The clinical effects of intrathecal morphine in contemporary surgery

M.V. Koning

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Mark Vincent Koning

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The Clinical Effects of Intrathecal Morphine in Contemporary Surgery

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Introduction and Aim of Thesis

Chapter 1

Postoperative analgesia

Postoperative pain management is important for clinical outcome

Postoperative pain requires adequate treatment, not only for ethical reasons, but also for medical reasons. Pain increases neuro-humoral activation with subsequent cardiovascular and immunological compromise. It may also immobilize a patient with subsequent risks for ileus and pneumonia. Furthermore, it may increase the risk for chronic pain.[1] Consequently, the treatment of pain should aim to reduce pain and avoiding complications in the postoperative course, while facilitating fast recovery of surgery. In addition, pain management has to be effective and reliable and the benefits has to outweigh the risks. The cure should not be worse than the cause.

The most effective method of postoperative analgesia depends on surgical, patient and logistic factors. The type of surgery determines the location, duration and severity of postoperative pain.[2] Pain management should fit within such a profile. The goals of the postoperative phase should be considered, since after some surgical procedures early mobilization is not possible, while after other procedures it is crucial. This affects pain and analgesic options. Patient factors include the preoperative presence of chronic pain with secondary sensitization, chronic analgesics use, contra-indications to types of analgesia and interactions with comorbidities or medication. Logistic factors such as the availability of a pain service, sufficient nursing staff, local experience and the availability of devices such as infusion-pumps are important for the analgesia options.

These considerations require an adaptive pain management per hospital and the preferred analgesic method per type of surgery needs to be adjusted to patient specific factors.

Since surgical techniques have changed for abdominal surgery, analgesic techniques has to adapt as well.

The preferred method of postoperative analgesia is primarily determined by the type of surgery. In the past twenty years, laparoscopic surgery has evolved to a main technique of abdominal surgical procedures and robot-assisted surgery is developing. Both approaches resulted in less tissue damage compared to open abdominal surgery, which lead to a shorter duration of postoperative pain.[2] In

addition, Enhanced Recovery Programs changed the course and goals of the postoperative phase for patients. Key elements of recovery after abdominal surgery are early mobilization and enteral nutrition.[3] The method of analgesia should facilitate these key elements, while side-effects such as sedation, nausea and vomiting should be minimized. Consequently, postoperative analgesia has to be adapted to the surgery-specific properties of postoperative pain and the goals of postoperative recovery. Thus when surgical techniques change, a change of the method of analgesia should be considered.

Which outcome measure is relevant for postoperative analgesia related research?

The effect of any analgesic method can be measured in several outcome measures. Specific pain-related outcome measures are available, such as pain scores, opioid consumption and time to first analgesic request. Other outcome measures of general aspects including patient satisfaction, quality of recovery, time to fit-for-discharge, length of hospital stay or the occurrence of complications are in part influenced by analgesic management as well.

Each outcome measure has inherent disadvantages. Pain scores can be affected by the interviewer or methods of surveying, which reduces the objectivity.[4] Postoperative opioid consumption is affected by availability and side effects of opioids, making it not solely a reflection of pain.[5] General outcome measures of recovery are influenced by many other factors than pain and provide a more general perspective of recovery, but may lack sensitivity for a specific analgesic intervention.[6]

Because all these types of outcome measures are in part unreliable, a study investigating only one outcome measure risks an incomplete and thus unreliable perspective of the intervention. Ideally, studies measuring post-operative analgesia should measure a combination of outcome measures, consisting of at least a subjective pain score, a measurement of analgesia consumption and a general recovery outcome measure. The latter should be determined by the type of surgery. For example, in intestinal surgery, the length of hospital stay is mainly determined by postoperative intestinal recovery. Postoperative analgesia influences intestinal recovery, making the time to fit-for-discharge a relevant

outcome measure in this situation. Conversely, the time to hospital discharge in Robot-Assisted Laparoscopic Prostatectomy is predominantly set by a time to detect early complications and not influenced by post-operative recovery. In this situation, the quality of analgesia is not reflected in the length of hospital stay.

There is no golden standard to determine the quality of postoperative analgesia. Therefore, a study involving pain management should investigate multiple types of outcome measures, since only the combination will provide sufficient information regarding the overall effect of analgesia.

Intrathecal morphine

Pharmacological considerations of intrathecal morphine as postoperative analgesia

Intrathecal morphine has been used since 1979 for analgesia.[7] A continuous infusion is used for chronic pain, but a single shot technique is often used for perioperative analgesia. The latter is predominantly used in lower extremity surgery and caesarean sections, but it has been a common method of analgesia in cardiac surgery as well.[8]

From a pharmacodynamical perspective, intrathecally administered morphine acts specifically on the opioid-receptor in the spinal cord and in some degree even on a supraspinal level.[9] Unlike other opioids, such as meperidine, low dose morphine acts only on the opioid-receptor.[10] This results in an antinociceptive effect without side effects due to sympathetic or motor nerve block, such as hypotension or paralysis.

Pharmacokinetics are a major determinant of the analgesic profile of intrathecal morphine. A low dose of intrathecally administered morphine has a duration of action over 24 hours and does not result in a clinically effective concentration of morphine in the blood.[11] This effect is mainly caused by the hydrophilic nature of morphine, which results in a slow diffusion out of the cerebrospinal fluid and thus a slow clearance from the effect site. Furthermore, due to its small volume of distribution, a low dose of morphine yields a high concentration in the cerebrospinal fluid, with a corresponding high potency. The volume of distribution of the other compartments is much larger, making the concentration of morphine insignificant.[12] This is schematically displayed in figure 1.

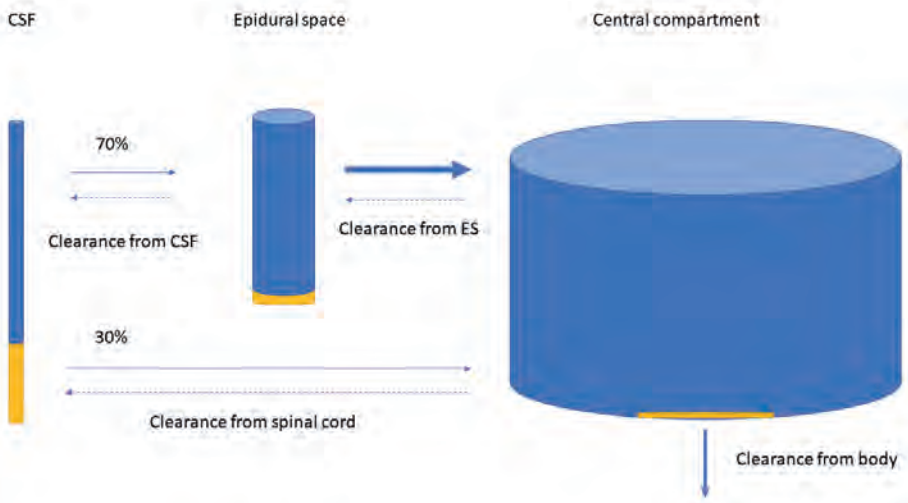

Figure 1. *A simplified display of pharmacokinetics of intrathecal morphine, based on data from Ummenhofer et al.[12]. When a dose of morphine (yellow bar) is injected in to the cerebrospinal fluid (CSF), a high concentration is achieved, due to a low volume of distribution. The slow clearance of the morphine out of the CSF into the epidural space (arrow) is driven by the concentration gradient. Approximately 30% of the morphine is cleared through the venous plexus of the spinal cord. The volume of distribution of the epidural space (ES) is larger, resulting in low concentrations (yellow bar) and no redistribution (dotted arrow). Similarly, morphine is cleared from the ES to the central compartment, where this is hepatically cleared from the body. The central compartment has a much larger volume of distribution, yielding low concentrations of morphine in this compartment as well (yellow bar).*

Another pharmacokinetic aspect is the rostral spread of lumbar injected morphine. Morphine appears not to readily dissolve in the CSF, because a concentration gradient between the injection site and distant sampling sites remains.[12-14] The high concentration found near the injection site, is slowly carried upwards with the bulk flow of the cerebrospinal fluid and exerts a respiratory depressive effect when it reaches the brain.[15]

Anatomical considerations of intrathecal morphine

The anesthesiologist needs to consider the anatomical pathways in order to choose an optimal method of abdominal analgesia. Abdominal pain can be divided in visceral pain and somatic pain, both of which are present in postoperative pain after abdominal surgery (Figure 2).

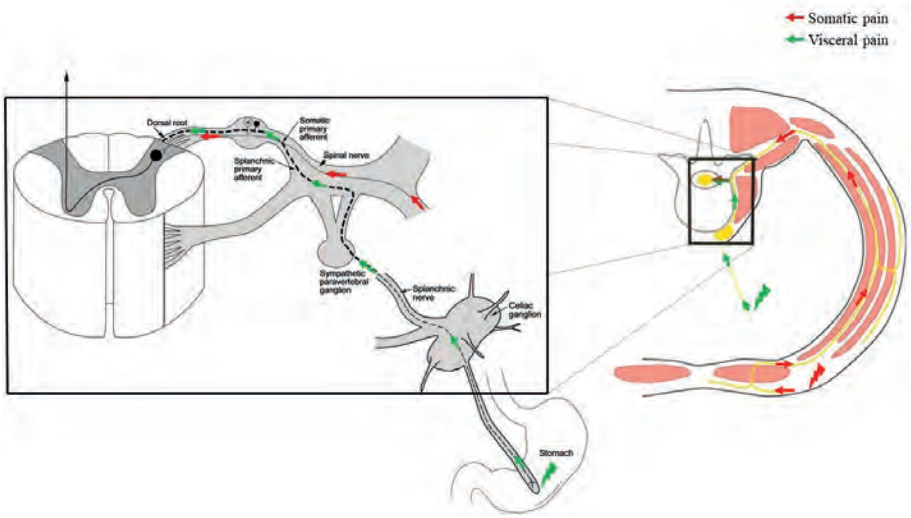

***Figure 2**. An illustration of abdominal pain pathways. Abdominal pain can originate from visceral or somatic pathways. The overall schematic of the abdominal wall on the right side illustrates that somatic pain originates from the abdominal wall and visceral pain originates from the viscera. Both pathways travels through the dorsal root towards the spinal cord and towards the brain. Adapted from Abram.[16]*

Visceral pain is caused by noxious stimuli of the intra-abdominal nociceptors, which is conducted by Aδ and C fibers, via the hypogastric and celiac plexus, to the dorsal root, into the spinal cord. In the dorsal horn of the spinal cord, the primary afferent synapses with the spinothalamic tract and the pain sensation is transferred to the brain.[16] Depending on the localization of the stimuli, the level of entrance in the spinal cord can be in the lumbosacral region for lower abdominal pain or lower thoracic region for higher abdominal pain.[16] In addition, multiple primary afferent nerves may be stimulated and entrance of pain sensation into the spinal cord may occur at multiple levels.[17]

Somatic pain is caused by noxious stimuli of the abdominal wall and Aδ and C fibers in the peripheral nerves transfer the stimuli to the dorsal root, into the spinal cord after which they are transferred via the spinothalamic tract to the brain.[16] The level of entrance in the spinal cord is also dependent on the localization of the stimuli and follows dermatomal distribution.[16]

These pathways are important to consider when understanding the effects of a neuraxial or regional method of analgesia. Peripheral nerve blocks or wound-

infiltration analgesia only block the somatic pathway, while neuraxial techniques block both the visceral and the somatic pathway.

Methods of analgesia for abdominal surgery: epidural analgesia, regional analgesia, systemically administered opioids and intrathecal morphine.

Several methods of analgesia are available for the treatment abdominal analgesia,. Most commonly used are epidural analgesia, regional nerve blocks (transverse abdominal plain (TAP-)block), systemically administered opioids and intrathecal hydrophilic opioids. The systemically administered opioids can be administered either orally, intramuscularly or intravenously per patient controlled analgesia-pump (PCA-pump). Properties of these methods of analgesia are summarized in table 1.

Epidural analgesia is commonly administered continuously through a catheter. The advantage of the catheter is the ability for prolonged analgesia, but the disadvantages of a catheter are the risk of dislocation and the incompatibility with use of anticoagulation. Epidural analgesia blocks both visceral and somatic pain pathways by the use of local anesthetics. These local anesthetics also block sympathetic nerves, which results in vasodilation, hypotension and urinary retention. To some extent, even motor nerves may be blocked, resulting in muscle weakness, which may hamper mobilization. Lipophilic opioids are often added to the epidural infusion, in order to reduce the dose of local anesthetics and thus the side effects. Unfortunately, lipophilic opioids are quickly absorbed systemically, which may result in side effects as well. Furthermore, the reported success rate of epidural analgesia is around 80% and declines over the duration of epidural analgesia.[18]

The most reported regional nerve block for abdominal surgery is the TAP-block.[19] This block is an ultrasound-guided technique in which the peripheral nerves conducting the somatic pain are blocked by local anesthetics. This technique does not address the visceral pain pathway. Most often, a single shot technique is used, which results in a duration of analgesia of approximately 12-24 hours, which is limited compared to catheter-techniques. The benefits of a TAP-block are the opioid sparing effects, the ease of administration, the limited adverse effects such as absence of motor block or the need for urinary catheter.

Systemically administered opioids can be administered as needed or routinely and through different routes, such as orally, intravenously, subcutaneously or intramuscularly. Commonly, opioids are administered by a PCA-pump, in which patients can self-administer opioids as needed, within set limits. Dosing of systemic opioids can be repeated or continued, providing a duration of action as long as required. The main benefit of the systemic opioids is the ease of administration, because no advanced techniques are required for analgesic effect. No specific pain pathway is blocked, because all opioid-receptors in the body are agonized. The downside is the limited analgesic effect, possibly due to the side-effects, which are nausea, vomiting, somnolence, obstipation and delirium. It is common practice to add other analgesics with other modes of analgesia, such as paracetamol, non-steroidal anti-inflammatory drugs, gabapentinoids or intravenous lidocaine. This multimodal analgesia aims to decrease opioid consumption and consequently side-effects, but the extent of opioid sparing effect varies per study, combination of medication and type of surgery.

Intrathecally administered morphine is an alternative method of administration of opioids which stimulates the opiate receptor in the dorsal horn in the spinal cord, which inhibits both visceral and somatic pain pathways. The duration of analgesia is around 24 hours and cannot be prolonged when analgesia has worn off. The success rate of an intrathecal injection is higher than the success rate of insertion of an epidural catheter.[18,20] Additionally, because the analgesic effect is caused by opiate receptors, sympathic and motor nerves remain intact, resulting in no vasodilation or muscle weakness. Disadvantages are related to the side-effects, which are nausea, pruritus and urinary retention. Furthermore, due to the slow rostral spread of morphine towards the brain, a late respiratory depression may occur. Typically, this effect is reported around 3.5 to 12 hours after intrathecal injection and is dose dependent.[21] However, this adverse event seems to be dose dependent and unlikely to occur in low doses.[21]

Based on these properties, intrathecal morphine may be a suitable technique for laparoscopic abdominal surgery, because the duration of action matches the duration of pain[12], both somatic and visceral pain pathways are blocked, it has little systemic or sedative effects and is it unlikely to inhibit mobilization and tolerance to enteral nutrition. Still, its clinical value in laparoscopic surgery has yet to be determined.

Table 1: Summary of the properties of the four common methods of analgesia for laparoscopic surgery.

	Epidural analgesia	Regional nerve blocks	Systemic opioids	Intrathecal morphine
Advanced Technique	Catheter technique, operator dependent	Single Shot Technique, operator dependent	No advanced technique	Single Shot Technique, operator dependent
Type of analgesia	Visceral and somatic analgesia	Somatic analgesia	Peripheral and central anti-nociception	Visceral and somatic analgesia
Duration of action	As long as the catheter is in place	18-24 hours	As long as dosing is continued or repeated	24-30 hours
Success rate	80-90%, decreasing over the duration of analgesia	85-95%	100%	>95%
Common side effects	Motor block, hypotension, pruritus and urinary retention	None	Nausea, vomiting, constipation, pruritus, urinary retention and sedation	Nausea, vomiting, pruritus and urinary retention
Anticoagulation	Prohibited during placement, treatment and up to 24 hours after removal of the catheter.	Independent of coagulation status	Independent of coagulation status	Prohibited during injection and up to 24 hours after injection.

Not only for abdominal surgery?

As described previously, intrathecal morphine is also used for analgesia after lower extremity surgery, especially in elective hip or knee replacement surgery.[8] For this indication it has been proven to reduce opioid consumption.[22] However, in these types of surgery the urinary retention is a limitation for the postoperative course, because of the need for urinary catheter might hamper mobilization and increase the risk of a urinary tract infection.[23]

These contraindications are not applicable for emergency hip fracture surgery. Patients for this type of surgery are often old and frail and early postoperative mobilization is not as advocated as in elective lower extremity surgery. In addition most patients undergoing emergency hip fracture surgery already have an urinary catheter.

Moreover, the most common complication after hip fracture surgery is delirium.[24] Several risk factors for delirium are identified, which can be classified as modifiable and non-modifiable risk factors.[25] Pain and systemic opioid consumptions are identified as modifiable risk factors. Intrathecal morphine may reduce both factors and thereby reducing the incidence of delirium.

Thus, the potential benefits of intrathecal morphine may decrease the common complication of delirium and the need for a urinary catheter is not a disadvantage in this situation, Therefore, the advantages of intrathecal morphine may outweigh the disadvantages in this procedure.

So far, anesthesia for hip fracture surgery has predominantly focused on the question whether spinal anesthesia is better than general anesthesia on various outcome measures, such as mortality and postoperative complications.[26] This question is oversimplified, because there is no single type of spinal anesthesia, just as there is no single type of general anesthesia. The choice, timing and dose of the medication determines the anesthesia, not the route of administration only. Therefore, spinal anesthesia with local anesthetics only is not the same as spinal anesthesia with intrathecal morphine and studies comparing general anesthesia versus spinal anesthesia cannot be transferred to spinal anesthesia with intrathecal morphine. Whether spinal anesthesia with intrathecal morphine reduces postoperative delirium after emergency hip fracture surgery requires a study of its own.

Aim of thesis

This thesis aims to investigate intrathecal morphine in contemporary surgical practice and specifically investigate patient-related outcome measures.

Guidelines for analgesia in intestinal surgery recommend epidural analgesia, based on studies in open abdominal surgery.[27] This recommendation is transferred to laparoscopic surgery, although the level of evidence is limited.[3] Intrathecal morphine is mentioned in the current Enhanced Recovery After Surgery guidelines, but a lack of evidence hinders a firm recommendation.[3] So far, intrathecally administered morphine for laparoscopic colonic surgery was first investigated in 2002 and two small randomized trials has been reported.[28-30]

The following questions were raised:

1. What type of analgesia is used in the Netherlands for laparoscopic colorectal surgery? (Chapter 2)

2. Does intrathecal morphine lead to a faster postoperative recovery than systemic opioids after laparoscopic intestinal surgery in an Enhanced Recovery Program? (Chapter 3)

Robot-Assisted Radical Prostatectomy is nowadays a common method of prostatectomy, because it results in less bleeding, nerve damage and complications compared to open prostatectomy.[31] Still, a quality assessment in the Maasstad Hospital found that severe postoperative pain and bladder discomfort remains a problem in over 10 percent of the patients. This was in line with the results from observational studies.[31, 32] One of the side effects of intrathecal morphine, urinary retention, is not an issue following this surgery, since all patients receive an urinary catheter for a week. Thus, the use of intrathecal morphine could potentially have a beneficial effect on postoperative pain and quality of recovery, while it has minimally negative impact on the postoperative recovery. The question was raised:

- Does intrathecal morphine enhances quality of recovery after a robot-assisted radical prostatectomy compared to systemically administered opioids? (Chapter 4)

Multiple studies investigated the effects of an intrathecally administered hydrophilic opioid, in various types of abdominal surgery. This led to an opportunity to quantify the advantages and disadvantages of this method of analgesia in abdominal surgery. The main question was:

- What is the "opioid sparing" effect of intrathecal morphine in abdominal surgery? (Chapter 5)

As mentioned, the opioid sparing effects may also be beneficial in reducing the incidence of delirium elderly patients after surgery. Especially elderly patients receiving surgery for proximal femur fractures suffer from a high incidence of delirium.[24] The cause seems to be multifactorial, two of which are systemic opioid use and pain.[25] Administration of intrathecal morphine may exert a systemic opioid sparing effect and provide adequate levels of analgesia for these patients, which could contribute to a lower incidence of delirium. This led to the following question:

- Can the opioid sparing-effect of intrathecal morphine reduce the incidence of delirium after proximal femur fractures? (Chapter 6)

Since the dose of intrathecal morphine is important for the risk-benefit-ratio, it is important to consider how this dose is achieved. In daily practice, two common options are to dilute the morphine from a high concentration manually or to use pharmacy-prepared concentrations of morphine. Still, a high dose can be administered inadvertently and early recognition and supportive care is important to avoid adverse effects. Therefore we had the following questions:

- Is manually diluted morphine safe to administer in terms of dose and contamination? (Chapter 7)

- What are the symptoms of an inadvertent overdose of intrathecal morphine? (Chapter 8)

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Ambiguous policies in anesthetic pain management in laparoscopic colonic surgery: A national survey

E.E. van Houwelingen, M.V. Koning, A.J.W. Teunissen, R.J. Stolker

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Chapter 2

Abstract

Background

The goal of postoperative care is no longer solely adequate pain relief since other outcomes (e.g. mobilization, length of hospital stay) have become increasingly important. Enhanced Recovery After Surgery (ERAS)-guidelines recommend the use of epidural analgesia and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). However, this practice have been challenged, due to the association of epidural analgesia with prolonged recovery and the use of NSAIDs with anastomotic leakage. Aim of this survey was to investigate the extent of difference in postoperative pain management after colonic surgery.

Methods

Anesthesiology departments from all 86 Dutch hospitals were contacted and a questionnaire was submitted. Respondents were questioned about pain management, which drugs are used and experience with intrathecal opioids in laparoscopic colonic surgery.

Results

The response rate was 85%. 55% of the hospitals used epidural analgesia and 21% used patient controlled analgesia as primary pain modality ($P<0.01$). Epidural analgesia was used more in general hospitals than in university hospitals (58% vs. 14% respectively, $P = 0.045$). NSAIDs were prescribed in 45 Dutch hospitals (62%). Overall use of intrathecal long acting opioids for postoperative pain was 22%. 48% was unfamiliar with the use of intrathecal opioids for laparoscopic colonic surgery.

Conclusions

Epidural analgesia is used in the majority of Dutch hospitals for laparoscopic colonic surgery. NSAID's are predominantly used in combination with Patient Controlled Analgesia. The use of single shot intrathecal morphine is not common, especially not for laparoscopic surgery. This survey gives an adequate reflection of Dutch anesthetic management in laparoscopic colonic surgery.

Introduction

The goal of postoperative care is no longer solely adequate pain relief since other outcomes (e.g. mobilization, length of hospital stay, return of bowel function and prevention of adverse events) have become increasingly important. This is reflected in guidelines for Enhanced Recovery After Surgery (ERAS) after colonic surgery.[1] In this guideline it is recommended to use as few opioids as possible by administering multimodal analgesia with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and epidural analgesia.

Regarding postoperative pain management in laparoscopic colonic surgery, controversies arose in the past years. Laparoscopic surgery is still associated with high postoperative pain intensities in the first 24 hours after surgery.[2] However, some reported that epidural analgesia prolongs length of hospital stay (LOS) after surgery.[4-7] Other modalities of pain management, such as Patient Controlled Analgesia (PCA) or single shot spinal anesthesia with long acting opioids might be attractive alternatives due to the high effectiveness of analgesia and less effect on length of hospital stay and mobilization.[5,8, 9] Another controversy is the use of NSAIDs. Some retrospective reports state that the use of NSAIDs is associated with increased anastomotic leakage, although two recent meta-analyses could not confirm this statement.[10, 11]

The Dutch guideline of postoperative pain management leaves space for local variation.[12] We undertook a national survey to study the practice of pain management in laparoscopic colonic surgery. The objective of this survey is to investigate the extent of difference in pain management, the familiarity with intrathecal analgesia for laparoscopic colonic surgery and the rationale for their preferred method of analgesia. With this knowledge, we aim to give insight in daily practice and considerations with regard to anesthetic pain management in laparoscopic colonic surgery.

Methods

The survey was conducted from November 2014 to Match 2015. The attending anesthesiologists from all 86 anesthesiology departments in the Netherlands were contacted by telephone to ask for cooperation with the survey. The questionnaire could be answered by telephone or by email. Up to three reminders were send when the respondent opted for cooperation. Anonymity was guaranteed for the publication of data, however the investigators were not blinded.

The respondents were questioned about the following aspects of pain management in laparoscopic colonic surgery, 1) what kind of pain management is used in your hospital in what percentage of the patients, 2) which drugs are used, 3) why is the chosen pain management preferred and 4) which co-analgesics are given. In order to investigate the familiarity with intrathecal opioids the respondents were questioned 5) are intrathecal long-acting opiates given in any type of surgery, 6) what experience do you have with long acting opiates and 7) if long acting opiates are administered, are there any specific arrangements or precautions undertaken. After this section, respondents were asked 8) what would be necessary to implement single shot long acting opiates in laparoscopic colonic surgery, 9) are you familiar with single shot long acting opiates in the pain management of laparoscopic colonic surgery? The full questionnaire is included in appendix A. It was emphasized that the answers should reflect departmental policies rather than individual practice.

Based on the first question, the respondents were classified according to primary technique. Primary technique was defined as the technique used in 75% or more of the patients. It was categorized as “Epidural”, “PCA”, “combination” and “other”. The combination group consisted of hospitals which used epidural and PCA-analgesia, but neither one was a primary technique. The category of “other” consisted of hospitals which used oral or intramuscular opioids, sometimes combined with ketamine and/or gabapentinoids.

Data are presented as percentages or numbers of respondents. For categorical data a Fisher’s exact test is performed by SPSS 23.0 (IBM, Armonk, NY, U.S.A.).

Results

The overall response rate by mail (n=9) or telephone (n=64) of the questionnaire was 85% (73 hospitals in the Netherlands). Seven of the 8 Dutch university hospitals responded (88%).

Current pain management in laparoscopic colonic surgery

Table 1 displays the frequency of the used analgesic modality. Fifty-five percent of the hospitals used epidural analgesia and 21% used PC A-administered opioids as a primary modality. The most used drugs for epidural analgesia were bupivacaine (56%), ropivacaine (36%) and levobupivacaine (8%). Except one, all hospitals used bupivacaine/ropivacaine in combination with an opioid (sufentanil 86%, morphine 8%, fentanyl (4%). One hospital added clonidine to a mixture of a local anesthetic and an opioid. The most commonly used combination was bupivacaine 0.125% with sufentanil 0.5-2 mcg/ml. Eleven percent used other analgesics than epidural analgesia or PCA, which were predominantly oral oxycodone or subcutaneous opioids. Another 13% had no primary technique and was applying various methods of analgesia between patients, most often epidural analgesia and PCA. General hospitals used epidural analgesia more often than university hospitals as a primary modality (58% vs. 14%, P=0.045). Only 1 of all 73 hospitals administered intrathecal opioids in 1-25% of the patients for elective laparoscopic colonic surgery.

Table 1. The frequencies of primary technique of analgesia (defined as >75% of the patients) are presented as n(%). PCA: Patient Controlled Analgesia, NSAID: Non-Steroidal Anti-Inflammatory Drugs. * p=0.045, ^ p=0.013.

	Epidural	PCA	Combination	Otherwise
All Hospitals	40 (55%)	15 (21%)	10 (13%)	8 (11%)
Academic	1 (14%)*	2 (29%)	3 (43%)	1 (14%)
General	39 (58%)*	13 (20%)	7 (11%)	7 (11%)
Co-analgesia				
NSAIDs	19 (48%)^	13 (87%)^	6 (60%)	7 (88%)
Only acetaminophen	21 (52%)	2 (13%)	4 (40%)	1 (12%)

Co-analgesics

All hospitals prescribed paracetamol as a co-analgesic. However, NSAIDs were prescribed in 45 Dutch hospitals (62%), without a difference between the

university and general hospitals (71% vs 61% respectively, p=0.70). Table 1 also shows that NSAIDs were prescribed less when epidural analgesia was the primary form of pain management when compared with PCA (48% and 87%, P=0.013). In 8 hospitals (11%) other pain medication was prescribed, such as ketamine, clonidine or gabapentinoids in addition to paracetamol, NSAIDs and opioids per requisite as standard pain management.

Reasons for using primary technique

Table 2 displays the percentage of reported reason for using a primary modality. The return of bowel function was the most reported argument for epidural analgesia. In general, when epidural analgesia was not the primary technique, non-invasiveness was an important argument.

Table 2. The reported reasons why an analgesic modality was chosen. Percentage is the percentage of respondents reporting that argument. Multiple arguments per respondent were possible. PCA: Patient Controlled Analgesia. ERAS: Enhanced Recovery After Surgery.

Epidural	PCA	Other analgesics
Fast return of bowel function (49%)	Epidural not indicated (40%)	PCA/epidural not necessary (57%)
High success rate (33%)	Non-invasive nature (33%)	Non-invasive nature (43%)
ERAS-protocol (26%)	High success rate (20%)	High success rate (29%)
Less systemic opioids (26%)	Low-risk modality (13%)	Convenience for nursing staff (14%)

Familiarity with intrathecal opioids

The overall use of intrathecally administered long acting opioids in Dutch hospitals was 22%, it was mostly used in orthopedic surgery and cesarean sections and morphine was the only opioid reported. Dosage ranged from 100 to 500 mcg. The most associated or feared adverse effects of intrathecal long acting opioids were pruritus (70%), nausea (29%), respiratory insufficiency (18%), urinary retention (5%), hypotension (3%) and dosage errors (3%). Respiratory insufficiency appeared to be reported less by hospitals that used intrathecal morphine when compared to hospitals that did not (7% vs. 22%, p=0.177). Sixty-nine percent of the hospitals take no additional measures for postoperative monitoring. In 6% of the hospitals, patients stayed on the intensive care unit for one night and in 13% patients got a urinary catheter.

Implementation of intrathecal long acting opioids for laparoscopic colonic surgery

Forty-eight percent of the respondents were unfamiliar with the use of intrathecal opioids for laparoscopic colonic surgery. For implementation the respondents reported that more research was needed (52%), a guideline was desirable (19%) and 26% reported that intrathecal opioids were not necessary at all. The hospitals with experience with intrathecal morphine seem to request more often additional research before implementation (55% vs 36%, p=0.152).

Discussion

This national survey has a high response rate. Key findings of this survey were the clear differences in policies concerning pain management in laparoscopic colonic surgery in Dutch hospitals. In most of the Dutch hospitals (59%) epidural analgesia is the primary technique, while PCA is the second most used modality (21%).

In the past decennium several studies investigated pain management for laparoscopic surgery. Laparoscopic surgery is still associated with high postoperative pain intensities in the first 24 hours after surgery.[2] And although the use of epidural analgesia gives excellent pain relief during the initial period after surgery, this benefit is limited by a relatively high failure rate.[13,14] Another perceived benefit of epidural analgesia is its positive effect on bowel function, as showed by a meta-analysis.[15] However this conclusion is based predominantly on two studies without an ERAS-program and with a relatively long length of hospital stay.[15-17] Epidural analgesia was associated with prolonged length of hospital stay and delayed medical recovery when an ERAS-program was followed. This was due to the need of vasoactive medication treating hypotension.[4,5] Furthermore, it probably serves no benefit for gastrointestinal function in laparoscopic surgery as opposed to laparotomic surgery.[18] Even though these studies indicate that the benefits of epidural analgesia may not outweigh the disadvantages, it still remains the most common method of analgesia in the Netherlands. Interestingly, the most reported reason in this survey for using epidural analgesia (enhanced return of bowel function) is not supported by literature.

A difference was seen in the use of epidural analgesia between general hospitals and university hospitals (58% vs. 14% respectively, P=0.045). This difference might have numerous explanations, such a difference in success rate of epidural

analgesia, perhaps due to young residents, local experience, type of surgery, co-morbidity of patients and its related medications (e.g. anticoagulants) or an earlier translation of recent research findings[4,5] into clinical practice in the academic hospitals. However, this remains speculation since this study was not designed to comment on this difference.

NSAIDs were used in 48% of the hospitals when epidural analgesia is the primary technique, while they were prescribed in 87% of the hospitals which used predominantly PCA. The use of NSAIDs is recently challenged because a claimed association with anastomotic leakage.[10,19,20] Especially non-selective NSAIDs may be associated with anastomotic leakage compared to selective cyclooxygenase-2-inhibitors after colorectal surgery.[21] However, this association is based on non-randomized prospective and retrospective studies. In a recent meta-analysis, the power of these pooled results was too low to detect any significant difference in anastomotic leakage.[11] Moreover, in randomized controlled trials the use of NSAIDs have demonstrated to lower pain scores, decreased use of systemic opioids, shortened length of hospital stay and reduced postoperative bowel impairment after colonic surgery.[22,23] For epidural analgesia, however, one can question the addition of NSAIDs. In cesarean sections it appears that the addition of NSAIDs to epidural analgesia leads to less or delayed use of rescue analgesics but it made no difference in pain perception, patient satisfaction or functional recovery.[24,25]

Intrathecal opioids for laparoscopic surgery were used in only one hospital. The only long acting intrathecal opioid reported to be used in the Netherlands is morphine. It is administered in 22% of the hospitals, in particular in orthopedic surgery and cesarean sections in doses of less than 500 micrograms. Respondents associated intrathecal morphine with pruritus, nausea, respiratory insufficiency and urinary retention. Assumedly, these side effects may limit it widespread use in Dutch practice, while in other European countries it is more commonly used.[26,27] Regarding the side effects, pruritus is more common after intrathecal administration of morphine with relative risk of 1.8 (95%-CI 1.4-2.2), but nausea and vomiting are not more common than with intravenous opioids when a dose $<$300 mcg is used.[28] Furthermore, both 5-HT_3 receptor antagonists and droperidol are effective and recommended in the prophylaxis of pruritus due to intrathecal opioids.[29,30] There is a large variance in the incidence of respiratory depression, due to the lack of a clear definition and a large variance in administered dosage. Two

meta-analysis reported two different conclusions. Meylan et al. stated that there is an increased risk in respiratory depression, although they did not search for a dose-dependent effect.[31] Gehling et al. stated that an intrathecal dose < 300 mcg of morphine does not lead to an increased incidence of respiratory depression, while larger doses did so indeed.[28] A dose < 300 mcg of morphine is also recommended in abdominal surgery.[32] Another concern are medication errors which are easily made when morphine has to be diluted to lower concentrations.

Ten percent of the respondents feels that ready to use ampoules should be available and that this could lower the probability of a medication error. Urinary retention is indeed a common side effect of intrathecal morphine use.[33]

Intrathecal morphine in a dose of 300 mcg could be a promising technique of analgesia for laparoscopic gastrointestinal surgery.[5-7,28,32] Still, its benefit has yet to be proven in regard to patient satisfaction or functional recovery after surgery. We initiated a randomized controlled trial to investigate this in Dutch practice (registered at clinicaltrials.gov with number NCT02284282). Remarkable is that many respondents (26%) stated that implementation of intrathecal morphine as an analgesic modality is not necessary, even if it proves to lead to enhanced recovery and better patient satisfaction.

Even though this survey leads to an insight in Dutch practice it has several limitations. One limitation is that almost all respondents were approached by telephone during daytime, which could lead to rushed interviews. However, an internet based questionnaire was offered, as well as phone call on a different day. Furthermore, the telephonic interview has the advantage for elaboration, explanations and clarification of questions or answers. Another limitation was the fact that only one representative in a hospital was questioned instead of the entire department. However, it was emphasized that the answers should reflect hospital policies rather than individual practice. We have chosen this strategy in order to achieve a high response rate, which we believe gives an adequate reflection of common practice in Dutch hospitals.

In conclusion, this survey shows that epidural analgesia is used in the majority of Dutch hospitals for laparoscopic colonic surgery, despite recent investigations challenging the superiority of this form of pain management. Despite some concerns, NSAIDs are commonly used, predominantly in combination with PC A.

Single shot intrathecal morphine is not common in Dutch hospitals, especially not for laparoscopic surgery. It is a remarkable finding that despite evidence 26% of the respondents finds it not necessary to implement the use of intrathecal opioids. This survey gives an adequate reflection of Dutch anesthetic management in laparoscopic colonic surgery.

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Appendix A. Questionnaire

(translated from Dutch).

1. Please state how often the following analgesia methods are applied in your hospital for laparoscopic gastro-intestinal surgery (e.g. Hemicolectomy, (partial) gastric resections, sigmoidectomy, etc.). Please give in percentage of the patients.
   - PCA … %
   - Epidural analgesia …%
   - Spinal analgesia …%
   - Otherwise …% (such as:……)

2. Which medication and what dose do you use per method applied in question 1.

3. What is the reason for the preference of the most applied method of analgesia (multiple answers are possible):
   - non-invasive nature
   - high successive rate
   - sympathic blockade
   - positive effect on bowel function
   - too limit the use of systemic opioids
   - the lack of necessity for postoperative visits
   - otherwise, such as:…..

4. Which co-analgetics are prescribed:
   - Acetaminophen
   - NSAID's
   - Metamizole
   - Others (gabapentin/pregabalin/ketamine/lidocaine/ketamine/clonidine)
   - Others (not yet mentioned), such as:….

5. Do you use intrathecal long acting opioids (such as morphine) for any type of surgery?
   - Yes/No

6. If so, which opioid, what dose and which indications?

7. Which effects do you see/associate with intrathecal long acting opioids? (multiple answers are possible)
   - Nausea
   - Beneficial effect on pain
   - Hypotension
   - Pruritus
   - A limited effect on pain
   - Respiratory depression
   - Otherwise, such as.....

8. Do you take postoperative measures or precautions when intrathecal long acting opioids are used?

9. What would be necessary to implement intrathecal long acting opioids as analgesia for laparoscopic gastro-intestinal surgery?
   - More research/scientific articles
   - A national guideline with recommendations for dose and indication
   - Ready to use ampoules
   - More or prolonged postoperative monitoring abilities
   - Others, such as....

10. Were you familiar with the use of a single shot intrathecal injection with long acting opioids as method of analgesia for laparoscopic surgery?
    - Yes/No

Intrathecal morphine for laparoscopic segmental colonic resection: a randomized controlled trial

M.V. Koning, A.J.W. Teunissen, E. van der Harst, E.J. Ruijgrok, R.J. Stolker.

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Chapter 3

Abstract

Background

Management of postoperative pain after laparoscopic segmental colonic resections remains controversial. We compared 2 methods of analgesia within an Enhanced Recovery After Surgery (ERAS) program. The goal of the study was to investigate whether administration of intrathecal bupivacaine/morphine would lead to an enhanced recovery.

Methods

A single-center, randomized, double-blind controlled trial was performed (NL43488.101.13). Patients scheduled for laparoscopic segmental intestinal resections were considered. Exclusion criteria were patients in whom contraindications to spinal anesthesia were present, conversion to open surgery, and gastric and rectal surgery. The intervention group received single-shot intrathecal bupivacaine/morphine (12.5 mg/300 μg), with an altered dose for older patients. The control group received a sham procedure and a bolus of piritramide (0.1 mg/kg). Both groups received standardized general anesthesia and a patient-controlled intravenous analgesia pump as postoperative analgesia. All patients were treated according to an ERAS protocol. A decrease in days to "fit for discharge" was the primary outcome.

Results

Fifty-six patients were enrolled. Intervention group patients were fit for discharge earlier (median of 3 vs 4 days, $P = 0.044$). Furthermore, there was a significant decrease in opioid use and lower pain scores on the first postoperative day in the intervention group. There were no differences in adverse events (except for more pruritus), time to mobilization, fluid administration, or patient satisfaction.

Conclusions

This randomized controlled trial shows that intrathecal morphine is a more effective method of postoperative analgesia in laparoscopic surgery than intravenous opioids within an ERAS program. Recovery is faster and less painful with intrathecal morphine. Other studies have confirmed these results, although data on faster recovery are new and require confirmation in future trials.

Introduction

Enhanced Recovery After Surgery (ERAS) programs have changed postoperative management for abdominal surgery in the past decade. One of the recommendations in an ERAS protocol for colorectal surgery is to limit opioid use via administration of multimodal analgesics, including regional anesthesia techniques.[1] Thoracic epidural analgesia is recommended for open surgery; however, its use in laparoscopic surgery is associated with a prolonged length of hospital stay due to delayed mobilization.[2,3]

Pain after laparoscopic surgery is intense, but relatively short-lived when compared with open surgery, and the analgesia should be tailored accordingly.[4] Two common methods for post- operative analgesia in laparoscopic surgery are systemic opioids per requisite (e.g. patient-controlled intravenous analgesia [PCIA]) or intrathecal morphine.[2,5,6] The benefit of intrathecal morphine is limited systemic uptake due to its hydrophilic properties and thus a minor effect on bowel motility. Proclaimed disadvantages include the risk of an intrathecal injection, pruritus, and delayed respiratory depression.[7,8] However, when a low dose of morphine is used, there seems to be no more respiratory depression than with systemic opioids.[7] Patient-controlled intravenous analgesia has the benefit that the dose of opioids is matched to the patient's need, although its analgesic effect is limited by the patient's understanding and the adverse effects of the opioid.[9,10]

Previous studies on laparoscopic colonic resections have shown a decrease in systemic opioid use with an increase of quality of analgesia for intrathecal morphine when compared with PCIA.[2,5,6] However, recovery was measured only as length of hospital stay, and recovery protocols were not standardized. We therefore designed a confirmation trial with a few methodological adaptations in an existing ERAS program to investigate whether intrathecal bupivacaine and morphine can increase the speed of recovery after laparoscopic colonic resections. These adaptations include higher intrathecal morphine dose, similar postoperative analgesia, fluid-restrictive management rather than goal-directed fluid management, predefined "fit for discharge" (FFD) criteria, and a longer follow-up period. We hypothesized that intrathecal bupivacaine and morphine would enhance the speed of recovery by decreasing systemic opioid utilization and concomitant systemic adverse effects.

Methods

Study Design

The SALMON study (SpinAL MOrphiNe) was an investigator-initiated, single-center, randomized trial performed in a large teaching hospital. The study was approved by the ethics committee of Maasstad Hospital (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam, the Netherlands, NL43488.101.13) and CCMO (Dutch abbreviation for Central Committee on Research Involving Human Subjects). Patients provided written informed consent before enrollment. The study was registered as NCT02284282 at ClinicalTrials.gov on November 6, 2014, and as NTR4870 at trialregister.nl on October 29, 2014. This article adheres to the applicable EQUATOR guidelines.

Participants

All patients who were scheduled for laparoscopic gastrointestinal surgery between October 2014 and October 2016 were asked to participate. Exclusion criteria were as follows:

1. rectal and bariatric surgery;
2. contraindications to spinal anesthesia (e.g. severe aortic stenosis, increased intracranial pressure, coagulation disorders);
3. contraindications to study medication (allergy for morphine, local anesthetics [amides], nonsteroidal anti-inflammatory drugs, paracetamol, or glomerular filtration rate <30 mL/min);
4. conversion to an open procedure; and
5. scheduled postoperative intensive care unit admission.

Patients who were considered eligible for the study were informed on the preoperative screening unit with written and oral information. Within a week, the patients were called for further ex- planation and definitive inclusion. After inclusion of 2 patients for gastric resection, we concluded that this type of surgery has a different recovery profile than segmental colonic resections, and we eliminated them from analysis.

Randomization, Allocation, and Blinding

Randomization was conducted by using sealed, opaque envelopes. An independent colleague randomized these envelopes in blocks of 6 with a ratio of 1:1. These envelopes were stacked and stored. The upper envelope was taken by the attending anesthesiologist when an included patient arrived on the preparation ward. The patient, the surgical team, the nurses on the ward, and the researchers were all blinded. Only the attending anesthesiology team and the nurse on the recovery ward were aware of the randomization, in case there was an emergency. They were instructed not to tell the patient in which group he/she was allocated.

Study Protocol

All patients were prepared according to the ERAS protocol, consisting of a carbohydrate drink the night before surgery and no bowel preparation; 1000 mg intravenous (IV) cefazolin was administered 30 minutes before surgery. No sedative premedication was given. In the operation theater, the patients received standard monitoring (pulse oximetry, 3-lead electrocardiogram, automatic non-invasive blood pressure measurements every 3 minutes). After the time-out procedure, the surgical team left the theater for blinding. According to the envelope, the patient received either an intrathecal injection of bupivacaine/morphine or a sham procedure. In both cases, the patient was placed in an upright sitting position, and the skin over the lumbar region of the back was cleaned with chlorhexidine, and sterile drapes were placed.

For the intrathecal injection, the skin was infiltrated with 3 mL of lidocaine 1%. A sterile 27-gauge pencil-point needle (Pencan; Braun Melsungen AG, Melsungen, Germany) was used to enter the intrathecal space at the L2-3 or L3-4 interspace. After obtaining cerebrospinal fluid, medication was administered through a single injection; 12.5 mg isobaric bupivacaine and 300 µg morphine in 5 mL were administered when the age of the patient was younger than 76 years, and 10 mg isobaric bupivacaine and 240 µg morphine in 4 mL were given when the age was older than 75 years.

For the sham procedure, the skin was infiltrated with 3 mL of lidocaine 1%. After this, the anesthesiologist pressed on the skin with a finger and talked as if he/she gave an intrathecal injection. The patients who were randomized to the control group received 0.1 mg/kg piritramide intravenously during surgery, which was common practice in our hospital.

Standardized general anesthesia was administered immediately after the puncture. After preoxygenation, 0.4 μg/kg sufentanil, 2 mg/kg propofol, and 0.6 mg/kg of rocuronium were administered, and the trachea was intubated. Sterile drapes were placed after positioning of the patient, and the surgery was started as soon as possible. Pneumoperitoneum was installed by needle insufflation through a small periumbilical incision with an insufflation pressure of 14 mmHg and changed at the discretion of the surgeon. Standard IV medication of 1000 mg paracetamol, 1000 mg metamizol, 0.625 mg droperidol, and 4 mg ondansetron were given before the end of surgery. Ten micrograms of IV sufentanil was administered when an increase in heart rate or blood pressure of greater than 10% occurred compared with a stable phase during surgery. Ten milligrams of IV rocuronium was administered when ventilator dyssynchronization or abdominal wall contraction occurred that remained after 10 μg IV sufentanil. Vasoactive medication was given at the discretion of the executive anesthesiologist (i.e. phenylephrine, ephedrine, and norepinephrine). Every patient received an IV drip with 500 mL lactated Ringer's solution to keep an open IV line, and the targeted fluid balance was less than +750 mL. Blood loss was compensated with a blood transfusion according to the Dutch national guidelines, maintaining the hemoglobin level between 6.4 and 9.4 g/dL or Voluven (HES 130/0.4 [6%]; Fresenius Kabi, Bad Homburg, Germany) in a 1:1 manner, at the discretion of the anesthesiologist.

After completion of surgery, patients were allowed to wake up and were extubated in the operation theater. Nasogastric tubes were removed. A train-of-4 measurement was done in order to exclude residual relaxation. If necessary, rocuronium was antagonized with atropine/neostigmine or sugammadex at the discretion of the anesthesiologist.

Standard monitoring continued in the recovery ward. Pain scores (on a numerical rating scale [NRS]) were noted at admission to and discharge from the recovery ward and regularly at a 10-minute interval by the recovery nurse; 2.5 mg piritramide IV was administered when the patient reported an NRS of greater than 4 and repeated every 10 minutes if necessary. Nausea was treated with a repeated dose of 0.625 mg IV droperidol. Intravenous propofol 30 mg was available for complaints of pruritus. Discharge from the recovery unit to the ward was allowed when the patient was hemodynamically and respiratory stable, reported an NRS of less than 4, and had a Glasgow Coma Scale score of greater than 14. All patients

received 2 L of oxygen per minute by nasal cannula. Paracetamol 1000 mg 4 times a day, metamizol 1000 mg 4 times a day, and piritramide by PCIA system were prescribed as postoperative analgesic management. The PCIA was set up to give 1 mg of piritramide per bolus with a lockout time of 6 minutes. The PCIA system was stopped on the second postoperative day. Four milligrams of ondansetron per requisite was available for nausea, and 1 mg clemastine per requisite was available for pruritus. All patients received daily macrogol 13.7 g as a laxative.

An ERAS protocol has been fully functional for multiple years on the ward. It consisted of early enteral feeding (e.g. drinks immediately on arrival on the ward, a small meal on the night of surgery), early mobilization, and removal of the urinary catheter the day after surgery.

Data Collection

Baseline characteristics and laboratory results were noted from the patient data file. The anesthesia team was asked to fill in a case record form during the surgery and the recovery phase.

The patients were asked to fill in a questionnaire 3 times a day regarding pain scores (NRS 0-10), nausea (yes/no), pruritus (yes/no), drowsiness (yes/no), and satisfaction regarding pain management (0-3, where 0 is “very unsatisfied,” and 3 is “very satisfied”). They were also asked to note the time for first drinks, first food, first full meal, first mobilization, first flatus, and first bowel movement. This was then converted to hours after discharge from the recovery room, which was T = 0. An anesthetic nurse visited the patient daily for a reminder of the questionnaire and for checking and explaining the pain medication. The PCIA system was electronically checked for demands and delivered boluses.

Outcomes

Primary outcome was the number of days until FFD since the day of the surgery (which is day 0). Fit for discharge was defined as a patient who

1. was taking only oral pain medication,
2. was able to walk around in the room independently,
3. was tolerating a full oral diet and had bowel movements,
4. was hemodynamic and respiratory stable, and
5. had no drains or urinary catheters in situ.

Patients were checked for the criteria once a day during morning rounds. This assessment continued during the admission, even if the patient was FFD earlier.

