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Intravenous Versus *Epidural Administration of Hydromorphone*

Effects on Analgesia and Recovery after Radical Retropubic Prostatectomy

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Background: **It remains unclear whether epidural administration of hydromorphone results in spinal analgesia or clinical benefit when compared with intravenous administration. Therefore, we undertook this study to determine whether epidural administration of hydromorphone resulted in decreased opioid requirement, improved analgesia, reduced side effects, more rapid return of gastrointestinal function, or shorter duration of hospital stay than intravenous administration.**

Methods: **Sixteen patients undergoing radical retropubic prostatectomy were randomized in a double-blind manner to receive either intravenous or epidural hydromorphone *via* patient-controlled analgesia (PCA) for postoperative analgesia. All patients underwent a standardized combined epidural and general anesthetic and all received ketorolac for 72 h postoperatively. To decrease variability, patients were cared for according to a standardized protocol and were deemed ready for discharge according to prospectively defined criteria.**

Results: **Patients in the intravenous PCA group required approximately twice as much opioid than the epidural PCA group ($P < 0.008$), but there were no differences between groups in pain scores or patient satisfaction. Epidural administration resulted in a greater incidence of pruritus ($P = 0.02$). Gastrointestinal function recovered quickly in all patients with little variation, and there were no differences between groups. All patients were deemed ready for discharge by the third postoperative day, and removal of surgical drains was the last discharge criterion reached in all patients.**

Conclusions: **Our results indicate that epidural administration of hydromorphone results in spinally mediated analgesia. However, epidural administration did not provide significant benefits in terms of postoperative analgesia, recovery of gastrointestinal function, or duration of hospitalization. Furthermore, we suggest that radical retropubic prostatectomy no longer be used as a model to assess the effects of analgesic technique on postoperative recovery, because control of discharge criteria revealed that hospital discharge was primarily dependent on removal of surgical drains. (Key words: Anesthetic techniques: epidural; patient-controlled analgesia. Anesthetics, opioids: hydromorphone. Pain, postoperative: gastrointestinal motility.)**

HYDROMORPHONE is an opioid intermediate in lipid solubility between morphine (less lipid-soluble than hydromorphone) and fentanyl (more lipid-soluble). Intermediate lipid solubility may improve the ability of an opioid to provide spinal analgesia,[2] and previous studies have reported that epidural administration of hydromorphone results in rapid onset of analgesia,[3] low incidence of side effects,[4] and a low risk of delayed respiratory depression.[5] However, there is no conclusive evidence that epidural administration of hydromorphone results in spinal analgesia. Furthermore, little information is available to assess whether epidural administration of hydromorphone offers advantages over intravenous administration for postoperative analgesia or recovery.

Previous studies suggest that patients receiving epidural opioids may have faster postoperative recovery of gastrointestinal function than those receiving intravenous opioids.[3,6] Because return of gastrointestinal

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function is often the rate-limiting step to hospital discharge in patients undergoing intraabdominal operations, we hypothesized that epidural administration of hydromorphone may accelerate recovery of gastrointestinal function and shorten hospitalization. Thus, we undertook this study to determine whether epidural administration of hydromorphone could reduce opioid requirement, improve analgesia, reduce side effects, speed recovery of gastrointestinal function, or shorten duration of hospital stay after radical retropubic prostatectomy when compared to intravenous administration of hydromorphone.

Methods

After Institutional Review Board approval and informed consent were obtained, 16 patients undergoing radical retropubic prostatectomy with or without pelvic lymph node dissection were enrolled in this study. Exclusion criteria included history of chronic pain or narcotic dependence, presence of contraindications to epidural catheter placement (coagulation defects, infection at puncture site, patient's refusal to undergo epidural anesthesia), presence of contraindication to patient-controlled analgesia (PCA; inability to understand patient-controlled analgesia, history of drug abuse), American Society of Anesthesiologists (ASA) physical classification > 3, patient age younger than 18 yr or older than 80 yr, and contraindications to ketorolac use (serum creatinine < 2 $mg \cdot dl^{-1}$, history of hemorrhagic peptic ulcer disease, history of hypersensitivity to aspirin).

