The use of Sedation Analgesia during the Implantation of a Neurostimulator: Dexmedetomidine versus Propofol

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Het gebruik van sedatie analgesie tijdens de implantatie van een neurostimulator: dexmedetomidine versus propofol

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Voor mijn lieve ouders

1

Introduction and outline of the thesis

Dexmedetomidine

In 1999, dexmedetomidine was approved by the US Food and Drug Administration (FDA) for short-term sedation analgesia for less than 24 hours in the intensive care unit (ICU). In 2008, the FDA approved its use during procedural sedation analgesia. The European Medicines Agency (EMA) approved dexmedetomidine in 2011 for use in the ICU; and recently, in 2018, approval was obtained for the use of dexmedetomidine during procedural sedation. Dexmedetomidine is a highly selective, long-lasting presynaptic alpha-2 receptor agonist, with sedative, anxiolytic, and analgesic characteristics (1, 2). Dexmedetomidine sedation induces a state of consciousness that mimics superficial natural sleep in which the patient is easily arousable, no decline in cognitive skills or cooperation occurs and in which the patient is quickly reversible to the sedated state (3, 4). Because it acts primarily at the locus coeruleus in the pons, dexmedetomidine will almost never lead to respiratory depression. It is associated with a low incidence of delirium (5). Furthermore, the use of opioids is limited because of the analgesic properties of dexmedetomidine. Side effects including hypotension and bradycardia have been reported (6-8). During awake procedures (e.g., awake craniotomy and deep brain stimulation) the sedative agent dexmedetomidine has shown promising results (9-11).

Surgical placement of spinal cord neurostimulator leads

The implantation of a spinal cord neurostimulator is part of this spectrum of "awake procedures." Neurostimulation is a direct clinical application of the gate control theory (12). The presumed mechanism of action is that electrical stimulation of the large ascending fibers in the dorsal horn (Ab-fibers) results in inhibition of pain impulses, entering from the dorsal root (Aδ and C-fibers), although supraspinal mechanisms and peripheral GABA-related mechanisms seem to play a role as well (12). The classical primary targets for neurostimulation are the dorsal column and the (intraspinal) nerve roots. It is an acknowledged method of treatment for chronic neuropathic pain. Its efficacy in pain treatment has been demonstrated with failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and painful diabetic polyneuropathy. For these indications, there is a moderate quality of evidence for clinically relevant pain relief and improvement in functionality and quality of life (13). There is a general consensus that neurostimulation be used only when other conventional therapies for chronic neuropathic pain have failed.

Since the mid-90s, neurostimulation has become a well-established practice in the Netherlands, with over 12,000 registered neurostimulation procedures performed between 2010 and 2017 (14). Today, different methods of neurostimulation are available, including spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRG). In the last year, new studies have been published on the effectiveness and proper use of

different stimulation frequencies and stimulation patterns, such as variable frequency and duration of burst stimulation (15). Neurostimulation is considered to be a safe and cost-effective therapy (16, 17).

Awake versus anatomical

There are some differences between the European and American neurostimulation procedures. The differences in methods of lead placement and the associated anesthesia technique are relevant to this thesis. In Europe, the majority of patients undergoing the implantation of a neurostimulator receive sedation analgesia to provide a comfortable situation in which they are able to give reliable feedback. Patient feedback is required during electrical mapping for the assessment of the degree of paresthesia coverage of the painful area. In the United States, the neurostimulators are also implanted under general anesthesia, taking an anatomical approach. In a study regarding the implantation of a neurostimulator, the anatomical approach (without patient feedback) was compared with the awake approach (with patient feedback) under propofol sedation. This study found a preference for the anatomical approach, due to less frequent device failures. In addition, it reports difficulties during the awake approach. Patients proved to be disoriented and agitated, which interfered with reliable communication and control of difficult-to-manage pain during the wake-up (18). The question remains as to whether these results are due to the anatomical procedure or a consequence of the side effects of the sedation. Likewise, cognition was the primary endpoint in a trial of dexmedetomidine and propofol, applying cooperative sedation. The result of this trial is clear: dexmedetomidine allowed for a better cognitive function compared to propofol (19). This might indicate a more difficult production of arousable sedation using propofol compared to dexmedetomidine sedation. When taking the anatomical approach, a tailormade arousable sedation is evidently unnecessarily time-consuming.

Regarding the anatomical approach, effectivity is only proven for the implantation of 10-kHz high-frequency SCS (20). For neurostimulators using other frequencies, the effectivity of the anatomical approach remains a matter of debate. Therefore, the approach involving patient feedback remains the standard method of treatment. During the procedure, the patient must cooperate in the provision of feedback; preferably they must be alert, comfortable, and in as little pain as possible. This can be difficult when the patient is lying in a prone position and the procedure lasts for a longer period of time. Furthermore, there are limited options for local anesthesia because, in order to guarantee the required feedback, the deeper structures cannot be anesthetized. This procedure is performed under procedural sedation analgesia in combination with local anesthesia to accomplish the aforementioned dual goal. The level of sedation during the implantation of a neurostimulator is equal to the level of moderate sedation analgesia, see Table 1 (21).

Table 1. Continuum of depth of sedation, following the report of ASA, 2018 (6)

	Minimal sedation (anxyiolysis)	Moderate sedation analgesia (conscious sedation)	Deep sedation/ analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

**Reflex withdrawal from a painful stimulus is NOT considered a purposeful response*

Propofol

The standard sedation analgesia regimen applied in the current neurostimulation practice in the Netherlands is a combination of propofol and a short-acting opioid called “remifentanil.” Propofol is a sedative-hypnotic agent, acting as an agonist on the GABA-A receptors. This action inhibits the acetylcholine release in the hippocampus and prefrontal cortex and mediates the sedative effects of propofol. Propofol is known for its rapid onset, short duration of action, and relatively low cost. However, possible side effects include patient discomfort and confusion (6). Consequently, patients treated with this agent could have difficulty with adequately reporting the degree of paresthesia coverage during the test stimulation.

Aim

Based on the information given above on the profiles and from the existing literature on the agents propofol (acting on the GABA receptors, which is well-known, widely used, and low-cost) and dexmedetomidine (acting on the alfa-2 receptors, recently approved for sedation analgesia, leaving the patient easily arousable, allowing quick return to the sedated state), this thesis is based on the information given above and intended to answer the following questions:

1. What is documented in the literature regarding the use of dexmedetomidine regarding pain level, patient satisfaction, operator satisfaction, procedure duration, recovery time, and hemodynamic and respiratory characteristics during small diagnostic and therapeutic procedures in adults and in children?
2. What kind of sedation analgesia do Dutch pain specialists use during the implantation of a neurostimulator, and what is their knowledge of and experience with dexmedetomidine?
3. Is dexmedetomidine feasible as a sedative agent during a neurostimulation procedure?

4. Are there differences in patient satisfaction and/or patient safety for the standard sedative agent (propofol) and dexmedetomidine during the implantation of a neurostimulator?
5. What is the financial impact of the use of dexmedetomidine as a sedative agent during a neurostimulation procedure, compared to that of propofol?
6. Do the long-term effects of using dexmedetomidine or propofol during a neurostimulation implantation procedure differ?

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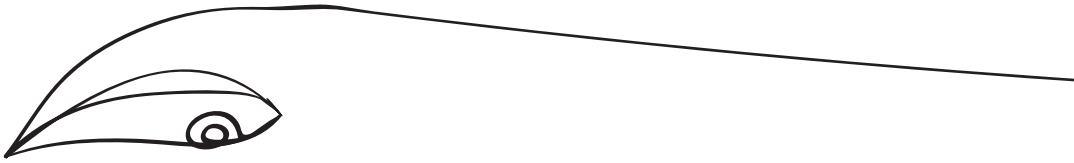
II

Sedation analgesia in small diagnostic and therapeutic procedures



Chapter I

Efficacy of dexmedetomidine as a sole sedative agent in small diagnostic and therapeutic procedures: a systematic review

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ABSTRACT

Dexmedetomidine is an upcoming agent with sedative, anxiolytic and analgesic properties. This review summarizes empirical evidence for the efficacy of dexmedetomidine as a sole sedative agent, and its effectiveness for small diagnostic and therapeutic procedures, in comparison with other frequently used sedatives. All randomized controlled trials on the effect of dexmedetomidine were reviewed. Pain level, patient satisfaction, operator satisfaction, procedure duration, recovery time, and hemodynamic and respiratory characteristics were examined. A total of 1993 patients (1,621 adults; 372 children) from 35 studies were included. In the adult studies, dexmedetomidine yielded significantly lower pain levels compared to the other sedatives (in 31.3% of the included studies) and significantly more patient satisfaction (68.2%). In studies on children, more favorable results concerning respiratory safety and the level of adequate sedation were found compared to the control sedatives. Implications for future studies are discussed.

INTRODUCTION

The level of sedation can be divided into minimal, conscious, deep, and general anesthesia (1). A sedative decreases the level of consciousness, allows a patient to sustain a painful procedure (whether or not in combination with a local anesthetic), and minimizes discomfort and memory of the procedure. Minimal-to-moderate sedation is generally sufficient to maintain spontaneous respiration and airway protective reflexes (2,3).

Therefore, for many small diagnostic and therapeutic procedures (ranging from dental to gastrointestinal procedures) a sedative in combination with a local anesthetic is often preferred over general anesthesia.

An increasingly used sedative is dexmedetomidine, a highly selective presynaptic alpha-2-receptor agonist with sedative, anxiolytic and analgesic properties. Use of dexmedetomidine does not lead to respiratory depression, or to a decline in cognitive skills or patient cooperation. This is because dexmedetomidine acts on the alpha-2 receptors in the locus coeruleus, in contrast to other sedatives (e.g. midazolam and propofol) which act on GABA receptors/cerebral cortex. Possible side effects include hypotension and bradycardia (4,5).

In 1999 dexmedetomidine was approved by the Food and Drug Administration (FDA) for use as a short-term medication (within 24 hours) for analgesia and sedation in mechanically ventilated patients in the intensive care unit. Then, in 2008, the FDA approved a new indication for nonintubated patients requiring sedation before and/or during small diagnostic and therapeutic procedures. During some small procedures, because the patient may have to cooperate, sedation need only be moderate. The procedures mentioned in this review are small diagnostic and therapeutic procedures performed under conscious sedation and therefore comparable with minimal invasive pain treatment procedures like the implantation of a neuromodulation system. During these kind of procedures an equilibrium between patient cooperation and patient comfort is required for an optimal outcome. Dexmedetomidine, whether or not in combination with a local anesthetic, can induce this required level of sedation (minimal/conscious) (6). Several randomized controlled trials (RCTs) have investigated the use of dexmedetomidine as a sole sedative agent during small procedures (7,8).

The aim of the present study is to systematically review the evidence for the efficacy of dexmedetomidine in both adults and children during small diagnostic and therapeutic procedures, compared with other commonly used sedatives.

MATERIALS AND METHODS

Search strategy

A systematic search was made in Embase, Medline, Web of Science, Scopus, Cochrane, PubMed publisher and Google Scholar using a predefined strategy (see Appendix 1).

Selection criteria

Only RCTs were eligible for inclusion in this review. Effectiveness in terms of pain level and patient satisfaction were the primary outcomes. Secondary outcomes were operator satisfaction, duration of procedure, recovery time, and hemodynamic and respiratory characteristics. Excluded were trials with designs other than a RCT, animal trials, studies not using dexmedetomidine as the sole sedative pre-, peri- and postoperatively, use in an intensive care unit, use during relatively extensive procedures (requiring general anesthesia), and the use of general anesthesia during short procedures. Articles not published in English were also excluded. Records were retrieved from the inception of each scientific database until end March 2014 (Figure 1).

Publication retrieval

All retrieved abstracts were independently screened for eligibility by two reviewers (IE and FtB). For each eligible abstract a full copy of the publication was reviewed. All reasons for excluding an article were noted and any disagreement was resolved by discussion between the reviewers until consensus was reached. If further information was required about the trial, the first author of the publication was contacted. The references of the included publications were also screened for additional eligible publications.

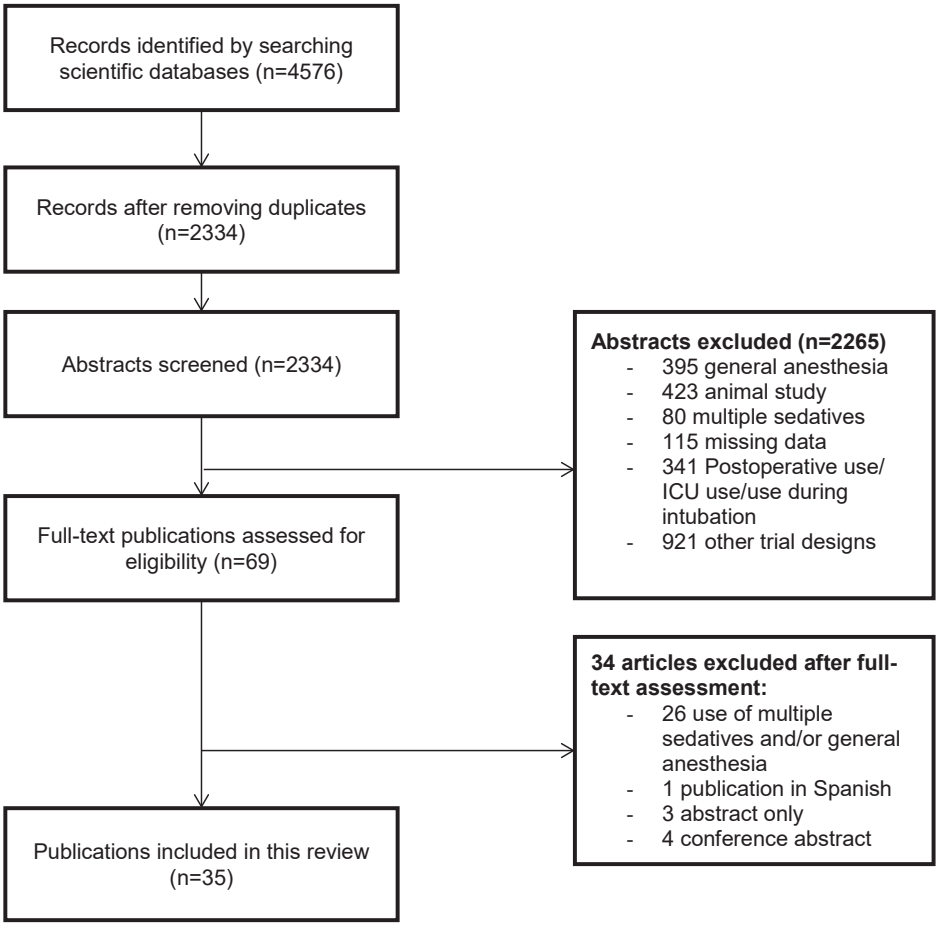

Figure 1. Flowchart showing the process of article selection.

RESULTS

Number of studies

After removing duplicate studies, the search yielded 2,334 potentially relevant articles. Of these, 2,265 articles were excluded because (based on title and abstract) they did not meet the inclusion criteria. Of the remaining 69 articles, the full text was assessed for eligibility and 35 studies were finally selected for inclusion: Table S1 to S5 present details of studies in adults and Table S6 of studies in children. A condensed representation of the study results is added.

Study characteristics

Of the 35 included articles all but four reported on 2-arm studies; the remaining four reported on 3-arm studies. In total, 31 trials compared intravenous (IV) dexmedetomidine with an IV control; one trial compared IV dexmedetomidine with intranasal (IN) dexmedetomidine; another trial compared IV dexmedetomidine with intramuscular (IM) dexmedetomidine; and one trial compared IM use of dexmedetomidine with an IM control (Tables S1-S6).

Of the 35 trials, 30 assessed adults and five assessed children. In total, 1,993 patients were investigated (1,621 adults, 372 children). Regarding geographic location, 23 trials were conducted in nine different Asian countries, nine were conducted in Egypt, and one trial each was conducted in the USA, Brazil and Poland.

Use of Dexmedetomidine in Adults

Dexmedetomidine Vs. Placebo

In 7 trials dexmedetomidine was compared to a placebo (Table S1). Only one trial showed a significant difference in pain level between the groups, that is a lower mean pain level in the dexmedetomidine group (7). Patient satisfaction was assessed in 3 trials using a Visual Analogue Scale (VAS) score (9,10) or a Likert-type verbal rating score (8); in two of these trials a significantly higher level of patient satisfaction was observed in the dexmedetomidine group (8,9). In two of three studies, operator satisfaction was significantly higher in the dexmedetomidine group (8,9); no significant difference in procedure duration was found in the four trials assessing this parameter (9,11,12). In five of six trials, a significantly lower level of mean arterial pressure (MAP) and heart rate (HR) was found in the dexmedetomidine group (8,10,12-14). Peripheral oxygen saturation (SpO_2) was significantly decreased in one of four trials assessing this parameter (12).

Dexmedetomidine Vs. Propofol

Dexmedetomidine was compared to propofol in nine trials (Table S2). In three trials, there was a significantly lower level of pain in the dexmedetomidine group, measured with a VAS score (2,15,16). Patient satisfaction was assessed in seven trials using a VAS score (score from 0-10) (15-17), a Likert-like verbal rating scale (2,8,18) or the IOWA satisfaction with anesthesia scale (ISAS)(19). Of these seven trials, five showed a significantly higher level of patient satisfaction with dexmedetomidine compared to the propofol group (2,15,16,18,19). In only one of two trials operator satisfaction with propofol showed a significantly lower level than the dexmedetomidine group (8). No significant difference in procedure duration was found in the seven trials assessing this parameter (2,16-21). For recovery time, the Aldrete score was used; only one of four tri-

als showed a significantly shorter recovery time in the dexmedetomidine group (16). Muller et al. showed a significantly prolonged recovery time, measured as a higher level of sedation in the recovery room, for the dexmedetomidine group (21). Of the nine trials that measured MAP, five showed a significantly lower (15,18-21) and two a significantly higher MAP (8, 16) in the dexmedetomidine group. In seven of nine trials, a significantly lower HR was found in the dexmedetomidine group(8,15-18,20,21). Finally, four of nine trials showed a significantly higher level of SpO_2 during dexmedetomidine infusion (2,15,17,18).

Dexmedetomidine Vs. Midazolam

Dexmedetomidine was compared to midazolam in 11 trials (Table S3). Pain level was measured using a VAS score: one of four trials showed a significantly higher level of pain in midazolam group (measured by amount of rescue medication based on VAS score) (22) and one of four trials showed a significantly lower level of pain in the dexmedetomidine group (23). Four of eight trials assessing patient satisfaction (using different scoring measures) showed a significantly higher level with dexmedetomidine (23-26) and one trial showed a significantly lower level with dexmedetomidine(22). Two of six trials showed a significantly higher level of operator satisfaction in the dexmedetomidine group, measured with a NRS and a VAS (23-27). Only one of 10 trials showed a significantly prolonged duration of procedure with dexmedetomidine (28). The Aldrete score was assessed in three trials; in only two trials, a significantly prolonged recovery time was found in the dexmedetomidine group (22,26). Two trials used the *Modified Post Anesthesia Discharge Scoring System* (MPADSS) score for recovery time, and both trials showed a significantly prolonged recovery time in the dexmedetomidine group (28,29). In nine of 11 trials, in the dexmedetomidine group a significantly lower MAP (12,23-26,28-31) was seen and in 10 of 11 trials a significantly lower HR was seen (12,22-26,28-31). Two of three trials showed a significantly lower SpO_2 in the dexmedetomidine group (22,31) and only 1 of 3 trials showed a significantly higher level of SpO_2 in the dexmedetomidine (30).

Dexmedetomidine Vs. Opioids

Dexmedetomidine was compared to an opioid in five trials (Table S4). Only one of three trials showed a significantly lower level of pain (measured with a VAS score) in the dexmedetomidine group (7). Patient satisfaction was significantly higher with dexmedetomidine in three of four trials assessing this parameter (7,32,33). No significant differences in operator satisfaction were found. Five trials measured procedure duration: one trial showed a significantly shorter duration (7) and one showed a significantly prolonged duration with dexmedetomidine (28). Only one of two trials assessing recovery time showed a significantly prolonged time in the dexmedetomidine group (28). MAP

was significantly lower in 4 of 5 trials (7,28,33,34) and HR was significantly lower in the dexmedetomidine group in all trials (7,28, 32-34). In 2 of 5 trials, a significant increase in SpO_2 was shown in the dexmedetomidine group (7,32).

Intravenous Vs. Intranasal Dexmedetomidine

Two trials analyzed differences between intravenous (IV) and intranasal (IN) dexmedetomidine (Table S5). Zhang et al. compared IV and IN dexmedetomidine and found a significantly lower MAP and HR in the IV group (13). Nooh et al. compared IN dexmedetomidine with IN placebo and found no significant difference in pain level, but a significantly lower level of MAP and HR in the IN dexmedetomidine group (35).

Use of Dexmedetomidine in Children

Five trials investigated the effectiveness of dexmedetomidine in children (Table S6), but not in terms of pain level and patient satisfaction. All trials used the Ramsey sedation score (range 4-6) to measure level of sedation (Table S7). Dexmedetomidine compared with propofol showed a significantly prolonged recovery time, which was defined as the time from discontinuation of drug intake until achievement of a Steward Recovery Score of 6. HR was significant lower in the dexmedetomidine group (6). Tammam and Wahba compared IV and IM dexmedetomidine (37). In the IV dexmedetomidine group significantly more rescue medication was required and a lower operator satisfaction score (VAS score) was found. The Aldrete score was used for discharge time and showed a significantly shorter time to discharge in the IV group. In the IM dexmedetomidine group a significantly later onset of sedation and a lower sedation level were found. A significantly lower MAP and HR was seen in the IV group. Tammam et al. compared IM dexmedetomidine with IM ketamine and IM dexmedetomidine plus ketamine (DK) (36). The DK group showed significantly less sedation failure and the need for rescue medication was significantly lower. Al Taher et al. also compared dexmedetomidine with midazolam plus propofol and showed a significantly faster recovery time post procedure (measured as the time from stoppage of drug infusion until reaching a Ramsey score 2), and a significantly higher MAP in the dexmedetomidine group (38). Koroglu et al. compared dexmedetomidine with midazolam and showed significantly less use of rescue medication and a higher rate of adequate sedation for the dexmedetomidine group, without any significant differences in MAP, HR and SpO_2 in both arms (39). All trials in children showed respiratory safety during dexmedetomidine infusion compared to the control group (6, 36-39).

DISCUSSION

Adults

The evidence on the use of dexmedetomidine in small diagnostic and therapeutic procedures indicates that it is associated with a significantly lower pain level compared with other commonly used sedative agents. In the 16 trials measuring pain level, five (31.3%) showed a significantly lower level and one a significantly higher level of pain with dexmedetomidine. Similarly, of the 22 trials measuring patient satisfaction 16 showed a significant difference; of these, 15 trials (68.2%) reported a significantly higher level of patient satisfaction with dexmedetomidine.

Of all assessments, in seven trials a significantly higher saturation level was shown (23.3%) with dexmedetomidine. Additionally, of the 13 trials measuring recovery time, five showed a significantly prolonged recovery time (38.5%) and one showed a significantly reduced recovery time with dexmedetomidine. However, no differences in procedure duration were found.

Variability in procedures

Although all included studies are RCTs they are methodologically heterogeneous, differing in the control sedative used, whether or not they were blinded, in the outcome parameters, and in their operationalization.

The studies were also clinically diverse regarding the study populations, ways of administration, the local anesthetic used, and ways of measuring the administration of the drugs. Although the results are relatively consistent across studies, we also evaluated whether this methodological and clinical heterogeneity might explain some of the variability in the results.

Pain

Sixteen trials measured pain level directly using a pain score, and nine used the amount of rescue medication as an indirect pain measurement. In almost all trials, the findings of the indirect measurement ran parallel with the direct measurement. We have no explanation for the differences in pain relief in terms of methodological inconsistency, except perhaps in the propofol group, i.e. the non-significant result found in one of the four trials might be due to the relatively smaller sample size. Moreover, the investigators in this later trial used a different operationalization of the pain measurement (17).

A fixed dose of dexmedetomidine and/or a highly invasive procedure can lead to lack of analgesic management with dexmedetomidine and, therefore, a higher need for rescue

medication. This may explain some of the inconsistency in the present results. In one trial a high dose of rescue medication probably caused a respiratory depressant effect during dexmedetomidine infusion; however, this result is not consistent with other reports (22).

Satisfaction

Of the 22 trials measuring patient satisfaction, 16 showed a significant difference and, of these, 15 (68.2%) showed a significantly higher level of patient satisfaction. However, Zeyneloglu et al. showed a significantly lower level of patient satisfaction: this was probably due to the fixed dose of dexmedetomidine used for a painful procedure (outpatient shock wave lithotripsy) leading to higher pain levels and, moreover, the control group received midazolam and additional fentanyl (22).