Secondary outcomes included use of piritramide per PCIA in milligrams, patient satisfaction, pain scores and occurrence of adverse effects, difficulty of surgery, laboratory results, and adverse events.

Definitions

Time of surgery was defined as the time between start of pneumoperitoneum and the start of emergence of anesthesia. The time on the recovery ward was defined as the time between arrival and the call to the ward for picking up the patient. A conversion of surgical approach was defined as an unforeseen change in incision. An ileus was defined as an insertion of a draining nasogastric tube and nothing by mouth lasting more than 24 hours. An anastomotic leakage was defined as an intra-abdominal infection that required surgery or percutaneous drainage.

Statistical Analysis

A power analysis showed that we needed 46 subjects in order to detect a difference in FFD from 5 ± 1 day to 4 ± 1 day with a 2-sided power of 90% and P = 0.05. We suspected a 20% loss to follow-up, for which we added 10 patients. Therefore, we needed a minimum of 56 patients, which we set to n = 60. The values we used were in accordance with previous studies.[11,12]

We performed a per-protocol analysis. Data are described in median (interquartile range) (range). Comparisons for non-normally distributed outcomes were made by a Mann-Whitney U test. For ordinal data, a Fisher exact test was used. P = 0.05

was considered statistically significant. Values were calculated with SPSS version 21.0 (IBM, Armonk, New York), and graphics were made by GraphPad Prism version 7.1 (GraphPad Software, San Diego, California).

Results

Sixty patients were randomized. Two patients who were randomized into the intervention group were treated as a control because in 1 patient the study medication was unavailable and a misconception occurred in the other patient. Because we performed a per-protocol analysis, these patients were analyzed as a control group. Two other patients in the control group were converted to an open procedure because of adhesions and were excluded from analysis. Patients with gastric resections (n=2) were excluded from analysis (see Methods). A flowchart is presented in Figure 1.

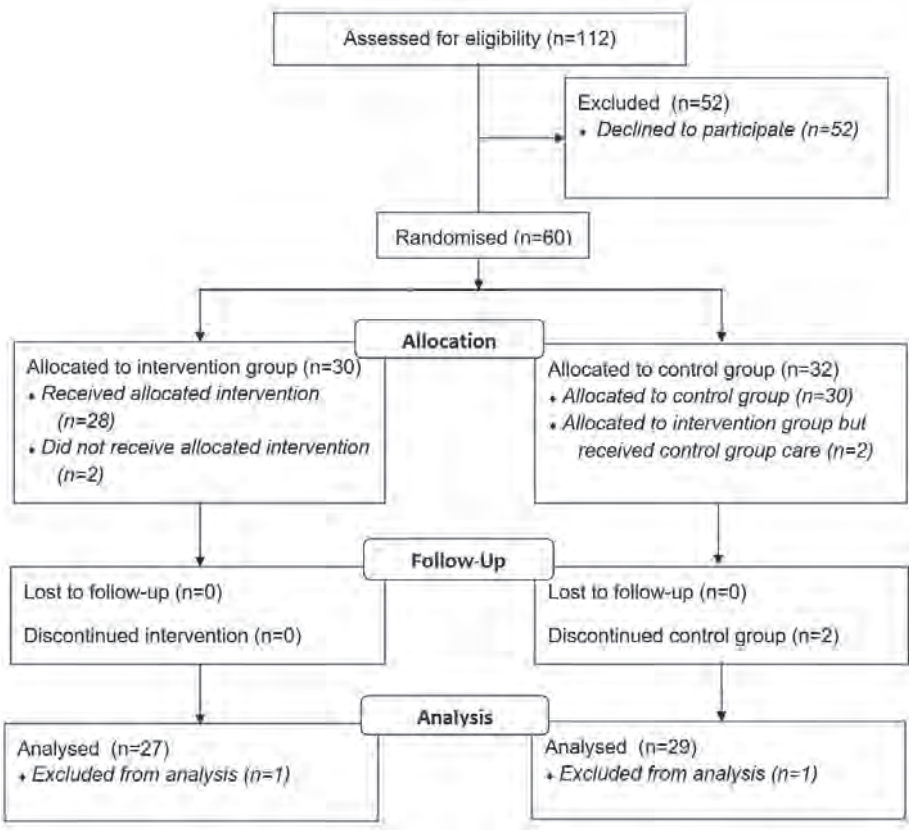


Figure 1. Flowchart of inclusion. See text for specifications.

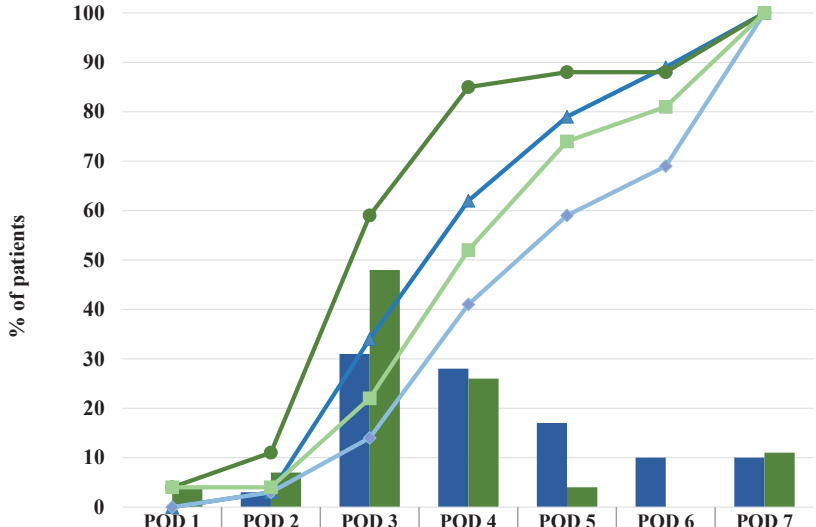
Baseline characteristics are presented in Table 1. There were more sigmoidal resections in the intervention group, whereas there were more right-sided hemicolectomies in the control group. Age and comorbidities were non-significantly different. For the intervention group, all attempts for intrathecal injection succeeded, because cerebrospinal fluid was obtained in all patients.

Table 1. Baseline characteristics. Data is presented as N (%) or median (IQR)[range]. cm = centimeter, BMI: Body Mass Index, ASA: American Society of Anesthesiology.

	Control (n=29)	**Intervention (n=27)**
Male (%)	15 (51.7%)	18 (66.7%)
Age (years)	69 (62.5-77)[41-85]	68 (61-71)[49-80]
Length (cm)	174 (168.5-181)[158-189]	178 (170-182)[163-200]
BMI (kg/m²)	27.3 (24.9-30)[21.1-37.2]	27.5 (25.6-30.6)[21.1-50.2]
ASA class (1/2/3) (%)	6/17/6 (21/59/21%)	8/12/7 (30/44/26%)
Time of start of surgery (hh:mm)	11:30 (9:15-13:00)[8:00-15:30]	10:30 (8:30-12:30)[8:00-14:00]
Type of surgery		
Left hemicolectomy	2 (7%)	2 (7%)
Right hemicolectomy	20 (69%)	14 (52%)
Ileocoecal resection	1 (3%)	1 (4%)
Sigmoidal resection	6 (21%)	10 (37%)
Malignancy as indication	26 (90%)	23 (85%)

Primary Outcome Parameters

Patients in the intervention group were FFD earlier than patients in the control group (median, 3 [3-4] [1-28] vs 4 [3-5] [2-25] days; P = 0.044). After 3 days, 16 patients (59%) in the intervention group versus 10 patients (34%) were FFD (Figure 2), P = 0.056. No difference was detected for actual length of stay (median, 4 [4-6] [1-33] vs 5 [4-7] [2-26] days; P = 0.270). No regression to “not FFD” occurred in any patient when scored as being FFD. Also, no readmissions occurred within 30 days after discharge.



	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7
Control - FFD	0	3	31	28	17	10	10
Intervention - FFD	4	7	48	26	4	0	11
Control - FFD	0	3	34	62	79	89	100
Intervention - FFD	4	11	59	85	88	88	100
Control - aLOS	0	3	14	41	59	69	100
Intervention - aLOS	4	4	22	52	74	81	100

Figure 2. Patients in the intervention group were earlier fit for discharge (4 (3-5)[2-25] vs. 3 (3-4)[1-28] days, p=0.044). The bars in the chart corresponds with the upper two rows in the table and represent the percentage of patients who met the "Fit for discharge"-criteria (FFD) per day. The dark lines represent the cumulative percentage of patients who met the FFD-criteria and the light lines represent the cumulative percentage of the actual Length of Stay (aLOS). These lines corresponds with the middle two and the lower two rows in the table, respectively. The table displays the percentages in a numeric fashion. aLOS: actual Length of Stay, FFD: Fit for Discharge, POD: Postoperative Day.

Secondary Outcome Parameters

All patients were treated according to an ERAS protocol. No difference was detected in time to first drinks, foods, meals, mobilization, flatus, or defecation (Table 2).

Pain scores were lower in the intervention group on the first postoperative day, as indicated by lower NRS scores (Table 3). This effect was despite a lower opioid use per PCIA in the intervention group. The difference in use of PCIA lasted for the first 20 hours after surgery (Figure 3). The difference in opioid use occurred in the first 20 hours, which led to a difference in piritramide dose of 9 mg (3-17) [0-36] versus 33 mg (26-61)[13-112], P < 0.001. The difference was 15 mg (4-25)[0-

60] versus 44 mg (33-77)[14-127], P < 0.001, after 48 hours. Only 5 patients used additional opioids (10 mg long-acting oxycodone by mouth) when the PCIA pump was removed: 1 patient (4%) in the intervention group compared with 4 (14%, no difference, P = 0.353) in the control group.

Patients in the intervention group received less intraoperative sufentanil (30 µg (25-35) [15-50] vs 45 µg (35-50) [20-75], P < 0.001), had lower pain scores upon arrival on the recovery (0 (0-3) [0-6] vs 4 (1-6) [0-9], P = 0.001), and had less pain by discharge to the ward (0 (0-2) [0-3] vs 3 (2-4) [0-4], P < 0.001). No difference was detected in difficulty for the surgeon, duration of surgery, duration on the recovery ward, blood loss, or fluid administration.

Residual sensory block was tested in all intervention patients and was detected below a median of Th10 (Th7-Th12) [none-L2]. No motoric blockade could be detected in any intervention patient.

More patients with intrathecal morphine had pruritus than the control group (41% vs 8%, P = 0.014), although solely on the first day (Table 3). Interestingly, none of the patients asked for treatment of the pruritus. There was no difference detected in nausea, drowsiness, or adverse events.

One patient in the control group died on the eighth postoperative day because of septic shock. The focus for shock was most likely to be an abdominal focus, although an autopsy was not performed. Two patients in the control group were converted to an open procedure. An ileus occurred in 3 patients (11%) in the intervention group versus 5 patients (17%) in the control group (non-significant), and in both groups, there was 1 patient with anastomotic leakage. Other non-anastomotic leakage infections occurred in 3 patients (10%) in the control group versus 2 patients (7%) of the intervention group (non-significant). There were 3 other minor complications in the control group (severe pain requiring rescue medication [n = 1], exacerbation chronic obstructive pulmonary disease [n= 1], and severe hypokalemia [n= 1]), whereas no other complications were noted in the intervention group.

Table 2. Indicators of ERAS-adherence. Timing is presented in hours after discharge from the recovery ward. Data is presented as median (IQR)[range].

	Control	Intervention	P
Time to first drink	3 (1-5)[0-16]	2 (1-4)[0-19]	0.461
Time to first food	16 (9-19)[3-24]	14 (4-19)[1-24]	0.308
Time to first meal	19 (17-28)[14-66]	22 (16-24)[1-44]	0.826
Time to first mobilization	20 (17-23)[14-116]	20 (17-24)[8-48)	0.984
Time to first flatulence	42 (19-54)[0-100]	30 (21-45)[10-68]	0.306
Time to first defecation	65 (46-82)[22-96]	54 (46-68)[16-144]	0.510

No statistically significant differences were found between groups regarding patient satisfaction, even though a trend was observed on the day of surgery (40% vs 71% were very satisfied with the analgesia, P = 0.071, and 13% vs 0% were unsatisfied regarding pain control, P = 0.236) (Table 3).

Table 3. Patients' self-reported scores. Mean pain scores was the mean NRS score from 0-10 over tree time points during the day. Nausea, pruritus and drowsiness was a yes or no question, and incidence is reported. Satisfaction was asked on a four-point scale, from which 0 and 1 was defined as "unsatisfied" and 2 was "normally satisfied". "Very satisfied" was indicated by the number 3. Data is presented as median (IQR)[range] or as n (%).

	Control	Intervention	P
Mean pain scores			
POD 0	2 (2-7)[0-7]	1.5 (0-4)[0-6]	0.075
POD 1	2.3 (1.3-4.3)[0.7-5.3]	0.3 (0-3.8)[0-6.3]	0.004
POD 2	1.7 (1.3-3)[1-4]	0.8 (0-2.5)[0-4.7]	0.147
POD 3	1.3 (0.7-2.3)[0-4]	0.3 (0-1.3)[0-3]	0.389
Nausea			
POD 0	6 (24%)	11 (52%)	0.068
POD 1	11 (42%)	6 (24%)	0.237
POD 2	11 (44%)	6 (30%)	0.372
POD 3	8 (36%)	9 (42%)	0.760
Pruritus			
POD 0	2 (8%)	9 (41%)	0.014
POD 1	1 (4%)	6 (26%)	0.044
POD 2	1 (4%)	1 (5%)	1.000
POD 3	0 (0%)	0 (0%)	N/A
Drowsiness			
POD 0	16 (64%)	9 (41%)	0.148
POD 1	10 (40%)	4 (17%)	0.117
POD 2	4 (16%)	0 (0%)	0.114
POD 3	1 (6%)	0 (0%)	1.000

	Control	Intervention	P
Unsatisfied			
POD 0	3 (13%)	0 (0%)	0.236
POD 1	3 (12%)	2 (9%)	1.000
POD 2	3 (12%)	1 (5%)	0.614
POD 3	1 (5%)	0 (0%)	1.000
Very satisfied			
POD 0	10 (40%)	15 (71%)	0.071
POD 1	12 (48%)	14 (61%)	0.401
POD 2	14 (56%)	15 (72%)	0.363
POD 3	15 (68%)	15 (75%)	0.738

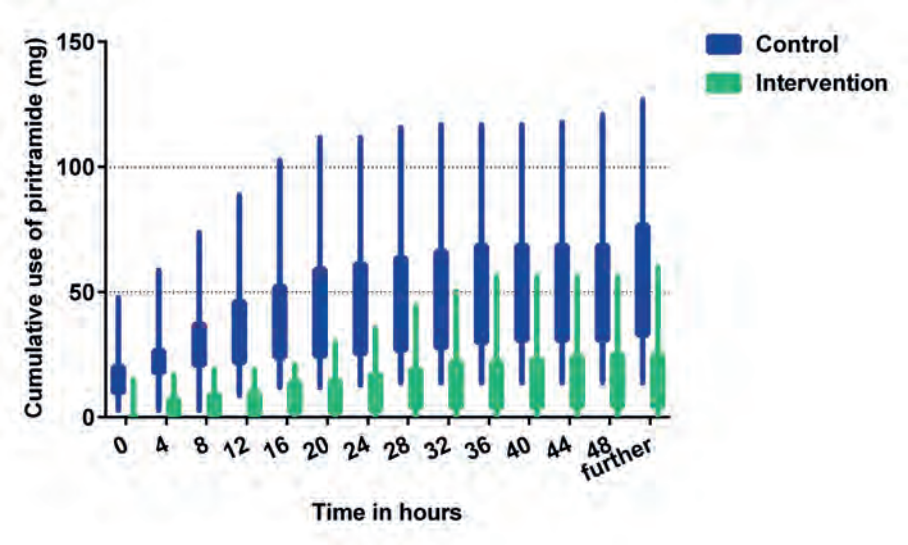


Figure 3. Cumulative use of piritramide per PCIA.

Discussion

This study shows that a single intrathecal injection of bupivacaine/morphine when compared with patients on systemic opioids leads to a faster recovery in a laparoscopic surgery enhanced recovery protocol. Less PCIA opioids were used in the first 20 hours after laparoscopic surgery, and patients reported lower pain scores with intrathecal morphine. There was a higher incidence of pruritus. Our study was unable to detect a difference in patient satisfaction.

The faster recovery is displayed in the fact that patients were FFD earlier. We believe that meeting the FFD criteria reflects recovery better than the length of stay, because the latter is also influenced by social or non-medical decisions (e.g. no place available in the nursing home, discharge preferred during workdays). Our FFD criteria were in accordance with international consensus.[13]

The reason for the faster recovery is unclear, because both groups had similar adherence to the ERAS protocol. The difference in faster recovery could be explained by the preoperative fitness, although there are no signs that differences in preoperative fitness played a role, because the groups were well randomized in other aspects. However, the use of systemic opioids and the pain scores were lower in the intervention group, which could lead to a difference in the extent of mobilization or enteral feeding. For example, first mobilization could have been 5 steps in the room or a walk to the coffee machine in the hall. Unfortunately, this was not measured.

Our results differ from the study of Wongyingsinn et al[6], which did not find a faster recovery. That study measured the actual length of hospital stay instead of FFD criteria, with the aforementioned limitations. Furthermore, different postoperative regimens for analgesia were used (PCIA vs oral oxycodone), and a different dose of intrathecal morphine was used. Still, the recovery profile was deemed very comparable in regard to pain scores, opioid use, and duration of intense pain.

A large variance in PCIA use was observed in the control group, whereas in the intervention group the variance was less. Still, a substantial amount of systemic piritramide was saved in the intervention group during the first 20 hours, which indicates the effect of a single shot of intrathecal morphine. Moreover, pain scores were lower in the intervention group, despite the same availability of PCIA piritramide. This indicates that even though PCIA is used, patients still have room left for lowering the pain scores. Explanations for this observation are either the patient does not need a lower pain score or the PCIA is unable to achieve lower pain scores because of patient knowledge gaps, inadequate medication or settings of the PCIA, or occurrence of adverse effects. Unfortunately, this study was not set up to investigate this.

Pain scores and PCIA piritramide use were similar after the first day, indicating that either the effect of intrathecal morphine or the pain of laparoscopic surgery has worn off.[14,15] In both groups, only small amounts of opioids were used after the

first day, and no rebound pain was observed during the follow-up period. These facts suggest that the duration of analgesia of intrathecal morphine is appropriate to cover the pain for this type of surgery.

Appropriate analgesia without serious adverse effects and delaying recovery is the primary goal of analgesia in the ERAS program.[1] In this study, this dose proved to provide appropriate analgesia during the first 24 hours. Furthermore, apart from pruritus, neither significant adverse effects nor any adverse events were observed, although the number of patients may be too low for detection. The dose of 300 μg of morphine was chosen based on a meta-analysis and a review.[7,16] To our knowledge, a dose-finding study of intrathecal morphine for laparoscopic surgery has not been published.

Ten to 12.5 mg of bupivacaine was added to enhance intraoperative analgesia, and its effect is displayed in the lower intraoperative sufentanil use. It could also have contributed to the lower pain scores on the recovery ward. A preemptive analgesic effect might be involved as well, although there are no data available to support this claim. However, because we observed no adverse events related to bupivacaine (e.g. prolonged motor blockade or sympatholysis), we would recommend adding bupivacaine to the intrathecal mixture.[17] Common doses of vasopressors were used in this study, and a fluid-restrictive management was still achieved in both groups, without a significant difference between groups.

The intervention group suffered from a higher incidence of pruritus, despite the use of prophylactic measures.[7,18 20] Interestingly, patients did not ask for medication to treat the pruritus, even though it was available and prescribed on demand for them. A trend toward more nausea on the first day for the intervention group was observed, but this was reversed on the second postoperative day. Perhaps administration of dexamethasone at induction of anesthesia and/or prescribing 5-HT_3 antagonists at standardized times rather than per requisite would alter the nausea.

A well-known adverse effect of intrathecal morphine is delayed respiratory depression.[21,22] In this study, all patients received supplemental oxygen by nasal cannula, and sedatives were prohibited during the first night. None of the patients' vital signs were monitored after discharge from the recovery ward. We did not study respiratory frequency or oxygen saturation during the first night, so we cannot comment on the occurrence of a delayed respiratory depression; however,

no clinically relevant consequences were observed. This observation is in line with the meta-analysis of Gehling and Tryba[7], which concluded that at less than 500 µg intrathecal morphine does not cause serious respiratory adverse events. Another meta-analysis does warn for respiratory depression, but it did not investigate whether there was a dose dependency.[8] A few case reports suggest respiratory depression after intrathecal morphine with a dose lower than 500 µg, but it is not clearly related to morphine as multiple sedatives were used as well.[23,24] Therefore, we prohibited sedative medication to prevent an interaction with the intrathecal morphine.

We found no difference in patient satisfaction, which indicates that both groups perceived pain levels to their expectations. Although a trend was observed, it did not reach statistical significance. We measured satisfaction on a non-validated 4-point scale, which could be too insensitive to measure any effect. However, in our opinion, a smaller effect is hardly clinically relevant.

This study has several strengths, which contribute to the search for a fitting method of analgesia for laparoscopic colonic resections.[2,5,6,12] Its follow-up lasts for the total time of admission, the departments were used to an ERAS program, the 2 study arms received similar postoperative care, and it was a double-blind study. Unlike Levy et al[2], we did not use goal-directed fluid management, but rather we used a fluid-restricted management and early oral hydration. This was more in line with contemporary guidelines for fluid management in patients without severe cardiovascular comorbidity.[25]

This study has several limitations. First, we excluded the converted surgeries, so we cannot comment on the effect of intrathecal morphine on laparotomy surgery. However, it seems reasonable to assume that intrathecal morphine still has an analgesic effect after open surgery during the first day and still exerts an advantage in this setting. Second, we did not measure the magnitude of mobilization, which could be the underlying explanation for the faster recovery in the intervention group. Third, the measurement of patient satisfaction may be too insensitive, as mentioned previously. Unfortunately, we did not use a Quality-of-Recovery questionnaire, which is recommended by the European Society of Anaesthesiology for measuring quality of recovery. Fourth, allocation went wrong in 2 patients. Because it was a per-protocol analysis, we analyzed these patients in the control group. This mistake was due to implementation of the study in the daily work

and unrelated to the patient. Furthermore, the sample size is relatively low, so a confirmatory trial is necessary, especially for the faster recovery. In addition, we did not measure the cost-effectiveness of the intervention. The intervention will probably become cost-effective when the actual length of stay is reduced, because the costs of an admission day are higher than the intervention. Thus, additional efforts are needed to reduce the actual length of stay in order to reduce the costs.

Further research should focus on a confirmatory trial using fitness for discharge as the primary outcome, evaluating extent of mobilization as an explanation for how intrathecal morphine enhances recovery and to also clarify how the time between FFD and actual discharge can be minimized. Also, given the large variance of postoperative opioid use, investigations for which patients benefit most from this intervention should be initiated.

In conclusion, this randomized controlled trial shows that intrathecal bupivacaine/morphine provides a short-lasting analgesic effect during the first postoperative day after laparoscopic surgery. Most important, this method of analgesia leads to faster recovery, lower pain scores, and less opioid use after laparoscopic gastrointestinal surgery when compared with patients on systemic opioids. There is more pruritus in the intervention group, but no patient required treatment for this adverse effect. We recommend further research regarding intrathecal bupivacaine/morphine within an ERAS program, because recovery could be further enhanced with this method of analgesia.

Acknowledgements

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The effect of intrathecal bupivacaine/morphine on quality of recovery in robot-assisted radical prostatectomy: a randomized controlled trial

M.V. Koning, R. de Vlieger, A.J.W. Teunissen, M. Gan, E.J. Ruijgrok, J.C. de Graaff, J.S.H.A. Koopman, R.J. Stolker.

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Chapter 4

Abstract

Background

Robot-assisted radical prostatectomy causes discomfort in the immediate postoperative period. This randomized controlled trial investigated if intrathecal bupivacaine/morphine in addition to general anesthesia could be beneficial for the postoperative quality of recovery.

Methods

One hundred and fifty-five patients were randomly allocated to an intervention group that received intrathecal 12.5 mg bupivacaine/300 µg morphine (20% dose reduction in patients >75 years) or a control group receiving a subcutaneous sham injection and an intravenous loading dose of 0.1 $mg.kg^{-1}$ morphine. Both groups received standardized general anesthesia and the same postoperative analgesic regimen. The primary outcome was decrease in the Quality of Recovery-15 (QoR-15) questionnaire score on postoperative day 1.

Results

The intervention group (n=76) had less reduction in QoR-15 on postoperative day 1; median (IQR [range]) 10% (1-8 [-60-50%]) vs. 13% (5-24 [-6-50%]), p=0.019, and used less morphine during the admission; 2 mg (1-7 [0-41 mg]) vs 15 mg (12-20 [8-61 mg]), p<0.001, compared to the control group (n=79). Furthermore, they perceived lower pain scores during exertion; NRS 3 (1-6 [0-9]) vs. 5 (3-7[0-9]), p=0.001; less bladder spasms (NRS 1 (0-2[0-10]) vs. 2 (0-5[0-10]), p=0.001 and less sedation; NRS 2 (0-3[0-10]) vs. 3 (2-6[0-10]), p=0.005. Moreover, the intervention group used less rescue medication. Pruritus was more severe in the intervention group; NRS 4 (1-7[0-10]) vs. 0 (0-1[0-10]), p=0.000.

Conclusion

We conclude that despite a modest increase in the incidence of pruritus, multimodal pain management with intrathecal bupivacaine/morphine remains a viable option for robot-assisted radical prostatectomy.

Introduction

Robot-assisted radical prostatectomy causes considerable discomfort, mainly during the first postoperative day. The discomfort originates from abdominal pain, bladder spasms and transurethral catheter irritation.[1] Various techniques such as dorsal penal nerve block, transversus abdominus plane block, administration of intravesical ropivacaine, suprapubic catheters and intrathecal morphine were investigated and resulted in moderate analgesic effects.[2-6] This emphasizes the necessity for improvement of postoperative care in the first days after robot-assisted radical prostatectomy.

An ideal analgesic method has maximal benefit and few side-effects, and this ratio is likely to be reflected in the quality of recovery. The analgesic effects of intrathecal morphine have been demonstrated to last for 20-48 h.[6,7] The side-effects, however, have not been studied sufficiently in this type of surgery. One of the side-effects of intrathecal morphine is urinary retention. This is relieved as a direct result of this procedure, since all patients receive a urinary catheter following surgery.[8] Moreover, bladder spasm-related discomfort may be effectively reduced by intrathecal morphine, since it reduces bladder contractions.[9] These properties of intrathecal morphine suggest that it is a potentially suitable technique for improving the quality of recovery after robot-assisted radical prostatectomy.

The aim of this study was to evaluate quality of recovery after administration of intrathecal bupivacaine/morphine after robot-assisted radical prostatectomy surgery. Besides length of stay and surgical conditions, this study investigated the positive and negative effects of intrathecal morphine. We hypothesized that, due to a reduction in pain and discomfort, intrathecal bupivacaine/morphine would lead to improved quality of recovery on the first postoperative day compared with the control group.

Methods

This study was a single-center, observer and patient-blinded randomized clinical trial performed in a teaching hospital and national referral center for robot-assisted radical prostatectomy (Maasstad Hospital, the Netherlands). The study was approved by the local ethics committee (Toetsingcommissie Wetenschappelijk Onderzoek Rotterdam e.o., the Netherlands) and the CCMO (Dutch abbreviation for Central Committee on Research involving Human Subjects).

All patients scheduled for robot-assisted radical prostatectomy with or without pelvic lymph node dissection between October 2016 and June 2018 were eligible for participation. Exclusion criteria were: age < 18 y; contraindications to study medication (such as allergy or glomerular filtration rate < 30 $ml.min^{-1}$); contraindications to spinal anesthesia (such as severe aortic stenosis, coagulation disorders, increased intracranial pressure); scheduled postoperative ICU admission; and patient refusal to participate.

Patients were informed about the study during the pre-operative screening unit. Weeks before surgery the patients were called for further explanation, informed consent and the baseline Quality of Recovery-15 (QoR-15) questionnaire. Patients provided written informed consent before the start of randomization in the holding area.

Randomization was by the use of sealed, opaque envelopes. An independent colleague randomized these envelopes in blocks of 10 with a 1:1-ratio to produce an equal distribution of intervention across the whole study period. The envelopes were stacked and stored. When an included patient arrived in the holding area, the upper envelope was opened by the attending anesthesiologist. The patient, surgical team, nurses on the ward and researchers were all blinded. Only the attending anesthetic team and the nurse on the recovery ward were aware of the group allocation. They were not involved in further patient care or data collection, other than filling in the case record form during the surgical procedure and recovery phase.

All patients received 1000 mg intravenous (i.v.) cefazolin 30 min before surgery. No sedative premedication was given. In the operating theatre the patients received standard monitoring. After the time-out procedure the surgical team left

the theatre for blinding purposes. In accordance with randomization, the patient received either an intrathecal injection of bupivacaine/morphine or a sham procedure.

In both treatment allocation groups, the patient was placed in an upright sitting position, the skin over the lumbar region of the back was cleaned with chlorhexidine and sterile drapes were positioned. In both groups the skin was infiltrated with 3 ml lidocaine 1%. In the intervention group a sterile 27-g pencil-point needle (Pencan; Braun Melsungen AG, Melsungen, Germany) was inserted at the L2–3 or L3–4 interspace. After obtaining cerebrospinal fluid, medication was administered with a single injection; 12.5 mg isobaric bupivacaine and 300 μg morphine in 5 ml. For patients over 75 years of age, 10 mg isobaric bupivacaine and 240 μg morphine in 4 ml were given. The medication was prepared by the Pharmacy Department. No additional i.v. morphine was administered during the procedure.

Patients in the control group received a sham procedure after the aforementioned skin infiltration with 3 ml lidocaine 1%. After this, the anesthesiologist pressed on the skin with a finger to simulate intrathecal injection. The patients who were randomized to the control group received 0.1 $mg.kg^{-1}$ morphine i.v. during surgery, which was standard practice in our hospital.

For both groups, standardized general anesthesia was administered immediately after the spinal puncture. After pre-oxygenation, 0.4 $\mu g.kg^{-1}$ sufentanil, 2 $mg.kg^{-1}$ propofol and 0.6 $mg.kg^{-1}$ of rocuronium were administered and the trachea intubated. Thereafter the patient was positioned in lithotomy, the operative field disinfected, and sterile drapes positioned. A transurethral catheter was inserted. Pneumoperitoneum was achieved by insufflation of CO_2 up to a pressure of 15 mmHg through a 12 mm camera trocar inserted through a periumbilical incision. After insertion of the remaining five trocars (three 8 mm robotic trocars, a 15 mm and a 5 mm assisting trocar), the intra-abdominal pressure was decreased to 12 mmHg and the patient placed in the Trendelenburg position. In this position the robot surgery system (Da Vinci Si System, Intuitive Surgical, Sunnyvale, CA, USA) was docked and surgery commenced.

Ten micrograms of i.v. sufentanil was administered when an increase in heart rate or blood pressure > 10% occurred in comparison with a stable phase during surgery.

Rocuronium 10 mg i.v. was administered when ventilator desynchronisation or abdominal wall contraction occurred. Vasoactive medication was given at the discretion of the attending anesthesiologist (i.e., phenylephrine, ephedrine, or noradrenaline). Every patient received an i.v. infusion of 500 ml lactated Ringer's solution with a targeted fluid balance of less than 750 ml surplus.

Standard medication of 1000 mg paracetamol, 1000 mg metamizol, 0.625 mg dehydrobenzperidol and 4 mg ondansetron were given i.v. before the end of surgery. A train-of-4 measurement was performed in order to exclude residual relaxation after surgery. If necessary, rocuronium was antagonized with atropine/neostigmine or sugammadex at the discretion of the anesthesiologist. After completion of surgery, patients were extubated in the operating room and transferred to the post-anesthesia care unit (PACU) for at least 30 min of observation.

In the PACU, a nurse (unblinded to the randomization) administered 2.5 mg morphine i.v. if the pain score was > 4 on a numeric rating scale (NRS). This was evaluated every 10 min and morphine administration was repeated if necessary up to a maximum of 20 mg. If the patient was still in pain after 20 mg of morphine, other analgesics were administered at the discretion of the attending anesthesiologist and consisted of i.v. esketamine, i.v. clonidine, oral oxybutynin or i.v. hyoscine. Pain scores were registered on arrival and discharge from the PACU. Nursing staff were able to administer an additional dose of 0.625 mg i.v. dehydrobenzperidol for nausea according to their own clinical judgement. Similarly, 30 mg of i.v. propofol was allowed to be administered for pruritus. In both treatment arms the patient- controlled analgesia (PCA) pump was connected and instructions given to the patient when they were sufficiently awake and pain free. It was set to administer 1 mg of morphine i.v. per bolus with a lockout time of 6 min. Discharge to the ward was allowed when the patient had an Aldrete score > 8 and pain, nausea and other side effects were well managed.

All patients received 2 $l.min^{-1}$ of oxygen by nasal cannula during the first night. Oxygen was to be increased when $SaO_2 < 92\%$. To reduce the risk of late respiratory depression, patients in both groups were not allowed to receive benzodiazepines or opioids other than PCA morphine. No other precautions were taken to prevent late respiratory depression. Postoperative pain treatment included paracetamol up to 4000 $mg.day^{-1}$ and metamizol 1000 mg. Morphine administered by the PCA

system was prescribed as postoperative analgesic management. The PCA system was stopped on the first postoperative day (POD 1). Ondansetron 4 mg was administered when required for nausea and pruritus, 5 mg of oxybutynin was prescribed for bladder spasms. The urinary catheter remained in situ for 7 days after surgery.

Patients were discharged home after a minimum of one night in hospital when they: were able to mobilize; achieved adequate pain control with oral medication; able to eat and drink; had vital signs within normal limits; had sufficient home care.

The primary outcome was percentage decrease in QoR-15 at POD 1 from the baseline score that was established within the weeks prior to surgery. On POD 1 the QoR-15-questionnaire was assessed by an anesthetic nurse blinded to the randomized group. Furthermore, the QoR-15 on POD 1 was analyzed both as an absolute decrease and as a single score. The five subdomains of QoR-15 measurements were also analysed.[10]

The QoR-15 (range 0-150, in which 150 is the best possible outcome) is a validated questionnaire, commonly used in the peri-operative setting and recommended as an outcome measure by the ESA-ESICM joint taskforce on peri-operative outcome measures.[11] The QoR-15 is reported as absolute decrease, relative decrease and single score.[10] We chose the relative decrease in percentage as the primary outcome measure because population values of absolute thresholds for QoR-15 in patients undergoing robot-assisted radical prostatectomy were not available when the study was initiated. After initiation of the study, a minimal clinically important difference was determined at 8.0 and an acceptable symptom state of 118 was determined.[12]

The intra-operative secondary outcomes (duration of different stages of the anesthesia, sufentanil and rocuronium administration, i.v. fluid administration, blood loss, pain scores and complications) were noted on a case record form that was filled in by the anesthesia team and PACU nurse (who were unblinded to randomization) during surgery and the recovery phase. Furthermore, the attending urologist (blinded for assigned treatment) was asked to score the surgical difficulty of the procedure on a NRS, ranging from 0 (easy) to 10 (very difficult) after surgery. The PCIA system was checked electronically for total morphine consumption and bolus demands.

For the postoperative secondary outcomes, an anesthetic nurse (blinded to the group allocation) visited the patients on POD 1. In addition to the QoR-15, seven items related to the potential benefits and side effects of intrathecal morphine: physical discomfort; pain during exertion; bladder spasms; sedation; sleep; pruritus and general satisfaction were recorded with a NRS ranging from 0 (low or absent) to 10 (high or severe) (see appendix B).

One week after surgery a trained medical secretary (blinded to group allocation), telephoned the patient to assess the QoR-15 on postoperative day 7 (POD 7). Additionally, 12 questions were asked regarding the hospital admission in a retrospective manner on a NRS ranging from 0 (low or absent) to 10 (high or severe, see appendix B). These 12 questions consisted of the same seven items asked on POD 1. The objective of these seven questions was to assess recollection of symptoms after a week. The five other items inquired about: nausea; pain at rest; current use of analgesics and the current state of physical and mental abilities.

Clinical follow-up, which included occurrence of complications, pathology results and laboratory results (serum creatinine, hemoglobin level, C-reactive protein and leucocyte count) were obtained from the electronic hospital medical record. The duration of follow-up for complications was 2 months after surgery. Respiratory depression was defined as that for which medical intervention was necessary.

Thresholds for QoR-15 in patients undergoing robot-assisted radical prostatectomy were not available at the time of initiation of the study; we therefore estimated a decrease in QoR-15 at POD 1 of 35% in the control group and 25% in the intervention group, with a standard deviation of 16%. We calculated that 160 patients (134 patients with 20% loss to follow-up) were needed in total for a two-sided power of 95% and a p-value of 0.05.

Data is presented as median (IQR [range]) or n (%). Data was analyzed for normal distribution and Mann-Whitney U-tests were performed for continuous data. For ordinal data a Fisher exact test was used. A p-value < 0.05 was deemed statistically significant. A p-value <0.02 was deemed statistically significant for secondary outcomes after correcting for multiple testing. An intention-to-treat and per-protocol analysis was performed as a sensitivity analysis to detect difference resulting from protocol violations. Values were calculated with SPSS version 21.0 (IBM, Armonk, NY, USA) and graphics were produced using GraphPad Prism version 7.1 (GraphPad Software, San Diego, CA, USA).

Results

Four hundred and fifty-nine patients were screened, of which 12 were excluded and 287 declined to participate (Figure 1). Three patients in the intervention group withdrew consent after randomization. All attempts at intrathecal injection in the intervention group produced return of cerebrospinal fluid through the needle.

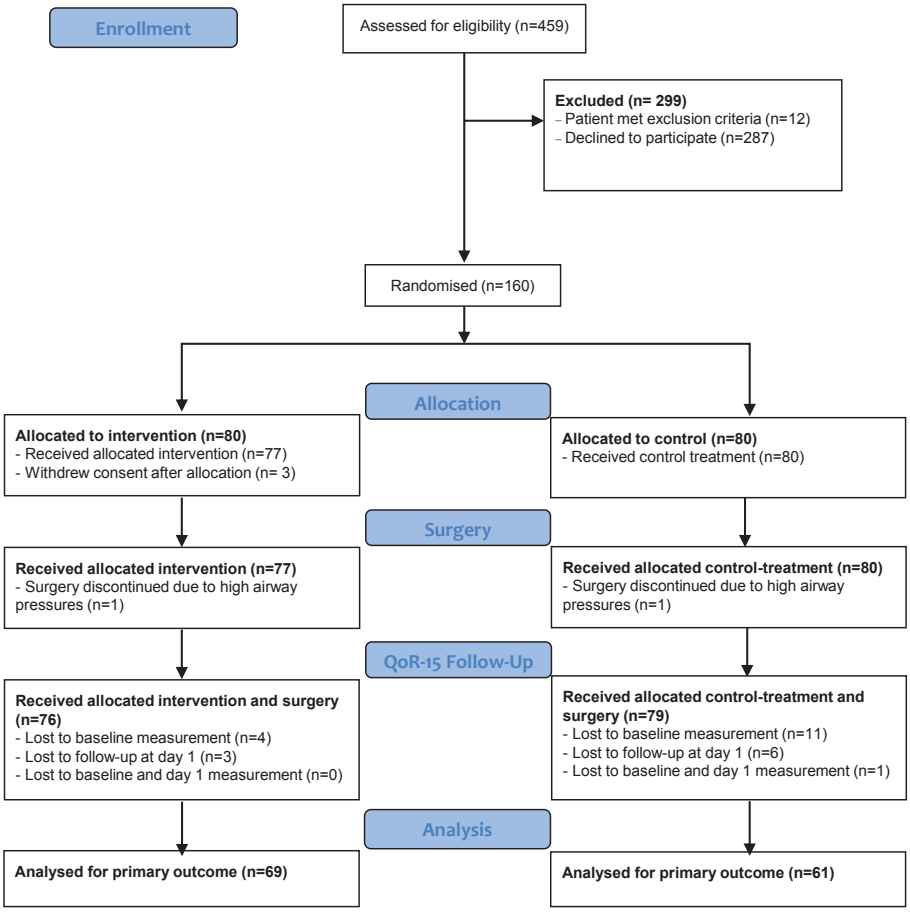

Figure 1. Flow diagram of the participants of the study. Since the primary outcome was a paired measurement, analysis was performed only when both the preoperative Quality of Recovery (QoR)-15 and the QoR-15 on postoperative (POD) 1 were available. Other outcome measures were analyzed when available.

Five patients in the intervention group inadvertently received an i.v. loading dose of 0.1 mg.kg^{-1} morphine also. Five patients received a robot-assisted simple prostatectomy (two in the intervention group, three in the control group). These patients were included for the intention-to-treat analysis, and a per-protocol analysis showed no difference in morphine consumption and QoR-15-scores for these violations. No other protocol violations were observed. Baseline characteristics are displayed in Table 1. The groups were comparable; only lymph node dissection was performed more often in the intervention group.

Table 1. Baseline characteristics. Values presented as median (IQR [range]), number (proportion).

	Intervention (n=76)	**Control (n=79)**
Age; y	67 (63–70 [50-78])	66 (61-71 [44-82])
BMI*	26.3 (25.0-29.7 [20.9-37.0])	26.2 (24.6-28.1 [18.8-33.3])
ASA physical status; (1/2/3) %	22 (29%) /42 (55%) /12 (16%)	27 (34%) /43 (54%) /9 (11%)
Malignancy	73 (96%)	75 (95%)
T2	47 (64%)	53 (71%)
T3	26 (36%)	22 (29%)
Lymph node dissection	36 (47%)	21 (27%)
Duration of surgery; min	129 (103-160 [60-263])	133 (106-150 [71-259])
Duration of PACU admission; min	57 (40-73 [24-341])	60 (46-70 [25-147])
Pre-op PSA; ng.l^{-1}	9.7 (6.7-13.1 [0.5-90.0])	8.1 (6.5 – 12.2 [1.3-35.4])
Days between baseline QoR-15 and day of surgery	11 (5-18 [0-43])	10 (5-20 [0-45])

PSA, prostate specific antigen, QoR-15: Quality of Recovery-15

Primary outcome

The completion rate for QoR-15 was 89.7% pre-operatively, 93.5% for POD 1 and 99.4% for POD 7. Since both the pre-operative and the POD 1 QoR-15 were required to assess primary outcome, 89.6% in the intervention group and 77.2% in the control group were available for analysis of the primary outcome (Figure 1).

The percentage decrease in QoR-15 on POD 1 was significantly less in the intervention group than the control group; 10% (1-8 [-60-50%]) vs. 13% (5-24 [-6-50%]), p=0.019. Absolute values of QoR-15 were similar; 123 points (106-137 [72-150]) vs. 118 points (105-130 [66-150]), p=0.077 at POD 1 (Figure 2). The absolute decrease in QoR-15 and subdomains are presented in Table 2. Analyses of QoR-15 subdomains showed that only the decline in 'pain' was significantly lower in the

intervention group than in the control group on POD 1 (Table 2). All the absolute values and individual questions of the QoR-15 are described in appendix B.

Closer inspection of the domain "pain" (range from 0-20, 0 = severe pain, 20 = no pain) on POD 1 showed that the number of patients with extreme pain (scores < 10) was decreased; 13 (18.3%) vs. 2 (2.8%), p=0.002 in the intervention and control groups, respectively.

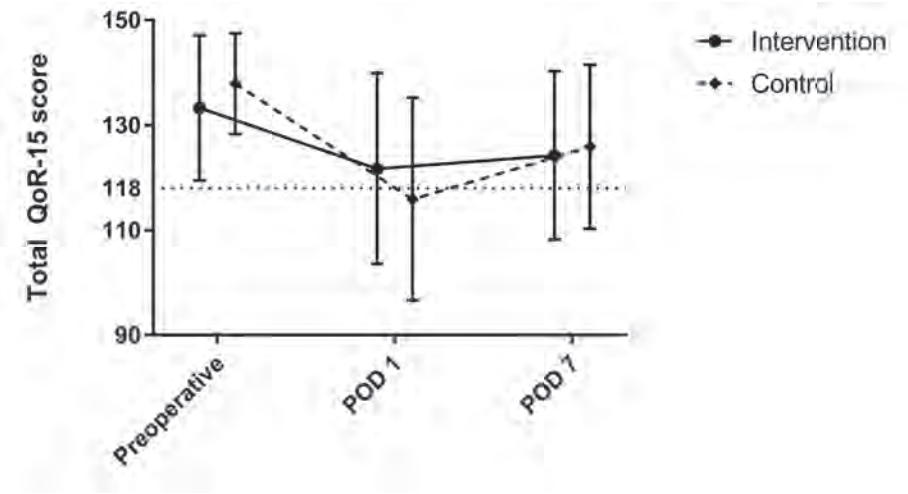

Figure 2. The total Quality of Recovery (QoR)-15 scores per timepoint. The data is presented as mean with SD error bars. The percentage and absolute decrease between preoperative QoR-15 and postoperative (POD) 1 were different (p=0.019 and p=0.013) between intervention and control group. There were no significant differences between absolute values between the groups. A score of 118 (dashed line) is defined as acceptable symptom state.[12]

Secondary Outcomes

The intervention group had less pain as assessed by the NRS and consumed less opioids than the control group on POD 1 (Table 3). Only one patient (allocated to the control group) received additional dehydrobenzperidol for treatment of nausea. No treatment for pruritus was necessary on the PACU. There were no differences regarding the surrogate markers for laparoscopic workspace.

Table 2. Decline in QoR-15 and scores for the additional questions. The QoR-15 outcomes are the absolute decline compared to the preoperative QoR-15. A negative value indicates an increase in QoR-15 score. The additional questions are in NRS-scales from 0-10, where 10 signifies maximal agreement with the statement. For POD 7, it was explicitly mentioned that the additional questions regarded hospital admission. Values are median (IQR [range]).

	POD 1		**P**	**POD 7**		**p value**
QoR-15 (absolute decrease)	Intervention	Control		Intervention	Control	
	n=69	n=61		n=72	n=67	
QoR-15	14 (1.5-25.0 [-47 to 70])	18 (6.5-35.0 [-9 to 64])	0.013§	6.5 (1.0-16.8 [-37 to 70])	9.5 (3.0-19.0 [-11 to 63])	0.197
Domain 'pain'	2 (0.0-4.0 [-13 to 14])	6 (3.0-9.0 [-4 to 14])	0.000§	2 (0.0-3.3 [-17-14])	2 (0.0-4.0 [-4 to 20])	0.352
Domain 'physical Comfort'	4 (0.0-11.0 [-9 to 25])	6 (2.0-10.3 [-6 to 23])	0.170	2 (-1.0-4.3 [-11-23])	2 (0.0-4.5 [-9 to 16])	0.430
Domain 'physical independence'	3 (0.3-8.0 [-2 to 20])	5 (1.0-9.0 [-1 to 18])	0.124	3 (1.0-4.0 [-2-15])	3 (1.0-4.0 [-3 to 10])	0.557
Domain 'psychological support'	0 (-4.0-0.0 [-13 to 10])	0 (-1.0-0.0 [-10 to 16])	0.084	0 (-3.0-0.0 [-13-6])	0 (-0.5-1.0 [-10 to 8])	0.104
Domain 'emotional support'	2 (-1.0-4.5 [-6 to 17])	2 (-1.8-6.8 [-10 to 26])	0.624	0 (-1.0-5.0 [-8-26])	1 (0.0-4.0 [-12 to 19])	0.708
Additional questions (NRS)	n=66	n=71		n=76	n=78	
Severity of physical discomfort	5 (2-7 [0-9])	6 (3-7 [0-10])	0.079	3 (1-6 [0-10])	4 (2-6 [0-10])	0.235
Severity of pain during exertion	3 (1-6 [0-9])	5 (3-7 [0-9])	0.001§	3 (2-7 [0-10])	5 (2-7 [0-10])	0.072
Severity of bladder spasms	1 (0-2 [0-10])	2 (0-5 [0-10])	0.001§	0 (0-4 [0-10])	0 (0-6 [0-10])	0.098
Severity of sedation	2 (0-3 [0-10])	3 (2-6 [0-10])	0.005§	1 (0-3 [0-10])	2 (0-5 [0-8])	0.339
Severity of insomnia	1 (0-6 [0-10])	5 (1-7 [0-10])	0.070	1 (0-6 [0-10])	5 (1-7 [0-10])	0.174
Severity of pruritus	4 (1-7 [0-10])	0 (0-1 [0-10])	<0.001	1 (0-5 [0-9])	0 (0-0 [0-9])	<0.001
General satisfaction	9 (8-10 [0-10])	8 (7-10 [0-10])	0.820	8 (8-10 [1-10])	9 (8-10 [0-10])	0.414
Severity of nausea	n/a			0 (0-3 [0-10])	0 (0-3 [0-10])	0.365
Severity of pain in rest	n/a			0 (0-3 [0-9])	0 (0-3 [0-9])	0.085

Table 3. Secondary outcomes. Values are median (IQR [range])

		Intervention (n=76)	Control (n=79)	p
Opioid consumption	Intra-operative sufentanil use; µg	35 (25-45 [15-100])	45 (35-50 [20-90])	<0.001
	Intra-operative morphine consumption; mg	0 (0-0 [0-10])	9 (8-10 [5-20])	<0.001
	Morphine consumption in recovery ward; mg	0 (0-0 [0-16])	0 (0-0 [0-14])	0.053
	Morphine consumption per PCIA during hospital admission; mg	1.5 (1-6 [0-41])	5 (2-11 [0-61])	<0.001
	Total morphine consumption during hospital admission; mg	2 (1-7 [0-41])	15 (12-20 [8-61])	<0.001
Pain/non-opioid analgesics	Pain scores on PACU (NRS)	0 (0-0 [0-5])	0 (0-4 [0-8])	<0.001
	Additional non-opioid analgesia	5.3%	27.8%	<0.001
	Additional oxybutynin on the ward	30.3%	50.6%	0.014
Laparo-scopic workspace	Rocuronium consumption; mg	50 (50-58 [25-105])	50 (50-60 [35-115])	0.278
	Difficulty of surgery; NRS	3 (1-4 [0-10])	4 (2-6 [0-9])	0.119
	Duration of surgery; min	129 (105-160 [60-263])	133 (105-150 [71-259])	0.987
	Estimated blood loss; ml	200 (140-325 [5-1300])	200 (150-400 [0-2300])	0.623

PCIA, patient-controlled intravenous analgesia; NRS, numeric rating scale; PACU, post-anaesthesia care unit.

