

# Postoperative Analgesia after Radical Retropubic Prostatectomy

## A Double-blind Comparison between Low Thoracic Epidural and Patient-controlled Intravenous Analgesia

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**Background:** Postoperative pain after radical retropubic prostatectomy can be severe unless adequately treated. Low thoracic epidural analgesia and patient-controlled intravenous analgesia were compared in this double-blind, randomized study.

**Methods:** Sixty patients were randomly assigned to receive either low thoracic epidural analgesia (group E) or patient-controlled intravenous analgesia (group P) for postoperative pain relief. All patients had general anesthesia combined with thoracic epidural analgesia during the operation. Postoperatively, patients in group E received an infusion of 1 mg/ml ropivacaine, 2 µg/ml fentanyl, and 2 µg/ml adrenaline, 10 ml/h during 48 h epidurally, and a placebo patient-controlled intravenous analgesia pump intravenously. Patients in group P received a patient-controlled intravenous analgesia pump with morphine intravenously and 10 ml/h placebo epidurally. Pain, the primary outcome variable, was measured using the numeric rating scale at rest (incision pain and "deep" visceral pain) and on coughing. Secondary outcome variables included gastrointestinal function, respiratory function, mobilization, and full recovery. Health-related quality of life was measured using the Short Form-36 questionnaire, and plasma concentration of fentanyl was measured in five patients to exclude a systemic effect of fentanyl.

**Results:** Incisional pain and pain on coughing were lower in group E compared with group P at 2–24 h, as was deep pain between 3 and 24 h postoperatively ( $P < 0.05$ ). Maximum expiratory pressure was greater in group E at 4 and 24 h ( $P < 0.05$ ) compared with group P. No difference in time to home discharge was found between the groups. The mean plasma fentanyl concentration varied from 0.2 to 0.3 ng/ml during 0–48 h postoperatively. At 1 month, the scores on emotional role, physical functioning, and general health of the Short Form-36 were higher in group E compared with group P. However, no group × time interaction was found in the Short Form-36.

**Conclusions:** The authors found evidence for better pain relief and improved expiratory muscle function in patients receiving low thoracic epidural analgesia compared with patient-

controlled analgesia for radical retropubic prostatectomy. Low thoracic epidural analgesia can be recommended as a good method for postoperative analgesia after abdominal surgery.

POOR pain control in the postoperative period can lead to chronic pain syndromes,<sup>1</sup> increased postoperative morbidities,<sup>2</sup> and poor quality of life.<sup>3</sup> Therefore, good postoperative pain management is imperative for the patient and is one of the new pain management standards recommended recently.<sup>4</sup> Postoperative pain after radical retropubic prostatectomy can be moderate to severe but is often self-limiting and of short duration (< 48 h), and it is therefore important to use anesthetic and analgesic techniques that provide good pain relief, specifically in the early postoperative period. In addition to good postoperative pain relief and a low incidence of complications associated with analgesic techniques, early postoperative mobilization and home discharge are important milestones in recovery of full function after major surgery.<sup>3,5,6</sup> Gottschalk *et al.*<sup>7</sup> found that preemptive epidural analgesia results in better pain control even at home after home discharge, and increased activity levels without affecting other postoperative outcomes.

Epidural analgesia using a combination of local anesthetic and opioids has been a popular method for postoperative pain relief, and many studies, including some meta-analyses, have shown beneficial effects not only on the pain intensity, but also on certain outcomes such as lower incidence of respiratory complications, deep vein thrombosis, and even cardiac morbidity.<sup>8–10</sup> Because the incidences of some of these major postoperative complications are low, well-controlled prospective studies have only shown reduction in pain intensity and only rarely other benefits on outcome.<sup>11–13</sup> One recent double-masked study on patients undergoing open aortic aneurysm surgery found no benefit of epidural analgesia compared with patient-controlled analgesia (PCA).<sup>12</sup> This has resulted in many questions being raised about the potential benefits *versus* risks of epidurals for anesthesia and analgesia.<sup>14</sup>

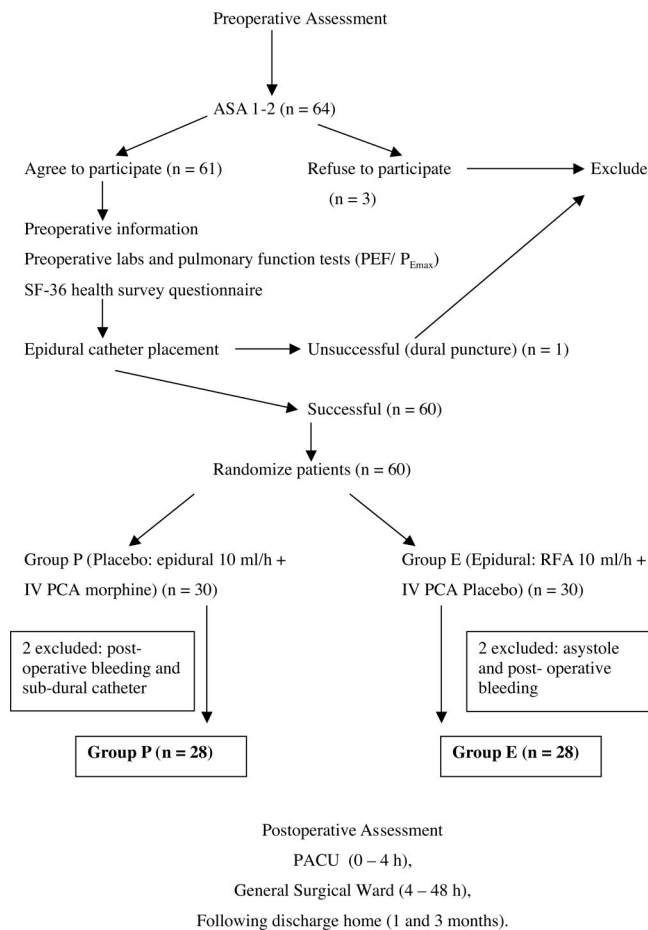
This study was performed with the primary aim of comparing intravenous PCA with thoracic epidural analgesia on postoperative pain during the first 48 h after radical retropubic prostatectomy. The secondary aims were to assess certain respiratory functions, the time to mobilization, home readiness, and actual duration of hospital stay. Plasma concentrations of fentanyl were

