Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: a dose-finding study

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Purpose: A dose-finding study to investigate the use of epidural infusions of ropivacaine for postoperative analgesia following orthopaedic surgery.

Methods: This was a randomized, double-blind study. Surgery was performed using a combination of a lumbar epidural block utilizing ropivacaine 0.5% and a standardized general anaesthetic. Postoperatively, an epidural infusion of the study solution (saline, ropivacaine 0.1%, 0.2% or 0.3%) was started at the rate of 10 ml·hr⁻¹ and continued for 21 hr after arrival in the PACU. Analgesia was supplemented with PCA morphine (dose = 1.0 mg, lock-out = 5 min).

Results: Forty-four patients completed the study. The ropivacaine 0.1%, 0.2%, 0.3% groups required less morphine over the 21 hr than the saline group ($P < 0.01$). The VAS pain scores were also lower in the three ropivacaine groups ($P < 0.001$). The ropivacaine groups maintained sensory anaesthesia to pinprick when compared with saline ($P < 0.05$). The motor block in the 0.3% group was significantly higher than the saline group at all times ($P < 0.05$), and higher than the

0.1% group at eight hours ($P < 0.01$), while the 0.2% group had higher Bromage scores than saline at 4 and 21 hr ($P < 0.05$).

Conclusions: The use of continuous epidural infusions of ropivacaine 0.1%, 0.2% and 0.3% at 10 ml·hr⁻¹ improved postoperative pain relief and decreased PCA morphine requirements in patients undergoing major orthopaedic surgery. The 0.1% and 0.2% concentrations produced similar sensory anaesthesia with less motor blockade than the 0.3% concentration.

Objectif: Déterminer la dose de ropivacaine administrée en perfusion épidurale pour l'analgesie postopératoire en chirurgie orthopédique.

Méthode: Cette étude est randomisée et en double aveugle. La chirurgie est réalisée sous épidurale lombaire à la ropivacaine 0,5% associée à une chirurgie générale standardisée. En postopératoire, une perfusion épidurale continue d'une des solutions à l'étude (sol. physiologique, ropivacaine 0,1%, 0,2% ou 0,3%) est débutée à la vitesse de 10 ml·hr⁻¹ et continuée pendant 21 h après l'admission en salle de réveil. L'analgesie est suppléementée par de la morphine en PCA (dose = 1,0 mg, intervalle de sécurité = 5 min).

Résultats: Quarante-quatre patients ont complété l'étude. Les groupes ropivacaine 0,1%, 0,2% et 0,3% ont des besoins moindres de morphine pendant ces 21 h que le groupe sol. physiologique ($P < 0,01$). Les scores sur l'EVA sont aussi plus bas dans les groupes ropivacaine ($P < 0,001$). Les groupes ropivacaine demeurent insensibles à la piqure d'aiguille contrairement au dernier groupe ($P < 0,05$). Le bloc moteur du groupe 0,3% est plus marqué que dans le groupe sol. physiologique à tous les instants ($P < 0,05$), et plus marqué que dans le groupe 0,1% à la huitième heure ($P < 0,02$), alors que le groupe 0,02% avait des scores plus élevés sur l'échelle de Bromage que le groupe sol. physiologique à la 4e et la 21e h ($P < 0,05$).

Conclusions: Les perfusions continues de ropivacaine 0,1%,

Key words

ANAESTHETIC TECHNIQUES: epidural;
PAIN: postoperative;
ANAESTHETICS, LOCAL: ropivacaine.

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Accepted for publication 24th September, 1995.

0,2% et 0,3% à 10 ml·hr⁻¹ améliorent le soulagement et diminuent les besoins en morphine des patients soumis à une chirurgie orthopédique. Les concentrations à 0,1% et à 0,2% produisent des résultats identiques avec un bloc moteur moins important que la concentration à 3%.

Ropivacaine is a new amide local anaesthetic structurally similar to bupivacaine possessing a propyl substitution for the butyl side chain of bupivacaine. Unlike bupivacaine it is produced as the S(-) enantiomer instead of a racemic mixture.¹ Studies in both animals,²⁻⁵ and in human volunteers⁶ have indicated that these differences result in lower cardiotoxicity when compared with bupivacaine. This is an important improvement since bupivacaine is thought to be more cardiotoxic than other amide local anaesthetics.⁷

Epidural use of ropivacaine has been shown to produce safe and effective surgical anaesthesia similar to that of bupivacaine.^{8,9} Epidural infusions of bupivacaine have been utilized to provide postoperative analgesia following orthopaedic procedures,¹⁰ upper and lower abdominal surgery,^{11,12} and thoracotomy.¹³ In some of these studies, the use of these infusions has however resulted in potentially toxic systemic concentrations.¹³ Substitution of ropivacaine for bupivacaine should theoretically minimize this risk of toxicity. No published studies have investigated the analgesic effectiveness of continuous postoperative epidural infusions of ropivacaine. The purpose of this study was to investigate the use of epidural infusions of varying concentrations of ropivacaine to provide postoperative analgesia following major orthopaedic surgery.