Table 2 shows the results of the additional questions asked on POD 1. On the first postoperative day, the intervention group reported less pain during exertion, less severe bladder spasms, less sedation, but more pruritus than the control group. No patient required treatment for pruritus, and only one patient (allocated to the intervention group) received additional treatment for nausea. No difference in severity of nausea or general satisfaction was detected between groups. Furthermore, no differences in laboratory results such as creatinine levels, C-reactive protein or hemoglobin values were detected (see appendix B).

There was no significant difference in QoR-15 (including subdomains) on POD 7 (Figure 2). The retrospective scores of symptom severity regarding the hospital admission showed lower scores than on POD 1 in both groups. Only the difference for the severity of pruritus remained (Table 2). There was no difference in the use of analgesics 1 week after surgery (p=0.137); patients used no analgesics at all (33% vs. 51%), only paracetamol (62% vs. 45%) or paracetamol with the addition of non-steroidal anti-inflammatory drugs or opioids (5% vs. 4%) for the intervention and control groups, respectively. A minority of patients felt physically limited in their activities beyond the limitations set by the urologist (16% vs. 15%, p=1.000). Perceived mental restrictions were similar in both groups (p=0.347); if patients reported them, they were minor (9% vs. 6%) or moderate (1% vs. 5%).

Hospital length of hospital stay was similar in both groups; 1 day (1-2 [1-3]) vs. 1 day (1-2 [1-3]), p=0.490. No patient had clinically relevant respiratory depression.

Subgroup analysis for prostatectomy with or without lymph node dissection showed similar results as the total group for morphine consumption and QoR-15 at POD 1.

Discussion

This study showed that QoR-15 decreased less in patients that received intrathecal bupivacaine/morphine than in the control group after robot-assisted radical prostatectomy. Furthermore, the intervention decreased opioid consumption, pain, sedation, bladder spasms, use of rescue analgesia and oxybutynin administration on POD 1. The intervention especially reduced the number of patients in severe pain. Pruritus was increased in the intervention group compared with control. No difference in outcomes could be detected 1 week after surgery. Addition of a lymph node dissection to the robot-assisted radical prostatectomy did not affect the outcomes.

The present study showed a significant difference in individual patient decreases in QoR-15 between groups, but not absolute values of QoR-15. Changes relative to baseline value are preferred because it addresses individual patient changes and corrects for differences within a group.[11,13] Still, the difference between groups is marginal, the decrease in QoR-15 was less than estimated in the sample size calculation and the absolute scores were comparable with 'minor' or 'intermediate surgery'.[12] As such, these findings indicate that the intervention had a limited effect on the QoR-15 in a robot-assisted radical prostatectomy procedure.

A clinically important effect was found in pain reduction. The distribution of scores in the domain "pain" showed that the number of patients in pain was reduced, which led to a six-fold decrease in patients in severe pain (domain 'pain' < 10). In our opinion, this is the value of the intrathecal bupivacaine/morphine. Furthermore, morphine consumption, rescue analgesia, rescue oxybutynin and bladder spasms were reduced in the intervention group compared with the control group. This shows that rescue analgesia is not as effective as intrathecal bupivacaine/morphine in reducing pain and bladder spasms after robot-assisted radical prostatectomy.

Bae et al. investigated the use of 300 µg intrathecal morphine in 30 patients undergoing robot-assisted radical prostatectomy and measured morphine consumption as the primary outcome.[6] They found a median reduced morphine consumption of 12 mg and reduced pain scores in the intervention group. The current study confirmed these findings in a larger sample and added some other useful features. Firstly, bupivacaine was added to the intrathecal morphine, which prolongs the analgesic effect.[14] No disadvantages of the bupivacaine were

observed, such as severe hemodynamic compromise or residual motoric blockade which prevented mobilization. Secondly, in the current study paracetamol and non-steroidal anti-inflammatory drugs were administered as part of a multimodal postoperative analgesic regimen. This may have reduced the opioid-sparing effect attributed to intrathecal morphine, because a multimodal analgesic regimen also leads to less opioid consumption. Still, the opioid-sparing effects of the intrathecal morphine persisted longer than the effects of the paracetamol and non-steroidal anti-inflammatory drugs. Finally, due to the five-fold increase in the number of participants compared with the earlier study, the present study allowed detection of differences in side-effects and allowed subgroup analysis for patients with lymph node dissection.

The increased severity of pruritus in the intervention group is clinically relevant and in accordance with other studies.[15] This appeared not to affect the QoR-15, probably because pruritus is not included in QoR-15. Ondansetron and dehydrobenzperidol were the only one-time administered prophylactic drugs against pruritus.[16] Remarkably, no patient requested treatment for these side-effects. The continuation of 5-HT_3-antagonists at fixed times could further decrease the incidence and severity of pruritus, but this aspect of management was not included in the present study protocol.[17] Additionally, management of patients' expectations by providing information and explanation may limit this discomfort, since unexpected symptoms may be perceived as more severe.[18] Postoperative nausea was not increased by the use of intrathecal morphine, even though this is a well-known side-effect.[19] This could be explained to some extent by the prophylactic use of ondansetron, dehydrobenzperidol and the male gender of the study population.[16]

Our hypothesis that intrathecal bupivacaine would lead to increased laparoscopic workspace due to motor block is not supported by this study. Even though we were unable to measure true laparoscopic workspace in this study, the surrogate markers did not differ. Nevertheless, the addition of bupivacaine might have the beneficial effect of producing analgesia before the onset of the intrathecal morphine and prolong duration of action[14], but this was not investigated in the present study.

The most feared side effect of intrathecal morphine, late respiratory depression, did not occur in any patients. Incidence is difficult to estimate, since the definition of respiratory depression varies from a SaO_2 < 94% and/or a $PaCO_2$

> 6 kPa to a respiratory rate <6 breaths per min.[20]. Most reported cases of late respiratory depression with the use of < 500 µg intrathecal morphine required no intervention.[19] Therefore, we installed no specific monitoring for this complication, since clinically relevant respiratory depression is unlikely to occur more often with low dose intrathecal morphine (< 500 mcg) than with PCIA morphine.[19,21] Sedatives and opioids (other than as needed in PCIA) were contra-indicated on the night after surgery because of the potential to interact with intrathecal morphine and cause severe respiratory depression.[22]

This study has several limitations. One limitation is the protocol violation in five patients who received an i.v. loading dose of morphine in addition to the intrathecal bupivacaine/morphine. These patients were monitored for 12 h on the PACU for increased chance for late respiratory depression, but this did not occur. Since this might have affected the quality of recovery, a sensitivity analysis was performed that showed the same results. A second limitation is the omission of 5-HT_3-antagonist prophylaxis against pruritus on the ward, which could reduce incidence and severity of pruritus, and perhaps further increase the quality of recovery. A third limitation is that the anesthesia team and recovery nurses were unblinded for group allocation, which could have influenced the administration of additional analgesics or the scoring of pain. However, this was deemed inevitable to guarantee patient safety in case of emergencies. A fourth limitation was the loss of QoR-15 data. This was caused by the incorporation of the study into daily practice, during which forms were lost or patients had no time to answer the questionnaire by phone and were not reached a second time prior to surgery. Finally, the percentage of decrease in QoR-15 was chosen as the primary outcome. Other values, such as the minimally clinically important difference and acceptable symptom state were determined during the execution of this study and were therefore not used in the power analysis.

The current trial offers two recommendations for subsequent studies. First, the QoR-15 appears to be a difficult instrument to interpret. Its main advantage is the overall view of patients' experience, measured by five subscales. The disadvantage is the possibility that if an intervention reduces one item it may be obscured by the other items, reducing sensitivity. In addition, the variance in baseline values indicate that inter-patient comparisons may obscure differences even further, but individual patient change may correct for this. Values such as the minimal clinically

important difference and the acceptable symptom state are of assistance in this regard.[10,12] We prefer measuring traditional outcomes as well (such as morphine consumption and pain scores) in addition to the QoR-15 to reduce the risk of a false-negative intervention. Second, after several studies comparing interventions with i.v. opioids in robot-assisted radical prostatectomy procedures, a new study may aim to compare two interventions, e.g. intrathecal analgesia vs. transversus abdominus plane block. We believe that an intervention should have been compared with the least invasive strategy first before an additional value could be concluded. For intrathecal morphine in a robot-assisted radical prostatectomy procedure, this was insufficiently done when this study was initiated.

In conclusion, this study showed that a single shot of intrathecal bupivacaine/morphine reduced the decrease in quality of recovery in the first 24 h after robot-assisted radical prostatectomy in a limited manner. There were important reductions in opioid consumption, sedation, bladder spasms, number of patients with severe pain and need for rescue medication. Despite a modest increase in the incidence of pruritus, multimodal pain management with intrathecal bupivacaine/morphine remains a viable option for robot-assisted radical prostatectomy.

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Appendix B

Content:

1. Quality of Recovery-15, Dutch version

Deel A: Over de afgelopen 24 uur:	Nooit/niet										Altijd/wel
Ik kan makkelijk ademen	0	1	2	3	4	5	6	7	8	9	10
Ik heb trek om te eten	0	1	2	3	4	5	6	7	8	9	10
Ik voel me uitgerust	0	1	2	3	4	5	6	7	8	9	10
Ik heb goed geslapen	0	1	2	3	4	5	6	7	8	9	10
Ik kan zonder hulp naar toilet en voor mijn persoonlijke hygiëne zorgen.	0	1	2	3	4	5	6	7	8	9	10
Ik kan met vrienden en familie communiceren	0	1	2	3	4	5	6	7	8	9	10
Ik krijg steun van dokters en/of verpleegkundigen	0	1	2	3	4	5	6	7	8	9	10
Ik kan mijn dagelijkse bezigheden uitvoeren	0	1	2	3	4	5	6	7	8	9	10
Ik voel me comfortabel en heb de controle	0	1	2	3	4	5	6	7	8	9	10
Ik voel me over het algemeen gezond	0	1	2	3	4	5	6	7	8	9	10
Deel B: Over de afgelopen 24 uur:	Nooit/niet										Altijd/wel
Ik had milde pijn	10	9	8	7	6	5	4	3	2	1	0
Ik had ernstige pijn	10	9	8	7	6	5	4	3	2	1	0
Ik was misselijk/overgeven	10	9	8	7	6	5	4	3	2	1	0
Ik voelde me bezorgd/angstig	10	9	8	7	6	5	4	3	2	1	0
Ik voelde me verdrietig/depressief	10	9	8	7	6	5	4	3	2	1	0

2. Additional questions postoperative day 1

A. Dutch version

Vragenlijst: Over de afgelopen 24 uur:	Niet										Erg
Hoe erg was het lichamelijke ongemak?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de pijn bij inspanning (hoesten, lopen)?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg waren de blaaskrampen?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg is de sufheid?	0	1	2	3	4	5	6	7	8	9	10
Heeft u goed kunnen slapen na de operatie?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de jeuk?	0	1	2	3	4	5	6	7	8	9	10
Bent u in het algemeen tevreden met uw herstel?	0	1	2	3	4	5	6	7	8	9	10

B. English translation

Questionnaire: Regarding the past 24 hours:	Not										Very
How severe was the physical discomfort?	0	1	2	3	4	5	6	7	8	9	10
How severe was the pain in exertion (e.g. coughing, walking)?	0	1	2	3	4	5	6	7	8	9	10
How severe were the bladder spasms?	0	1	2	3	4	5	6	7	8	9	10
How severe was the drowsiness?	0	1	2	3	4	5	6	7	8	9	10
Were you able to sleep well after the surgery?	0	1	2	3	4	5	6	7	8	9	10
How severe was the itching?	0	1	2	3	4	5	6	7	8	9	10
How satisfied are you in general with your recovery?	0	1	2	3	4	5	6	7	8	9	10

3. Additional questions postoperative day 7

A. Dutch version

Vragenlijst: Over de ziekenhuisopname:	Niet										Erg
Hoe erg was het lichamelijke ongemak?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de pijn bij inspanning (hoesten, lopen)?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg waren de blaaskrampen?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de sufheid?	0	1	2	3	4	5	6	7	8	9	10
Heeft u goed kunnen slapen na de operatie?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de misselijkheid?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de pijn in rust?	0	1	2	3	4	5	6	7	8	9	10
Hoe erg was de jeuk?	0	1	2	3	4	5	6	7	8	9	10
Bent u in het algemeen tevreden met uw herstel?	0	1	2	3	4	5	6	7	8	9	10
Gebruikt u nu nog pijnstillers? (welke)	.....										
Ik kan dezelfde lichamelijke inspanning verrichten als vóór de operatie (b.v. traplopen, boodschappen doen)	.....										
Ik kan dezelfde geestelijke inspanning verrichten als vóór de operatie (b.v. concentratie, geheugen)	.....										

B. English translation

Questionnaire: Regarding the hospital admission:	Not 0 1 2 3 4 5 6 7 8 9 10 Very
How severe was the physical discomfort?	0 1 2 3 4 5 6 7 8 9 10
How severe was the pain in exertion (e.g. coughing, walking)?	0 1 2 3 4 5 6 7 8 9 10
How severe were the bladder spasms?	0 1 2 3 4 5 6 7 8 9 10
How severe was the drowsiness?	0 1 2 3 4 5 6 7 8 9 10
Were you able to sleep well after the surgery?	0 1 2 3 4 5 6 7 8 9 10
How severe was the nausea?	0 1 2 3 4 5 6 7 8 9 10
How severe was the pain in rest?	0 1 2 3 4 5 6 7 8 9 10
How severe was the itching?	0 1 2 3 4 5 6 7 8 9 10
How satisfied are you in general with your recovery?	0 1 2 3 4 5 6 7 8 9 10
Do you currently use any pain medication (if so, which)?	.....
I can perform the same physical activities as before the surgery (e.g. walking a flight of stairs, doing groceries)	.....
I can perform the same mental activities as before the surgery (e.g. concentration, memory)	.....

4. Absolute QoR-15-scores for the total QoR-15 and the five domains. POD: Post-Operative Day.

	Group	Preoperative	P	POD 1	P	POD 7	P
Total QoR-15	Intervention	133.3 ± 13.8	0.099	121.7 ± 18.2	0.077	124.3 ± 16.0	0.569
	Control	137.9 ± 9.6		115.9 ± 19.3		125.9 ± 15.6	
Pain	Intervention	18.4 ± 3.6	0.473	16.1 ± 3.6	0.000	17.2 ± 3.2	0.642
	Control	19.3 ± 1.6		13.2 ± 4.3		16.7 ± 4.2	
Physical comfort	Intervention	45.0 ± 4.5	0.581	39.7 ± 7.3	0.530	43.3 ± 5.6	0.749
	Control	45.4 ± 4.2		38.9 ± 7.1		43.5 ± 4.4	
Physical independence	Intervention	19.3 ± 1.4	0.644	14.7 ± 4.9	0.081	16.3 ± 2.8	0.367
	Control	19.1 ± 1.6		13.3 ± 5.1		16.7 ± 2.9	
Psychological support	Intervention	16.8 ± 4.1	0.260	18.6 ± 2.1	0.141	18.6 ± 1.8	0.731
	Control	17.6 ± 3.4		18.0 ± 2.9		18.5 ± 2.4	
Emotional support	Intervention	35.4 ± 4.6	0.608	33.5 ± 5.9	0.792	33.2 ± 6.2	0.267
	Control	35.8 ± 4.0		32.9 ± 6.5		34.1 ± 6.4	

5. Absolute values of the QoR-15 per question, presented as Median (IQR). * notes a P-value < 0.05. POD = postoperative day, I: Intervention, C: control.

Question		Preoperative	P	POD 1	P	POD 7	P
Breathing	I	10 (9-10)	0.482	10 (9-10)	0.442	10 (10-10)	0.564
	C	10 (9-10)		10 (9-10)		10 (9-10)	
Food	I	10 (9-10)	0.582	9 (8-10)	0.199	10 (9-10)	0.514
	C	10 (9-10)		8 (7-10)		10 (8-10)	
Rest	I	8 (8-10)	0.243	8 (7-10)	0.372	8 (7-9)	0.617
	C	9 (8-10)		8 (7-8)		8 (6-9)	
Sleep	I	9 (8-10)	0.798	8 (5-9)	0.158	7 (6-10)	0.839
	C	9 (7-10)		6 (5-8)		8 (7-9)	
Hygiene	I	10 (10-10)	0.215	9 (6-10)	0.096	10 (10-10)	0.211
	C	10 (10-10)		8 (5-10)		10 (10-10)	
Communication	I	10 (10-10)	0.363	10 (9-10)	0.233	10 (10-10)	0.711
	C	10 (9-10)		10 (9-10)		10 (10-10)	
Support	I	9 (6-10)	0.080	10 (9-10)	0.432	10 (8-10)	0.583
	C	9 (8-10)		10 (8-10)		10 (9-10)	
Return to work	I	10 (9-10)	0.767	8 (6-10)	0.113	7 (6-8)	0.513
	C	10 (9-10)		7 (4-9)		7 (5-8)	
Feeling in control	I	10 (9-10)	0.445	9 (7-10)	0.349	8 (7-10)	0.901
	C	10 (9-10)		8 (6-9)		7 (6-9)	
Well-being	I	9 (8-10)	0.855	9 (8-10)	0.990	9 (8-10)	0.737
	C	9 (8-10)		9 (7-10)		8 (7-10)	
Moderate pain	I	10 (8-10)	0.489	8 (4-9)	0.000*	8 (8-10)	0.644
	C	10 (9-10)		5 (3-8)		8 (5-10)	
Severe pain	I	10 (10-10)	0.227	10 (8-10)	0.018*	10 (7-10)	0.532
	C	10 (10-10)		9 (7-10)		10 (10-10)	
Nausea	I	10 (10-10)	0.433	9 (5-10)	0.247	10 (10-10)	0.049
	C	10 (10-10)		10 (7-10)		10 (10-10)	
Anxiety	I	10 (7-10)	0.907	10 (8-10)	0.621	10 (7-10)	0.050
	C	9 (7-10)		9 (8-10)		10 (8-10)	
Depressed	I	10 (9-10)	0.722	10 (9-10)	0.646	10 (10-10)	0.351
	C	10 (9-10)		10 (8-10)		10 (10-10)	

6. The absolute difference between pre-operative and post-operative score per question. A positive value indicates a decline in quality of recovery. * notes a P-value < 0.05. POD: Post-operative Day, I: Intervention, C: control.

Question		POD 1	p	POD 7	p
Breathing	I	0 (0-0)	0.290	0 (-1-0)	0.307
	C	0 (0-0)		0 (-1-0)	
Food	I	0 (0-2)	0.274	0 (0-0)	0.332
	C	1 (0-2)		0 (0-1)	
Rest	I	0 (-1-2)	0.178	0 (0-2)	0.165
	C	1 (0-2)		1 (0-2)	
Sleep	I	1 (0-3)	0.112	1 (0-3)	0.896
	C	2 (0-4)		1 (0-2)	
Hygiene	I	1 (0-3)	0.146	0 (0-0)	0.069
	C	2 (0-5)		0 (0-0)	
Communication	I	0 (0-0)	0.784	0 (0-0)	0.571
	C	0 (0-1)		0 (0-0)	
Support	I	-1 (-3-0)	0.014*	0 (-2-0)	0.083
	C	0 (-1-0)		0 (0-1)	
Return to work	I	2 (0-5)	0.150	3 (1-4)	0.905
	C	2 (1-5)		3 (1-4)	
Feeling in control	I	1 (0-2)	0.393	2 (0-3)	0.403
	C	1 (0-3)		2 (0-4)	
Well-being	I	0 (-1-2)	0.943	0 (0-1)	0.872
	C	0 (0-2)		0 (0-1)	
Moderate pain	I	1 (0-3)	0.000*	1 (0-3)	0.304
	C	4 (2-7)		2 (0-3)	
Severe pain	I	0 (0-1)	0.014*	0 (0-0)	0.703
	C	0 (0-3)		0 (0-0)	
Nausea	I	1 (0-4)	0.314	0 (0-0)	0.365
	C	0 (0-3)		0 (0-0)	
Anxiety	I	0(-2-1)	0.596	0 (-2-0)	0.173
	C	0 (-1-1)		0 (-2-0)	
Depressed	I	0 (0-1)	0.998	0 (0-0)	0.868
	C	0 (0-1)		0 (0-0)	

7. Additional outcome measures:

	Intervention	Control	P
Preoperative hemoglobin level (mmol/L)	9.3 (8.8-9.7)	9.2 (8.8-9.7)	0.831
Postoperative hemoglobin level (mmol/L)	8.0 (7.4-8.4)	8.0 (7.5-8.4)	0.470
Difference between preoperative and postoperative hemoglobin (mmol/L)	1.3 (0.9-1.8)	1.2 (0.9-1.7)	0.273
Preoperative Creatinine (µmol/L)	82 (74-88)	81 (72-89)	0.905
Postoperative Creatinine (µmol/L)	86 (77-98)	81 (72-89)	0.033
Difference between preoperative and postoperative Creatinine (µmol/L)	-5 (-11-2.5)	-1 (-7- -4)	0.074
Post-operative C-reactive Protein (CRP) (mg/L)	39 (29-53)	34 (23-54)	0.210
Postoperative leucocyte count (10^9/L)	9.7(8.0-11.2)	9.3 (8.2-11.1)	0.769
Postoperative Prostate Specific Antigen > 0.2 ng/L	6 (8.6%)	9 (12%)	0.591
Cristalloid administration (ml)	1000 (1000-1500)	1100 (1000-1500)	0.686
Colloid administration (ml)	0 (0-0)	0 (0-0)	0.072
Residual neuromuscular block at end of surgery	6 (7.9%)	7 (9.2%)	1.000
Emergence Delirium	0 (0%)	3 (3.8%)	0.245

Intrathecal hydrophilic opioids for abdominal surgery: a meta-analysis, meta-regression and trial sequential analysis

M.V. Koning, M. Klimek, K. Rijs, R.J. Stolker, M.A. Heesen.

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Chapter 5

Abstract

Background

Intrathecal hydrophilic opioid decreases systemic opioids consumption after abdominal surgery and potentially suits an Enhanced Recovery Program. A meta-analysis is needed to quantify the risks and benefits.

Methods

A systematic search was performed to find randomized controlled trials investigating intrathecal hydrophilic opioids in abdominal surgery. Caesarean sections and continuous regional or neuraxial techniques were excluded. Several subgroup analysis were prespecified. A conventional meta-analysis, meta-regression, trial sequential analysis (TSA) and provision of a GRADE score were planned.

Results

The search yielded 40 trials consisting of 2500 patients. A difference was detected in "intravenous morphine consumption" at day 1 (Mean Difference -18.4 mg (95%CI: -22.3, -14.4)) and day 2 (MD -25.5 mg (95%CI: -30.2, -20.8)), pain scores at day 1 in rest (MD -0.9 (95%CI: -1.1, -0.7)) and during movement (MD -1.2 (95%CI: -1.6. -0.8)), length of stay (MD -0.2 days (95%CI: -0.4, -0.1)) and pruritus (Relative Risk 4.3 (95%CI: 2.5, 7.5)) but not in nausea or sedation. A difference was detected for respiratory depression (OR 5.5 (95%CI: 2.1, 14.2) but not when two small outlying studies were excluded (OR 1.4 (95%CI: 0.4, 5.2)). The level of evidence was graded as high for the morphine consumption, also because the required information size was reached.

Conclusion

This study showed important opioid sparing effects of intrathecal hydrophilic opioids. Our data suggest a dose dependent relationship between the risk of respiratory depression and the dose of intrathecal opioids. Excluding two high-dose studies, intrathecal opioids have a comparable incidence as the control group.

Introduction

Enhanced Recovery Programs (ERP) provide multiple recommendations, one of which is sufficient postoperative analgesia.[1] A promising analgesic approach is the use of intrathecal hydrophilic opioids, which have been used for decades and renewed interest was caused by a recent study that was able to show an enhanced recovery in abdominal surgery.[2,3] Still, the risks and benefits needs to be quantified before the widespread use in abdominal surgery can be advocated.

The benefits of intrathecal hydrophilic opioids, compared to intravenous administration, are believed to be caused by a higher potency and a prolonged action, due to a small distribution volume of the cerebrospinal fluid and a slow diffusion, respectively.[4] Used as a single bolus technique, intrathecal hydrophilic opioids have an intravenous opioid sparing effect, facilitate mobilization and – due to a lack of peripheral vasodilation - a restrictive fluid management can easily be achieved.[5] These properties may lead to a faster recovery after abdominal surgery.

The risks, however, are pruritus, nausea and late respiratory depression. Especially the fear for latter has limited the use of intrathecal hydrophilic opioids. Previously, Meylan *et al.* performed a meta-analysis regarding intrathecal morphine and they found higher rates of pruritus and respiratory depression.[6] However, that meta-analysis involved predominantly studies in cardiac surgery and a wide range in dosages were used. This limits the transfer of the found risks and benefits to abdominal surgery, which requires a meta-analysis of its own.

Therefore, we performed a meta-analysis to quantify the risks and benefits of intrathecal hydrophilic opioids. Our study had two goals: firstly, we set out to identify the studies published in the last decade in order to come to an up-dated evaluation of the benefits and risks of intrathecal morphine. Secondly, we focused on a particular patient group, i.e. abdominal surgery patients undergoing both open and laparoscopic procedures. Furthermore, in recent years Trial Sequential Analysis (TSA) has emerged as a statistical technique that maintains the Type 1 error-rate in meta-analyses at a prespecified level, which contributes to the certainty of a conclusion in a meta-analysis.[7] This technique will be applied to the data obtained from trials on intrathecal hydrophilic opioids for abdominal surgery.

Methods

Our meta-analysis was performed in accordance with the PRISMA statement.[8] The meta-analysis was registered at PROSPERO with registration number CRD42018090682.

A systemic literature search was performed in December 2019. We searched the databases of Medline, Embase, CINAHL, LILACS, Cochrane CENTRAL, Web of Science, ClinicalTrials.gov and Google Scholar. Filters or language restriction were not applied. The search combined terms for "intrathecal", "hydrophilic opioid" and "abdominal surgery" (See Appendix C). Morphine, hydromorphone, diamorphine, pethidine, and dihydromorphine were considered hydrophilic opiates. The search was managed with EndNote and duplicates were removed. Bibliographies of selected studies were also screened for studies of interest. The search included trial registers and these records were checked for completion and publication.

Inclusion and exclusion criteria were defined a priori and only randomized trials were considered. The inclusion criteria were defined according to a PICO-search, in which the Patients were adults undergoing abdominal surgery, the Intervention was the administration of intrathecal hydrophilic opioids, with or without additives, such as local anesthetics, the Comparator was analgesia without intrathecal hydrophilic opioids. The primary outcome measures were intravenous (IV) morphine-equivalents consumption at 24 and 48 hours. The secondary outcome measures were pain scores in rest and during movement at 24 and 48 hours, time to fit for discharge, length of hospital stay, time to first analgesic request, intraoperative sufentanil-equivalent consumption, incidence of nausea, pruritus, sedation and respiratory depression.

Exclusion criteria were caesarean section and the use of concomitant continuous regional anesthesia or neuraxial anesthesia.

Two authors (MVK and MK) screened the abstracts for eligible studies. Full texts of these studies were analyzed and data was extracted if the study was considered includable. The extracted data were authors, year of publication, type of surgery, details of intervention, details of control, post-operative analgesia and urinary catheter management. If the mean and standard deviation were not reported in the paper, we derived the mean and standard deviation from the median and

range using the formula by Hozo et al.[9] Morphine equivalents were calculated. The conversion factor for piritramide was 0.7[10], for papaveretum 0.665[11], for fentanyl 10012, for pethidine 0.133[13] and for tramadol 0.1[12]. The conversion factor to calculate fentanyl into sufentanil equivalents for intraoperative analgesia was 0.1.[14] If multiple groups with intrathecal morphine were compared, we combined those groups and used the mean dose of intrathecal morphine. The continuous outcome measures of such as study were the mean values of the groups and the largest SD of the groups. Addition of events and patients were used for binary data. If a trial used multiple groups that could serve as control group (i.e. without intrathecal hydrophilic opioids), the group with the control treatment as similar as possible with the intervention group was used.

The methodological quality of each study was evaluated by two authors (MVK and MH) based on the Cochrane Risk of Bias tool.[15] This tool includes assessment of the risks of selection bias (random sequence generation, allocation concealment), performance bias (blinding of participant and personnel), detection bias (blinding of assessor), attrition bias and other bias (e.g. multiple treatment groups, comparable baseline values and number of participants).

We used Review Manager (RevMan, version 5.1, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for meta-analysis. We considered meta-analyses worthwhile only if at least three studies with at least 100 patients per treatment arm were available for analysis. In order to deal with the expected clinical and methodological heterogeneity across studies, a random effects model with inverse variance was applied. For dichotomous data the Mantel-Haenszel-method was used. Risk ratio (RR) and 95% confidence interval (95% CI) were calculated for binary outcome and mean Difference (MD) and 95% CI were calculated for continuous outcomes. The Peto Odds Ratio was used to analyze the risk of respiratory depression, due to the low incidence. The I^2 statistic was used to assess heterogeneity and an $I^2 > 50\%$ was considered important heterogeneity.[16] A P value of <0.05 was taken to indicate statistical significance. We performed the following pre-specified subgroup analyses: laparoscopic surgery, laparotomic surgery, addition of bupivacaine to the intrathecal hydrophilic opioids, solely intrathecal hydrophilic opioids, studies with an Enhanced Recovery Program (ERP) and studies with a sham-procedure in the control group for blinding purposes. For the latter, only studies with a lumbar needle insertion in the control group, either

subcutaneously or intrathecally and regardless if medication was administered, were included in this subgroup.

Asymmetry in conventional funnel plots can exist without true asymmetry, and reasons other than publication bias can result in asymmetry.[17,18] For this reason, contour-enhanced funnel plots were performed. This was done if there were 10 or more studies in the meta-analyses of the outcomes.[15] We used the test described by Egger et al. to test for plot asymmetry.[19]

We hypothesized that the effect of the dose of intrathecal opioid could influence the outcome variables. To test for possible heterogeneity, we performed mixed-effects meta-regression (unrestricted maximum likelihood) to determine the effect of the dose of intrathecal opioid. R version 3.1.3 with the 'meta' package (version 4.2-0) and 'metafor' package (version 1.9-7) was used.

Furthermore, similar to interim analyses of primary clinical trials, meta-analyses have been found to be prone to type-1 (falsely positive results) and type-2 error (falsely negative results) during statistical analysis.[20,21] Trial Sequential Analyses (TSA) is a method to avoid type-1 errors and were performed for the primary outcomes of our meta-analyses, in order to consider the risk of random error and better estimate the uncertainty in our findings.[22,23] Trial sequence analyses methodology was described elsewhere.[24] Sequential monitoring boundaries are made to decide whether a trial could be terminated early because of a sufficiently small p value. When the cumulative z-curve crosses the monitoring boundaries, an acceptable small chance of a false positive result can be assumed. We calculated the required information size allowing for a type-1 error of 0.05, and type-2 error of 0.20, with the mean difference from the effect estimate from the conventional random effects model[25], and heterogeneity estimated by the diversity (D2) in the included trials. For the analyses we used Trial Sequential Analysis Viewer (TSA Viewer. Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, 2016).

In order to rate the quality of evidence and strength of recommendation of our primary outcomes, the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) was used.[26] We assessed the following criteria: risk of bias, inconsistency, indirectness, imprecision and publication bias. When one of the above items was assessed as a risk, the evidence was downgraded by two

levels (very serious risk) or one level (serious risk). In addition, when the Required Information Size was not reached or the sequential boundary was not crossed, the evidence was downgraded one level as well. One of the following four grades was assigned: high quality (further research is very unlikely to alter the confidence in the estimate of the effect); moderate quality (further research is likely to alter the confidence in the estimate of the effect); low quality (further research is very likely to alter the confidence in the estimate of the effect); or very low quality (the confidence in the effect estimate is very little).

Results

The flow chart of our literature search is presented in Figure 1. 40 studies were included in the quantitative analysis and study characteristics are presented in Table 1. Only Child et al., Day et al. and Levy et al. used diamorphine, all others used morphine as intrathecal opioid.[5,37,39] The dose varied between 100 and 800 µg of morphine and except for two studies that administered a body weight adjusted dose of 15 µg/kg and 50 µg/kg morphine.[47,55]

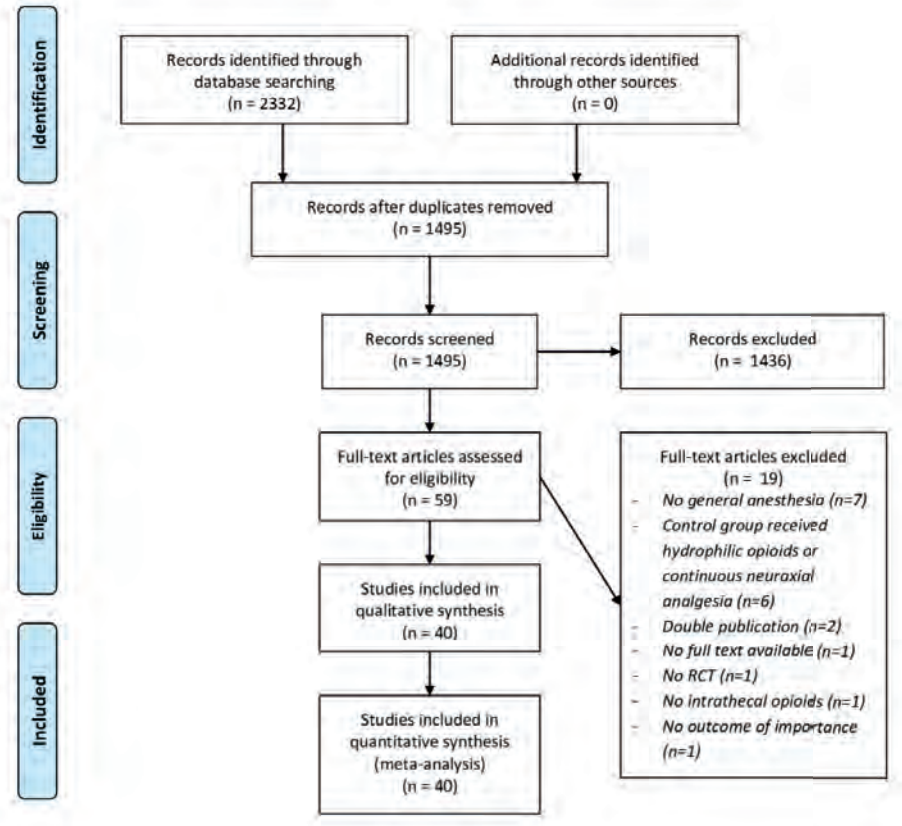


Figure 1. Flow chart.

Table 1. Characteristics of included studies. PCA: Patient Controlled Analgesia, NSAID: non-steroidal anti-inflammatory drugs.

First author, year of publication	Type of surgery	Number of participants (intervention vs. Control)	Intervention	Comparator	Postoperative analgesic regimen	Sham procedure	Subgroup	Urinary Catheter
Abd El-Rahman, 2018[27]	Major Abdominal Cancer surgery	30 vs 30	300 µg morphine, 10 mg bupivacaine, 0.1 mg/kg ketamine	10 mg bupivacaine, 0.1 mg/kg ketamine	PCA morphine	IT medication	A	Unspecified
Abdel-Ghaffar, 2016[28]	Major Abdominal Cancer surgery	30 vs 30	500 µg morphine, 10 mg bupivacaine	10 mg bupivacaine	PCA morphine	IT medication	A	Urinary catheter removed on POD1
Andreoni, 2002[29]	Percutaneous Nephrolithotomy	9 vs 11	0.3-0.5 µg/kg morphine	Local infiltration with ropivacaine	Unspecified	None	B	Nephrostomy catheter, no urinary catheter
Andrieu, 2009[30]	Retropubic Radical Prostatectomy	17 vs 16	4 µg/kg morphine, maximum of 300 µg	No additional medication	Paracetamol, PCA morphine	None	B, D	Unspecified
Bae, 2017[31]	Robotic Assisted Laparoscopic Prostatectomy	15 vs 15	300 µg morphine	No additional medication	PCA morphine, pethidine rescue dose	None	B, C	Urinary catheter for one week
Beaussier, 2006[32]	Colonic surgery	26 vs 26	300 µg morphine	No additional medication	Paracetamol, PCA morphine	SC saline	B	Unspecified
Beltrutti, 2002[33]	Hysterectomy	15 vs 14	4.3 µg/kg morphine	1.3 µg/kg buprenorphine IV	IV buprenorphine	IT saline	B, D	No postoperative urinary catheter in a part of the patients

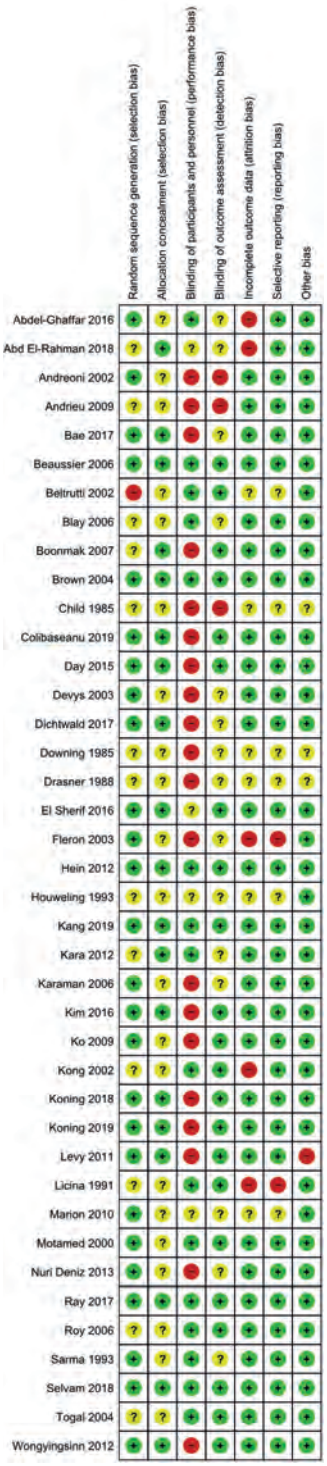
First author, year of publication	Type of surgery	Number of participants (intervention vs. Control)	Intervention	Comparator	Postoperative analgesic regimen	Sham procedure	Subgroup	Urinary Catheter
Blay, 2006[34]	Abdominal aortic surgery	15 vs 15	200 µg morphine	No additional medication	Paracetamol, nefopam, morphine rescue dose	SC saline	B, D	Urinary catheter of unknown duration
Boonmak, 2007[35]	Kidney surgery	40 vs 40	300 µg morphine	No additional medication	PCA morphine	None	B, D	Unspecified
Brown, 2004[36]	Radical prostatectomy	49 vs 50	200 µg morphine, 15 mg bupivacaine, 75 µg clonidine	15 mg bupivacaine, 75 µg clonidine	Paracetamol, Ketorolac, PCA morphine	SC saline	A, D	Unspecified
Child, 1985[37]	Colonic surgery	8 vs 8	50 µg/kg diamorphine	3-5 µg/kg fentanyl IV	Unspecified	None	B, D	Unspecified
Colibaseanu, 2019[38]	Colorectal surgery	98 vs 102	100 µg morphine	Bilateral TAP-block with liposomal bupivacaine	Multimodal analgesia, unspecified	None	B, E	Unspecified
Day, 2015[39]	Colorectal surgery	60 vs 60	250 µg diamorphine, 12.5 mg bupivacaine	10 mg morphine IV and PCA morphine	Tramadol and morphine PO as needed, diclofenac, paracetamol	None	A, C	Urinary catheter removed on POD1
Devys, 2003[40]	Mixed abdominal surgery	30 vs 30	300-400 µg morphine	No additional medication	PCA morphine	None	B	Unspecified
Dichtwald, 2017[41]	Hepatopancreatic surgery	23 vs 26	4 µg/kg morphine	IV loading dose of 0.15 µg/kg morphine	PCA morphine, paracetamol and dypirone rescue doses	None	B, D	Urinary catheter of unknown duration
Downing, 1985[42]	Cholecystectomy	10 vs 10	800 µg morphine	IV titration of papaveretum during surgery	IV papaveretum rescue dose	None	B, D	Unspecified

First author, year of publication	Type of surgery	Number of participants (intervention vs. Control)	Intervention	Comparator	Postoperative analgesic regimen	Sham procedure	Subgroup	Urinary Catheter
Drasner, 1988[43]	Major gynaecological surgery	10 vs 10	750 µg morphine	IM 750 µg morphine	Unspecified	None	B, D	Unspecified
El-Sherif, 2016[44]	Laparoscopic bariatric surgery	50 vs 50	300 µg morphine, 6 mg bupivacaine	IT 6 mg bupivacaine and saline	Paracetamol, ketorolac, PCA morphine, wound infiltration with ropivacaine	IT medication	A, C	Removal of urinary catheter after surgery
Fleron, 2003[45]	Abdominal aortic surgery	102 vs 115	8 µg/kg morphine, 1 µg/kg sufentanil	Continuous IV sufentanil	Paracetamol, PCA morphine	None	D	Urinary catheter of unspecified duration
Hein, 2012[46]	Abdominal hysterectomy	102 vs 34	Mean 200 µg morphine, 12 mg bupivacaine	IT 12 mg bupivacaine	Paracetamol, PCA morphine	IT medication	A, D	Unspecified
Houweling, 1993[47]	Abdominal Aortic surgery	18 vs 18	50 µg/kg morphine	IT 150 µg sufentanil	500 µg morphine IT	IT medication	B, D	Urinary catheter of unspecified duration
Kang, 2019[48]	Laparoscopic partial hepatectomy	27 vs 27	400 µg morphine	Bilateral ESP-block with ropivacaine	Paracetamol, ibuprofen, PCA fentanyl, IV meperidine	None	B, C, E	Urinary catheter of unspecified duration
Kara, 2012[49]	Major gynaecological surgery	30 vs 30	300 µg morphine	No additional medication	PCA morphine	SC needle introduction	B	Unspecified
Karaman, 2006[50]	Abdominal hysterectomy	12 vs 12	5 µg/kg morphine	No additional medication	Diclofenac, PCA morphine	None	B, D	Unspecified

First author, year of publication	Type of surgery	Number of participants (intervention vs. Control)	Intervention	Comparator	Postoperative analgesic regimen	Sham procedure	Subgroup	Urinary Catheter
Kim, 2016[51]	Kidney surgery	22 vs 23	300 µg morphine	No additional medication	PCA morphine, pethidine rescue dose	None	B, D	Unspecified
Ko, 2009[52]	Liver transplantation donors	20 vs 20	400 µg morphine	No additional medication	PCA fentanyl	None	B, D	Urinary catheter of unspecified duration
Kong, 2002[53]	Laparoscopic colorectal surgery	18 vs 17	200 µg morphine, 15 mg bupivacaine	15 mg bupivacaine	PCA morphine	IT medication	A, C	Unspecified
Koning, 2018[3]	Laparoscopic colonic surgery	27 vs 29	300 µg morphine, 12.5 mg bupivacaine	IV 0.1 mg/kg piritramide	Paracetamol, diclofenac, PCA piritramide	SC lidocaine	A, C	Urinary catheter removed on POD1
Koning, 2019[54]	Robot-Assisted radical prostatectomy	76 vs 79	300 µg morphine, 12.5 mg bupivacaine	IV 0.1 mg/kg morphine	Paracetamol, diclofenac, PCA morphine	SC lidocaine	A, C	Urinary catheter for one week
Levy, 2010[5]	Laparoscopic colorectal surgery	31 vs 30	250 µg diamorphine, 12.5 mg bupivacaine	IV 10 mg morphine	Paracetamol, diclofenac, tramadol or morphine	None	A, C	Urinary catheter removed on POD1
Licina, 1991[55]	Mixed abdominal surgery	12 vs 12	15 µg/kg morphine	No additional medication	Unspecified	SC saline	B, D	Unspecified
Marion, 2010[56]	Abdominal hysterectomy	35 vs 32	200 µg morphine, 10 µg fentanyl, 12.5 mg bupivacaine	IT 10 µg fentanyl, 12.5 mg bupivacaine	Paracetamol, diclofenac and PCA ketobemidone	IT medication	A, D	Unspecified
Motamed, 2000[57]	Laparoscopic cholecystectomy	17 vs 17	100 µg morphine, 5 mg bupivacaine	No additional medication	PCA morphine, Paracetamol and ketoprofen rescue doses	SC saline	A, C	No catheterisation

First author, year of publication	Type of surgery	Number of participants (intervention vs. Control)	Intervention	Comparator	Postoperative analgesic regimen	Sham procedure	Subgroup	Urinary Catheter
Nuri Deniz, 2013[58]	Retropubic radical prostatectomy	28 vs 28	200 µg morphine	No additional medication	PCA tramadol, paracetamol and diclofenac rescue doses	None	B, D	Unspecified
Ray, 2017[59]	Major abdominal surgery	46 vs 46	750 µg morphine, 10 mg bupivacaine	IV 0.2 mg/kg morphine, SC 0.1 mg/kg morphine	Paracetamol, SC morphine	IT saline	A	Urinary catheter of unspecified duration
Roy, 2006[60]	Partial hepatic resections	10 vs 10	500 µg morphine, 15 µg fentanyl	No additional medication	PCA morphine	SC needle introduction	D	Unspecified
Sarma, 1993[61]	Abdominal hysterectomy	60 vs 20	Mean 300 µg morphine	No additional medication	Pethidine rescue dose	IT saline	B, D	Urinary catheter removed on POD1
Selvam, 2018[62]	Laparoscopic hysterectomy	16 vs 15	200 µg morphine, 5 mg bupivacaine	IT 5 mg bupivacaine	Paracetamol, PCA fentanyl	IT medication	A, C	Unspecified
Togal, 2004[63]	Abdominal hysterectomy	25 vs 25	100 µg morphine	No additional medication	PCA morphine	IT saline	B, D	Urinary catheter removed on POD1
Wongy-ingsinn, 2012[64]	Laparoscopic colonic resection	24 vs 25	200 µg morphine, 10 mg bupivacaine	PCA morphine	Paracetamol, naproxen, oxycodone	None	A, C	Urinary catheter removed on POD1

"No additional medication" under Comparator means that no additional medication to the postoperative analgesic regimen was administered. A = Addition of bupivacaine to intrathecal hydrophilic opioids, B= Only intrathecal hydrophilic opioids, C= laparoscopic procedures, D= open procedures, E= Regional Anesthesia.



◂**Figure 2.** Risk of bias assessment for included studies.

Risk of bias analysis is presented in Figure 2. Main limitations were allocation concealment and blinding of personnel and participants.

Primary outcomes:

Meta-analysis showed a mean difference in IV morphine equivalent consumption after 24 and 48 hrs of -18.4 mg (95%CI -22.3, -14.4) and -25.5 mg (95%CI -30.2, -20.8), respectively, in favor of the intrathecal opioids (Figure 3).

Secondary outcomes (Table 2):

The pain scores (converted to a range of 0-10) both in rest and during exertion were reduced in the intrathecal opioid group after 24 hours. The lower pain scores persisted during exertion after 48 hours, but were no longer different in rest. Intraoperative sufentanil-equivalents consumption was reduced and time-to-first analgesic request was prolonged in the intrathecal opioid group.

No increased risk for nausea or sedation was detected. The risk for pruritus was increased. Only Boonmak et al. reported the incidence of pruritus over different timepoints during the first two postoperative days, thus no data on duration and timing could be retrieved.35 All other studies reported an incidence of pruritus and monitored over 20-48 hours.

Due to the heterogeneity in definition of respiratory depression, only the cases in which medication was administered or mechanical ventilation was necessary were scored as respiratory depression in the meta-analysis. An increased risk for respiratory depression was found between intrathecal and intravenous opioids (Peto Odds Ratio 5.49 (95% CI 2.12, 14.24). The incidence of respiratory depression was 18/974 in the intrathecal opioids group versus 4/888 in the control group. The timing of respiratory depression after administration of intrathecal opioids was only reported by Dichtwald et al., which was after a mean of 6 hours after injection.[41] Licina *et al.* and Houweling *et al.* reported the highest incidence of respiratory depression with 11/12 patients and 2/18 patients respectively.[47,55] Both studies also used a much higher dose of intrathecal morphine than the other studies (15 μcg/kg and 50 μcg/kg respectively, resulting in 1200 μcg and 4000 μcg in a 80 kg patient).

However, when those two outlying high-dose studies were excluded[47,55], the incidence of respiratory depression was 5/944 for the intrathecal opioids group and 4/858 for the control group. This led to a Peto Odds Ratio of 1.39 (95% CI 0.37, 5.21).

