Original Article

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

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Summary

Robot-assisted radical prostatectomy causes discomfort in the immediate postoperative period. This randomised controlled trial investigated if intrathecal bupivacaine/morphine, in addition to general anaesthesia, could be beneficial for the postoperative quality of recovery. One hundred and fifty-five patients were randomly allocated to an intervention group that received intrathecal 12.5 mg bupivacaine/300 μg morphine (20% dose reduction in patients > 75 years) or a control group receiving a subcutaneous sham injection and an intravenous loading dose of 0.1 $mg.kg^{-1}$ morphine. Both groups received standardised general anaesthesia and the same postoperative analgesic regimen. The primary outcome was a decrease in the Quality of Recovery-15 (QoR-15) questionnaire score on postoperative day 1. The intervention group (n = 76) had less reduction in QoR-15 on postoperative day 1; median (IQR [range]) 10% (1–8 [−60% to 50%]) vs. 13% (5–24 [−6% to 50%]), p = 0.019, and used less morphine during the admission; 2 mg (1–7 [0–41 mg]) vs. 15 mg (12–20 [8–61 mg]), p < 0.001. Furthermore, they perceived lower pain scores during exertion; numeric rating scale (NRS) 3 (1–6 [0–9]) vs. 5 (3–7 [0–9]), p = 0.001; less bladder spasms (NRS 1 (0–2 [0–10]) vs. 2 (0–5 [0–10]), p = 0.001 and less sedation; NRS 2 (0–3 [0–10]) vs. 3 (2–6 [0–10]), p = 0.005. Moreover, the intervention group used less rescue medication. Pruritus was more severe in the intervention group; NRS 4 (1–7 [0–10]) vs. 0 (0–1 [0–10]), p = 0.000. We conclude that despite a modest increase in the incidence of pruritus, multimodal pain management with intrathecal bupivacaine/morphine remains a viable option for robot-assisted radical prostatectomy.

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Introduction

Robot-assisted radical prostatectomy causes considerable discomfort, mainly during the first postoperative day. The discomfort originates from abdominal pain, bladder spasm and transurethral catheter irritation [1]. Various techniques such as dorsal penile nerve block, transversus abdominus

plane block, administration of intravesical ropivacaine, suprapubic catheters and intrathecal morphine were investigated and resulted in moderate analgesic effects [2–6]. This emphasises the necessity for improvement of postoperative care in the first days after robot-assisted radical prostatectomy.

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

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

Methods

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

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

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

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

All patients received 1000 mg intravenous (i.v.) cefazolin 30 min before surgery. No sedative premedication was given. In the operating theatre the patients received standard monitoring. After the time-out, the surgical team left the theatre for blinding purposes. In accordance with random allocation, the patient received either an intrathecal injection of bupivacaine/morphine or a sham procedure.

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

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

For both groups, standardised general anaesthesia was administered immediately after the spinal puncture. After

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

Ten micrograms of i.v. sufentanil was administered when an increase in heart rate or blood pressure > 10% occurred in comparison with a stable phase during surgery. Rocuronium 10 mg i.v. was administered when ventilator desynchronisation or abdominal wall contraction occurred. Vaso-active medication was given at the discretion of the attending anaesthetist (i.e. phenylephrine, ephedrine or noradrenaline). Every patient received an i.v. infusion of 500 ml lactated Ringer's solution with a targeted fluid balance of less than 750 ml surplus.

Standard medication of 1000 mg paracetamol, 1000 mg metamizol, 0.625 mg dehydrobenzperidol and 4 mg ondansetron was given i.v. before the end of surgery. A train-of-four measurement was performed in order to exclude residual neuromuscular blockade after surgery. If necessary, rocuronium was antagonised with atropine/neostigmine or sugammadex at the discretion of the anaesthetist. After completion of surgery, the patient's trachea was extubated in the operating room and transferred to PACU for at least 30 min of observation.

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

All patients received 2 l.min^{-1} of oxygen by nasal cannulae during the first night. Oxygen was to be increased when SaO_2 < 92%. To reduce the risk of late respiratory depression, patients in both groups were not allowed to receive benzodiazepines or opioids other than PCA morphine. No other precautions were taken to prevent late respiratory depression. Postoperative pain treatment included paracetamol up to 4000 mg.day^{-1} and metamizol 1000 mg. Morphine administered by the PCA system was prescribed for postoperative analgesic management. The PCA system was stopped on the first postoperative day (POD 1). Ondansetron 4 mg was administered when required for nausea and pruritus, 5 mg of oxybutynin was prescribed for bladder spasms. The urinary catheter remained in situ for 7 days after surgery.