Methods

After institutional ethics committee approval and written informed consent, patients scheduled for either elective total hip or knee arthroplasty were eligible for study in this double-blind, randomized, multi-centre trial. Patients were excluded for the presence of any of the following: contraindications to epidural anaesthesia (e.g., local infection, sepsis, coagulation abnormality), ASA status >III/V, age <18 or >80 yr, weight <50 or >110 kg, allergy to amide local anaesthetics, preexisting neurological deficit, psychiatric history, or alcohol or narcotic dependence.

Surgery was performed using a combination of the functioning epidural and a standardized general anaesthetic. Following a crystalloid fluid bolus of 500 ml, an epidural catheter was inserted in an L₄₋₅-L₂₋₃ interspace. A 3 ml test dose of ropivacaine 0.5% was utilized to rule out subarachnoid placement and was followed five minutes later by a 10-15 ml dose injected incrementally

over a five minute period. Upper and lower sensory anaesthesia to pinprick was then measured every five minutes. The epidural was considered effective if this resulted in a minimum upper level of T₁₀. If after 30 min a T₁₀ level of anaesthesia was not present, a further 5 ml ropivacaine 0.5% were injected. Patients were excluded from the study if after a further 15 min they still did not exhibit a T₁₀ level of sensory anaesthesia. General anaesthesia with tracheal intubation was then induced utilizing thiopentone, muscle relaxant, isoflurane, nitrous oxide/oxygen, and fentanyl (maximum 2.0 µg·kg⁻¹ on induction). Intraoperatively, 5 ml ropivacaine 0.5% were given every second hour or when signs of an inadequate block developed (increased heart rate, blood pressure, etc.). The time between consecutive epidural doses was limited to every 30 min. During the procedure intravenous fentanyl was limited to 50 µg boluses when further epidural supplementation was not allowed and complementary analgesia was required. Upon completion of the operation, the inhalational agents were discontinued, the neuromuscular block was reversed, the trachea was extubated and the patient was transferred to the post-anaesthesia care unit (PACU).

Within 30 min of arrival in the PACU, an epidural infusion of the blinded study solution (saline, ropivacaine 0.1%, 0.2%, or 0.3% prepared by the Department of Pharmacy, Astra Pain Control AB, Sodertalje, Sweden) was started at a rate of 10 ml·hr⁻¹ and continued for 21 hr. Supplemental analgesia was provided by PCA morphine set to deliver a dose of 1 mg with a delay of five minutes and no basal infusion. Antiemetic therapy consisted of droperidol 0.5 mg or metoclopramide 10 mg *iv* as required. Measurements of pain at rest (VAS, 0 = no pain, 100 mm = worst pain), patients' impressions of their quality of treatment (1 = poor, 2 = fair, 3 = good, 4 = excellent), and morphine usage were recorded at 4, 8, and 21 hr after starting the infusion. The occurrence at any time of side effects including bradycardia (heart rate <50 beats·min⁻¹), hypotension (systolic blood pressure <80 mmHg or >30% decrease from preoperative value), nausea and vomiting, and urinary retention were noted during the 21 hr. Assessments of sensation (pinprick) and motor block (Bromage scale)¹⁰ were made every two hours excluding the hours 2200 to 0800 the following morning, until the return of normal sensation and motor function. Pulmonary function was also assessed preoperatively and on the first and second days postoperatively. Measurements of FEV₁, PEFR, and FVC were made with the patient in the supine position using a hand-held spirometer.

Statistical methods included chi-square testing for sex distribution and side effects, Wilcoxon rank sum testing for sensory and motor block and analysis of variance