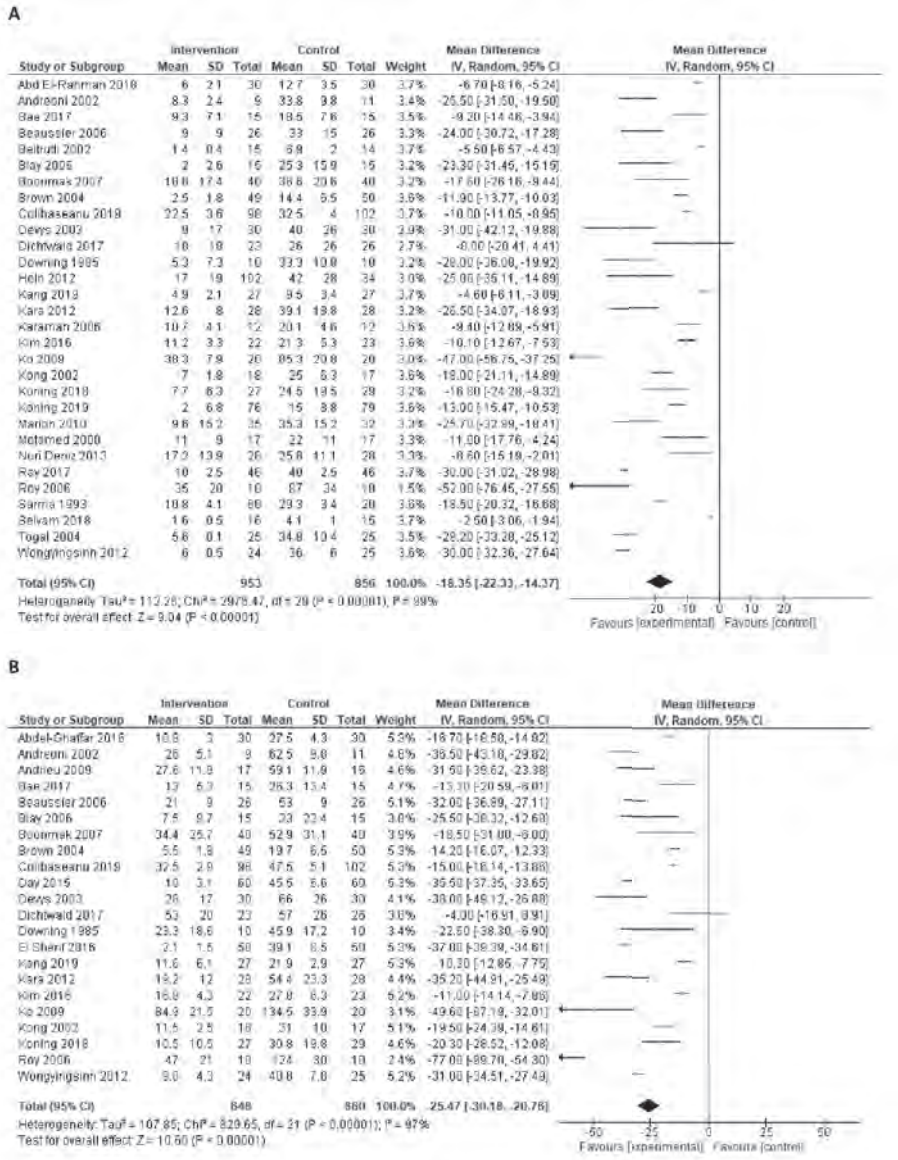


Figure 3. Forest plot of A. Morphine-equivalent consumption after 24 hours and B. 48 hours.

The length of hospital stay (LOS) was reduced with a mean difference of -0.2 days (95%CI -0.4, -0.1). In addition, patients in the intervention group were earlier fit-for-discharge as well (-0.3 days (95%CI -0.5, -0.1).

Table 2. Summary of the meta-analyses. I^2 describes the heterogeneity, RIS: Required Information Size as measured by TSA, Egger test describes the risk for publication bias. MD: Mean Difference, 95%CI: 95% Confidence Interval, NRS: Numeric Rating Scale, RIS: Required Information Size, RR: Relative Risk, mcg: microgram, mg: milligram

Variable	Studies (n)	Participants (n)	Value (95%CI)	I^2	RIS	Egger Test	Grade
Benefit			***Mean Difference***				
Morphine consumption day 1 (mg)	30	1809	-18.4 (-22.3, -14.4)	99%	266	0.03	High
Morphine consumption day 2 (mg)	22	1309	-25.5 (-30.2, -20.8)	97%	103	0.21	High
Pain scores in rest, day 1 (NRS)	33	2164	-0.9 (-1.1, -0.7)	93%		0.03	
Pain in exertion, day 1 (NRS)	19	1099	-1.2 (-1.6, -0.8)	79%		0.79	
Pain scores in rest, day 2 (NRS)	19	1114	-0.4 (-0.7, -0.1)	97%		0.94	
Pain in exertion, day 2 (NRS)	13	639	-0.4 (-0.7, -0.1)	50%		0.14	
Intraoperative sufentanil use (µg)	11	625	-12.9 (-19.3, -6.5)	91%		0.07	
Time to first analgesic request (hours)	8	309	9.7 (4.9, 14.5)	99%		0.01	
Time to Fit-for-discharge (days)	4	233	-0.3 (-0.5, -0.1)	28%		0.80	
Length of hospital stay (days)	17	1416	-0.2 (-0.4, -0.1)	88%		0.12	
Risk			***Risk Ratio***				
Incidence of nausea	25	1412	1.1 (0.9, 1.4)	48%		0.12	
Incidence of pruritus	23	1282	4.3 (2.5, 7.5)	57%		0.05	
Incidence of sedation	12	644	0.7 (0.5, 1.1)	2%		0.53	
Incidence of respiratory depression	31	1862	5.5 (2.1, 14.2)	14%		0.17	
Incidence of respiratory depression (<500 µg)	26	1473	1.1 (0.2, 8.2)	21%		N/A	

I^2 describes the heterogeneity, RIS: Required Information Size as measured by TSA, Egger test describes the risk for publication bias.

Management of urinary catheter was reported in 19 studies (Table 1). The majority inserted a catheter for at least one day or for an unspecified duration. These studies reported no interventions for urine retention after removal of the urinary catheter. More specifically, the studies that removed the catheter after 24 hours did not report any re-catheterisation.[3,5,28,39,61,63] Three studies used no postoperative urinary catheter, which allowed evaluation for urinary retention.[33,44,57] El Sheriff *et al*. found no urinary retention in 50 patients, Beltrutti *et al*. found urinary retention in 4 of 7 patients in the intervention group versus 3 of 9 patients in the control group although none required re-catheterization. Motamed *et al*. found 4 of 17 patients in the intervention group versus 1 of 17 patients in the control group with urinary retention. Of the 4 of the intervention group, 2 were managed with naloxone and 2 were managed with a urinary catheter.

Publication bias:

The search included trial registries and yielded 26 trial registrations of which 12 were published and already included. Six trials were still recruiting. Two trials were completed and added to the database.[38,54] Two other, completed studies were of potential interest but no publication could be found (NCT03620916 and NCT03675646).

Contour enhanced funnel plots were generated and only 24 hour IV morphine equivalent consumption pain scores in rest after 24 hours and time to first analgesic request had Egger tests with a p-value <0.05 (Figure 4). Asymmetry in the 24 hour IV morphine equivalents and pain score in rest after 24 hours seemed to originate from the lack of studies with low Standard Error with a large effect size or from the lack of small studies. Based on visual inspection of the two contour-enhanced funnel plots, the asymmetry was unlikely to exaggerate the effect size, which makes as *small study effect* unlikely. The lack of studies with a large benefit and a small standard error is unlikely to be caused by publication bias. Time to first analgesic request included 8 studies, which limits its power. The funnel plots are presented in appendix C. Based on these findings the risk of publication bias seems low.

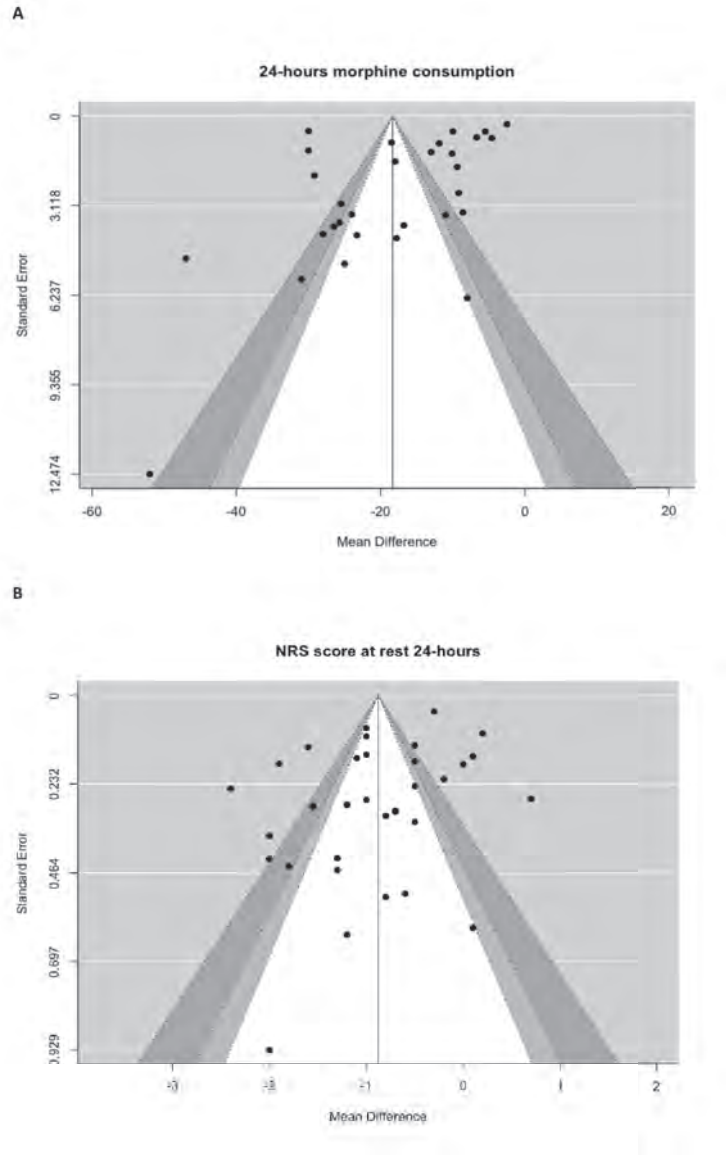


Figure 4. Contour-enhanced funnel plot of A. 24 hour morphine equivalent consumption and B. pain score in rest after 24 hours.

Subgroup analyses (see appendix C):

Five subgroup analyses were performed, which were solely intrathecal hydrophilic opioids, the addition of intrathecal bupivacaine, laparoscopic surgical procedures, laparotomic surgical procedures and the studies that involved an Enhanced Recovery Program (ERP). The first four mentioned subgroups showed no difference to the general comparison (see appendix C). Five studies described the use of an ERP.[3,5,38,39,64] In these studies the Length of Stay was -0.2 days (95% CI: -0.5, 0.1), I^2 93%. Fit-for-Discharge had too little subjects (82 vs 84) to produce a reliable analysis. In addition, a sensitivity analysis was performed including only studies with a patient-blinding procedure in the control group for the outcomes "pain scores", morphine consumption, nausea and pruritus.[3,27,28,32-34,36,44,46,47,49,53-57,59-63] This analysis showed comparable outcomes to the general comparison.

Meta-regression:

Meta-regression analyses were performed to detect a dose dependent effect in 24 hour and 48 hour IV morphine equivalents consumption, pain scores in rest and during movement, nausea, pruritus, sedation and respiratory depression (see appendix C). The variation in doses was limited since the most commonly used dose was 300 µg and all but six studies varied between 100 and 400 µg of intrathecal morphine. A dose dependency was observed only for pain scores in rest after 48 hours (slope of 0.006/µg morphine (95% CI: 0.001, 0.011)) and incidence of pruritus (slope of 0.005/µg morphine (95% CI: 0.002, 0.007))(see appendix C).

Trial Sequential Analysis:

Trial sequential analysis showed a required information size of n=266 for 24 hour IV morphine equivalent consumption, n=103 for 48 hour IV morphine equivalent consumption.

GRADE recommendations:

GRADE recommendations were made for the outcomes "IV morphine equivalent consumption after 24 hours", "IV morphine equivalent consumption after 48 hours". Inconsistency was detected, since conventional meta-analyses showed an I^2 >74% and a p-value for heterogeneity >0.05. The inconsistency was not

explained by subgroup analysis or by different types of studies, since all studies were prospective randomized trials. Moreover, no studies were in the opposite direction, thus important clinical inconsistency was deemed unlikely. Since the confidence interval of the outcomes were within a clinical useful range, we did not downgrade the level of evidence due to inconsistency. No publication bias was detected by contour-enhanced funnel plots and all outcomes were directly measured. The risk of bias was high due to limited blinding of participants or outcome assessors in a number of studies, but the sensitivity analysis of only blinded studies with a sham procedure did not show different results. Therefore, the insufficient blinding probably had a limited effect and the level of evidence was not downgraded. The required information size was reached for both outcomes. Therefore, we graded the outcomes of 24 and 48 hours IV morphine equivalent consumption as a high level of evidence.

Discussion

Our meta-analysis of 40 studies including 2500 patients found a reduced postoperative IV morphine equivalent consumption of -18.4 mg (95%CI -22.3, -14.4) in the first 24 and -25.5 mg (95%CI -30.2, -20.8) in the first 48 hours in the intrathecal hydrophilic opioids group. Moreover, we found clinically relevant reductions by intrathecal hydrophilic opioids for the following secondary outcomes: pain scores in rest and during movement after 24 hours, pain scores during movement after 48 hours, time to first analgesic request, length of hospital stay and intraoperative sufentanil equivalent consumption. The risk of pruritus was increased and a dose dependent effect was found. Overall, the risk of respiratory depression was increased (Peto Odds Ratio 5.49 (95%CI: 2.12, 14.24), but when two outlying studies of doses >1000 μg of intrathecal morphine were excluded, similar incidence of respiratory depression as the control group was found (Peto Odds Ratio of 1.39 (95% CI 0.37, 5,21). Subgroup analysis for laparoscopic, laparotomic, addition of bupivacaine and solely hydrophilic intrathecal opioids yielded no substantial differences compared to the total group for all the outcomes.

These results led to different conclusions than the results of a previous meta-analysis.[6] This meta-analysis shows that the use of intrathecal hydrophilic opioids in abdominal surgery has several benefits, which are the reduced systemic opioid consumption, lower pain scores and a slightly reduced length of stay. The risks

consist mostly of pruritus. Urinary retention was not evaluated in the majority of the included trials. The risk of respiratory depression was not increased when the studies with a dose over 1000 µg were excluded. It appeared that a specific indication (i.e. abdominal surgery), a specific definition of respiratory depression and more recent studies led to an acceptable safety profile. While in the other meta-analysis it was suggested to abandon this analgesic technique, this study shows the positive effects may be substantial in abdominal surgery and the risks are limited.[6]

The reduction in IV morphine equivalents consumption may not come as a surprise, since this effect has already been described for many years.65 However, we feel that our finding of a reduction in postoperative morphine consumption of 18.4 mg (95%CI -22.3, -14.4) in the first 24 hours is clinically relevant. In addition, difference in morphine consumption further increased to 25.5 mg (95%CI -30.2, -20.8) after 48 hours, a finding that is unique in our study and which was not shown by Meylan et al.[6] These findings are based on sufficient data, as displayed by Trial Sequential Analysis.

In addition, the mean morphine equivalent consumption allows to compare this method with other opioid sparing techniques such as intravenous lidocaine (-4.5 mg (95%CI: -6.3, -2.8)[66], high dose pregabalin (-13.4 mg (95%CI: -22.8, -4.0)[67] and ketamine -10.3 (95%CI -13.8, -6.8)[68]. This is not a direct scientific comparison, so it should be interpreted with caution, but it may provide an intuitive effect size. Of importance is that the opioid sparing effect in our meta-analysis is in addition to paracetamol and NSAIDs, since most studies used this medication as a basal multimodal analgesia regimen. We believe that the use of additional opioid sparing strategies, such as intrathecal hydrophilic opioids, intravenous lidocaine, pregabalin or ketamine, should be regarded as addition to the use of paracetamol and NSAIDs, since these are most consolidated in clinical practice.

This work supports the use of intrathecal hydrophilic opioids within an Enhanced Recovery Program (ERP), since the lower pain scores during movement caused by intrathecal hydrophilic opioids may facilitate early mobilisation.[69] Additionally, other goals such as to minimize systemic opioids and still produce low pain scores are achieved as well.[70] This mechanism could explain the reduced postoperative length of stay. In line with previous research, we interpreted the difference in length of stay as one out of every five patients leaves the hospital a day earlier,

because in most studies the length of stay was scored per full day and not in half or quarter days. Still, this outcome must be interpreted with caution, because the subgroup analysis of studies which implemented an ERP did not show any difference and length of stay may be influenced by non-medical issues, making fit-for-discharge perhaps a better variable for reflecting recovery.[3]

Other studies reported that the use of intrathecal hydrophilic opioids was associated with adverse effects, such as urinary retention, pruritus, nausea and the risk of late respiratory depression.[71] By contrast, our meta-analysis was unable to detect a difference in nausea. Urinary retention was not measured, since the majority of the included studies used an urinary catheter for at least the first postoperative day. Interestingly, none of these studies reported a case of catheterization or urinary retention beyond that period.

The most common side-effect of intrathecal hydrophilic opioids is pruritus and we found a dose-dependent effect for pruritus in the range of 100-800 µg of intrathecal morphine. We have to point out that a previous meta-analysis of Meylan *et al.* did not detect a dose- dependent effect which may be due to the lower number of studies in that analysis.[6] Studies that have purposely investigated the relationship between the dose and the incidence of pruritus were able to detect a correlation.[72] Theoretically, severe pruritus might delay hospital discharge, albeit the pruritus probably lasts shorter than the time for recovery. The duration of pruritus was only investigated in the study of Boonmak *et al.* during 48 hours, which showed a decline of incidence after 24 hours.[35] This is in accordance with other studies.[3,73] Late respiratory depression is an adverse effect of concern and probably limits the widespread use of intrathecal hydrophilic opioids.[74] Since only one study explicitly investigated the time to respiratory depression, we are unable to draw conclusions on this aspect.[35] In our analysis we detected similar incidences of respiratory depression (5/944 for the intrathecal opioids group and 4/844 in the control group) by the use of intrathecal opioids in low dosage. This led to a markedly different conclusion than a previous meta-analysis, which found 6/504 in the intrathecal morphine group and 0/440 in the control group. This difference can be explained by a different definition of respiratory depression, the difference in dosage and the different type of surgery (i.e. abdominal versus cardiac surgery).

The definitions of respiratory depression varies amongst studies, which makes the incidence and severity of respiratory depression less than clear.[75] For our

analysis respiratory depression was only scored when a medical intervention (i.e. mechanical ventilation or medication) was installed. This is a high threshold to score respiratory depression, but we believe that this definition excludes respiratory failure due to other pathology (e.g. atelectasis, diaphragm dysfunction, pneumothorax or hemothorax). Meylan et al. used a different definition and included patients after cardiac surgery, which have higher incidences of this type of pathology than abdominal surgery.[6] Although the upside of a high threshold for scoring is that only the clinically important respiratory depression is scored, the downside is the risk of missing respiratory depression that does not require a medical intervention but may impact the clinical course of the patients.

Gehling et al. found a dose dependent effect for respiratory depression with a cut-off of 300 μg.[76] In our meta-regression a dose dependent effect was visible, but the confidence interval was too wide for statistical significance. In our analysis with the exclusion of two outlying studies, the incidence of respiratory depression that required a medical intervention was still similar to the control group. When excluding these two outlying high-dose studies the maximum dose included in our analysis was 800 μg, but the majority of the studies used a dose less than 500 μg. For safety measures, we would recommend using doses less than 500 μg, because these doses were predominantly investigated.

The incidence of respiratory depression in our control group seems to be in line with reported incidences in PCA opioids in a Cochrane review.[77] Still, the Cochrane review used a lower threshold for scoring respiratory depression, making this comparison to be interpreted with caution. However, because the incidences of respiratory depression is likely to be within the same range for low dose intrathecal morphine as for PCA opioids, we suggest the same monitoring as for patients with a PCA opioids should be applied.[77,78] The ERAS society recommends this as well.1 Nonetheless, coadministration of benzodiazepines and routinely administered systemic opioids should be avoided during the first 24 hours, since respiratory depression may occur due to interaction.[79]

This meta-analysis contains a high level of heterogeneity, which was not explained by the subgroup analysis, meta-regression or methodological differences of the included studies. The differences in type of surgery is a likely cause of heterogeneity, but further subgroup analysis was not prespecified and could increase the chance of a type 1-error. The post-operative analgesic regimen consisted in most studies

of paracetamol, NSAID and PCA opioids, but variation adds to heterogeneity as well. Still, the confidence intervals are within clinical significant limits and the effects of individual studies were predominantly in the same direction, therefor we did not alter the GRADE level of evidence based on heterogeneity.

Besides the inherent downside of a meta-analysis by the methodological limitations of the included studies, an additional limitation of this study is the probability of missing studies. We were unable to retrieve a full text of Togal et al.[80] Another issue is the low number of patients for some outcomes. Of importance is the respiratory depression, for which no increased ratio was found. This too could be because of the low number of events and patients. Some outcomes have been reported in dichotomous and continuous variables, such as patient satisfaction and sedation, which limited the ability to pool the data. A third limitation is the pooling of various types of abdominal surgery which adds to heterogeneity. We mentioned in the introduction that only similar types of surgery should be analyzed and even though only abdominal surgery was included, a variance within abdominal surgery is still expected. Subgroup analyses were performed to restrict this limitation. Fourth, not all included studies described characteristics of the recovery phase such as time to oral feeding, mobilization and extent of mobilization and therefore no comments regarding this subject can be made. Finally, high levels of bias for blinding and allocation concealment in the individual studies cause limitations for the meta-analysis as well.

In conclusion, intrathecal hydrophilic opioids reduce intraoperative and postoperative opioid consumption, pain scores and length of hospital stay in abdominal surgery. These properties make it a potentially important contributor to the overall effects of an ERP and we feel this technique should be considered more frequently. The risk for pruritus is increased in a dose dependent fashion. In our opinion, anesthesiologists are reluctant to administer intrathecal morphine because of fear for respiratory depression. An increased incidence of respiratory depression was found, but this was predominantly caused by two studies using high doses of intrathecal morphine. When these two studies were excluded, this rare complication was not more common in the intervention group than in the control group with systemic opioids. Still, the majority of the studies used a dose less than 500 µg, thus the evidence is predominantly based on this range of doses. We recommend to take similar precautions as with the use of systemically administered opioids for the duration of at least 12 hours.

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Appendix C

Content:

1. Search terms
2. Forest plots
3. Funnel plots
4. Subgroup analyzes
5. Meta-regression
6. Trial sequential analyzes

Appendix C.1 Search terms

Embase

('spinal anesthesia'/exp OR 'intrathecal drug administration'/de OR 'intrathecal drug administration':lnk OR 'intradural drug administration'/de OR 'intradural drug administration':lnk OR (rachianaesthes* OR rachianesthes* OR intrathecal* OR intra-thecal* OR intradural* OR subdural* OR ((spinal* OR subarachnoid* OR lumbar*) NEAR/3 (anesthes* OR anaesthes* OR analges* OR block* OR inject* OR techn*))):ab,ti,kw) AND ('morphine derivative'/exp OR 'opiate agonist'/exp OR 'methadone'/de OR 'pethidine'/de OR (morphin* OR morfin* OR diamorphin* OR methadon* OR hydromorphon* OR pethidin* OR meperidin* OR opiate* OR opioid* OR dihydromorphon* OR dilaudid* OR palladone* OR Demerol*):ab,ti,kw) AND ('abdominal surgery'/exp OR 'hysterectomy'/exp OR 'prostatectomy'/exp OR 'kidney surgery'/de OR 'nephrectomy'/exp OR 'nephrotomy'/de OR 'pyelolithotomy'/de OR 'pyeloplasty'/de OR 'pyelotomy'/de OR 'bladder surgery'/exp OR 'adrenalectomy'/de OR 'ovariectomy'/de OR 'salpingooophorectomy'/de OR (laparoscop* OR laparotom* OR laparoendoscop* OR hysterectom* OR uterus-extirpat* OR prostatectom* OR prostat*-resect* OR nephrectom* OR pyelotomy* OR nephrotom* OR pyelolithotom* OR pyeloplast* OR pancreatectom* OR pancreaticoduodenectom* OR pancreaticojejunostom* OR gastrectom* OR gastroduodenostom* OR gastroenterostom* OR gastrojejunostom* OR gastrostom* OR gastrotom* OR cystectom* OR bladder*-reconstruct* OR splenectom* OR adrenalectom* OR cholecystectom* OR ovariectom* OR ovarectom* OR salpingooophorectom* OR salping*-oophorectom* OR salpingoophorectom* OR salpingo-ophorectom* OR adnexectom* OR enterotom* OR ((abdomin* OR abdomen* OR digestiv*-system* OR kidney* OR renal* OR pancrea* OR liver* OR hepat* OR stomach* OR gastric* OR gastro* OR bladder* OR cystic* OR rectum* OR rectal* OR spleen* OR adrenal* OR gallbladder* OR biliar* OR bile-duct* OR ovary OR ovarian OR intestin* OR colon* OR colorect* OR Gynecolog*) NEAR/6 (surger* OR surgical OR operat* OR resect*))):ab,ti,kw) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim)

Cochrane

((rachianaesthes* OR rachianesthes* OR intrathecal* OR intra-thecal* OR intradural* OR subdural* OR ((spinal* OR subarachnoid* OR lumbar*) NEAR/3 (anesthes* OR anaesthes* OR analges* OR block* OR inject* OR techn*))):ab,ti,kw) AND ((morphin* OR morfin* OR diamorphin* OR methadon* OR hydromorphon* OR pethidin* OR meperidin* OR opiate* OR opioid* OR dihydromorphon* OR dilaudid* OR palladone* OR Demerol*):ab,ti,kw) AND ((laparoscop* OR laparotom* OR laparoendoscop* OR hysterectom* OR uterus-extirpat* OR prostatectom* OR prostat* NEXT resect* OR nephrectom* OR pyelotomy* OR nephrotom* OR pyelolithotom* OR pyeloplast* OR pancreatectom* OR pancreaticoduodenectom* OR pancreaticojejunostom* OR gastrectom* OR gastroduodenostom* OR gastroenterostom* OR gastrojejunostom* OR gastrostom* OR gastrotom* OR cystectom* OR bladder* NEXT reconstruct* OR splenectom* OR adrenalectom* OR cholecystectom* OR ovariectom* OR ovarectom* OR salpingooophorectom* OR salping* NEXT oophorectom* OR salpingoophorectom* OR salpingo-ophorectom* OR adnexectom* OR enterotom* OR ((abdomin* OR abdomen* OR digestiv* NEXT system* OR kidney* OR renal* OR pancrea* OR liver* OR hepat* OR stomach* OR gastric* OR gastro* OR bladder* OR cystic* OR rectum* OR rectal* OR spleen* OR adrenal* OR gallbladder* OR biliar* OR bile-duct* OR ovary OR ovarian OR intestin* OR colon* OR colorect* OR Gynecolog*) NEAR/6 (surger* OR surgical OR operat* OR resect*))):ab,ti,kw)

Web of Science

TS=(((rachianaesthes* OR rachianesthes* OR intrathecal* OR intra-thecal* OR intradural* OR subdural* OR ((spinal* OR subarachnoid* OR lumbar*) NEAR/2 (anesthes* OR anaesthes* OR analges* OR block* OR inject* OR techn*)))) AND ((morphin* OR morfin* OR diamorphin* OR methadon* OR hydromorphon* OR pethidin* OR meperidin* OR opiate* OR opioid* OR dihydromorphon* OR dilaudid* OR palladone* OR demerol*)) AND ((laparoscop* OR laparotom* OR laparoendoscop* OR hysterectom* OR uterus-extirpat* OR prostatectom* OR prostat*-resect* OR nephrectom* OR pyelotomy* OR nephrotom* OR pyelolithotom* OR pyeloplast* OR pancreatectom* OR pancreaticoduodenectom* OR pancreaticojejunostom* OR gastrectom* OR gastroduodenostom* OR gastroenterostom* OR gastrojejunostom* OR gastrostom* OR gastrotom* OR

cystectom* OR bladder*-reconstruct* OR splenectom* OR adrenalectom* OR cholecystectom* OR ovariectom* OR ovarectom* OR salpingooophorectom* OR salping*-oophorectom* OR salpingoophorectom* OR salpingo-ophorectom* OR adnexectom* OR enterotom* OR ((abdomin* OR abdomen* OR digestiv*-system* OR kidney* OR renal* OR pancrea* OR liver* OR hepat* OR stomach* OR gastric* OR gastro* OR bladder* OR cystic* OR rectum* OR rectal* OR spleen* OR adrenal* OR gallbladder* OR biliar* OR bile-duct* OR ovary OR ovarian OR intestin* OR colon* OR colorect* OR Gynecolog*) NEAR/5 (surger* OR surgical OR operat* OR resect*)))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man)) AND (random* OR factorial* OR crossover* OR cross-over* OR placebo* OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups))

Medline

(Anesthesia, Spinal/ OR Injections, Spinal/ OR (rachianaesthes* OR rachianesthes* OR intrathecal* OR intra-thecal* OR intradural* OR subdural* OR ((spinal* OR subarachnoid* OR lumbar*) ADJ3 (anesthes* OR anaesthes* OR analges* OR block* OR inject* OR techn*))).ab,ti,kf.) AND (exp Morphine Derivatives/ OR Analgesics, Opioid/ OR exp Methadone/ OR exp Meperidine/ OR (morphin* OR morfin* OR diamorphin* OR methadon* OR hydromorphon* OR pethidin* OR meperidin* OR opiate* OR opioid* OR dihydromorphon* OR dilaudid* OR palladone* OR Demerol*).ab,ti,kf.) AND (exp Digestive System Surgical Procedures/ OR exp Hysterectomy/ OR exp Prostatectomy/ OR exp Nephrectomy/ OR exp Nephrotomy/ OR Cystectomy/ OR Cystotomy/ OR Cystostomy/ OR Adrenalectomy/ OR exp Ovariectomy/ OR (laparoscop* OR laparotom* OR laparoendoscop* OR hysterectom* OR uterus-extirpat* OR prostatectom* OR prostat*-resect* OR nephrectom* OR pyelotomy* OR nephrotom* OR pyelolithotom* OR pyeloplast* OR pancreatectom* OR pancreaticoduodenectom* OR pancreaticojejunostom* OR gastrectom* OR gastroduodenostom* OR gastroenterostom* OR gastrojejunostom* OR gastrostom* OR gastrotom* OR cystectom* OR bladder*-reconstruct* OR splenectom* OR adrenalectom* OR

cholecystectom* OR ovariectom* OR ovarectom* OR salpingooophorectom* OR salping*-oophorectom* OR salpingoophorectom* OR salpingo-ophorectom* OR adnexectom* OR enterotom* OR ((abdomin* OR abdomen* OR digestiv*-system* OR kidney* OR renal* OR pancrea* OR liver* OR hepat* OR stomach* OR gastric* OR gastro* OR bladder* OR cystic* OR rectum* OR rectal* OR spleen* OR adrenal* OR gallbladder* OR biliar* OR bile-duct* OR ovary OR ovarian OR intestin* OR colon* OR colorect* OR gynecolog*) ADJ6 (surger* OR surgical OR operat* OR resect*))).ab,ti,kf.) AND (exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti,kf.) NOT (exp Animals/ NOT Humans/)

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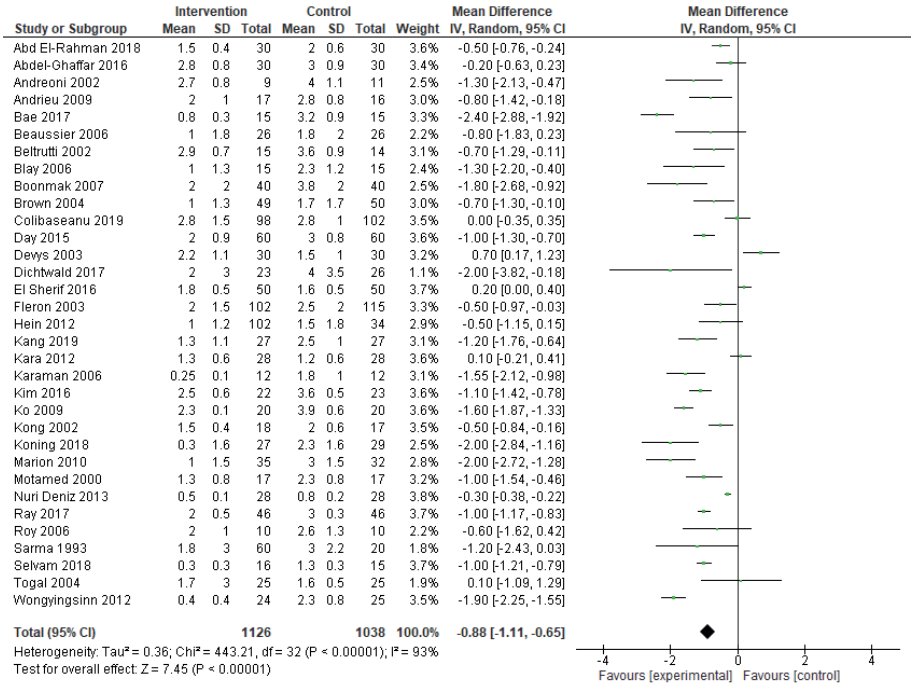
intrathecal|intradural|subdural|"spinal|lumbar
anesthesia | anaesthesia| analgesia" morphin|opiate|opioid
"abdominal|abdomen|kidney|pancreas|liver|stomach|gastric|cystic|rectum|spleen|ovary|intestinal|colon surgery|surgical|operation|resection" trial

Appendix C.2 Forest plots

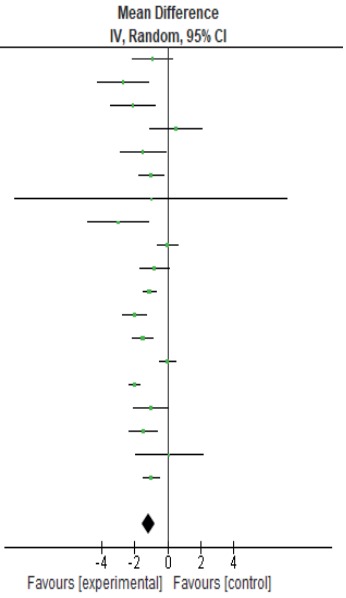
1. Pain scores in rest at day 1



2. Pain scores in exertion at day 1

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andrieu 2009	3.3	1.8	17	4.2	1.8	16	4.7%	-0.90 [-2.13, 0.33]
Bae 2017	2.8	2.1	15	5.5	2.3	15	3.6%	-2.70 [-4.28, -1.12]
Beaussier 2006	3.2	2.5	26	5.3	2.5	26	4.2%	-2.10 [-3.46, -0.74]
Blay 2006	3.8	2	15	3.3	2.4	15	3.6%	0.50 [-1.08, 2.08]
Boonmak 2007	4.5	4	40	6	2	40	4.2%	-1.50 [-2.89, -0.11]
Brown 2004	1.8	1.6	49	2.8	2.2	50	6.4%	-1.00 [-1.76, -0.24]
Devys 2003	4	23	30	5	1.3	30	0.2%	-1.00 [-9.24, 7.24]
Dichtwald 2017	4	3	23	7	3.5	26	3.1%	-3.00 [-4.82, -1.18]
Hein 2012	2	1.2	102	2	1.8	34	6.8%	0.00 [-0.65, 0.65]
Karaman 2006	1.5	0.9	12	2.3	1.3	12	5.9%	-0.80 [-1.69, 0.09]
Kim 2016	4.8	0.8	22	5.9	0.6	23	7.6%	-1.10 [-1.51, -0.69]
Ko 2009	3.8	1.3	20	5.8	1	20	6.5%	-2.00 [-2.72, -1.28]
Kong 2002	3	0.8	18	4.5	1.1	17	6.8%	-1.50 [-2.14, -0.86]
Koning 2019	3	1.5	76	3	1.5	79	7.4%	0.00 [-0.47, 0.47]
Lew 2011	4	0.8	31	6	0.5	30	7.8%	-2.00 [-2.33, -1.67]
Marion 2010	3	1.8	35	4	2.5	32	5.3%	-1.00 [-2.05, 0.05]
Motamed 2000	2.3	1.3	17	3.8	1.3	17	5.9%	-1.50 [-2.37, -0.63]
Roy 2006	4.5	2.3	10	4.4	2.4	10	2.6%	0.10 [-1.96, 2.16]
Wongyingsinn 2012	3.3	1	24	4.3	0.8	25	7.3%	-1.00 [-1.51, -0.49]
Total (95% CI)			**582**			**517**	**100.0%**	**-1.16 [-1.56, -0.76]**

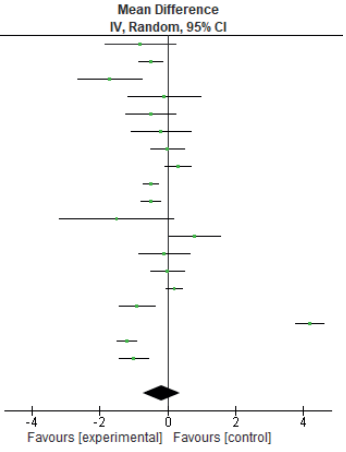
Heterogeneity: Tau² = 0.51; Chi² = 83.39, df = 18 (P < 0.00001); I² = 78%
Test for overall effect: Z = 5.69 (P < 0.00001)



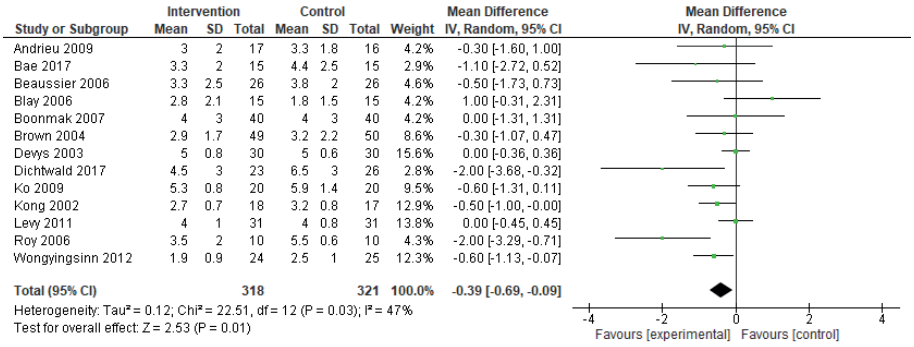
3. Pain scores in rest at day 2

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andreoni 2002	3.7	1.1	9	4.5	1.3	11	4.8%	-0.80 [-1.85, 0.25]
Andrieu 2009	0.5	0.5	17	1	0.5	16	5.6%	-0.50 [-0.84, -0.16]
Bae 2017	0.8	0.6	15	2.5	1.8	15	4.9%	-1.70 [-2.66, -0.74]
Beaussier 2006	1.5	2	26	1.6	2	26	4.7%	-0.10 [-1.19, 0.99]
Blay 2006	0.5	0.7	15	1	1.3	15	5.2%	-0.50 [-1.25, 0.25]
Boonmak 2007	2	2	40	2.2	2	40	5.0%	-0.20 [-1.08, 0.68]
Brown 2004	1.4	1.3	49	1.4	1.3	50	5.5%	0.00 [-0.51, 0.51]
Colibaseanu 2019	2.8	1.5	98	2.5	1.3	102	5.6%	0.30 [-0.09, 0.69]
Day 2015	1	0.5	60	1.5	0.8	60	5.7%	-0.50 [-0.74, -0.26]
Devys 2003	1	0.6	30	1.5	0.5	30	5.6%	-0.50 [-0.78, -0.22]
Dichtwald 2017	2	2.5	23	3.5	3.5	26	3.8%	-1.50 [-3.19, 0.19]
Kang 2019	3.2	1.7	27	2.4	1	27	5.2%	0.80 [0.06, 1.54]
Kara 2012	0.9	0.4	28	1	2	28	5.2%	-0.10 [-0.86, 0.66]
Ko 2009	3.5	0.8	20	3.5	0.8	20	5.5%	0.00 [-0.50, 0.50]
Kong 2002	1.3	0.4	18	1.1	0.3	17	5.7%	0.20 [-0.03, 0.43]
Koning 2018	0.8	1.2	27	1.7	0.8	29	5.4%	-0.90 [-1.44, -0.36]
Roy 2006	5	0.6	10	0.8	0.3	10	5.6%	4.20 [3.78, 4.62]
Selvam 2018	0.3	0.3	16	1.5	0.5	15	5.6%	-1.20 [-1.49, -0.91]
Wongyingsinn 2012	0.5	0.5	24	1.5	1	25	5.5%	-1.00 [-1.44, -0.56]
Total (95% CI)			**552**			**562**	**100.0%**	**-0.18 [-0.74, 0.38]**

Heterogeneity: Tau² = 1.42; Chi² = 545.53, df = 18 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.62 (P = 0.53)



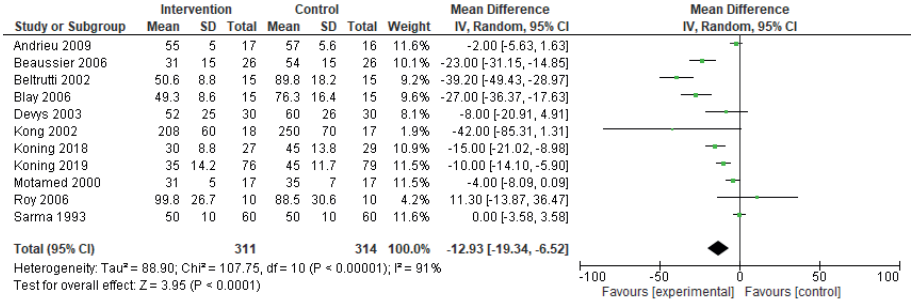
4. Pain scores in exertion at day 2



Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andrieu 2009	3	2	17	3.3	1.8	16	4.2%	-0.30 [-1.60, 1.00]
Bae 2017	3.3	2	15	4.4	2.5	15	2.9%	-1.10 [-2.72, 0.52]
Beaussier 2006	3.3	2.5	26	3.8	2	26	4.6%	-0.50 [-1.73, 0.73]
Blay 2006	2.8	2.1	15	1.8	1.5	15	4.2%	1.00 [-0.31, 2.31]
Boonmak 2007	4	3	40	4	3	40	4.2%	0.00 [-1.31, 1.31]
Brown 2004	2.9	1.7	49	3.2	2.2	50	8.6%	-0.30 [-1.07, 0.47]
Dewys 2003	5	0.8	30	5	0.6	30	15.6%	0.00 [-0.36, 0.36]
Dichtwald 2017	4.5	3	23	6.5	3	26	2.8%	-2.00 [-3.68, -0.32]
Ko 2009	5.3	0.8	20	5.9	1.4	20	9.5%	-0.60 [-1.31, 0.11]
Kong 2002	2.7	0.7	18	3.2	0.8	17	12.9%	-0.50 [-1.00, -0.00]
Lew 2011	4	1	31	4	0.8	31	13.8%	0.00 [-0.45, 0.45]
Roy 2006	3.5	2	10	5.5	0.6	10	4.3%	-2.00 [-3.29, -0.71]
Wongyingsinn 2012	1.9	0.9	24	2.5	1	25	12.3%	-0.60 [-1.13, -0.07]
Total (95% CI)			**318**			**321**	**100.0%**	**-0.39 [-0.69, -0.09]**

Heterogeneity: Tau² = 0.12; Chi² = 22.51, df = 12 (P = 0.03); I² = 47%
Test for overall effect: Z = 2.53 (P = 0.01)

5. Intraoperative sufentanil use

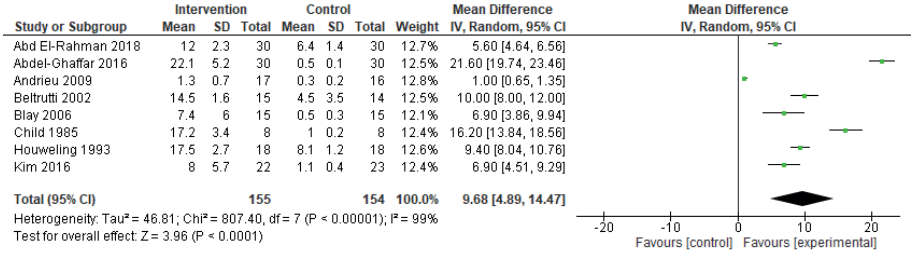


Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andrieu 2009	55	5	17	57	5.6	16	11.6%	-2.00 [-5.63, 1.63]
Beaussier 2006	31	15	26	54	15	26	10.1%	-23.00 [-31.15, -14.85]
Beltrutti 2002	50.6	8.8	15	89.8	18.2	15	9.2%	-39.20 [-49.43, -28.97]
Blay 2006	49.3	8.6	15	76.3	16.4	15	9.6%	-27.00 [-36.37, -17.63]
Dewys 2003	52	25	30	60	26	30	8.1%	-8.00 [-20.91, 4.91]
Kong 2002	208	60	18	250	70	17	1.9%	-42.00 [-85.31, 1.31]
Koning 2018	30	8.8	27	45	13.8	29	10.9%	-15.00 [-21.02, -8.98]
Koning 2019	35	14.2	76	45	11.7	79	11.5%	-10.00 [-14.10, -5.90]
Motamed 2000	31	5	17	35	7	17	11.5%	-4.00 [-8.09, 0.09]
Roy 2006	99.8	26.7	10	88.5	30.6	10	4.2%	11.30 [-13.87, 36.47]
Sarma 1993	50	10	60	50	10	60	11.6%	0.00 [-3.58, 3.58]
Total (95% CI)			**311**			**314**	**100.0%**	**-12.93 [-19.34, -6.52]**

Heterogeneity: Tau² = 88.90; Chi² = 107.75, df = 10 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.95 (P < 0.0001)

6. Time to first analgesic request.

Note that time to first analgesic request is prolonged in the experimental group, which is beneficial thus favours the experimental-group.