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**Fig. 1. Patient flowchart.** ASA = American Society of Anesthesiologists; IV = intravenous; PACU = postanesthesia care unit; PCA = patient-controlled analgesia; PEF = peak expiratory flow;  $P_{E_{max}}$  = maximum expiratory pressure; RFA = ropivacaine, fentanyl, adrenaline; SF-36 = Short Form-36.

measured in five patients to assess whether there was a significant absorption of fentanyl from the epidural space. After discharge, the patients were followed up during a 3-month period to assess their quality of life at home.

## Materials and Methods

Ethics committee approval was obtained from the institutional review board at the University Hospital, Örebro, Sweden, before the start of the study, and informed verbal and written consent was obtained from 60 patients undergoing radical retropubic prostatectomy for prostatic cancer (fig. 1). Exclusion criteria were chronic pain, use of preoperative opioid analgesics, known contraindications for epidural analgesia, intolerance to morphine or local anesthetics, and age older than 70 yr.

### Randomization and Blinding

The Hospital Pharmacy, which also prepared the drugs, randomized patients into two groups using com-

puter-generated randomized numbers. The patients and surgeons, anesthesiologists, and nurses involved in patient treatment were unaware of the method of analgesia, and every precaution was taken to achieve double blinding. After successful insertion of the epidural catheter, patients were randomized into two groups:

Group P (PCA: morphine): 10 ml/h normal saline epidurally for 48 h (= 480 ml), and PCA morphine intravenously.

Group E (epidural: 1 mg/ml ropivacaine + 2  $\mu$ g/ml fentanyl + 2  $\mu$ g/ml adrenaline): 10 ml/h epidurally for 48 h (= 480 ml), and PCA placebo (normal saline) intravenously.

The hospital pharmacy sent two double-blinded bags, one for epidural use (total volume 500 ml) and the other for intravenous use (total volume 200 ml), according to the randomization described above.

### Preoperative Preparation

The patients were informed in detail about the operation and anesthesia, and postoperative pain relief and physiotherapy. Preoperatively, expiratory functions (see Respiratory Functions), a health-related quality-of-life questionnaire (Short Form-36 [SF-36]), and pain scores (numeric rating scale [NRS], 0-10) were obtained from all patients. Preoperative anxiolysis was achieved using 10 mg diazepam orally 1 h before planned surgery. Intravenous access was achieved and 200-300 ml acetated Ringer's solution was given intravenously before insertion of the epidural catheter. When required, 1-2 mg midazolam was given intravenously during epidural catheter placement.

### Epidural Technique

An 18-gauge epidural needle was inserted at the Th10-12 interspace using the hanging-drop or loss-of-resistance technique with the patient in the sitting position in the holding area. The epidural catheter was inserted and subsequently tested for subarachnoid or intravascular placement using 3 ml mepivacaine, 2%, with adrenaline, which is standard practice at our hospital. A bolus dose of 3-4 ml mepivacaine, 2%, with adrenaline was subsequently injected, and a loss of sensation to cold was determined after 10 min. If a sensory block up to the Th8 dermatomal level was achieved, the patient was considered to be ready for induction of anesthesia. If not, a further dose of 2-3 ml mepivacaine, 2%, with adrenaline was injected epidurally. If this did not achieve the desired block, it was assumed that the catheter was incorrectly placed, and the patient was offered the choice of one more attempt at epidural catheter placement or exclusion from the study.

### Anesthetic Technique

Anesthesia was induced with 1-2 mg/kg propofol (patients 1-55) or 3-5 mg/kg thiopentone (patients 56-60)

for reasons described below; 2  $\mu\text{g}/\text{kg}$  fentanyl was given as an analgesic before induction of anesthesia, and 0.5 mg/kg rocuronium was used as a muscle relaxant for intubation. After tracheal intubation, the patients were ventilated with 33% oxygen in nitrous oxide and 1–3% sevoflurane using volume-controlled ventilation. Monitoring included indirect, noninvasive blood pressure and heart frequency, oxygen saturation, end-tidal concentration of anesthetic gases and carbon dioxide, neuromuscular transmission, and anesthetic depth monitoring using the Bispectral Index. Perioperative analgesia was maintained using an infusion of 2% mepivacaine with 2–5 ml/h adrenaline by epidural infusion in all patients. Adequate anesthetic depth was obtained by adjusting the inspired concentration of sevoflurane to maintain a Bispectral Index value between 40 and 50. Hypotension was treated with volume replacement and, when necessary, with intravenous ephedrine in incremental doses of 5 mg. Bradycardia (heart frequency < 50 beats/min) was treated with 0.5 mg atropine if needed. Intravenous fluids were administered to maintain adequate blood pressure and basal fluid requirement, and colloids or blood was administered when deemed necessary by the attending anesthesiologist. At the end of the operation and after the last suture, muscle relaxation was reversed using 0.2 mg glycopyrrolate and 2.5 mg neostigmine. When spontaneous respiration had returned, the train-of-four stimulation showed greater than 70% recovery, and the patient was able to open his eyes on command, the trachea was extubated, and the patient was transferred to the postoperative ward. Immediately before transfer to the postoperative ward, the epidural infusion was turned off.

