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Intrathecal Anesthesia and Recovery from Radical Prostatectomy

A Prospective, Randomized, Controlled Trial

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Background: **Previous studies suggest that intraoperative anesthetic care may influence postoperative pain and recovery from surgery. The authors tested the hypothesis that the addition of intrathecal analgesia to general anesthesia would improve long-term functional status and decrease pain in patients undergoing radical retropubic prostatectomy.**

Methods: **One hundred patients received either general anesthesia supplemented with intravenous fentanyl or general anesthesia preceded by intrathecal administration of bupivacaine (15 mg), clonidine (75 μg), and morphine (0.2 mg). Patients and providers were masked to treatment assignment. All patients received multimodal pain management postoperatively. Primary outcomes included pain and functional status over the first 12 postoperative weeks.**

Results: **Patients receiving intrathecal analgesia required more intravenous fluids and vasopressors intraoperatively. Pain was well controlled throughout the study (mean numerical pain scores < 3 in both groups at all times studied). Intrathecal analgesia decreased pain and supplemental intravenous morphine use over the first postoperative day but increased the frequency of pruritus. Pain and functional status after discharge from the hospital did not differ between groups. Intrathecal analgesia significantly decreased the duration of hospital stay (from 2.8 ± 2.0 to 2.1 ± 0.5 days; $P < 0.01$) as a result of five patients in the control group who stayed in the hospital more than 3 days.**

Conclusions: **The benefits of improved immediate analgesia and decreased morphine requirements resulting from intrathecal analgesia must be weighed against factors such as pruritus, increased intraoperative requirement for fluids and vasopressors, and resources needed to implement this modality. Further studies are needed to determine the significance of the decrease in duration of hospital stay.**

POSTOPERATIVE pain is a significant problem in the United States: Current practice fails to provide adequate pain relief in approximately half of postoperative patients.[1] Postoperative pain may prolong recovery[2–6] and lead to the development of chronic pain syndromes.[6] Although it is unlikely that all postoperative pain can be eliminated, better pain control might be expected to decrease morbidity and hasten the recovery of functional status.

A recent study of patients undergoing radical retropubic prostatectomy (RRP) reported significantly decreased postoperative pain during hospital stay in patients who received epidural narcotics and local anesthetics instituted before surgical incision and maintained postoperatively.[6] In addition, the activity level after discharge from the hospital was increased, and pain was decreased in these patients, suggesting that the perioperative analgesic technique in RRP could affect postoperative pain and functional status. Although this study was carefully performed and the findings were statistically significant, its clinical implications are less clear. The only significant improvement in median pain score occurred at 9.5 weeks postoperatively, whereas activity was significantly improved only at 3.5 weeks postoperatively. Furthermore, the postoperative protocol used (epidural analgesia for 3 days postoperatively) is not consistent with current practice for this procedure in many locations. The current duration of stay after this procedure is 2–3 days at many institutions. Therefore, although there may be benefit to the anesthetic regimen used in this study, it may not be possible to use this regimen in other practice locations.

Intrathecal analgesia is another technique that potentially could improve pain control and long-term functional status in patients undergoing RRP. The duration of action of intrathecal opioids may be better suited to the anticipated duration of hospital stay in current practice, and a single injection is easier to implement in clinical practice. Studies in patients undergoing laparoscopic cholecystectomy[7] and orthopedic surgery[8] have shown intrathecal analgesia to improve pain control during the immediate postoperative period. The effects on more long-term outcomes, such as pain and functional status after discharge from the hospital, are unknown.

The current study is a randomized, masked clinical trial investigating the effect of preincisional intrathecal analgesia on recovery from RRP. We tested the hypothesis that the addition of intrathecal analgesia to general anesthesia would improve postoperative pain and recovery of functional status.

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Materials and Methods

Recruitment

After approval by the institutional review board, all patients scheduled to undergo elective RRP for the treatment of prostate cancer were screened for enrollment in the study. Exclusion criteria included (1) gross neurologic impairment, (2) chronic painful conditions, (3) preoperative narcotic use, (4) coagulation abnormalities, (5) narcotic or anesthetic agent allergy, (6) personal or family history of malignant hyperthermia, (7) American Society of Anesthesiologists physical status IV or greater, (8) suspected difficult airway requiring awake fiberoptic intubation, (9) inability to complete questionnaires, (10) serum creatinine concentration greater than 1.3 g/dl, (11) age younger than 35 yr or older than 85 yr, (12) preoperatively determined need for postoperative intensive care unit care, and (13) any comorbid condition, in the judgment of the consulting urologic surgeon or intraoperative anesthesiologist, that would proscribe the patient from any aspect of the study.

After written informed consent was obtained, a research assistant administered a health survey and introduced the scoring systems used for pain assessment. Patients were randomly assigned to a treatment group using a sealed envelope determined by a computer-generated list that made assignments based on enrollment number.