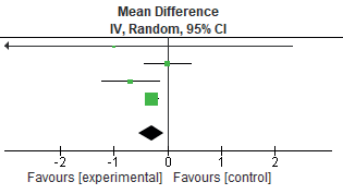
Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abd El-Rahman 2018	12	2.3	30	6.4	1.4	30	12.7%	5.60 [4.64, 6.56]
Abdel-Ghaffar 2016	22.1	5.2	30	0.5	0.1	30	12.5%	21.60 [19.74, 23.46]
Andrieu 2009	1.3	0.7	17	0.3	0.2	16	12.8%	1.00 [0.65, 1.35]
Beltrutti 2002	14.5	1.6	15	4.5	3.5	14	12.5%	10.00 [8.00, 12.00]
Blay 2006	7.4	6	15	0.5	0.3	15	12.1%	6.90 [3.86, 9.94]
Child 1985	17.2	3.4	8	1	0.2	8	12.4%	16.20 [13.84, 18.56]
Houweling 1993	17.5	2.7	18	8.1	1.2	18	12.6%	9.40 [8.04, 10.76]
Kim 2016	8	5.7	22	1.1	0.4	23	12.4%	6.90 [4.51, 9.29]
Total (95% CI)			**155**			**154**	**100.0%**	**9.68 [4.89, 14.47]**

Heterogeneity: Tau² = 46.81; Chi² = 807.40, df = 7 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.96 (P < 0.0001)

7. Time to Fit for discharge

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Koning 2018	3	6.8	27	4	5.8	29	0.5%	-1.00 [-4.32, 2.32]
Lewy 2011	2.6	0.8	31	2.6	0.9	30	21.5%	0.00 [-0.43, 0.43]
Marion 2010	2.2	1.5	35	2.9	0.6	32	15.2%	-0.70 [-1.24, -0.16]
Wongyingsinn 2012	3	0.1	24	3.3	0.3	25	62.8%	-0.30 [-0.42, -0.18]
Total (95% CI)			**117**			**116**	**100.0%**	**-0.30 [-0.53, -0.07]**

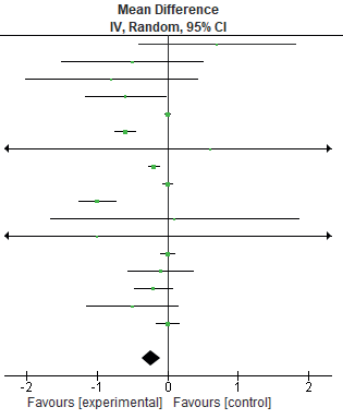
Heterogeneity: Tau² = 0.02; Chi² = 4.18, df = 3 (P = 0.24); I² = 28%
Test for overall effect: Z = 2.51 (P = 0.01)



8. Length of hospital stay

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andreoni 2002	3.9	1.5	9	3.2	0.9	11	1.3%	0.70 [-0.42, 1.82]
Beaussier 2006	7.9	2	26	8.4	1.7	26	1.5%	-0.50 [-1.51, 0.51]
Blay 2006	11.5	1.2	15	12.3	2.1	15	1.1%	-0.80 [-2.02, 0.42]
Brown 2004	2.1	0.5	49	2.7	2	50	3.7%	-0.60 [-1.17, -0.03]
Colibaseanu 2019	3	0.2	98	3	0.1	102	12.0%	0.00 [-0.04, 0.04]
Day 2015	2.3	0.3	60	2.9	0.5	60	10.6%	-0.60 [-0.75, -0.45]
Dichtwald 2017	11.2	9.5	23	10.6	8	26	0.1%	0.60 [-4.35, 5.55]
El Sherif 2016	1.3	0.2	50	1.5	0.2	50	11.7%	-0.20 [-0.28, -0.12]
Fleron 2003	10	0.2	102	10	0.3	115	11.8%	0.00 [-0.07, 0.07]
Kang 2019	7	0.5	27	8	0.5	27	8.1%	-1.00 [-1.27, -0.73]
Ko 2009	10.8	2.8	20	10.7	2.9	20	0.5%	0.10 [-1.67, 1.87]
Koning 2018	4	8	27	5	6	29	0.1%	-1.00 [-4.72, 2.72]
Koning 2019	1	0.3	76	1	0.3	79	11.5%	0.00 [-0.09, 0.09]
Lewy 2011	2.7	1.1	31	2.8	0.7	30	4.9%	-0.10 [-0.56, 0.36]
Motamed 2000	1	0.3	17	1.2	0.5	17	7.9%	-0.20 [-0.48, 0.08]
Sarma 1993	6	1.2	60	6.5	1.3	20	3.1%	-0.50 [-1.15, 0.15]
Wongyingsinn 2012	3.3	0.3	24	3.3	0.3	25	10.2%	0.00 [-0.17, 0.17]
Total (95% CI)			**714**			**702**	**100.0%**	**-0.23 [-0.37, -0.10]**

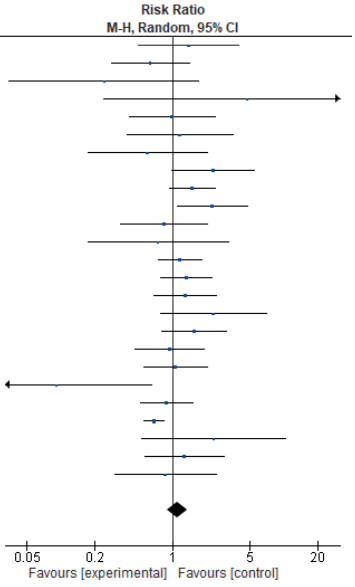
Heterogeneity: Tau² = 0.04; Chi² = 133.56, df = 16 (P < 0.00001); I² = 88%
Test for overall effect: Z = 3.47 (P = 0.0005)



9. Incidence of nausea

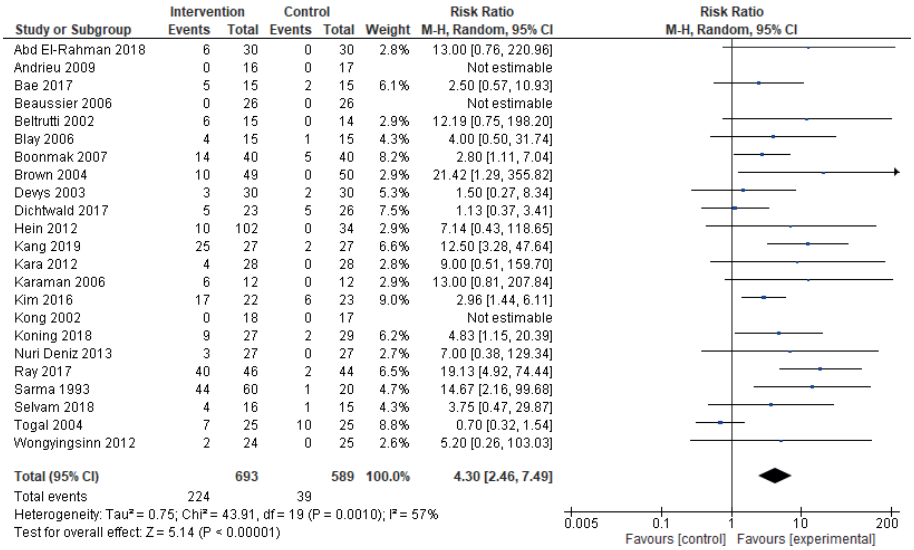
Study or Subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abd El-Rahman 2018	7	30	5	30	3.0%	1.40 [0.50, 3.92]
Abdel-Ghaffar 2016	7	30	11	30	4.2%	0.64 [0.29, 1.42]
Andreoni 2002	1	9	5	11	1.0%	0.24 [0.03, 1.73]
Andrieu 2009	2	17	0	16	0.5%	4.72 [0.24, 91.41]
Bae 2017	6	15	6	15	3.7%	1.00 [0.42, 2.40]
Beltrutti 2002	5	15	4	14	2.7%	1.17 [0.39, 3.49]
Blay 2006	3	15	5	15	2.3%	0.60 [0.17, 2.07]
Boonmak 2007	14	40	6	40	3.9%	2.33 [1.00, 5.46]
Brown 2004	25	49	17	50	6.8%	1.50 [0.93, 2.41]
Devys 2003	16	30	7	30	4.6%	2.29 [1.10, 4.74]
Dichtwald 2017	6	23	8	26	3.6%	0.85 [0.35, 2.08]
El Sherif 2016	3	50	4	50	1.8%	0.75 [0.18, 3.18]
Hein 2012	49	102	14	34	7.1%	1.17 [0.74, 1.83]
Kang 2019	16	27	12	27	6.3%	1.33 [0.79, 2.25]
Kara 2012	13	28	10	28	5.3%	1.30 [0.69, 2.46]
Karaman 2006	7	12	3	12	2.7%	2.33 [0.78, 6.94]
Kim 2016	12	22	8	23	5.0%	1.57 [0.80, 3.09]
Kong 2002	8	18	8	17	4.7%	0.94 [0.46, 1.94]
Koning 2018	11	27	11	29	5.2%	1.07 [0.56, 2.06]
Nuri Deniz 2013	1	27	11	27	1.0%	0.09 [0.01, 0.66]
Ray 2017	16	46	18	46	6.2%	0.89 [0.52, 1.52]
Sarma 1993	39	60	19	20	9.5%	0.68 [0.55, 0.85]
Selvam 2018	5	16	2	15	1.7%	2.34 [0.53, 10.30]
Togal 2004	9	25	7	25	4.1%	1.29 [0.57, 2.91]
Wongyingsinn 2012	5	24	6	25	2.9%	0.87 [0.30, 2.47]
Total (95% CI)		**757**		**655**	**100.0%**	**1.11 [0.90, 1.37]**
Total events	286		207			

Heterogeneity: Tau² = 0.11; Chi² = 46.34, df = 24 (P = 0.004); I² = 48%
Test for overall effect: Z = 1.00 (P = 0.32)

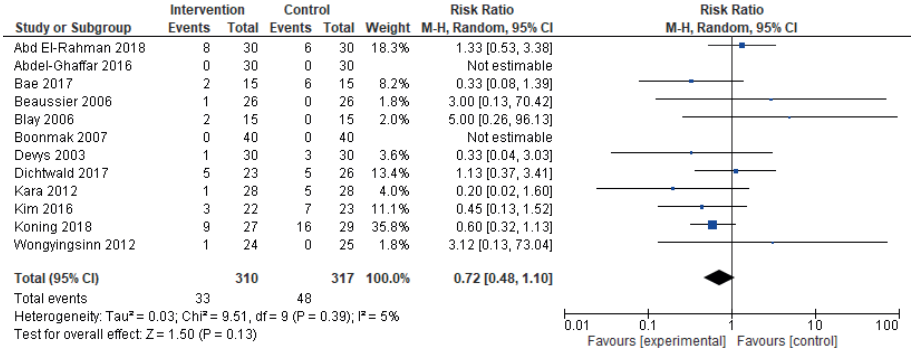


10. Incidence of pruritus.

Note that the risk favors the experimental group, which means that the risk for pruritus is higher in the experimental group.



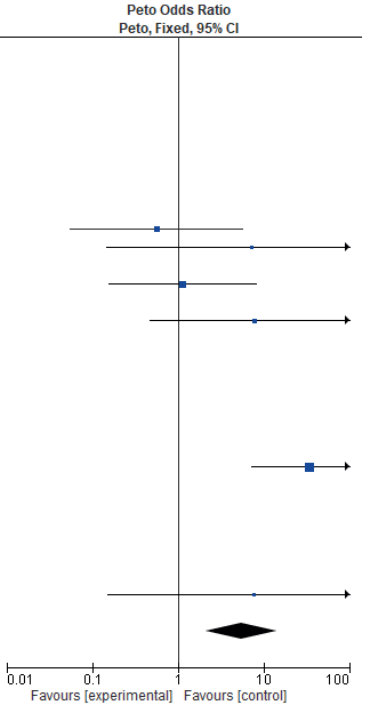
11. Incidence of sedation



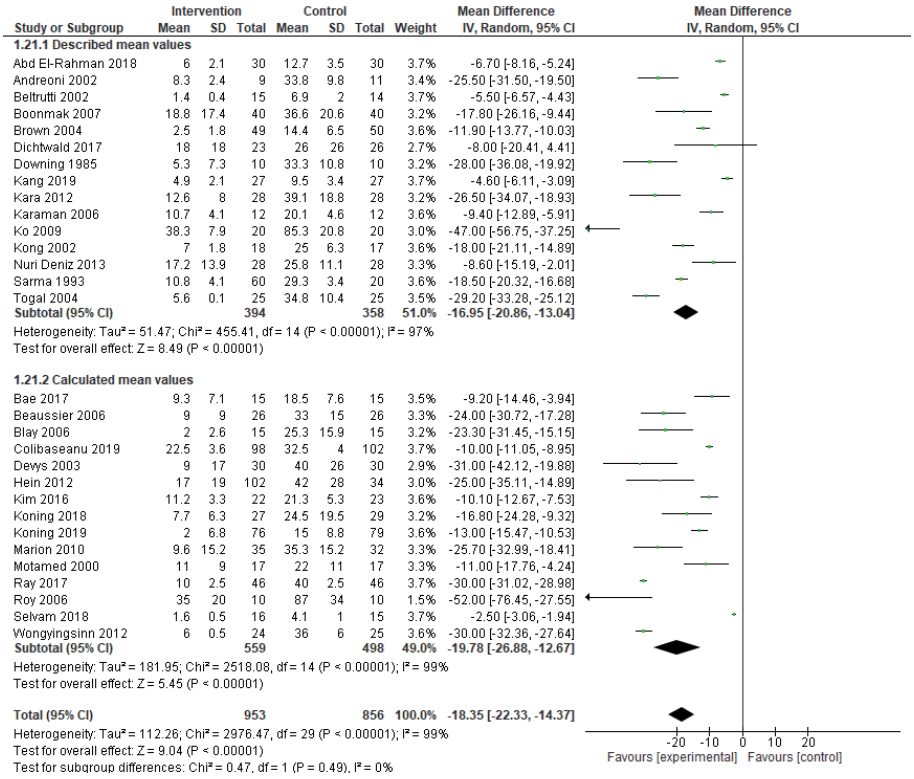
12. Incidence of respiratory depression

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Abdel-Ghaffar 2016	0	30	0	30		Not estimable
Andreoni 2002	0	9	0	11		Not estimable
Andrieu 2009	0	17	0	16		Not estimable
Bae 2017	0	15	0	15		Not estimable
Beaussier 2006	0	26	0	26		Not estimable
Beltrutti 2002	0	15	0	14		Not estimable
Blay 2006	0	15	0	15		Not estimable
Boonmak 2007	0	40	0	40		Not estimable
Brown 2004	0	49	0	50		Not estimable
Devys 2003	0	30	0	30		Not estimable
Dichtwald 2017	1	23	2	26	16.9%	0.57 [0.06, 5.73]
Drasner 1988	1	10	0	10	5.9%	7.39 [0.15, 372.38]
El Sherif 2016	0	50	0	50		Not estimable
Fleron 2003	2	102	2	115	23.2%	1.13 [0.16, 8.16]
Hein 2012	0	102	0	34		Not estimable
Houweling 1993	2	18	0	18	11.5%	7.84 [0.47, 130.46]
Kang 2019	0	27	0	27		Not estimable
Karaman 2006	0	12	0	12		Not estimable
Kim 2016	0	22	0	23		Not estimable
Ko 2009	0	20	0	20		Not estimable
Kong 2002	0	18	0	17		Not estimable
Koning 2018	0	27	0	29		Not estimable
Koning 2019	0	76	0	79		Not estimable
Licina 1991	11	12	0	12	36.7%	34.41 [7.14, 165.76]
Nuri Deniz 2013	0	28	0	28		Not estimable
Ray 2017	0	46	0	46		Not estimable
Roy 2006	0	10	0	10		Not estimable
Sarma 1993	0	60	0	20		Not estimable
Selvam 2018	0	16	0	15		Not estimable
Togal 2004	0	25	0	25		Not estimable
Wongyingsinn 2012	1	24	0	25	5.9%	7.70 [0.15, 388.55]
Total (95% CI)		**974**		**888**	**100.0%**	**5.49 [2.12, 14.24]**
Total events	18		4			

Heterogeneity: Chi² = 11.50, df = 5 (P = 0.04); I² = 57%
Test for overall effect: Z = 3.51 (P = 0.0005)

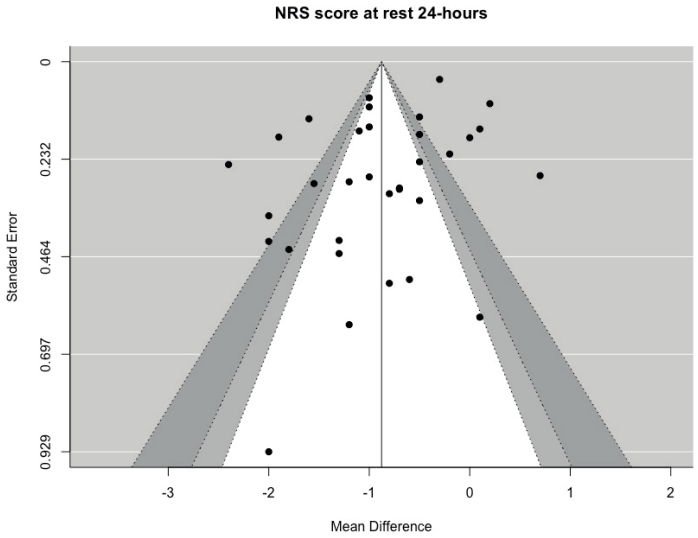


13. Subgroup analysis for calculated mean and standard deviation values for 24 hour morphine equivalent consumption.



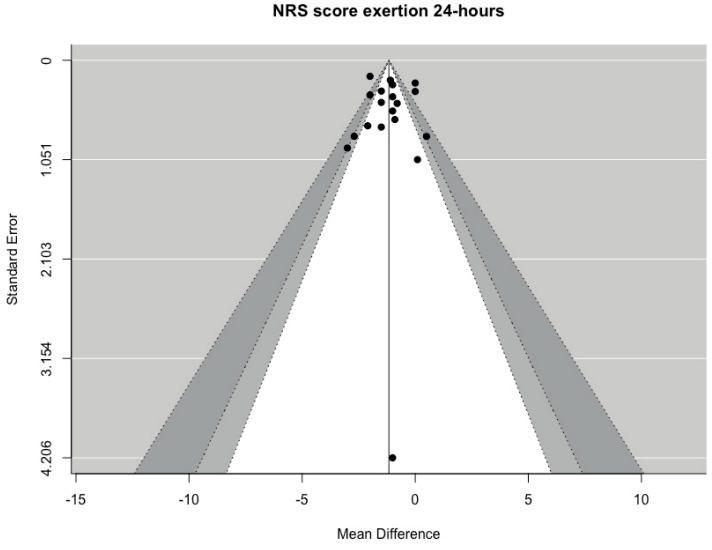
Appendix C.3 Funnel plots

1. Pain scores in rest at day 1



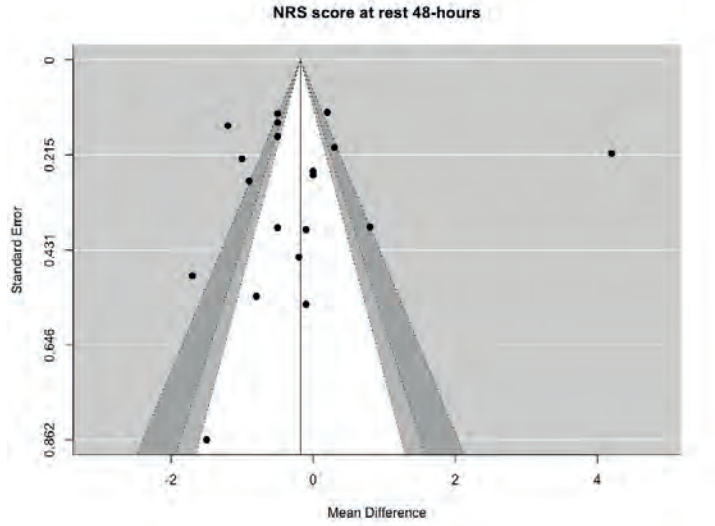
Egger test p = 0.0264

2. Pain scores in exertion at day 1



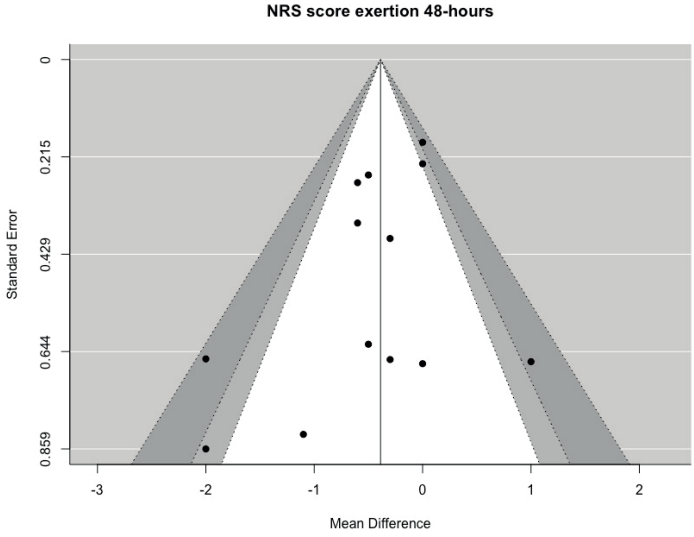
Egger test p = 0.7928

3. Pain scores in rest at day 2



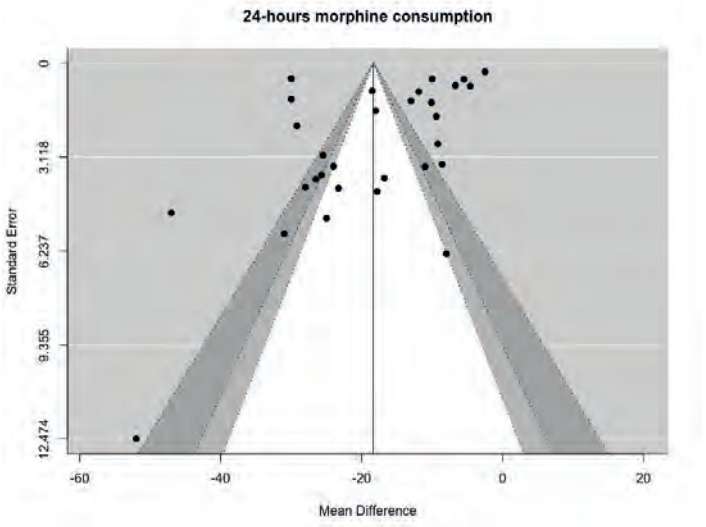
Egger test p = 0.9445

4. Pain scores in exertion at day2



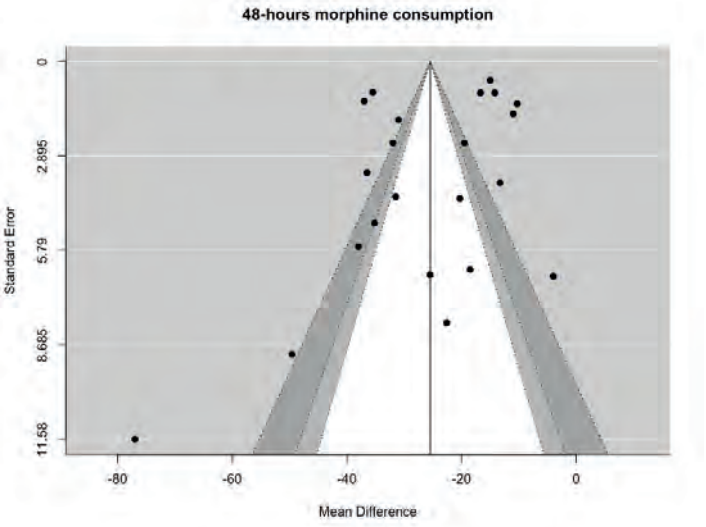
Egger test p = 0.1418

5. Morphine consumption at day 1



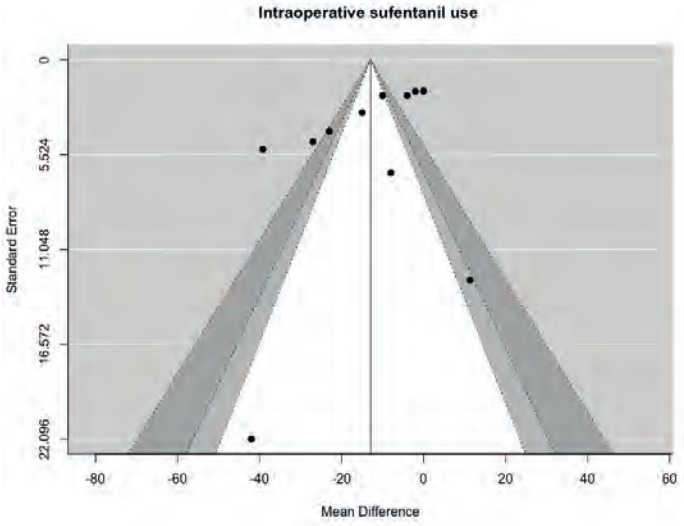
Egger test p = 0.0321

6. Morphine consumption at day 2



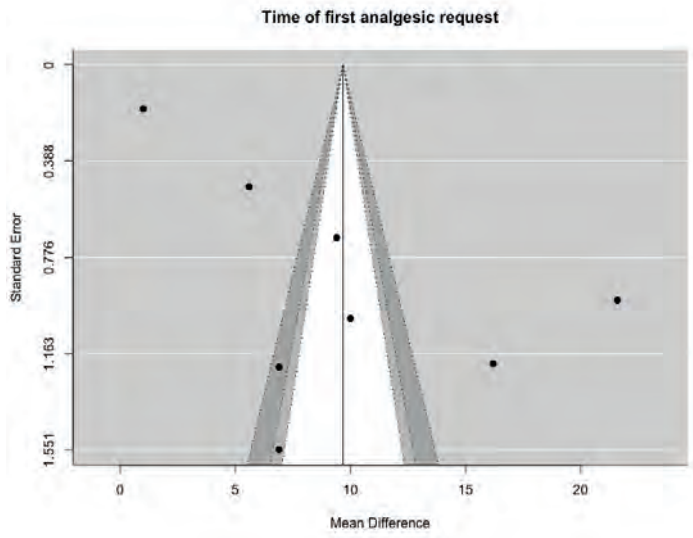
Egger test p = 0.2111

7. Intraoperative sufentanil use



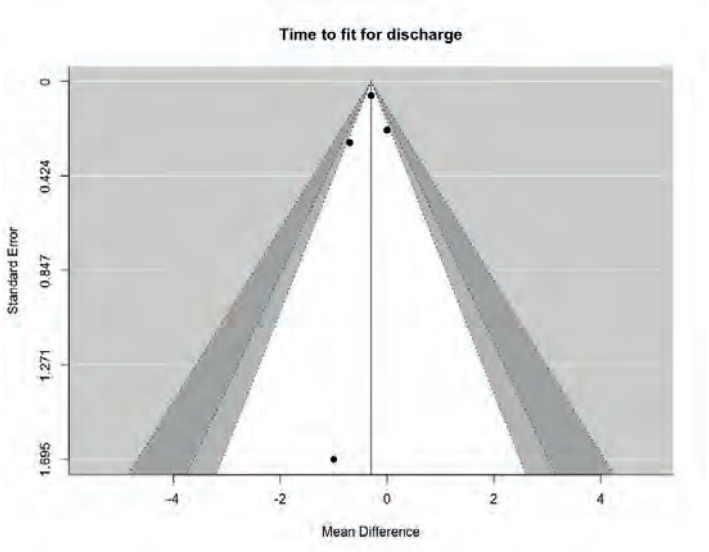
Egger test p = 0.0682

8. Time to first analgesic request



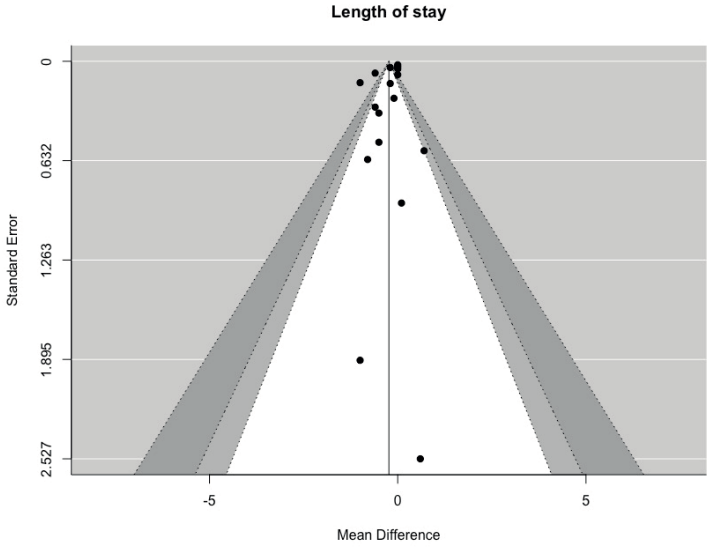
Egger test p = 0.0085

9. Time to fit for discharge



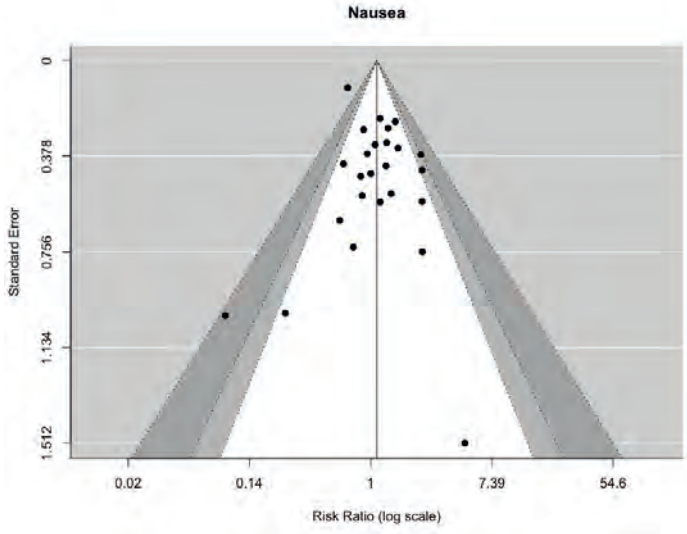
Egger test p = 0.7996

10. Length of stay



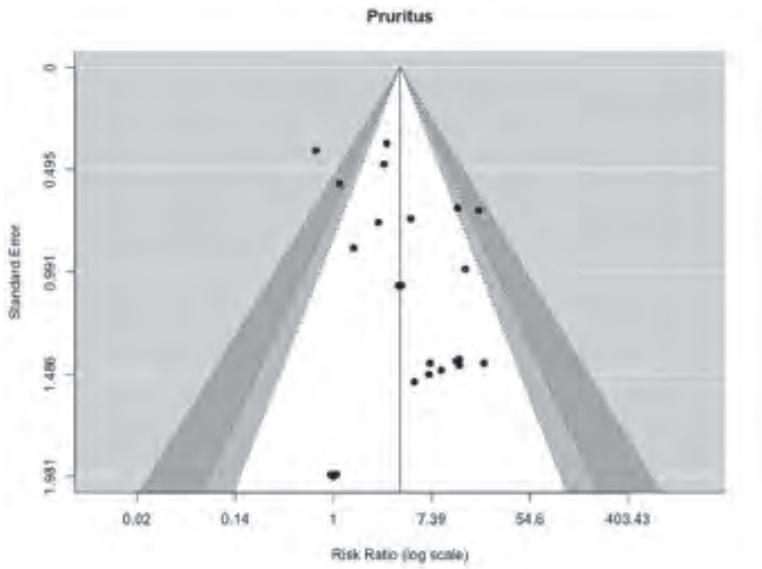
Egger test p = 0.1160

11. Incidence of nausea



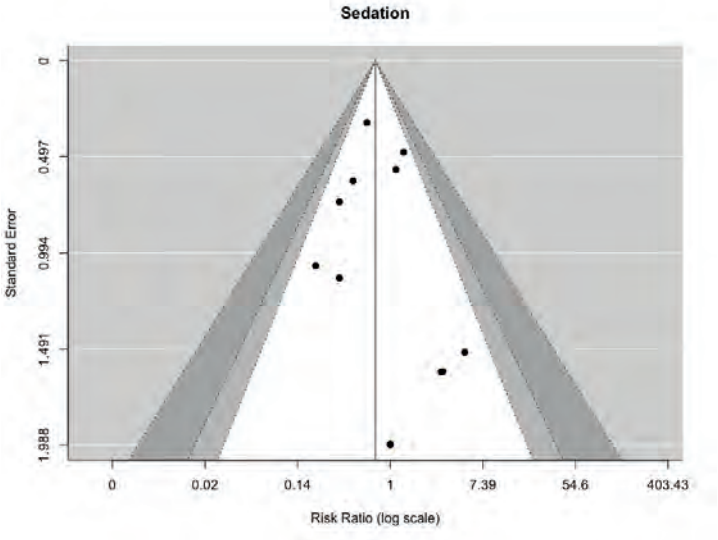
Egger test p = 0.1196

12. Incidence of pruritus



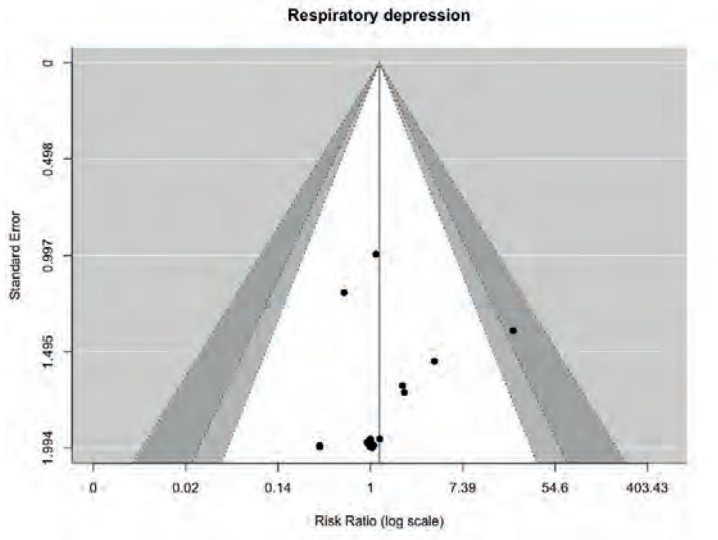
Egger test p = 0.0509

13. Incidence of sedation



Egger test p = 0.5255

14. Incidence of respiratory depression



Egger test p = 0.1724

Appendix C.4 Subgroup analyses

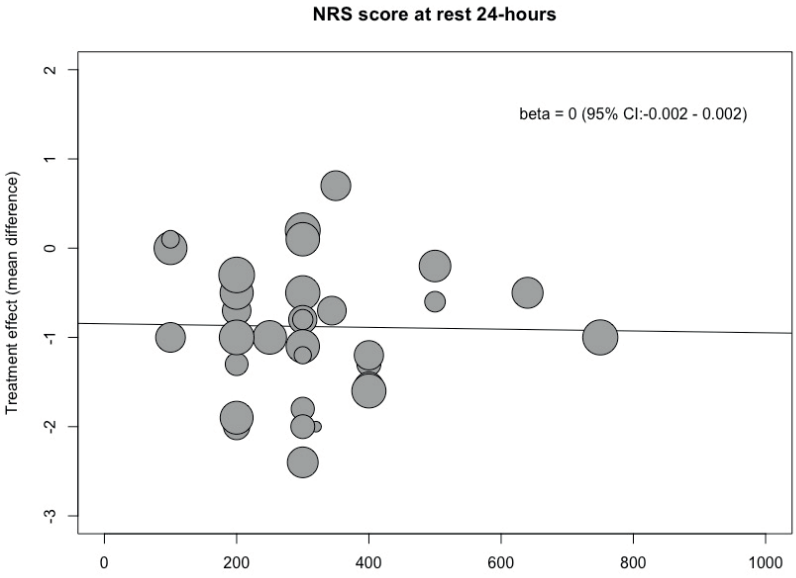
Outcome	Number of studies – participants	Effect (mean (95%CI))	I^2
Pain scores in rest, day 1 (NRS)	33 – 2164	-0.9 (-1.1, -0.7)	93%
- *Addition of intrathecal bupivacaine*	13 – 939	-0.9 (-1.2, -0.5)	93%
- *Solely intrathecal hydrophilic opioids*	18 – 988	-0.9 (-1.3, -0.5)	93%
- *Laparoscopic procedures*	10 – 529	-1.1 (-1.7, -0.6)	95%
- *Laparotomic surgery*	15 – 1035	-1.0 (-1.4, -0.7)	91%
- *Studies with a placebo or sham procedure*	18- 1087	-0.7 (-1.0, -0.4)	89%
Pain in exertion, day 1 (NRS)	19 – 1099	-1.2 (-1.6, -0.8)	79%
- *Addition of intrathecal bupivacaine*	8 – 636	-1.0 (-1.6, -0.4)	89%
- *Solely intrathecal hydrophilic opioids*	10 – 443	-1.4 (-1.9, -0.9)	56%
- *Laparoscopic procedures*	7 – 384	-1.3 (-2.0 -0.5)	89%
- *Laparotomic surgery*	10 – 603	-1.0 (-1.5, -0.6)	70%
- *Studies with a placebo or sham procedure*	9 – 628	-0.8 (-1.3, -0.2)	73%
Pain scores in rest, day 2 (NRS)	19 – 1114	-0.4 (-0.7, 0.1)	97%
- *Addition of intrathecal bupivacaine*	6 – 390	-0.6 (-1.1, -0.1)	93%
- *Solely intrathecal hydrophilic opioids*	12 – 704	-0.3 (-0.6, 0.0)	68%
- *Laparoscopic procedures*	8 – 395	-0.5 (-1.0, -0.1)	91%
- *Laparotomic surgery*	6 – 331	-0.3 (-0.6, 0.0)	21%
- *Studies with a placebo or sham procedure*	8 -379	-0.4 (-0.8, 0.1)	98%
Pain in exertion, day 2 (NRS)	13 – 639	-0.4 (-0.7, -0.1)	50%
- *Addition of intrathecal bupivacaine*	4 – 245	-0.3 (-0.6, 0.0)	14%
- *Solely intrathecal hydrophilic opioids*	8 – 374	-0.3 (-0.8, 0.2)	47%
- *Laparoscopic procedures*	5 – 196	-0.6 (-1.1, -0.1)	61%
- *Laparotomic surgery*	6 – 331	-0.3 (-0.9, 0.3)	58%
- *Studies with a placebo or sham procedure*	5 – 236	-0.5 (-1.1, 0.2)	62%
Morphine consumption day 1 (mg)	30 -1809	-18.4 (-22.3, -14.4)	99%
- *Addition of intrathecal bupivacaine*	11 – 814	-17.2 (-25.7, -8.8)	100%
- *Solely intrathecal hydrophilic opioids*	18 – 975	-17.7 (-21.2, -14.2)	96%
- *Laparoscopic procedures*	9 – 464	-15.0 (-22.0, -8.1)	99%
- *Laparotomic surgery*	14 – 805	-18.6 (-23.1, -14.0)	93%
- *Studies with a placebo or sham procedure*	16 – 1022	-19.7 (-26.1, -13.3)	99%
Morphine consumption day 2 (mg)	22 – 1308	-25.5 (-30.2, -20.8)	97%
- *Addition of intrathecal bupivacaine*	7 – 519	-25.0 (-33.3, -16.7)	99%
- *Solely intrathecal hydrophilic opioids*	14 – 769	-23.4 (-28.4, -18.5)	93%
- *Laparoscopic procedures*	8 – 464	-27.9 (-36.9, -18.9)	98%
- *Laparotomic surgery*	8 – 396	-19.9 (-25.8 -14.0)	86%
- *Studies with a placebo or sham procedure*	9 – 508	-28.0 (-35.6, -20.4)	97%

Outcome	Number of studies – participants	Effect (mean (95%CI))	I^2
Time to first analgesic request (hours)	8 – 309	9.7 (4.9, 14.4)	99%
Time to fit-for-discharge (days)	4 – 233	-0.3 (-0.5, -0.1)	28%
- *Enhanced Recovery Programs*	3 – 166	-0.3 (-0.4, -0.2)	0%
Length of hospital stay (days)	17 – 1416	-0.2 (-0.4, -0.1)	88%
- *Addition of intrathecal bupivacaine*	8 – 674	-0.2 (-0.4, 0.0)	87%
- *Solely intrathecal hydrophilic opioids*	8 – 525	-0.3 (-0.9, 0.2)	88%
- *Laparoscopic procedures*	8 – 629	-0.3 (-0.5, -0.1)	92%
- *Laparotomic surgery*	6 – 515	-0.3 (-0.6, 0.1)	38%
- *Enhanced Recovery Programs*	5 – 486	-0.2 (-0.5, 0.1)	93%
Intraoperative sufentanil use (µg)	11—625	-12.9 (-19.3, -6.5)	91%
- *Addition of intrathecal bupivacaine*	4 – 280	-10.0 (-16.2, -3.8)	75%
- *Solely intrathecal hydrophilic opioids*	6 – 325	-16.1 (-27.0, -5.1)	95%
Incidence of nausea	25 – 1412	1.1 (0.9, 1.4)	48%
- *Addition of intrathecal bupivacaine*	10 – 718	1.1 (0.9, 1.4)	0%
- *Solely intrathecal hydrophilic opioids*	15 – 694	1.2 (0.8, 1.6)	65%
- *Laparoscopic procedures*	7 -355	1.1 (0.8, 1.5)	0%
- *Laparotomic surgery*	12 – 709	1.1 (0.8, 1.7)	68%
- *Studies with a placebo or sham procedure*	14 – 914	1.0 (0.8, 1.3)	42%
Incidence of pruritus	23 -1282	4.3 (2.5, 7.5)	57%
- *Addition of intrathecal bupivacaine*	8 – 556	8.9 (4.2, 18.9)	0%
- *Solely intrathecal hydrophilic opioids*	15 – 726	3.2 (1.7, 6.0)	59%
- *Laparoscopic procedures*	6 -255	5.3 (2.6, 11.1)	0%
- *Laparotomic surgery*	12 – 709	3.4 (1.6, 7.0)	66%
- *Studies with a placebo or sham procedure*	13 – 804	6.4 (2.3, 18.1)	70%
Incidence of sedation	12 – 644	0.7 (0.5, 1.1)	2%
Incidence of respiratory depression	31 – 1862	2.4 (0.8, 7.4)	14%
- *Addition of intrathecal bupivacaine*	10 – 813	7.7 (0.2, 388.6)	N/A
- *Solely intrathecal hydrophilic opioids*	19 – 812	9.0 (2.9, 27.8)	64%
- *Laparoscopic procedures*	9 – 530	3.3 (0.1, 83.9)	N/A
- *Laparotomic surgery*	17 – 1048	3.7 (0.6, 24.5)	57%
Mortality	6 – 554	0.4 (0.1, 1.1)	0%

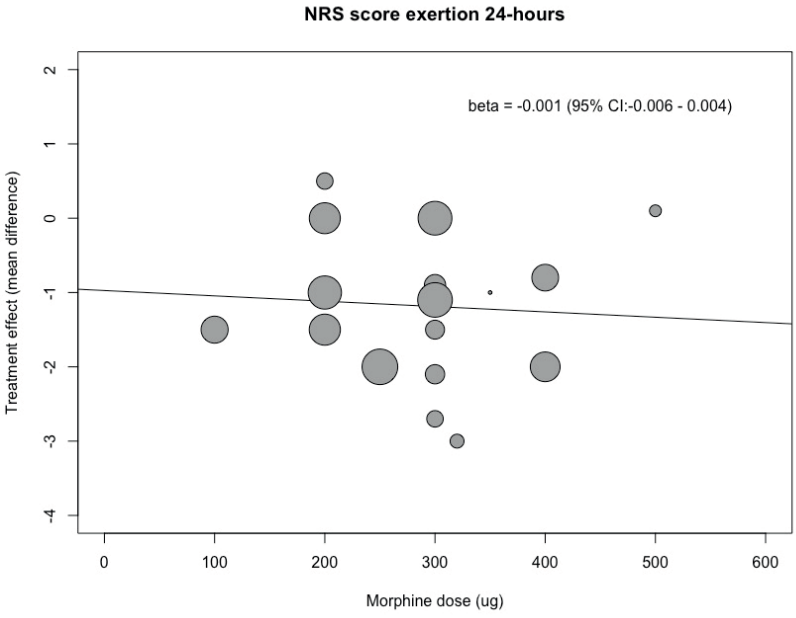
Data presented in mean difference (95% CI) for continuous outcomes and RR (95% CI) for dichotomous variables (i.e. incidences). For the incidence of respiratory depression the Peto Odds Ratio was calculated.

Appendix C.5 Meta-regression

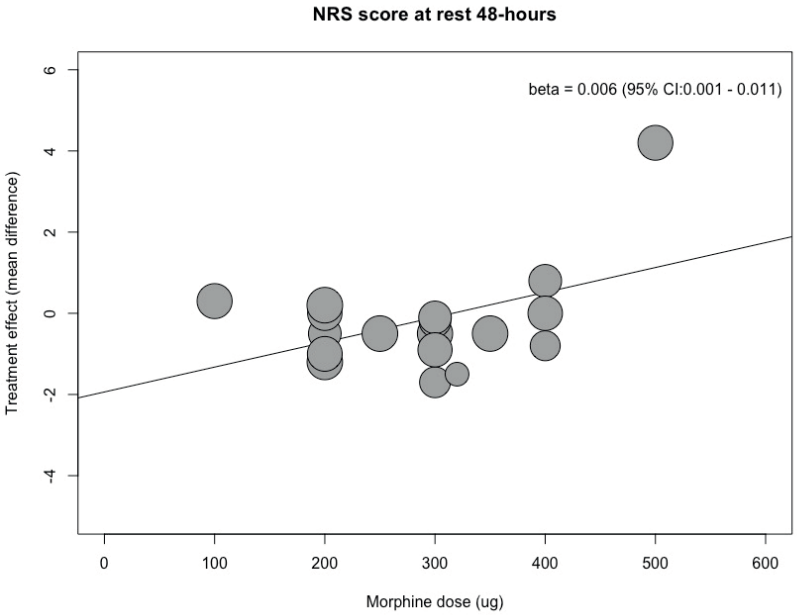
1. Pain scores in rest at day 1



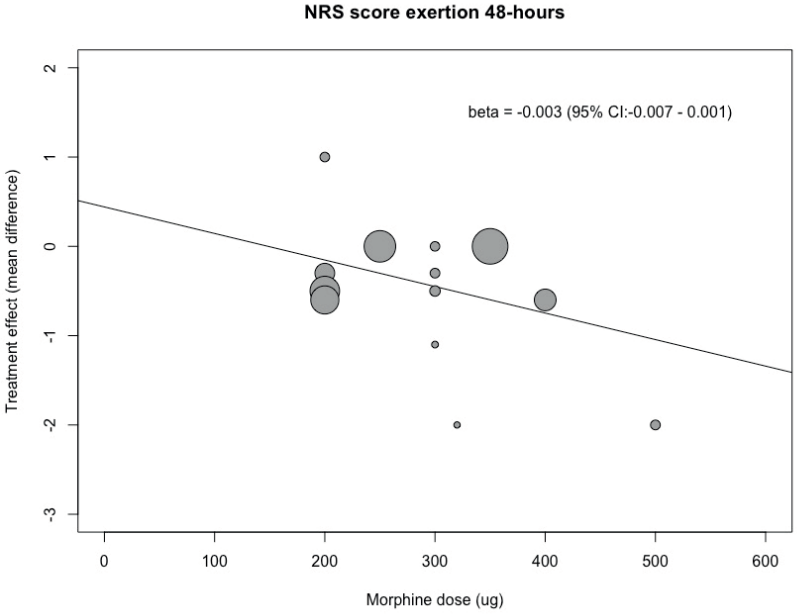
2. Pain scores in exertion at day 1



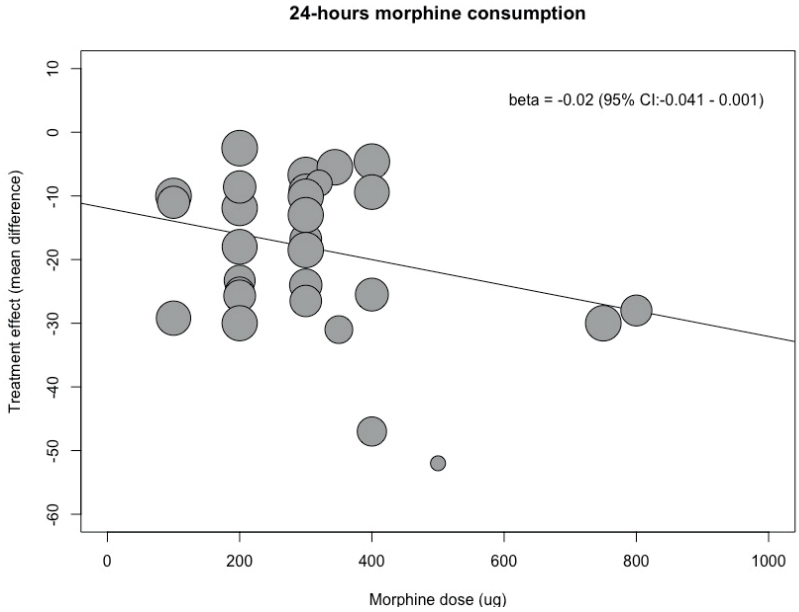
3. Pain scores in rest at day 2



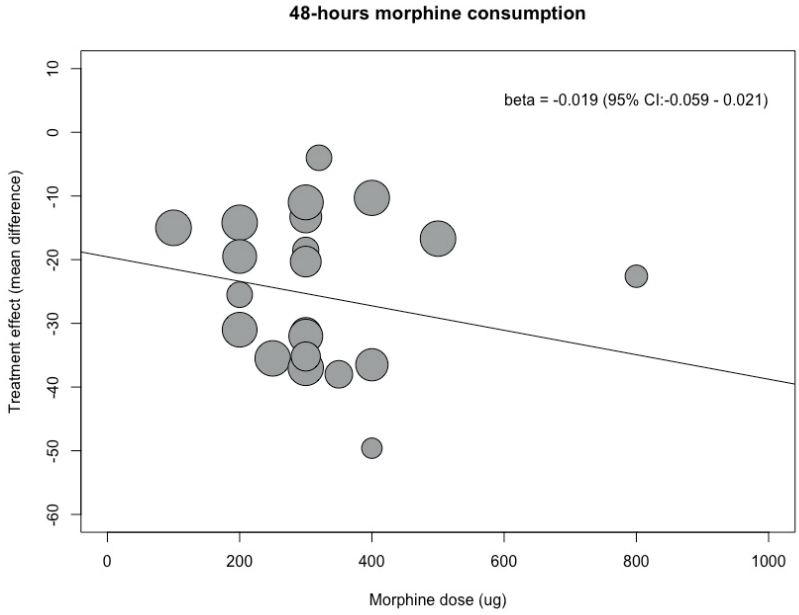
4. Pain scores in exertion at day 2



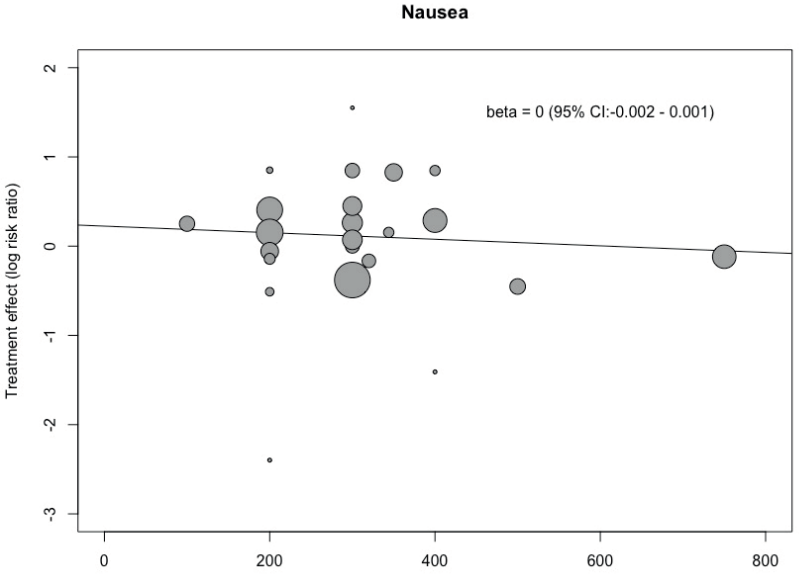
5. Morphine consumption at day 1



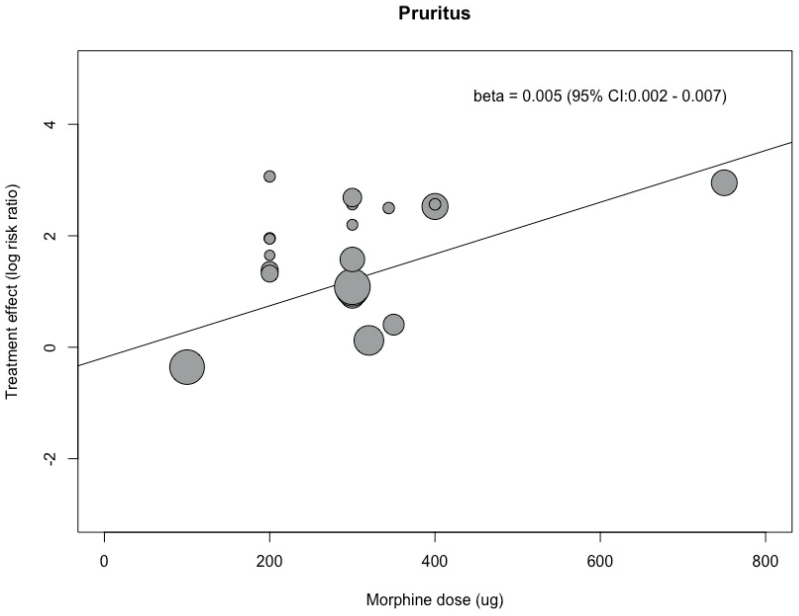
6. Morphine consumption at day 2



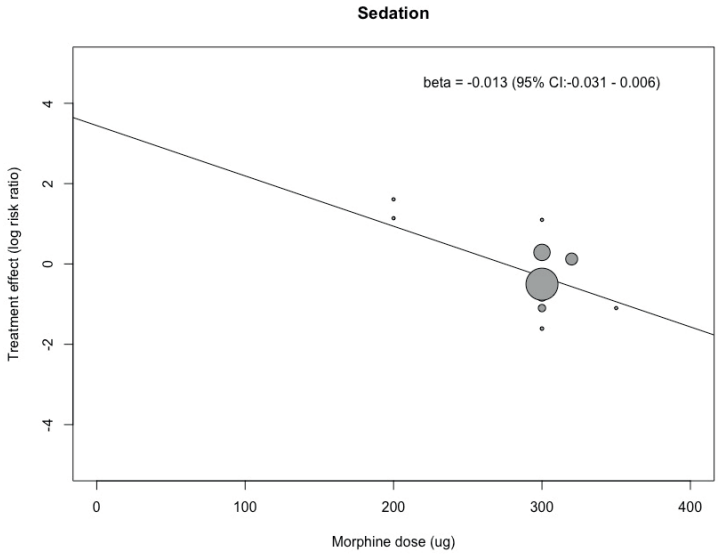
7. Incidence of nausea



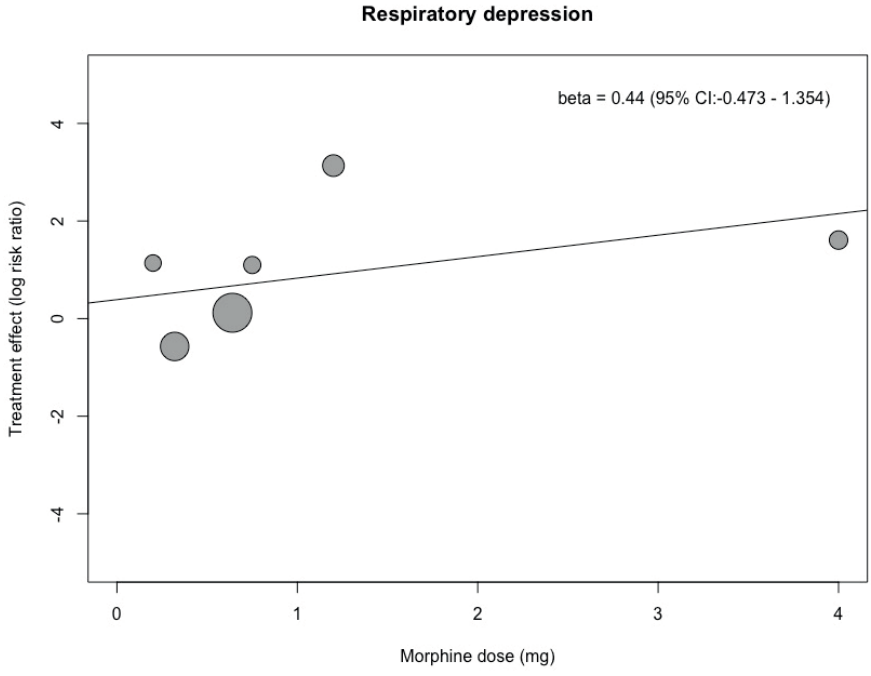
8. Incidence of pruritus



9. Incidence of sedation

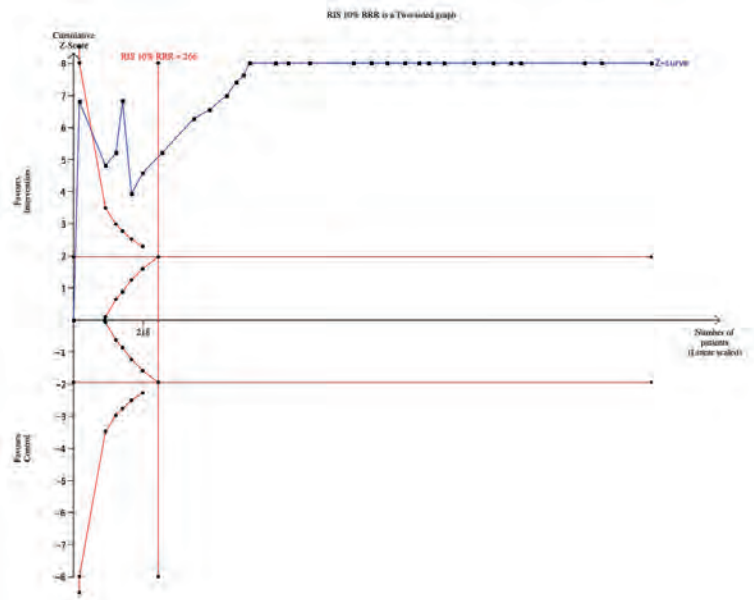


10. Incidence of respiratory depression

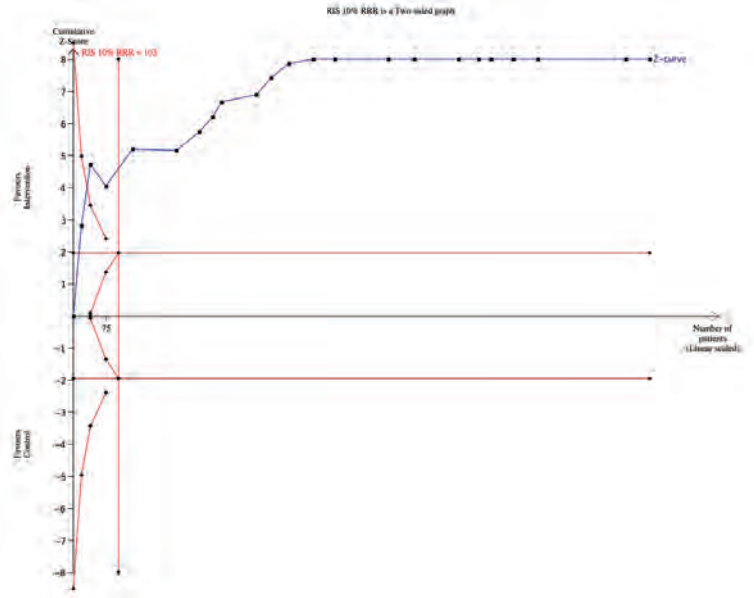


Appendix C.6 Trial Sequential Analyses

1. Morphine consumption at day 1



2. Morphine consumption at day 2



Intrathecal Morphine is Associated With Less Delirium Following Hip Fracture

Surgery: A Register Study

M.V. Koning, M. van der Sijp, R.J. Stolker, A.H.P. Niggebrugge.