### *Surgical Technique*

Radical retropubic prostatectomy was performed as described by Walsh.<sup>15</sup> A unilateral or bilateral nerve-sparing technique was applied when the tumor and patient characteristics permitted. In some patients, bilateral pelvic lymphadenectomy was performed according to the Swedish guidelines. A drain was left *in situ* for 48 h in all patients, which is a routine at our hospital.

### *Postoperative Analgesia and Rescue Medication*

On arrival in the postanesthesia care unit, the study drug (saline or ropivacaine-fentanyl-adrenaline) was started epidurally at a constant rate of 10 ml/h. All patients were provided with an intravenous PCA device with either 1 mg/ml morphine or placebo (0.9% saline) in group P and group E, respectively. The PCA device was programmed to give a bolus dose of 1 mg (1 ml) with a lockout time of 6 min (10 mg/h maximum) and used in case of inadequate analgesia (NRS score > 3), when the patient was fully awake, which is the standard at our hospital. A nurse, also blinded to the study arm, was allowed to administer a bolus of 1–2 mg morphine

as needed to all patients in the event of inadequate pain relief (NRS score > 5) during 0–48 h. All patients received 1 g paracetamol orally before and every 6 h after the operation during the hospital stay.

### *Outcome Measures*

**Primary Outcome Measure.** Postoperative pain (NRS) at rest (incision site and “deep abdominal” pain) and on coughing was measured every 1 h for 4 h, every 4–6 h during 8–24 h, and every 12 h during 24–48 h. Analgesic consumption during 0–4 h in the postanesthesia care unit; total PCA consumption at each 24-h period for 48 h; and opioid-related side effects, including postoperative nausea and vomiting (PONV), sedation (1–4; 1 = fully awake, 4 = deep asleep), and tiredness (0–10; 0 = fully alert, 10 = extremely tired), were also measured.

### **Secondary Outcome Measures.**

**Duration of Stay in the Hospital.** Time to home readiness (see appendix for home readiness criteria) and discharge were measured once a day until home discharge.

**Gastrointestinal Function.** Time to drinking and eating, and PONV were recorded.

**Mobilization.** Time to sit at the edge of the bed, stand, and walk with support were recorded.

**Respiratory Functions.** Peak expiratory flow rate (Airmed, London, United Kingdom) and maximum expiratory pressure ( $P_{\text{Emax}}$ ; MicroMedical, Moreton-in-Marsh, United Kingdom) were measured at 0 h (preoperatively), 4 h, 24 h, and 48 h after the end of the operation.  $P_{\text{Emax}}$  was measured providing a leakage of 0.3 l/min to minimize the effect of buccal muscles on the generated expiratory pressure.

**Infections Parameters.** C-reactive proteins and leukocyte count on day 1 were recorded.

**Complications.** All complications were recorded.

**Quality of Life.** The SF-36 (see Quality-of-life Questionnaire) was given before and 1 and 3 months after the operation to each patient.

Seven milliliters of blood was obtained from the last 15 patients at the end of the operation and after 4, 24, and 48 h to determine plasma fentanyl concentration. After centrifugation of the blood and separation of plasma, the sample was frozen to  $-70^{\circ}\text{C}$ , and all samples were analyzed at the end of the study after the codes had been broken.

### *Quality-of-life Questionnaire (SF-36)*

The SF-36 is a validated health-related quality of life survey consisting of 36 questions that measure eight health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations secondary to emotional problems, and mental health. In addition, two summary scores are available: a standardized physical component and a standardized mental component. Each

**Table 1. Preoperative Characteristics**

	Group E (Epidural)	Group P (PCA)	P Value
Age, yr	64.5 ± 4.9	61.1 ± 4.3	0.007
Height, cm	177.0 ± 5.9	176.6 ± 6.2	0.85
Weight, kg	82.2 ± 7.9	81.5 ± 8.7	0.76
ASA status, median (range)	1.5 (1–2)	1.0 (1–2)	0.045
Gleason score, median (range)	6 (5–9)	6 (5–9)	0.08
Blood pressure, mmHg			
Systolic	143 ± 15	144 ± 20	0.79
Diastolic	85 ± 11	85 ± 10	0.99
Heart frequency, beats/min	70 ± 14	65 ± 11	0.14
Level of epidural catheter placement, median (range)	Th10–11 (8/9–11/12)	Th10–11 (9/10–11/12)	0.73
Epidural block (sensory) after 10 min,* median (range)			
Upper level	Th6 (3–8)	Th6 (4–11)	0.14
Lower level	L1 (1–5)	L1 (1–5)	0.84

Preoperative characteristics and epidural catheter placement. All results are expressed as mean ± SD unless otherwise stated.

\* Five patients with inadequate block were given a supplementary dose after 10 min.