Anesthesia Protocol

All patients were premedicated with 0.04 $mg \cdot kg^{-1}$ midazolam and 1.25 $\mu g \cdot kg^{-1}$ fentanyl intravenously. Epidural catheters were placed in all patients (T10–L1) immediately before surgery. Epidural catheters were tested with 3 ml 1.5% lidocaine with 1:200,000 epinephrine followed by an additional 7 ml 1.5% lidocaine with epinephrine. All patients then received 2–5 $mg \cdot kg^{-1}$ thiopental and 1.5 $mg \cdot kg^{-1}$ succinylcholine intravenously. The trachea was intubated and ventilation controlled. Anesthesia was maintained with oxygen (50%), nitrous oxide (50%), and isoflurane as needed. The epidural catheter was injected with 3 ml 1.5% lidocaine with 1:200,000 epinephrine every 45 min. Muscular relaxation was provided using pancuronium in doses titrated to neuromuscular monitoring of the adductor pollicis. Neuromuscular blockade was antagonized with 0.05 $mg \cdot kg^{-1}$ neostigmine and 0.01 $mg \cdot kg^{-1}$ glycopyrrolate at the end of surgery. One hour before the anticipated conclusion of surgery, all patients received 30 mg ketorolac tromethamine intramuscularly. No intraoperative opioids were given by either the intravenous or the epidural route.

Postoperative Analgesic Protocol

The trachea of each patent was extubated immediately after completion of surgery. In the recovery room, a PCA device (Abbott Life Care 4100, North Chicago, IL) was connected with a stopcock to both their intravenous and epidural catheters in all patients. Patients were randomized into one of two treatment groups: epidural PCA hydromorphone or intravenous PCA hydromorphone. Patients in the epidural PCA group had the stopcock opened to the epidural catheter, and those in the intravenous PCA group had the stopcock opened to the intravenous catheter. The stopcock was adjusted by the recovery room nurse, who secured and concealed the stopcock position. Neither patients, surgeons, floor nurses, nor investigators were aware of stopcock position. On complaint of pain, patients were given an initial loading dose of 1,050 μg hydromorphone *via* the PCA device. Initial PCA settings were bolus of 150 μg hydromorphone as a 75 $\mu g \cdot ml^{-1}$ solution and lockout period of 15 min. Inadequate analgesia was initially treated with a 300 μg load *via* the PCA device and 50-μg incremental increases of the PCA bolus dose every hour up to a bolus dose of 300 μg. If analgesia remained inadequate, the lockout interval was decreased to 10 min. If analgesia remained inadequate after 1 h, the bolus dose was increased in increments of 50 μg every hour until adequate analgesia was achieved. The doses and lockout intervals were based on our clinical experience and results from a previous study.[3] Intramuscular ketorolac (15 mg) was administered every 6 h after the initial intraoperative dose for a total of 72 h. We chose to administer ketorolac because it possesses potent analgesic effects and may hasten postoperative recovery of gastrointestinal function.[7,8] PCA was continued until hospital discharge criteria were met, at which time patients were switched to oral analgesics. On discontinuation of PCA analgesia, patients in the epidural group received 5 ml 1.5% lidocaine through their epidural catheter to verify correct placement. If a dermatomal band of analgesia to pinprick did not develop, results from the patient

would be excluded from the study. No other form of analgesia was provided.

Recovery Protocol

To decrease variability, all patients underwent a standardized recovery program. Nasogastric tubes were not placed.[9] On the morning after surgery, all patients were given a standardized low-fat, full-liquid diet, which was maintained until discharge.[10,11] Patients were allowed to eat as much of this diet as they wished. All patients ambulated the morning after surgery.[12]

Postoperative Assessments

Patient assessments were performed at 3 h postoperatively and in the mornings of postoperative days 1–3. Pain was quantified by the patient with a 10-cm visual analog scale (VAS) graded from 0 (no pain) to 100 (worst pain) at rest, after cough, and with ambulation. Patients were questioned as to presence of nausea, vomiting, and pruritus. Presence of sedation was noted by the observer. Hydromorphone consumption was quantified with a printout of each patient's PCA usage every morning and afternoon. Presence of bowel tones and flatus were checked by investigators every morning and afternoon. In addition, patients were instructed to record the time at which first passage of flatus was noted. Daily calorie counts and oral intake were recorded by staff dieticians and nurses.

Discharge criteria were prospectively agreed on with our surgeons. Patients were deemed ready for discharge from the hospital when output from surgical drains was less than 50 $ml \cdot day^{-1}$, patients were afebrile, oral nutrition was tolerated without discomfort, and bowel function (defined as first passage of flatus) had returned. Surgeons and the research team assessed patients every morning and afternoon to determine whether patients were ready for discharge.

An analgesia satisfaction questionnaire was mailed to every study patient after hospital discharge. Patients marked their overall satisfaction with pain relief on a paper VAS continuously graded from 1 (poor) to 10 (excellent). Patients were also asked whether they would choose their method of pain management again.