Four of 12 trials measuring operator satisfaction showed a significantly higher level of operator satisfaction (33.3%) with dexmedetomidine.

Dose and route of administration

Initial loading doses of IV dexmedetomidine ranged from 0.5 to 4.0 mcg/kg for 10 minutes, whereas 1.0 mcg/kg for 10 minutes is the commonly used dose (in 20 of the trials, i.e. 57%); most trials also included a maintenance dose of dexmedetomidine infusion with rates ranging from 0.1 to 2.0 mcg/kg/hour, whereas doses of 0.1-0.5 mcg/kg/h are commonly used until the end of the procedure.

Zhang et al. compared IV and IN dexmedetomidine. The advantages of IN administration described are safety and ease of administration, noninvasiveness, possibility of self-medication, and tolerance, especially in patients with nausea and vomiting. However, results show a lower bioavailability and a prolonged time till maximal sedative effect is reached (13).

We found no reports on excessive sedation: The dexmedetomidine dose can easily be changed and relatively large amounts of dexmedetomidine can be used (although may not be necessary to achieve the intended result). Although dexmedetomidine contains analgesic features, some trials used an additional local anesthetic to support pain management. In 27 trials (77.1%) a local anesthetic was used, i.e. mostly lidocaine, which was used in 16 studies (66.7%). Lidocaine was used in variety of combinations, e.g. with ephedrine (26,29,32) or with cocaine (31).

Recovery time

Of the 13 trials reporting recovery time, five showed a significantly prolonged recovery time; this might be due to the relatively long half-life (± 2 hours) of dexmedetomidine (40). The recovery time is reduced if the infusion is stopped at an earlier moment during the procedure.

Earlier investigations, reported in the summary of product characteristics (SPC) of dexmedetomidine, showed that its adverse effects can include hypertension, hypotension and bradycardia (2). In almost all trials included in the present review, at least one of these adverse effects was reported but had no clinically relevant outcome in any of the patients. Three trials reported a significantly lower level of SpO2 during dexmedetomidine infusion compared to controls: the first trial found a minimum of 95.7% (20); in the second trial 20% of the patients in the dexmedetomidine group had a saturation level ≤ 90% (31); and the third trial showed lower mean oxygen saturation values in the dexmedetomidine group (22). This latter finding is probably attributable to the higher frequency of rescue analgesic used in the dexmedetomidine group.

Children

This review indicates that, compared to other sedatives used for children, dexmedetomidine as a sole sedative agent (whether or not in combination with a local anesthetic) is effective for small diagnostic and therapeutic procedures. The dexmedetomidine group showed better respiratory safety compared to propofol (6). Operator satisfaction was significantly lower for IV dexmedetomidine compared to IM dexmedetomidine (36,37). A decrease in HR was found in 60% of the assessments. The adequacy of sedation with dexmedetomidine is higher compared to midazolam (39). In addition this sedative showed a shorter time till recovery (38). Tammam and Wahba reported a preference for IM over IV use of dexmedetomidine on the basis of a number of relevant outcome parameters (37).

The studies were clinically diverse regarding the study participants, ways of administration, and use of local anesthetic; also, the age of the children ranged from 1-14 years. Although age may have influenced the outcomes, no definite conclusions can be drawn about this.

Although all studies were RCTs, they were methodologically heterogeneous; they differed in control sedative used, outcome parameters and their operationalization. Due to this diversity and the relatively small number of trials in children, we are unable to draw firm conclusions about the efficacy of dexmedetomidine. Nevertheless, the pooled data give a relatively favorable impression of the use of dexmedetomidine in children.

Sedation

A higher sedation level (compared with adults) in terms of the Ramsey score was found: range 4 to 6. This implies that children are more heavily sedated and are less able to clearly communicate their feelings, satisfaction and/or severity of pain; this is probably why the pain level is not measured in children. To assess efficacy, these trials included measurement of recovery time, operator satisfaction, level of adequate sedation, need for rescue medication, duration of procedure, and hemodynamic and respiratory values. Based on the higher level of sedation in children, a longer recovery time might be expected; however, Taher et al. reported a shorter time to recovery in the dexmedetomidine group (38). Furthermore, in one trial the sedation level was more adequate in terms of the need for rescue medication in the dexmedetomidine group than in the control group (midazolam) (39).

Tammam et al. compared IM dexmedetomidine with IM ketamine with a IM combination of dexmedetomidine and ketamine (DK) (36). Remarkably, DK was the preferred choice due to fewer adverse events. The disadvantages of dexmedetomidine and ketamine as sole sedatives can be counterbalanced when used in combination; dexmedetomidine has an alpha-2 agonist effect on the sympathetic ganglia, and it produces dose-dependent decreases in blood pressure and heart rate. Dexmedetomidine and ketamine have opposite hemodynamic side effects of each other where dexmedetomidine as counterbalance provides to the sympathetic stimulation and dexmedetomidine attenuates the hyperadrenergic state associated with ketamine. Use of dexmedetomidine as premedication was noted to be effective in attenuating the cardio-stimulatory and post-anesthetic delirium effects of ketamine (36). However, the optimal regimen for the combination of dexmedetomidine and ketamine in pediatric sedation still needs to be established (41).

Route of administration

An advantage of dexmedetomidine for children is the possibility of different routes of administration; IV, IM or IN. Tammam and Wahba. compared IV dexmedetomidine with IM dexmedetomidine and showed that operator satisfaction was higher and need for rescue medication lower in the IM dexmedetomidine group. This might be due to the requirement for supplemental sedation for successful sedation with IV dexmedetomidine. In addition IM dexmedetomidine may allow a depot of the investigational drug to be released gradually into the systematic circulation over a certain period of time. This reduces the most serious risks and complications, and frequent titration for sedation is not necessary (37). IN dexmedetomidine use seems to be a good alternative because no injection is necessary.

Table 1. Condensed Representation of the Results (For Detailed View See Appendix 2). (a) Effect on Pain. (b) Effect on Rescue Medication. (c) Effect on Patient Satisfaction. (d) Effect on Operator Satisfaction. (e) Effect on Duration of Procedure. (f) Effect on MAP. (g) Effect on SBP. (h) Effect on DBP. (i) Effect on HR. (j) Effect on SpO2. (k) Effect on Recovery Time

Study design	Percentage of trials*	Procedure	Route of administration	Results
(a)				
Dexmedetomidine versus placebo	1 of 2 (50%)	Cataract surgery	IV	In favor of dex
Dexmedetomidine versus propofol	3 of 4 (75%)	CAUP	IV	In favor of dex
		Vitreoretinal surgery	IV	In favor of dex
		Septoplasty	IV	In favor of dex
Dexmedetomidine versus midazolam	1 of 5 (25%)	Outpatient shockwave lithotripsy	IV	In favor of midazolam
Dexmedetomidine versus opioid	1 of 4 (20%)	Awake fibreoptic nasotracheal intubation	IV	In favor of dex
Intranasal dexmedetomidine	0 of 1 (0%)			
(b)				
Dexmedetomidine versus placebo	0 of 2 (0%)			
Dexmedetomidine versus propofol	1 of 2 (50%)	ERCP	IV	In favor of propofol
Dexmedetomidine versus midazolam	2 of 3 (66,6%)	Tympanoplasty	IV	In favor of dex
		Outpatient shockwave lithotripsy	IV	In favor of midazolam
Dexmedetomidine versus opioid	0 of 1 (0%)			
Intranasal dexmedetomidine	0 of 1 (0%)			
(c)				
Dexmedetomidine versus placebo	2 of 3 (66,6%)	LASIK	IV	In favor of dex
		Cataract surgery	IV	In favor of dex
Dexmedetomidine versus propofol	5 of 7 (71,4%)	CAUP	IV	In favor of dex
		Anterior segment opthlamic surgery	IV	In favor of dex
		Cataract surgery	IV	In favor of dex
		Vitreoretinal surgery	IV	In favor of dex
		Septoplasty	IV	In favor of dex

Table 1. Condensed Representation of the Results (For Detailed View See Appendix 2). (a) Effect on Pain. (b) Effect on Rescue Medication. (c) Effect on Patient Satisfaction. (d) Effect on Operator Satisfaction. (e) Effect on Duration of Procedure. (f) Effect on MAP. (g) Effect on SBP. (h) Effect on DBP. (i) Effect on HR. (j) Effect on SpO2. (k) Effect on Recovery Time (*continued*)

Study design	Percentage of trials*	Procedure	Route of administration	Results
Dexmedetomidine versus midazolam	5 of 8 (62,5%)	Tympanoplasty	IV	In favor of dex
		Dental surgery	IV	In favor of dex
		Outpatient shockwave lithotripsy	IV	In favor of midazolam
		Third molar surgery	IV	In favor of dex
		Cataract surgery	IV	In favor of dex
Dexmedetomidine versus opioid	3 of 4 (75%)	Awake fibreoptic nasotracheal intubation	IV	In favor of dex
		Awake fibreoptic nasotracheal intubation	IV	In favor of dex
		Awake fibreoptic nasal intubation	IV	In favor of dex
Intranasal dexmedetomidine	0 of 0 (0%)			
(d)				
Dexmedetomidine versus placebo	2 of 3 (66,6%)	LASIK	IV	In favor of dex
		Cataract surgery		In favor of dex
Dexmedetomidine versus propofol	1 of 2 (50%)	LASIK	IV	In favor of dex
Dexmedetomidine versus midazolam	2 of 6 (16,7%)	Tympanoplasty	IV	In favor of dex
		Upper endoscopy	IV	In favor of dex
Dexmedetomidine versus opioid	0 of 1 (0%)			
Intranasal dexmedetomidine	0 of 0 (0%)			
(e)				
Dexmedetomidine versus placebo	0 of 4 (0%)			
Dexmedetomidine versus propofol	0 of 7 (0%)			
Dexmedetomidine versus midazolam	0 of 10 (0%)			
Dexmedetomidine versus opioid	1 of 5 (20%)	Awake fibreoptic nasotracheal intubation	IV	In favor of dex
Intranasal dexmedetomidine	0 of 2 (0%)			

Table 1. Condensed Representation of the Results (For Detailed View See Appendix 2). (a) Effect on Pain. (b) Effect on Rescue Medication. (c) Effect on Patient Satisfaction. (d) Effect on Operator Satisfaction. (e) Effect on Duration of Procedure. (f) Effect on MAP. (g) Effect on SBP. (h) Effect on DBP. (i) Effect on HR. (j) Effect on SpO2. (k) Effect on Recovery Time (*continued*)

Study design	Percentage of trials*	Procedure	Route of administration	Results
(f)				
Dexmedetomidine versus placebo	3 of 4 (75%)	LASIK	IV	In favor of placebo
		Awake fibreoptic intubation	IV	In favor of placebo
		Upper gastrointestinal endoscopy	IV	In favor of placebo
Dexmedetomidine versus propofol	4 of 6 (66,6%)	LASIK	IV	In favor of dex
		CAUP	IV	In favor of propofol
		Anterior segment ophthalmic surgery	IV	In favor of propofol
		ERCP	IV	In favor of propofol
Dexmedetomidine versus midazolam	6 of 8 (75%)	Tympanoplasty	IV	In favor of midazolam
		Upper gastrointestinal endoscopy	IV	In favor of midazolam
		Third molar extraction	IV	In favor of midazolam
		Third molar surgery	IV	In favor of midazolam
		Cataract surgery	IV	In favor of midazolam
		Colonoscopy	IV	In favor of midazolam
Dexmedetomidine versus opioid	3 of 4 (75%)	Awake fibreoptic nasotracheal intubation	IV	In favor of opioid
		Tension-free vaginal tape surgery	IV	In favor of opioid
		Colonoscopy	IV	In favor of opioid
Intranasal dexmedetomidine	0 of 0 (%)			
(g)				
Dexmedetomidine versus placebo	2 of 3 (66,6%)	Electrochemotherapy	IV	In favor of placebo
		Ophthalmic surgery	IV	In favor of placebo
Dexmedetomidine versus propofol	3 of 3 (100%)	Cataract surgery	IV	In favor of propofol
		Septoplasty	IV	In favor of dex
		Minor oral surgery	IV	In favor of propofol
Dexmedetomidine versus midazolam	3 of 3 (100%)	Dental surgery	IV	In favor of midazolam
		Flexible bronchoscopy	IV	In favor of midazolam
		Third molar surgery	IV	In favor of midazolam
Dexmedetomidine versus opioid	1 of 1 (100%)	Awake fibreoptic nasal intubation	IV	In favor of opioid

Table 1. Condensed Representation of the Results (For Detailed View See Appendix 2). (a) Effect on Pain. (b) Effect on Rescue Medication. (c) Effect on Patient Satisfaction. (d) Effect on Operator Satisfaction. (e) Effect on Duration of Procedure. (f) Effect on MAP. (g) Effect on SBP. (h) Effect on DBP. (i) Effect on HR. (j) Effect on SpO2. (k) Effect on Recovery Time (*continued*)

Study design	Percentage of trials*	Procedure	Route of administration	Results
Intranasal dexmedetomidine	2 of 2 (100%)	Electrochemotherapy	IN	In favor of IV/IN placebo
		Third molar extraction	IN	In favor of IN placebo
(h)				
Dexmedetomidine versus placebo	0 of 2 (0%)			
Dexmedetomidine versus propofol	1 of 2 (50%)	Minor oral surgery	IV	In favor of propofol
Dexmedetomidine versus midazolam	2 of 3 (66,6%)	Dental surgery	IV	In favor of midazolam
		Third molar surgery	IV	In favor of midazolam
Dexmedetomidine versus opioid	0 of 1 (0%)			
Intranasal dexmedetomidine	0 of 0 (0%)			
(i)				
Dexmedetomidine versus placebo	5 of 7 (71,4%)	LASIK	IV	In favor of placebo
		Electrochemotherapy	IV	In favor of placebo
		Awake fibreoptic intubation	IV	In favor of placebo
		Endoscopy		In favor of placebo
		Ophthalmic surgery	IV	In favor of placebo
Dexmedetomidine versus propofol	7 of 9 (77,8%)	LASIK	IV	In favor of propofol
		CAUP	IV	In favor of propofol
		Anterior segment ophthalmic surgery	IV	In favor of propofol
		Fibreoptic nasotracheal intubation	IV	In favor of propofol
		Septoplasty	IV	In favor of propofol
		Minor oral surgery	IV	In favor of propofol
		ERCP	IV	In favor of propofol

Table 1. Condensed Representation of the Results (For Detailed View See Appendix 2). (a) Effect on Pain. (b) Effect on Rescue Medication. (c) Effect on Patient Satisfaction. (d) Effect on Operator Satisfaction. (e) Effect on Duration of Procedure. (f) Effect on MAP. (g) Effect on SBP. (h) Effect on DBP. (i) Effect on HR. (j) Effect on SpO2. (k) Effect on Recovery Time (*continued*)

Study design	Percentage of trials*	Procedure	Route of administration	Results
Dexmedetomidine versus midazolam	10 of 11 (90,9%)	Tympanoplasty	IV	In favor of midazolam
		Dental surgery	IV	In favor of midazolam
		Flexible bronchoscopy	IV	In favor of midazolam
		Outpatient shock wave lithotripsy	IV	In favor of midazolam
		Upper gastrointestinal endoscopy	IV	In favor of midazolam
		Third molar extraction	IV	In favor of midazolam
		Third molar surgery	IV	In favor of midazolam
		Third molar surgery	IV	In favor of midazolam
		Cataract surgery	IV	In favor of midazolam
		Colonoscopy	IV	In favor of midazolam
Dexmedetomidine versus opioid	5 of 5 (100%)	Awake fibreoptic nasotracheal intubation	IV	In favor of opioid
		Awake fibreoptic nasotracheal intubation	IV	In favor of opioid
		Tension-free vaginal tape surgery	IV	In favor of opioid
		Awake fibreoptic nasal intubation	IV	In favor of opioid
		Colonoscopy	IV	In favor of opioid
Intranasal dexmedetomidine	2 of 2 (100%)	Electrochemotherapy	IN	In favor of IV/IN placebo
		Third molar extraction	IN	In favor of IN placebo
(j)				
Dexmedetomidine versus placebo	0 of 5 (0%)			
Dexmedetomidine versus propofol	5 of 9 (55,5%)	CAUP	IV	In favor of dex
		Anterior segment	IV	In favor of dex
		Ophthalmic surgery	IV	In favor of dex
		Vitreoretinal surgery	IV	In favor of dex
		Fibreoptic nasotracheal intubation	IV	In favor of propofol
		Minor oral surgery		
Dexmedetomidine versus midazolam	3 of 11 (27,3%)	Flexible bronchoscopy	IV	In favor of dex
		Outpatient shockwave lithotripsy	IV	In favor of midazolam
		Third molar surgery	IV	In favor of midazolam

Table 1. Condensed Representation of the Results (For Detailed View See Appendix 2). (a) Effect on Pain. (b) Effect on Rescue Medication. (c) Effect on Patient Satisfaction. (d) Effect on Operator Satisfaction. (e) Effect on Duration of Procedure. (f) Effect on MAP. (g) Effect on SBP. (h) Effect on DBP. (i) Effect on HR. (j) Effect on SpO2. (k) Effect on Recovery Time (*continued*)

Study design	Percentage of trials*	Procedure	Route of administration	Results
Dexmedetomidine versus opioid	2 of 5 (40%)	Awake fibreoptic nasotracheal intubation Awake fibreoptic nasotracheal intubation	IV IV	In favor of dex In favor of dex
Intranasal dexmedetomidine	0 of 2 (0%)			
(k)				
Dexmedetomidine versus placebo	0 of 1 (0%)			
Dexmedetomidine versus propofol	1 of 6 (16,7%)	Septoplasty	IV	In favor of dex
Dexmedetomidine versus midazolam	3 of 5 (60%)	Outpatient shockwave lithotripsy Third molar extraction Cataract surgery	IV IV IV	In favor of midazolam In favor of midazolam In favor of dex
Dexmedetomidine versus opioid	0 of 2 (0%)			
Intranasal dexmedetomidine	0 of 0 (0%)			

Only one trial used a local anesthetic (lidocaine) in addition to dexmedetomidine. This was necessary because this study investigated an invasive procedure (oro-dental) in contrast to the other trials involving endoscopy and imaging techniques (38).

CONCLUSION

In conclusion, there is evidence to support dexmedetomidine as a potential sole sedative agent in small diagnostic and therapeutic procedures, whether or not in combination with a local anesthetic. This evidence applies, in particular, to pain relief and patient satisfaction as measured during procedures in adults, and to respiratory safety in the procedures involving children. The routes of administration of dexmedetomidine and the possibility of sedating adults and children, have been discussed. Future research should examine in which procedures dexmedetomidine can be used as a sole sedative agent (or in combination with a local anesthetic) in preference to other sedatives.

Appendix 1: Search strategy

Embase.com

(dexmedetomidine/de OR (dexmedetomidine OR dexamedetomidine OR 'mpv 1440' OR mpv1440 OR precedex O primadex OR dexdomitor OR dexdor):ab,ti) AND (('conscious sedation'/de OR 'anesthesia level'/de OR 'Ramsay Sedation Scale'/de OR wakefulness/de OR (((conscious* OR moderate* OR light OR depth OR level) NEAR/3 (sedat* OR anesth* OR anaesth*)) OR Ramsay OR wakeful* OR awake*):ab,ti) OR ((sedation/de OR anesthesia/de OR 'anesthetic agent'/de OR 'intravenous anesthetic agent'/de OR 'intravenous regional anesthesia'/de OR 'analgesic agent'/de OR 'anxiolytic agent'/de OR 'tranquilizing activity'/de OR (sedati* OR anesthe* OR anaesthe* OR analgesi* OR anxioly* OR tranquiliz*):ab,ti) AND ('ambulatory surgery'/de OR 'local anesthesia'/de OR 'diagnostic procedure'/de OR 'digestive system examination'/exp OR 'mouth examination'/exp OR 'respiratory tract examination'/exp OR radiodiagnosis/exp OR (((day*) NEAR/3 (surg* OR anesthe* OR anaesthe*)) OR ambula* OR outpatient* OR ((minor OR small*) NEAR/3 (intervent* OR procedure*)) OR ((local OR regional) NEAR/3 (anesthe* OR anaesthe*)) OR ((diagnos* OR dental) NEAR/3 (procedure* OR interven*)) OR ((respirator* OR mouth* OR digestive) NEAR/3 (examination*)) OR radiodiagnos* OR mri OR 'magnetic resonance' OR ct OR tomograph* OR pet OR nonoperat* OR (outside NEAR/3 (operat* OR surg*)) OR non NEXT/1 (anesthesiolog* OR anesthaesiolog*)):ab,ti)))

Medline (OvidSP)

(dexmedetomidine/ OR (dexmedetomidine OR dexamedetomidine OR "mpv 1440" OR mpv1440 OR precedex OR primadex OR dexdomitor OR dexdor).ab,ti.) AND (("conscious sedation"/ OR wakefulness/ OR (((conscious* OR moderate* OR light OR depth OR level) ADJ3 (sedat* OR anesth* OR anaesth*)) OR Ramsay OR wakeful* OR awake*).ab,ti.) OR ((exp Anesthesia/ OR "anesthetics"/ OR "Anesthesia, Conduction"/ OR "analgesics"/ OR "Anti-Anxiety Agents"/ OR "Tranquilizing Agents"/ OR (sedati* OR anesthe* OR anaesthe* OR analgesi* OR anxioly* OR tranquiliz*).ab,ti.) AND (exp "Ambulatory Surgical Procedures"/ OR "Anesthesia, Local"/ OR "Physical Examination"/ OR exp "Diagnostic Techniques and Procedures"/ OR (((day*) ADJ3 (surg* OR anesthe* OR anaesthe*)) OR ambula* OR outpatient* OR ((minor OR small*) ADJ3 (intervent* OR procedure*)) OR ((local OR regional) ADJ3 (anesthe* OR anaesthe*)) OR ((diagnos* OR dental) ADJ3 (procedure* OR interven*)) OR ((respirator* OR mouth* OR digestive) ADJ3 (examination*)) OR radiodiagnos* OR mri OR "magnetic resonance" OR ct OR tomograph* OR pet OR nonoperat* OR (outside ADJ3 (operat* OR surg*)) OR non ADJ (anesthesiolog* OR anesthaesiolog*)).ab,ti.)))