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

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

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

The intra-operative secondary outcomes (duration of different stages of the anaesthesia, sufentanil and

rocuronium administration, i.v. fluid administration, blood loss, pain scores and complications) were noted on a case record form that was filled in by the anaesthetic team and PACU nurse (who were unblinded) during surgery and the recovery phase. Furthermore, the attending urologist (blinded) was asked to score the surgical difficulty of the procedure on a numeric rating scale (NRS), ranging from 0 (easy) to 10 (very difficult) after surgery. The PCA system was checked electronically for total morphine consumption and bolus demands.

For the postoperative secondary outcomes, an anaesthetic nurse (blinded) visited the patients on POD 1. In addition to the QoR-15, seven items related to the potential benefits and side-effects of intrathecal morphine: physical discomfort; pain during exertion; bladder spasms; sedation; sleep; pruritus; and general satisfaction – were recorded with a NRS ranging from 0 (low or absent) to 10 (high or severe) (see also Supporting Information, Data S1).

One week after surgery, a trained medical secretary (blinded), telephoned the patient to assess the QoR-15 on postoperative day 7 (POD 7). Additionally, 12 questions were asked regarding the hospital admission in a retrospective manner on a NRS ranging from 0 (low or absent) to 10 (high or severe, see also Supporting Information, Data S1). These 12 questions consisted of the same seven items asked on POD 1. The objective of these seven questions was to assess recollection of symptoms after a week. The five other items inquired about: nausea; pain at rest; current use of analgesics; and the current state of physical and mental abilities.

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

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

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

Results

Four hundred and fifty-nine patients were screened, of whom 12 were not included and 287 declined to participate (Fig. 1). Three patients in the intervention group withdrew consent after random allocation. All attempts at intrathecal injection in the intervention group produced return of cerebrospinal fluid through the needle. Five patients in the intervention group accidently also received an i.v. loading dose of 0.1 $mg.kg^{-1}$ morphine. Five patients received a robot-assisted simple prostatectomy (two in the intervention group, three in the control group). These patients were included in the intention-to-treat analysis, and a per-protocol analysis showed no difference in morphine consumption and QoR-15 scores for these violations. No other protocol violations were observed. Baseline characteristics are displayed in Table 1. The groups were comparable; only lymph node dissection was performed more often in the intervention group.

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

The percentage decrease in QoR-15 on POD 1 was significantly less in the intervention group than the control group; 10% (1–8 [−60% to 50%]) vs. 13% (5–24 [−6% to 50%]), p = 0.019. Absolute values of QoR-15 were similar; 123 points (106–137 [72–150]) vs. 118 points (105–130 [66–150]), p = 0.077 at POD 1 (Fig. 2). The absolute decrease in QoR-15 and subdomains are presented in Table 2. Analyses of QoR-15 subdomains showed that only the decline in 'pain' was significantly lower in the intervention group than in the control group on POD 1 (Table 2). All the absolute values and individual questions of the QoR-15 are described in the Supporting Information Data S1.

Closer inspection of the domain 'pain' (range from 0 to 20, 0 = severe pain, 20 = no pain) on POD 1 showed that