Statistical Analysis

Our initial power analysis from retrospective, uncontrolled data indicated several endpoints depending on outcome examined. For example, 6 subjects per group would be sufficient to determine a 50% difference in opioid consumption, whereas 16 subjects per group would be needed to determine a difference of 1 day in return of gastrointestinal function, and 18 for hospital discharge. Our study was designed primarily to examine recovery of gastrointestinal function, and we intended to enroll 18 patients per group. However, we anticipated that recovery of gastrointestinal function and hospital stay probably would be affected by our study protocol, because postoperative recovery and discharge would be standardized. Thus, an interim analysis after acquiring eight subjects per group was planned. This would be a sufficient number of subjects to fulfill our power analysis for differences in opioid consumption and allow us to perform a new power analysis on return of gastrointestinal function. The interim analysis indicated we had adequate power to determine a difference of 1 day in recovery of gastrointestinal function (power = 0.8, $P < 0.001$). Therefore, we decided to terminate the study without a formal stopping rule.

Demographics were analyzed with unpaired, two-tailed t test. VAS scores were compared with repeated measures analysis of variance. Hydromorphone consumption was analyzed with the Mann-Whitney rank sum test.[13] Daily incidences of side effects were compared with Fisher's exact test. Calorie counts, daily oral intake, and time until first passage of flatus were compared with unpaired, two-tailed t test. Times until return of bowel tones and duration of postoperative hospitalization were analyzed with a contingency table for each assessment period. Patient satisfaction was analyzed with the Mann-Whitney rank sum test and contingency tables.

Results

There were no differences between groups in demographics (table 1). Each group included one patient without pelvic lymph node dissection. All patients were

Table 1. Patient Demographic Data

	Epidural	iv
Age (yr)	60 ± 8	59 ± 11
Height (inches)	71 ± 2	68 ± 3
Weight (kg)	89 ± 17	82 ± 12
Surgical duration (min)	181 ± 29	187 ± 33
Operative blood loss (ml)	1,407 ± 598	1,092 ± 622
Total dose of epidural lidocaine (mg)	330 ± 30	345 ± 33

Values are mean ± SD.

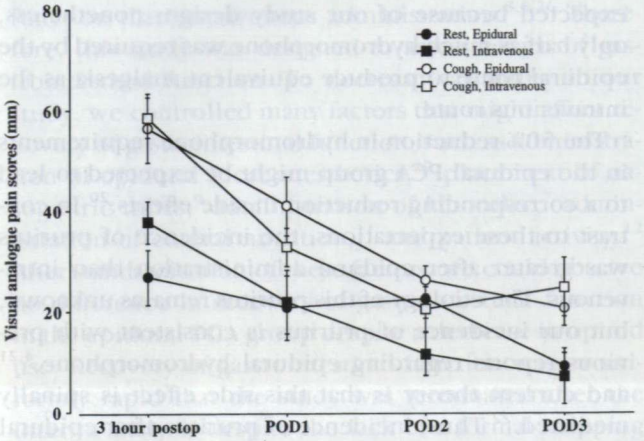

Fig. 1. Visual analog scale pain scores at rest and with cough. Mean and standard error displayed.

ASA physical status 2 except for one ASA physical status 3 patient in the epidural group. There were no differences between groups in VAS scores at rest or after cough (fig. 1). VAS scores with ambulation were intermediate between scores at rest and after cough and also decreased with time. The intravenous PCA group required approximately twice as much hydromorphone as the epidural PCA group ($P < 0.008$) to achieve equivalent comfort at each assessment period (fig. 2). There were no differences between groups in incidence of side effects except for a greater incidence of pruritus in the epidural PCA group on postoperative days 1 and 2 (table 2). No treatment was required for opioid side effects other than diphenhydramine for pruritus. All subjects had bowel tones detected on the morning of postoperative day 1 and tolerated oral nutrition on the morning of postoperative day 1. There were no differences between groups in time until return of bowel function, and clinically insignificant differences were seen in calorie counts and oral intake (table 3). All drains were removed on the morning of postoperative day 3, and all patients were deemed ready for discharge in the morning of postoperative day 3.