Cochrane

((dexmedetomidine OR dexamedetomidine OR 'mpv 1440' OR mpv1440 OR precedex OR primadex OR dexdomitor OR dexdor):ab,ti) AND (((((conscious* OR moderate* OR light OR depth OR level) NEAR/3 (sedat* OR anesth* OR anaesth*)) OR Ramsay OR wakeful* OR awake*):ab,ti) OR (((sedati* OR anesthe* OR anaesthe* OR analgesi* OR anxioly* OR tranquiliz*):ab,ti) AND ((((day*) NEAR/3 (surg* OR anesthe* OR anaesthe*)) OR ambula* OR outpatient* OR ((minor OR small*) NEAR/3 (intervent* OR procedure*)) OR ((local OR regional) NEAR/3 (anesthe* OR anaesthe*)) OR ((diagnos* OR dental) NEAR/3 (procedure* OR interven*)) OR ((respirator* OR mouth* OR digestive) NEAR/3 (examination*)) OR radiodiagnos* OR mri OR 'magnetic resonance' OR ct OR tomograph* OR pet OR nonoperat* OR (outside NEAR/3 (operat* OR surg*)) OR non NEXT/1 (anesthesiolog* OR anesthaesiolog*)):ab,ti)))

Web-of-science

TS=(((dexmedetomidine OR dexamedetomidine OR "mpv 1440" OR mpv1440 OR precedex OR primadex OR dexdomitor OR dexdor)) AND (((((conscious* OR moderate* OR light OR depth OR level) NEAR/3 (sedat* OR anesth OR anaesth*)) OR Ramsay OR wakeful* OR awake*)) OR (((sedati* OR anesthe* OR anaesthe* OR analgesi* OR anxioly* OR tranquiliz*)) AND ((((day*) NEAR/3 (surg* OR anesthe* OR anaesthe*)) OR ambula* OR outpatient* OR ((minor OR small*) NEAR/3 (intervent* OR procedure*)) OR ((local OR regional) NEAR/3 (anesthe* OR anaesthe*)) OR ((diagnos* OR dental) NEAR/3 (procedure* OR interven*)) OR ((respirator* OR mouth* OR digestive) NEAR/3 (examination*)) OR radiodiagnos* OR mri OR "magnetic resonance" OR ct OR tomograph* OR pet OR nonoperat* OR (outside NEAR/3 (operat* OR surg*)) OR non NEAR/1 (anesthesiolog* OR anesthaesiolog*))))))

Scopus

TITLE-ABS-KEY(((dexmedetomidine OR dexamedetomidine OR "mpv 1440" OR mpv1440 OR precedex OR primadex OR dexdomitor OR dexdor)) AND (((((conscious* OR moderate* OR light OR depth OR level) W/3 (sedat* OR anesth* OR anaesth*)) OR Ramsay OR wakeful* OR awake*)) OR (((sedati* OR anesthe* OR anaesthe* OR analgesi* OR anxioly* OR tranquiliz*)) AND ((((day*) W/3 (surg* OR anesthe* OR anaesthe*)) OR ambula* OR outpatient* OR ((minor OR small*) W/3 (intervent* OR procedure*)) OR ((local OR regional) W/3 (anesthe* OR anaesthe*)) OR ((diagnos* OR dental) W/3 (procedure* OR interven*)) OR ((respirator* OR mouth* OR digestive) W/3 (examination*)) OR radiodiagnos* OR mri OR "magnetic

resonance" OR ct OR tomograph* OR pet OR nonoperat* OR (outside W/3 (operat* OR surg*)) OR non W/1 (anesthesiolog* OR anesthaesiolog*))))))

PubMed publisher

(dexmedetomidine[mh] OR (dexmedetomidine OR dexamedetomidine OR "mpv 1440" OR mpv1440 OR precedex OR primadex OR dexdomitor OR dexdor)) AND ((("conscious sedation"[mh] OR wakefulness[mh] OR (((conscious*[tiab] OR moderate*[tiab] OR light OR depth OR level) AND (sedat*[tiab] OR anesth*[tiab] OR anaesth*[tiab])) OR Ramsay OR wakeful*[tiab] OR awake*[tiab])) OR ((Anesthesia[mh] OR "anesthetics"[mh] OR "Anesthesia, Conduction"[mh] OR "analgesics"[mh] OR "Anti-Anxiety Agents"[mh] OR "Tranquilizing Agents"[mh] OR (sedati*[tiab] OR anesthe*[tiab] OR anaesthe*[tiab] OR analgesi*[tiab] OR anxioly*[tiab] OR tranquiliz*[tiab])) AND ("Ambulatory Surgical Procedures"[mh] OR "Anesthesia, Local"[mh] OR "Physical Examination"[mh] OR "Diagnostic Techniques and Procedures"[mh] OR (((day*[tiab]) AND (surg*[tiab] OR anesthe*[tiab] OR anaesthe*[tiab])) OR ambula*[tiab] OR outpatient*[tiab] OR ((minor OR small*[tiab]) AND (intervent*[tiab] OR procedure*[tiab])) OR ((local OR regional) AND (anesthe*[tiab] OR anaesthe*[tiab])) OR ((diagnos*[tiab] OR dental) AND (procedure*[tiab] OR interven*[tiab])) OR ((respirator*[tiab] OR mouth*[tiab] OR digestive) AND (examination*[tiab])) OR radiodiagnos*[tiab] OR mri OR "magnetic resonance" OR ct OR tomograph*[tiab] OR pet OR nonoperat*[tiab] OR (outside AND (operat*[tiab] OR surg*[tiab])) OR non ADJ (anesthesiolog*[tiab] OR anesthaesiolog*[tiab])))))) AND publisher[sb]

Google Scholar

Dexmedetomidine "conscious|moderate|light sedation|anesthesia|anaesthesia"|Ramsay|wakeful|awake

Appendix 2: Summary of included studies (Table 1 – 6)

Legend:
*Significant difference ($p < 0.05$)
↑ = Increased value compared to control group
↓ = Decreased value compared to control group
→ = Unchanged values compared to the control group
/ = No difference between two out of three groups
IV = intravenous; IN = Intranasal; pain = pain during procedure; pain LA = pain from local anesthetic; LA = local anesthetic; VAS = Visual analogue
scale (pain score); NRS = Numeric rating scale (pain score); MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood
pressure HR = Heart rate; SpO2 =peripheral capillary oxygen saturation; RR = respiratory rate; Recovery time = time till patient is recovered after
procedure; Aldrete = time until Aldrete score is 10; Rescue medication = medication needed because current medication is not sufficient; Ramsey = Ramsey
sedation scale; OAA/S = Observer's Assessment of Alertness/Sedation; BIS = Bispectral Index Score ; RASS = Richmond Agitation Sedation
Scale

Appendix Table 1. Summary of included studies reporting dexmedetomidine versus placebo in adults

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter(s)	Results
Eskandr, 2014	Cataract surgery	Adults (18-70)	Yes	60	IV dexmedetomidine (D) + LA *versus* LA	Subtenon (Lidocaïne + Bupivacaine)	OAA/S	Pain (VAS) Duration of procedure MAP HR	↓ ↓ ↓ ↓
Wang, 2014	Laser assisted in situ keratomileusis (LASIK)	Adults (18-31)	Yes	30	IV dexmedetomidine (D) *versus* IV propofol (P) *versus* IV placebo	Topical proparacaine	Ramsay	Patient satisfaction Operator satisfaction Recovery time MAP HR SpO2	Placebo < P / D* Placebo < P < D* P < D P < D / placebo* D < P / placebo* →
Zhang, 2013	Electrochemotherapy	Adults (18-60)	Yes	60	IV dexmedetomidine (IV-D) *versus* IN dexmedetomidine (IN-D) *versus* IV/IN saline (C)	Ropivacaine	OAA/*S*	Rescue medication Duration of procedure SBP HR SpO2	IV-D < IN-D < C IV-D < IN-D < C IV-D < IN-D < C* IV-D < IN-D < C* →
Bergese, 2010	Awake fiberoptic intubation	Adults (≥ 18)	Yes	105	IV dexmedetomidine *versus* IV saline	Lidocaïne	Ramsay	Rescue medication Patient satisfaction Operator satisfaction MAP HR SpO2	↓* → → ↓* ↓* →
Hashiguchi, 2008	Upper gastrointestinal endoscopy	Adults (38-54)	No	40	IV dexmedetomidine (D) *versus* IV midazolam (M) *versus* placebo	Lidocaïne	Ramsay	Duration of procedure SBP DBP HR SpO2	M < D < placebo D < M < placebo* D < M < placebo* D < M / placebo* D /M < placebo*

Appendix Table 1. Summary of included studies reporting dexmedetomidine versus placebo in adults (*continued*)

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter(s)	Results
Erdurmus, 2008	Cataract surgery	Adults (≥ 18)	Yes	44	IV dexmedetomidine *versus* IV placebo	Topical (lidocaïne rescue)	Ramsay	Pain (VAS) Patient satisfaction Operator satisfaction Duration of procedure SBP DBP HR SpO2	↓* ↑* ↑* → ↓ ↓ ↓ →
Abdalla, 2006	Ophthalmic surgery	Adults (47-74)	Yes	40	IV dexmedetomidine *versus* IV placebo	Topical proparacaine	BIS	SBP DBP HR	↓* ↓ ↓*

Appendix Table 2. Summary of included studies reporting dexmedetomidine versus propofol in adults

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Wang, 2014	Laser assisted in situ keratomileusis (LASIK)	Adults (18-31)	Yes	30	IV dexmedetomidine (D) *versus* IV propofol (P) *versus* IV placebo	Topical proparacaine	Ramsay BIS	Patient satisfaction Operator satisfaction Recovery time MAP HR SpO2	Placebo < P / D* Placebo < P < D* P < D P < D / placebo* D < P / placebo* →
Ma, 2012	Coblation-assisted upper airway procedure (CAUP)	Adults (34-62)	No	60	IV dexmedetomidine *versus* IV propofol	Lidocaïne	Ramsey BIS	Pain (VAS) Rescue medication Patient satisfaction (VAS) Recovery time (Aldrete) MAP HR SpO2	↓* ↓* ↑ → ↓* ↓* ↑
Darwish, 2012	Anterior segment ophthalmic surgery	Adults (40-60)	No	100	IV dexmedetomidine *versus* IV propofol	Levobupiva-caine + Lidocaïne	RASS BIS	Patient satisfaction Duration of procedure Recovery time (Aldrete) MAP HR SpO2	↑ ↓ ↑ ↓* ↓* ↑
Na, 2011	Cataract surgery	Adults (20-75)	No	31	IV dexmedetomidine *versus* IV propofol-Alfentanil	Proparacaine	Ramsay	Patient satisfaction Duration of procedure SBP HR SpO2	↑ → ↓* → →
Ghali, 2011	Vitreoretinal surgery	Adults (39-55)	Yes	60	IV dexmedetomidine *versus* IV propofol	Subtenon (ropivacaine)	Ramsay	Pain (VAS) Patient satisfaction Operator satisfaction Duration of procedure Recovery time (Aldrete) MAP HR SpO2	↓* ↑ ↑ → ↑ → → ↑

Appendix Table 2. Summary of included studies reporting dexmedetomidine versus propofol in adults (*continued*)

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Tsai, 2010	Fibreoptic nasotracheal intubation	Adults (46-64)	Yes	40	IV dexmedetomidine *versus* IV propofol	Topical Lidocaïne	Entropy	Pain (sore troat) Patient satisfaction Duration of procedure MAP HR SpO2	↓ → ↑ → ↓* ↑*
Dogan, 2010	Septoplasty	Adults (18-70)	No	60	IV dexmedetomidine *versus* IV propofol + fentanyl	Lidocaïne	Ramsay	Pain (VAS) Patient satisfaction Duration of procedure Recovery time (Aldrete) SBP DBP HR SpO2	↓* ↑* ↑ ↓* ↑* → ↓* →
Taniyama, 2009	Minor oral surgery	Adults (19-43)	No	14	IV dexmedetomidine *versus* IV propofol	Lidocaïne	Mackenzie	Duration of procedure SBP DBP HR SpO2 Comfort	↓ ↓* ↓* ↓* ↓* ↓
Muller, 2008	Endoscopic retrograde cholangiopancreatography (ERCP)	Adults (20-78)	Yes	26	IV dexmedetomidine *versus* IV propofol + fentanyl	*none*	RASS	Rescue medication Duration of procedure Recovery time MAP HR SpO2	↑* ↑ ↑ ↓* ↓* →

Appendix Table 3. Summary of included studies reporting dexmedetomidine versus midazolam in adults

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Parikh, 2013	Tympanoplasty	Adults (18-60)	Yes	90	IV dexmedetomidine *versus* IV midazolam/ fentanyl	Lignocaine	Ramsay	Pain (VAS) Rescue medication Patient satisfaction Operator satisfaction Duration of procedure MAP HR SpO2	↓ ↓* ↑* ↑* ↓ ↓* ↓* →
Fan, 2013	Dental surgery	Adults (19-38)	Yes	60	IV dexmedetomidine *versus* IV midazolam	Lidocaïne	OAA/S BIS	Patient satisfaction Duration of procedure SBP DBP HR SpO2 Safety	↑* → ↓* ↓* ↓* → ↑
Liao, 2012	Flexible bronchoscopy	Adults (49-68)	No	197	IV dexmedetomidine *versus* IV midazolam	Lidocaïne	Ramsay	Duration of procedure SBP DBP HR SpO2 Comfort	↓ ↓* → ↓* ↑* →
Zeyneloglu, 2008	Outpatient shockwave lithotripsy	Adults (35-60)	Yes	49	IV dexmedetomidine *versus* IV midazolam/ fentanyl	*None*	OAA/S	Pain (VAS) Rescue medication Patient satisfaction Operator satisfaction Duration of procedure Recovery time (Aldrete) MAP HR SpO2	↑* ↑* ↓* → ↑ ↑* → ↓* ↓*

Appendix Table 3. Summary of included studies reporting dexmedetomidine versus midazolam in adults (*continued*)

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Hashiguchi, 2008	Upper gastrointestinal endoscopy	Adults (38-54)	No	40	IV dexmedetomidine (D) *versus* IV midazolam (M) *versus* placebo	Lidocaïne	Ramsay	Duration of procedure SBP DBP HR SpO2	M < D < placebo D < M < placebo* D < M < placebo* D < M / placebo* D /M < placebo*
Fawzy, 2007	Third molar extraction	Adults (20-40)	Yes	40	IV dexmedetomidine *versus* IV midazolam	Lidocaïne	BIS	Rescue medication Patient satisfaction Operator satisfaction Duration of procedure Recovery time MAP HR SpO2 Comfort	↓ → → ↑ ↑* ↓* ↓* → ↑
Demiraran, 2007	Upper endoscopy	Adults (18-60)	Yes	50	IV dexmedetomidine *versus* midazolam	Topical lidocaïne spray	Somno-lence score	Patient satisfaction Operator satisfaction Duration of procedure Recovery time MAP HR SpO2 Comfort	↑ ↑* ↓ → → → → →
Cheung, 2007	Third molar surgery	Adults (18-50)	Yes	60	IV dexmedetomidine *versus* IV midazolam	Lidocaïne	Ramsay	Pain (NRS) Patient satisfaction Operator satisfaction Duration of procedure MAP HR SpO2	→ → ↑ → ↓* ↓* ↓*

Appendix Table 3. Summary of included studies reporting dexmedetomidine versus midazolam in adults (*continued*)

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Ustun, 2006	Third molar surgery	Adults (17-28)	Yes	20	IV dexmedetomidine *versus* IV midazolam	Artricaine	Ramsay	Pain LA (VAS) Patient satisfaction (VAS) Duration of procedure SBP DBP HR SpO2	↓ ↑* → ↓* ↓* ↓* →
Alhashemi, 2006	Cataract surgery	Adults (18-80)	Yes	44	IV dexmedetomidine *versus* IV midazolam	Bupivacaine + Lidocaïne	Ramsay	Patient satisfaction Operator satisfaction Recovery time (Aldrete) MAP HR SpO2	↑* → ↓* ↓* ↓* ↑
Jalowiecki, 2005	Colonoscopy	Adults (18-60)	Yes	64	IV dexmedetomidine (D) *versus* IV meperidine/ midazolam (M) *versus* IV fentanyl (F)	*None*	OAA/S	Quality of sedation/pain (NRS) Duration of procedure Recovery time MAP HR SpO2	→ F < M < D D < M < F* D < M < F* D < M < F* →

Appendix Table 4. Summary of included studies reporting dexmedetomidine versus opioids in adults

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Shen, 2014	Awake fibreoptic nasotracheal intubation	Adults (19-65)	Yes	40	IV dexmedetomidine *versus* IV sufentanil	Lidocaïne	Ramsay	Pain (throat pain) Patient satisfaction Operator satisfaction Duration of procedure MAP HR SpO2	↓* ↑* ↑ ↓* ↓* ↓* ↑*
Hu, 2013	Awake fibreoptic nasotracheal intubation	Adults (22-54)	Yes	40	IV dexmedetomidine *versus* IV remifentanil	Lidocaïne	Ramsay	Rescue Patient satisfaction Duration of procedure MAP HR SpO2	→ ↑* ↓ → ↓* ↑*
Turan, 2011	Tension-free vaginal tape surgery	Adults (44-62)	Yes	49	IV dexmedetomidine *versus* Epidural bupivacaine/fentanyl	Lidocaïne	Ramsay	Pain Patient satisfaction Duration of procedure Recovery time (Aldrete) MAP HR SpO2	→ ↑ ↑ → ↓* ↓* →
Chua, 2010	Awake fibreoptic nasotracheal intubation	Adults (42-65)	Yes	30	IV dexmedetomidine *versus* IV fentanyl	Cocaine + Lidocaïne	State entropy value	Pain (throat pain) Patient satisfaction Duration of procedure SBP DBP HR SpO2	↑ ↑* ↓ ↓* → ↓* →

Appendix Table 4. Summary of included studies reporting dexmedetomidine versus opioids in adults (*continued*)

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Jalowiecki, 2005	Colonoscopy	Adults (18-60)	Yes	64	IV dexmedetomidine (D) *versus* IV meperidine/ midazolam (M) *versus* IV fentanyl (F)	*None*	OAA/S	Quality sedation/pain (NRS) Duration of procedure Recovery time MAP HR SpO2	→ F < M < D D < M < F* D < M < F* D < M < F* →

Appendix Table 5. Summary of included studies reporting intranasal dexmedetomidine in adults

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Zhang, 2013	Electrochemotherapy	Adults (18-60)	Yes	60	IV dexmedetomidine (IV-D) *versus* IN dexmedetomidine (IN-D) *versus* IV/IN saline (C)	Ropivacaine	OAA/*S*	Rescue medication Duration of procedure HR SBP SpO2	IV-D < IN-D < C IV-D < IN-D < C IV-D < IN-D < C* IV-D < IN-D < C* →
Nooh, 2013	Third molar extraction	Adults (20-28)	Yes	18	IN dexmedetomidine *versus* IN placebo	Lidocaïne	OAA/S BIS	Pain LA (NRS) Duration of procedure SBP HR SpO2	→ ↓ ↓* ↓* →

Appendix Table 6. Summary of included studies reporting on dexmedetomidine use in children

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Hasanin, 2014	Gastrointestinal endoscopy	Children (1-14)	No	80	IV dexmedetomidine *versus* IV propofol	*None*	Ramsay	Duration of procedure Recovery time MAP HR SpO2	→ ↑* → ↓* ↑*
Tammam, 2013	MRI sedation	Children (2-8)	Yes	90	IV dexmedetomidine *versus* IM dexmedetomidine	*None*	Ramsay	Rescue medication Operator satisfaction Duration of sedation Recovery time (Aldrete) Sedation failure MAP HR SpO2	↑* ↓* ↓ ↓* ↑* ↓* ↓* →
Tammam, 2013	MRI sedation	Children (2-7)	Yes	62	IM dexmedetomidine (D) *versus* IM ketamine (K) *versus* IM dexmedetomidine+ ketamine (DK)	*None*	Ramsay	Rescue medication Operator satisfaction Duration of sedation Recovery time (Aldrete) Sedation failure MAP HR SpO2	DK < K < D* D < K < DK* DK < D < K* DK < D < K* DK < K < D* D < DK < K* D < DK < K* K < D < DK*
Al Taher, 2010	Oro-dental procedures	Children (4-10)	Yes	60	IV dexmedetomidine *versus* IV midazolam/ propofol	Lidocaïne	Ramsay	Duration of procedure Recovery time MAP HR SpO2	↑ ↓* ↑* → →

Appendix Table 6. Summary of included studies reporting on dexmedetomidine use in children (*continued*)

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Anesthetic addition	Sedation scale	Outcome parameter	Results
Koroglu, 2005	MRI sedation	Children (1-7)	No	80	IV dexmedetomidine *versus* IV midazolam	*None*	Ramsay	Rescue medication Adequate sedation Duration of procedure Recovery time MAP HR SpO2	↓* ↑* ↑ ↓ → → →

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III

Sedation analgesia regimens in the awake implantation of a neurostimulator in the Netherlands

Chapter 2

Survey on sedation analgesia regimens, in particular the use of dexmedetomidine, among Dutch implanters of spinal cord neurostimulators

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ABSTRACT

Background and aims

During implantation of most spinal cord neurostimulators, patients need to be cooperative to give feedback during lead placement, and also be comfortable. Sedation and analgesia can support these conditions. This survey aimed to provide an overview of the sedation analgesia regimens currently used among Dutch pain specialists. The survey focused on the sedative agent 'dexmedetomidine' due to its attractive pharmacological profile and its promising results during awake procedures.

Methods

A 27-item survey was sent to the 65 pain specialists involved in neurostimulation in the Netherlands. The survey consisted of questions related to different aspects of sedation and analgesia during neurostimulation, e.g. the current regimen, the opinion on and experience with dexmedetomidine as a sedative agent, and preferences regarding different aspects of sedation (i.e., production of arousable sedation, pain management, quality of patient's feedback and overall preference).

Results

Of 65 pain specialists, 45 (69%) completed the survey. Most commonly used sedative was propofol (91%) and most common used analgesic was remifentanil (78%). Of the 45 respondents, 21 (47%) considered the use of dexmedetomidine, whereas 13 (29%) had experience with dexmedetomidine during neurostimulation. The most frequently mentioned positive property of dexmedetomidine was the easy production of arousable sedation. Most respondents who used dexmedetomidine preferred dexmedetomidine sedation over propofol sedation regarding all aspects of sedation.

Conclusions

The most commonly used sedation analgesia regimen is the combination of propofol-remifentanil during the implantation of a neurostimulator among Dutch pain specialists. Only a small percentage of respondents had experience with the use of dexmedetomidine, despite its reported advantages.

Implications

When implanting a spinal cord neurostimulator, dexmedetomidine could be considered as a sedative, given its allowance for and preservation of a state of easy arousable sedation.

Keywords
Neurostimulation; dexmedetomidine; pain specialists; hypnotics and sedatives; pain management; survey

INTRODUCTION

Since the start of neurostimulation in the mid-1990s, pain practice in the Netherlands has developed a well-established practice of neurostimulation. Between 2010 and 2017, a total of 12,947 neurostimulation procedures were performed in 26 pain centers throughout the Netherlands. The various indications for neurostimulation include: failed back surgery syndrome (FBSS), peripheral nerve pain, Complex Regional Pain Syndrome (CRPS), central pain, angina pectoris, and ischemic leg pain. The strongest indication (covering most neurostimulation procedures) is FBSS. In the Netherlands, 23% of the anesthesiologist-pain specialists is involved in neurostimulation (1).

Varying approaches are used for lead placement between and within countries. Two commonly applied approaches used during electrical mapping are (i) the anatomical approach and (ii) the approach based on patient feedback. Although the anatomical approach has proven effective for implantation for 10-kHz high-frequency spinal cord stimulation therapy, its use is still debated for neurostimulators that use low frequencies (2-4).

In the Netherlands (and also in our center), the approach mostly used for lead placement is based on patient feedback. When this approach is used, sedation and analgesia is required to maintain “moderate sedation”, defined as “a drug-induced depression of consciousness during which patients respond adequately to verbal commands” (5,6). Maintaining this level of sedation is often challenging, since the patient needs to be as cooperative and comfortable as possible.

In contrast to other more traditional sedative agents e.g., propofol or midazolam, acting on the GABA receptors, dexmedetomidine acts on the α2-receptor to achieve sedative, analgesic and anxiolytic effects. Studies on awake procedures indicate that dexmedetomidine, due to its fore mentioned pharmacological profile, is capable of achieving moderate sedation with easy arousability and no decline in cognitive skills. Furthermore, it does not lead to respiratory depression. However, side effects like hypotension and bradycardia have been reported (7-10). Based on these findings, our goal was also to ascertain the extent to which dexmedetomidine has a place in Dutch clinical practice during implantation of a neurostimulator. Since dexmedetomidine was not approved for procedural sedation in Europe by the European Medicines Agency (EMA) until 2018 and the most commonly used approach in Europe for lead placement matches the approach based on patient feedback, the data of this Dutch study will probably be representative and easily translatable to the rest of Europe.

Therefore, a survey was conducted among Dutch pain specialists involved in neurostimulation. The aim was to present an overview of (i) practice related to the sedation analgesia regimen during implantation of a neurostimulator, and of (ii) knowledge of and experience with dexmedetomidine.

METHODS

Based on current Dutch medical ethical regulations, no institutional review board approval was necessary for the survey.

Eligible for the survey were pain specialists working in a pain center specialized in spinal cord neurostimulation procedures and also involved in neurostimulation. A total of 65 pain specialists from 26 centers, were personally approached by email (by non-responding maximally three times) to participate in this survey. Although there are ≅ 80 pain centers in the Netherlands, not all perform neurostimulation procedures. Furthermore, pain specialists not involved in neurostimulation procedures were excluded.

Table 1. Data on respondents: age, hospital type and years of experience in neurostimulation

	Respondents n (%)
Age group (years)	
31-40	6 (13%)
41-50	15 (33%)
51- 60	19 (42%)
61 - 70	5 (11%)
Hospital type	
University hospital	12 (27%)
Peripheral hospital	32 (71%)
Private sector	2 (4%)
Years of experience in neurostimulation: mean (SD)	10.6 (7.7)

Since no established/validated survey for experience/preference regarding a sedation analgesia regimen is available, we designed a structured survey (see Supplement). The survey was conducted via telephone and data were digitally processed in Google Forms. Responses to the open questions were (individually) categorized based on content by two authors (FtB and DS).

The survey covered different aspects of sedation during a neurostimulation procedure, divided into the following sections: (1) current sedation analgesia regimen for a neurostimulation procedure, (2) specialists' knowledge of and experience with dexmedetomidine as a sedative agent, (3) the production of arousable sedation, (4) pain management, (5) quality of patient's feedback, and (6) overall preference. If a pain specialist had experience with more than one sedation analgesia regimen, the respondent was asked to indicate his/her preference for one specific regimen (with the reasons for this preference).

Descriptive statistics were used to determine the frequency of the demographic variables and the outcome parameters. Data were analyzed using IBM SPSS version 24.

RESULTS

From 1 March through 31 July 2018, 45 pain specialists from 24 centers completed the survey (response rate 69%) (Table 1).

Standard sedation analgesia regimen during neurostimulation

All respondents used standard monitoring of blood pressure, heart rate and saturation, whereas only 33 respondents (73.3%) used capnography. Regarding local anesthetic, 88.9% of the respondents used lidocaine; others reported the use of ropivacaine, bupivacaine, xylocaine and prilocaine, or a combination thereof. Besides local anesthetics, all respondents had experience with the use of a sedative and/or analgesic agent during the procedure. Some respondents included more than one sedative or analgesic agent in their standard sedation analgesia regimen (Table 2).