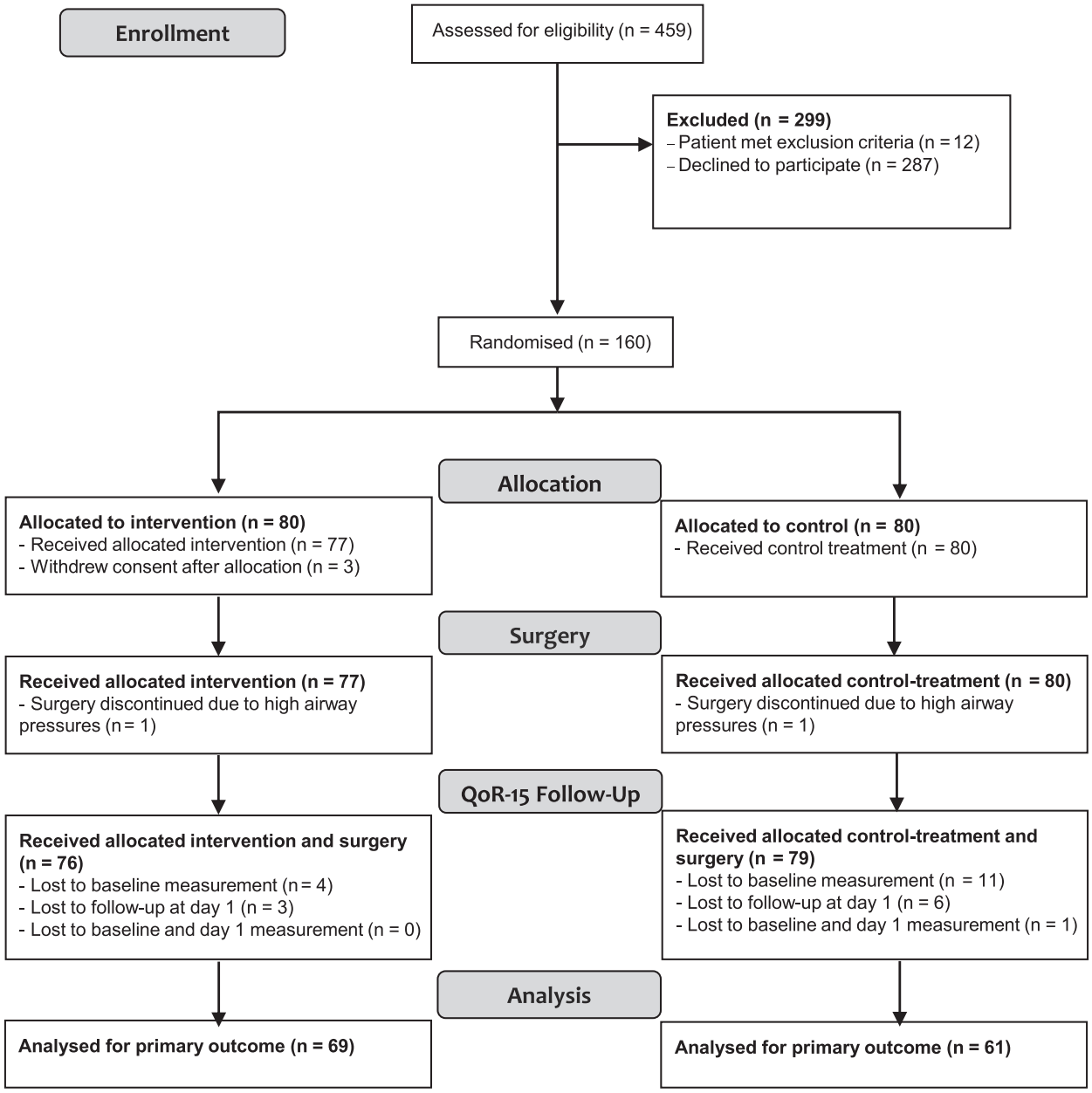

Figure 1 Flow diagram of the participants of the study. Since the primary outcome was a paired measurement, analysis was performed only when both the pre-operative Quality of Recovery (QoR)-15 and the QoR-15 on postoperative day 1 were available. Other outcome measures were analysed when available.

the number of patients with extreme pain (scores < 10) was decreased; 13 (18.3%) vs. 2 (2.8%), p = 0.002 in the intervention and control groups, respectively.

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

Table 2 shows the results of the additional questions asked on POD 1. On the first postoperative day, the intervention group reported less pain during exertion, less severe bladder spasms, less sedation, but more pruritus than the control group. No patient required treatment for pruritus, and only one patient (allocated to the intervention group) received additional treatment for nausea. No

Table 1 Baseline characteristics. Values are median (IQR [range]) or number (proportion).

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

BMI, body mass index; PACU, postoperative care unit; PSA, prostate specific antigen, QoR-15: Quality of Recovery-15.

difference in severity of nausea or general satisfaction was detected between groups. Furthermore, no differences in laboratory results such as creatinine levels, C-reactive protein or haemoglobin values were detected (see also Supporting Information, Data S1).

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

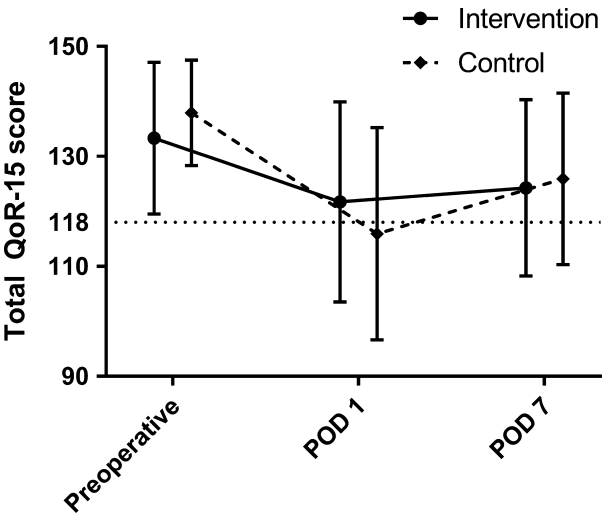

Figure 2 The total Quality of Recovery (QoR)-15 scores per time-point. The data are presented as mean with SD error bars. The percentage and absolute decrease between pre-operative QoR-15 and postoperative 1 were different (p = 0.019 and p = 0.013) between the intervention and control groups. There were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