ASA = American Society of Anesthesiologists; PCA = patient-controlled analgesia.

summary score is derived from four scale scores: The physical component score is derived from physical problems, role limitations—physical, bodily pain, and general health, whereas the mental component score is derived from vitality, social functioning, role limitations—emotional, and mental health. The scores are calibrated so that a higher score indicates an improved level of function, *e.g.*, a higher score in bodily pain indicates a low level of body pain, whereas a higher score in social functioning indicates an improved level of social functioning. The questionnaire is available and validated in the Swedish language. For further details of the questionnaire and the meaning derived from its individual components, please see Ware and Sherbourne<sup>16</sup> and Ware *et al.*<sup>17</sup>

### Statistics

To determine the number of patients that should be recruited for the study, we used pain on coughing at 4 h after the operation as the primary variable. We were interested in achieving a 50% reduction in pain intensity as measured by the NRS in the epidural group compared with the intravenous PCA group (5.0 to 2.5 and with an SD of 2.5). We determined that 50 patients would be needed (25 in each group) to achieve statistical significance ( $\alpha = 0.05$  and  $\beta = 0.2$ ) and therefore recruited 30 patients/group to account for loss of data and patient dropout. Results are presented as mean and SD or median and range as appropriate. Demographic data, operation/anesthesia times, bleeding times, and drug requirements perioperatively were assessed using the unpaired Student *t* test. The NRS score was treated as a nonparametric variable and analyzed at 4, 12, 24, and 48 h using the Mann-Whitney U test followed by the Bonferroni-Holm test. Postoperative pain and the SF-36 were analyzed using repeated-measures analysis of variance followed by the Fisher protected least significance difference test. Duration of hospital stay and times to

achieve recovery indices were analyzed using the Mann-Whitney U test, and chi-square test was used to analyze ordinal variables. Statistical significance was considered when  $P < 0.05$ .

### Results

Of the 60 patients randomly assigned into the study after successful catheter placement, 4 patients were subsequently excluded: one due to subdural catheter position suspected due to high thoracic analgesia and confirmed on day 1 by computerized tomography with contrast injection (group P), one due to postoperative bleeding requiring reoperation (group P), one after a short period of asystole after anesthetic induction (group E), and one due to postoperative bleeding that subsided with conservative management (group E). A total of 56 patients (28 in each group) thus completed the study.

No differences were found in demographic data and between the groups except for a higher American Society of Anesthesiologists physical status and age in group E (table 1). The median level of epidural catheter insertion and the spread of analgesia after 10 min, as well as preoperative blood pressure and heart frequency, were similar between the groups. Intraoperative operation/anesthesia times, drug requirements, perioperative bleeding, and fluid (crystalloid and colloids) requirements were similar between the groups (table 2). Postoperative bleeding during 0–48 h and crystalloid requirements during 0–24 h were similar between the groups (table 2).

Postoperative pain in the two groups during 1–48 h is shown in figures 2–4. Median pain at rest at the incision site was low ( $< 4$ ) and significantly lower in group E compared with group P at 4–24 h after the operation (fig. 2). Similarly, “deep” pain and pain on coughing were also significantly lower at 4–24 and 4–48 h, re-

**Table 2. Intraoperative Characteristics**

	Group E (Epidural)	Group P (PCA)	P Value
Duration of operation, min	103 ± 33	114 ± 22	0.13
Duration of anesthesia, min	149 ± 33	151 ± 36	0.80
Total dose propofol, mg	188 ± 37	194 ± 42	0.58
Fentanyl requirement, μg	149 ± 38	147 ± 17	0.86
Ephedrine given, mg	18 ± 16	18 ± 13	0.92
Intraoperative bleeding, ml	1,150 ± 884	939 ± 397	0.26
Blood requirement perioperatively, n	6	7	0.84
Fluids given, ml			
Crystalloids	2,554 ± 836	2,242 ± 630	0.13
Plasma expanders	607 ± 438	679 ± 366	0.51

Intraoperative characteristics, including drugs, blood loss, and fluids given. All results are expressed as mean ± SD. PCA = patient-controlled analgesia.

spectively, in group E compared with group P (figs. 3 and 4). Postoperative morphine consumption during the postoperative period is shown in table 3. No difference was seen during 0–4 h between the groups. Thereafter, the median morphine consumptions in group P during 4–24 and 24–48 h were 32 and 16 mg, respectively. No patients in the epidural group required supplemental morphine during 4–48 h.

The median times to recovery of function and mobilization were similar between the groups (table 4), and the median duration of hospital stay did not differ between the groups. No difference was found in the times to home discharge between the groups (table 4).

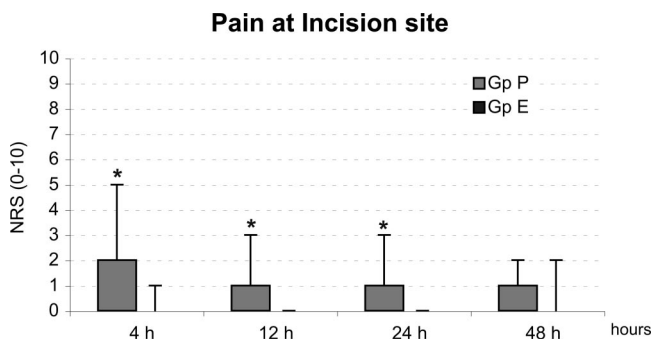
Peak expiratory flow rate values decreased in both groups postoperatively at 4 h, but no significant difference was seen between the groups at any time (table 3). The  $P_{Emax}$  values also decreased with time and were significantly different at 4 and 24 h compared with preoperative values. There was also a statistically significant difference in  $P_{Emax}$  values between the groups at 4 and 24 h ( $P < 0.01$ ).