Anesth Pain Med 2020 26;10:e106076

Chapter 6

Abstract

Background

Delirium is a common complication after proximal femoral fracture surgery, with pain and opioid consumption as the contributing factors. The administration of intrathecal morphine may decrease these factors postoperatively and potentially reduce delirium.

Objective

This research aimed to study the association between the use of intrathecal morphine and the occurrence of delirium.

Methods

A retrospective analysis of a prospectively register kept in a non-academic hospital in the Netherlands was performed. The register contained data of all patients with proximal femur fractures that were surgically treated with osteosynthesis or prosthesis. Patients receiving spinal anesthesia (SA-group) were compared with patients receiving spinal anesthesia with the addition of intrathecal morphine (SIM-group). The administration of either SA or SIM was based on the preference of the anesthesiologist. The primary outcome was the incidence of delirium, as defined by the DSM-V classification. The follow-up lasted until hospital discharge. Both univariate and multivariate analyses were performed.

Results

The SA-group consisted of 451 patients and the SIM-group included 34 patients. Delirium occurred in 19.7% in the SA-group versus 5.9% in the SIM-group (p=0.046). This association remained significant after correction in multivariate analysis (OR of delirium in the SA group, 95% CI: 1.062 - 21.006, p=0.041). Additionally, multivariate analysis revealed that age, gender, preoperative cognitive impairment, and fracture treatment (osteosynthesis or prosthesis) were independently associated with delirium.

Discussion

This retrospective study found an independent association between the use of intrathecal morphine and a lower incidence of delirium. This clinically relevant decrease in delirium should be studied in a prospective randomized study.

Introduction

Delirium is one of the most prevalent perioperative complications of proximal femoral fracture surgery.[1] It is associated with an increased mortality, prolonged admission time, and impaired functional recovery, and is prognostic for cognitive impairments and dementia.[2] Amongst the factors influencing the incidence of delirium during admissions are pain and systemic opioid use.[3,4] Both pain and systemic opioid use decrease with the administration of intrathecal morphine, which provides adequate analgesia for approximately 24 to 48 hours.[5] Consequently, intrathecal morphine could potentially reduce the prevalence of postoperative delirium in proximal femoral fracture patients.

In contrast, the Royal College of Physicians recommends against the routine use of intrathecal morphine due to the risk of side effects, including postoperative confusion.[6] This claim seems questionable since only one study has investigated intrathecal morphine in proximal femoral fracture patients, which detected no difference in complications, although it was underpowered for this outcome measure.[7,8] Furthermore, studies involving intrathecal morphine in older patients undergoing elective hip surgery did not find an increased risk of postoperative delirium.[9-11]

The goal of this study was to investigate if the administration of intrathecal morphine is associated with a lower incidence of delirium when compared to spinal anesthesia without intrathecal morphine in patients treated surgically for a proximal femoral fracture. All patients admitted with a proximal femoral fracture were registered in a prospective database in the study hospital. A minority of the anesthesiologists added morphine to the intrathecal bupivacaine for spinal anesthesia, which made it possible to allocate patients to different groups. A retrospective analysis of that database was performed as a hypothesis-generating study.

Methods

A retrospective analysis was performed with data that were routinely and prospectively registered in a database. The database was not specifically designed for anesthesia-related influences on delirium. Data were registered simultaneously with the clinical registrations during admission by clinicians as part of routine care for all patients admitted with a proximal femoral fracture to the 'Hip Fracture Centre' of the Haaglanden Medical Centre Bronovo in The Hague, the Netherlands. All treatment aspects and data registrations presented in this study are documented in the local care pathway protocol. All data were handled in agreement with the 'Code of Conduct for Health Research' of the Council of the Federation of Medical Scientific Societies. The personal data were handled according to the Dutch Personal Data Protection Act. The methodology of the data collection and any subsequent observational studies was approved by the institutional Medical Research Ethics Committee (METC Southwest Holland; protocol number 18-029) without the need for individual patient consent due to the observational nature of the study.

Patients

Data were used from all patients surgically treated under intrathecal anesthesia between 19-12-2016 and 14-01-2019. The patients were divided into two groups, based on the type of anesthesia, including Spinal Anesthesia (SA) or Spinal anesthesia with Intrathecal Morphine (SIM). The choice of administration of intrathecal morphine was only at the discretion of the treating anesthesiologist.

Methods

After the radiological diagnosis of a proximal femoral fracture, patients were admitted to the surgical ward. The EKG and laboratory investigations were performed and additional preoperative investigations initiated when necessary. Screening for cognitive impairments was routinely performed using the Six-item Cognitive Impairment Test (6CIT) for all older patients (age >70) without a known diagnosis of dementia or other cognitive impairments.[13] The 6CIT was designed to assess the global cognitive status in dementia. Developed in the 1980s as an abbreviated version of the 26-item Blessed Information-Memory Concentration Scale, the 6CIT is an internationally used, well-validated screening tool. It was

designed principally for use in primary care, but has also found application in secondary care settings.

The patients' delirium risk was assessed using the (Dutch) National Safety Management System (VMS) theme 'Frail Elderly' by the ward nurses.[14] Patients with elevated delirium risk and patients with a clinical suspicion of delirium were screened three times daily by trained nurses using the Delirium Observation Screening Scale (DOSS).[15] The DOSS is an observation scale consisting of 13-items (see Appendix D). It is a validated, nurse-led screening tool that can be completed within five minutes. The DOSS score varies between 0 and 13, which is correlated with the severity of delirium.[16] When delirium was suspected (DOSS score >3), a psychiatrist was consulted to diagnose delirium using the DSM-V criteria.

Perioperative pain management consisted of paracetamol 1000 mg q.i.d., diclofenac 50 mg t.i.d. and subcutaneous piritramide 5-10 mg when requested. Regional nerve blocks were not routinely administered in this cohort.

All patients received a type of anesthesia depending on the preference of the patient and the attending anesthesiologist. Only severe aortic valve stenosis (Aortic Valve Area < 0.8 cm^2), pulmonary hypertension (mean Pulmonary Arterial Pressure >50 mmHg), or coagulation disorders (PT>1.8 INR, use of clopidogrel) were absolute contraindications for spinal anesthesia. Spinal anesthesia was performed with bupivacaine 5 mg/ml and the dose was at the discretion of the anesthesiologist. Morphine was added to the intrathecal mixture based on individual preferences by the anesthesiologists. Preservative-free morphine was diluted from 10 mg/ml to 100 μg/ml by a double dilution technique. To administer the intrathecal injection, patients were sedated with propofol/esketamine or propofol/alfentanil for positioning, depending on the preference of the anesthesiologist. It is common practice in our institution to sedate the patient with spinal anesthesia with continuous infusion of propofol during surgery. Propofol was targeted at a BIS value >45 (Bispectral Index System, Medtronic, Minneapolis, MN, USA) or a maximum of 2.5 mg/kg/h.

Patients without intrathecal morphine received 5-10 mg piritramide subcutaneously in the recovery ward as a loading dose. Further intravenous titration of piritramide with increments of 2.5 mg was available on the recovery ward for all patients. After surgery, pain management was resumed as previously described.

Patients recovered on a special 10-bed division of the surgical ward dedicated to proximal femoral fracture patients. Routine delirium preventative measures for patients with elevated risk consisted of providing a clearly visible clock, the immediate appliance of hearing and visual aids, stimulation of normal day-night rhythm and providing familiar items, and the possibility of rooming-in of family members. Patients were visited daily during the rounds by the ward doctor, a surgeon, and a senior nurse.

Patients were discharged only if they were hemodynamically and respiratory stable, the functionality corresponded with the discharge location, there were no signs of complications for which diagnostics or treatments were indicated (e.g. infection, electrolyte disorders), and the pain was controlled with oral medication.

Methods of Assessment

The primary outcome was defined as the occurrence of delirium during admission. The secondary outcomes were pain, length of hospital stay, and complications including infection, respiratory failure, and mortality. The duration of follow-up was set to the length of hospital stay until discharge since no pharmacotherapeutic effect of intrathecal morphine is expected beyond this timepoint. The missing data were not imputed or replaced.

Definitions of the complications, treatment aspects and data collection have been presented previously in more detail by Sijp et al. 2017.[12] Applicable definitions for this study are as follows:

- Cognitive impairment was defined as previously diagnosed dementia or an abnormal 6-CIT score (<11) used to screen for cognitive impairments during admission in the ED.[13]
- The pain was scored three times daily during admission on a Numeric Rating Scale (NRS) with the range of 0-10. The highest postoperative pain score for each patient was registered.
- Systemic infections were pooled and scored when a patient had a temperature >38.5 degrees of Celsius, elevated C-Reactive Protein (CRP) levels (>10 mg/L), or a white blood cell count >12.5 x 10^6/ml, a clinically susceptible site of infection, and (antibiotic) therapy use.

- Respiratory insufficiency was defined as a need for supplemental oxygen or intubation after surgery.
- All patients with elevated DOS-scores were evaluated by a physician. Delirium was diagnosed according to the DSM-V-criteria.[17]

Statistical Analysis

Patients were allocated according to their method of anesthesia, as described previously. Categorical variables are presented as frequency (percentage) and were com- pared using the chi-square test or Fisher's exact test if the data were insufficiently large (expected cell counts ≤ 5). Continuous data were presented as median with the interquartile range (IQR) and compared using the independent sample t-test and the Mann-Whitney U-test, depending on the data distribution. A multiple linear regression analysis was used to study the effect size of the anesthesia type (intrathecal anesthesia either with or without morphine) concerning the incidence of delirium during admission. Factors included for multivariate analysis were suspected confounding factors and factors identified in the univariate analysis with a P value of < 0.10. The one-in-ten rule was applied to limit the number of adjusting variates. A P value of 0.05 was considered statistically significant for all other outcomes. All statistical analyses were performed using IBM SPSS version 25.0 software (IBM, Armonk, New York).

Results

A total of 1,028 patients were admitted to the study hospital with a proximal femoral fracture between 19 December 2016 and 14 January 2019. From these, 999 (97.1%) patients were treated surgically. However, 514 (50.7%) patients who were surgically treated received general anesthesia and were consequently not included in the study. Of the 485 remaining patients, 451 (93.0%) were treated with spinal anesthesia and 34 (7.0%) with spinal anesthesia with intrathecal morphine. The dose of intrathecal morphine ranged between 100 and 150 µg. The baseline characteristics were comparable (Table 1). Of the treatment aspects, only the operating time (skin-to-skin) differed significantly between the groups (SA: 52 min (10-164) vs. SIM: 69 min (27-129), $P<0.001$).

No statistically significant differences were observed in the clinical outcomes (Table 2). From all studied perioperative complications, only the incidence of delirium varied significantly between the two study groups (19.7% vs. 5.9%, P=0.047). One patient in the SIM group died because of persistent hypotension after treatment with a prothesis, clinically attributed to the use of cement intraoperatively.

Multivariate analysis was performed to exclude factors confounding the association between delirium and “the type of intrathecal anesthesia”. Potential confounding factors identified in the univariate analysis were “operating time” and “treatment type”. Suspected confounding factors were “age”, “gender”, “ASA-classification”, and “cognitive impairment”. The analysis affirmed an association between intrathecal morphine use and a lower incidence of delirium (OR: 4.723, 95%CI: 1.062-21.006; P=0.042) (Table 3).

Table 1 Baseline characteristics.

		SA n= 451 (93.0%)	SIM n=34 (7.0%)	P-value
Age (years)		83 (75-90)	84 (75-89)	0.903
Sex (% female)		313 (69.4)	22 (64.7)	0.568
BMI (Kg/m²)		23.3 (21.2-25.5)	24.0 (21.3-27.6)	0.243
ASA classification	I	31 (7.0)	0 (0.0)	
	II	175 (39.6)	11 (32.4)	
	III	217 (49.1)	20 (58.8)	
	IV	19 (4.3)	3 (8.8)	0.187
Katz-ADL	0-2	323 (73.4)	26 (76.5)	
	3-4	62 (14.1)	5 (14.7)	
	5-6	55 (12.5)	3 (8.8)	0.820
Living situation	Independent	272 (60.3)	19 (55.9)	
	Homecare or residential home	86 (19.1)	10 (29.4)	
	Nursing home	82 (18.2)	5 (14.7)	
	Other	11 (2.4)	0 (0.0)	0.415
Cognitive impairment		159 (36.1)	8 (23.5)	0.138
Fracture type	FNF	266 (59.0)	22 (64.7)	
	PFF	174 (38.6)	12 (35.3)	
	Other	11 (2.4)	0 (0.0)	0.579
Time to surgery (h)		21 (14-28)	23 (15.5-31.5)	0.472
Pre-operative nerve block		25 (9.8)	5 (18.5)	0.183[1]
Fracture treatment	Prosthesis	201 (44.5)	20 (58.8)	
	Osteosynthesis	251 (55.5)	14 (41.2)	0.105
Operating time (min)		52 (40-68)	69 (55-79)	*<0.001*

SA: spinal anesthesia, SIM: spinal anesthesia with intrathecal morphine, SD: Standard deviation, f: female, FNF: femoral neck fracture, PFF: pertrochanteric femoral fracture, h: hours, min: minutes, Katz-ADL: Katz Index of Independence in Activities of Daily Living: a scale from 0-6 indicating level of independence, [1]Fisher's exact test (two-tailed), *italics* indicate statistical significance.

Table 2 Clinical outcomes.

		SA n= 451 (93.0%)	SIM n=34 (7.0%)	P-value
Admission time (days)		4 (3-7)	5 (4-7)	0.273
Reason for prolonged admission	Comorbidities	15 (7.3)	1 (5.0)	
	Complications	54 (26.3)	8 (40.0)	
	Logistics	116 (56.6)	11 (55.0)	
	Other	3 (1.5)	0 (0.0)	0.504
Highest postoperative pain score (NRS)		4 (3-6)	3 (2-6)	0.170
Opioid use at discharge		114 (25.2)	7 (20.6)	0.547
Delirium		89 (19.7)	2 (5.9)	*0.047*
POWI	Superficial	2 (0.4)	0 (0.0)	1.000[1]
	Deep	0 (0.0)	0 (0.0)	-
Systemic infections		44 (9.7)	2 (5.9)	0.760
Renal failure		17 (3.8)	1 (2.9)	1.000[1]
Myocardial Infarction		1 (0.2)	1 (2.9)	0.135[1]
Stroke		2 (0.4)	0 (0.0)	1.000[1]
Respiratory insufficiency		11 (2.4)	0 (0.0)	1.000[1]
In-hospital mortality		7 (1.5)	1 (2.9)	0.443[1]

NRS: numeric rating scale, DOS: delirium observational scale, POWI: postoperative wound infection, MI: myocardial infarction, [1]Fisher's exact test (2-sided), *italics* indicate statistical significance.

Table 3 Multivariate analysis (logistic regression) for delirium

		Adjusted OR	95%CI	P-value
Age (y)		1.050	1.016-1.085	*0.003*
Sex	Male	Ref		
	Female	0.455	0.261-0.791	*0.005*
ASA classification	I	Ref		
	II	>999	0.000 – NA	0.998
	III	>999	0.000 – NA	0.998
	IV	>999	0.000 – NA	0.998
Cognitive impairment	No	Ref		
	Yes	1.950	1.135 - 3.350	*0.016*
Operating time (min)		1.002	0.991 - 1.013	
Intrathecal anesthesia	SIM	Ref		
	SA	4.723	1.062 – 21.006	*0.041*
Fracture treatment	Prosthesis	Ref		
	Osteosynthesis	0.476	0.278 – 0.815	*0.007*

OR: Odds Ratio, CI: confidence interval (of the OR), SA: spinal anesthesia, SIM: spinal anesthesia with intrathecal morphine, y: years, min: minutes, Ref: reference, NA: not available, *italics* indicate statistical significance.

Discussion

This hypothesis-generating, retrospective study showed that the use of intrathecal morphine for postoperative pain in patients with proximal femoral fractures was independently associated with a lower incidence of postoperative delirium. This association remained significant after correction for age, gender, ASA-classification, pre-existing cognitive impairment, duration of surgery and fracture treatment.

The pathogenesis of delirium is not fully elucidated, although multiple factors are associated with its occurrence.[18] The well-known risk factors are age, gender, ASA classification, premorbid cognitive impairment, fracture treatment, pain, and medication, including opioids.[19,20] The current study identified previously known risk factors for delirium, which demonstrates the reproducibility of this cohort. Furthermore, the incidence of delirium is in line with the findings of other studies.[21]

The study effects are attributed to intrathecal morphine, although the lack of a subcutaneous loading dose of piritramide in the recovery room could be a cause, as well. These two factors were the only differences in the analgesic regimen between the SA and the SIM groups. Even though the administration of a loading dose is controversial, in our practice, it is common to administer some opioids, because pain may contribute to the development of delirium, as well. This practice is supported by the fact that emergency hip fracture surgery is so painful that patients need postoperative opioids.[22] This would imply that leaving out a loading dose would not decrease the opioid consumption, because patients would require opioids anyway. In addition, paracetamol and diclofenac were used as basal analgesic regimens because of the opioid-sparing effects. The study effect persisted despite the use of this basal analgesic regimen.

To date, only one study has prospectively investigated the use of intrathecal morphine for postoperative pain in patients undergoing surgery for proximal femoral fractures, but the occurrence of delirium was not measured.[8] Since delirium is a predominant complication after surgical treatment of proximal femoral fractures in elderly patients with significant consequences, a possible reduction through the use of intrathecal morphine may be clinically relevant and should be studied prospectively.

A possible mechanism by which intrathecal morphine reduces postoperative delirium is likely to involve reduced postoperative pain and reduced systemic

opioid administration.[23] Both factors are associated with delirium and are reduced by the use of intrathecal morphine.[5,20] The systemic effects of opioids are possibly involved in delirium and due to its hydrophilic nature, intrathecal morphine exerts a selective spinal effect with few systemic effects.[24]

Continuous regional or neuraxial anesthesia might be an alternative to reduce postoperative pain scores and systemic opioid consumption and thus, could potentially reduce delirium, as well.[25] However, these analgesic methods may cause a motor block, which might hamper mobilization and rehabilitation through early postoperative physiotherapy, making it less attractive as a postoperative analgesic. Additionally, peripheral nerve blocks might not completely block the innervation of the proximal femur, which limits the analgesic effects in some patients.[26-28] These disadvantages do not occur with intrathecal morphine, since this produces an analgesic effect at a spinal level and does not inhibit motoric function. Furthermore, the prolonged analgesic effect of continuous regional techniques relies on the position of a catheter, while intrathecal morphine can be administered with a single-shot technique.

Several important limitations inherent in our study design should be considered. First, due to the observational nature of this study, no causative effect can be concluded. Second, a vast majority of patients (93.0%) were treated without intrathecal morphine due to an uneven division of the anesthesiologists based on their personal preference and professional experience. The third limitation, as mentioned previously, is that the study effect could be attributed to the lack of a piritramide loading dose, rather than the administration of the intrathecal morphine in the SIM-group. As discussed, we believe that the loading dose would be required anyway, making this theory unlikely. Fourth, other anesthesia- or anesthesiologist-related treatment aspects, which may have differed between the minority group of anesthesiologists using intrathecal morphine and the other anesthesiologists, may have contributed to the observed study outcomes. As this study was based on a routine prospective register, variables available for study purposes were limited. Additional study outcomes of interest would include the actual postoperative opioid consumption of patients, daily pain scores during admission, sedation scores, the time and extent of enteral nutrition after surgery, and the time and extent of the first mobilization after surgery. Because these were unavailable, the hypothesized mechanism for the reduced incidence of delirium

could not be tested in this study. Fifth, the number of preoperative nerve blocks was low in both groups. These nerve blocks could decrease the use of preoperative opioids and pain scores, which might affect delirium, as well. Finally, the risk of bias was considerable, e.g. because nurses were more reluctant to administer opioids in patients with intrathecal morphine.

In conclusion, this retrospective study generated a hypothesis that the use of intrathecal morphine might reduce the incidence of delirium. Lower pain scores and less opioid consumption in the postoperative period is the proposed mechanism that causes less delirium. This result urges for further explorations of this analgesic method in the occurrence of delirium in a randomized study, since this study carries a high risk of bias.

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Appendix D

Delirium Observation Screening Scale (DOSS).

The patient:

1. Dozes during conversation or activities
2. Is easy distracted by stimuli form the environment
3. Maintains attention to conversation of action
4. Does not finish question or answer
5. Gives answers which do not fit the question
6. Reacts slowly to instructions
7. Thinks to be somewhere else
8. Knows which part of the day it is
9. Remembers recent event
10. Is picking, disorderly, restless
11. Pulls IV tubes, feeding tubes, catheters etc.
12. Is easy or sudden emotional (frightened, angry, irritated)
13. Sees/hears things that are not there

Absent is 0 points, Present is 1 point. Except for items 3, 8 and 9, which are scored in reverse.

Measurement of drug concentration and bacterial contamination after diluting morphine for intrathecal administration: an experimental study

M.V. Koning

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Chapter 7

Abstract

Background

Low concentrations of morphine are required for safe dosing for intrathecal injections. Sometimes, manual dilution of morphine is performed to achieve these low concentrations, but risks dilution errors and bacterial contamination. The primary goal was to compare the concentrations of morphine and bupivacaine between four methods of preparation. The secondary goal was to investigate the contamination rate between these groups.

Methods

Twenty-five experienced anesthesia providers were prescribed to prepare a mixture of bupivacaine 2.0 mg/ml and morphine 60 µg/ml according to three written prescriptions as clean and precise as possible. The fourth method used was the aspiration from ampoules prepared by the hospital pharmacy department. The concentrations of morphine and bupivacaine were measured by High-Pressure Liquid Chromatography (HPLC). The medication was cultured for bacterial contamination. Data are presented in median (interquartile range)[range].

Results

Method 1 (median 60 µg/ml (59-80)[54-287]) had 3 outliers with morphine concentrations above 180 µg/ml. Method 2 (76 µg/ml (70-82)[57-93]) and 3 (69 µg/ml (66-69)[54-88]) were consistently higher than the target concentration of 60 µg. Method 4 (pharmacy) was precise and accurate (59 µg/ml (59-59)[59-60]). In method 2 and 4 one sample was contaminated with a spore-forming aerobic gram-positive rod.

Conclusion

Manually diluted morphine is at risk for deviating concentrations, which could lead to a subtherapeutic doses or an increased number and severity of side-effects. Medication prepared by the hospital pharmacy was highly accurate. If this is unavailable, we recommend using a method with the fewest dilutions and the lowest starting concentration of morphine. Furthermore, even when precautions are undertaken, contamination of the medication is a serious risk and may occur unrelated to the dilution process.

Introduction

Intrathecal administration of morphine is an effective method of analgesia. A single dose of 100-300 µg of morphine produces analgesia that lasts over 24 hours.[1, 2] However, adverse events due to intrathecal morphine, such as late respiratory depression and pruritus, are described to be dose dependent.[3] The risk for adverse events may increase in doses > 500 µg.[4-6] Given this narrow therapeutic range, accurate dosing of intrathecal morphine is paramount.

To achieve a safe dose of intrathecal morphine, low concentrations of morphine are necessary.

However, commercially available concentrations of morphine in the Netherlands are 1 mg/ml, 10 mg/ml and 20 mg/ml. Often, only 10 mg/ml is available in the operating theatres, because these concentrations are useful for intravenous administration and multiple ampoules of morphine with different concentrations may lead to medication errors. Some health care providers use 0.15 ml of 10 mg/ml morphine to achieve a dose of 150 µg, others dilute the morphine manually.[7-9] This leaves room for error with potentially fatal outcomes as a result.

In addition, precautions should be taken to prevent a contaminated injection, since the introduction of bacteria into the cerebrospinal fluid can lead to meningitis.[10] Even though the incidence of meningitis after an intrathecal injection is estimated to be 1:53.000, manipulations for manual dilution could contaminate the injectate and increase this incidence.[11]

Previous studies have investigated the dilution of morphine, but the generalizability to our clinical situation was limited since the method of dilution was at the disposal of the subject preparing the diluted morphine[8] or a limited number of subjects diluted the morphine.[9] The first study showed that dilution decreased the precision and the accuracy of the concentration of the entire mixture, while the latter study did not confirmed that finding, but demonstrated the heterogeneity within a mixture after dilution. Furthermore, bacterial contamination was not measured in both studies. We hypothesized that the number of maneuvers increases the risk for a dilutional error and bacterial contamination. Therefore, we aim to define the precision and accuracy of morphine and bacterial contamination in syringe preparations for intrathecal with target concentrations 2.0 mg/ml bupivacaine and

60 µg/ml morphine as prepared by experienced anesthesia providers according to three standardized methods of dilution and syringes extracted from Ready-to-Use (RTU) ampoules prepared by the department of pharmacy.

Methods

For this experimental study, medical ethical approval was waived by the medical ethical committee of the Maasstad Hospital (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o., February 5, 2018). The primary outcome was the precision and accuracy in morphine concentration within groups. The secondary outcome the difference in contamination rate between these methods.

Twenty-five anesthesiologists and nurse anesthetists with at least 3 years of clinical experience were instructed to prepare a mixture of bupivacaine and morphine according to predefined methods. The instructions were provided in text and a researcher was present to clarify the instructions if required and made sure the anesthesia providers followed the instructions. The characteristics of these methods are described in Table 1. The target concentrations were 2.0 mg/ml bupivacaine and 60 µg/ml morphine. They were provided with medication, sterilely packed syringes and needles and aseptic measures, as written below.

Table 1. Characteristics of dilution per method.

	Starting concentration	Number of dilutions	Dilution volume
Method 1	10 mg/ml morphine 5 mg/ml bupivacaine	1	100 ml NaCl 0.9%
Method 2	10 mg/ml morphine 5 mg/ml bupivacaine	2	9 ml NaCl 0.9%, twice
Method 3	1 mg/ml morphine 5 mg/ml bupivacaine	1	9 ml NaCl 0.9%
Pharmacy	60 µg/ml morphine 2.5 mg/ml bupivacaine	0	N/A

Medication

For this study, commercially available medication was used for the first three methods: bupivacaine 5 mg/ml (5 ml), morphine 1 mg/ml (1 ml) and morphine 10 mg/ml (1 ml). For the method Pharmacy, the hospital pharmacy provided RTU ampoules of 5 ml, containing a combined solution of 2.5 mg/ml bupivacaine and 60 µg/ml morphine. The ampoules were prepared under Good Manufacturing

Practice (GMP) conditions by the pharmacy that is GMP certified by the Dutch Health Care Inspectorate. One batch of 50 sterile ampoules were prepared. The solution was prepared in a Grade A with Grade C background aseptic cleanroom and glass ampoules were filled under nitrogen. The fluid was filtered through a 0.22 µm bacterial filter. The ampoules were sterilized in the autoclave for 15 minutes in 121 degrees Celsius. Quality control tests in a GMP accredited laboratory included sterility, fill volume, shelf-life, and concentration. The only available RTU ampoules contained concentrations of 2.5 mg/ml bupivacaine and 60 µg/ml morphine. We have chosen to use a different concentration of bupivacaine in the dilution methods, because if the target concentration of bupivacaine was 2.5 mg/ml in 5 ml, it would require 2.5 ml of 5 mg/ml bupivacaine. This leaves 2.5 ml to contain 300 mcg morphine, leading to a concentration after dilution of 120 µg/ml morphine. This would require dilution steps that are uncommon in clinical practice.

Experimental design

The participants received written and oral instructions by one of the researchers for preparation of the solutions. It was stressed that the mixtures needed to be as aseptic and precise as possible. The preparation of medication was performed on the Post Anesthesia Care Unit, on a clean table, specifically used for preparation of medication. As aseptic measures, caps and non-sterile nitrile gloves, but not facemasks were worn by the participants. All ampoules were swiped with 70% ethanol before opening. The medication was immediately aspirated after opening of the ampoule. The outside of the ampoules was not touched by the BD blunt fill needles (BD, Oxford, United Kingdom). After each diluting step, the providers used a new needle.

There were four methods to which a participant was obliged to prepare a syringe. Method 1 was diluting 10 mg/ml of morphine in a single step. It started with drawing up 1 ml of 10 mg/ml morphine. This was injected in a container of 100 ml NaCl 0.9%. Three ml of this mixture was aspirated into a 5 ml syringe and 2 ml of 5 mg/ml bupivacaine was added. Method 2 was a double-dilution method from 10 mg/ml of morphine. It started with drawing up 1 ml of 10 mg/ml morphine in a 10 ml syringe. This was diluted with 9 ml of NaCl 0.9% in the same syringe. After mixing, 9 ml of this content was discarded and the remaining 1 ml was diluted again with 9 ml of NaCl 0.9%. After mixing, 3 ml of this mixture was aspirated in a

5 ml syringe and 2 ml of 5 mg/ml bupivacaine was added. Method 3 was a single dilution step of 1 mg/ml morphine. It started with aspiration of 1 ml of 1 mg/ml morphine into a 10 ml syringe. This was diluted with 9 ml of NaCl 0.9%. After mixing, 3 ml of this mixture was aspirated in a 5 ml syringe and 2 ml of 5 mg/ml bupivacaine was added. Method 4 (Pharmacy) was aspirating the aforementioned 5 ml ready-to-use ampoule of bupivacaine and morphine as prepared by the department of pharmacy into a 5 ml syringe.

After each prepared syringe, the participants changed nitrile gloves. Participants could perform their tasks at their own speed. Two syringes per method were prepared, leading to a total of 8 syringes per provider. Syringes were marked after each preparation. The participants started with method 1, then method 2, then method 3 and ended with method 4. Per method, one syringe was analyzed for drug concentration and one for bacterial contamination. No materials were re-used for method 2, 3 and 4. For method 1, two samples were taken from the same 100 ml 0.9% NaCl-container.

After preparation, all the syringes were capped and analyzed the same day in the pharmacy department for drug concentrations and bacterial contamination. The syringes were tested for concentration of morphine and bupivacaine by High-Pressure Liquid Chromatography (HPLC) at 285 nm in a 125 mm X 4 mm fluid column. Testing of the microbiological culture was done with the standardized method of the pharmacy department by injecting the fluid through a 0.22 µm bacterial filter which was cultured for 7 days. The contaminating microbes were identified if the culture was positive.

Outcomes

Primary outcomes were the precision and accuracy of the methods. Accuracy was defined as the average concentrations of morphine and bupivacaine per method. The precision of a method was calculated as the difference between the individual measurements and the target-concentration. In addition, the number of morphine concentrations outside the clinical acceptable range was measured. Secondary outcomes were the number of contaminated samples per method and a relationship between anesthesia provider and the precision, accuracy and contamination.

Statistics

Data is described as n (%, with 95% Confidence Interval (CI)) or as median (interquartile range(IQR))[range] after testing for non-normality (defined as a Shapiro-Wilk-test p-value <0.05). Kruskal-Wallis was used for the testing the difference of morphine concentrations between the methods and anesthesia providers. The Chi-square-test was used to compare the number of contaminated samples between the methods. A $p<0.005$ was considered appropriate and Bonferroni correction was applied when necessary. All testing was performed with SPSS 25.0 (IBM, Armonk, New York) and figure 1 was made by GraphPad Prism version 7.1 (GraphPad Software, San Diego, California).

A sample size calculation was performed with GPower 3.1. For a targeted dose of 300 µg we consider a range from 240 µg to 360 µg clinically sufficient. This corresponds with a clinical acceptable concentration between 48 µg/ml and 72 µg/ml of morphine when 5 ml of 60 µg/ml was targeted. A concentration was deemed clinically acceptable if the concentration was in the range between 80% and 120% of the target concentration. A standard deviation of 20% with normal distribution was assumed. In order to detect a clinically unacceptable range of concentrations for a dilution method, using an alpha of 0.05 and a beta of 0.8, 10 samples per group were necessary. To increase accuracy and correct for multiple testing, 25 samples per group were obtained.

Results

The accuracy was the highest in the method 4 (Pharmacy) (59 µg/ml (59-59)[59-60]). The morphine concentrations in method 2 and 3 were in higher than targeted and the method 4 ($p<0.01$, Figure 1). The median concentrations of method 1 were as targeted, but had three outliers with morphine concentrations of 189, 246 and 287 µg/ml. None of the methods resulted in concentrations below the predetermined clinically acceptable concentration, but 72% of the syringes method 2 contained higher concentrations than deemed clinically acceptable. Further details of morphine and bupivacaine concentrations are presented in Table 2.

No statistical difference in precision between method 2 and 3 was detected (16 µg (10-20)[2-33] vs. 9 µg (6-9)[1-28], p=0.329). Method 4 was the most precise (1 µg (1-1)[0-1], $p<.001$ for all comparisons with methods 1, 2 and 3). No difference in precision between methods 1 and 3 was detected (2 µg (1-2)[0-227] vs. 9 (6-9) [1-28], p=0.645).

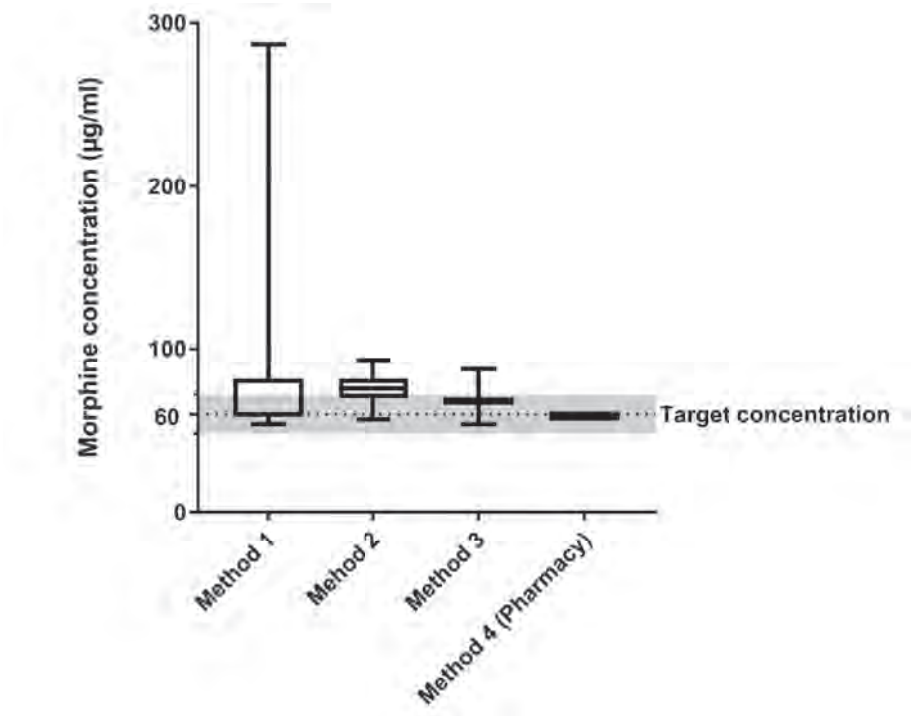

Figure 1. Morphine concentrations. Box and whiskers demonstrate the median, interquartile range and range**.** The grey bar reflects the range of clinical acceptable concentration between 48 µg/ml to 72 µg/ml.

Bupivacaine concentrations were not different between methods 1-3 (p>.999 for all comparisons). Since method 4 had a higher concentration, we calculated the difference between the target and the measured concentrations. Again, no difference was detected (p<.999 for all comparisons).

There was no relation detected between the anesthesia provider and the precision of the morphine concentrations (P=0.462).

Two samples had positive cultures with spore-forming aerobic gram-positive rods (method 2 and 4) (p<.999). These were prepared by the same anesthesia provider. In one sample a fiber was detected (method 2).

Table 2. Details of concentrations of morphine and bupivacaine.

	Method 1	**Method 2**	**Method 3**	**Method 4 (Pharmacy)**
	N=25	**N=25**	**N=25**	**N=25**
Morphine concentration (µg/ml)	60 (59-80) [54-287]	76 (70-82) [57-93]	69 (66-69) [54-88]	59 (59-59) [59-60]
Bupivacaine (mg/ml)	1.98 (1.93-2.03) [1.80-2.09]	2.00 (1.94-2.04) [1.83-2.20]	1.97 (1.92-2.01) [1.59-2.09]	2.54 (2.54-2.54) [2.54-2.57]
Morphine Out-of-range (<80%)	0 (0%) [0-14]	0 (0%) [0-14]	0 (0%) [0-14]	0 (0%) [0-14]
Morphine Out-of-range (>120%)	7 (28%) [12-49]	18 (72%) [51-88]	3 (12%) [3-13]	0 (0%) [0-14]
Bupivacaine Out-of-Range (<80%)	1 (4%) [0-20]	0 (0%) [0-14]	1 (4%) [0-20]	0 (0%) [0-14]
Bupivacaine Out-of-Range (>120%)	0 (0%) [0-14]	1 (4%) [0-20]	0 (0%) [0-14]	0 (0%) [0-14]

Data presented as median (IQR)[range] or n (%)[95% CI] where appropriate.

Discussion

Our results show that manual dilution of morphine for intrathecal administration is prone for large and potentially dangerous concentrations, even by experienced personnel. The concentrations in the method 4 (Pharmacy) were precise and accurate. Method 3, which had the lowest starting concentration and only 1 dilution step, led to the most accurate and precise concentrations of the manual dilution methods. This means that a lower starting concentration leads to a higher precision and accuracy, but variation remains present with every dilution. Contamination occurred in method 2 and method 4 and seemed to be related with medication handling, since it was associated with the same anesthesia provider.

The dilution regime according to method 1 resulted in three cases with outlying concentrations which could result in respiratory depression when injected intrathecally. Five milliliters of the target concentration result in a clinically acceptable dose of 300 µg of intrathecal morphine, but five milliliters of these manual diluted solutions might have resulted in an intrathecal administered dose of 1 to 1.5 mg of morphine. Therefore, this method should not be used. It illustrates that this dilution process is at risk of creating dangerously high morphine concentrations. The erroneous high concentration is possibly achieved because no new extraction needle was used and by the lack of rinsing off the first extracting needle in this protocol, thereby leaving a small volume of high concentration morphine in the needle. A second explanation may be because the solution did not mix properly in the 100 ml container.[9]

The accuracy of group 2 and 3 was clinically acceptable, even though the precision was limited. When these methods of dilution are clinically applied, one has to aim for the lower limit of the therapeutic range of intrathecal morphine to prevent an inadvertently high dose. The higher concentration is possibly caused by the excess volume of a 1.0 ml morphine ampoule, which has to be more than 1.0 ml to allow an extractable volume of 1.0 ml.[12] We believe that methods 2 and 3 are inherently safer methods, because the needle is rinsed if no new needle is used and the solution is mixed by aspiration of 9 ml of saline. This is supported by the study of Benkhadra et al., which shows that mixing of the syringe results in a homogenous distribution of the solution.[9] Even though this was a relatively minor effect, every cause for imprecision should be excluded.

Most remarkably, method 2 and 4 (Pharmacy) contained a contaminated sample, despite wearing non-sterile gloves and caps and swiping the ampoule with 70% ethanol before opening. In addition, this study was performed in the Post Anesthesia Care Unit, a room where medication is commonly prepared, even though it has no air flow-control. We did not instruct the participants to wear face masks, because we prepared the solutions as in daily practice. Dilution steps did not appear to increase bacterial contamination. Given the rate of contamination, it is surprising that the incidence of bacterial meningitis after an intrathecal injection is around 1: 53.000.[11] This may be explained by the fact that not every contamination leads to infection, especially for low-pathogenic bacteria or by the antibacterial action by bupivacaine. Alternatively, if sterilely packed ampoules or Ready-to-Administer (RTA) medication are commonly used, our found contamination rate may not reflect clinical practice.

Several pathways for contamination of intrathecal injection are described. One pathway consists of bacteria originating from the oropharynx of the healthcare provider falling on the sterile area and instruments. The aerobic spores are predominantly found on skin and materials, but seldom in the human oral cavity, making it unlikely that wearing a face mask during preparation would change the results. A second pathway is that contaminated particles fall in the ampoule when this is opened.[10,13] Based on the identified spores, this pathway is more likely. This study shows contaminated medication could be an important pathway of introducing a microorganism into the cerebrospinal fluid and our precautions fail to prevent contamination by this spore-forming aerobic gram-positive rods.[14]

This contamination with gram-positive rods is most likely Bacillus cereus, which is also part of the human skin flora and commonly associated with contamination.[15] The spores of Bacillus cereus are alcohol-resistant.[16] In healthy patients, the possibility of a Bacillus cereus infection in the central nervous system is low because of intact host resistance. In immunocompromised patients, however, Bacillus cereus was identified as causative microorganism for meningitis leading to fatal outcomes.[17, 18] The inability to remove the spores with alcohol might pose a risk in immunocompromised patients, even though a Bacillus cereus-meningitis is rare. It is possible to remove this pathogen by using disinfection procedures with solutions containing chlorine or hydrogen peroxide.

Bupivacaine was added to measure control of volume. This study showed that the aspiration of 2 ml into a 5 ml syringe is accurate. Furthermore, bupivacaine has antibacterial properties, making it of interest for the measurement of contamination.[19] Despite this antibacterial effect, contamination occurred in 2% of the syringes. The difference in bupivacaine concentration between group pharmacy (2.5 mg/ml) and the other groups (2.0 mg/ml) is unlikely to affect the contamination rate.[20, 21]

A few recommendations can be made based on this study. Firstly, RTU medication should be preferred in clinical practice. In some countries, dilution of medication is regarded as compounding of medication and is subject to strict regulations.[22,23] If RTU medication is not available, one should dilute from the lowest possible starting concentration and mix the syringe during the process. Secondly, sterile precautions should be undertaken when medication for intrathecal use is prepared, since bacterial contamination is likely to occur as shown by Zacher et al.[13] Several hospitals routinely prepare drugs with high microbiological risk, such as intrathecal administrations, in a cleanroom environment, either centrally in the hospital pharmacy or decentral in a laminar flow cabinet in close proximity to the operation theatres. Risk of contaminating medication occurs during dilution or aspiration of medication. Our study fails to demonstrate a lower risk of contamination with RTU medication, because the contamination rate was low and both contaminations occurred with one anesthesia provider. Prefilled sterile syringes, which are RTA could be an alternative for RTU medication. Use of these prefilled syringes would avoid drawing up the medication. The effects of using prefilled sterile syringes on contamination should be investigated further. Thirdly, clinical studies regarding intrathecal morphine sometimes do not describe the manufacturing process[24] or dilute manually[25]. Manually diluted drugs could yield a variance in dose with a different effect/side effect ratio. Therefore, the manufacturing process should be described in clinical studies. Finally, these recommendations are applicable to other diluted medication, as well. Of course this is highly relevant to morphine for intrathecal use, because of the single shot technique, the prolonged duration of action and the narrow range of the clinical acceptable dose of intrathecal morphine

A limitation of this study is that a Hawthorne-effect may have occurred, because the dilution protocol was strict and the anesthesia providers were aware of the goal

of the study, which may underestimate the variation in morphine concentration in clinical practice. Second, the use of low-volume aspirating needles and syringes may lead to a higher precision, but this does not reflect our clinical practice. Third, even though the anesthesia providers were instructed to shake the syringe to obtain a homogenic mixture, this was not specified or measured. This may have been a cause for the variation in concentration. A fourth limitation is that the pharmacy department prepared a single batch of medication for method 4. This means that method 4 does not reflect the accuracy and precision of the method of pharmacy department, but rather serves as a control group for the dilution methods. A limitation regarding the contamination is that we did not determine the species beyond the gram-stain. Gram positive aerobe spore forming bacteria are either Bacillus antracis or Bacillus cereus. The first would be very unlikely. Additionally, the bupivacaine concentration in the group pharmacy differed from the other groups, although this range of bupivacaine is unlikely to affect the contamination rate of Bacillus cereus.[21] Also, the incidence of contamination was not less in the pharmacy group. A seventh limitation is the location of the study, since the PACU is placed downstream from the operating theatre in terms of pressure hierarchy and has no air flow-control system. Per Dutch regulation, the PACU resides in the operating theatre complex and has the same air refreshment management.[26] In addition, intrathecal injections are administered in the PACU in our institution, which makes it clinically applicable to our situation. Finally, the sample size calculation was based on the assumption of a normal distribution of concentration, which appeared to be false. Still, the sample size of this study meets the rule of thumb stating that 15% should be added for a non-normal distribution.