All patients returned their analgesia satisfaction questionnaire and were equivalently satisfied with their

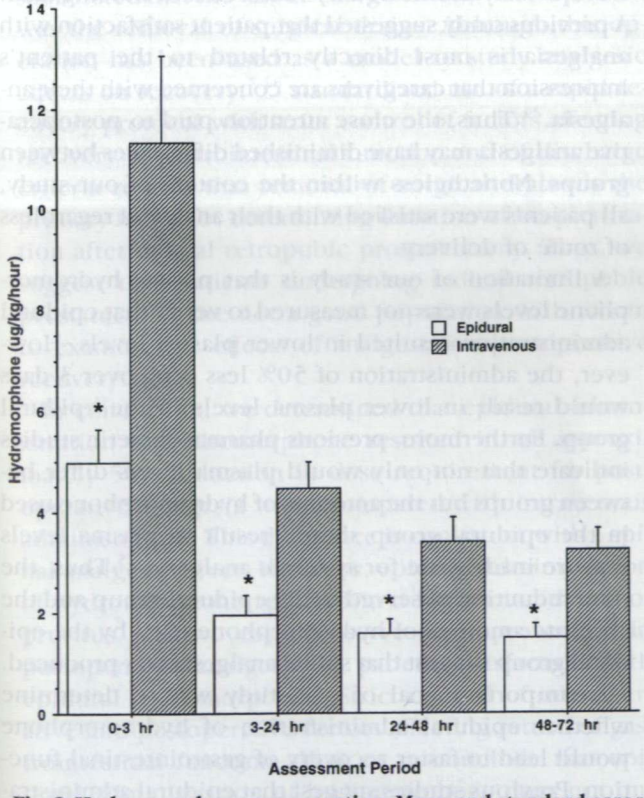

Fig. 2. Hydromorphone consumption. Mean and standard error displayed. *Different from intravenous group ($P < 0.008$).

Table 2. Side Effects from Epidural and Intravenous Administration of Hydromorphone

	3 h		POD1		POD2		POD3	
	iv	Epid	iv	Epid	iv	Epid	iv	Epid
Pruritus (% incidence)	13	63	13	75*	13	75*	13	25
Nausea	25	25	25	38	25	13	13	13
Vomiting	13	13	0	0	0	13	0	0
Sedation	13	25	13	25	25	25	25	25

iv = intravenous group; Epid = epidural group.

* Different from iv ($P = 0.02$).

Table 3. Comparison of Recovery of Gastrointestinal Function Between Groups

	Epidural	iv	Difference (epidural − iv) (95% confidence interval)
Time from last injection of epidural lidocaine until first request for hydromorphone (min)	33 ± 10	35 ± 7	−2 (−4 to 8)
Time until first flatus (h after surgery)	30 ± 5	29 ± 6	1 (−3 to 5)
Daily calorie count (kcal)	890 ± 66	800 ± 72	90 (48 to 132)
Daily oral intake (ml)	770 ± 65	720 ± 58	50 (7 to −93)

Values are mean ± SD.

analgesia. Patients in the epidural group rated their overall quality of analgesia as 8.8 ± 0.8 (mean ± SD) out of a maximum of 10. Patients in the intravenous group rated their overall quality of analgesia as 8.9 ± 0.7, and scores were not different (95% confidence interval for difference between means ranges from −0.51 to 0.71). All patients in each group would choose the same method of analgesia again.

Discussion

Our results demonstrate that epidural administration of hydromorphone reduces dose requirement for postoperative analgesia when compared to intravenous administration (approximately 50% less drug). This is within the range of a previous unblinded study reporting that PCA intravenous hydromorphone dose requirements are 3–4 times greater than PCA epidural administration for postcesarean section analgesia.[3] Reduced dose requirement for epidural administration of opioid is characteristic of spinal analgesia. For example, epidural administration of morphine consistently results in spinal analgesia[14] and an approximately eightfold reduction in dose requirement compared to intravenous administration.[15] In contrast, effects of epidural administration of fentanyl are controversial, because dose requirements are nearly equivalent after epidural administration.[16,17] Therefore, our finding of increased potency with epidural hydromorphone is consistent with a spinal analgesia.

Provision of spinal analgesia with epidural hydromorphone did not result in lower VAS pain scores than after intravenous administration. This observation may be explained by several factors. First, it is possible that epidural lidocaine produced a preemptive analgesic effect.[18] If so, intraoperative epidural anesthesia may have reduced postoperative pain in both groups, thereby reducing the ability to detect differences. Second, ketorolac was administered in both groups. Ketorolac is a potent analgesic with demonstrated ability to reduce epidural and systemic opioid requirements.[7] Reduction in severity of postoperative pain from ketorolac administration also may have diminished potential differences between groups. Finally, our use of a PCA device to administer hydromorphone may have diminished potential differences in analgesia. Although PCA devices are useful to quantitate opioid use, they allow patients to titrate to equivalent analgesia across study groups and thereby minimize differences in analgesia.[19] Thus, the similarity in VAS pain scores was expected because of our study design; nonetheless, only half as much hydromorphone was required by the epidural route to produce equivalent analgesia as the intravenous route.