The incidence of side effects is shown in table 3. No differences were found between the groups in the incidence of PONV, but the total number of patients requesting antiemetics during 0–2 days was greater in group E ( $P < 0.05$ ). A majority of these antiemetics were administered in the early postoperative ward (0–4 h) (5 vs. 1

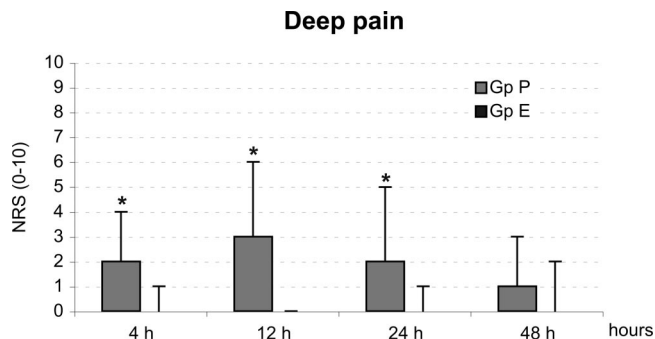
in groups E and P, respectively). Mild sedation ( $\geq 2$ ) was recorded in a similar number of patients in both groups, and even tiredness (visual analog scale score  $\geq 6$ ) was similar between the groups. Two patients in group E had perioperative complications: One had an infection of the wound requiring antibiotic medication, and one patient underwent repeat surgery on day 4 because of an accidental perioperative rectal perforation requiring sigmoidostomy. In group P, one patient was readmitted after discharge because of fever, which subsided after 1–2 days of antibiotic treatment, and was subsequently discharged home. One patient had a short period of asystole requiring approximately 20 s of cardiac massage immediately after induction of anesthesia with propofol. He recovered completely, without any residual effects.

Five of the 15 patients in whom blood was taken for plasma fentanyl concentration measurement had thoracic epidural analgesia (TEA) with ropivacaine–fentanyl–adrenaline. The plasma concentration of fentanyl in these patients was found to be between 0.13 and 0.40 ng/ml at 0–48 h postoperatively, with only small variations at different time periods and between the patients (fig. 5).

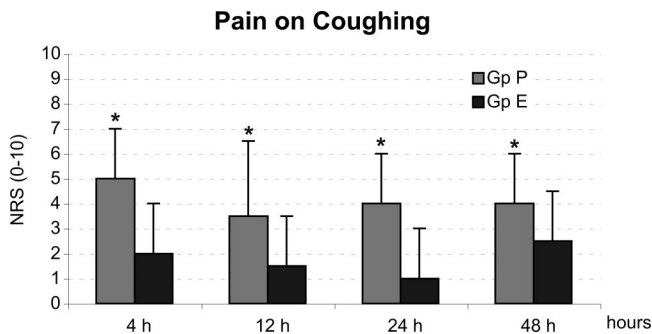
The results of the quality-of-life questionnaire (SF-36) at 1 and 3 months are shown in table 5. A significant difference was found between the groups in physical functioning, general health, and role limitation due to



**Fig. 2. Pain at the site of incision, shown as median (interquartile range). \*  $P < 0.05$  between groups. Gp E = epidural group; Gp P = patient-controlled analgesia pump group; NRS = numeric rating scale.**



**Fig. 3. Deep abdominal pain, shown as median (interquartile range). \*  $P < 0.05$  between groups. Gp E = epidural group; Gp P = patient-controlled analgesia pump group; NRS = numeric rating scale.**



**Fig. 4. Pain on coughing, shown as median (interquartile range). \*P < 0.05 between groups. Gp E = epidural group; Gp P = patient-controlled analgesia pump group; NRS = numeric rating scale.**

emotional problems, with a higher score in group E compared with group P in all variables at 1 month. Except for general health and mental health, all other variables were significantly reduced in both groups at 1 month but returned to preoperative values at 3 months. However, no group × time interaction was found in the SF-36.

**Discussion**

Significantly lower pain scores were found in the epidural group compared with the intravenous PCA group in patients undergoing radical retropubic prostatectomy during the first 24 h postoperatively. This resulted in improved expiratory muscle function as measured by the maximum expiratory pressure. However, the improvement in pain relief with epidural analgesia did not translate into a reduction in minor or major postoperative complications or duration of hospital stay. Quality of life was poorer in both groups at 1 month compared with preoperative values, but no interaction was seen in group × time during the study period. The benefits of TEA should be weighed against the rare complications seen, the possible higher costs, and the increased time taken in patient preparation.

Poor pain management in the postoperative period has been shown to result in chronic pain syndromes,<sup>1,18,19</sup> delayed recovery, and increased cardiac and renal complications.<sup>20</sup> Shir *et al.*<sup>21</sup> showed that