Conclusion

Manual dilution of medication may lead to inaccurate concentrations. We recommend using prepared solutions from the hospital pharmacy. If these are not available, it is advised to use the lowest starting concentration available. In studies, the medication should be produced by the pharmacy department since manual dilution can cause an erroneous dose. Contamination of medication is a serious risk and precautions should be taken seriously, even though in this study it appeared to be unrelated to the method used.

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Serious adverse events after a single shot of intrathecal morphine: a case series and systematic review

M.V. Koning, E. Reussien, B.A.N. Vermeulen, S. Zonneveld, E.M. Westerman, J.C. de Graaff, B.M. Houweling.

Submitted

Chapter 8

Abstract

Background

The dose of intrathecal morphine is important, because of its narrow therapeutic range. Due to a compounding error, the ready-to-use syringes contained 1 mg ml^{-1} morphine instead of the intended 50 mcg ml^{-1}. This study aims to describe the serious adverse events in six patients that received this inadvertent dose and a systematic review is added to describe the serious adverse events after intrathecal morphine.

Methods

A retrospective case series described all six patients that received the erroneous morphine intrathecally for analgesia after laparoscopic segmental colonic resections. The patients' charts were reviewed for the occurrence, timing, duration and management of adverse events, the vital signs at the night post-surgery and length of hospital stay. A systematic review investigated characteristics of serious adverse events after intrathecal morphine in a perioperative setting.

Results

Four out of six patients had an adverse event, which was somnolence combined with respiratory depression (n=3) and hypotension (n=1). The review yielded 63 cases with serious adverse events, predominantly somnolence and/or respiratory depression. The onset occurred between 2 and 24 hours after injection. The severity of symptoms varied and life-threatening respiratory depression only occurred after a dose > 900 mcg or when potentiating medication was used. Naloxone did not affect analgesia. No prolonged sequalae occurred.

Conclusions

This study reveals that respiratory depression and somnolence are the predominant serious adverse events after an intrathecal dose of morphine in a peri-operative setting. We recommend routine supplemental oxygen, avoidance of doses < 900 mcg and concomitant use of potentiating medication.

Introduction

Intrathecal morphine provides effective postoperative analgesia.[1] Due to its hydrophilic properties, intrathecally administered morphine remains in the cerebrospinal fluid for a prolonged period of time, which results in a duration of action up to 36 hours, but simultaneously carries the risk of a delayed respiratory depression.[2-4] Several studies suggest a dose-dependent incidence of delayed respiratory depression.[5-7] The incidence of respiratory depression after a dose of less than 1 mg intrathecally administered morphine varies between 0.5 and 3.0% in studies including 492 until 5705 patients.[5,6,8-11] This variance in the incidence is for an important part caused by the heterogeneity in definition of respiratory depression.[4]

This heterogeneity in definition also impairs the interpretation of the severity of respiratory depression. It varies amongst studies for a range of low respiratory rate, hypercapnia and hypoxemia.[4] Life supporting therapy is seldom required.[8] Furthermore, the onset, duration, accompanying symptoms and risk factors are also not fully elucidated. Amongst the accompanying symptoms is somnolence of interest, because it is associated with an increased risk for respiratory depression.[12] These characteristics require further clarification, in order to interpret the clinical importance and provide a basis for recommendations for precautions or monitoring.[13]

Recently, our hospital initiated the routine use of intrathecal morphine as postoperative analgesia for patients undergoing laparoscopic segmental colonic resections, based on the positive results of several studies.[14-16] Ready-to-use syringes of 2.5 mg mL^{-1} bupivacaine and 50 mcg mL^{-1} morphine were used for this purpose. Unfortunately, due to a human error during the pharmaceutical compounding process by an external compounding pharmacy, the morphine concentration was 1000 mcg mL^{-1} instead of the labelled 50 mcg mL^{-1}. Consequently, a total of six patients accidentally received 3000 to 5000 mcg morphine intrathecally, until this error was discovered after a critical review of four cases with serious adverse events. A retrospective review of these patients who received a twenty-fold dose of intrathecal morphine offers an unique opportunity to describe the severity of the adverse events after intrathecal morphine.

This study aims to elucidate the severity and characteristics of serious adverse events after the administration of intrathecal morphine, which may guide recommendations for monitoring. Our study has two methods: firstly, a retrospective case series describes the severity and characteristics of adverse events. Secondly, a systematic review of the literature for individual cases of serious adverse events after the use of intrathecal morphine in a perioperative setting aims to describe the onset, the duration, accompanying symptoms, the severity and risk factors.

Methods

We performed a retrospective study of all six patients who have received intrathecal morphine between May 31st 2019 and June 7th 2019 in a teaching hospital in The Netherlands (Haaglanden MC, The Hague). All patients received medication from the same batch of erroneously prepared medication and no medication of this batch was administered to other patients. The study protocol was approved by the local hospital ethics committee (Leiden-Den Haag-Delft G20.094), because patients were not subjected to investigational actions. All patients provided informed consent for the anonymous use of their data. The data were retrieved from the electronic hospital medical records (HIX 6.1, Chipsoft, Amsterdam, The Netherlands).

Medication error

The use of intrathecal bupivacaine/morphine as method of analgesia was initiated on the first of May 2019. The hospital pharmacy provided the medication with 5 ml syringes labeled to contain an isobaric concentration of 2.5 mg ml^{-1} bupivacaine and 50 mcg ml^{-1} morphine. The syringes from the erroneously prepared batch were available for clinical use from the 31st of May 2019 until the decision to stop this method of analgesia on the 7th June 2019. During that time, no other batch of bupivacaine/morphine was concurrently used. On the 7th June 2019, it was noted that four patients had serious side effects which were associated with an intrathecal high dose of morphine in a short period of time. The medication was recalled to the pharmacy department on 12 June 2019. All but six syringes were send to the pharmacy department, since these six have been used for patient care. Analysis showed that the ready-to-use syringes contained 2.5 mg mL^{-1} bupivacaine and 1000

mcg mL^{-1} morphine. A human error in the compounding process and no routine in-process drug concentration analysis before release of the batch were identified as causes for this medication error. Routine in-process drug concentration analysis was not required by the Dutch Regulations and the EU-GMP, since this analysis is only required in large batches of medication and when the pharmacist deems it required based on the risks of the medication. It was reported to authorities and practice has changed according to the recommendations. One of which was routinely performing drug concentration analysis.

Standard Care

Intrathecal bupivacaine/morphine was exclusively administered to patients undergoing laparoscopic segmental colonic resections. On the day of surgery, patients were admitted to the hospital and no sedative premedication was routinely administered.

Spinal anesthesia was administered through a 27-G pencil point needle (Pencan, Braun, Melsungen AG, Melsungen, Germany) in a sterile manner. Per local protocol, 3-5 mL of a ready-to-use syringe produced by an external compounding pharmacy as described before was administered for spinal anesthesia in the operation room. The dose of intrathecal morphine was at the discretion of the anesthesiologist and in the local protocol it was recommended to use 4-5 mL (i.e. 200-250 mcg of morphine) for patients under 71 years of age, while 3-4 mL (i.e. 150-200 mcg of morphine) was used for elder patients. Thereafter, general anesthesia was administered at the discretion of the anesthesiologist using a combination of an opioid (sufentanil or remifentanil) an anesthetic agent (propofol or sevoflurane) and neuromuscular blockade (rocuronium). A urinary catheter was inserted before surgery commenced.

During surgery, 1000 mg of paracetamol, 75mg of diclofenac, 4 mg of dexamethasone and 4 mg of ondansetron were routinely administered. Intravenous fluids were targeted at a fluid balance of less than 750 ml surplus. Administration of phenylephrine and norepinephrine as vasopressors were at the discretion of the attending anesthesiologist. At the end of surgery, a Train-of-Four-ratio-measurement was routinely performed to measure residual neuromuscular blockade. If necessary this was antagonized with sugammadex. If the patient was

arousable and protective airway reflexes and sufficient spontaneous ventilation were present, the trachea was extubated and the patient was transferred to the Post Anesthesia Care Unit (PACU).

At the PACU, 2.5 mg piritramide was administered intravenously by a nurse if pain scores were >4 on a Numeric Rating Scale (NRS). Additional ondansetron or 0.6-1.2 mg dehydrobenzperidol was administered for nausea or pruritus if needed, at the discretion of the anesthesiologist. The patient was discharged to the ward when pain scores were <4 NRS, no nausea or other side-effects were present and the Aldrete score was > 8.

At the ward, postoperative analgesia was continued with 1000 mg paracetamol four times daily, naproxen 250 mg three times daily and short-acting oxycodone 5 mg if needed. Up to three doses of 4 mg ondansetron and 1 mg haloperidol were allowed for nausea and pruritus if needed. Heart rate, non-invasive blood pressure, pulse oximetry, respiratory rate and consciousness were routinely measured at least every 4 hours. Three liter min^{-1} of oxygen was routinely administered by nasal cannula and adjusted to maintain a SpO_2 > 94%. Based on a Modified Early Warning Score (MEWS), the nurses consulted the attending physician and/or the intensive care unit if the score was higher than 3.[17] The house officer and intensive care physician were 24 hours per day available and usual response time was within 5 minutes. The choice to call the house officer or the intensive care physicians depended on the severity and judgement of the attending nurse. The attending nurse could call the intensive care physicians directly without consulting the surgical resident first.

Data Collection

Patient characteristics, all administered drugs on the day of surgery and first postoperative day, duration of surgery, duration of anesthesia, time spent on the PACU and worst vital signs measured on the ward were noted. The patient's chart was investigated for any adverse events during hospital admission and on the first out-patient visit. In case of an adverse event, time and symptoms of this adverse event were registered, as well as the undertaken diagnostic measures, the treatment and duration of treatment.

Systematic review of literature

In order to elucidate the severity and characteristics of the adverse events after intrathecal morphine, a literature search for these outcomes was performed in March 2021. The registration was declined by Prospero for not meeting the inclusion criteria. The databases Medline, Embase, Cochrane CENTRAL and Web of Science were used. No language restrictions applied. The search combined the terms "Intrathecal" OR "Spinal" AND "Morphine" and excluded the terms "Chronic", "Pump" or "Caesarean Section" (see appendix E for search strategy). Duplicates were removed using Endnote. The bibliographies from selected studies were screened for relevant studies. The cases of the current case series were included as well.

Because the review aimed to investigate characteristics of serious adverse events, individual case data were required. Therefore, inclusion criterium was any individual case description of one or more patients with an adverse event after the use of a single shot of intrathecal morphine in a perioperative setting. All types of studies were included and data from cohort studies were only used when individual patient data were identifiable. Exclusion criteria were aggregate data, obstetric cases and intrathecal morphine administered through an intrathecal pump or for chronic use. The latter two exclusion criteria were based on the reason that obstetric and non-opioid-naïve patients are likely to have a different response than opioid-naïve surgical patients. In addition, the time of onset and dose are difficult to determine after continuous infusions and postoperative patients may have other causes of hypoxemia compared to out-clinic patients, such as atelectasis.

Two authors (MVK and BMH) screened the titles and abstracts. A study was included for a full text analysis when at least one author deemed it of interest. Both investigators (MVK and BMH) independently read the full-texts of these citations. Data extracted from the full text was the author, year of publication, age and gender of the patient, type of surgery, dose of intrathecal morphine, the concomitant use of other intrathecal medication, the use of sedative medication on the day of surgery, the presenting symptoms, the time between injection and symptoms, the duration of the symptoms, the use and dose of antagonizing agents, the vital signs (blood pressure, heart rate, respiratory rate, pCO_2, pO_2, SpO_2 and consciousness) upon presentation, the use of mechanical ventilation or other types of life support and the overall outcome.

Outcomes

All cases were screened for the criteria of serious adverse event, defined as an impaired vital sign, including either somnolence, defined as a Glasgow Coma Scale < 14 or described as "difficult to arouse", respiratory depression, defined as a respiratory rate below 10 breaths per minute, a PaCO2 > 7.0 kPa or an SaO2 < 90%, or cardiovascular instability, defined as a heart rate < 50 bpm or > 120 bpm or a mean arterial blood pressure < 55 mmHg or > 110 mmHg. The cases were also screened for a life-threatening respiratory depression, which was defined as a respiratory rate < 4 breaths per minute, a SpO2 <85% or other signs of hypoxemia or a PCO2 > 8 kPa.

Statistics

Data are presented as median (interquartile range)[minimum-maximum] or as N (%) when applicable.

Results

Case series

A total of six patients (age 63-80, 3 female, 3 male) received intrathecal analgesia with medication from the erroneous batch (Table 1). Four patients had serious adverse events, which were respiratory depression combined with somnolence (n=3) and hypotension (n=1). In the other two patients no events were detected and recovery from surgery appeared uneventful. These two patients had uneventful intrathecal injection and signs of an intrathecal block due to the bupivacaine. None of the patients required any additional opioids after surgery. All four cases with serious adverse events are described in Appendix F. Respiratory depression consisted of hypoxemia (Patient 4), hypercapnia (Patient 1, 4 and 6) and a respiratory rate < 10 breaths per minute (Patient 1 and 4). Hypercapnia was present in all three patients in whom CO_2 was measured. In all three patients the respiratory depression resolved after administration of supplemental oxygen and naloxone, none of the patients required mechanical ventilation. One patient was admitted to the Intensive Care Unit (patient 4) and 2 patients were treated on the ward.

Table 1. Patient characteristics.

Patient	Age – Gender – type of laparoscopic surgery	Dose of ITM (mcg)	Time between ITM and symptoms (hours)	Duration of symptoms (hours)	Vital Signs when symptoms were detected^	Class of SAE	Treatment	ICU admission	Length of Hospital stay (days)
1	80 – F Right hemicolectomy	5000	5	19	E3M6V5, 6 brpm, 7.1 kPa, 97%, 2 L min^{-1}, 118/54, 71 bpm	S, RD	100 mcg Naloxone, at 10 and 22 hours after ITM injection	No	8
2	73 – M Rectosigmoidresection	5000				None		No	8
3	72 – M Rectosigmoidresection	4000*	4	24	E4M6V5, 17 brpm, 100%, 1 L min^{-1}, 102/31, 54 bpm	H	Norepinephrine-infusion for 24 hours	Yes	4
4	74 – F Right hemicolectomy	5000*	2	36	E2M5V2, 8 brpm, 7.3 kPa, <70%, 0 L min^{-1}, 100/65, 70 bpm	S, RD	Oxygen and naloxone-infusion for 36 hours	Yes	5
5	68 – F Right hemicolectomy	3000				None		No	4
6	63 – M Sigmoidresection	3000	13	6	E2M5V2, 12 brpm, 8.2 kPa, 97%, 1 L min^{-1}, 164/95, 94 bpm	S, RD	100 mcg Naloxone	No	4

* Received benzodiazepines preoperatively. ^: displayed as: Glasgow Coma Score, Respiratory Rate, pCO_2, SaO_2, supplemental oxygen, non-invasive bloodpressure and heart rate. Bpm: beats per minute; brpm: breaths per minute; F: Female; H: hypotension, ICU: Intensive Care Unit; ITM: Intrathecal morphine, M: Male, RD: Respiratory Depression, S: Somnolence

These three patients (patient 1, 4 and 6) also suffered from somnolence. The onset time differed, since patient 4 was immediately unarousable after a 2 hour surgery and the other two patients were somnolent after 5 (patient 1) and 13 hours (patient 6) after intrathecal injection, respectively. Patient 4 received alprazolam prior to surgery, although patient 3 received midazolam prior to surgery and did not suffer from somnolence (Table 1). All cases of somnolence were accompanied with respiratory depression.

Patient 3 was hypotensive without tachycardia after a period of normotension. This patient had no signs of sedation or respiratory depression and showed no signs of hemorrhage, hypovolemia or other causes of shock. He was already admitted to the ICU because of comorbidities as planned preoperatively. A continuous infusion of norepinephrine for 24 hours resolved the hypotension. All other patients did not have any hemodynamic consequences.

The serious adverse events occurred between 2 and 20 hours after injection and lasted from 1 to 37 hours (Table 1). No patients received additional opioids in the post-operative phase. All six patients survived and did not sustain any permanent damage related to adverse event caused by the intrathecal morphine.

Review of literature

The search obtained 2007 articles, from which 1903 studies were excluded after screening of abstracts. The flow diagram is presented in Figure 1. From the remaining 104 studies, 44 papers were included and yielded 68 case descriptions of adverse events after the use of intrathecal morphine. With the inclusion of the data from the current case series, 72 cases were analyzed (see Appendix G). Sixty-three patients had disturbed vital signs and were deemed as a serious adverse event. The non-serious adverse events (n=9) consisted of nystagmus (n=2), fascia dehiscence after lumbar surgery (n=2), meningitis (n=1), hypothermia and/or diaphoresis (n=3) and pain (n=1). Two patients deemed as a serious adverse events also had an accompanying adverse events, which were a nystagmus and a Transient Ischemic Attack. Two patients deemed as a serious adverse events also had accompanying adverse events, which were a nystagmus and a Transient Ischemic Attack (Appendix G). The TIA was believed to be caused by hypercapnia, leading to an intracerebral steal phenomenon.

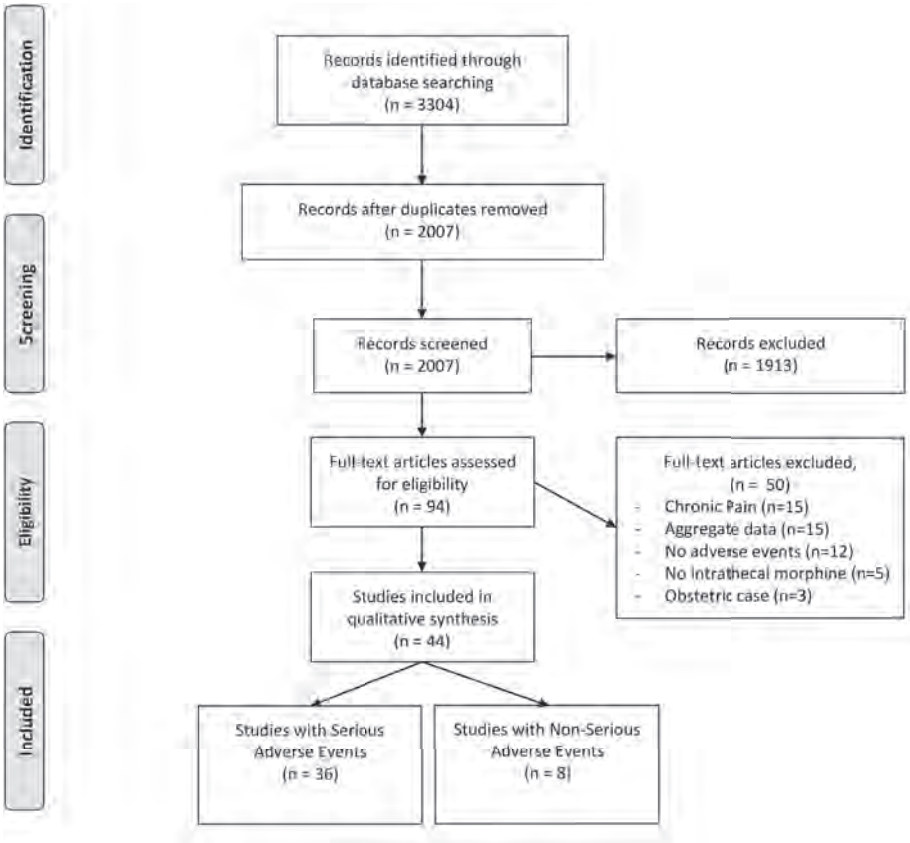

Figure 1. Flow diagram of the systematic review.

The sixty-three serious adverse events were classified as somnolence (n=28), respiratory depression (n=54), and hypotension with relative bradycardia (n=2). Eighteen patients were both somnolent and respiratory depressed. Table 2 displays the characteristics of the cases with somnolence, respiratory depression and hypotension. The administered dose in the cases with respiratory depression and/or somnolence is displayed in Figure 2. Accidental overdosing was reported in two studies[18,19], one study administered morphine at the level of T3 after a spinal tap for epidural analgesia[20] and one study reported manual dilution of the morphine[21]. No fatalities were reported.

Somnolence was often described as "difficult to arouse". More specific data are displayed in Table 2. Treatment consisted of naloxone (n=23, 82%), which was

repeatedly or continuously administered in five cases. In one case cerebrospinal fluid irrigation was performed[22] and another case resolved after the administration of flumazenil since benzodiazepines were coadministered[21]. The duration of somnolence was infrequently reported, but either resolved after a continuous naloxone administration or spontaneously after 12-24 hours. Somnolence was combined with respiratory depression in 19 cases, which was 68% of all the cases presenting with somnolence.

Respiratory depression was reported in 54 cases and the definition varied from an elevated $PaCO_2$> 6.6 kPa to a respiratory rate below 10 breaths per minute. The reported respiratory rates during the symptoms varied between apnea and 16 breaths per minute. CO_2 levels varied between 6.8 and 15.1 kPa. Respiratory depression was combined with somnolence in 19 cases, which was 33% of all the cases presenting with respiratory depression. Thirty-eight patients were antagonized with naloxone, which was repeatedly or continuously administered in 8 patients. Twelve patients (23%) received ventilatory support, although often patients were already ventilated as part of routine postoperative cardiosurgical care or before administration of naloxone. Naloxone resolved the respiratory depression in all but two cases. Sidi et al. noted no effect of 400 mcg naloxone after 4000 mcg of intrathecal morphine and ventilated the patient mechanically.[23] Krenn et al. noted no effect on respiratory depression of 800 mcg naloxone after 100 mcg of intrathecal morphine, even though other non-serious effects resolved.[24] The patient required no ventilatory support and the respiratory depression resolved spontaneously.

The criteria of *life-threatening respiratory depression* were met in 25 cases. Four cases recovered spontaneously without the need for therapy or life support. Another four patients were mechanically ventilated and 19 patients were antagonized. The criterium of hypoxemia was reported in our case after 4000 mcg morphine and six other cases appeared “centrally cyanotic” after 10,000-15,000 mcg morphine.[18,25,26] A respiratory rate <4 breaths per minute was reported in 7 cases after 3000-15,000 mcg morphine[18,23,27,28] and in one patient with a Cheyne-Stokes breathing pattern after 100 mcg morphine[24]. The remaining cases met the criterium of a pCO2 > 8 kPa. Benzodiazepines were administered concomitantly in some of these cases and flumazenil was required as well to antagonize the respiratory depression in one case.[21]

Four cases received a dose less than 900 mcg of intrathecal morphine, yet still had life-threatening respiratory depression (figure 2). Two of these cases had co-administration of benzodiazepines and in one case flumazenil was administered and resolved the respiratory depression.[21] The other case subsided spontaneously.[29] The third case received continuous IV fentanyl postoperatively.[30] In the fourth patient naloxone resolved the nausea, but not the Cheyne-Stokes breathing.[24] No ventilatory support was required in this patient. Since the patient received granisetron, ondansetron and metoclopramide for the nausea, the authors hypothesized that the opioid analgesia was potentiated through a dopamine-2-receptor antagonism.[24]

Hypotension without tachycardia was reported in two cases, several hours after the intrathecal injection. One case was reported in the present case series (see Appendix F), another case involved a female patient who received 400 mcg of intrathecal morphine in 5% dextrose, combined with 40 mg of lidocaine for an orthopedic procedure.[31] Several hours later, she had a respiratory rate of 6 bpm, a heart rate of 46 beats per minute and an arterial blood pressure of 70/50 mmHg. All her vital signs improved after a single dose of 400 mcg naloxone.

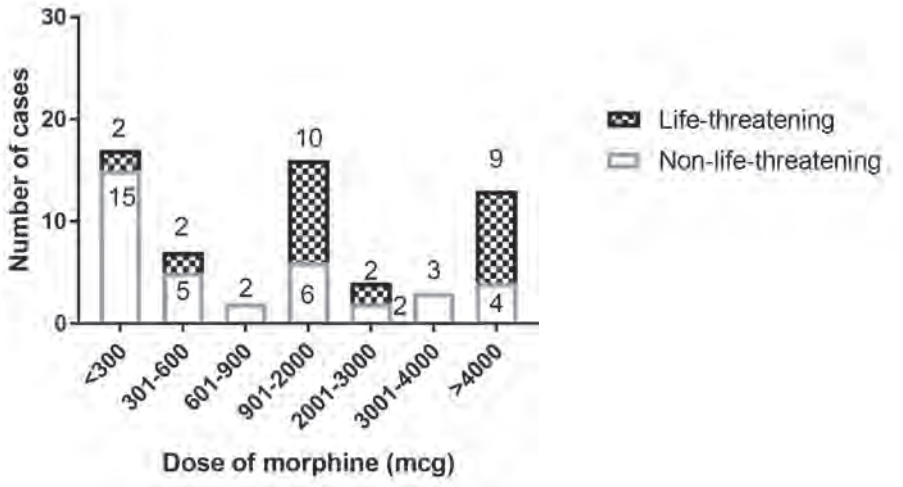

Figure 2. The number of reported cases with somnolence and/or respiratory depression, reported per range of intrathecal morphine dose.

Table 2. Data from the review of literature. Patients showing multiple symptoms are included in both groups. Missing data resulted in varying size of the groups and percentages are calculated over the reported data. Data is presented as N(%) or median (interquartile range)[range].

	Somnolence	Respiratory Depression	Hypotension
N	28	54	2
Male (%)	11 (48%)	15 (38%)	1 (50%)
Age (years)	73 (63-78)[40-90]	72 (66-79)[40-90] (n=20)	73[72-74]
Time of onset (h)	5 (2-6)[1.5-13] (n=22)	6 (3-7)[1-24] (n=35)	8 (4-12)
Dose (mcg)	2000 (250-5000)[60-15,000] (n=27)	1000 (350-3000)[100-20,000] (n=54)	2200 (400-4000)
Concomitant Local Anesthetics	16 (57%)	21 (40%)	2 (100%)
Systemic sedatives	7 (25%)	10 (19%)	2 (100%)
Naloxone	23 (82%)	38 (70%)	1 (50%)
Positive response to naloxone	22 (96%)	36 (95%)	1 (100%)
Dose of naloxone (mcg)	200 (100-200)[80-400] (n=14)	300 (160-400)[80-1600] (n=29)	400

Discussion

The case series showed that an unintentional high dose of intrathecal morphine causes symptoms with a variety of severity and timing. The review of the literature showed that somnolence and respiratory depression were the most frequently reported symptoms. These symptoms were often co-existing, although both could also appear separately. The onset time of somnolence and respiratory depression occurred between 2 and 24 hours after injection. The dose of morphine associated with adverse events varied. Doses less than 900 mcg of morphine resulted in respiratory depression, but this was only life-threatening when potentiating medication was co-administered. Life-threatening adverse events were associated with doses over 1000 mcg of morphine. All but two patients responded well to naloxone and prolonged administration was sometimes necessary. None of the patients had prolonged sequalae due to the adverse effects of intrathecal morphine.

Somnolence and respiratory depression often coincide, but only one of these symptoms was present in 62% of the reported cases. Possibly respiratory depression was not of sufficient severity or duration to cause somnolence. However, somnolence also occurred without signs of respiratory depression, which is in line with the finding that distinct pathways are involved for both symptoms.[32] Our results did not identify a factor that differed between patients that were either somnolent or respiratory depressed after intrathecal morphine. Two patients in our case series received benzodiazepines, one of them had no signs of respiratory depression. Possibly, the sedative effects may have worn off in the patient without respiratory depression.

Our analysis included two cases of hypotension with a relative bradycardia, but uncertainty remains if this was caused by intrathecal morphine. Hypotension is rarely reported as a consequence of intrathecal morphine, yet experimental data shows that intrathecal morphine can exert a hypotensive effect.[33,34] All other patients included in the current review remained normotensive. Actually, most patients with a high dose of intrathecal morphine are relatively hypertensive and tachycardic due to the hypercapnia. In our case series, the patient had comorbidities that could contribute to hypotension as well. This adds to the uncertainty to conclude that the hypotension in these cases is a consequence of the intrathecal morphine.

This review also demonstrates that the onset of symptoms may not always be delayed, but may also be present immediately after surgery. The latter is unexpectedly fast, considering that the morphine injected at a lumbar level requires rostral spread to reach a supraspinal level.[3] According to the theory of rostral spread in the CSF, the onset of symptoms should be dependent on CSF volume of distribution, the distance to cerebrum or CSF flow. Volume of distribution and distance to the cerebrum could be related to the patients height, but no correlation between onset and the patients' height was found in the our case series. CSF flow depends on CSF production, ciliary function, respiratory rate and heart rate.[35] Especially inspiration is a major contributor, which may affect onset.[36] The current review was unable to determine this effect. In addition, we cannot exclude spinal pathology, such as spinal stenosis. Some authors suggested that baricity of morphine when dissolved in dextrose combined with the position of the patient may result in an earlier onset of respiratory depression[23,31], but we were unable to demonstrate this, because an early onset also occurred with the use of isobaric morphine.

The severity of respiratory depression in the literature varies from a mildly elevated CO_2 to a life-threatening hypoxemia or apnea.[4] We assume that the cases found in our review of the literature are likely the worst cases, because mild cases may not be detected or published. Our review found twenty-five cases that may be regarded as life-threatening. None of these cases resulted in a fatality. These cases were all after > 900 mcg of morphine[18,23,25-28,37-39] or after low dose of morphine with coadministration of potentiating medication[21,24,29,30]. The latter consisted of one case of 100 mcg of self-diluted, intrathecal morphine and 3 mg of IV midazolam, in which flumazenil resolved the respiratory depression[21], one case in which 400 mcg of intrathecal morphine and 4 mg of IV lorazepam resulted in a pCO2 of 8.5 kPa which resolved spontaneously[29], one case with concomitant continuous IV fentanyl[30] and one case in which 100 mcg of intrathecal morphine combined with intravenous metoclopramide and granisetron resulted in a Cheyne-Stokes breathing pattern (CSBP)[24]. This CSBP may not be related to morphine, because it did not respond to naloxone and CSBP is unlikely to be caused by opioids.[40] Furthermore, no further life support or treatment was installed for this CSBP, which downgrades its severity.[24] In these four cases with coadministration of potentiating medication it is questionable if the life-threatening respiratory depression is caused solely by intrathecal morphine.

Respiratory depression may result in hypoxemia. Hypoxemia caused by opioid-induced respiratory depression results from a decreased alveolar pO_2 due to the hypercapnia, as depicted by Dalton's law. This can be treated with a small increase in FiO_2, for which we suggest to routinely administer 3 L min^{-1} of supplemental oxygen after the use of intrathecal morphine.

Treatment with relatively low dose naloxone antagonized the adverse effects in all but two patients while analgesic effects remained. A concomitant effect of potentiating medication is not excluded in these two cases.[23,24] It is known that analgesic effects remain, while respiratory depression and somnolence are reversed with naloxone after neuraxial morphine.[41] A proposed mechanism of this phenomenon is that the morphine concentration is the highest around the injection site, which is the substantia gelatinosa in the lumbar region.[42] This higher concentration of morphine would require a higher concentration of antagonist, compared to the lower concentrations of morphine in the respiratory center. Based on this differential effect, an approach can be to administer continuous naloxone routinely, to prevent respiratory depression but maintain analgesia.[43,44] However, this strategy requires further research regarding effectiveness and side effects.

This paper partially contradicts the recommendations from the American Society of Anesthesiologists, which recommends monitoring respiratory rate, oxygenation and level of consciousness every hour for the first 12 hour and every 2 hours for 12 hours thereafter.[13] First, our case series demonstrates that the onset may be sudden, which questions the ability of an hourly monitoring to detect an adverse event. Second, such a strategy is likely to be inefficient, since the majority of the cases are not life-threatening, which is supported by the data from Gwirtz *et al*.[8] Third, such a strategy adds nursing workload, which may be unfeasible or limit the use of an effective analgesic technique. However, the cases that were life-threatening, all had co-administration of potentiating medication such as benzodiazepines or used doses over 900 mcg morphine. Furthermore, the incidence, timing and severity of respiratory depression are comparable to systemically administered opioids per Patient Controlled Analgesia-pump.[45-47] Therefore, the results of the present study suggest avoidance of co-administration of benzodiazepines, avoiding doses over 900 mcg of intrathecal morphine and applying the same monitoring as for PCA-administered opioids in combination with the previous mentioned routinely administration of supplemental oxygen.

Alternatively, if potentiating medication is required, an intensive monitoring strategy with continuous monitoring of vital signs is warranted for 24 hours.

This study has several limitations to consider. First, the review does not provide incidences of adverse events after the use of intrathecal morphine. For that information, an observational study of Gwirtz et al. regarding 5969 patients using 200-800 mcg of intrathecal morphine remains the most robust study, which detected an incidence of 3.0% of respiratory depression, defined as a respiratory rate < 10 bpm or a pCO_2 > 50 mmHg.[8] Of these patients, none had life-threatening respiratory failure[8]. Other studies with various doses of intrathecal hydrophilic opioids found incidences of 3.0% of 1022 patients[9], 1.5% of 1039 patients[10], 1.0% of 492 patients[11], 3.0% of 327 patients[5] and 0.5% of 944 patients[6], with varying definitions of respiratory depression. Second, the majority of the data of this review resulted from case reports, which are inherently retrospective of nature, just as our case series. This leads to missing data, as exemplified by our case series in which pCO_2 was only determined in three patients. If in all patients pCO_2 had been determined, possibly more patients could have been defined with respiratory depression. In addition, observational and randomized trials were screened and included in this analysis, but these contributed little because individual patient data were seldomly reported. Third, two patients we classified as asymptomatic in our case series might have been truly asymptomatic, or the symptoms were not detected in our clinical setting which might result in a false sense of safety. Fortunately, it did not lead to permanent adverse sequelae. This applies to the review as well, since patients that were classified as asymptomatic might be symptomatic but undetected. Fourth, a review is inherently limited by publication bias. One can argue that the most severe cases are likely to be reported, although it is not excluded that a clinician is reluctant to report an inadvertent fatal case. Fifth, this review of the literature did not include adverse events related to intrathecal morphine in patients with intrathecal infusion pumps or in patients treated for chronic pain. We believe that such a clinical setting is not transferable to adverse effects of a single shot of intrathecal morphine in a perioperative setting, unless a serious medication error occurs. Still, massive doses of intrathecal morphine may result in neurotoxicity, psychosis, myoclonias, epilepsy, allodynia and motor block.[48-55]

In conclusion, this paper showed that somnolence and/or respiratory depression were the most serious adverse events after a single dose of intrathecal morphine in

a perioperative setting. The onset and duration are unpredictable and symptoms may occur after any dose of intrathecal morphine. The life-threatening cases of respiratory depression were associated with a dose over 900 mcg morphine or with concomitant use of potentiating medication. Naloxone antagonized the adverse effects in the majority of the cases without affecting analgesia. No patient had prolonged sequelae due to the use of intrathecal morphine. We suggest routine supplemental nasal oxygen, avoidance of administering more than 900 mcg of intrathecal morphine and concomitant use of potentiating medication in order to reduce the risk for life-threatening respiratory depression. The therapeutic range of intrathecal morphine is narrow, making drug concentration analysis warranted when it is compounded.

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Appendix E – search strategy

embase.com	1360	1353
Medline ALL Ovid	459	65
Web of Science SCI-EXPANDED & SSCI	457	191
Cochrane CENTRAL register of Trials	360	50
Preliminary PubMed-search	668	348
TOTAL	**3304**	**2007**

embase.com 1360

(((morphine/de OR opiate/de OR 'morphine derivative'/exp) AND ('intrathecal drug administration'/de OR 'intraspinal drug administration'/de OR 'spinal anesthesia'/de)) OR 'morphine'/dd_tl OR opiate/dd_tl OR ((morphine OR opiate* OR opioid* OR narcotic*) NEAR/6 (intrathecal* OR intra-thecal* OR spinal* OR cerebrospinal* OR intra-spinal* OR subarachnoid*)):ab,ti) AND ('adverse event'/de OR 'drug fatality'/de OR 'adverse drug reaction'/de OR 'respiration depression'/de OR hypoxia/exp OR hypercapnia/de OR somnolence/exp OR morbidity/de OR death/de OR fatality/de OR mortality/exp OR 'respiratory failure'/de OR 'respiratory arrest'/de OR intoxication/de OR 'drug overdose'/exp OR 'drug intoxication'/de OR (adverse OR ((respirat* OR CNS OR nervous-system*) NEAR/3 (depress* OR inhibition* OR effect* OR arrest* OR failure*)) OR hypoxi* OR hypercapni* OR somnolen* OR hypersomnolen* OR sleepiness* OR morbidit* OR death OR fatal* OR mortalit* OR ((severe OR serious) NEAR/3 side-effect*) OR intoxicat* OR overdos*):ab,ti) NOT (obstetrics/mj OR 'intrathecal pump'/mj OR 'malignant neoplasm'/exp/mj OR 'cesarean section'/exp/mj OR childbirth/exp/mj OR (obstetric* OR pump OR chronic* OR malign* OR cancer* OR cesarean* OR caesarea* OR c-sectio* OR labour* OR labor OR childbirth* OR child-birth* OR deliver*):ti) NOT (juvenile/exp NOT adult/exp) NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim NOT ((review/exp OR 'meta analysis'/de OR (review OR meta-analy*):ti) NOT ('case report'/de OR 'case study'/exp OR case*:ti))

Medline ALL Ovid 459

(((Morphine/ OR Opiate Alkaloids/) AND (Injections, Spinal / OR Anesthesia, Spinal/)) OR ((morphine OR opiate* OR opioid* OR narcotic*) ADJ6 (intrathecal* OR

intra-thecal* OR spinal* OR cerebrospinal* OR intra-spinal* OR subarachnoid*)).ab,ti.) AND (exp Drug-Related Side Effects and Adverse Reactions/ OR Respiratory Insufficiency/ OR Hypoxia/ OR Hypercapnia/ OR Sleepiness/ OR Morbidity/ OR Death/ OR exp Mortality/ OR Drug Overdose/ OR (adverse OR ((respirat* OR CNS OR nervous-system*) ADJ3 (depress* OR inhibition* OR effect* OR arrest* OR failure*)) OR hypoxi* OR hypercapni* OR somnolen* OR hypersomnolen* OR sleepiness* OR morbidit* OR death OR fatal* OR mortalit* OR ((severe OR serious) ADJ3 side-effect*) OR intoxicat* OR overdos*).ab,ti.) NOT (*Obstetrics / OR *intrathecal pump/ OR exp * Neoplasms / OR * Cesarean Section / OR * Parturition / OR (obstetric* OR pump OR chronic* OR malign* OR cancer* OR cesarean* OR caesarea* OR c-sectio* OR labour* OR labor OR childbirth* OR child-birth* OR deliver*).ti.) NOT ((exp child/ OR exp infant/ OR pediatrics/ OR adolescent/) NOT exp adult/) NOT (exp animals/ NOT humans/) NOT ((review/ OR Systematic Review/ OR meta-analysis/ OR (review OR meta-analy*).ti.) NOT (case reports/ OR case*.ti.))

Web of Science SCI-EXPANDED & SSCI 457

TS=((((morphine OR opiate* OR opioid* OR narcotic*) NEAR/5 (intrathecal* OR intra-thecal* OR spinal* OR cerebrospinal* OR intra-spinal* OR subarachnoid*))) AND ((adverse OR ((respirat* OR CNS OR nervous-system*) NEAR/2 (depress* OR inhibition* OR effect* OR arrest* OR failure*)) OR hypoxi* OR hypercapni* OR somnolen* OR hypersomnolen* OR sleepiness* OR morbidit* OR death OR fatal* OR mortalit* OR ((severe OR serious) NEAR/2 side-effect*) OR intoxicat* OR overdos*))) NOT TI=((obstetric* OR pump OR chronic* OR malign* OR cancer* OR cesarean* OR caesarea* OR c-sectio* OR labour* OR labor OR childbirth* OR child-birth* OR deliver* OR child* OR infan* OR pediatr* OR paediatr* OR review* OR meta-analy* OR case*)) AND DT=(article)

Cochrane CENTRAL register of Trials 360

(((morphine OR opiate* OR opioid* OR narcotic*) NEAR/6 (intrathecal* OR intra NEXT thecal* OR spinal* OR cerebrospinal* OR intra NEXT spinal* OR subarachnoid*)):ab,ti) AND ((adverse OR ((respirat* OR CNS OR nervous NEXT system*) NEAR/3 (depress* OR inhibition* OR effect* OR arrest* OR failure*)) OR hypoxi* OR hypercapni* OR somnolen* OR hypersomnolen* OR sleepiness* OR

morbidit* OR death OR fatal* OR mortalit* OR ((severe OR serious) NEAR/3 side NEXT effect*) OR intoxicat* OR overdos*):ab,ti) NOT ((obstetric* OR pump OR chronic* OR malign* OR cancer* OR cesarean* OR caesarea* OR c NEXT sectio* OR labour* OR labor OR childbirth* OR child NEXT birth* OR deliver*):ti)

Preliminary PubMed-search 668

(intrathecal OR spinal) AND (morphine) NOT (chronic) NOT (pump) NOT (caesarean section)

Appendix F – cases

Patient 1:

A 80 year old female was scheduled for a laparoscopic right hemicolectomy. She had no contributing medical history and used no medication. Intrathecal anesthesia was administered with the use of a ready-to-use syringe containing 12.5 mg of bupivacaine and 250 mcg of morphine, which was 5000 mcg of morphine in reality. During general anesthesia with sevoflurane, 7.5 mcg of sufentanil was administered. Surgery ensued uneventful and lasted 80 minutes. The patient regained consciousness, the trachea was extubated and she was transferred to the Post Anesthesia Care Unit (PACU). She remained at the PACU for 1 hour and her vital signs remained normal. Five hours after intrathecal injection, the nursing staff was alarmed because of the somnolence and the slow respiration. Upon arrival, the attending physician detected no signs of airway obstruction, normal vital signs (NIBP 118/54, heart rate of 71 bpm, SpO2 97% with 2 L/min of nasal oxygen and respiratory rate of 12 breaths per minute) and a Glasgow Coma Scale of E3M6V5 after firm stimuli without signs of lateralization. The patient was re-evaluated 4 hours later by the same physician and no significant change was noted, other than a decrease in respiratory rate to 6 breaths per minute. An arterial bloodgas analysis showed a pCO2 of 7.1 kPa. 100 mcg naloxone was administered intravenously 10 hours after the intrathecal injection and the patient recovered to a normal conscious state and was without pain. She remained on the ward and somnolence re-occurred after two hours. No ICU admission was required as judged by the attending intensivist. The next morning she was too somnolent for mobilization and another 100 mcg naloxone was administered. No further repeat-dose was required. Later that first postoperative day, she was found to have an intra-abdominal hemorrhage based on a declining hemoglobin level and a repeat laparoscopy was needed. During induction of general anesthesia she aspirated and developed a pneumonia. She was discharged home 8 days after the first surgery.

Patient 3:

A 72 year old male was scheduled for a laparoscopic rectosigmoid resection. He had a history of hypertension, insulin-dependent Diabetes Mellitus, chronic renal failure for which he received intermittent hemodialysis, stroke and multiple

myeloma. He did not use antihypertensive medication or beta-blocking agents. He was administered 5 mg of midazolam intravenously prior to the intrathecal injection for anxiety. Intrathecal anesthesia was administered with the use of a ready-to-use syringe containing 10 mg of bupivacaine and 200 mcg of morphine, which was 4000 mcg of morphine in reality. General anesthesia was maintained with sevoflurane and remifentanil. Surgery ensued uneventful and lasted 107 minutes. The patient regained consciousness, the trachea was extubated and he was transferred to the Intensive Care Unit, which was scheduled because of his comorbidities. Four hours after the intrathecal injection, his blood pressure dropped to 102/31 mmHg and his heart rate was 54 beats per minute. His respiratory rate was 17 breaths per minute and his consciousness was unaltered. He was continuously given norepinephrine for 24 hours, after which it could be stopped. No further sequalae occurred and he was discharged home 4 days after surgery.

Patient 4:

A 74 year old female was scheduled for a laparoscopic right hemicolectomy. She had a history of anxiety, for which she used 0.5 mg alprazolam as needed, which was the case one hour prior to surgery. Intrathecal anesthesia was administered with the use of a ready-to-use syringe containing 12.5 mg of bupivacaine and 250 mcg of morphine, which was 5000 mcg of morphine in reality. General anesthesia was maintained with sevoflurane and remifentanil. Surgery ensued uneventful and lasted 137 minutes. After the surgery, she was not arousable, but had an adequate spontaneous minute ventilation and protective airway reflexes. Her trachea was therefore extubated. Directly after extubation her oxygen saturation dropped to 70%, for which a nasal-pharyngeal airway was inserted and 5 L min^{-1} of oxygen per face mask was administered. One hour after surgery, her Glasgow Coma Score was still E3M5V2, although without signs of lateralization. At first, this was attributed to the alprazolam the patient received before surgery for severe anxiety. Four hours after the intrathecal injection, 400 mcg naloxone was administered, after which she was fully awake without pain. Shortly after she became somnolent again with a respiratory rate of 8 breaths per minute and was admitted to the ICU. At the ICU an additional dose of 400 mcg naloxone was administered, after which a continuous infusion was started. Continuation of this infusion was needed

until the next evening (+36 hours after intrathecal injection). Initially, when the naloxone was tapered, she became somnolent and with hypopnea again. After the continuous infusion was stopped the next day, no signs of somnolence re-occurred. She was discharged home 5 days after surgery.

Patient 6:

A 63 year old male was scheduled for a laparoscopic sigmoid resection. He had no contributing medical history and used no medication. Intrathecal anesthesia was administered with the use of a ready-to-use syringe containing 7.5 mg of bupivacaine and 150 mcg of morphine, which was 3000 mcg of morphine in reality. During general anesthesia with sevoflurane, 15 mcg of sufentanil was administered. Surgery ensued uneventful and lasted 95 minutes. The patient regained consciousness, his trachea was extubated and he was transferred to the Post Anesthesia Care Unit (PACU). He remained at the PACU for 3 hours, predominantly for the treatment of nausea, for which two doses of 4 mg of ondansetron were provided. His vital signs remained within normal limits.

Thirteen hours after the intrathecal injection, during a meal on the ward, the patient was found unconscious. The Intensive Care Unit was consulted and upon arrival the patient was found less responsive, with food in his mouth, but with an unobstructed airway. His Glasgow Coma Scale was E2M5V2 without signs of lateralization. His vital signs were a heart rate of 94 bpm, blood pressure of 164/95, a SpO2 of 97% with 1 L/min of nasal oxygen, a respiratory rate of 12 breaths per minute and arterial pCO2 of 8.2. He was given 100 mcg of naloxone and within minutes he was fully awake without pain. He was observed on the ward and somnolence re-occurred during the four hours after ICU consultation, but not as severe as earlier. Further recovery went uneventful and he was discharged home 4 days after surgery.