Table 2. Standard sedation analgesia regimen

Sedative agent	**Respondents n (%)**
Propofol	41 (91%)
Dexmedetomidine	8 (18%)
No sedative agent	4 (9%)
Analgesic agent	
Remifentanil	35 (78%)
Alfentanil	14 (31%)
Sufentanil	1 (2%)
No analgesic agent	0 (0%)

Analgesia regimen

Four respondents (9%) used an analgesic regimen of remifentanil without a sedative agent. All respondents mentioned good pain management, the possibility of fast and adequate communication with the patient, and no occurrence of deep sedation. Negative aspects included lack of sedation, discomfort, and side-effects related to the use of remifentanil.

Dexmedetomidine

Of 45 respondents, 21 (47%) considered the use of dexmedetomidine, whereas only 13 (29%) had actual experience with dexmedetomidine during a neurostimulation procedure (Table 3). The positive/negative aspects reported by respondents using dexmedetomidine during neurostimulation (n = 13) are presented in Table 4. Furthermore, respondents mentioned that the effectiveness of dexmedetomidine was related to the amount of experience of the administering practitioner [6 (43%)], age of the patient [2 (14%)] and the number and/or severity of comorbidities [3 (21%)].

Table 3. Number of respondents using dexmedetomidine vs. those considering dexmedetomidine

		Use of dexmedetomidine during neurostimulation		
		Yes	**No**	**Total**
Considered using dexmedetomidine during neurostimulation	**Yes**	13	8	21
	No	0	24	24
	Total	13	32	45

Table 4. Positive and negative rating of the use of dexmedetomidine

Positive aspects of the use of dexmedetomidine Respondents n (%)		**Negative aspects of the use of dexmedetomidine** Respondents n (%)	
Easy production of arousable sedation	10 (77%)	Hemodynamic side-effects	6 (46%)
Positive postoperative conditions i.e., a fast recovery time	2 (15%)	Difficult production of arousable sedation	4 (31%)
Stable respiratory profile	1 (8%)	Negative postoperative conditions i.e., a slow recovery time	1 (8%)
		High costs	1 (8%)

Comparison between propofol and dexmedetomidine

All respondents who considered to use and actually used dexmedetomidine [13 (29%)] also had experience with the use of propofol; they reported a preference for either of these in terms of different aspects of sedation (Table 5).

Table 5. Preference between dexmedetomidine or propofol as sedative agent regarding different aspects of sedation

	Preference dexmedetomidine (No. of respondents (%))	**Preference propofol** (No. of respondents (%))	**No preference** (No. of respondents (%))
Production of arousable sedation	8 (62%)	4 (31%)	1 (8%)
Pain management	5 (38%)	4 (31%)	4 (31%)
Quality of patient's feedback	11 (85%)	1 (8%)	1 (8%)
Overall preference	9 (69%)	4 (31%)	0 (0%)

Respondents considering, but not using dexmedetomidine

Eight respondents considered using dexmedetomidine, but did not. They had considered its use due to "promising stories" [4 (50%)], "positive respiratory aspects" [2 (25%)] and "better production of arousable sedation" [3 (38%)]. However, they did not actually use dexmedetomidine because of "satisfaction with the current regimen" [2 (25%)], "little or no experience with dexmedetomidine by the administrating practitioner" [3 (38%)], "expected difficulty to produce arousable sedation" [1 (13%)], and "unavailability of dexmedetomidine" [1 (13%)].

Respondents not considering nor using dexmedetomidine

Reasons given for not using nor considering dexmedetomidine were "satisfaction with current regimen" [14 (58%)], "little or no experience of administering practitioner" [16 (66%)] and "unavailability of dexmedetomidine" [5 (21%)]. They also mentioned "high costs" [1 (4%)] and "expected difficulty to produce arousable sedation" [2 (8%)].

DISCUSSION

Neurostimulation is an effective and widely applied treatment for chronic pain. Studies on this procedure have mainly focused on clinical effects and the occurrence of adverse events. During lead placement, the patient has to be awake to give feedback during electrical mapping regarding paresthesia testing. At the same time, the patient needs to be comfortable and with as little pain as possible. Sedation and analgesia can help provide both cooperation and comfort. Since few studies have investigated the sedation analgesia regimen, the present survey aimed to provide an overview of the regimens used during neurostimulation, focusing on the experience with and use of dexmedetomidine, as currently used in most neurostimulation centers in the Netherlands.

The combination of 'propofol-remifentanil' is most commonly used in Dutch practice. Of all our respondents, only four used an analgesic regimen. Although communication with

the patient was fast and adequate there was also discomfort, probably because the patient was not sedated. In our opinion a sedative agent should have been added, thereby enabling more comfort for the patient while preserving easy arousable sedation.

Only a small proportion of the respondents had experience with dexmedetomidine. Only respondents in this group, approximately half of them, reported hemodynamic side-effects i.e., the side-effects as mentioned in the literature (11). It is unclear if the reported side-effects were associated with (dis)continuing dexmedetomidine. Moreover, this survey suggest that the main reason(s) for the small amount of respondents who had experience with dexmedetomidine are limited experience by the administering practitioner and/or satisfaction with the current regimen, together with unavailability of dexmedetomidine and/or high costs. Further research on the cost-effectiveness of dexmedetomidine during procedural sedation analgesia seems warranted.

The survey showed that, the greater the number of systems the pain specialist had implanted using dexmedetomidine as sedative agent, the more positive their opinion on dexmedetomidine. This is probably because sedation with dexmedetomidine requires a certain amount of experience to more effectively provide stable sedation with easy arousability.

Limitations

Since this survey was limited to Dutch practice only, it may not be representative for practices in other countries. Also, a response rate of 69% may indicate that selective dropout may have occurred, thereby compromising the internal validity of this study; however, the response rate related to the total number of included pain centers was high (92%). Furthermore, this survey focused particularly on the sedative agent(s) and their ability to provide an easy arousable sedation, adequate patient's feedback and on good pain management. Nonetheless, the latter aspect can also be achieved through adequate use of analgesia and so in our survey more emphasis on analgesia would have been justified (12).

CONCLUSION

This survey shows that, in Dutch pain practice, the most commonly used sedation analgesia regimen is the combination of propofol and remifentanil. Almost 50% of the respondents considered the use of dexmedetomidine sedation due to its potential advantages regarding the production of arousable sedation. Of those respondents who

were able to make a comparison between dexmedetomidine and propofol, the majority preferred dexmedetomidine over propofol during a neurostimulation procedure.

Previous studies on awake procedures reported positive findings concerning the effectiveness of dexmedetomidine; however, neurostimulation was not included in these latter procedures. Therefore, we recommend to perform a randomized controlled trial focusing on the effectiveness of dexmedetomidine during neurostimulation procedures. Furthermore we believe that this study can serve as the basis for an European investigation regarding sedation analgesia during neurostimulation implant procedures.

SUPPLEMENT

SURVEY

SEDATION ANALGESIA REGIMEN

NEUROMODULATION

- 27 ITEMS -

In General

Q1. In what kind of hospital do you work?

○ Academic hospital
○ Peripheral hospital
○ Private clinic

Q2. What is your age?

○ 21 - 30 years
○ 31 - 40 years
○ 41 - 50 years
○ 61 - 70 years
○ 71 - 80 years

Q3. How many years of experience do you have with the implantation of a neurostimulator?

..... years

Standard Sedation Analgesia Regimen

Q4. Do you use a sedation analgesia regimen during the implantation of a neurostimulator? If no, give the reason why.

○ Yes
○ No, because **.....**

Q5. If you use a sedation analgesia regimen, who is the administrating practitioner?

○ Anesthesiologist (separate from operator)
○ Anesthesiologist (same as operator)
○ Sedationist
○ Anesthetic nurse
○ Resident Anesthesiology
○ Not applicable

Q6. Do you use premedication? If yes, which premedication do you use?

○ Yes **.....**
○ No

Q7. Which local anesthetic do you use?

○ Lidocaïne
○ Bupivacaïne
○ Ropivacaïne
○ Other **.....**

Q8. What is your standard sedation analgesia regimen?

○ Propofol
○ Remifentanil
○ Midazolam
○ Fentanyl
○ Sufentanil
○ Alfentanil
○ Clonidine
○ Dexmedetomidine
○ Ketamine
○ Unknown
○ Other **.....**

Q9. What kind of standard monitoring of vital parameters do you use?

○ Blood pressure
○ Heart rate / ECG
○ Pulse oximetry
○ Capnography
○ Unknown
○ Other **.....**

Dexmedetomidine

Q10. Do you have, in general, experience with dexmedetomidine?

○ Yes
○ No

Q11. If yes at Q10, regarding which procedure?

.....

Q12. Have you ever considered the use of dexmedetomidine during this procedure? If yes, if no, give reason(s) why.

○ Yes, because **.....**
○ No, because **.....**

Q13. Have you ever used dexmedetomidine during this procedure?

○ Yes, go to Q14
○ No, go to Q16

Q14. If yes at Q13, give a estimation of how many patients you have implanted using dexmedetomidine sedation

..... patients

Q15. What was your experience with the use of dexmedetomidine? Go to Q17.

.....

Q16. Why did you not use dexmedetomidine during this procedure?

.....

Preferences

Q17. What kind of monitoring do you use for the production of arousable sedation?

○ None
○ Ramsay Sedation Score
○ OAA/S scale
○ Verbal communication with the patient
○ Non-verbal communication with the patient (like snoring)
○ Not applicable
○ Other **.....**

Q18. Regarding the production of arousable sedation, which sedation analgesia regimen has your preference?

.....

Q19. Please provide reasons why.

.....

Q20. What kind of monitoring do you use for the level of pain intensity?

○ None
○ NRS-score
○ Verbal communication with the patient
○ Non-verbal communication with the patient
○ Non-verbal expressions of the

patient
○ Not applicable
○ Other **.....**

Q21. Regarding level of pain intensity, which sedation analgesia regimen has your preference?

.....

Q22. Please provide reasons why.

.....

Q23. How do you measure the quality of the patient's feedback?

.....

Q24. Regarding quality of patient's feedback, which sedation analgesia regimen has your preference?

.....

Q25. Please provide reasons why.

.....

Conclusion

Q26. Which sedation analgesia regimen has in general your preference?

.....

Q27. Please provide reasons why.

.....

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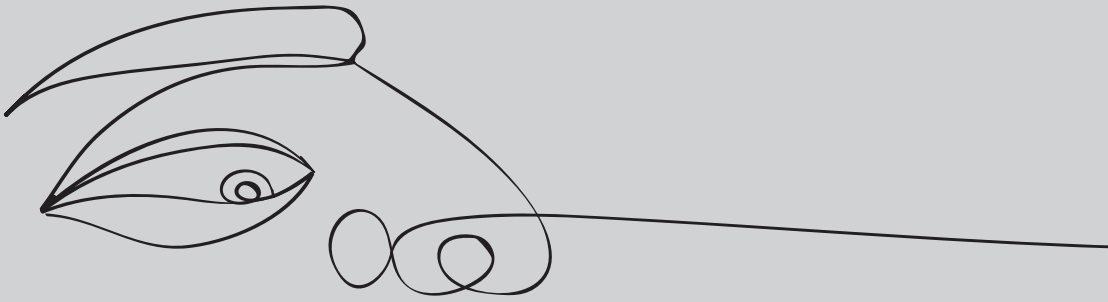
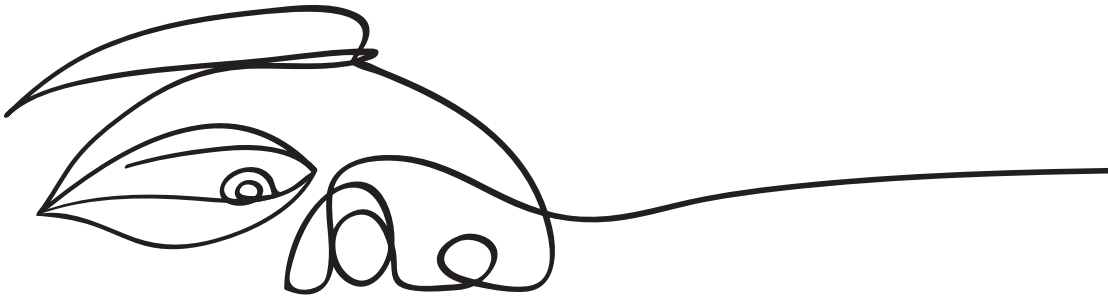


IV

Sedative agents during the implantation of a neurostimulator: dexmedetomidine versus propofol



Chapter 3

Dexmedetomidine as a Sedative in the Awake Implantation of a Neuromodulative System

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Pain Pract. 2017 Feb;17(2):208-213.

ABSTRACT

Objective

During implantation of a neuromodulative system, high patient satisfaction is closely associated with the equilibrium between an effective analgesia and sedation regimen, and the possibility for the patient to be awake and cooperative during procedure. This study assessed the efficacy of the sedative dexmedetomidine to achieve this balance, with patient satisfaction as the primary outcome.

Methods

Ten patients undergoing implantation of a dorsal column and dorsal root ganglion stimulator received dexmedetomidine (1 mcg/kg over 10 minutes, followed by 0.6 mcg/kg/hour) in combination with remifentanil at a set dose (3 mcg/kg/hour). Sedation was titrated to a Ramsay Sedation Score of 3. Recorded were as follows: patient satisfaction score, patient comfort score, operator comfort score, pain score, rescue medication and number of adjustments of dexmedetomidine intra-operatively, as well as sedation level, hemodynamic (blood pressure and heart rate) and respiratory characteristics (SpO_2).

Results

Scores were high on patient satisfaction (median 8.5; IQR 2.0), patient comfort (3.0; IQR 1.25) and operator comfort (4.0; IQR 1.0). In all patients, intra-operative heart rate and mean arterial pressure were lower compared with baseline values. No respiratory depression or other complications related to anesthesia were reported. Moments of incident pain were effectively treated in 6 patients requiring an extra bolus of remifentanil.

Conclusion

In this study group, dexmedetomidine combined with remifentanil provided a high level of patient satisfaction and comfort, as well as operator comfort, without any clinically relevant adverse events. All patients were highly cooperative and instructable; incident pain needs to be closely monitored.

Keywords

Sedation, dexmedetomidine, neuromodulation, chronic pain

INTRODUCTION

To place neurostimulation leads, most of the currently available systems require the cooperation of the patient. The overlap between neurostimulation-induced paresthesia and the pain area can only be specified by the patient. For patients, the procedure can be frightening, uncomfortable (due to the prolonged prone position) and sometimes painful due to inadequate analgesia. Therefore, adequate information and guidance is essential. In addition, besides local anesthesia, the use of anxiolytics, sedatives and more general analgesics can be helpful. However, a potential disadvantage of these adjuvants is that, due to the sedative effect of these drugs, patients may be insufficiently cooperative with the instructions and questions posed by physicians and nurses.

A promising analgosedative is dexmedetomidine, a highly selective, long-lasting presynaptic α2-receptor agonist with sedative, anxiolytic and analgesic properties. With dexmedetomidine there is no decline of cooperation or of cognitive skills. Due to its pharmacologic profile dexmedetomidine acts on the α2 receptors in the locus coeruleus, in contrast to other sedatives which act on GABA receptors/cerebral cortex (eg,. midazolam and propofol), and there is no respiratory depression. Furthermore, in combination with intravenous opioids (such as remifentanil), dexmedetomidine allows for lower doses of opioids. Earlier randomized controlled trials evaluating the use of dexmedetomidine alone during small diagnostic and therapeutic procedures showed promising results (1-3). However, a potential disadvantage of dexmedetomidine is its hemodynamic side effects, which include hypotension and bradycardia (4,5).

Therefore, this study aimed to examine the applicability of dexmedetomidine for the placement of neurostimulation leads for procedures in which the patient's cooperation is required. Applicability is operationalized as measurement of patient satisfaction, patient and operator's comfort, pain relief and rescue medication, the number of adjustments made to the administration of dexmedetomidine, sedation level, and hemodynamic and respiratory monitoring.

METHODS

Study design, selection of patients

The study protocol was approved by the Medical Ethics Committee of Erasmus Medical Center and registered with the Netherlands Clinical Trials Registry (NL 49012.078.12).

This is a proof-of-concept, prospective observational study. After providing informed consent, we enrolled 10 consecutive patients (aged 18 to 65 years) with an indication for trial implantation of a neurostimulation system, for which cooperation of the patient during lead placement is required. Exclusion criteria included hypersensitivity to either of the drugs involved, atrioventricular block (II-III), acute cerebrovascular disease, heart rate ≤ 60 bpm, pregnancy, acute epilepsy, severe liver dysfunction, use of beta blocking agents, psychological instability, and/or a communication problem.

Study site, measurements

Before the procedure, all patients received standard education and were guided perioperatively by a nurse. All patients were commenced on a dexmedetomidine infusion in the operating room, using an intravenous cannula. Sedation was performed by an independent anesthesiologist not involved in the interventional procedure. Implantation of the neuromodulative system was performed by another anesthesiologist-pain specialist not involved in the sedation. An independent observer, not involved in the sedation or the interventional procedure, performed all study measurements. During each procedure, measurements were made at 7 predefined moments: a preoperative measurement, at start of dexmedetomidine, at start of remifentanil, at start of the procedure, at midline incision (incision of the skin for anchoring the lead on the subcutaneous fascia and subcutaneous tunnelling of the lead), at end of the procedure, and postoperatively on the ward.

Patients were administered a loading dose of dexmedetomidine of 1 mcg/kg over 10 minutes to achieve the required level of sedation according to the Ramsay Sedation Scale (score 2 to 3) (Table 1)(6).This scale was used before the initiation of sedation and at 5-min intervals until the end of the procedure. The dose was adjusted depending on the required level of sedation (ie, a Ramsay score of 2 when the patient is required to be cooperative, and a score of 3 to 4 when the patient requires increased sedation). The maintenance dose of dexmedetomidine is 0.1-1.4 mcg/kg/hour; in the present study a maintenance dose of 0.6 mcg/kg/hour was used.

Ten minutes after commencement of the loading dose of dexmedetomidine, remifentanil infusion was started at a set dose (3 mcg/kg/hour) to achieve a high analgesic effect. Standard care involves the use of 1% lidocaine in combination with adrenaline (1:200,000) at the start of the procedure, during the midline incision, and at end of the procedure. When a patient complained of pain during the procedure, the anesthesiologist administered an additional bolus of remifentanil (25-50 mcg).

Table 1. Details of Ramsey Sedation Scale

Clinical score	Level of sedation
1	Patient is anxious and agitated or restless or both
2	Patient is cooperative, oriented and tranquil
3	Patient responds on command
4	Patient exhibits a brisk response to a light glabellar (between the eyebrows) tap or loud auditory stimulus
5	Patient exhibits a sluggish response to a light glabellar tap or loud auditory stimulus
6	Patient exhibits no response to stimulus

Our primary outcome parameter was patient satisfaction, as measured with a postoperative overall patient satisfaction questionnaire (consisting of 7 questions) (table 2) (6). Secondary outcomes were pain relief, patient's comfort and operator's comfort (using a comfort score) (table 3) (4), number of adjustments made during dexmedetomidine titration, scores on the Ramsay Sedation Scale. and intra-operative standard monitoring including noninvasive mean arterial pressure (MAP), heart rate (HR) via ECG, pulse oximetry (SpO_2) and end tidal CO_2 ($EtCO_2$).

Table 2. Patient Satisfaction Questionnaire

Q1	On a scale from 1 to 10 (1 least satisfied, 10 most satisfied), how satisfied were you with your anesthesia during your operation?
Q2	Do you remember awakening during the procedure?
Q3	If yes, was the experience distressful?
Q4	If you were to have the operation again, would you choose the same anesthesia?
Q5	Do you recall problems at home after discharge with anesthesia (hangover)?
Q6	Do you know of any complications from the anesthetic used?
Q7	If yes, what complications?

Data analysis

At each measurement moment, mean values of the outcomes were collected and reported as outcome per time moment. These values differ for each measurement moment, depending on the duration of the procedure, as measurements are made every 5 minutes.

Statistical analysis

Descriptive statistics were used to determine the frequencies of the demographic variables and the outcome parameters, and to describe measures of central tendency and of variability, depending on the shape of the distribution. All analyses were performed using IBM SPSS Statistics version 21 (Armonk, NY, USA).

Table 3. Patient Comfort and Operator Comfort Score

Criteria	*Score*
Excellent	1
Good	2
Fair	3
Poor	4

Table 4. Details of the included patients

Variables	**Patients (n = 10)**
Age in years (median; IQR)	53.3; 17,75
Female gender, n (%)	7 (70%)
BMI (kg/m^2): mean (SD)	28.47 (4.35)

Table 5. Data on Overall Patient Satisfaction

Patient satisfaction (median; IQR)	8.5; 2.0
Awake	Yes (100%
Stressful	Yes (20%)
Would choose same anesthesia again?	Yes (100%)
Home problems?	Not applicable
Were there complications related to anesthesia?	No (100%)

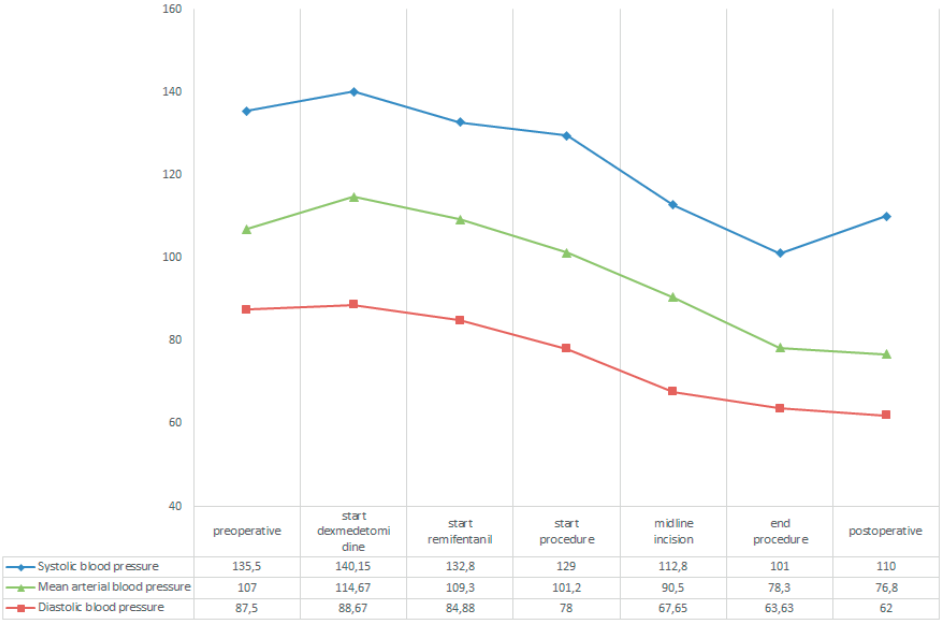
RESULTS

A total of 10 patients were included (Table 4).

All patients completed the study; the median score of patients' overall satisfaction was 8.5 (IQR, 2.0) (Table 5). All patients reported to be awake during the implantation and 20% experienced the procedure as stressful. In case of a repeat procedure, all patients stated they would request the same anesthetic procedure again. None of the patients reported complications related to the anesthesia. The median score for patient comfort was 3.0 (IQR, 1.25) and for operators' perioperative comfort it was 4.0 (IQR, 1.0).

In case of unacceptable pain management, patients received a bolus of remifentanil of 25 mcg. Six patients required an extra bolus of remifentanil during insertion of the Tuohy needle, or during subcutaneous tunneling. One patient needed 1 bolus of remifentanil, three patients received 2 boluses, and two patients needed ≥ 3 boluses. During the procedure only one patient needed an increase of 0.2 mcg/kg/h dexmedetomidine to achieve an adequate sedation level.

Median SBP, DBP, MAP and mean HR decreased during the procedure (Figures 1 and 2); however, none of these changes were clinically relevant. No patient required any airway intervention.



	preoperative	start dexmedetomidine	start remifentanil	start procedure	midline incision	end procedure	postoperative
Systolic blood pressure	135,5	140,15	132,8	129	112,8	101	110
Mean arterial blood pressure	107	114,67	109,3	101,2	90,5	78,3	76,8
Diastolic blood pressure	87,5	88,67	84,88	78	67,65	63,63	62

Figure 1. Systolic, diastolic and median arterial blood pressure at each measurement

The mean duration of the procedure was 115.4 (SD 34.84) minutes and the median duration was 118.5 (IQR, 56.25) minutes.