**Table 3. Postoperative Characteristics**

	Group E (Epidural)	Group P (PCA)	P Value
Postoperative nausea, n			
0–4 h	8	4	NS
4–24 h	3	1	NS
24–48 h	0	3	NS
Postoperative vomiting, n			
0–4 h	1	0	NS
4–24 h	1	0	NS
24–48 h	0	1	NS
Antiemetics, n	8	2	< 0.05
Tiredness (VAS score ≥ 6), n			
2 h	5	3	NS
4 h	0	1	NS
24 h	1	3	NS
Postoperative sedation (≥ 2), n			
2 h	3	7	NS
4 h	4	3	NS
24 h			
Bleeding, ml			
0–24 h	185 ± 127	243 ± 247	NS
24–48 h	81 ± 38	83 ± 37	NS
Crystalloids, ml	1,817 ± 911	1,472 (540)	NS
0–24 h			
Morphine requirements, median (range), mg			
0–4 h	2 (0–17)	3 (0–28)	NS
4–24 h	—	32 (7–66)	
24–48 h	—	16 (1–43)	
PEF, l/min			
Preoperatively	527 ± 72	504 ± 90	NS
4 h	409 ± 104	351 ± 97	NS
24 h	454 ± 103	417 ± 72	NS
48 h	446 ± 95	438 ± 87	NS
P <sub>E<sub>max</sub></sub> , mmHg			
Preoperatively	91 ± 37	88 ± 27	NS
4 h	67 ± 29	42 ± 16	< 0.001
24 h	78 ± 29	58 ± 21	< 0.01
48 h	63 ± 21	71 ± 19	NS

Postoperative characteristics. P values refer to differences between groups.

NS = not significant; PCA = patient-controlled analgesia; PEF = peak expiratory flow; P<sub>E<sub>max</sub></sub> = maximum expiratory pressure; VAS = visual analog scale.

**Table 4. Times to Recovery and Mobilization**

	Group E (Epidural)	Group P (PCA)	P Value
Time to start drinking, h	5.0 (0.5–29)	5.25 (1.0–51.0)	0.73
Time to start eating, h	16.3 (4.0–31.0)	18.5 (5.0–56.0)	0.45
Time to sitting, h	19.0 (5–22.5)	20.5 (4.0–32.0)	0.14
Time to walking with support, h	20.0 (15.25–27.5)	21.0 (15.0–48.0)	0.21
Time to first defecation, days	3.5 (2.0–5.0)	3.0 (2.0–4.0)	0.21
Number of patients ready for discharge, n (%)			
Day 1	0	0	
Day 2	15/28 (54%)	8/28 (29%)	0.058
Day 3	23/27 (85%)	18/27 (67%)	0.23
Time to actual discharge home, median (range), days	4 (3–12*)	5 (3–6)	0.69

Times to mobilization and recovery. All results are shown as median (range) unless otherwise stated. For home-readiness criteria, see the appendix.

\* One patient underwent repeat surgery because of a rectal perforation.

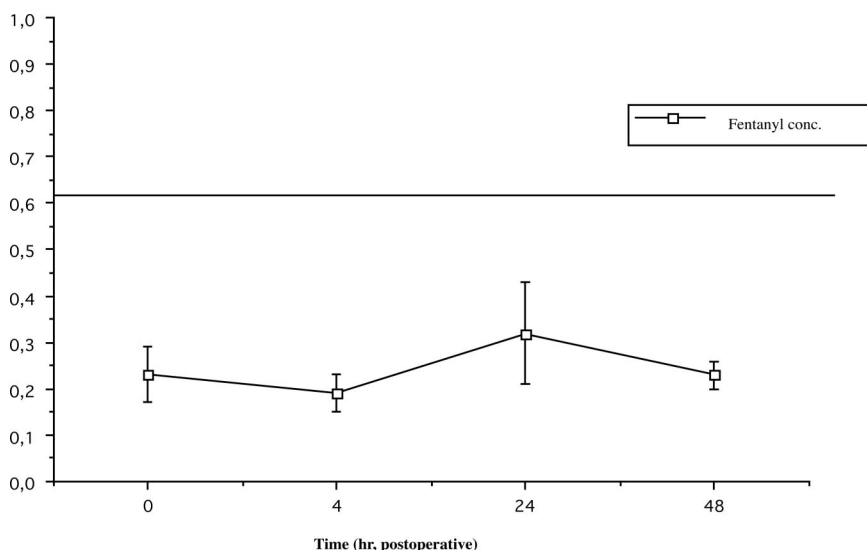
PCA = patient-controlled analgesia.

intraoperative epidural analgesia resulted in less postoperative analgesic requirements for similar efficacy compared with general anesthesia alone and that the blockade of afferent noxious input preoperatively was important in the management of postoperative pain after radical prostatectomy. In addition to better pain relief, epidural analgesia during radical retropubic prostatectomy has been shown to result in a reduction in blood loss<sup>22,23</sup> and earlier return of bowel function.<sup>23</sup> For these reasons, we believed that it was important to use epidural analgesia combined with general anesthesia in all patients during the operation. We found that the intraoperative blood loss was between 1,000 and 1,200 ml, which is comparable to the finding of other authors using epidural analgesia with or without general anesthesia,<sup>22</sup> and cardiovascular stability was maintained throughout the perioperative period.