Appendix G – table of studies

First author	Age, gender	Type of surgery	Dose of morphine (mcg)	Concomitant administration of LA or sedatives?	Somnolence, Respiratory Depression or Hypotension	Life Threatening?	Treatment
Bernard[1]		Spinal column	300		RD		N
		Spinal column	300		RD		N
		Spinal column	300		RD		N
		Spinal column	300		RD		N
Bowrey[2]		Orthopedic	200		RD, S		N
Chaney[3]		Cardiac surgery	4000		S		-
Fitzpatrick[4]		Cardiac surgery	1000		RD, S		N
		Cardiac surgery	2000		RD, S		N
Gehling[5]		Orthopedic	100	LA	RD		-
		Orthopedic	200	LA	RD		-
		Orthopedic	200	LA	RD		-
Gjessing[6]	73, F	Orthopedic	2000	LA	RD	Yes	-
	62, M	Orthopedic	1400	LA	RD		-
	72, F	Orthopedic	1400	LA	RD	Yes	N
	78, M	Orthopedic	1200	LA	RD	Yes	-
	85, F	Orthopedic	1000	LA	RD	Yes	N
	81, F	Orthopedic	1000	LA	RD	Yes	N
	82, F	Orthopedic	1000	LA	RD	Yes	N
	75, F	Abdominal surgery	2000	Sed	RD	Yes	-

First author	Age, gender	Type of surgery	Dose of morphine (mcg)	Concomitant administration of LA or sedatives?	Somnolence, Respiratory Depression or Hypotension	Life Threatening?	Treatment
	71, F	Abdominal surgery	1200	Sed	RD	Yes	N
	67, F	Abdominal surgery	1000	Sed	RD		-
Gray[7]		Thoracic surgery	800		RD		N
Jun[8]	59, F	Abdominal surgery	400	Sed	RD, S	Yes	Mechanical Ventilation
Kalso[9]	F	Orthopedic	400	LA, Sed	RD	Yes	-
		Orthopedic	400	LA	RD		-
Samii[10]			1600		RD		N
			1600		RD		N
Sebel[11]		Cardiac surgery	4000		RD		N
Shapiro[12]	72, F	Orthopedic	200	LA	RD, S		-
Suksompong[13]	69, F	Thoracic surgery	300	Sed	RD		N, Mechanical Ventilation
Wongyingsinn[14]	81	Abdominal surgery	150	LA	RD		Ventilatory support
	75	Abdominal surgery	150	LA	S		-
Akodjenou[15]	83, M	Abdominal surgery	1000	LA	RD	Yes	Mechanical Ventilation
Baskoff[16]	72, M	Abdominal surgery	10000	LA	RD, S	Yes	N, Mechanical Ventilation
Bicalho[17]	44, F	Abdominal surgery	100	LA, Sed	Diaphoresis		-
D'Oyley[18]	60, M	Abdominal surgery	800		RD		-
De All[19]	67, M	Abdominal surgery	400		Vertical nystagmus		N
De Gans[20]	61, M	Major vascular	3000		Meningitis		Antibiotics

First author	Age, gender	Type of surgery	Dose of morphine (mcg)	Concomitant administration of LA or sedatives?	Somnolence, Respiratory Depression or Hypotension	Life Threatening?	Treatment
De Morais[21]	45, M	Orthopedic	4000	LA	Diaphoresis		N
Dworzak[22]	72, F	Inguinal surgery	100	LA, Sed	RD, S	Yes	N, Flumazenil
Eran[23]	51, F	Thoracic surgery	500		S, PRES		-
Glass[24]	74, F	Orthopedic	400	LA, Sed	RD, H		N
Glynn[25]	71, M	Thoracic surgery	5000		S		N
	74, F	Abdominal surgery	3000		RD		N
Ip Yam[26]	76, M	Thoracic surgery	2000		RD, S, TIA	Yes	N
Kaiser[27]	81, M	Abdominal surgery	5000	LA	S		CSF-irrigation
Karpos[28]	27, F	Spinal column	500		Fascia dehiscence		Surgical treatment
	34, F	Spinal column	9500		Fascia dehiscence		Surgical treatment
King[29]	64, M	Abdominal surgery	400	LA	RD, S		N
Koning	80, F	Abdominal surgery	5000	LA	RD, S		N
	72, M	Abdominal surgery	4000	LA, Sed	H		Norepinephrine
	74, F	Abdominal surgery	5000	LA, Sed	RD, S	Yes	N
	63, M	Abdominal surgery	3000	LA	RD, S	Yes	N
Korff[30]	59, F	Abdominal surgery	600	LA, Sed	Vertical nystagmus		-
Krenn[31]	72, F	Abdominal surgery	100	LA	RD, Nystagmus	Yes	N, minor effect
Liolios[32]	67, M	Abdominal surgery	15000		RD, S	Yes	N, mechanical ventilation
Lim[33]	74, M	Lower extremity	100	LA, Sed	S		N

First author	Age, gender	Type of surgery	Dose of morphine (mcg)	Concomitant administration of LA or sedatives?	Somnolence, Respiratory Depression or Hypotension	Life Threatening?	Treatment
Neustein[34]	73, F	Thoracic surgery	250		S		N
Odoom[35]	73, F	Major vascular	3000	Sed	RD		N
	82, M	Major vascular	3000	Sed	RD	Yes	N
Ong[36]	39, F	Abdominal surgery	250	LA, Sed	Pain		
Paulus[37]	55, M	Inguinal surgery	20,000	LA, Sed	RD		N
Perrot[38]	42, M	Orthopedic	8000	Sed	RD, S	Yes	N
Pomonis[39]	90, F	Orthopedic	15,000	LA	RD, S	Yes	Nalorphine
	82, F	Orthopedic	15,000	LA	RD, S	Yes	Nalorphine
	61, M	Orthopedic	15,000	LA	RD, S	Yes	Nalorphine
	78, M	Orthopedic	15,000	LA	RD, S	Yes	Nalorphine
Rutili[40]	81, F	Abdominal surgery	60	LA, Sed	S		N
Ryan[41]	57, F	Orthopedic	150	LA, Sed	Hypothermia		Lorazepam
Scammell[42]	76, F	Orthopedic	400	LA, Sed	RD, S		N
Sidi[43]	40, M	Abdominal surgery	4000	S	RD, S	Yes	N, no effect
Vijayan[44]	F	Orthopedic	"Inadvertantly large dose"	LA	S		N

Abbreviations: H: Hypotension, F: Female, LA: Local Anesthetic, M: Male, mcg: microgram, N: naloxone, RD: Respiratory Depression, Sed: Sedative, S: somnolence. Missing data is left open. PRES: Posterior Reversible Encephalopathy Syndrome.

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General discussion

Chapter 9

General discussion and future perspectives:

From a historical perspective, intrathecal morphine was once a common method of analgesia. In the years 1995-2005 it was used less frequently, as the duration or intensity of postoperative pain did not match the duration or intensity of analgesia provided by intrathecal morphine.[1,2] For cardiac surgery, high doses of morphine were required for a prolonged duration of analgesia, which resulted in side effects such as respiratory depression. This was not a problem when patients were mechanically ventilated overnight, but cardiac surgical and anesthesiological management changed and patients were extubated within hours after surgery. This made delayed respiratory depression a major disadvantage. For open abdominal surgery, the use of low dose intrathecal morphine provided analgesia of insufficient duration. Continuous epidural analgesia was able to provide prolonged analgesia without major side effects, making this the preferred method of analgesia for open abdominal surgery.[3,4]

Nowadays, laparoscopic surgery is the predominant method of abdominal surgery and the duration of postoperative pain has shortened with this technique.[5,6] The benefits of epidural analgesia in laparoscopic surgery are not as clear as in open abdominal surgery.[3] Intrathecal morphine might be an attractive alternative in laparoscopic surgery, because the duration of analgesia matches the duration of pain. Additionally, it has the benefits of a single-shot technique and it does not hamper mobilization. However, side effects, such as pruritus, nausea, urinary retention and late respiratory depression may occur even at low doses and benefits should be weighed against the side effects of this analgesic method for every type of surgery.

The overall aim in Enhanced Recovery Programs is to reduce the length of hospital stay by means of, amongst others, reducing pain and systemic opioid consumption as the primary aims of analgesia. With respect to these two aims, this thesis demonstrated superiority of intrathecal morphine over systemic opioids in abdominal surgery.[7-9] Multiple prospective studies have now demonstrated less pain and less opioid consumption with the use of intrathecal morphine in laparoscopic colorectal surgery.[7,10-12] It is still unclear if the use of intrathecal morphine results in a shortened time to fit-for-discharge, because results of studies are ambiguous. This outcome needs to be investigated in multicenter

randomized clinical trials involving over 200 patients. If the shortened time to fit-for-discharge is confirmed, the benefits of intrathecal morphine are even more clinically relevant.

Until such a study is performed, intrathecal morphine may thus be preferred over systemic opioids for laparoscopic colorectal surgery based on the analgesic properties. These properties being visceral and somatic analgesia for the duration of 24-48 hours, with virtually no systemic action, hypotension or motor block. This intrathecal method of analgesia may also be beneficial in other types of abdominal surgery. Especially patients undergoing procedures resulting in severe postoperative pain for the first day could benefit from intrathecal morphine, because the pain profile matches the analgesic properties of duration and intensity. This method of analgesia is well established and investigated in various abdominal procedures.[9] Still, further studies should define the specific procedure-related benefits. This should not only be targeted at lower pain scores and opioid consumption, but also at more generic outcome measures such as length of hospital stay and quality of recovery, as mentioned in the introduction.

The importance of procedure-specific research was demonstrated in the study involving robot-assisted radical prostatectomy (RARP), where the benefits of intrathecal morphine were less clear than in laparoscopic colorectal surgery. The use of intrathecal morphine resulted in less pain and opioid consumption, but only in a limited manner.[8,13] Consequently, only a small effect on the Quality-of-Recovery-15 was observed.[8] This finding could result from a limited effect of pain on the total Quality-of-Recovery-15 score, but may also be caused by the non-normal distribution of severe pain after this procedure. Pain is generally of minor intensity after RARP, but a part of the patients suffer from severe postoperative pain. This number of patients may not be large enough to affect the overall Quality of Recovery-15, but it may still be worthwhile to reduce the number of patients with severe pain. Our trial demonstrated a reduced incidence of severe pain in the intrathecal morphine group of 2.8%, compared to 18.3% in the control group. This resulted in a number needed to treat of 6.4 patients. We were unable to define the subgroup of patients with severe post-operative pain, aiming to reduce the number needed to treat. In order to provide a recommendation for clinical practice, patient preference should be considered as well. If a patient prefers to limit pain or opioid consumption but is willing to accept a higher chance of

pruritus, the use of intrathecal morphine could be a useful method. Conversely, if a patient is willing to accept more pain and opioid consumption, administration of intrathecal morphine has little patient-related benefits.

To maximize the benefit-harm ratio of intrathecal morphine, side effects should be managed. Pruritus occurs in 35-45% of the patients although the incidence is dose dependent.[9] As prophylaxis, but also as therapy, ondansetron, droperidol and propofol limit the incidence and severity.[14-16] Post-operative nausea and vomiting is reported to have an incidence of 30-40% after the use of intrathecal morphine, but this is reduced to 15-25% with the use of prophylactic dexamethasone.[9,17] Prophylactic ondansetron and droperidol reduce the incidence of nausea and vomiting as well, to approximately 10%.[18,19] Furthermore, intrathecal morphine causes a dose dependent suppression of detrusor contractility and a decreased sensation of urge, which results in urinary retention.[20] Urinary catheterization for the duration of action of morphine is recommended.[2] Alternatively, one may choose to observe bladder content with ultrasound and catheterize once urinary retention is present, but this may lead to higher workload for the nursing staff and risks a too late catherization, which may result in prolonged bladder dysfunction.[21]

Late respiratory depression is a rare but potentially serious side effect. The severity and incidence is less than clear, because in studies the definition varies from different levels of hypoxemia, hypercapnia and respiratory rate.[22] Hypercapnia and low respiratory rates are strongly related with respiratory depression, since opioids cause a decrease in minute ventilation. Hypoxemia may be a consequence, because an elevated CO_2 causes alveolar hypoxia as stated by Dalton's law. In addition, opioids also reduce the ventilatory response to hypoxemia, and thus hypoxemia can be regarded as a side effect of a opioid. However, (isolated) hypoxemia may result from atelectasis as well, which is common after general anesthesia and abdominal surgery. This is hard to differentiate and studies including hypoxemia in the definition of respiratory depression may overestimate the true incidence of respiratory depression caused by intrathecal morphine.

The incidence of respiratory depression does not only depend on the definition, but also on the administered dose. Several studies, with varying doses of intrathecal morphine, reported an incidence respiratory depression between 0.5 and 3.0%.[1,9,23-27] The meta-analysis in this thesis scored respiratory depression when an individual study reported this event according to their own definition.[9] The

meta-analysis found a incidence of 1.8%, but this was 0.5% when two high-dose, outlying studies were excluded. The non-intrathecal opioid group reported an incidence of 0.5% as well. The largest observational study reported an incidence of 3% respiratory depression, defined as a respiratory rate < 8 breaths per minute of a PaCO2 over 50 mmHg.[23] None of these patients required airway management or mechanical ventilation. All patients responded when naloxone was administered. The authors discuss that the 3% reflects potential respiratory depression, but this was never life-threatening. In our case series and systematic review we did not find any fatal case despite administration of supraclinical dose of morphine (3000 to 5000 µg). Perhaps no fatality occurred because all patients were managed just in time, or because the potential life-threatening respiratory depression is not severe enough to cause a respiratory arrest. Virtually all patients responded to naloxone, except when concomitant sedatives were used.[27] The cases fitting the definition of life-threatening respiratory depression all received a dose over 900 µg of morphine or concomitant sedatives. Therefore, one should not use a high dose of intrathecal morphine and avoid concomitant benzodiazepines or routinely administered opioids, in order to limit the incidence and consequences of respiratory depression.[27] Moreover, it is questionable if a dose over 300 µg of morphine provides better analgesia.

To avoid severe consequences of respiratory depression, the American Society of Anesthesiologists recommends monitoring oxygenation, sedation and ventilation every hour for the first 12 hours after administration of intrathecal morphine and every two hours for the following 12 hours.[28] This recommendation is only based on the consensus of the members of the task force, but not on any scientific evidence due to insufficient literature. Such an intense monitoring strategy may be clinically unfeasible and inefficient, as the incidence and severity of respiratory depression is low. Moreover, this strategy is unlikely to exert a protective effect, since the onset may be sudden and thus be missed by hourly and two-hourly visits.[27] Still, the timing of onset, severity and incidence of respiratory depression is not different between PCA opioids and intrathecal morphine.[9,29,30] One could consider applying the same monitoring strategy after the use of intrathecal morphine as with PCA opioids.

Recommendations for monitoring for respiratory depression with the use of PCA-administered opioids differs per society. Commonly, it is recommended to monitor every 2.5 hourly for the first day and every 4.5 hours after that day. However, these

standards were not clinically feasible.[31] This illustrates the need for a continuous, reliable and low-resource demanding monitoring strategy. Wearable devices are under development, but so far are unable to monitor the respiratory rate reliably.[32,33] Until such a strategy is available, one needs to balance the benefits of analgesia to the risks of the analgesic technique and consider alternative method of analgesia. This thesis demonstrated that the risks of low dose intrathecal morphine are comparable to PCA-administered opioids, but the analgesia is better. Since PCA-opioids are widely used in the Netherlands, the ability for monitoring should not be a threshold to administer intrathecal morphine. Therefore, applying the same monitoring strategy as with PCA-administered opioids might be suitable.

Alternatively, an interesting method to avoid respiratory depression is to routinely and continuously administering intravenous naloxone for 24 hours, which antagonizes the respiratory depression but not analgesics effects of morphine.[34] Still, further research is required to elucidate analgesic properties and respiratory effects of this method.

The dose is important to reduce the risks of intrathecal morphine. This thesis demonstrated that manual dilution poses a risk for deviating concentrations and thus an administration of an inadvertently high dose.[35] Unfortunately, compounding by a pharmacy is not a process without errors, as is every process.[27] This is the reality for every medication, but the consequences of an error are severe when morphine for intrathecal use is involved. The safest method is pharmaceutical compounding with measurement of the concentration as a safety check. However, Dutch regulation does not require to analyze every charge of medication.[36] The safest method for administration of intrathecal morphine is thus by using only compounded medication of an analyzed charge or by using commercially available low-volume low-concentration morphine. Unfortunately, errors may occur anywhere in the process and can never be fully excluded. It is vital to remain vigilant for any medication error, which is no different for intrathecal morphine. If this occurs, one may administer an opioid antagonist and monitor the patient on a high-dependency ward for re-occurrence of respiratory depression or sedation.

Alternative methods of analgesia, other than intrathecal morphine and systemic opioids, were presented in the introduction of this thesis, which were epidural

analgesia and the TAP-block. This thesis compared intrathecal morphine to the use of systemic opioids in laparoscopic surgery, but what are the analgesic effects of intrathecal morphine compared to the other two modalities?

Only one randomized study compared intrathecal diamorphine with epidural analgesia and found that epidural analgesia prolonged the length of stay after laparoscopic colorectal surgery, possibly due to a larger amount of administered fluid and a delay in mobilization.[11] Similar results were found in a retrospective analysis.[37] Unfortunately, further studies are lacking. Moreover, it is unlikely that randomized trials will be designed that compare epidural with intrathecal analgesia, since epidural analgesia is being abandoned in current guidelines regarding laparoscopic colorectal surgery, because evidence suggests that less-invasive alternatives are more attractive. It is likely that observational data from "change-of-practice" studies will be the highest level of evidence gathered in the foreseeing future.

Prospective studies comparing intrathecal morphine and a TAP-block are mainly performed in patients undergoing caesarean sections. In this type of surgery, a TAP-block is not as effective for postoperative pain as intrathecal morphine.[38] One randomized controlled trial compared intrathecal hydromorphone with a TAP-block in colorectal surgery and concluded that a TAP-block was not as effective as intrathecal hydromorphone in lowering pain scores and opioid consumption.[39] Such findings were confirmed in observational studies.[40] Furthermore, studies comparing epidural analgesia to TAP-blocks found no major difference.[41-44] In conclusion, the evidence is scarce, but epidural analgesia may prolong length of hospital stay and a TAP-block has inferior analgesic properties when compared to intrathecal morphine in laparoscopic colorectal surgery. A randomized controlled trial comparing intrathecal morphine to a TAP-block is required to confirm or refute the findings of Colibaseanu et al. and should specifically measure pain, opioid consumption and time to fit-for-discharge.[39]

The results from the research in this thesis show that intrathecal morphine is preferred over systemic opioids for laparoscopic colorectal surgery. For other abdominal procedures, intrathecal morphine may be considered, as well. Implementation of this method of analgesia requires to address several pitfalls. Because some effects are dose-dependent, the administered dose should be

precise. Low concentration preservative-free morphine is highly recommended.[35] Other recommendations are prophylactic administration of dexamethasone, ondansetron and droperidol, as mentioned earlier. Routine urinary catheterization for 24 hours prevents urinary retention and long-term bladder dysfunction. The medical and nursing staff should be informed treatment of pruritus and nausea. They also should be informed that late respiratory depression may occur and benzodiazepines or routinely administered opioids should be prohibited at the night after surgery. Furthermore, because non-anesthesiologist may confuse intrathecal analgesia with epidural analgesia, it should be stressed that hypotension and motor block cannot be explained by intrathecal morphine, and other causes should be diagnosed.

Besides the mentioned limitations per study in each chapter, the thesis in general has limitations that need to be considered. Every study was performed in a single hospital in the Netherlands, which limits the generalizability and increases the chances for a Hawthorne effect and an investigator bias, despite blinding measures. Still, the results of our studies are in line with other studies from different locations and general management is in line with common practice. The randomized studies both have a relatively small sample size, even though the sample size calculations were met. These two studies used intravenous morphine as the comparator because it is the least invasive method of analgesia, while perhaps alternative methods of analgesia may be more suitable. Another limitation is that only 300 mcg of intrathecal morphine was administered for both studies, which was the suggested dose by an experts' review. Perhaps different doses may have led to different risk-benefit ratio with different outcomes. This was only investigated in the meta-analysis, which is not a robust method for finding an optimal dose. Additionally, all the studies have been performed in and during clinical practice, which had led to missed inclusions and outcome measurements. Finally, the limited funding did not allow for resource-demanding outcome measurements, such as transcutaneous CO_2 or continuous respiratory rate measurements, extent of mobilization and muscle strength measurements, laparoscopic workspace measurements and certain laboratory measurements.

Further research remains to be performed, especially for procedure-specific indications of intrathecal morphine. First, a randomized trial should investigate if the use of intrathecal morphine reduces the incidence of delirium in proximal

femur fracture surgery. Such a study is initiated (Dutch Trial Register ID: NL9390). Second, the added value of intrathecal morphine should be investigated in other laparoscopic types surgery than laparoscopic colorectal procedures. Third, further studies should confirm our finding of an earlier fit-for-discharge with the use of intrathecal morphine within an Enhanced Recovery Program in laparoscopic colorectal surgery. Fourth, monitoring strategies should be investigated on the ability to detect respiratory depression after less than 500 µg intrathecal morphine. New technological developments such as wearable devices that continuously vital signs, including respiratory rate, may be appropriate monitoring accompanied with a low nursing workload. However, such a study may be difficult to perform, because the low incidence of a clinically relevant respiratory depression leads to a high number of patients. Alternatively, some investigators routinely administer a continuous infusion of naloxone when intrathecal morphine is used, because naloxone antagonizes the respiratory depression with minimal effect on the analgesic properties of intrathecally administered morphine.[34] This is theoretically a sound practice, but clinical studies should compare this strategy with a continuous intravenous placebo. Finally, alternative methods of analgesia should be compared to intrathecal morphine. These alternative methods may not have the side effects of urinary retention and the risk for respiratory depression and may therefore be preferred. Still, analgesic properties, success rate and other side effects should be considered before choosing one method over the other.

With the limitations and the suggestions for further research in mind, I conclude that of all the opioid sparing techniques for abdominal surgery, intrathecal morphine is one of the most reliable techniques with a high success rate. So far, the only other method of blocking somatic and visceral pain is the more invasive epidural analgesia, but this has a lower success rate and less ability to mobilize the patients early than intrathecal morphine. Dosing is important, because not the benefits but the side-effects appear to have a dose dependency, resulting in more side effects at higher doses, but not more benefits. The arbitrarily chosen 300 mcg of morphine in the randomized trials may be the upper limit. Side-effects should definitely be limited, and if done properly, patients are likely to perceive the benefits. It will be intriguing to investigate the effects on delirium after hip fracture surgery, because reducing the incidence of delirium will be truly beneficial for these patients. For now, the use of intrathecal morphine is ready to be adopted more widely in laparoscopic abdominal surgery.

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Summary

Chapter 10

This thesis aimed to investigate the effect of intrathecal morphine on patient related outcome measures in contemporary surgical procedures. We hypothesized that due to the development of less invasive surgical techniques, such as laparoscopic and robotic-assisted surgery, analgesic properties of intrathecal morphine fits the duration and severity of postoperative pain after abdominal surgery.

In 2015, we performed a survey amongst Dutch anesthesiology departments and demonstrated that the most common methods of analgesia for laparoscopic abdominal surgery in The Netherlands were epidural analgesia (55%) and opioids administered by a PCA-pump (21%) (**Chapter 2**). Intrathecal morphine was rarely administered, mostly due to unfamiliarity and fear for side effects such as pruritus and respiratory depression. The interviews were conducted by telephone during the daytime, which could have resulted in rushed answers. Still, with this approach a response rate of 88% was achieved. Another limitation is that only one representative of the department was interviewed, which may not reflect department policy.

As epidural analgesia was associated with a prolonged length of stay after laparoscopic intestinal surgery, we compared two alternatives in a double-blinded, single-center, randomized controlled trial **(Chapter 3**). Included patients underwent laparoscopic colorectal surgery and were managed according an enhanced recovery program. Twenty-seven patients randomized to the intervention arm received 12.5 mg bupivacaine combined with 300 µg of morphine intrathecally. Twenty-nine patients randomized to the control arm received a subcutaneous injection of lidocaine as a sham procedure and an intravenous loading dose of 0.1 mg/kg piritramide. Further analgesic management was similar in both arms and consisted of paracetamol, diclofenac and piritramide per PCA-pump. The study demonstrated that patients who received intrathecal bupivacaine/morphine had a shorter length of stay (median 3 (3–4) vs. 4 (3–5) days; $p = 0.044$), used less systemic opioids in 48 hours (median 15 mg piritramide (4–25) vs. 44 mg piritramide (33–77); $p < 0.001$) and had less pain compared to patients in the control group. However, a per-protocol analysis was performed, thus the results reflect the method of analgesia rather than what one would achieve in clinical practice.

An important development for prostatectomy surgery was the robot-assisted technique. Compared to an open technique, the Robot-Assisted Radical Prostatectomy (RARP) was associated with less surgical trauma and blood loss.

Patients were commonly discharged the day after surgery, indicating a quick functional recovery. Nonetheless, in a local evaluation of postoperative pain in the Maasstad Hospital, around 10 percent of the patients suffered from severe abdominal pain and bladder discomfort on the first postoperative day after a RARP. We performed a double-blinded, single-center, randomized controlled trial to investigate if bupivacaine combined with morphine intrathecally improved the quality of recovery by reducing pain, bladder discomfort and postoperative opioid consumption (**Chapter 4)**. The 76 patients in the intervention arm received the intrathecal mixture of 12.5 mg bupivacaine and 300 µg morphine, the 79 patients in the control group received a subcutaneous injection of lidocaine as a sham procedure and an intravenous loading dose of 0.1 mg/kg morphine. Both groups received similar analgesic management, consisting of paracetamol, diclofenac and a PCA-pump with morphine. This study demonstrated that intrathecal morphine reduced the decline in Quality of Recovery-15 score after surgery (10% (1-8) vs. 13% (5-24); p = 0.019), which was a minor effect. Furthermore, the use of intrathecal morphine reduced pain scores on a Numeric Rating Scale (NRS) (3 (1-6) vs. 5 (3-7); p = 0.001), the incidence of severe pain (2 (2.8%) vs. 13 (18.3%), p=0.002), bladder discomfort (NRS 1 (0-2) vs. 2 (0-5); p = 0.001) and postoperative opioid consumption (2 mg (1-7) vs. 15 mg (12-20); $p < 0.001$). Unfortunately, a limitation of this study was the missing data of the preoperative Quality of Recovery-15 score in 16% of the patients, caused by logistical limitations in clinical practice.

A meta-analysis on randomized controlled trials involving intrathecal hydrophilic opioids for abdominal surgery included 40 studies with 2500 patients and morphine was the used hydrophilic opioid in 37 studies (**Chapter 5**). This meta-analysis demonstrated that the use of intrathecal hydrophilic opioids reduced systemic morphine equivalent consumption with 18.4 mg (95% confidence interval (CI): 22.3-14.4) on the first postoperative day and 25.5 mg (95% CI: 30.2-20.8) over the first two postoperative days. Moreover, pain scores were 0.9 points (95% CI: 1.1-0.7) and 1.2 points (95% CI: 1.6-0.8) lower on a 10-point Numeric Rating Score in rest and during movement on postoperative day 1, respectively. However, pruritus is 4.3 times (95%CI: 2.5-7.5) increased, resulting in an incidence of 32%, and a dose dependent effect was present. No difference in the incidence of sedation or nausea was found. Respiratory depression occurred more often with the use of intrathecal hydrophilic opioids with a risk ratio of 5.5 (95% CI: 2.1-14.2), resulting in an incidence of 2% for the hydrophilic opioid group and 0.5% in

the non-hydrophilic opioid group. However, two studies that used high doses of intrathecal morphine were outliers. When only studies using a dose < 500 µg of intrathecal morphine were included (n=1473 patients), the risk ratio was 1.1 (95% CI: 0.2-8.2), corresponding with incidences of 0.3% in both groups. A limitation of this study was the pooling of different types of laparoscopic surgery. While subgroup analyses were performed, the pooling remains a potential cause of heterogeneity.

One patient category that may benefit particularly from the opioid sparing effects are elderly patients undergoing proximal femur fracture surgery. One of the most predominant complications of such a surgery is delirium, for which pain and opioid consumption are important risk factors. Since the use of intrathecal morphine may decrease these two risk factors, delirium may be decreased by the use of intrathecal morphine. In a retrospective analysis of prospectively kept register, we demonstrated that patients who received intrathecal bupivacaine and morphine suffered from less delirium (5.9% vs 19.7%, p=0.046) compared to patients receiving intrathecal bupivacaine only. This difference remained significant in multivariate analysis (**Chapter 6**). Still, the risk of bias was high due to the retrospective study design.

The meta-analysis **(Chapter 5)** demonstrated a dose dependent effect for the side-effects, making dosing important. Because low concentrations of morphine are not commercially available, a clinician can either dilute the medication him/herself or ask the pharmacy department to manufacture morphine with a low concentration. In an experimental study, we demonstrated that three different methods of manual dilution targeting a concentration of 60 µg/ml resulted in significant higher concentrations. One method diluted 10 mg/ml of morphine in 100 ml of NaCl 0.9% and resulted in a median concentration of 60 µg/ml (59-80) [54-287], from which 3 samples had concentrations over 180 µg/ml. A second method diluted 10 mg/ml morphine in two steps with 9 ml of NaCl 0.9%, which resulted in a median concentration of 76 µg/ml (70-82)[57-93]. A third method diluted 1 mg/ml morphine in one step with 9 ml of NaCl 0.9% and resulted in a median concentration of 69 µg/ml (66-69)[54-88]. As a control, the pharmacy department provided ampoules with a median morphine concentration of 59 µg/ml (59-59)[59-60](**Chapter 7**). Bacterial contamination did not occur more often with manual dilution (1.3% vs. 4.0%, p>.999). Preferably, morphine for intrathecal

injections should be provided by the pharmacy department. One should consider a study-effect when interpreting these results. All participants were aware that medication was diluted for a study, which may have resulted in more precise actions than one would do in clinical practice.

Still, medication errors may even occur when low concentrations of morphine are provided by a pharmacy department, as demonstrated by the case series in **Chapter 8**. This case series described six patients who received a twenty-fold dose of intrathecal morphine, due to an error by an external compounding pharmacy. Four of these patients had an serious adverse event. A systematic review investigated the severity and characteristics of serious adverse events after intrathecal morphine in 63 cases with individual patient data. It was found that respiratory depression and somnolence were the most reported serious adverse events. The onset of symptoms is between 2 and 24 hours after injection. These serious adverse events may occur after any dose of morphine, but only meets the criteria of a life-threatening state in doses >900 µg or when potentiating medication is administered concomitantly. Still, no fatalities were reported and 92% of the cases responded to naloxone if administered. Potentiating medication was used in the two cases that did not respond to naloxone. Other studies found that the incidence of these serious adverse events after intrathecal morphine was below 3.0%, depending on the used definition and dose. The incidence, timing and severity of adverse events after intrathecal morphine were similar to PCA opioids. Therefore the results suggests that applying the same monitoring as used in patients with PCA opioids, administering supplemental nasal oxygen routinely, avoiding doses over 900 µg of intrathecal morphine and concomitant use of potentiating medication might reduce the risk for life-threatening respiratory depression. These recommendations are based on the systematic review of case reports, which inherently holds a potential risk of publication bias.

In conclusion, this thesis demonstrated a beneficial role of intrathecal morphine in a variety of surgical procedures. Because side effects are dose dependent, dosing is important for achieving a beneficial effect and limiting the side effects.

Nederlandstalige samenvatting:

Chapter 11

Het doel van dit proefschrift was het effect van intrathecaal morfine bij hedendaagse chirurgie op patiënt-gerelateerde uitkomsten te onderzoeken. De hypothese was dat intrathecaal morfine een passende methode van pijnbestrijding is bij nieuwe chirurgische technieken, die tot minder ernstige en langdurige postoperatieve pijn leiden.

In 2015 hebben we een enquête uitgevoerd onder Nederlandse anesthesiologie afdelingen. Deze enquête toonde dat epidurale pijnstilling (55%) en PCA-opiaten (21%) de meest gebruikte vormen van pijnstilling waren bij laparoscopische darmchirurgie (**Hoofdstuk 2**). Intrathecaal morfine werd zelden toegepast, hoofdzakelijk vanwege onbekendheid met deze methode en de angst voor bijwerkingen, zoals jeuk en respiratoire depressie. De interviews werd telefonisch en overdag afgenomen, wat zou geleid kunnen hebben tot gehaaste antwoorden. Aan de andere kant, dit leidde wel dat 88% van de anesthesiologie afdelingen de vragen beantwoorde. Een andere beperking is dat per afdeling één anesthesioloog werd geïnterviewd, wat mogelijk niet het beleid van de afdeling zou kunnen zijn.

Omdat epidurale pijnstilling bij laparoscopische darmchirurgie is geassocieerd met een verlengde ligduur, hebben we twee alternatieve vormen van pijnstilling onderzocht in een dubbelblinde, gerandomiseerde studie (**Hoofdstuk 3**). Alle geïncludeerde patiënten werden behandeld volgens een Enhanced Recovery Program omtrent laparoscopische colorectale chirurgie. Zevenentwintig patiënten werden gerandomiseerd voor de interventie groep en kregen 12.5 mg bupivacaïne en 300 µg morfine intrathecaal toegediend. Negenentwintig patiënten werden gerandomiseerd voor de controle groep en een subcutane injectie met lidocaïne in de lumbale regio als schijnprocedure en een intraveneuze oplaaddosering met 0.1 mg/kg piritramide. De rest van de pijnstilling was in beide groepen hetzelfde en bestond uit paracetamol, diclofenac en piritramide middels een PCA-pomp. De patiënten in de interventie groep hadden een kortere ligduur (mediaan 3 dgn (3-4) vs. 4 dgn (3-5), p=0.044), gebruikten minder systemische opiaten gedurende 48 uur (mediaan 15 mg piritramide (4-25) vs. 44 mg piritramide (33-77), $p < 0.001$) en hadden lagere pijnscores. Van belang is dat een per-protocol is uitgevoerd, dus deze resultaten reflecteren meer de methode van pijnstilling dan wat uiteindelijk in de klinische praktijk bereikt zal worden.

De mogelijkheid van de robot-geassisteerde radicale prostatectomieeën (RARP) is een belangrijke ontwikkeling geweest. Een RARP is geassocieerd met minder chirurgisch trauma en bloedverlies in vergelijk met een open techniek. Het

merendeel van de patiënten gaat een dag na de RARP naar huis, wat duidt op een snel functioneel herstel. Toch bleek uit een lokale kwaliteitsevaluatie 10% van de patiënten ernstige pijn te hebben op de eerste dag na een RARP. Daarom hebben we een dubbelblinde gerandomiseerde studie uitgevoerd, zodat onderzocht kon worden of intrathecaal bupivacaïne/morfine de kwaliteit van herstel verbeterde, doordat patiënten minder pijn, minder blaaskrampen en minder opiaatconsumptie hadden (**Hoofstuk 4**). De interventie groep (n=76) kreeg een intrathecale injectie van 12.5 mg bupivacaïne en 300 µg morfine toegediend. De controle groep (n=79) kreeg een schijnprocedure toegediend, bestaande uit subcutaan lidocaïne in de lumbale regio, en een intraveneuze oplaaddosering van 0.1 mg/kg morfine. Beide groepen kregen dezelfde postoperatieve pijnstilling, bestaande uit paracetamol, diclofenac en morfine middels een PCA-pomp. Dit onderzoek toonde dat de daling in Quality-of-Recovery-15 score ten opzichte van de uitgangswaarde minder daalde dan in de controle groep (10% (1-8) vs. 13% (5-24), p=0.019), hoewel dit maar een klein effect was. In de interventie groep waren ook de pijnscores (NRS 3 (1-6) vs. NRS 5 (3-7), p=0.001), de incidentie van ernstige pijn (2 (2.8%) vs. 13 (18.3%), p=0.002), de ernst van blaaskrampen (NRS 1 (0-2) vs. NRS 2 (0-5), p=0.001) en de postoperatieve opiaatconsumptie (2 mg (1-7) vs. 15 mg (12-20), $p < 0.001$) lager. Een beperking van deze studie is dat de preoperatieve Quality-of-Recovery-15 score in 16% van de patiënten mistte, veroorzaakt door logistieke beperkingen in de klinische praktijk.

Vervolgens werd een meta-analyse verricht over gerandomiseerde studies met het gebruik van intrathecale hydrofiele opiaten als pijnstilling bij abdominale chirurgie. Deze meta-analyse bevatte 2500 patiënten vanuit 40 verschillende studies (**Hoofdstuk 5**) en toonde aan dat het gebruik van intrathecale hydrofiele opiaten het systemische morfine-equivalent gebruik verminderde met 18.4 mg (95% BI: 22.3-14.4) in de eerste 24 uur en met 25.5 mg (95% BI: 30.2-20.8) in de eerste 48 uur na abdominale chirurgie. Bovendien waren de pijnscores met 0.9 (95% BI: 1.1-0.7) lager in rust en 1.2 (95% BI: 1.6-0.8) lager tijdens beweging op de dag na de operatie, op een 10-punts NRS-schaal. Patiënten met intrathecale hydrofiele opiaten hadden een 4.3 (95% BI 2.5-7.5) grotere kans op jeuk, wat leidde tot een incidentie van 32% en hier was een dosis-afhankelijk effect gevonden. De incidentie van misselijkheid en sufheid was niet verhoogd. Respiratoire depressie kwam vaker voor bij het gebruik van intrathecale hydrofiele opiaten, met een risico-ratio van 5.5 (95% BI: 2.1-14.2), wat bleek uit een 2% incidentie bij de patiënten

met intrathecale hydrofiele opiaten en 0.5% bij patiënten zonder intrathecale hydrofiele opiaten. Dit verschil bleek echter hoofdzakelijk op twee buiten liggende studies met een hoge dosering te berusten. Als alleen de studies met een dosis van < 500 µg morfine werden geïncludeerd (n=1473) was dit verschil in respiratoire depressie niet meer te vinden (incidentie van 0.3% in beide groepen, risico-ratio van 1.1 (95% BI: 0.2-8.2)). Een beperking van deze studie was dat verschillende typen van abdominale chirurgie werden gepoold. Ondanks subgroep analyses bleef heterogeniteit een potentieel risico op de interpretatie.

Oudere kwetsbaren die geopereerd worden aan een gebroken heup is een categorie die bij uitstek nut kunnen hebben van intrathecaal morfine. Een delier is één van de meest voorkomende complicaties na een dergelijke operatie, hiervoor zijn onder meer pijn en systemische opiaat gebruik belangrijke risicofactoren. Doordat intrathecaal morfine beide risicofactoren verminderd, zou het potentieel ook leiden tot minder delier. Dit is aangetoond in een retrospectieve analyse van een prospectief bijgehouden database, waaruit bleek dat patiënten die spinaal anesthesie met intrathecaal morfine minder delier hadden dan patiënten met alleen spinaal anesthesie (5.9% vs. 19.7%, p=0.046). Dit verschil bleef bestaan na correctie in een multivariate analyse (**Hoofdstuk 6**). Hierbij moeten worden aangetekend dat er een hoog risico op bias in deze studie aanwezig is, onder andere vanwege het retrospectieve karakter.

De meta-analyse in **hoofdstuk 5** toonde een dosis-afhankelijk effect in bijwerkingen, wat het belang van de dosis onderstreept. Dusdanig lage concentraties van morfine zijn niet commercieel verkrijgbaar, waardoor of de lokale apotheek het moet bereiden of de artsen moeten de morfine zelf verdunnen. In een experimentele studie zijn morfine concentraties van drie handmatige verdunningsmethoden vergeleken met apotheek-bereide morfine concentraties (**Hoofdstuk 7**). Hierin werd aangetoond dat handmatige verdunning leidde tot hogere concentraties dan de beoogde 60 µg/ml. Een methode verdunde 10 mg/ml morfine in 100 ml NaCl 0.9% en verkreeg een mediane morfine concentratie van 60 µg/ml (59-80) [54-287], waarbij in drie samples een concentratie boven de 180 µg/ml werd gemeten. Een tweede methode verdunde 10 mg/ml morfine via twee stappen met 9 ml NaCl 0.9% en verkreeg een mediane morfine concentratie van 76 µg/ml (7082)[57-93]. Een derde methode verdunde 1 mg/ml morfine met 9 ml NaCl 0.9% en verkreeg een mediane morfine concentratie van 69 µg/ml (66-69)[54-88]. De ampullen die door de apotheek werden bereid bevatten 59 µg/ml (59-59)[59-

60] morfine. Bacteriële contaminatie van de samples kwam niet meer voor bij handmatige verdunning (1.3% vs. 4.0%, p>.999). Concluderend zou morfine voor intrathecaal gebruik bij voorkeur moeten worden verdund door de apotheek. In dit onderzoek is een studie-effect niet uit te sluiten. De deelnemers waren bewust van dat de medicatie verdund werd voor een studie, wat zou kunnen leiden dat de deelnemers preciezer waren dan in de dagelijkse praktijk.

Zelfs als medicatie door de apotheek wordt bereid kunnen er medicatiefouten optreden, zoals beschreven in de casuïstiek in **Hoofdstuk 8**. Hier werden 6 patiënten beschreven die een twintigvoudige dosis van intrathecaal morfine kregen, doordat er een fout in het productieproces van een externe farmaceut optrad. Vier van deze patiënten had een serieuze bijwerking. Een systematische review onderzocht de ernst en karakteristieken van de serieuze bijwerkingen na intrathecaal morfine in 63 patiënten waarin individuele patiënt data werd beschreven. Hieruit bleek dat somnolentie en respiratoire depressie de meest gerapporteerde serieuze bijwerkingen zijn. Dit treedt op tussen de 2 en 24 uur na injectie. De bijwerkingen kunnen optreden na elke dosis van intrathecaal morfine, maar voldeed alleen aan de criteria van levensbedreigend als er een dosis > 900 µg werd toegediend of als er versterkende medicatie werd toegediend. Desondanks is er niemand aan overleden en reageerde 92% van de patiënten op naloxone, indien het werd toegediend. De twee patiënten die niet reageerden op naloxone hadden versterkende medicatie toegediend gekregen. Andere studies vonden dat de incidentie van serieuze bijwerkingen na intrathecaal morfine onder de 3% ligt, afhankelijk van de gebruikte definitie en dosis. De incidentie, ernst en timing van serieuze bijwerkingen komen daarmee overeen met die van PCA-toegediende opiaten. De review suggereert dat met dezelfde monitoring als bij PCA-opiaten, routinematig toediening van nasale zuurstof, doseringen < 900 µg intrathecaal morfine gebruiken en het vermijden van versterkende medicatie het risico op een levensbedreigende respiratoire depressie sterk wordt gereduceerd. Deze aanbevelingen berusten op een systematische review van patiënt beschrijvingen, wat een inherent risico op publicatie bias heeft.

Concluderend toont dit proefschrift de voordelen van intrathecaal morfine in verschillende vormen van hedendaagse chirurgie. De dosering van morfine is belangrijk om de maximale werking en tegelijkertijd de minimale bijwerkingen te hebben, omdat de bijwerkingen dosis-afhankelijk zijn.

Portfolio, List of Publications, Acknowledgements, Curriculum Vitae

Chapter 12

Portfolio

PhD training	Year
Good Clinical Practice-course	2013
Good Clinical Practice-refresher	2018
Scientific Writing (KNMG)	2011
(Inter)National Presentations	
ISOTT 2014, London	2014
NVA Wetenschapsdag, Amsterdam	2017
Euroanesthesia 2017, Geneva	2017
Nederlandse Vereniging voor Endoscopische Chirurgie-congres, Amsterdam	2018
NVA-dagen, Maastricht	2019
Webinar “Acute/In-hospital pain”, Faculty of Pain Medicine, Royal College of Anaesthetists	2021
Attendence international conferences	
ISOTT London	2014
ASA-conference	2015, 2018
Euroanesthesia	2016-2020
ESICM Lives Physiology, Prague	2020
Teaching	
Generic Instructor Course	2012
Basiskwalificatie Onderwijs (BKO), Erasmus MC	2017
Supervision of (medical) students and residents for research	2019-
Instructor ACLS	2012-2020
Instructor “Reanimatietrainingen AIOS”	2012-2016
Narrative review in A&I	2019
Teacher Scheepvaart en Transport College, Rotterdam	2016-2017
Teacher Care Group Training, Renal, Circulation and Ventilation Practitioners	2020-
Miscellaneous	
Diplomate of the European Society of Anesthesiology (ESA/ESAIC)	2016
European Diploma of Intensive Care (ESICM)	2017
Co-author of the Dutch guideline “Electroconvulsive Therapy”	2019-2021
Examinator for the EDAIC part 2 examination	2020-
Member of the NVA exam-committee	2021-

List of publications, related to this thesis:

1. van Houwelingen EE, Koning MV, Teunissen AJW, Stolker RJ. Ambiguous policies in anesthetic pain management in laparoscopic colonic surgery: A national survey. *Nederlands Tijdschrift voor Anesthesiologie 2016 Sept; 124-128.*
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3. Koning MV, de Vlieger R, Teunissen AJW, Gan M, Ruijgrok EJ, de Graaff JC, Koopman JSHA, Stolker RJ. The effect of intrathecal bupivacaine/morphine on quality of recovery in robot-assisted radical prostatectomy: a randomized controlled trial. *Anaesthesia. 2020 May;75(5):599-608.*
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6. Teunissen AJW, Koning MV, Ruijgrok EJ, Liefers WJ, de Bruijn B, Koopman SA. Measurement of drug concentration and bacterial contamination after diluting morphine for intrathecal administration: an experimental study. Based on: *BMC Anesthesiol. 2020 Sep 25;20(1):244*

List of publications, unrelated to this thesis:

1. Koning MV, Loffeld RJ. Rectal bleeding in patients with haemorrhoids. Coincidental findings in colon and rectum. *Fam Pract* 2010;27:260-2
2. Koning MV, Loffeld RJ. A survey of abnormalities in the colon and rectum in patients with haemorrhoids. *BMC Gastroenterol* 20107;10:74.
3. Nurmohamed SA, Koning MV, Vervloet MG, Groeneveld AB. Delivered dose of continuous venovenous hemofiltration predicts outcome in septic patients with acute kidney injury: a retrospective study. *J Crit Care* 2011;26:213-20
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6. Koning MV, Koning NJ, Koning HM, van Kleef M. Relationship between Sensory Stimulation and Side Effects in Percutaneous Radiofrequency Treatment of the Trigeminal Ganglion. *Pain Pract* 2014;14:581-7.
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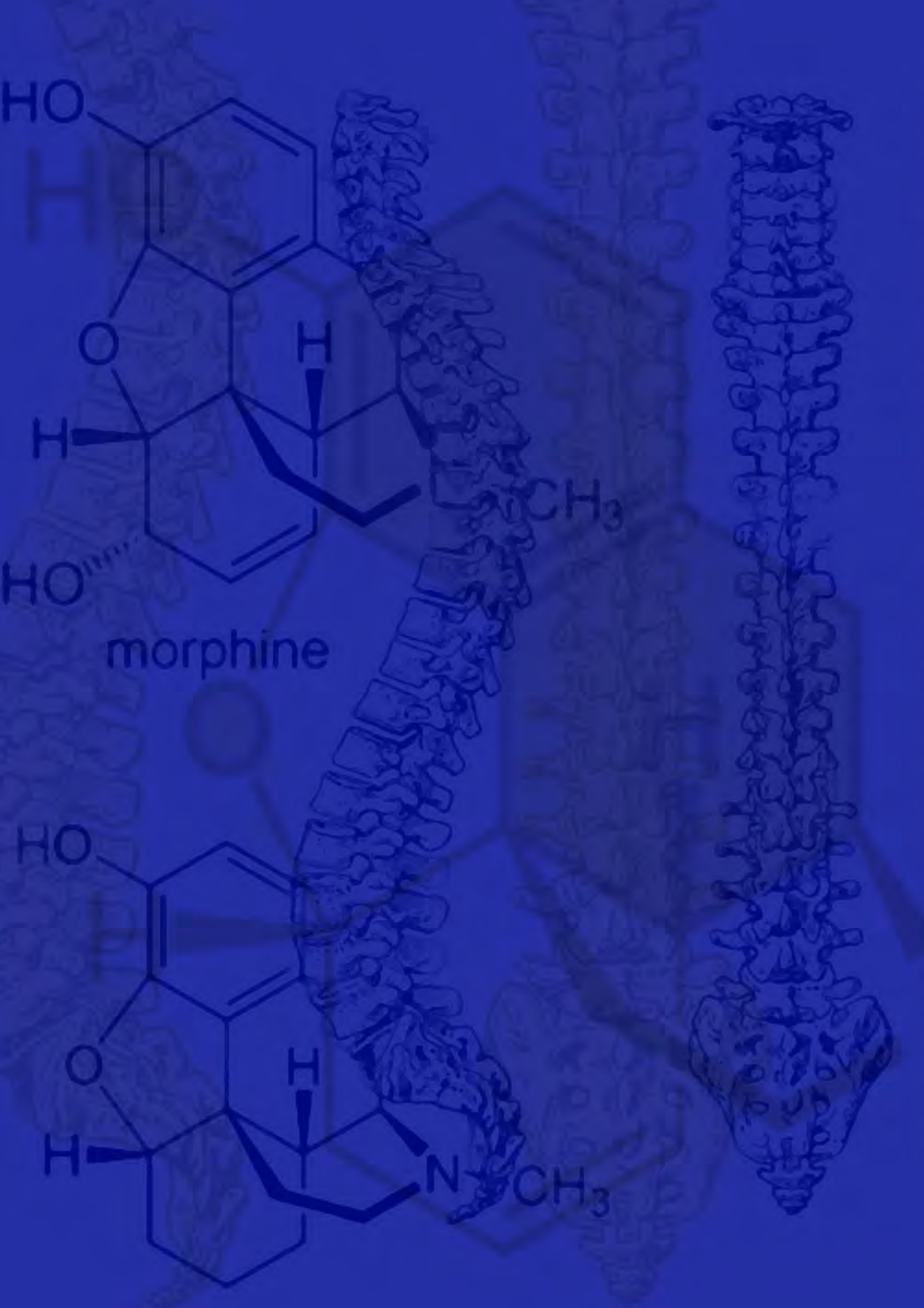
Curriculum Vitae:

Mark Vincent Koning was born on the 28th of April, 1986 in Nieuwegein, The Netherlands. He graduated from the secondary school (VWO, OSG Piter Jelles, Leeuwarden) in 2004. From 2004 to 2010 he studied Medicine at the Free University of Amsterdam. He worked as ANIOS at the cardiac Intensive Care at the Isala Klinieken, Zwolle until starting with his residency training in Anesthesiology at the Erasmus Medical Center, Rotterdam (prof. dr. R.J. Stolker). His residency included a year of training at the Maasstad Hospital, Rotterdam, under supervision of drs. A.J.W. Teunissen. The research of this thesis started in this hospital. After becoming an anesthesiologist in 2016, he further specialized in Intensive Care Medicine at the Erasmus Medical Center, Rotterdam (prof. D.A.M.P.J. Gommers) in 2017. During those trainings, he passed the European exams of the European Society Anesthesiology (EDAIC) and the European Society of Intensive Care Medicine (EDIC). He also obtained a certification in teaching (Basis Kwalificatie Onderwijs, Erasmus Medical Center, Rotterdam) in 2017.

After working in the Sint Antonius Hospital, Nieuwegein and Haaglanden Medical Center, The Hague as an anesthesiologist, he now works as an anesthesiologist and intensivist in the Rijnstate Hospital, Arnhem since 2018.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