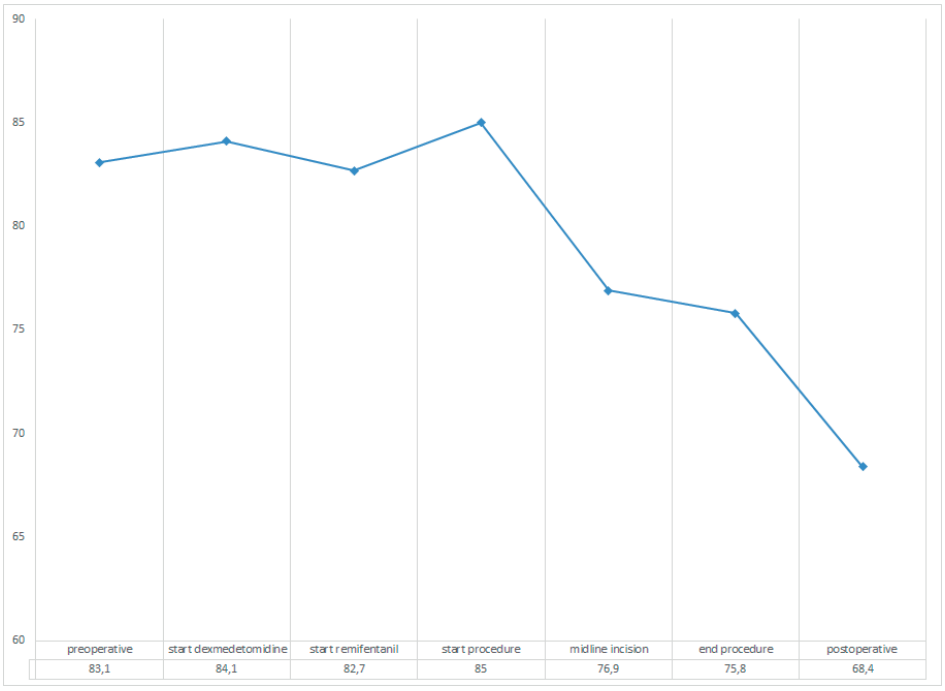


Figure 2. Mean heart rate at each measurement

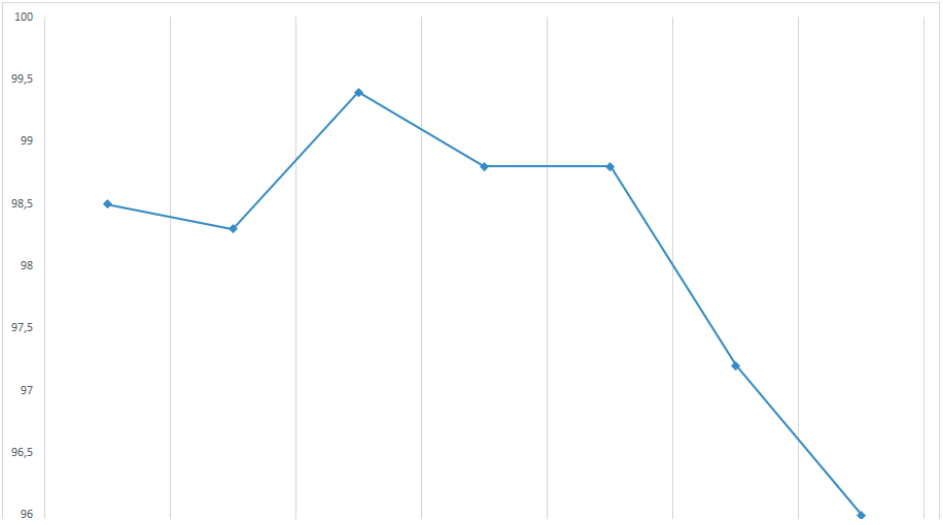


Figure 3. Median oxygen saturation level (SpO2) at each measurement

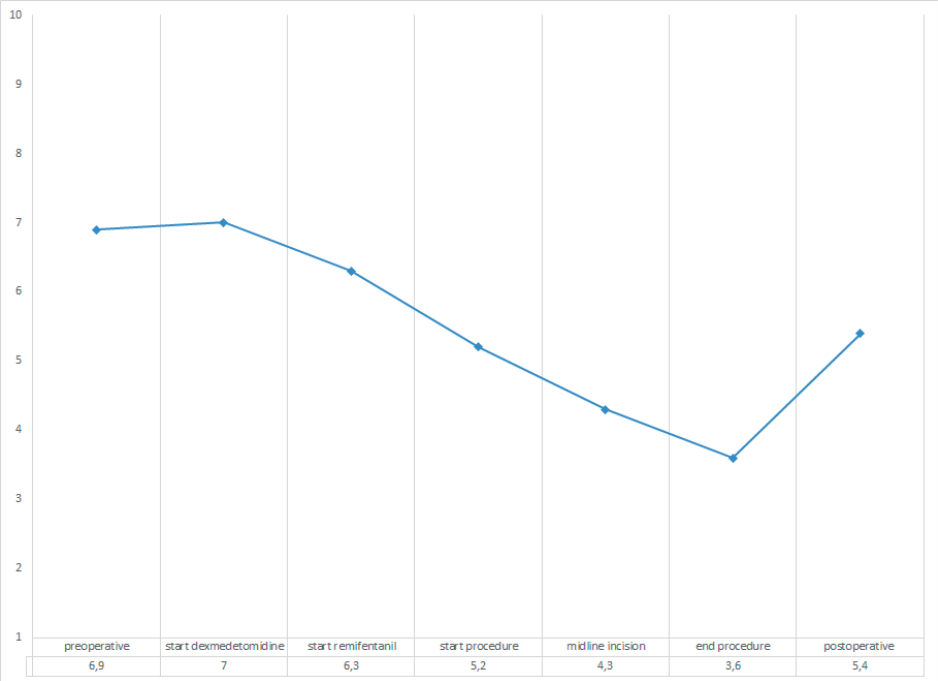


Figure 4. Mean Numeric Rating Scale (NRS) pain score of each measurement

DISCUSSION

When a patient is required to be awake during a surgical procedure, this is generally experienced as a stressful and uncomfortable situation. Therefore, an effective sedation analgesic regimen is necessary. During implantation of a neuromodulative system (classified as a small therapeutic procedure), patients need to be cooperative and able to follow instructions. Dexmedetomidine may be useful for this clinical situation, as its benefits have been reported in various types of procedures (7,8).

In the present study, patients reported a high level of satisfaction (median 8.5; IQR 2.0). Moreover, all patients would choose the same anesthesia regimen again in case of future comparable interventions, and only 20% experienced the implantation as a stressful procedure. Patient comfort was good (median 3.0; IQR 1.25) and operator comfort was excellent (median 4.0; IQR 1.0).

During the procedure, scores on the Numeric Rating Scale (NRS) decreased in nearly all patients, demonstrating adequate pain relief using dexmedetomidine in combination with remifentanil (Figure 4). However, dexmedetomidine is not suitable for incident pain. In our study, incident pain occurred during insertion of the Tuohy needle or tun-

neling, during which pain scores rose to 8-10. This was dealt with by administering a bolus of remifentanil of 25 mcg before the start of tunneling, or a comparable procedure.

In the post-operative period, heart rate and saturation went down (Figure 2 and 3), however the pain score increased. This might be due to the fact that the patient was not experiencing fear any more after the procedure (heart rate decreased) and didn't get any oxygen support (saturation). The decrease in heart rate and saturation were not clinically relevant. Pain score increased postoperatively probably because of pain around the wound, made during surgery. The neuromodulative system was not active at that moment.

This proof-of-concept study demonstrates that a sedation regimen of dexmedetomidine and remifentanil allows implantation of a neuromodulative without the need for airway support. Safety during a procedure depends on airway tone, and controlling this factor will potentially increase patient safety. In our study airway stability was maintained and no respiratory depression in prone position was observed. This latter result was expected, because dexmedetomidine does not act on GABA receptors (9).

During all procedures, hypotension and bradycardia were observed in all patients (Figures 1 and 2) but stayed within an acceptable range. No patient required atropine or any form of hemodynamic support. Patient cooperation and level of instructability were excellent during all procedures. Patients were asleep during the procedure but awakened immediately upon hearing a verbal command. During the procedure, patients had a Ramsay score of 2 to 3 when using a loading infusion of 1 mcg/kg/hour for 10 minutes and a maintenance dose of 0.6 mcg/kg/hour for the remainder of the procedure; this is the desired level of sedation. During the entire procedure a set dose of remifentanil of 3 mcg/kg/hour was administered. Moreover, the use of dexmedetomidine allowed to use a lower set dose of remifentanil as compared with standard care.

The use of dexmedetomidine in neuromodulation surgery including Deep Brain Stimulation (DBS) is well described. Outcomes show promising results, such as good surgical conditions, patient comfort and analgesia. Furthermore dexmedetomidine provided a comparable hemodynamic stability during DBS implantation and this trial (10,11). A limitation of the present study is that we used an observational design with a small sample size, because our first aim was to examine the applicability of dexmedetomidine. Furthermore we did not add the management of bradycardia in the study protocol because this is part of standard care. Any form of hemodynamic support using atropine was not necessary. A follow-up study will compare dexmedetomidine with more conventional regimens of sedation, as well as its cost-effectiveness.

CONCLUSION

In summary, in this patient group, dexmedetomidine combined with remifentanil provided a high level of patient satisfaction and comfort, as well as good operator comfort, without any clinically relevant adverse events. All patients were asleep during the procedure but were highly cooperative and instructable when required; moreover, there was no report of respiratory depression. A randomized controlled trial is required to further investigate the role of dexmedetomidine for the implantation of a neuromodulative system.

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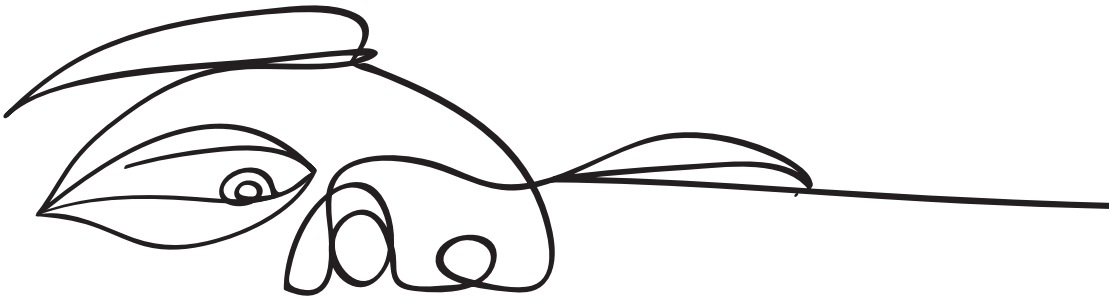

Chapter 4

Dexmedetomidine vs propofol as sedation for implantation of neurostimulators: A single-center single-blinded randomized controlled trial

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ABSTRACT

Background

During the lead implantation of most spinal cord neurostimulators, the patient has to be comfortable and without pain. However, the patient is expected to provide feedback during electrical mapping. Titrating sedatives and analgesics for this double goal can be challenging. In comparison with our standard sedative agent propofol, the pharmacological profile of dexmedetomidine is more conducive to produce arousable sedation. The latter, however, is associated with hemodynamic side effects. We investigated whether dexmedetomidine is preferable over propofol during neurostimulator implantation.

Methods

This single-center single-blinded randomized controlled trial included 72 patients with an indication for a neurostimulator, randomized to sedation with either propofol (0.5mg/kg for 10 minutes, followed by 2.0mg/kg/h) or dexmedetomidine (1µg/kg for 10 minutes, followed by 0.6µg/k/h). The primary outcome was patient satisfaction with the sedation. The secondary outcomes were patient's and operator's comfort, number of titration adjustments, standard intraoperative hemodynamic and respiratory parameters and side effects.

Results

Data of 69 patients (dexmedetomidine n=35; propofol n=34) were analyzed. Those receiving dexmedetomidine were more satisfied with the sedation than those receiving propofol; i.e. with sedation delivery (median 100.0 vs 83.3, $p < .01$), procedural recall (median 95.8 vs 83.3, $p = .03$) and sedation side effects (median 90.0 vs 83.3, $p = .01$). Fewer changes in the dexmedetomidine titration were necessary to maintain arousable sedation. Over time, mean arterial pressure and heart rate were significantly lower in the dexmedetomidine group. Hemodynamic side effects were comparable across groups.

Conclusions

Dexmedetomidine sedation resulted in higher patient satisfaction and allowed for better arousable sedation than sedation with propofol. Although differences in hemodynamic parameters were found between the groups, these differences were not regarded as clinically relevant.

INTRODUCTION

For correct lead placement of most spinal cord neurostimulators, the patient's feedback on the overlap between the area of neurostimulation-induced paresthesia and the pain area is essential (1). Being awake in prone position during a lead implant procedure can be uncomfortableand possibilities for local anesthesia are limited because the deeper structures should preferably not be anaesthetized. Because the patient is expected to give immediate and adequate feedback, a superficial local anesthesia combined with arousable sedation analgesia is often used in these interventions (2,3) .

Our standard sedative agent so far has been propofol, which acts on $GABA_A$ receptors. An alternative to this is the use of dexmedetomidine, a highly selective, long-lasting presynaptic α2-adrenoreceptor agonist with sedative, anxiolytic and analgesic characteristics. It induces a state mimicking natural sleep with easy arousability and no decline in cognitive skills or cooperation. A return to sedated state after arousal by external stimulation is achieved within a few minutes (4-7). The use of dexmedetomidine does not result in respiratory depression, and is associated with a lower incidence of delirium, as well as lower opioids consumption. On the other hand, side effects such as hypotension and bradycardia have been reported (8-11). Recently, the use of dexmedetomidine was found beneficial during other procedures requiring arousable sedation, such as an awake craniotomy (12-14).

We hypothesized that sedation with dexmedetomidine could provide a more stable situation for the patient than sedation with propofol. The primary aim of this study was to determine patient satisfaction with each of these methods of sedation. Secondary aims included determining patient's and operator's comfort, ease of arousable sedation, standard intraoperative hemodynamic and respiratory parameters, and side effects associated with the use of dexmedetomidine and that of propofol during the implantation of a neurostimulator.

MATERIALS & METHODS

Study design

This was a single-blinded, randomized controlled study. The study protocol was approved by the Medical Ethics Review Board of Erasmus University Medical Center and registered with the Netherlands Clinical Trials Registry on 17 September 2015 (NL52755.078.15) and the ISRCTN registry on 03 December 2015 (ISRCTN46302353). All participants provided a written informed consent.

Inclusion of patients

From October 2015 to April 2018, we included 72 consecutive patients (aged 18-65 years) with an indication for implantation of a neurostimulator. Exclusion criteria were hypersensitivity to either of the drugs investigated, atrioventricular block (II-III), acute cerebrovascular disease, HR ≤ 60 bpm, pregnancy, recent acute epilepsy or uncontrolled seizure, severe liver dysfunction, use of beta blocking agents, psychopathology, or a communication problem. The assignment of patients to either the experimental group (i.e., receiving dexmedetomidine) or the group receiving propofol was randomized by the hospital pharmacy using a randomization list compiled by a statistician. To ensure blinding, the hospital pharmacy provided white lines for infusion and covering material for the syringe.

Blinding

Sedation was performed by an anesthesiologist who could not be blinded to the study group allocation because the sedation protocols for dexmedetomidine and propofol are different. The patient and the operator however were blinded to the study group allocation. In addition, a blinded observer, not involved in the sedation or the interventional procedure, enrolled the patients and performed all perioperative study measurements. If a medical emergency would have occurred during the intervention, the blinding would have been broken and the reason for it reported.

Procedural details

Before the procedure, all patients received a standard explanation about the procedure from a specialized pain nurse. Intraoperative standard monitoring parameters , i.e. non-invasive mean arterial pressure (MAP) and heart rate (HR) via ECG, peripheral oxygen saturation (SpO_2), and end tidal CO_2 ($etCO_2$) were measured from the preoperative moment till the postoperative moment.

Before the start of the procedure, the patient received 1cc lidocaine (1%) iv to cover possible pain due to the administration of propofol. Both dexmedetomidine and propofol were infused through an iv cannula.

Standard care involved supplemental oxygen by nasal prongs.

To provide analgesia, 1% lidocaine in combination with adrenaline (1:200 000) was infiltrated to the skin prior to the skin incision by the operator. The level of the mid line incision (T5), dissected till the fascia of the paravertebral muscles, was determined by on the stimulation target on the spinal cord or concerned dorsal root(s).

In addition to lidocaine, a set dose of remifentanil (3 µg/kg/h) was administered ten minutes after administration of the loading dose of dexmedetomidine or propofol. Any pain during the procedure that could not be locally treated with lidocaine, was treated with an additional bolus of remifentanil (25 µg).

The patient's pain problem determined the choice for spinal cord stimulation or dorsal root ganglion stimulation and the number of leads were to be implanted. The preferred location of the battery was the left buttock, unless the patient wished otherwise. The procedure was performed in the surgical day care unit.

Sedation protocol

Patients in the dexmedetomidine group received a loading dose of dexmedetomidine of 1 µg/kg over 10 minutes to achieve the required level of sedation, followed by a maintenance dose of 0.6 µg/kg/h. Subjects in the propofol group received a loading infusion of 0.5 mg/kg propofol 1% over 10 minutes followed by a maintenance dose of 2.0 mg/kg/h. The level of sedation during procedure was measured by the Ramsey Sedation Scale immediately before the initiation of sedation and at 5-min intervals until the end of the procedure. The required depth of sedation was equal to a Ramsey score of 3, corresponding to 'Awake, responds only to commands' (15). If the level of sedation was inadequate, the dose of sedative was adjusted. Dexmedetomidine was increased or decreased with steps of 0.1 µg/kg/h with an acceptable range of 0.6 - 1.4 µg/kg/h. Propofol was increased or decreased with steps of 1 $mg \cdot kg^{-1} \cdot h^{-1}$ with an acceptable range of 2.0 - 4.0 mg/kg/h. All such adjustments were recorded and used as an indicator for the production of arousable sedation. Sedation was not stopped during the procedure.

Measurements

The primary outcome parameter was patient satisfaction with the sedation, measured with the Patient Satisfaction with Sedation Index (PSSI), a valid and reliable instrument (16). The PSSI consists of four subscales, i.e., sedation delivery (2 items), procedural recall (4 items), sedation side-effects (10 items), and global satisfaction (4 items). Subscale scores can range from 0-100, with higher scores indicating higher patient satisfaction. Since the study population was Dutch-speaking, three Dutch physicians (native speakers) who were fluent in English had translated the U.S. version of the PSSI into Dutch. Differences between the three translations were discussed until consensus was reached, resulting in a single Dutch translation. Back translation into English resulted in hardly any difference with the original English version (17).

The secondary outcomes were: (a) patient's comfort and operator's comfort throughout the procedure, measured as the response to the question "What score would you give to

the comfort during the procedure?" – from 1 (bad) till 4 (excellent); (b) number of adjustments made during dexmedetomidine or propofol titration; (c) level of sedation measured with the Ramsey Sedation Scale; (d) sedation side effects (18) (i.e., desaturation, airway intervention, laryngospasm, hypotension, bradycardia, vomiting and unwanted movement) and (e) intraoperative standard monitoring parameters – i.e. noninvasive MAP and HR via ECG, SpO_2, and $etCO_2$.

Data collection

The measurements were performed every 5 minutes during the procedure.

Each procedure was divided into nine predefined phases (preoperative and T1-T8). Measurements were made at the following predefined moments: a preoperative measurement baseline measurement in the outpatient clinic during preoperative screening; (T1) at lidocaine infusion; (T2) at start of infusion of dexmedetomidine or propofol; (T3) at start of remifentanil; (T4) at start of the procedure; (T5) at midline incision (incision of the skin for anchoring the lead of the subcutaneous fascia and subcutaneous tunneling of the lead); (T6) at the end of the procedure; (T7) in the recovery room; and (T8) postoperatively on the ward.

The mean values of the measurements made during each predefined served as the outcomes of the phases. Mean values were calculated because the predefined phases varied in duration.

Statistical Analysis

The sample size calculation was based on the primary outcome parameter: patient satisfaction measured by the validated Patient Satisfaction with Sedation Index (PSSI). A statistically detectable and clinically relevant effect size (d) of 0.45 was chosen on the basis of *Vargo et al* (16). The power of the study (1 - β) was chosen to be 0.8, the allocation ratio to be 1:1, and the two-sided level of significance (α) to be 0.05. The required a priori total sample size computed by this method is 72.

Descriptive statistics were used to determine the frequencies of the demographic variables and the outcome parameters, and to describe measures of central tendency and variability, depending on the shape of the distribution.

All distributions were checked for normality using the Kolmogorov-Smirnov test. If a parameter appeared to be normally distributed, its features are presented as mean ± standard deviation (SD). When not normally distributed, data are presented as median and interquartile range (IQR).

Differences between the two groups in variables measured only once were tested with the independent-samples Mann-Whitney U test if the parameter was not normally distributed, or with the independent samples t-test if the parameter was normally distributed.

Differences in relative frequencies between the two groups were tested with Fisher's Exact test.

The repeated measured parameters (i.e. MAP, HR and SpO_2) were analyzed using a repeated measures MANOVA. The factor group (the dexmedetomidine group and the propofol group) and the factor time (i.e. all phases of the implantation procedure (Pre-operative and T1-T8)) served as independent parameters. Dependent variables were the repeated parameters mentioned above.

The MANOVA for repeated measurements within factors model requires that each dependent variable entered into the analysis be normally distributed. However, if the distribution of repeated measured parameters was non-normally distributed the MANOVAs were still used, because the Monte Carlo experiments have shown that, for sample sizes of 3 or 5, it is possible to analyze distributions quite dissimilar to normal ones. These latter experiments demonstrated that the empirically determined rejection region of the F-distribution would be no larger than $\alpha = 0.08$ when the usual 5% rejection is used (Keppel 1973 (19). For all statistics, α was set at the 0.05 level.

RESULTS

Patient Characteristics

Three of the 72 included patients dropped out from the study: one because the patient's back anatomy necessitated lead placement guided by a MRI-scan (which was not available), and two patients for logistical reasons (study measurements performed by a non-blinded person). *Table 1* presents the characteristics of the patients for both groups.

Patient satisfaction

The scores of the patients in the dexmedetomidine group on 3 of the 4 subscales of the PSSI were significantly higher than those of the patients in the propofol group, which shows a greater satisfaction of the former *(see table 2).* We excluded item 20 of the subscale 'Global satisfaction', which measures satisfaction with the current intervention compared to that of a previous one, from the analysis because three quarters of the patients did not have a previous one.

Table 1. Patient characteristics by study group

	Dexmedetomidine group (n=35)	Propofol group (n=34)
Age (yr), median [IQR]	46.9 [52.9-40.9]	46.4 [56.2-36.7]
Female gender, n (%)	23 (65.7)	25 (73.5)
BMI (kg/m^2), mean (SD)	27.2 (5.8)	27.2 (5.3)
NRS-score preoperative, median [IQR]	7.9 [8.8-6.5]	7.7 [8.3-6.6]
Medications, n (%)		
- None	6 (17)	3 (8)
- Paracetamol	10 (29)	14 (41)
- NSAID	8 (23)	8 (24)
- Gabapentinoids	16 (46)	9 (27)
- Weak opioids	1 (3)	3 (8)
- Strong opioids	17 (49)	15 (44)
- Antiepileptic's	1 (3)	2 (6)
- Antidepressants	14 (40)	14 (41)
- Benzodiazepines	7 (20)	9 (27)
Smoking, n (%)		
- Non-smoker	22 (63)	22 (65)
- Smoker	8 (23)	10 (29)
- Unknown	5 (14)	4 (12)
Alcohol use, n(%)		
- Yes	22 (63)	14 (41)
- No	4 (11)	15 (44)
- Unknown	9 (26)	5 (15)
Neurostimulator indication, n (%)		
- CRPS I & II upper extremity	6 (17)	8 (24)
- CRPS I & II lower extremity	14 (40)	11 (32)
- Neuropathy	6 (17)	6 (18)
- Failed Back Surgery Syndrome	9 (26)	7 (21)
- Other	0 (0)	2 (6)

Abbreviations: CRPS, complex regional pain syndrome; NRS pain score, numeric rating scale (11-point NRS 0-10); NSAIDs, non-steroidal anti-inflammatory drugs; weak opioids: codeine or tramadol; strong opioids: morphine, oxycodone, tapentadol, fentanyl, methadone, extended release morphine.

Patient's and operator's comfort

In both groups, the median patient's comfort score was 3.00 [IQR 1.0](p = .75). The operators' comfort score in the dexmedetomidine group was 3.00 [IQR 1.0] versus 3.00 [IQR .63] in the propofol group (p = .50).

Hemodynamic variables

Mean arterial pressure

The MAP showed a bigger decrease over time in the dexmedetomidine group than in the propofol group (factor "Time x Group" $F_{(4.0, 268.0)} = 3.5$, $p < .01$). There was a difference regarding the factor time (factor "Time" $F_{(4.0, 268.0)} = 81.8$, $p < .01$) and regarding the factor group (factor "Group" $F_{(1, 67)} = 4.8$, $p = .03$). The post hoc test revealed only a significant difference at T8 (p = 0.005) (*see figure 1)*.