Protocol

Regional Procedure. After standard anesthesia monitors were applied, sedation with intravenous fentanyl citrate and midazolam (maximum 100 μg and 2 mg, respectively) and a fluid bolus (10 ml/kg lactated Ringer's solution) were administered. To maximize masking of the study, a consulting anesthesiologist familiar with the study but not responsible for the intraoperative care of the patient performed the regional procedure. During this time, the anesthesiologist and anesthetist (anesthesiology resident or certified registered nurse anesthetist) responsible for the clinical conduct of anesthesia left the operating room, such that they were not aware of treatment assignment. With the patient in the lateral position, the lumbar region was prepared and draped in a sterile fashion, and 1% lidocaine infiltrated subcutaneously in one of the lumbar interspaces between the second and fifth vertebral bodies. In the active intrathecal group, a mixture of bupivacaine (15 mg isobaric, 0.75%), preservative-free clonidine (75 μg), and morphine (0.2 mg) was slowly injected into the subarachnoid space through a 25-gauge Whitacre needle. The control group received a subcutaneous injection of sterile saline. Subjects were then positioned supine, and the intraoperative anesthesia team reentered the room and resumed care of the patient.

Intraoperative Management. After preoxygenation, general anesthesia was induced with sodium thiopental (4 mg/kg) and succinylcholine (1 mg/kg), and the patients were orotracheally intubated. Paralysis was maintained with cisatracurium titrated by twitch monitor to maintain less than 2 twitches of a train-of-four. Isoflurane (0.5–1.5% end-tidal) and nitrous oxide (50% inspired) were used to maintain general anesthesia. Patients in the control group received 4 μg/kg intravenous fentanyl citrate as a bolus immediately after induction of anesthesia, followed by a continuous infusion ($2\ \mu g \cdot kg^{-1} \cdot h^{-1}$) until fascial closure began. Patients in the intrathecal group received an equal volume of saline as a bolus and infusion. The anesthesia team was blinded to the identity of the bolus and infusion. When the study drug infusion was discontinued, ketorolac (30 mg) was administered intravenously to both groups. No other nonsteroidal antiinflammatory drugs were administered during the remainder of the perioperative period. Intravenous fluid therapy consisted of lactated Ringer's solution at the discretion of the anesthesia team, supplemented with up to 1,000 ml Hespan (6%) and blood products as indicated. Phenylephrine and ephedrine were used as needed to maintain an adequate blood pressure as determined by the anesthesia team. At the conclusion of surgery, neuromuscular blockade was reversed, isoflurane and nitrous oxide were discontinued, and the patient was extubated at the discretion of the anesthesia team.

Postoperative Management. Management in the postanesthesia recovery room included supplemental oxygen as needed to maintain oxygen saturation as measured by pulse oximetry (Spo_2) greater than 94%, morphine sulfate for pain (1–2 mg intravenously every 10 min as needed), droperidol for nausea (0.625 mg intravenously), and diphenhydramine (25 mg intravenously) for pruritus. Postanesthesia recovery room nurses documented the presence or absence of neurologic blockade as part of their routine patient assessment.

In addition to routine hemodynamic monitoring, postoperative management included hourly determination of respiratory rate and Spo_2 during the first 18 h after the regional procedure (active or control) by floor nurses according to routine clinical practice for patients receiving intrathecal morphine. Postoperative pain management included scheduled ketorolac (15 mg intravenously every 6 h for six doses) and patient-controlled analgesia morphine (1-mg bolus, 10-min lockout, no basal infusion) for 24 h. After at least 24 h and when tolerating oral fluids, patients switched from patient-controlled analgesia to acetaminophen with codeine (650 mg/30 mg orally every 6 h as needed for pain). Pruritus was managed initially with diphenhydramine (25–50 mg intravenously every 6 h as needed) and then naloxone infusion (20 μg/h intravenously up to 30 h after intrathecal injection) if symptoms persisted. Nausea

and emesis were managed initially with droperidol (0.625 mg intravenously every 6 h) and then naloxone (same dosing/administration route as for pruritus) if symptoms persisted.

Study Assessments

Pain and functional status were the primary outcomes. Pain was assessed by an 11-point verbal numerical pain scale (NPS) with 0 indicating no pain and 10 indicating the worst pain imaginable.[9] Pain assessment was performed preoperatively by a research assistant and at 06:00, 14:00, and 22:00 h (± 2 h) by floor nursing staff when patients were in the hospital, for up to 3 days postoperatively. Patients were asked to score pain at the time of assessment (current pain) and to score pain at its best and worst over the period since the last determination. Postoperative narcotic requirements (milligrams morphine or equivalent) were also recorded.