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

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

Discussion

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

Table 2 Decline in Quality of Recovery (QoR-15) and scores for the additional questions. The QoR-15 outcomes are the absolute decline compared with the pre-operative QoR-15. A negative value indicates an increase in QoR-15 score. The additional questions are in numeric rating scales (NRS) from 0 to 10, where 10 signifies maximal agreement with the statement. For postoperative (POD) 7, it was explicitly mentioned that the additional questions regarded hospital admission. Values are median (IQR [range]). [Correction added on 9 Jan 2020, after first online publication: In Table 2, under QoR-15 ; Intervention and Domain 'pain'; Intervention and Control, error in data now revised in this version.]

	POD 1			POD 7		
	Intervention	**Control**	**p value**	**Intervention**	**Control**	**p value**
QoR-15 (absolute decrease)	n = 69	n = 61		n = 72	n = 67	
QoR-15	14 (2–25 [−47 to 70])	18 (7–35 [−9 to 64])	0.013	7 (1–17 [−37 to 70])	10 (3–19 [−11 to 63])	0.197
Domain 'pain'	2 (0–4 [−13 to 14])	6 (3–9 [−4 to 14])	0.000	2 (0–3 [−17 to 14])	2 (0–4 [−4 to 20])	0.352
Domain 'physical comfort'	4 (0–11 [−9 to 25])	6 (2−10 [−6 to 23])	0.170	2 (−1 to 4 [−11 to 23])	2 (0−5 [−9 to 16])	0.430
Domain 'physical independence'	3 (0−8 [−2 to 20])	5 (1−9 [−1 to 18])	0.124	3 (1.0−40 [−2 to 15])	3 (1−4 [−3 to 10])	0.557
Domain 'psychological support'	0 (−4 to 0 [−13 to 10])	0 (−1 to 0 [−10 to 16])	0.084	0 (−3 to 0 [−13 to 6])	0 (0 to 1 [−10 to 8])	0.104
Domain 'emotional support'	2 (−1 to 5 [−6 to 17])	2 (−2 to 7 [−10 to 26])	0.624	0 (−1 to 5 [−8 to 26])	1 (0−4 [−12 to 19])	0.708
Additional questions (NRS)	n = 66	n = 71		n = 76	n = 78	
Severity of physical discomfort	5 (2–7 [0–9])	6 (3–7 [0–10])	0.079	3 (1–6 [0–10])	4 (2–6 [0–10])	0.235
Severity of pain during exertion	3 (1–6 [0–9])	5 (3–7 [0–9])	0.001	3 (2–7 [0–10])	5 (2–7 [0–10])	0.072
Severity of bladder spasms	1 (0–2 [0–10])	2 (0–5 [0–10])	0.001	0 (0–4 [0–10])	0 (0–6 [0–10])	0.098
Severity of sedation	2 (0–3 [0–10])	3 (2–6 [0–10])	0.005	1 (0–3 [0–10])	2 (0–5 [0–8])	0.339
Severity of insomnia	1 (0–6 [0–10])	5 (1–7 [0–10])	0.070	1 (0–6 [0–10])	5 (1–7 [0–10])	0.174
Severity of pruritus	4 (1–7 [0–10])	0 (0–1 [0–10])	< 0.001	1 (0–5 [0–9])	0 (0–0 [0–9])	< 0.001
General satisfaction	9 (8–10 [0–10])	8 (7–10 [0–10])	0.820	8 (8–10 [1–10])	9 (8–10 [0–10])	0.414
Severity of nausea	n/a			0 (0–3 [0–10])	0 (0–3 [0–10])	0.365
Severity of pain in rest	n/a			0 (0–3 [0–9])	0 (0–3 [0–9])	0.085

n/a, not available.