At some time during the procedure, two patients in the dexmedetomidine group had a MAP < 60 mmHg, with a minimum perioperative pressure of 51 mmHg and 54 mmHg, respectively. Both were given a single ephedrine injection. In the propofol group one patient had a MAP < 60 mmHg (minimum 58 mmHg).

Heart rate

The HR course differed between the groups over time (factor "Time x Group" $F_{(3.6, 242.8)}$ = 9.6, p < .01). There was a difference regarding the factor time (factor "Time" $F_{(3.6, 242.8)}$ = 5.1, p < .01) and regarding the factor group (factor "Group" $F_{(1, 67)}$ = 8.4, p < .01). The post hoc test revealed a significant difference at the last three moments of measurements (T6-T8) (all p < .001) (*see figure 2)*.

In the dexmedetomidine group, two patients had, once or more, a perioperative HR < 50 bpm (minimum 38 and 49 bpm, respectively) for which one patient was given a single ephedrine injection. In the propofol group none of the patients had a HR < 50 bpm.

Peripheral oxygen saturation

No interaction of time and group was found regarding SpO_2 (factor "Time x Group" $F_{(5.0, 333.6)}$ =1.8, p = .12). The course of SpO_2 differed regarding the factor time (Factor "Time" $F_{(5.0, 333.6)}$ = 12.5, p < .01), however no difference was found regarding the factor group (factor "Group" $F_{(1,67)}$ = 0.1, p = .74). No significant differences were found at any moment of measurement as a result of the post hoc test (*see figure 3*).

In the dexmedetomidine group, desaturation (SpO_2 < 90%) was found in two patients on one or more moments during the procedure (89% and 88% minimum, respectively) compared with four patients in the propofol group (86%, 84%, 89% and 86% minimum, respectively).

Study and rescue medication

The mean amount of dexmedetomidine consumption was 74.79 µg (SD 36.0). The median of propofol consumption was 186.0 mg [IQR 240.0].

A rescue bolus of remifentanil 25 µg was given if a patient reported a high level of pain. In the dexmedetomidine group, eighteen patients received 1-5 rescue boluses and one patient received >5 rescue boluses. In the propofol group, 18 patients received 1-5 rescue boluses and three received >5 rescue boluses. In total, fifty in the dexmedetomidine and 61 in the propofol group (p = 0.523).

The median total amount of remifentanil administered, continuous and bolus infusion combined, was 342.80 [IQR 238.8] mcg in the dexmedetomidine group versus 336.90 [IQR 317.0] mcg in the propofol group (p = .75).

A remifentanil bolus can cause a respiratory depression. In the dexmedetomidine group, two patients showed a desaturation of SpO_2 <90% during the procedure, which in one patient occurred after a bolus administration. In the propofol group, four patients experienced desaturation; one patient experienced two desaturations; and three patients one. Four of these five desaturations occurred after a bolus administration.

Local anesthetic

The anesthetic solution used to provide local anesthesia contained 1% lidocaine plus adrenaline (1:200,000). The mean total volume of lidocaine administered in the dexmedetomidine group was 37.3 cc (equals 373 mg lidocaine and 186.5 µg adrenaline) versus 38.2 cc (equals 382 mg lidocaine and 191 µg adrenaline) in the propofol group (p = .74).

Side effects

One patient in the propofol group was subjected to a head tilt/chin lift after the sedation has suddenly deepened (up to Ramsey score 4) and the patient had lost consciousness. Three patients in the dexmedetomidine group were given a single ephedrine injection after MAP had decreased and/or HR decreased. One patient in the propofol group showed a vagal reaction at the start of the procedure, for which a single ephedrine injection was administered. The number of administered ephedrine injections did not differ between the groups (p = .61).

Production of arousable sedation

Regarding the production of arousable sedation, sedative titration was adjusted for 11 patients in the propofol group versus two patients in the dexmedetomidine group (p < .01) (*see table 3).*

Duration

The median duration from the start of procedure until median incision was 40.00 [IQR 26.0] minutes in the dexmedetomidine group and 36.00 [IQR 17.0] minutes in the propofol group (p = .81). The duration of the entire procedure was 71.00 [IQR 28.0] minutes in the dexmedetomidine group and 70.50 [IQR 34.3] minutes in the propofol group (p = .82). The median time elapsed from start of sedation till reaching a Ramsay score of 3 was 20.00 [IQR 6.0] minutes in dexmedetomidine group versus 20.00 [IQR 12.3] minutes in the propofol group (p = .41).

Table 2. Patient Satisfaction as assessed with the Patient Satisfaction Sedation Index (PSSI), patient satisfaction subscales and transformed scores: score 0 (= low satisfaction) to 100 (= high satisfaction) notated as median (IQR)

	Dexmedetomidine group (n=35)	Propofol group (n=34)	p-value
Sedation delivery	100.0 [100.0-91.7]	91.7 [93.8-83.3]	<.01
Procedural recall	91.7 [95.8-83.3]	83.3 [91.7-75.0]	.03
Sedation side-effects	90.0 [95.0-85.0]	83.3 [87.1-80.0]	.01
Global satisfaction (item 20 excluded)	94.4 [100.0-88.9]	88.9 [100.0-83.3]	.17

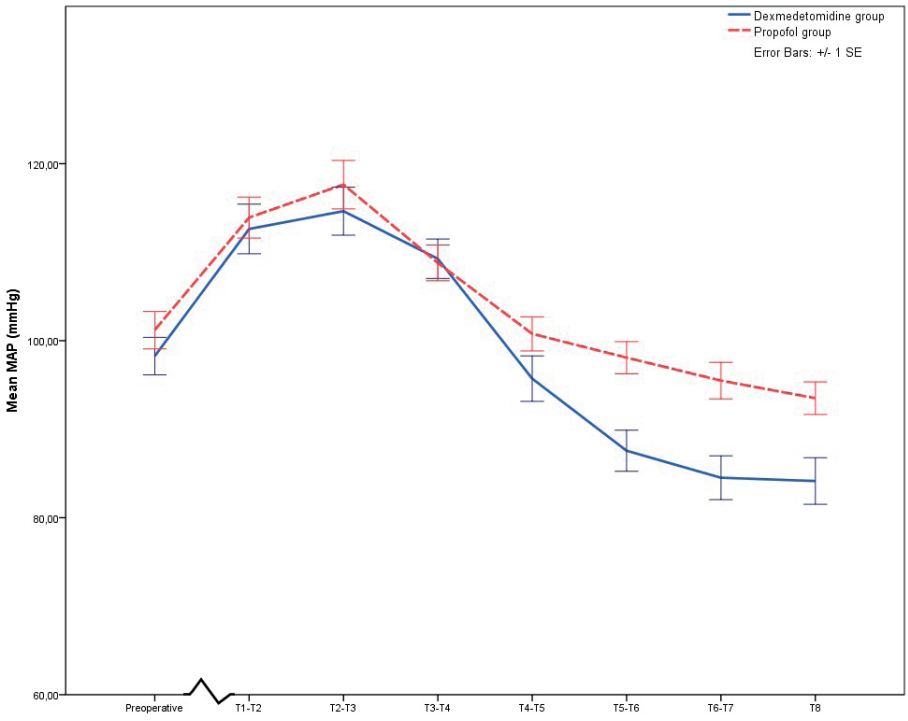

Figure 1. Data on MAP during the procedure. Predefined moments are a pre-operative measurement; (T1) at lidocaine infusion; (T2) at start of infusion of dexmedetomidine or propofol; (T3) at start of remifentanil; (T4) at start of the procedure; (T5) at midline incision; (T6) at the end of the procedure; (T7) in recovery; and (T8) post-operatively on the ward.

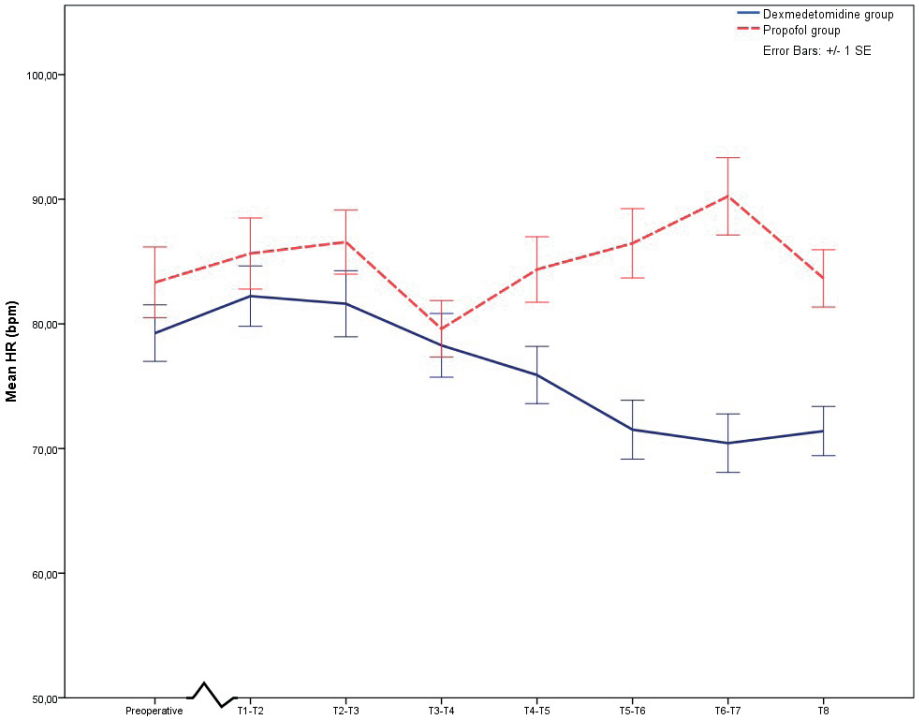

Figure 2. Data on HR during the procedure. Predefined moments are a pre-operative measurement; (T1) at lidocaine infusion; (T2) at start of infusion of dexmedetomidine or propofol; (T3) at start of remifentanil; (T4) at start of the procedure; (T5) at midline incision; (T6) at the end of the procedure; (T7) in recovery; and (T8) post-operatively on the ward.

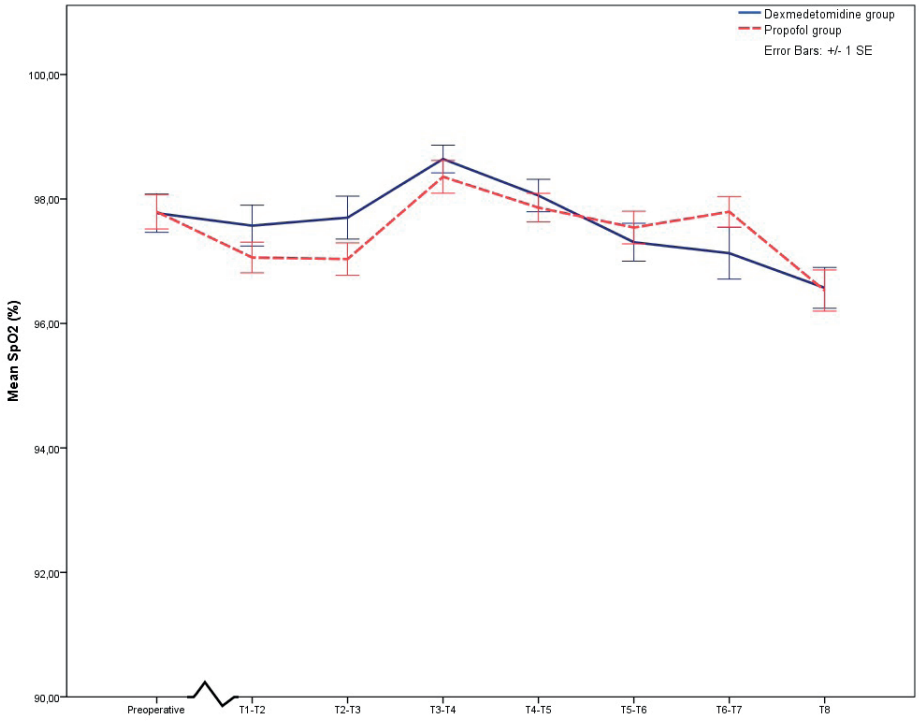

Figure 3. Data on SpO2 during the procedure. Predefined moments are a pre-operative measurement; (T1) at lidocaine infusion; (T2) at start of infusion of dexmedetomidine or propofol; (T3) at start of remifentanil; (T4) at start of the procedure; (T5) at midline incision; (T6) at the end of the procedure; (T7) in recovery; and (T8) post-operatively on the ward.

DISCUSSION

In this study, we compared the degree of the satisfaction with the sedative of patients undergoing implantation of a neurostimulator between those who received dexmedetomidine and those who received propofol as a sedative agent.

Satisfaction

Patients who had received dexmedetomidine were more satisfied with the sedation than those who had received propofol. This higher level of satisfaction was related to the sedation delivery, the procedural recall, and to the sedation side effects. Although patient satisfaction is important in its own right, it has also become increasingly important as an indicator of the quality of health care. Inevitably, it will also have an effect on reimbursements (20-22). However, the relative importance of aspects regarding sedation from the patient's perspective and from the clinical perspective can be questioned

considering that patient safety cannot be deduced from the patient's experience and needs to be based on clinical parameters.

Comfort

A cooperative and calm patient is important for the operator, but deeper sedation and being pain-free provides more comfort for the patient. Ideally, a patient and the operators are both highly satisfied with the situation, and a balance has been reached between each party's requirements (21). The results of this study show that this was achieved with each of the sedatives.

Although patients receiving dexmedetomidine were more satisfied than patients receiving propofol, they did not report a higher comfort. In hindsight, the operationalization of the concept of 'comfort' might have been capacious and ambiguous.

Table 3. No. of patients requiring titration adjustments and no. of patients experiencing side effects

	Dexmedetomidine group (n=35)	**Propofol group (n=34)**	**p-value**
Number of titration adjustments			
Patients (n (%))	2 (5.7)	11 (32.4)	<.01
No. of titration increasement	2	17	
No. of titration decreasement	1	16	
Side effects no. of patients (%)			
Desaturation	2 (5.7)	4 (11.8)	.43
Airway intervention	0 (0)	1 (2.9)	
Laryngospasm	0 (0)	0 (0)	
Hypotension (MAP <60 mmHg)	2 (5.7)	1 (2.9)	1.00
Bradycardia(HR <50 bpm)	2 (5.7)	0 (0)	.49
Vomiting	0 (0)	1 (2.9)	
Unwanted movement	0 (0)	2 (5.9)	

Production of arousable sedation

A Ramsey Sedation Score not equal to 3 after an auditory or painful stimulus, was an indication to adjust the infusion rate. Because the anesthesiologist was guided by the Ramsey score, we presume that the decisions of the anesthesiologist, although not blinded, have not biased our results. More infusion rate adjustments had been made in the propofol group. The lesser need for adjustment in the dexmedetomidine group indicates that dexmedetomidine permits easier arousable sedation.

A recently introduced alternative approach for the implantation of 10-kHz high-frequency Spinal Cord Stimulation therapy requires no intraoperative paresthesia testing

because it is based on anatomical lead placement (23-25). The value of this approach for other neurostimulators using different frequencies is still being discussed. Obviously, arousable sedation need not be produced when an anatomical approach is used. Nonetheless, Tuohy needle placement on levels above L2 in sedated and or anesthetized patients is heavily disputed. It has been argued that arousable sedation is required in anatomical placement as well.

Hemodynamic variables

Consensus on the safe ranges of MAP and HR during moderate sedation has not yet been reached, probably because patient populations, patient positioning, and procedures differ. Brady and colleagues express this as follows: "… *one size does not fit all"* (26). In the present study, although more hemodynamic side-effects were found in the dexmedetomidine group compared to the propofol group, only few emergency interventions were needed in either group. Hence we conclude that both the use of dexmedetomidine and that of propofol can provide a safe situation during sedation.

Theoretically, the differences the experimental groups found in hemodynamic variables could have been the result of the adrenaline contained in the local anesthetic solution. However, given the small amount of lidocaine administered, we consider this unlikely.

Pharmacokinetics

An alpha-2 agonist can cause a biphasic hemodynamic effect. This effect consists of a short-term hypertensive response via vasoconstriction through the alpha-2B receptors (peripheral smooth muscle cells), followed by a hypotensive response mediated through the alpha-2A receptors by inhibition of the firing of the locus coeruleus and the norepinephrine release at the neuroeffector junction (7,27,28). Although this phenomenon has been described in relation to clonidine, *Gerlach et al.* (29) reported that this is not common after dexmedetomidine infusion. In the present study, we found no evidence of a biphasic hemodynamic effect, possibly because dexmedetomidine was administered as a loading dose followed by a maintenance dose instead of a bolus.

Limitations

A limitation of the present study is that it was performed in a single center, which restricts the generalizability of our results. Furthermore, the primary outcome 'patient satisfaction' was measured using a back and forward translated (Dutch language) version of the PSSI, which has not been specifically validated for the Dutch population. In addition, the Ramsey score is a subjective measure of depth of sedation. Instead of this measurement, a more continuous and objective measurement by BIS monitoring could be recommendable. Also, two relevant parameters – i.e., (a) the time elapsed between

a stimulus and a coherent response from the patient and (b) the time course at the recovery – were not measured.

CONCLUSION

As patients receiving dexmedetomidine were more satisfied with the provided sedation than were patients receiving propofol, dexmedetomidine might be preferable over propofol for the implantation of a neurostimulator. Moreover, the use of dexmedetomidine achieved an easier production of arousable sedation – with lesser need for a change in titration. Regarding the hemodynamic outcomes, the MAP and HR values in the dexmedetomidine group were lower than the values in the propofol group. A difference in SpO_2 was found between the groups, without a consistent pattern. Although differences in hemodynamic parameters were found between the groups, these are regarded as clinically irrelevant.

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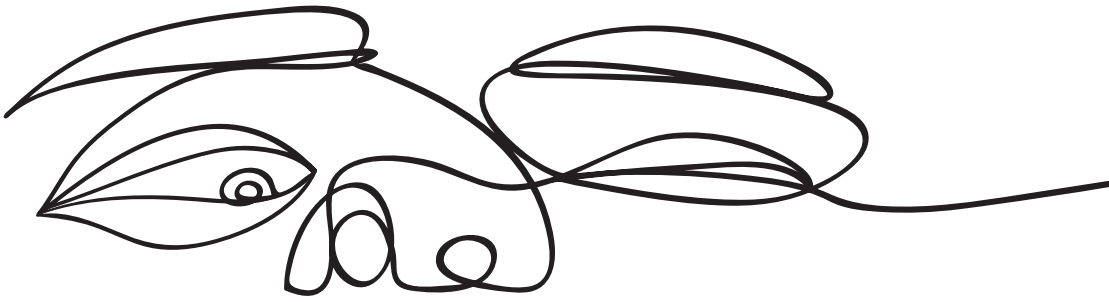

Chapter 5

Cost analysis of dexmedetomidine versus propofol during the implantation of a neurostimulator

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ABSTRACT

Objectives

During the implantation of a neurostimulator, procedural sedation analgesia is intended to contribute to the patient's comfort and cooperativeness. The aim of this study was to compare the financial costs of the sedative agent dexmedetomidine for this procedure, compared to that of propofol.

Methods

The cost analysis was based on the findings of a single-center single-blinded, randomized controlled trial (DexMedPro trial), which compared the effectiveness of dexmedetomidine with propofol in terms of patient satisfaction and patient safety. The cost analysis was conducted from the hospital perspective. The costs associated with the procedure were considered, namely the costs of the sedative agents, other medications, and the neurostimulation procedure itself. Costs were measured for the period between the start of the procedure and the patient's discharge from the recovery room.

Results

The base-case and sensitivity analysis showed that the mean costs for sedation in the dexmedetomidine group varied from €8.53 (SD4.1) to €8.77 (SD 4.2), versus €0.51 (SD 0.4) to €17.86 (SD 15.1) in the propofol group. Sedation costs represented less than 1% of the total costs associated with a neurostimulation procedure, for both a trial implant and a definitive implantation.

Conclusion

The cost difference between the use of propofol and dexmedetomidine during the implantation of a neurostimulator is statistically significant, but small. Based on this consideration and on the benefits to the patient of using dexmedetomidine instead of propofol, we believe that the choice of dexmedetomidine as a sedative in the implantation of a neurostimulator is justified.

INTRODUCTION

During the lead implantation of most spinal cord neurostimulators, the patient must be comfortable and preferably without pain. However, the patient is expected to provide feedback during electrical mapping. Titrating sedatives and analgesics for this double goal can be challenging.

We recently published a study entitled, "Dexmedetomidine vs propofol as sedation for implantation of neurostimulators: A single-center single-blinded randomized controlled trial." This trial (DexMedPro trial) compared dexmedetomidine with propofol during the implantation of a neurostimulator, being a proven cost-effective treatment for certain types of chronic pain (1-3). Dexmedetomidine resulted in higher patient satisfaction and allowed for better arousable sedation than propofol. Differences in hemodynamic parameters were found between the groups, but not regarded as clinically relevant (4).

There were three reasons to study the financial impact of dexmedetomidine versus propofol during the implantation of a neurostimulator.

First, notwithstanding the results of our abovementioned study, several anesthesiologists in our center did not consider the use of dexmedetomidine during the implantation of a neurostimulator. As it has only recently been approved – in 2018 – for sedation analgesia by the European Medicines Agency (EMA), they assumed dexmedetomidine would be more expensive than propofol.

Second, an European economic evaluation of the use of dexmedetomidine in intensive care units unexpectedly found that dexmedetomidine sedation was more cost-effective than the standard sedatives propofol and midazolam (4). This is despite the longer required duration of administration compared to that of the implantation of a neurostimulator (5).

Third, although the costs of a procedure are important in themselves, the quality of the health care from the perspective of the patient is increasingly seen as important. Considering this view and the results of our previous study, i.e., the higher patient satisfaction and the allowance for better arousable sedation using dexmedetomidine compared to propofol, we wondered whether a potentially somewhat higher cost would nevertheless be justified.

METHODS

Study design

This cost analysis was based on the findings of the previously mentioned DexMedPro trial.

Resource consumption and costs

The cost analysis was conducted in 2018 and from the hospital perspective. The costs associated with the procedure were those of the sedative agents (see Table 1), the other medications (see Table 2), and the neurostimulation procedure itself (see Table 3). Costs were measured for the period between the start of the procedure and the patient's discharge from the recovery room. All costs used in the analysis included VAT, as recommended by the "Dutch Manual for Costing in Economic Evaluations" (6).

Base-case and sensitivity analyses

Sensitivity analyses were performed to estimate the effect of varying the values of important input parameters on the results. In particular, the values of dexmedetomidine and propofol per vial were varied. These values were collected from "The Netherlands National Health Care Institute Medication Costs" (searchable database [in Dutch] of medicine prices [September 2018]). Regarding dexmedetomidine, there was one reference price (€22.79 ["sens 1"]). Values of propofol used in the sensitivity analysis were €9.56 and €36.68 per vial (respectively "sens 2" and "sens 3"), both much higher than the base case value of €1.05.

Table 1. Base case price and sensitivity range

	Dexmedetomidine	**Propofol**
Costs per ampoule/ flacon	Base case: €23.44* Sens 1: €22.79**	Base case: €1.05* Sens 2: €9.56** Sens 3: €36.68**

* Base case: price in Erasmus University Medical Center. **Sensitivity range: price extracted from "The Netherlands National Health Care Institute Medication Costs" (searchable database [in Dutch] of medicine prices [September 2018 (7)]); Sens 1: price of the original variant of dexmedetomidine; Sens 2: price of the generic variant of propofol; Sens 3: price of the original variant of propofol; sedative cost = mean costs per the amount of sedative agent used.

Sedative costs were calculated by multiplying the total study sedative dose consumed per patient by the following unit costs: €0.12 per 1 mcg dexmedetomidine (equals €23.44 per 200 mcg ampoule), €0.11 per 1 mcg dexmedetomidine (equals €22.79 per 200 mcg ampoule), €0.002 per 1 mg propofol (equals €1.05 per 500 mg vial), €0.02 per 1 mg propofol (equals €9.56 per 500 mg vial), and €0.07 per 1 mg propofol (equals €36.68 per 500 mg vial).

Table 2. Base case price – cost price for remifentanil and lidocaine in the Erasmus University Medical Center (2018)

Analgesic agents	
Remifentanil HCl 1 mg flacon	€8.99
Lidocaine 1% + adrenaline 1:200.000	€3.77

Table 3. Total rate of neurostimulation from the financial department of anesthesiology of the Erasmus University Medical Center, following the cost model of 2018 (Logex) of the Dutch Health Care Authority

Neurostimulation	
Trial implant	€5,018.50
Definitive implant	€22,885.33

Cost analysis

The analyses were performed in accordance with the Dutch national guidelines for economic evaluation (8), with the restriction that any costs incurred outside the hospital – for example, costs associated with a late complication of the neurostimulation procedure – were not included. In addition to a base case analysis, we also performed a sensitivity analysis in which prices of dexmedetomidine and propofol were varied according to acquisition prices.