To assess functional status, the SF-36 Health Survey was administered by a research assistant at the time of enrollment and 2, 4, 8, and 12 weeks (± 3 days) postoperatively by telephone interview. The SF-36 Health Survey measures perceived health status by assessing eight health components: (1) *physical functioning*: limitation in physical activity, including self-care activities; (2) *social functioning*: limitations in social activities due to emotional problems; (3) *role—physical*: work and activity limitations due to physical problems; (4) *role—emotional*: work and activity limitations due to emotional problems; (5) *bodily pain*: limitations due to pain; (6) *mental health*: emotional symptoms (*e.g.*, nervous, depressed); (7) *vitality*: energy *versus* fatigue; and (8) *general health*: overall self-rated health.[10]

In addition, there are two SF-36 summary composite scores based on the eight domains: physical composite score and mental composite score.[10] The eight SF-36 scales and the summary physical and mental components were scored using published software.[10,11] To adjust for age and sex differences, the SF-36 scores were standardized using the published age- and sex-specific reference norms for the general U.S. adult population.[10] SF-36 subscale scores are age- and sex-adjusted and scaled to have a mean of 50 and a SD of 10 for the reference sample. The average health-related quality of life of the U.S. adult population is represented by a scale *t* score of 50, with *t* scores higher than 50 reflective of better reported health than the general population, and *t* scores lower than 50 reflective of worse health than the general population. This questionnaire is a validated method of determining bodily pain and functional status over a 4-week period.[10,11] For the 2- and 4-week assessments, the SF-36 was modified by asking the patients to answer the questions based on a 2-week period. During the telephone interviews, the 11-point NPS used during inpatient pain evaluation was also used to further characterize chronic pain.

Secondary outcomes were also examined. Respiratory depression was defined as a respiratory rate less than 8 breaths/min that necessitated treatment with naloxone or mechanical ventilation. Patients receiving pharmacologic intervention for nausea/emesis or pruritus or an epidural blood patch for postdural puncture headache were considered to have experienced that side effect. Intraoperative variables studied included phenylephrine and ephedrine use and crystalloid and colloid volumes and blood products administered. Other perioperative outcomes assessed included myocardial ischemia (defined as new electrocardiographic changes or increases in cardiac enzymes consistent with myocardial ischemia and detected as part of routine care), unexpected need for postoperative intensive care, duration of hospital stay, and mortality.

Statistical Analysis

Sample-size/Power Calculations. Sample-size requirements were based on findings of an earlier study of preemptive analgesia for patients undergoing radical prostatectomy.[6] In the current study, an 11-point scale to measure pain was used to allow for telephone acquisition of data after patients were discharged. We assumed that an effect size expressed in SD units using an 11-point scale would be comparable to that observed using a visual analog scale in this previous study. Based on this assumption, a total sample size of 100 patients (50 patients/group) would provide a statistical power of 90% to detect an effect size as small as 0.65 SD units (using a two-sided test with an α level of 0.05). For long-term pain outcomes, Gottschalk *et al.*[6] reported that, compared with the control group, a significantly higher percentage of patients receiving preemptive analgesia reported no pain at 9.5 weeks after surgery (86% *vs.* 47%). We hypothesized that 45% of patients in the placebo group would report no pain (NPS of 0) at week 12. Based on this assumption, a sample size of 50 patients in each group would provide a statistical power of 90% to detect a 30% point increase (*i.e.*, 75% reporting no pain) for the preemptive analgesia group.

Statistical Analyses. This study used a simple, randomized design with no stratification factors. Therefore, all treatment group comparisons were performed using standard two-sample procedures with no covariate adjustments. In all cases, two-sided tests were performed with $P \leq 0.05$ used to indicate statistical significance. Unless otherwise indicated, data are presented as mean ± SD for continuous variables and percentages for categorical variables. Baseline patient and procedural characteristics were compared between groups using the rank sum test for continuous variables and the Fisher exact test for categorical variables. Postoperative NPS score (current, worst, least), intravenous morphine usage, duration of hospital stay, and SF-36 scale scores were compared between groups using the rank sum test.

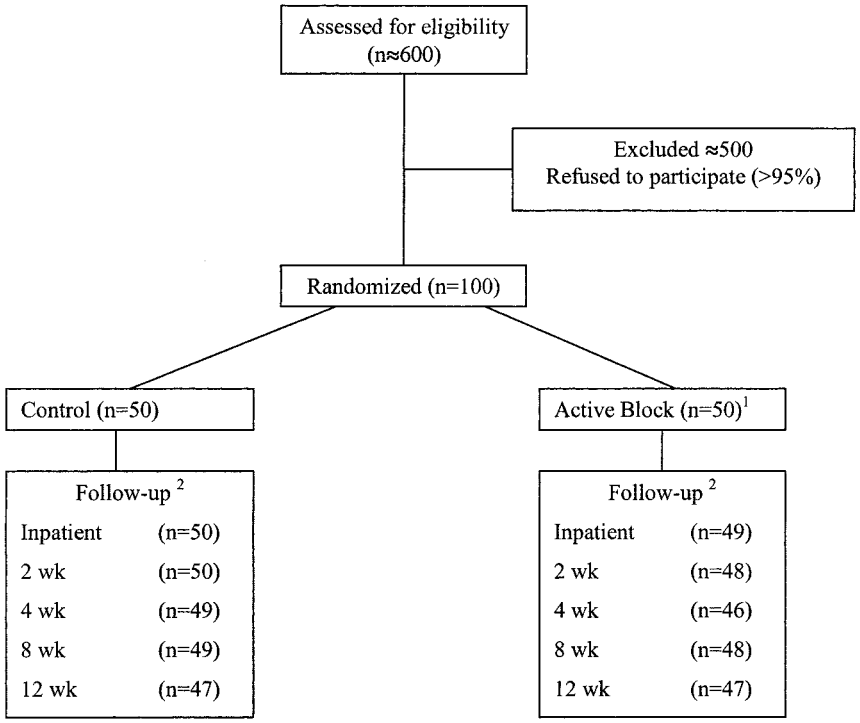

Fig. 1. Flow of participants through the trial. [1] One patient randomly assigned to the active block group had severe bradycardia after induction of anesthesia, and surgery was canceled. [2] Some patients could not be reached by telephone for outpatient follow-up. One subject in the control group could not be reached at the 8- and 12-week periods. The remainder of missing data was single time points for individual patients.