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

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

Bae et al. investigated the use of 300 μg intrathecal morphine in 30 patients undergoing robot-assisted radical prostatectomy and measured morphine consumption as the primary outcome [6]. They found a median reduced morphine consumption of 12 mg and reduced pain scores in the intervention group. The current study confirmed these findings in a larger sample and added some other useful features. Firstly, bupivacaine was added to the intrathecal morphine, which prolongs the analgesic effect [14]. No disadvantages of the bupivacaine were observed, such as severe haemodynamic compromise or residual motor blockade that prevented mobilisation. Secondly, in the current study paracetamol and non-steroidal anti-

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

	Intervention n = 76	**Control n = 79**	**p value**
Opioid consumption			
Intra-operative sufentanil use; μg	35 (25–45 [15–100])	45 (35–50 [20–90])	< 0.001
Intra-operative morphine consumption; mg	0 (0–0 [0–10])	9 (8–10 [5–20])	< 0.001
Morphine consumption in PACU; mg	0 (0–0 [0–16])	0 (0–0 [0–14])	0.053
Morphine consumption per PCA during hospital stay; mg	2 (1–6 [0–41])	5 (2–11 [0–51])	< 0.001
Total morphine consumption during hospital stay; mg	2 (1–7 [0–41])	15 (12–20 [8–61])	< 0.001
Pain/non-opioid analgesics			
Pain scores on recovery area; NRS	0 (0–0 [0–5])	0 (0–4 [0–8])	< 0.001
Additional non-opioid analgesia	4 (5.3%)	22 (27.8%)	< 0.001
Additional oxybutynin on the ward	23 (30.3%)	40 (50.6%)	0.014
Laparoscopic workspace			
Rocuronium consumption; mg	50 (50–58 [25–105])	50 (50–60 [35–115])	0.278
Difficulty of surgery; NRS	3 (1–4 [0–10])	4 (2–6 [0–9])	0.119
Duration of surgery; min	129 (105–160 [60–263])	133 (105–150 [71–259])	0.987
Estimated blood loss; ml	200 (140–325) [5–1300]	200 (150–400 [0–2300])	0.623

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

inflammatory drugs were administered as part of a multimodal postoperative analgesic regimen. This may have reduced the opioid-sparing effect attributed to intrathecal morphine, because a multimodal analgesic regimen also leads to less opioid consumption. Still, the opioid-sparing effects of the intrathecal morphine persisted longer than the effects of the paracetamol and non-steroidal anti-inflammatory drugs. Finally, due to the five-fold increase in the number of participants compared with the earlier study, the present study allowed detection of differences in side-effects and sub-group analysis for patients with lymph node dissection.

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

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

The most feared side-effect of intrathecal morphine, late respiratory depression, did not occur in any patients. Incidence is difficult to estimate, since the definition of respiratory depression varies from a SaO_2 < 94% and/or $PaCO_2$ > 6 kPa to a respiratory rate < 6 breaths per min [20]. Most reported cases of late respiratory depression with the use of < 500 μg intrathecal morphine required no intervention [19]. Therefore, we did not employ any specific monitoring for this complication, since clinically-relevant respiratory depression is unlikely to occur more often with low-dose intrathecal morphine (< 500 μg) than with PCA morphine [19, 21]. Sedatives and opioids (other than as needed in PCA) were contra-indicated on the night after surgery due to the potential to interact with intrathecal morphine and cause severe respiratory depression [22].

This study has several limitations. One limitation is the protocol violation in five patients who received an i.v. loading dose of morphine in addition to the intrathecal

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

The current trial offers two recommendations for subsequent studies. First, the QoR-15 appears to be a difficult instrument to interpret. Its main advantage is the overall view of patients' experience, measured by five subscales. The disadvantage is the possibility that if an intervention reduces one item it may be obscured by the other items, reducing sensitivity. In addition, the variance in baseline values indicates that inter-patient comparisons may obscure differences even further, but individual patient change may correct for this. Values such as the minimal clinically important difference and the acceptable symptom state are of assistance in this regard [10, 12]. We prefer measuring traditional outcomes as well (such as morphine consumption and pain scores) in addition to the QoR-15 to reduce the risk of a false-negative intervention. Second, after several studies comparing interventions with i.v. opioids in robot-assisted radical prostatectomy procedures, a new study may aim to compare two interventions, for example, intrathecal analgesia vs. transversus abdominus plane block. We believe that an intervention should have been compared with the least invasive strategy first before an additional value could be concluded. For intrathecal morphine in a robot-assisted radical prostatectomy procedure, this was insufficiently done when this study was initiated.