Statistical analysis

Descriptive statistics were used to determine the frequencies of the demographic variables and the outcome parameters and to describe measures of central tendency and of variability, depending on the shape of the distribution. All analyses were performed on the primary-analysis sample (i.e., all patients who received any amount of the study drug).

For the base-case analysis, the costs of study drugs were calculated from the perspective of the financial department of our hospital. One-way sensitivity analyses were conducted to highlight the effect of varying cost prices of sedative agents on the results of the total sedative costs.

The costs of the sedative agents and other medications were compared with independent-samples T-tests. The mean, standard deviation, and minimum and maximum values for each group were reported. For all statistics, α was set at the traditional 0.05 level.

All analyses were performed using IBM SPSS Statistics, version 21 (Armonk, NY, USA).

RESULTS

The costs of using dexmedetomidine were statistically significant higher than those of using propofol (see Table 4). The results of the sensitivity analysis were found to be consistent with this finding, with the exception of the original variant of propofol.

Table 4. Results of the base-case analysis and sensitivity analysis regarding costs of medication

	Dexmedetomidine group (n = 35)		**Propofol group (n = 34)**		**Cost difference**	**95% CI**	**p-value**
	Mean (min-max)	***SD***	***Mean (min-max)***	***SD***			
Sedative cost	Base case: €8.77* (€2.03-€17.26)	4.2	Base case: €0.51* (€0.04-€2.07)	0.4	€8.26	[6.8, 9.7]	<0.01
	Sens 1: €8.53** (€1.97-€16.78)	4.1	Sens 2: €4.66** (€0.38-€18.88)	3.9	€3.87	[1.9, 5.8]	<0.01
			Sens 3: €17.86** (€1.45-€72.45)	15.1	€-9.33	[-14.6, -4.1]	<0.01
Remifentanil cost	Base case: €4.81 (€0.86-€30.02)	5.6	Base case: €3.69* (€0.35-€9.85)	2.4	€1.12	[-0.1, 3.2]	0.29
Lidocaine costs	Base case: € 7.47 (€3.60-€11.20)	2.0	Base case: €7.64 (€3.20-€12.20)	2.3	€-0.17	[-1.2, 0.8]	0.74

** Base case: price in Erasmus University Medical Center. **Sensitivity range: price extracted from "The Netherlands National Health Care Institute Medication Costs" (searchable database [in Dutch] of medicine prices [September 2018 (7)]); Sens 1: price of the original variant of dexmedetomidine; Sens 2: price of the generic variant of propofol; Sens 3: price of the original variant of propofol; sedative cost = mean costs per the amount of sedative agent used; remifentanil costs = mean costs per amount of remifentanil used; lidocaine costs = mean costs per amount of lidocaine used.*

As the mean unit-cost of a neurostimulation procedure varied from €5.018,50 for a trial implant to €22.885,33 for a definitive implantation, the sedation costs represented less than 0.5% of the total costs associated with a neurostimulation procedure, both for a trial implant and a definitive implant.

DISCUSSION

This study compared the financial cost of dexmedetomidine with that of propofol during the implantation of a spinal cord neurostimulator. It found that the costs associated with dexmedetomidine were statistically significant higher than those associated with propofol. However, the cost impacts of both sedatives on the total implantation procedure were very small. This might be explained by the relatively short duration of sedative administration and the small amount of sedation needed to provide adequate sedation analgesia. The results of the sensitivity analysis were found to be consistent with the above-mentioned finding.

The total costs associated with neurostimulation might be considered high, mainly because the materials – such as leads, connectors, the battery, and so on – are expensive. Two scenarios of the neurostimulation procedures are described: a trial implant with and without the implantation of the battery during the same operation. Both require patient feedback during electrical mapping to test whether the leads are in the right place by providing paresthesia overlap. The costs of a definitive implant are higher than those of a trial implant primarily due to the internal neurostimulation battery. However, the total sedation costs for both groups were found to be very low compared to the mean total costs associated with both scenarios.

We believe the emphasis in choosing dexmedetomidine or propofol as a sedative to be usedin neurostimulation should be on the efficacy and safety of the sedation analgesia regimen. Firstly, because the sedative agent – both dexmedetomidine and propofol – represent a very small fraction of the costs.

Secondly, a prior investigation of us, namely the DexMedPro trial investigated the patient satisfaction and comfort associated with dexmedetomidine versus propofol during implantation of a neurostimulator. The results of this trial demonstrated a statistically significant higher patient satisfaction in the dexmedetomidine group compared to the propofol group. No significant difference regarding patient comfort were found between the groups.

Patient experience and satisfaction with health care is increasingly seen as an important indicator of the quality of health care (9, 10). The conversion of healthcare benefits, such as higher patient satisfaction, into financial terms is difficult to determine; therefore, willingness-to-pay data might be helpful. However, since the cost difference between the studied sedative agents is very small in itself – and certainly compared to the total costs of neurostimulation – the added contribution of willingness-to-pay analysis is questionable (11).

Some limitations of this study should be noted. First, the Erasmus University Medical Center, the hospital in which the DexMedPro trial was performed, uses the original and more expensive variant of propofol. However, the hospital pharmacy of the Erasmus University Medical Center received an undisclosed discount from the pharmaceutical industry. We expect that it would have been more accurate to use the costs of the generic variant of propofol in the cost analysis (sens 2 analysis, rather than the base-case analysis). This strategy might be more representative of other hospitals, both in our country and worldwide. Second, the DexMedPro study was performed in a single center. Both limitations may have negatively affected the external validity of the study. A third

limitation relates to the costs associated with neurostimulation used in our analysis. The total costs for the neurostimulation procedure are included in the analysis. These include overhead costs such as operating-room rental, operating-room equipment, day care admission, and radiology. The actual costs of the neurostimulation procedure itself were not included in the analysis because they were not available. However, the use of the actual costs (in place of the total costs) would probably not change the conclusion of the cost analysis, since the cost of sedation is a very small percentage.

In conclusion, the difference between the financial costs of using propofol and dexmedetomidine during the implantation of a neurostimulator is admittedly statistically significant, but actually very small. Based on this finding and on the benefits to the patient in terms of patient satisfaction and easy arousability when using dexmedetomidine in place of propofol, we believe that the choice of dexmedetomidine as a sedative is both preferable and justified.

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Chapter 6

Long term effects of dexmedetomidine versus propofol during the implantation of a neurostimulator — a post-trial follow-up analysis

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Submitted

ABSTRACT

Objectives

The success of neurostimulation depends partly on the amount of coverage of the neurostimulation-induced paresthesia of the painful area. This is often achieved by asking feedback from patients intraoperatively. If sedation analgesia is used, it is important that the patient is comfortable during sedation and easily arousable. If the patient is not well sedated or experiences residual effects of the sedation during testing, this can directly influence the ideal placement of the leads and indirectly the long-term effect of the treatment. It is our hypothesis that the quality of the sedation is directly coupled to the adequacy of lead placement and in this way in the result of the treatment. Dexmedetomidine is known for its easy production of arousable sedation. The aim of the present study was to compare the long-term effect of using dexmedetomidine with propofol during the implantation of a neurostimulator.

Methods

This is a post-trial follow-up analysis of the DexMedPro cohort. The primary outcome was global perceived effect (GPE). The secondary outcomes were the course of pain intensity, the emotional and physical functioning at the time of follow-up, and the course of neurostimulation treatment. In this study we used the patient satisfaction with sedation as a measure for sedation quality.

Results

Regarding the GPE, no statistically significant differences were found between the experimental groups in either subscale (i.e., recovery ($p=0.82$) and satisfaction with the neurostimulation treatment at follow-up ($p=0.06$)). The same was found regarding the secondary parameters. A correlation was found between patient satisfaction with sedation during the lead implantation (side effects and procedural recall) and satisfaction at follow-up.

Conclusions

Regarding the long-term efficacy of neurostimulation treatment, no statistically significant differences were found between the dexmedetomidine and the propofol group. We observed a trend towards greater satisfaction with the neurostimulation treatment at follow-up in the dexmedetomidine group, compared to the propofol group.

Keywords

Dexmedetomidine, propofol, chronic pain, neurostimulation, follow-up, retrospective studies

INTRODUCTION

Spinal cord neurostimulation is a proven effective but expensive treatment of chronic pain (1-3). The success of this intervention partially relies on stimulation-induced paresthesia and the extent of its coverage of the painful area(s) (4). Although, more recently, anatomical lead placement has received increasing attention, optimal paresthesia coverage is still often achieved by seeking feedback from patients intraoperatively (5). In our center, and elsewhere across Europe, the most common method of implantation is to apply sedation analgesia and wake up the patient during a test stimulation.

Optimal paresthesia coverage depends on the combination of stimulation parameters and the location of the lead(s) and it is achieved by using patients' feedback. Placement of the leads is easier with an adequate sedation. However, reliable feedback can be obtained if the patient is arousable – preferably easily. Different sedation analgesia strategies can facilitate this in varying degrees.

The most commonly used sedation analgesia regime during a neurostimulation procedure in the Netherlands is the combination of propofol-remifentanil (6). Propofol is frequently used partly because anesthesiologists have much experience with it. It provides a smooth and rapid induction and easily controllable and stable continuation of sedation, and its cost is relatively low (7). However, because propofol acts on the GABA receptors, difficulties may arise with regard to obtaining reliable feedback immediately after waking, due to the drowsiness of the patient.

Dexmedetomidine is an alfa-2 agonist with sedative, analgesic, and anxiolytic properties, known for its ability to produce arousable sedation in a moderately sedated patient, with spontaneous ventilation (8). Previous studies have reported promising results regarding the use of dexmedetomidine in awake procedures, such as during an awake craniotomy (9). In the DexMedPro trial, we compared dexmedetomidine with propofol during the implantation of a neurostimulator – as a sedative agent – in terms of patient satisfaction and safety. The results indicate higher satisfaction with sedation and an easier production of arousable sedation of patients who received dexmedetomidine, compared to the propofol group. The results indicated a safe and stable situation for both patient groups during the procedure (10).

A sedation that is too shallow can cause discomfort for the patient and the implantation team, which is to the detriment of the placement technique of the leads. A poorly awake patient during testing can lead to an inadequate assessment of the position of the leads. Both can have a negative effect on the results in the long term. In other

words, it is presumed that a more controllable agent such as dexmedetomidine leads to better sedation and better arousability and indirect to better lead placement with a better long-term effect. Therefore, our hypothesis was that a high-quality sedation regimen (dexmedetomidine or propofol sedation), indicated by a subjective outcome measurement (i.e., patient satisfaction with sedation) and an objective measurement (easy arousability during the intervention) could have a long-term impact on pain intensity and the emotional and physical functioning of the patients. Hence, the aim of this retrospective study was to examine the extent to which long-term efficacy is associated with the sedation regimen (dexmedetomidine versus propofol) during the implantation of a neurostimulator. The outcome parameters were global perceived effect, pain course, physical and emotional functioning, and course of neurostimulation treatment in terms of complications.

METHODS

This is a post-trial follow-up (PTFU) study of the DexMedPro trial (October 2015-April 2018; NL52755.078.15). This study was approved by the medical ethical committee of the Erasmus Medical Center in Rotterdam in March 2018.

Study design

A retrospective cohort study.

Subjects and treatment

Sixty-nine patients with an indication of a spinal cord neurostimulator were included in our previous DexMedPro trial. The aim of that trial was to examine whether the use of propofol versus dexmedetomidine as a sedative, leads to differences regarding patient satisfaction, ease of arousable sedation, and hemodynamic variables, during the implantation of a neurostimulator. Details regarding intra operative and postoperative data, dose of medication, indication for procedure, duration of procedure, level of sedation of the drugs are provided in the article about the DexMedPro trial (10).

The participants in this current PTFU study were those included in the DexMedPro trial. Patients were excluded if they had received an extra lead to the existing neurostimulation system and/or if they had had a negative trial period. Furthermore, patients who had undergone an explant were excluded as well.

Outcome parameters

All patients were evaluated by a review of the routine clinical records from the first intake at the department of Pain Medicine of the Erasmus Medical Center. Patient records, patient demographics, pain diagnosis, and device specifics are to be found in the article about the DexMedPro trial.

The outcome parameters were measured a questionnaire administered by telephone in the period from January to February 2020. The primary outcome parameter was global perceived effect, measured by the global perceived effect questionnaire (GPE), see Table 1 (11), at the time of the telephone interview, regardless of the duration of therapy to date. The secondary outcome parameters were pain course (measured by the NRS pain score), emotional functioning (measured by the Hospital Anxiety Depression Scale [HADS]), physical functioning (measured by the Short Form Health Survey [RAND-36]), and treatment course (measured by the occurrence of complications, see Table 2) (12).

Table 1. Seven-point scale of the Global Perceived Effect (GPE) questionnaire

Global Perceived Effect	
1. How would you rate the course of your recovery since the start of this study?	1. Completely recovered 2. Much improved 3. Slightly improved 4. Not changed 5. Slightly worse 6. Much worse 7. Worse than ever
2. How satisfied are you with the neurostimulation treatment?	1. Absolutely satisfied 2. Very satisfied 3. Slightly satisfied 4. Not satisfied nor dissatisfied 5. Somewhat dissatisfied 6. Very dissatisfied 7. Absolutely dissatisfied

Table 2. Long-term efficacy recorded according to the categorisation of Pope et al. (12)

Complications
Battery replacement
Complications requiring surgical intervention
Lead migration
Surgical site pain
Battery site pain
Fractured lead(s)
Lead revision
Infection
Seroma
Erosion
Epidural hematoma

Statistical analysis

Descriptive statistics were used to determine the frequencies of the demographic variables and the outcome parameters and to describe measures of central tendency and variability, depending on the shape of their distribution.

Using the Shapiro Wilk test all parameters appeared to be skewly distributed. Therefore, the measure for the central tendency is presented as the median and the measure for the dispersion as the midspread, i.e. the InterQuartile Range (IQR: Q1 –Q3). To be able to analyse a difference over time in pain level between the experimental groups, the difference between the preoperative pain and the pain at the time of the interview was calculated. Differences between the experimental groups in the continuous parameters were analysed using the Independent-Samples Mann-Whitney U Test. Spearman's rank correlation coefficient was used to test the degree of association between continuous variables. The difference in the proportion of the complications that did occur in the experimental groups was tested using the Fisher's exact test (two-sided). The difference in the length of time between the implantation until the completion of the questionnaire may have had an effect on the level of outcome parameters. Therefore we performed a analyses by dividing each experimental group into two groups using the median of the aforementioned length of time as the grouping criterion. Differences in the groups thus created were tested using the Independent-Samples Kruskal-Wallis Test. or all statistics, α was set at the traditional level of .05 level. Analyses were performed using IBM SPSS Statistics 22.

RESULTS

Following approval, 69 patients were included in the DexMedPro trial. If patients had had a negative trial period (n=7), received an extra lead (n=2), or died (n=2), they were excluded from this current trial. Nine patients underwent an explant of the neurostimulation system . We have no data for five patients because they could not be reached by telephone (3 patients from the dexmedetomidine group and 2 patients from the propofol group) . The remaining 44 patients were analysed.

The median number of days from implantation until completion of the questionnaire was 883 [IQR 706 – 1214] in the dexmedetomidine group and 837.5 [IQR 756.5 – 1104.5] in the propofol group (p=0.73).

Regarding the subscale recovery of the GPE scale, the scores of the dexmedetomidine group (2.0 [IQR 2.0 – 3.0]) did not differ from those of the propofol group (2.0 [IQR 2.0

– 3.0])(p=0.82). A trend was found in the subscale satisfaction in favor of the dexmedetomidine group (dexmedetomidine group 2.0 [IQR 1.0 – 3.0] vs propofol group 2.0 [IQR 2.0 – 3.0](p=0.06)).

We found a statistically significant negative correlation between the subscale satisfaction with neurostimulation treatment of the GPE and the subscale side effects of patient satisfaction with sedation index (PSSI) during the neurostimulation intervention administered at the end of the procedure and measured during the previous DexMedPro trial (r = -0.32; p=0.035). This indicates that greater patient satisfaction in terms of side effects is associated with greater satisfaction with the effect of neurostimulation treatment reported at follow-up. Although not statistically significant, there was also a correlation identified between the subscale procedural recall of the PSSI and both subscales of the GPE (i.e., satisfaction (r=-0.27; p=0.08) and recovery (r=-0.30; p=0.05)). The data suggest that greater patient satisfaction with sedation (procedural recall) is associated with greater satisfaction reported at follow-up with the effect of the treatment.

No correlation was found between the number of titration adjustments and the reported overall effect of the procedure in terms of satisfaction and recovery (GPE).

The preoperative pain score was compared with the pain score at follow-up. The median pain difference in the dexmedetomidine group was 1.7 [IQR 0.9 – 3.9] versus 1.5 [IQR 0.75 – 3.4] in the propofol group. No significant difference was found between the experimental groups in the difference between the level of preoperative pain and that at the time of the follow up (p=0.45).

Regarding the depression subscale of the HADS questionnaire, the median score was 6.0 [IQR 3.0 – 10.0] in the dexmedetomidine group versus 4.0 [IQR 1.5 – 7.0] in the propofol group. This indicates a trend towards more depression complaints in the dexmedetomidine group (p=0.07).

The median score for the anxiety subscale was 4.0 [IQR 1.0 – 7.0] in the dexmedetomidine group versus 5.0 [IQR 2.5 – 7.0] in the propofol group, implying no statistically significant difference between the median scores between both groups (p=0.95).

The same applied to the total median score on the HADS: 9.0 [IQR 5.0 – 15.0] in the dexmedetomidine group versus 8.0 [IQR 5.0 – 13.5]) in the propofol group (p=0.30).

Furthermore, no significant differences in the RAND-36 domains were found between the experimental groups, see Table 3.

Table 3. Median and IQR (Q1 – Q3) for the subscales of the RAND 36 by experimental group. Scale scores were calculated using the SF-36 scoring system

	Dexmedetomidine group (n=23)	Propofol group (n=21)	p
Physical functioning	50 (20 – 60)	35 (22.5 – 60)	0.84
Social functioning	50 (25 – 62.5)	50 (37.5 – 68.75)	0.64
Role limitations – physical	0 (0 – 25)	0 (0 – 25)	0.78
Role limitations – emotional	100 (33.3 – 100)	100 (66.7 – 100)	0.91
Mental health	80 (64 - 88)	80 (66 – 84)	0.47
Vitality	45 (25 – 55)	40 (32.5 – 55)	0.97
Pain	44.9 (22.4 – 55.1)	44.9 (22.4 – 47.0)	0.96
General health	45 (25 – 65)	40 (30 – 60)	0.48
Change in health	50 (50 – 75)	50 (37.5 – 75)	0.87

The occurrence of complications was analysed from the day of implantation to the time at which the questionnaire was obtained or the moment of explant (see Table 4). There were no complications registered regarding infection, seroma, erosion, or epidural hematoma.

Median number of complications per patient in the dexmedetomidine group is 1.0 (IQR 0 – 2.0) and in the propofol group 1.0 (IQR 0 – 1.0) (p = 0.11). The proportion of patients with one or more complications did not differ significantly between the dexmedetomidine group and the propofol group (p= 0.12).

Table 4. Complications that occurred by group, multiple complications were possible per patient

	Dexmedetomidine group (n=23)	**Propofol group (n=21)**
Patients with complications	17 (74%)	11 (52%)
Battery replacement	2 (9%)	2 (10%)
Complications requiring surgical intervention	3 (13%)	3 (14%)
Migration	4 (17%)	2 (10%)
Surgical site pain	5 (22%)	0 (0%)
Battery site pain	12 (52%)	10 (48%)
Lead revision	4 (17)	1 (5%)

The difference in the length of time between the implantation until the completion of the questionnaire may have had an effect on the level of outcome parameters. The results of these analyses did not differ from the previously performed.

DISCUSSION

In the DexMedPro trial, the satisfaction of the patients who received dexmedetomidine as a sedative during the implantation of a neurostimulator was found to be significantly higher compared to those who received propofol. In addition, dexmedetomidine provided an easier arousability than propofol. Given these differences, we were interested in whether better sedation and easier arousability would lead to better long-term effects of the neurostimulation procedure in the dexmedetomidine group, possibly due to a more targeted placement of the leads in this group.

In this follow-up trial, performed in January and February 2020, no significant differences were found between the dexmedetomidine group and the propofol group regarding all outcome parameters (i.e., global perceived effect, pain course, complaints of anxiety and depression, physical functioning, and treatment course). Nevertheless, it is notable that more surgical site pain occurred in the dexmedetomidine group than the propofol group (five vs zero patients with surgical site pain). We have no plausible explanation for this other than this result is coincidental.

In addition, it is worth mentioning that patients in both groups remain, even after a relatively long time, quite satisfied with the neurostimulation treatment.

Limitations

Several limitations of this study should be mentioned. This was a retrospective cohort study in which the results could be biased by patients' memory and a possible response shift leading to a reduced internal validity. The more so, given the relatively long period between the implantation and the completion of the questionnaire. The statistical power was most likely negatively affected due to the many exclusions. Furthermore, data from the medical charts were lost during the follow-up because they had not been recorded in a standardised manner and some data were missing. In addition, we did not adjust the error rate α for multiple testing because it would have reduced the power of the tests even more.

CONCLUSION

Regarding the long-term efficacy of neurostimulation treatment, based on the indirect influence of better sedation resulting in better lead placement, in terms of global perceived effect, pain course, and physical and emotional functioning, no statistically significant differences were found between the dexmedetomidine and the propofol group.

We found a trend towards greater satisfaction (subscale of GPE) in the dexmedetomidine group, compared to the propofol group. A correlation was found between patient satisfaction with sedation during neurostimulation intervention (side effects and procedural recall) and satisfaction with the neurostimulation treatment at follow-up.

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V

General discussion

Rationale of this thesis

In this thesis, we investigated the feasibility and safety of the use of dexmedetomidine, an alpha-2 receptor agonist, as a sedative agent, during the implantation of a neurostimulator. Sedation is traditionally performed with propofol in these procedures. The positive experience with dexmedetomidine in other procedures, such as the awake craniotomy, made us curious about the applicability in implantation procedures of a neurostimulator.

Considerations for the use of dexmedetomidine as a sedative in an implant procedure for neurostimulation

Dexmedetomidine has sedative, anxiolytic, and analgesic properties. The advantages of dexmedetomidine are its reported lower incidence of delirium and its opioid-sparing properties (1-4). Although the analgesic properties of dexmedetomidine are considered to be rather weak, acting in particular at the level of the spinal cord, synergy between opioids and the stimulating analgesic effect on the spinal cord from dexmedetomidine might explain the opioid-sparing properties (5). Therefore it is thought to reduce the need for opioids. However, in a neurostimulation implant procedure, complete elimination of opioid use (such as remifentanil) is not realistic, as the procedure can be painful. In addition, the ability to use a local anesthetic is limited, as the aim is to avoid anesthetizing the deeper structures, as this could interfere with potentially reliable patient feedback.

Since dexmedetomidine acts as an agonist on the alpha-2 receptor, dexmedetomidine may have a theoretical advantage over other sedatives, as it allows for easy-to-achieve arousable sedation with minimal respiratory depression. Respiratory depression is a particularly common side-effect when a sedative acts via a GABA receptor. Although dexmedetomidine does not act on the GABA receptors, recent findings suggest that sedation with dexmedetomidine sedation does not fully protect against upper-airway obstruction or respiratory depressant-effects (6, 7).

The literature describes the benefits of using dexmedetomidine during awake craniotomy. Fewer perioperative respiratory events are reported, compared to sedation with propofol-remifentanil (8). It creates reliable sedation (9) and allows for rapid and reliable clinical neurological assessment when the sedation is stopped (10). We have shown in a systematic review that dexmedetomidine, when used as a sole sedative, has advantages in small diagnostic and therapeutic procedures, such as ENT- and gastrointestinal medicine, in terms of pain relief and patient satisfaction (11).

In neurostimulation system implantation procedures, optimal lead placement is achieved through an optimal overlap of the area where pain is felt with the area where paresthesia is experienced. This is checked intraoperatively by waking up the patient to obtain feedback upon stimulation (12). The extent to which the paresthesia overlaps the area of pain is a predictor of pain relief and thus indirectly associated with the success of the neurostimulation therapy (13). In addition, the patient should feel as comfortable as possible and preferably be pain-free. Creating a situation of comfort for a patient who is awake can be challenging. We hypothesized that, based on its specific pharmacological profile, dexmedetomidine could have advantages over propofol in the implantation of a neurostimulator. To investigate this hypothesis, we conducted several studies.

In a prospective observational pilot study, we investigated the applicability of dexmedetomidine during the implantation of a neurostimulator in 10 patients and reported high patient satisfaction, good operator comfort, and a safe hemodynamic and respiratory situation for the patient (14).