For the SF-36 data, the rank sum test was also used to compare groups with respect to change from baseline to week 12. Because recently proposed guidelines for pain management (the Joint Commission on Accreditation of Healthcare Organizations proposed intensive care unit core measure profiles‡‡) have targeted an NPS score of 3 or less as acceptable pain control, the percentage of subjects meeting this criteria was also compared between groups using the Fisher exact test. The percentage of subjects experiencing postoperative adverse events (respiratory depression, pruritus, nausea/emesis, and positional headache) was compared between groups using the Fisher exact test. Not all patients had follow-up information available at each time point. In all cases, the results are presented from an analysis using available data only. To assess the impact of missing data, the analysis of postoperative pain was repeated using the approach of "last value carried forward," and in all cases, the findings were consistent.

Secondary Analyses. Scaled variables were compared between treatment groups using an appropriate two-sample comparison (*i.e.*, two-sample *t* test or rank sum test). Nominal variables were compared using the Fisher exact test.

Results

During the 22 months of recruitment, approximately 600 patients were screened (fig. 1). Less than 5% of the patients were excluded because of study criteria. Most of the remaining patients cited a preference in analgesic technique as the reason they declined to participate. Fifty patients were randomly assigned to each group. However, one patient randomly assigned to the active block group had surgery canceled after experiencing severe bradycardia after induction of general anesthesia. This patient was excluded from all analyses. Therefore, this report includes a total of 99 patients (50 control, 49 active block). Baseline characteristics are shown in table 1. There were no significant clinical or demographic differences at baseline. Health-related quality of life was better than average in the study population compared with the age- and sex-matched U.S. population, as shown by the mean values exceeding 50.

Surgical characteristics are shown in table 2. The intrathecal group received significantly more intravenous fluids and pressors during surgery. Morphine administration in the recovery room was significantly higher in the control group. No patients received blood products or were admitted to the intensive care unit. One patient assigned to the intrathecal group experienced significant bradycardia after the induction of general anesthesia and was withdrawn from the study after it was decided by the anesthesia team to cancel surgery. Subsequent evaluation of this patient, including serial electrocardiograms and biochemical markers of myocardial ischemia as well as echocardiography and cardiology consultation, provided no evidence for underlying cardiac disease or myocardial infarction.

Pain was relatively well controlled throughout the hospital stay in both groups, as reflected by a mean current

‡‡ Joint Commission on Accreditation of Healthcare Organizations. Available at: www.jcaho.org. Accessed May 15, 2003.

Table 1. Patient Demographics and Baseline Characteristics (n = 99)

Characteristic	Control (n = 50)	Active (n = 49)	*P* Value*
Age, yr	61.0 ± 7.5	61.6 ± 7.0	0.690
Body mass index, kg/m^2	29.6 ± 3.9	29.5 ± 3.7	0.761
ASA status			0.875
I	13 (26)	12 (25)	
II	30 (60)	32 (65)	
III	7 (14)	5 (10)	
Hypertension	14 (28)	9 (18)	0.342
Coronary artery disease	3 (6)	0 (0)	0.242
Previous myocardial infarction	2 (4)	1 (2)	1.000
SF-36 subscales†			
Bodily pain	56.3 ± 6.8	55.5 ± 6.9	0.568
General health perceptions	58.1 ± 6.8	58.0 ± 6.1	0.941
Mental health	51.5 ± 7.5	52.7 ± 6.9	0.359
Physical functioning	56.0 ± 4.9	57.3 ± 3.2	0.278
Role—emotional	53.0 ± 7.3	53.1 ± 6.9	0.589
Role—physical	54.7 ± 7.0	54.6 ± 6.6	0.928
Social functioning	53.0 ± 7.4	53.7 ± 5.7	0.594
Vitality	54.9 ± 8.4	55.3 ± 8.0	0.809
Physical composite score	57.4 ± 6.7	57.5 ± 4.8	0.677
Mental composite score	51.3 ± 7.0	52.0 ± 7.3	0.280

Categorical variables are presented as n (%), and continuous variables are presented as mean ± SD.

* *P* value from two-sample rank sum test for continuous variables and exact test for categorical variables. † SF-36 subscale scores are age- and sex-adjusted and scaled to have a mean of 50 and an SD of 10 for the reference sample. The average health-related quality of life of the U.S. adult population is represented by a scale *t* score of 50, with *t* scores higher than 50 reflective of better reported health than the general population and *t* scores lower than 50 reflective of worse health than the general population.