#### Postoperative Pain

Opioids given *via* intravenous PCA pumps have several disadvantages, including pruritus, PONV, sedation,

and a delay in the recovery of bodily functions such as bowel movement and mobilization.<sup>24,25</sup> Therefore, regional analgesia, specifically epidural analgesia, has been a popular alternative. Several studies have shown advantages of epidural analgesia over intravenous PCA. Interestingly, well-designed prospective double-blind studies have found only limited<sup>13</sup> or no benefits<sup>12</sup> of epidural analgesia over intravenous PCA techniques on outcome after major abdominal surgery. In the current study, using TEA, we found a significant reduction in pain intensity by 40–50% compared with intravenous PCA. Lower pain scores were found in static pain (incision site, “deep abdominal,” or visceral pain) as well as dynamic pain (on coughing). This was clearly evident in the early postoperative phase (< 24 h), specifically during coughing. Previous studies comparing epidural *versus* intravenous PCA have found similar reduction in pain after major abdominal surgery.<sup>10,13</sup> Not only did TEA result in a reduction in pain intensity, it even led to an improvement in expiratory function measured as  $P_{E_{max}}$ . This method has been used previously for measuring expiratory muscle strength and provides an ob-



**Fig. 5. Plasma concentration of fentanyl at different time periods. Minimum effective plasma concentration (shown by a line above) has been found to be approximately 0.63 ng/ml.<sup>30</sup> Time 0 = end of the operation.**

**Table 5. Health-related Quality-of-life Questionnaire (SF-36)**

	Preoperative		Postoperative (1 month)		Postoperative (3 months)		P Value, Group	P Value, Time	P Value, Group × Time
	Group E	Group P	Group E	Group P	Group E	Group P			
Physical functioning	95 ± 11	92 ± 9	84 ± 14	78 ± 17	94 ± 8	89 ± 13	0.040	0.0001	0.821
Role—physical	92 ± 28	84 ± 27	24 ± 39	9 ± 23	80 ± 35	69 ± 38	0.088	< 0.0001	0.589
Body pain	90 ± 17	84 ± 21	75 ± 23	68 ± 22	94 ± 13	90 ± 18	0.485	< 0.0001	0.639
General health	86 ± 11	77 ± 16	83 ± 16	74 ± 18	86 ± 13	78 ± 15	0.041	0.725	0.496
Vitality	83 ± 17	75 ± 18	67 ± 22	60 ± 27	83 ± 17	74 ± 20	0.140	0.0001	0.587
Social functioning	89 ± 18	88 ± 20	78 ± 26	66 ± 29	87 ± 24	83 ± 19	0.311	0.012	0.785
Role—emotional	86 ± 29	89 ± 27	78 ± 36	43 ± 45	90 ± 22	85 ± 27	0.040	0.0004	0.086
Mental health	85 ± 14	82 ± 15	87 ± 16	76 ± 21	88 ± 13	85 ± 15	0.408	0.122	0.509
Physical component score	55 ± 6	52 ± 6	43 ± 9	41 ± 6	53 ± 6	49 ± 8	0.059	< 0.0001	0.156
Mental component score	51 ± 8	50 ± 8	51 ± 11	43 ± 13	52 ± 7	51 ± 8	0.257	0.048	0.128

Scores on the health-related quality-of-life questionnaire (Short Form-36 [SF-36]) before and 1 and 3 months after radical prostatectomy. *P* values for group indicate intergroup values (group E [epidural] vs. group P [patient-controlled analgesia]) for each characteristic, whereas *P* values for time indicate a change over time (preoperative vs. 1 month vs. 3 months).

jective measure of the ability to cough.<sup>26</sup> The apparatus used by us provided for a small leak to compensate for the pressure that could be generated by the buccal muscles as previously described.<sup>27</sup> Although the peak expiratory flow rate has also been used as a measure of expiratory muscle function, it is less sensitive, and high flows can be generated despite poor abdominal muscle function. In this study, as in a previous study,<sup>26</sup> the peak expiratory flow rate was not equally sensitive as  $P_{Emax}$  in detecting differences between groups or over time. Improvement in the ability to cough would be expected to reduce respiratory complications in the postoperative period as has been shown in two published meta-analyses of the literature.<sup>8,28</sup> However, we did not find differences in respiratory complications postoperatively in the current study, which could be due to several reasons: The number of patients we studied were inadequate to detect differences in the low incidence of respiratory complications after lower abdominal surgery; the method used to detect respiratory complications such as the incidence of respiratory infections is not sufficiently sensitive in the present setting; and finally, the major benefits of reduction in postoperative pain, such as a lower incidence of atelectasis, are mostly seen after upper and not lower abdominal surgery.

The plasma concentration of fentanyl was found to be low at all time periods, with mean values between 0.2 and 0.3 ng/ml, which is approximately 30–50% of the minimum effective analgesic concentration of fentanyl (mean ± SD: 0.63 ± 0.25 ng/ml) in patients undergoing abdominal surgery.<sup>29</sup> However, in that study, the authors found a fivefold difference in the minimum effective analgesic concentration between patients (0.23–1.18 ng/ml), which would suggest that the systemic effects of fentanyl absorbed from the epidural space probably contributed to some of the analgesic effect seen. This was also the finding of Ginosar *et al.*,<sup>30</sup> who studied the effect of infusion of 30 μg/h fentanyl in human volunteers and found a linear relation between the analgesic

effect and plasma concentrations of fentanyl administered epidurally during 2.5 h. Therefore, our study confirms that significant quantities of fentanyl are absorbed systemically after epidural infusion but leaves open the question whether this contributed to the analgesic effects seen. When fentanyl is administered in doses of 20 μg/h epidurally, the plasma concentration does not increase markedly up to 48 h, which is interesting, and suggests that in these doses, fentanyl absorbed into the systemic circulation does not accumulate in the blood, and respiratory depression is therefore unlikely after prolonged use.