In a single-center, single-blinded, randomized, controlled trial with 72 patients, we compared the use of propofol with that of dexmedetomidine as sedatives during the implantation of a neurostimulator. Because the patient's perception of satisfaction and comfort is increasingly seen as an important indicator of the quality of an intervention, we chose patient satisfaction with sedation as the primary outcome parameter in this study. Sedation with dexmedetomidine resulted in higher patient satisfaction and enabled faster awakening, compared to propofol (15).

The most commonly reported hemodynamic adverse events with dexmedetomidine are hypertension (short hypertensive response via vasoconstriction by alpha-2B receptors), hypotension (hypotensive response by alpha-2A due to locus coeruleus inhibition and inhibition of noradrenaline release in neuroeffector junction), and bradycardia (16).

There is no consensus on which changes in blood pressure and heart rate during procedural sedation are safe, because "one size does not fit all" (17). Patient safety is just as important as the patient's experience and comfort. Therefore, in addition to the patients' experience, we studied the changes in the hemodynamic parameters in and between the two groups.

For this, a baseline measurement in the outpatient clinic during the preoperative assessment and intraoperative measurements were performed. We defined the perioperative cut-off value for bradycardia as a heart rate of < 50 beats per minute and hypotension as a mean arterial pressure of < 60 mmHg. Due to the rapidly transient or even absent

hypertension after induction, no threshold value for hypertension was defined. As expected, decreases in both blood pressure and heart rate were observed in both groups. The dexmedetomidine group showed a significant lower mean arterial pressure and heart rate over time, compared to the propofol group. This difference was not regarded as clinically significant. Thus, both sedatives are safe during sedation. A limitation of this conclusion is that it is not clear whether the administration of a local anesthetic with adrenaline was a confounding factor influencing the hemodynamic parameters (15).

Data monitoring

In this study the depth of sedation was measured with the Ramsay sedation score. This method depends on the subjective assessment of the anesthesiologists (18). It requires a verbal or painful stimulus for the evaluation of the depth of the sedation and reflects the moment of observation. In our studies, this measurement was performed by an independent non-blinded anesthesiologist who was responsible for the sedation. The desired Ramsay score during the procedure was 3, meaning "awake, responds only to commands." When the Ramsay score was unequal to 3, the infusion rate was adjusted. The ease with which this depth of sedation was achieved was operationalized in the number of changes in the infusion rate. Significantly more changes were required in the propofol group, showing that dexmedetomidine allows for easier achievement of stable sedation, compared to propofol.

The depth of sedation is increasingly measured using the Bispectral index (BIS) monitor. This uses raw EEG data, which are then translated via an algorithm into a score of 0-100 (19). Although we did not use this instrument, it could have been an interesting tool to measure the depth of sedation. BIS makes it possible to continuous track levels of consciousness in an objective manner (20, 21). In addition, it can better discriminate between deeper sedation levels (22). However, several limitations of BIS have also been reported. First, propofol and dexmedetomidine have different mechanisms of action, causing differences in EEG dynamics at the same sedation level and therefore potentially inducing differences in the BIS score (23). Second, movement of the facial muscles can cause artifacts in the BIS score (24). Third, no benefits were found with regard to clinical outcomes or resource utilization when the BIS monitor was compared head-to-head with the Ramsay sedation score in the ICU (25-27).

Costs

Dexmedetomidine was previously approved for long-term use (> 24h) at the ICU, before being approved as a sedative during procedural sedation analgesia. The literature states that dexmedetomidine might be preferred over other sedatives (e.g., propofol and midazolam) due to the shorter duration of mechanical ventilation, less frequent reported

delirium, and lower associated costs (28-31). However, the requirements for sedation on the ICU are clearly different from those for procedural sedation. The main differences are the duration of administration and outcome parameters (i.e., days of admission to the ICU or occurrence of delirium). The costs for the sedatives required for implantations of a neurostimulator are higher when using dexmedetomidine, compared to propofol. However, this difference is relatively small if total costs are included in the comparison.

Long-term effects of the use of dexmedetomidine

In a retrospective follow-up study, we investigated the possible long-term impact of the use of dexmedetomidine as a sedative during neurostimulator implantation and compared it with the use of propofol. The median time between implantation and follow-up was 863 days (IQR 1191-731). The outcome parameters were global perceived effect (GPE-score), course of pain intensity, and emotional and physical functioning at the time of follow-up. To evaluate these aspects, we looked at the course of neurostimulation treatment in terms of complications. The quality of sedation was measured both subjectively (i.e., patient satisfaction with sedation) and objectively (arousal during the intervention) measured. Regarding the long-term efficacy of neurostimulation treatment, no statistically significant differences in the above-parameters were found between the dexmedetomidine and the propofol group. A trend towards greater long-term satisfaction with treatment was found in the dexmedetomidine group. A correlation was found between patient satisfaction with sedation, in terms of side effects and procedural recall) and satisfaction at follow-up. We realize that many factors can influence those outcome parameters. By applying randomization between the two groups, we assume that a comparison of the long-term effects of the sedatives is warranted. Patients with a negative trial period, those who received an additional lead to the existing neurostimulation system, and those with an explant were excluded. Unfortunately, as a result, the sample size became so small that the power of the tests fell below the usual 80%. Despite this important limitation, we believe that we can infer from the data a preference for the use of dexmedetomidine over propofol as a sedative in the implantation of a neurostimulator.

Implementation of new knowledge

Current medicine focusses on protocol-based procedures. We support this peri-procedural working method. Nevertheless, highly detailed, prescribed methods can blind specialists to new possibilities and inhibit early adaptations. Our survey of Dutch pain specialists involved in neurostimulation showed that many were not familiar with dexmedetomidine. They reported a lack of experience, despite the possible theoretical advantages of dexmedetomidine reported in literature and outlined in this thesis (32). Hence, there is still a considerable task for the implementation here.

Future research

One interesting finding concerning dexmedetomidine was revealed in recent research. Namely, dexmedetomidine can have a neuroprotective effect by inhibiting the sympathetic nervous system, reducing oxidative stress, and minimizing the inflammatory response. Notably, the implantation of a neurostimulator itself can cause an increase in chronic pain. Therefore, dexmedetomidine could counteract this situation and thus be beneficial for chronic-pain patients (33). Further research on this subject is thus recommended.

In view of the beneficial effects of dexmedetomidine in the implantation of a neurostimulator, future research into its use in other interventional procedures – such as thermal radiofrequency of Gasser's ganglion — is also advisable.

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VI

Summary

Chapter 1

The introduction describes the rationale for this PhD thesis. The success of neurostimulation depends on the degree of overlap of the area where pain is felt with the area where the stimulation-induced paresthesia is experienced. To accomplish this overlap, patients' feedback is required. Ideally, sedation analgesia can support a situation where the patient is comfortable and experiences as little as pain as possible. If feedback is needed, however, it is preferable that the patient should be easily arousable and cooperative within a few minutes. During other awake procedures, such as an awake craniotomy, positive findings and an attractive pharmacological profile have been reported for the use of dexmedetomidine, a sedative agent. This prompted us to investigate the potential of the use of dexmedetomidine as a sedative during the implantation of a neurostimulator.

Chapter 2

This chapter presents a review of the current evidence for the efficacy of dexmedetomidine as a sole sedative agent administered during small diagnostic and therapeutic procedures, for example ear, nose and throat (ENT) procedures and gastrointestinal interventions. It concludes that, during such small procedures, dexmedetomidine might be considered the preferred choice of sole sedative agent. This is especially true with regard to pain relief and patient satisfaction with the intervention during procedures in adults and when considering respiratory safety in procedures involving children. The possibility of administering dexmedetomidine in different ways also supports the argument for its consideration as the sedative of choice.

Chapter 3

This chapter provides an overview of the use of sedation analgesia by Dutch pain specialists. In Dutch pain practice, the most commonly used regimen is a combination of propofol and remifentanil during the implantation of a neurostimulator. Almost half of the respondents said they had considered the use of dexmedetomidine sedation due to reports of its potential advantages regarding the production of arousable sedation, promising stories and positive respiratory aspects. However, they had not actually used dexmedetomidine, either because they were satisfied with the current regimen and/or had little or no experience with this alternative sedative. Of those respondents who were able to make a comparison between dexmedetomidine and propofol — because they had experience with both sedatives — the majority preferred dexmedetomidine over propofol during a neurostimulation procedure. From these findings, we can conclude that dexmedetomidine has considerable potential but this is not yet reflected in current Dutch clinical practice.

Chapter 4

In a multiple-case study, the potential of the use of dexmedetomidine in the implantation of a neurostimulator was investigated. The use of dexmedetomidine, combined with remifentanil, yielded high satisfaction and comfort on the part of the patients, as well as a good operators' comfort. Furthermore, no relevant adverse events and no respiratory depression were reported. Patients provided adequate feedback. These findings indicate the promising potential of dexmedetomidine as a sedative agent during the implantation of a neurostimulator.

Chapter 5

In this chapter, the results of a single-blind randomized controlled trial are presented. The primary aim of this study was to compare patient satisfaction with their sedation when using either dexmedetomidine or propofol during the implantation of a neurostimulator. Significantly greater patient satisfaction was found in the dexmedetomidine group versus the propofol group. With regard to the secondary outcome parameters, dexmedetomidine yielded a significantly easier production of arousable sedation, as was clearly evident from a lesser need for a change in titration. Concerning the hemodynamic outcomes, it turned out that during the procedure the dexmedetomidine group had a significantly lower mean arterial pressure and heart rate compared with the propofol group. Although more hemodynamic side-effects were found in the dexmedetomidine group compared with the propofol group, this difference is not regarded as clinically relevant since a limited number of interventions was required in both groups. From these findings we can conclude that dexmedetomidine is preferable over propofol as a sedative agent during the implantation of a neurostimulator.

Chapter 6

Dexmedetomidine has only been approved for procedural sedation in the operation room in Europe since 2018. This chapter describes the financial impact of dexmedetomidine versus propofol during the implantation of a neurostimulator. The costs of the use of dexmedetomidine were significantly higher than the costs of using propofol. However, the prices of dexmedetomidine or propofol are comparatively small in relation to the total costs involved in the implantation of a neurostimulator. Therefore, we believe that the choice of a sedation analgesia regimen during the implantation of a neurostimulator should be based on the clinical rather than financial aspects of this procedure.

Chapter 7

In this chapter, the long-term efficacy of the use of dexmedetomidine versus propofol during the implantation of a spinal cord neurostimulator is reported. Our hypothesis was that a high quality of sedation regimen, as measured in terms of both objective and

subjective outcomes, might have a long-term impact on the global perceived effect of the neurostimulation treatment, on pain intensity, and on the emotional and physical functioning of the patient. No significant differences were found, however, between the dexmedetomidine and propofol group regarding the above-mentioned outcomes. A trend towards more satisfaction with the neurostimulation treatment was found in the dexmedetomidine group. Furthermore, a correlation was found between patient satisfaction with sedation during neurostimulation intervention (side effects and procedural recall) and satisfaction with the neurostimulation treatment at follow-up.

Chapter 8

In this general discussion, the current state of knowledge and considerations regarding the use of dexmedetomidine as a sedative during procedural sedation are summarized. The results of the studies of its use during the implantation of a neurostimulator are also commented on, especially in comparison to the use of propofol. The results lead us to assume that both sedative agents are suitable during the implantation of a neurostimulator. However, dexmedetomidine might be preferable. This is because the use of dexmedetomidine results in higher patient satisfaction and because of its ability for a more easy arousal compared to the use of propofol, in combination with a safe situation for the patient. Until now, these favorable properties of dexmedetomidine are not reflected in the daily practice of the implantation of a neurostimulator in the Netherlands.

VII

Nederlandstalige samenvatting

Hoofdstuk 1

In dit inleidende hoofdstuk wordt de rationale voor dit proefschrift beschreven.

Idealiter biedt sedatie-analgesie een situatie waarin de patiënt zich tijdens een interventie op zijn gemak voelt en zo min mogelijk pijn ervaart. Het succes van de implantatie van een neurostimulator – een wakkere procedure - hangt af van de mate van overlap van het gebied waar pijn wordt gevoeld met het gebied waar de door stimulatie geïnduceerde paresthesie wordt ervaren. Om deze overlap tot stand te brengen, is bij een implantatie van de lead(s) enerzijds een patient nodig die zich op zijn gemak voelt en zo min mogelijk pijn ervaart en anderzijds adequate feedback kan geven. Dat wil zeggen dat de patiënt bij voorkeur gesedeerd moet zijn, maar waar nodig binnen enkele minuten gemakkelijk wekbaar en coöperatief moet zijn. Onderzoek naar het gebruik van dexmedetomidine als sedativum tijdens andere wakkere procedures, bijvoorbeeld de wakkere craniotomie, toonde positieve bevindingen en een aantrekkelijk farmacologisch profiel van dit sedativum. Dit was voor ons de reden om de mogelijkheden van het gebruik van dexmedetomidine als sedativum tijdens de implantatie van een neurostimulator te onderzoeken.

Hoofdstuk 2

In dit hoofdstuk wordt een overzicht gepresenteerd van de huidige empirische evidentie voor de werkzaamheid van het gebruik van dexmedetomidine als mono sedativum tijdens kleine diagnostische en therapeutische procedures, bijvoorbeeld KNO-procedures en gastro-intestinale procedures. De conclusie was dat het gebruik ervan, als mono sedativum, als eerste keus zou kunnen worden beschouwd, met name als het de pijnvermindering en patiënttevredenheid betreft tijdens procedures bij volwassenen en het respiratoir veilige profiel bij procedures met kinderen. De mogelijkheid om dexmedetomidine op verschillende manieren toe te dienen (zoals bijvoorbeeld intraveneus of intramusculair), kan ook een positief argument zijn bij de afweging van de keuze voor een sedativum.

Hoofdstuk 3

Dit hoofdstuk geeft een overzicht van het gebruik van sedatie-analgesie door de Nederlandse pijnspecialisten die neurostimulatoren implanteren. In de Nederlandse pijnpraktijk is de combinatie van propofol en remifentanil het meest gebruikte sedatie-analgesie regime bij deze procedure. Bijna de helft van de respondenten heeft overwogen om dexmedetomidine als sedatie te gebruiken vanwege de mogelijke voordelen met betrekking tot de productie van wakkere sedatie, de veelbelovende verhalen en de gunstige respiratoire eigenschappen. Ze meldden echter geen dexmedetomidine te gebruiken omdat ze tevreden waren met het huidige regime en / of weinig cq. geen ervaring had-

den met dexmedetomidine. Van de respondenten die een vergelijking konden maken tussen dexmedetomidine en propofol — omdat ze ervaring hadden met beide sedativa — gaf de meerderheid (69%) de voorkeur aan dexmedetomidine boven propofol tijdens een neurostimulatie procedure. Uit deze bevindingen concludeerden we dat dexmedetomidine van meerwaarde kan zijn, maar dat dat niet wordt weerspiegeld in de huidige Nederlandse klinische praktijk.

Hoofdstuk 4

In een meervoudige case study werd de doelmatigheid van het gebruik van dexmedetomidine bij de implantatie van een neurostimulator onderzocht. Het gebruik van dexmedetomidine, gecombineerd met remifentanil, resulteerde in een hoge tevredenheid en hoog comfort van de patiënten, evenals een goed comfort voor de operateur. Bovendien werden geen bijwerkingen met klinische consequenties gerapporteerd. De patiënt gaf voldoende adequate feedback over waar de stimulatie werd gevoeld. Deze bevindingen wezen op de goede doelmatigheid van dexmedetomidine als sedativum tijdens de implantatie van een neurostimulator.

Hoofdstuk 5

In dit hoofdstuk worden de resultaten van een enkelblinde gerandomiseerde studie gepresenteerd. Het primaire doel van deze studie was om de patiënttevredenheid met de sedatie te vergelijken bij het gebruik van dexmedetomidine of propofol tijdens de implantatie van een neurostimulator. Een significant grotere tevredenheid van de patiënt werd gevonden in de dexmedetomidine groep vergeleken met de propofol groep. Met betrekking tot de secundaire uitkomstparameters leverde dexmedetomidine procedureel een significant gemakkelijkere wakkere sedatie op, wat bleek uit een duidelijk kleinere behoefte aan een verandering in titratie van de sedativa. Wat betreft de hemodynamische uitkomsten bleek dat de dexmedetomidine groep, tijdens de procedure, een significant lagere gemiddelde bloedruk en hartslag had in vergelijking met de propofol groep. Hoewel er meer hemodynamische bijwerkingen werden gevonden in de dexmedetomidine groep, werd dit verschil als klinisch niet relevant beschouwd, aangezien in beide groepen een beperkt aantal interventies nodig was. Uit deze bevindingen concludeerden we dat het gebruik van dexmedetomidine de voorkeur heeft boven dat van propofol als sedativum bij de implantatie van een neurostimulator.

Hoofdstuk 6

Dexmedetomidine is in Europa sinds 2018 goedgekeurd voor procedurele sedatie op de operatiekamer. Dit hoofdstuk beschrijft de financiële kosten van dexmedetomidine en propofol tijdens de implantatie van een neurostimulator. De kosten van het gebruik van dexmedetomidine bleken significant hoger te zijn dan die van het gebruik van propofol.

De kosten van beide sedativa waren echter feitelijk laag als de totale kosten die gemoeid zijn met de implantatie van een neurostimulator, worden meegenomen in de analyses. Daarom zijn wij van mening dat de keuze voor een sedatie-analgesie regime tijdens de implantatie van een neurostimulator niet gebaseerd moet zijn op de financiële, maar op de klinische aspecten van deze procedure.

Hoofdstuk 7

In dit hoofdstuk worden de resultaten van ons onderzoek naar de lange termijn effecten van het gebruik van dexmedetomidine of propofol tijdens de implantatie van een ruggenmerg neurostimulator beschreven. Onze hypothese was dat een hoge kwaliteit van het sedatie-analgesie regime, gemeten in zowel objectieve als subjectieve uitkomstmaten, vanwege een theoretische verwachte technisch optimalere plaatsing van de leads, een impact zou kunnen hebben op het langere termijn effect van de neurostimulatie interventie, op de pijnintensiteit en op het emotionele en fysieke functioneren van de patiënt. Er werden geen significante verschillen gevonden tussen de dexmedetomidine- en propofol groep met betrekking tot bovengenoemde uitkomsten. Wel werd in de dexmedetomidine groep een trend naar meer tevredenheid gevonden. Er wordt een correlatie gevonden tussen de tevredenheid met de neurostimulatie interventie (betreffende de bijwerkingen en de herinnering aan de procedure) en de tevredenheid met de neurostimulatie behandeling op de langere termijn.

Hoofdstuk 8

In de algemene discussie worden de huidige kennis van en overwegingen met betrekking tot het gebruik van dexmedetomidine als sedativum tijdens procedurele sedatie samengevat. De resultaten van de onderzoeken naar het gebruik ervan tijdens de implantatie van een neurostimulator worden tevens besproken en dan met name in vergelijking met het gebruik van propofol. Op grond van de resultaten zijn wij van mening dat beide sedativa geschikt zijn voor het gebruik tijdens de implantatie van neurostimulator, maar dat dexmedetomidine de voorkeur verdient boven propofol vanwege de hogere patiënttevredenheid en gemakkelijker op te wekken sedatie in combinatie met een veilige situatie voor de patiënt. Helaas worden deze gunstige eigenschappen (nog) niet weerspiegeld in de dagelijkse praktijk van interventionele procedures uitgevoerd door Nederlandse pijnspecialisten.

IX

Curriculum vitae

List of publications

PhD portfolio

CURRICULUM VITAE

Feline Felice Janine Adine ter Bruggen was born on October 16th, 1992 in Tilburg, the Netherlands. In 2010 she graduated grammar school at the R.K. Gymnasium Beekvliet in Sint-Michielsgestel. In September 2010 she started her medical study at the Erasmus University in Rotterdam. In 2013 she obtained her bachelor's degree in Medicine and in 2017 her master's degree in Medicine. Consecutively she started her PhD candidacy at the Erasmus University Medical Center.

While pursuing her master's degree, she started her research career at the Center for Pain Medicine in the Erasmus University Medical Center in 2014. She was given the opportunity by Prof. Dr. F.J.P.M. Huygens to partly carry out her research project at the Center for Pain Medicine during her medical internship and continue it after obtaining her master's degree (promotor: Prof. Dr. F.J.P.M. Huygen; co-promotor: Dr. D.L. Stronks). In addition, while pursuing her PhD, she carried out clinical work for patients suffering from chronic pain admitted at the Center for Pain medicine. In 2019 she was selected to commence her anesthesiology residency at the Erasmus University Medical Center (Residency Program Director: Prof. Dr. R.J. Stolker).

LIST OF PUBLICATIONS

Succesvolle neuromodulatie behandeling van chronische post herpetische neuralgie met botuline neurotoxine-A
ter Bruggen FFJA, ter Bruggen JP
Nederlandstalig Tijdschrift Pijnbestrijding 39 (80). **2020**

Cost analysis of dexmedetomidine versus propofol during the implantation of a neurostimulator.
Ter Bruggen FFJA, Stronks DL, Huygen FJPM.
Acta Anaesthesiol Scand. **2020** Jul;64(6):861-862. doi: 10.1111/aas.13579. Epub 2020 Apr 14.
PMID: 32236939

Survey on sedation-analgesia regimens, in particular the use of dexmedetomidine, among Dutch implanters of spinal cord neurostimulators.
Ter Bruggen FFJA, Stronks DL, Huygen FJPM.
Scand J Pain. **2019** Aug 5;19(4):823-827. doi: 10.1515/sjpain-2019-0058. Print 2019 Oct 25.
PMID: 31377743

Dexmedetomidine vs propofol as sedation for implantation of neurostimulators: A single-center single-blinded randomized controlled trial.
Ter Bruggen FFJA, Ceuppens C, Leliveld L, Stronks DL, Huygen FJPM.
Acta Anaesthesiol Scand. **2019** Nov;63(10):1321-1329. doi: 10.1111/aas.13452. Epub 2019 Aug 9.
PMID: 31321763

Body mass index and complications following major gastrointestinal surgery: a prospective, international cohort study and meta-analysis.
EuroSurg Collaborative.
Colorectal Dis. **2018** Aug;20(8):O215-O225. doi: 10.1111/codi.14292. Epub 2018 Jul 9.
PMID: 29897171

Efficacy of Dexmedetomidine as a Sole Sedative Agent in Small Diagnostic and Therapeutic Procedures: A Systematic Review.
Ter Bruggen FFJA, Eralp I, Jansen CK, Stronks DL, Huygen FJPM.
Pain Pract. **2017** Jul;17(6):829-840. doi: 10.1111/papr.12519. Epub 2016 Dec 30.
PMID: 27862903

Dexmedetomidine as a Sedative in the Awake Implantation of a Neuromodulative System.
Ter Bruggen FF, Eralp I, Leliveld L, Jansen C, Stronks DL, Huygen FJ.
Pain Pract. **2017** Feb;17(2):208-213. doi: 10.1111/papr.12425. Epub 2016 Feb 23.
PMID: 26914618

PHD PORTFOLIO

Name: Drs. Feline Felice Janine Adine ter Bruggen
Erasmus MC department: Center for Pain Medicine, Department of Anesthesiology

PhD period: October 2017 – June 2019
Promotor: Prof. Dr. F.J.P.M. Huygen
Co-promotor: Dr. D.L. Stronks

Courses and Certificates

2019	English Biomedical Writing and Communication
2018	BROK-course (legislation and organization of clinical research)
2018	Medical Integrity course
2018	Biostatistical Methods I: Basic Principles Part A, NIHES
2015	EndNote workshop

Presentations / teaching activities

September	2019	European Pain Federation (EFIC), Valencia, Spain. Poster presentation "Survey on sedation analgesia regimens, in particular the use of dexmedetomidine, among Dutch implanters of spinal cord neurostimulators"
January	2019	Scientific Research Day Anesthesiology, Erasmus MC, Rotterdam Presentation about "Dexmedetomidine versus propofol in the awake implantation of a Neuromodulative System"
November	2018	Congres "Pijndagen", 's-Hertogenbosch Presentation about "Dexmedetomidine versus propofol in the awake implantation of a Neuromodulative System"
October	2018	Education to minor students following the minor Pain Medicine
May	2018	World Institute of Pain Congress, Dublin, Ireland Poster presentation " Dexmedetomidine versus Propofol in the Awake Implantation of a Neuromodulative System: Design for a Randomized Controlled Trial"
June	2015	International Neuromodulation Society Congress, Montreal, Canada Poster presentation "Dorsal root ganglion (DRG) stimulation for the management of chronic visceral pain in the thoracic region: a case report"
January	2015	Scientific Research Day Anesthesiology, Erasmus MC, Rotterdam Presentation about "Efficacy of Dexmedetomidine as a Sole Sedative Agent in Small Diagnostic and Therapeutic Procedures: A Systematic Review"

Grants

2015	St. Erasmus Pijnfonds