NPS score of less than 3 at all time points (table 3). Intrathecal analgesia improved current, least, and worst pain scores on the day of surgery and current and worst pain scores at 06:00 h the next day. There were no significant differences in any pain score between groups after this time. Morphine patient-controlled analgesia use was significantly higher in the control group through 14:00 h on the day after surgery. The frequency of pruritus was significantly greater in the intrathecal group (10 *vs.* 0 patients; $P < 0.001$). There was also a trend toward more nausea in the intrathecal group, but this did not reach significance (25 *vs.* 17 patients; $P = 0.11$). There was no reported respiratory depression or positional headache. Intrathecal analgesia produced a small but significant decrease in duration of hospital stay. This finding primarily reflected the fact that significantly more patients in the control group remained in the hospital more than 3 days after surgery (n = 5 in the control group, n = 0 in the intrathecal group; $P = 0.01$). Causes of delayed discharge in these control patients included anastomotic urine leaks (two patients) and delayed return of bowel function (three patients).

After discharge from the hospital, pain was well controlled during the 12 weeks of follow-up. No significant differences between groups in current, best, or worst pain scores were observed (table 4). No differences

Table 2. Surgical Characteristics (n = 99)

Characteristic	Control (n = 50)	Active (n = 49)	*P* Value*
Anesthesia duration, min	208.4 ± 38.3	199.6 ± 45.4	0.169
Crystalloid, ml	3,617 ± 1,052	4,424 ± 1,208	0.001
Hespan			0.192†
0 ml	44 (88)	38 (78)	
500 ml	4 (8)	8 (16)	
1,000 ml	2 (4)	3 (6)	
Packed erythrocytes, units	0 (0)	0 (0)	1.000
Phenylephrine, μg	56.0 ± 176.32	199.4 ± 315.9	0.007
Any phenylephrine	7 (14)	18 (37)	0.011
Ephedrine, mg	7.7 ± 9.7	25.1 ± 25.5	< 0.001
Preoperative hemoglobin, g/dl‡	14.7 ± 1.1	14.6 ± 1.3	0.487
Postoperative day 1 hemoglobin, g/dl§	10.7 ± 1.1	10.6 ± 1.2	0.504
Duration of recovery room stay, min	98.5 ± 32.2	99.1 ± 38.8	0.769
Morphine administered in recovery room, mg	5.0 ± 4.5	0.3 ± 1.0	< 0.001
Any morphine in recovery room	35 (70)	4 (8)	< 0.001

Categorical variables are presented as n (%), and continuous variables are presented as mean ± SD.

* *P* value from two-sample rank sum test for continuous variables and exact test for categorical variables. † Comparison of any Hespan *vs.* none. ‡ Preoperative hemoglobin was unavailable for 14 patients. § Postoperative day 1 hemoglobin was unavailable for two patients.

Table 3. Postoperative Characteristics for Patients Still in the Hospital (n = 99)

Characteristic	Control (n = 50)	Active (n = 49)	*P* Value*
Day of surgery: 22:00 h			
Current pain	2.4 ± 1.9	1.2 ± 1.4	< 0.001
Pain at its least	1.8 ± 1.9	0.6 ± 1.0	< 0.001
Pain at its worst	5.3 ± 2.8	2.6 ± 2.3	< 0.001
Intravenous morphine administered, mg	4.9 ± 6.0	1.2 ± 2.4	< 0.001
POD 1: 06:00 h			
Current pain	1.7 ± 1.7	1.0 ± 1.3	0.022
Pain at its least	0.9 ± 1.2	0.6 ± 1.0	0.142
Pain at its worst	2.8 ± 2.2	1.8 ± 1.6	0.034
Intravenous morphine administered, mg	4.5 ± 6.5	1.0 ± 1.8	< 0.001
POD 1: 14:00 h			
Current pain	1.8 ± 1.6	1.6 ± 1.6	0.514
Pain at its least	0.9 ± 1.1	0.7 ± 1.0	0.197
Pain at its worst	3.3 ± 2.3	2.9 ± 1.9	0.543
Intravenous morphine administered, mg	4.2 ± 7.4	1.4 ± 2.9	0.039
POD 1: 22:00 h			
Current pain	1.5 ± 1.5	1.7 ± 2.1	0.980
Pain at its least	1.0 ± 1.2	0.7 ± 1.2	0.144
Pain at its worst	3.1 ± 2.3	3.3 ± 2.4	0.587
Intravenous morphine administered, mg	1.0 ± 2.6	0.8 ± 2.8	0.596
POD 2: 06:00 h			
Current pain	1.4 ± 1.3	1.4 ± 1.3	0.927
Pain at its least	0.6 ± 1.0	0.6 ± 0.9	0.534
Pain at its worst	3.2 ± 2.2	2.9 ± 1.7	0.860
Intravenous morphine administered, mg	0.1 ± 0.6	0.8 ± 3.9	0.303
Any time while in the hospital			
Respiratory depression	0 (0)	0 (0)	1.000
Pruritus	0 (0)	10 (20)	< 0.001
Nausea/emesis	17 (34)	25 (51)	0.106
Positional headache	0 (0)	0 (0)	1.000
Duration of stay, days	2.7 ± 2.0	2.1 ± 0.5	0.010

Categorical variables are presented as n (%), and numerical pain scores and duration of stay are presented as mean ± SD. At 22:00 h on postoperative day (POD) 1, pain and intravenous morphine information was missing for one patient in the active group, and intravenous morphine information was missing for two patients in the control group. At 6:00 h on POD 2, pain and/or intravenous morphine information was missing for seven patients in the active group and eight patients in the control group. When the analysis was repeated with missing values imputed using the approach of "last value carried forward," the findings did not change.