The 50% reduction in hydromorphone requirements in the epidural PCA group might be expected to lead to a corresponding reduction in side effects.[20] In contrast to these expectations, the incidence of pruritus was greater after epidural administration than intravenous. The etiology of this pruritus remains unknown, but our incidence of pruritus is consistent with previous reports regarding epidural hydromorphone,[4,21] and current theory is that this side effect is spinally mediated.[22] Thus, incidence of pruritus after epidural hydromorphone may be inherently more common than after intravenous administration.

Despite differences in drug consumption and side effects, patients were equally satisfied with their pain management regardless whether hydromorphone was delivered intravenously or epidurally. This finding is consistent with previous studies reporting high patient satisfaction with PCA devices.[23] Another factor that may have influenced patient satisfaction is that all patients were closely monitored by research and nursing staff. A previous study suggested that patient satisfaction with analgesia is most directly related to the patient's impression that caregivers are concerned with their analgesia.[24] Thus, the close attention paid to postoperative analgesia may have diminished differences between groups. Nonetheless within the context of our study, all patients were satisfied with their analgesia regardless of route of delivery.

A limitation of our study is that plasma hydromorphone levels were not measured to verify that epidural administration resulted in lower plasma levels. However, the administration of 50% less drug over 3 days would result in lower plasma levels in the epidural group. Furthermore, previous pharmacokinetic studies indicate that not only would plasma levels differ between groups but the amounts of hydromorphone used in the epidural group should result in plasma levels that are inadequate for systemic analgesia.[25] Thus, the dose reduction observed in the epidural group and the absolute amounts of hydromorphone used by the epidural group suggest that spinal analgesia was produced.

An important goal of our study was to determine whether epidural administration of hydromorphone would lead to faster recovery of gastrointestinal function. Previous studies suggest that epidural administration of opioid may lead to faster recovery of colonic

function than intravenous administration.[3,6,26] Therefore, this study was designed to assess return of gastrointestinal function. To decrease variability in our study, we controlled many factors that might affect recovery of gastrointestinal function, such as administration of epidural local anesthetics,[27] placement of nasogastric tubes,[9] administration of ketorolac,[7] administration of enteral nutrition,[11] and patient activity.[12] After standardization of these factors, we could observe no difference in recovery of gastrointestinal function in the epidural PCA group despite a decrease in opioid use. Recovery of gastrointestinal function was so uniformly rapid that the study was terminated after the interim analysis despite the lack of a formal stopping rule.

Prospective definition of discharge criteria probably also resulted in the lack of variation in duration of hospitalization between groups, because all patients were deemed ready for discharge in the morning of postoperative day 3. Our clinical impression before beginning the study was that recovery of gastrointestinal function was the rate-limiting step to hospital discharge after radical retropubic prostatectomy. However, we soon noted that the last discharge criteria accomplished was the removal of surgical drains. Although this operation has been used as a model to study analgesic effects on recovery,[7,18] standardized use of a rapid recovery protocol with strict control of factors affecting recovery of gastrointestinal function and of discharge criteria reveals that removal of surgical drains is the primary factor for determining duration of hospitalization after radical retropubic prostatectomy. Thus, we suggest that patients undergoing radical retropubic prostatectomy are not a good population with whom to examine the effects of analgesia on postoperative recovery.

In conclusion, we determined that epidural administration of hydromorphone resulted in an approximately 50% reduction in dose requirement for postoperative analgesia when compared with intravenous administration. This difference is consistent with a spinal analgesic effect. However, epidural administration of hydromorphone resulted in a higher incidence of pruritus, and we could observe no improvement in postoperative analgesia or patient satisfaction with epidural hydromorphone. Strict control of intraoperative and postoperative factors affecting return of gastrointestinal function allow us to conclude that epidural administration of hydromorphone does not improve postoperative recovery of gastrointestinal function within the context of our accelerated recovery program: early enteral feeding, early ambulation, administration of ketorolac, and lack of a nasogastric tube. Finally, prospective definition of discharge criteria suggests that radical retropubic prostatectomy is not a good model to examine effects of analgesia on postoperative recovery, because removal of surgical drains appears to be the rate-limiting step for hospital discharge after this operation.

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