#### *Recovery, Mobilization, and Quality of Life*

In the past few years, several authors have stressed the importance of early feeding and mobilization as a path to quicker recovery, shorter duration of stay in the hospital, and earlier rehabilitation and return to work.<sup>24</sup> In keeping with these recommendations, we asked our patients to start drinking and eating as soon as possible after the operation and avoided the use of nasogastric tubes. Early mobilization is possible if the postoperative analgesia is good and there is no residual motor blockade of the lower limbs. This was achieved by using low TEA and combining low-dose ropivacaine with fentanyl and adrenaline, which has previously been shown to provide good pain relief with minimal motor block.<sup>31</sup> Using this method, we were able to achieve early enteral nutrition and mobilization that, although statistically similar in both groups, occurred numerically somewhat earlier in the epidural group compared with the intravenous PCA group. However, this did not translate into earlier home readiness or discharge for several reasons: patient and surgeon preferences on actual home discharge, the day of the week (weekday or weekend), and distance to home (close to the hospital or far away), as well as social factors (availability of caretakers at home or not). The median duration of stay in our study was similar to that reported by Gardner *et al.*<sup>32</sup>



To assess whether good postoperative pain relief also results in improvement in the quality of life after 1–3 months, all patients received a questionnaire that has been validated for use in the Swedish population. In general, patients in the epidural group had higher scores in all parameters compared with those in the intravenous PCA group, which suggests that these patients had a better level of function. This was statistically significant between the groups at 1 month for physical functioning, general health, and role limitation due to emotional problems. However, no difference was seen between the groups in any of the parameters at 3 months or when an interaction of group and time were considered. In a previous study, Wu *et al.*<sup>33</sup> showed that an increase in pain decreases a patient's quality of life in the immediate postoperative period as measured by the SF-12. Carli *et al.*<sup>3</sup> found a greater deterioration in the quality of life measured by the SF-36 at 3 and 6 weeks in the intravenous PCA group compared with the epidural group after surgery for colonic cancer. The absence of any group  $\times$  time interaction in our study may be due to several factors, such as the mild-moderate postoperative pain after radical prostatectomy, postoperative pain intensity being of minor importance in this special situation and factors such as vitality and physical functioning being more dominant than differences in pain management.

#### *Perioperative Complications*

One important aspect of a good analgesic regimen is the low incidence of side effects and complications. Good postoperative pain relief achieved at the cost of a high incidence of complications is unacceptable. The recent report by Moen *et al.*<sup>14</sup> serves to illustrate this problem, specifically when using epidurals. In our series of 60 patients receiving TEA, one patient had an accidental dural puncture with no residual long-term effects. In addition, in one patient, the catheter was placed subdurally (confirmed by computerized tomography with contrast). Therefore, 2 of 60 patients (3.3%) had minor complications of epidural analgesia with no residual effects and only short-term disability, which is lower than in some previous reports.<sup>34,35</sup> One other patient who was taking  $\beta$  blockers had a short period of cardiac arrest requiring approximately 20 s cardiac massage after induction with propofol. The combination of epidural analgesia and  $\beta$  blockers as well as fentanyl and propofol for induction of anesthesia may have created optimal conditions that lead to a cardiac arrest. We have seen a similar situation with another patient (not included in the current study) under similar circumstances but not taking  $\beta$  blockers. Both of these patients recovered fully, without any residual effects. In a meta-analysis of the literature, Tramer *et al.*<sup>36</sup> found a high incidence of bradycardia and asystole after induction of anesthesia with propofol. Other minor complications seen in both groups were mild and included PONV, tiredness, seda-

tion, and low-grade fever, all of which subsided with time and did not differ between the groups. The only other significant difference was a greater number of patients given antiemetics due to unresolved PONV in the epidural group. A majority of these episodes occurred in the postoperative ward and could be due to the residual postoperative effects of anesthetics in susceptible patients, and are unlikely to be an adverse outcome of epidural analgesia.

#### *Study Limitations*

Although every attempt was made to blind the patients, anesthesiologists, surgeons, and observers, it is possible that the patients may have deduced, with time, whether the epidural or the intravenous PCA pump had the active substance. This was impossible to control, and we could not have achieved better blinding in any other way. We connected the postoperative analgesics (epidural and intravenous PCA pump) after transfer to the postoperative ward, which may have resulted in some delay in achieving adequate analgesia, particularly in the epidural group because no bolus dose was given before the start of the epidural infusion. This was evident from the pain scores on arrival in the postoperative ward, in both groups, and could be considered as a drawback of this study. Finally, and to achieve satisfactory blinding, we did not allow for changes in the epidural infusion rate or bolus doses, which may have resulted in inadequate analgesia in some patients. Therefore, further improvement in analgesia in this group may have been achieved through the use of patient-controlled epidural analgesia. This could be considered as another weakness of this study.

#### **Conclusions**

We found evidence for lower pain scores and improved expiratory muscle function in patients receiving thoracic epidural analgesia for radical retropubic prostatectomy. This was achieved without delay in any of the milestones of recovery and can therefore be recommended as a satisfactory method for postoperative analgesia during abdominal surgery. Whether the analgesic effect seen is partly due to the systemic absorption of fentanyl remains unclear. The rare complications and increased costs of thoracic epidural analgesia should be weighed against its benefits as seen in the current study.

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## Appendix: Home Readiness

The criteria for home readiness were as follows:

1. Full mobilization without assistance
2. Return of gastrointestinal function (eating, drinking, bowel movement) to normal
3. Mild pain adequately controlled with oral analgesics
4. No PONV
5. No evidence of infection locally (redness, tenderness) or systemically (fever, increase in C-reactive protein or leukocyte count)
6. No other ongoing complications (bleeding, respiratory problems, deep vein thrombosis, etc.)