* *P* value from two-sample rank sum test for continuous variables and exact test for categorical variables.

Table 4. Postoperative NPS Scores at Phone Follow-up (n = 99)

Characteristic	Control	Active	*P* Value*
2-Week follow-up			
Current pain	0.9 ± 0.9	1.0 ± 1.1	0.64
Pain at its least	0.4 ± 0.8	0.4 ± 0.7	0.89
Pain at its worst	1.7 ± 1.7	2.1 ± 1.8	0.26
4-Week follow-up			
Current pain	0.7 ± 1.2	0.6 ± 0.9	0.96
Pain at its least	0.3 ± 0.8	0.4 ± 0.8	0.38
Pain at its worst	1.5 ± 1.8	1.1 ± 1.5	0.20
8-Week follow-up			
Current pain	0.2 ± 0.4	0.1 ± 0.4	0.29
Pain at its least	0.1 ± 0.3	0.0 ± 0.2	0.15
Pain at its worst	0.5 ± 0.9	0.3 ± 0.7	0.19
12-Week follow-up			
Current pain	0.1 ± 0.5	0.2 ± 0.7	0.50
Pain at its least	0.1 ± 0.5	0.1 ± 0.4	1.00
Pain at its worst	0.3 ± 0.8	0.4 ± 1.1	0.69

Data are numerical pain scale (NPS) scores presented as mean ± SD.

* *P* value from two-sample rank sum test. For weeks 2, 4, 8, and 12, respectively, the numbers of patients in the active group with data available were 48, 46, 48, and 47, and the numbers of patients in the control group with data available were 50, 49, 49, and 47. For each pain assessment, an additional analysis was performed where missing values were imputed using the "last value carried forward" technique, and the findings did not change.

between groups were observed when pain was expressed as the percentage of patients rating pain as greater than 3 (figs. 2 and 3). Finally, none of the eight subscales or two composite scores of the SF-36 health survey was significantly different between groups at any of the times studied. Twelve-week postoperative SF-36 scores are presented in table 5. No differences were found between groups at any

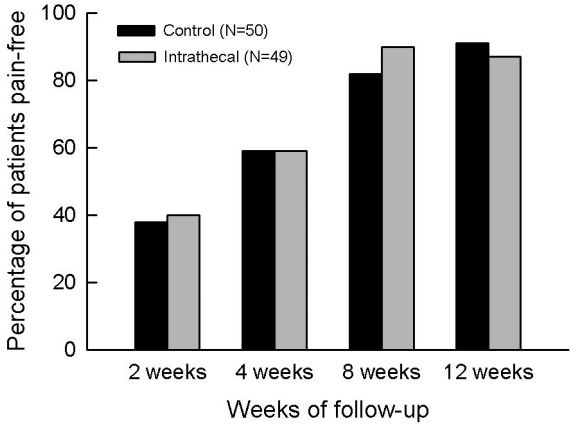

Fig. 2. Percentage of patients pain-free (numerical pain score = 0) at various time points after discharge from the hospital.

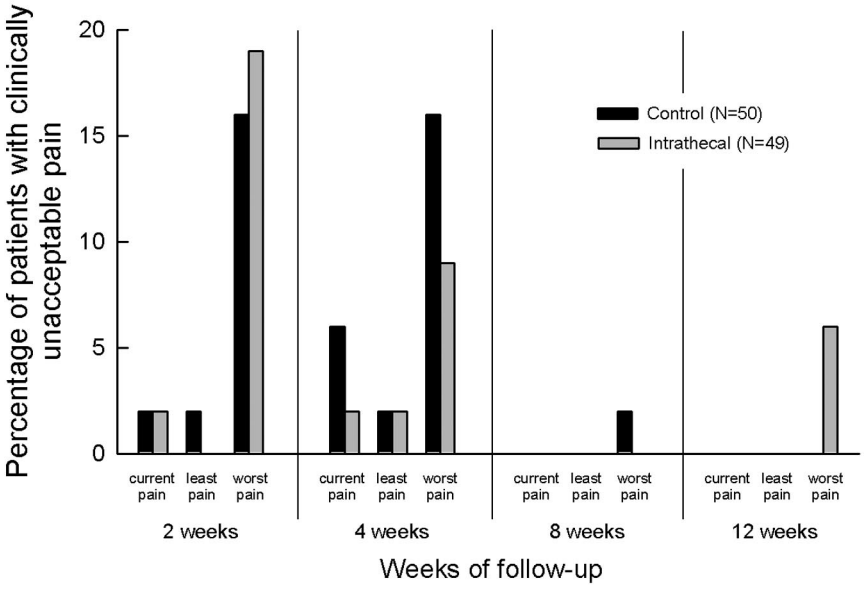

Fig. 3. Percentage of patients with clinically unacceptable pain (numerical pain score > 3) at various time points after discharge from the hospital.

of the times studied or between preoperative and 12-week postoperative values.