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

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References

1. Woldu SL, Weinberg AC, Bergman A, et al. Pain and analgesic use after robot-assisted radical prostatectomy. *Journal of Endourology* 2014; **28**: 544–8.
2. Weinberg AC, Woldu SL, Bergman A, et al. Dorsal penile nerve block for robot-assisted radical prostatectomy catheter related pain: a randomized, double-blind, placebo-controlled trial. *Springerplus* 2014; **3**: 181.
3. Dal Moro F, Aiello L, Pavarin P, Zattoni F. Ultrasound-guided transversus abdominis plane block (US-TAPb) for robot-assisted radical prostatectomy: a novel '4-point' technique-results of a prospective, randomized study. *Journal of Robotic Surgery* 2019; **13**: 147–51.
4. Fuller A, Vanderhaeghe L, Nott L, Martin PR, Pautler SE. Intravesical ropivacaine as a novel means of analgesia post-robot-assisted radical prostatectomy: a randomized, double-blind, placebo-controlled trial. *Journal of Endourology* 2013; **27**: 313–17.
5. Bertolo R, Tracey A, Dasgupta P, et al. Supra-pubic versus urethral catheter after robot-assisted radical prostatectomy: systematic review of current evidence. *World Journal of Urology* 2018; **36**: 1365–72.
6. Bae J, Kim HC, Hong DM. Intrathecal morphine for postoperative pain control following robot-assisted prostatectomy: a prospective randomized trial. *Journal of Anesthesia* 2017; **31**: 565–71.
7. Koning MV, Teunissen AJW, van der Harst E, Ruijgrok EJ, Stolker RJ. Intrathecal morphine for laparoscopic segmental colonic resection as part of an enhanced recovery protocol: a randomized controlled trial. *Regional Anesthesia and Pain Medicine* 2018; **43**: 166–73.
8. Fernandez MA, Karthikeyan S, Wyse M, Foguet P. The incidence of postoperative urinary retention in patients undergoing elective hip and knee arthroplasty. *Annals of the Royal College of Surgeons of England* 2014; **96**: 462–5.
9. Kontani H, Kawabata Y. A study of morphine-induced urinary retention in anesthetized rats capable of micturition. *Japanese Journal of Pharmacology* 1988; **48**: 31–6.

10. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013; **118**: 1332–40.
11. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *European Journal of Anaesthesiology* 2015; **32**: 88–105.
12. Myles PS. Clinically important difference in quality of recovery scores. *Anesthesia and Analgesia* 2016; **122**: 13–14.
13. Bowyer A, Jakobsson J, Ljungqvist O, Royse C. A review of the scope and measurement of postoperative quality of recovery. *Anaesthesia* 2014; **69**: 1266–78.
14. Tejwani GA, Rattan AK, McDonald JS. Role of spinal opioid receptors in the antinociceptive interactions between intrathecal morphine and bupivacaine. *Anesthesia and Analgesia* 1992; **74**: 726–34.
15. Boonmak S, Boonmak P, Bunsaengjaroen P, Srichaipanha S, Thincheelong V. Comparison of intrathecal morphine plus PCA and PCA alone for post-operative analgesia after kidney surgery. *Journal of the Medical Association of Thailand* 2007; **90**: 1143–9.
16. Horta ML, Morejon LC, da Cruz AW, et al. Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. *British Journal of Anaesthesia* 2006; **96**: 796–800.
17. Koju RB, Gurung BS, Dongol Y. Prophylactic administration of ondansetron in prevention of intrathecal morphine-induced pruritus and post-operative nausea and vomiting in patients undergoing caesarean section. *BMC Anesthesiology* 2015; **15**: 18.
18. Gibson MC, Keast D, Woodbury MG, et al. Educational intervention in the management of acute procedure-related wound pain: a pilot study. *Journal of Wound Care* 2004; **13**: 187–90.
19. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* 2009; **64**: 643–51.
20. Ko S, Goldstein DH, VanDenKerkhof EG. Definitions of "respiratory depression" with intrathecal morphine postoperative analgesia: a review of the literature. *Canadian Journal of Anesthesia* 2003; **50**: 679–88.
21. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database of Systematic Reviews* 2015; CD003348.
22. Dworzak H, Fuss F, Buttner T. Persisting respiratory depression following intrathecal administration of morphine and simultaneous sedation with midazolam. *Anaesthesist* 1999; **48**: 639–41.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. The supplementary data file contains the Dutch and English version of the questionnaire used in the study, the results per individual question and additional secondary outcome not reported in the manuscript.