Discussion

The major finding of this study is that pain is well controlled in patients undergoing RRP using general endotracheal anesthesia alone or combined with intrathecal analgesia followed by multimodal pain management, although intrathecal analgesia improves pain scores immediately (within approximately 18 h) after surgery. Intrathecal anesthesia was associated with a small but significant decrease in duration of hospital stay but an increase in minor side effects. Intrathecal analgesia did not affect pain or functional status after discharge from the hospital.

Although several studies have advocated the use of epidural anesthesia in patients undergoing prostatectomy,[6,12,13] the study methods or outcomes assessed have raised questions as to the applicability to general practice. Furthermore, changes in surgical techniques and efforts to control costs have decreased blood loss and expected duration of stay, confounding comparison of this study with previous work. Frank *et al.*[13] reported decreased blood loss and shorter hospital stay in a retrospective review of patients undergoing prostatectomy with either epidural anesthesia alone or combined epidural and general anesthesia compared with general anesthesia alone. More recent studies have shown perioperative blood transfusion to be an uncommon event in this group.[14] In the current trial, none of the 100 patients received blood products during their hospital stay. Furthermore, the duration of stay in the study of Frank *et al.* was 7 or more days, greater than in contemporary practice. Therefore, the benefits of regional analgesia in terms of blood loss and duration of stay shown in previous studies for patients undergoing prostatectomy may not be applicable to current practice.

Table 5. Health Status of Patients at 12-Week Phone Follow-up (n = 99)

	Control (n = 47)	Active (n = 47)	*P* Value*
Bodily pain	57.9 ± 6.1	58.4 ± 5.7	0.68
General health perceptions	58.8 ± 6.7	57.6 ± 8.1	0.40
Mental health	57.0 ± 4.6	55.6 ± 7.0	0.51
Physical functioning	56.0 ± 5.3	55.6 ± 5.7	0.93
Role—emotional	55.2 ± 2.9	53.5 ± 7.2	0.45
Role—physical	53.5 ± 8.7	51.3 ± 10.3	0.29
Social functioning	54.6 ± 4.6	53.7 ± 7.6	0.69
Vitality	56.3 ± 8.5	57.0 ± 7.7	0.61
Physical composite score	56.2 ± 7.8	55.8 ± 7.7	0.88
Mental composite score	55.9 ± 5.0	54.5 ± 8.7	0.82

Data are presented as mean ± SD.

* *P* value from two-sample rank sum test.

Shir *et al.*[12] reported pain and analgesic requirements during the 4 days after prostatectomy in three groups of patients. All patients received epidural bupivacaine and fentanyl patient-controlled analgesia postoperatively, though intraoperative care differed because one group received epidural bupivacaine alone, a second group received combined epidural and general endotracheal anesthesia, and a third group received general endotracheal anesthesia alone. Although documented pain scores were not considered to represent clinically significant pain in any group at any time (the NPS score in all groups during the first 4 postoperative days was ≤ 2), the NPS score was significantly lower on the first postoperative day in the epidural group compared with the general endotracheal anesthesia–alone group. This difference was not present on postoperative days 2–4. The excellent pain scores achieved in all groups makes it difficult to argue for routine placement of epidural cath-

eters for these cases if in-hospital pain management is the primary objective. The long-term outcomes and functional status of these patients were not reported, allowing for the possibility that such a management strategy might be justified by other outcomes.

A more recent study in prostatectomy patients by Gottschalk *et al.*[6] was designed to address long-term and global outcomes measures. Again, three groups of patients were studied, all receiving general anesthesia and epidural local anesthetic and narcotics at the time of fascia closure and continuing with postoperative epidural patient-controlled anesthesia. The groups differed in their intraoperative care because one group received epidural bupivacaine before incision and during surgery, another group received epidural fentanyl during the same period, and the final group received general anesthesia alone during surgery. These authors reported that patients who received epidural bupivacaine or fentanyl before the start of surgery, when compared with controls, were significantly more likely to have no pain when assessed 9.5 weeks after surgery, though no differences were found at 3.5 and 5.5 weeks. The same groups of patients were more active 3.5 weeks after surgery but not at 5.5 or 9.5 weeks compared with controls. These authors concluded that preemptive epidural analgesia improved postoperative pain control during the hospital stay and long after discharge and was associated with increased activity after discharge. Although the findings of this study were statistically significant, the clinical significance is less clear. Nonetheless, the potential for improved patient pain management and more rapid return of functional status has spurred investigators to identify optimal procedure-specific perioperative management strategies to improve long-term outcomes.

The objective of the current study was to determine whether the addition of intrathecal local anesthetic, narcotics, and the α-adrenergic agonist clonidine would improve short- and long-term pain management and shorten the recovery to functional status. We attempted to design a perioperative plan that would optimize pain control consistent with our current practice, including anticipated duration of stay. We chose to add intrathecal narcotics and clonidine to local anesthetics because this has been shown to improve immediate postoperative pain control.[15,16] The remainder of the multimodal pain management including administration of nonsteroidal antiinflammatory drugs reflected the current practice at our institution at the time of the study design.

Overall, pain scores were low at all points in both groups. Serlin *et al.*[17] have reported in cancer patients that numerical pain scores of 4 or less correspond to mild and limited impact on functional status. We chose to consider NPS scores of 3 or less as clinically acceptable pain control. Mean current NPS scores in both groups at all times studied were less than 3. Although pain scores were significantly lower during the initial two inpatient assessments, subsequent inpatient and all outpatient evaluations after this time and after discharge from the hospital revealed no differences between groups in terms of pain or functional status. By 12 weeks, there was no difference in pain or functional status compared with the preoperative assessment.

When evaluating the potential benefits of an anesthetic care plan, it is also important to consider potential drawbacks. One patient was withdrawn from the study because of significant bradycardia after administration of intrathecal drugs and during induction of general anesthesia. Bradycardia is a known side effect associated with clonidine administration, and we cannot rule this out as a causative factor. In addition, the intrathecal group received significantly more intraoperative pressors; it is not known whether this presents additional risk, and the relatively small number of patients studied is insufficient to evaluate any infrequent morbidity associated with the use of such pressors. Intrathecal analgesia produced a relatively high frequency of side effects such as pruritus and nausea, which produce significant, if transient, discomfort. Finally, at least in our practice, patients receiving intrathecal opioids are followed up by the acute pain service and thus require increased use of physician and paramedical resources.

The median duration of hospital stay was identical in both groups (2 days), but there was a small, significant difference in the duration of stay because five patients in the control group remained in hospital for more than 3 days. In two of the patients, the cause was a surgical complication and was unlikely related to anesthetic technique. In the other three patients, discharge was delayed because of slow recovery of bowel function. Opioids may contribute to impaired bowel motility, and other investigators have suggested that epidural analgesia may improve postoperative bowel function by reducing parenteral opioid use.[4,5] Patients in the control group did require significantly greater doses of morphine in the initial postoperative period, and it is possible that this may have contributed to the delayed return of bowel function. Given the relatively low frequency of this event, a study larger than ours would be necessary to evaluate the possibility that the narcotic-sparing effect of intrathecal analgesia improves postoperative bowel motility in this setting.

Limitations

We attempted to mask those caring for the patients and the patients themselves to treatment assignment as much as possible because effective masking may minimize any bias favoring a particular technique. However, the limitations of this approach must be acknowledged. Despite sedation, some subjects receiving intrathecal drugs may have been aware of their treatment assign-

ment before induction of general anesthesia. Furthermore, it is possible that the documented hemodynamic responses to induction of general anesthesia or surgical incision may have given clues to the assigned treatment group. Although the postanesthesia recovery room personnel and the patients themselves were aware of any residual effects of intrathecal bupivacaine, by the time of transfer to the floor, these effects were minimal. The subsequent personnel obtaining postoperative data were masked to treatment assignment.

We note that this trial was not designed to investigate the role of preemptive analgesia and postoperative outcomes. Although a preemptive neuronal block was likely present in the intrathecal group, we did not document sensory level before induction of general analgesia. Postoperative neurologic assessment identified a consistent residual neurologic blockade in the intrathecal group, suggesting that such neuronal input may have been attenuated. Our multimodal postoperative pain management protocol may have decreased our ability to detect a difference between groups. Furthermore, the potential interaction of general anesthesia and regional analgesia in this setting are not clear but may also have a confounding effect. Therefore, a variety of factors may have limited our ability to detect differences between groups.

The prerandomization exclusion rate was higher than anticipated. Few patients (< 5%) were excluded because of predefined exclusion criteria. Many patients wished to avoid general anesthesia, whereas others were adamantly opposed to regional techniques, even though they would also receive a general anesthetic. Virtually all patients undergoing prostatectomy have friends or acquaintances who have undergone this procedure, and it is possible that previous experience of these contacts or previous anesthetic experiences of the subject for other procedures contributed to the exclusion rate that we observed. The high prerandomization exclusion rate may have allowed for bias in the findings because the study population may not reflect the entire population that undergoes RRP. The randomized, masked study design and high degree of subsequent data collection should serve to limit such potential bias.

Finally, these results may not be applicable to other institutions or procedures. The patient demographics and surgical techniques of the current study population may not reflect those present in other institutions. In addition, the current study was conducted in men. Consequently, the findings of the current study may not be applicable to patients undergoing other types of surgical procedures or even the same procedure in a different environment.

Summary

Pain is well controlled in patients undergoing prostatectomy with either general anesthesia or combined intrathecal analgesia and general anesthesia followed by multimodal pain management. The addition of intrathecal analgesia did not improve pain management or functional status after discharge from the hospital. Although the duration of stay was significantly reduced in the group that received intrathecal analgesia, this small reduction was associated with an increase in minor side effects and resource utilization.

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