TABLE I Demographic and intraoperative data

	Saline	0.1%	0.2%	0.3%
Patients	10	12	11	11
Age (yr)	66.2 ± 8.5	67.0 ± 5.9	62.8 ± 12.5	62.7 ± 11.4
Height (kg)	165.4 ± 10.7	170.7 ± 6.6	171.8 ± 11.3	176.6 ± 12.0
Weight (kg)	81.4 ± 6.5	86.5 ± 16.6	83.8 ± 14.4	82.8 ± 15.3
Sex (m:f)*	2:8	10:2	4:7	8:3
Procedure (hips:knees)	7:3	4:8	6:5	6:5
Preoperative blockade				
– upper	T ₈ (T ₄ –T ₁₀)	T ₈ (T ₂ –T ₁₀)	T ₈ (T ₄ –T ₁₀)	T ₈ (T ₆ –T ₁₀)
– lower	S ₂ (L ₃ –S ₃)	S ₂ (S ₁ –S ₃)	S ₂ (S ₁ –S ₃)	S ₁ (S ₁ –S ₃)
Intraoperative fentanyl (μg)	140 ± 61	163 ± 70	138 ± 52	202 ± 139
Perioperative ropivacaine 0.5% (ml)	21.5 ± 5.6	21.4 ± 5.0	21.8 ± 5.2	22.9 ± 4.6
Fluid				
– crystalloid (L)	4.8 ± 1.4	5.4 ± 1.3	5.9 ± 2.3	6.1 ± 1.7
– colloid (ml)	320 ± 510	290 ± 580	670 ± 1000	640 ± 1030

Values are means ± SD, except blockade which is median (range).

* $P < 0.05$ for sex distribution among the four groups.

FIGURE 1 Pain at rest expressed as VAS scores. Values are mean ± SD. * $P < 0.001$ saline vs others, for the 21 hr study period.

FIGURE 2 PCA morphine utilization in mg for the given time frames. Values are mean ± SD. * $P < 0.01$ saline vs others, for the 21 hr study period.

(ANOVA) with Fisher's protected least significant difference post-Hoc testing for demographic data, and repeated measures ANOVA for VAS scores and morphine utilization. The last value carried forward to missing principle was utilized and $P < 0.05$ was considered significant.

Results

Forty-eight patients from three institutions were entered into the study. Four patients were excluded from the study due to one of the following problems: PCA printer error, infusion pump malfunction, patient reoperation, and loss of ropivacaine 0.5% through vial breakage. A fifth patient, who received ropivacaine 0.1%, developed persistent hypotension unresponsive to fluid and vasopressor therapy and was also removed from the study but included in demographic and side effect calculations. Subsequent evaluation of the patient revealed this

to be due to excessive blood loss. The patient was treated with a transfusion of red blood cells and recovered uneventfully. Patient demographics (age, height, weight, sex) and intraoperative data (procedure, preoperative block, amount of fentanyl, ropivacaine 0.5%, and fluids) are listed in Table I. There was no difference between the four groups in the distribution of these variables with the exception of sex.

Pain at rest as measured using mean VAS scores is shown in Figure 1. The three ropivacaine groups had better analgesia over the 21 hr than the saline group ($P < 0.001$), however, there was no difference among the three ropivacaine groups. Assuming a reduction in VAS pain scores of 20 to be clinically relevant, and using the calculations as described in Zar,¹⁴ the power of detecting a difference between the three ropivacaine groups was 0.50. Correspondingly, the mean PCA morphine

TABLE II Number of patients not requiring morphine for the time intervals shown

	Saline	0.1%	0.2%	0.3%
0-4 hr	2*	8	9	6
4-8 hr	0†	2	8	5
8-21 hr	0	0	2	1

* $P < 0.05$.

† $P < 0.01$ saline vs 0.1%, 0.2% and 0.3% ropivacaine.

FIGURE 3 Upper sensory level of block to pinprick. Error bars indicate 10 and 90 percentiles, while top, side and bottom of rectangles indicate 25, 50 and 75 percentiles respectively. * $P < 0.05$ saline vs 0.1% and 0.3% at 4 and 8 hours, * $P < 0.05$ saline vs 0.2%, at all times.

utilization during the 21 hr is shown in Figure 2, and the number of patients not requiring PCA morphine in Table II. The three ropivacaine groups also required less morphine than the saline group over the 21 hr study period ($P < 0.01$), but there was no difference in morphine consumption between the three ropivacaine groups. Assuming a reduction in morphine utilization of 20 mg over the 21 hr to be clinically significant, and using the same technique as before, the power of detecting a difference between the three ropivacaine groups was 0.77. The number of patients not requiring PCA morphine was also different for the saline group in the 0-4 hr ($P < 0.05$) and 4-8 hr ($P < 0.01$) periods when compared with the three ropivacaine groups.

The upper level of sensory block to pinprick is shown in Figure 3. The saline group was different from the ropivacaine groups at the times as shown. There was no difference among the three ropivacaine groups. The lower level of sensory block is shown in Figure 4. The saline group was also different from the ropivacaine groups at the times shown. There also was a difference between the ropivacaine 0.1% and 0.3% groups at the eight hour measurement ($P < 0.01$). The degree of motor

FIGURE 4 Lower sensory level of block to pinprick. Error bars indicate 10 and 90 percentiles, while top, middle and bottom of rectangles indicate 25, 50 and 75 percentiles respectively. * $P < 0.05$ saline vs 0.2% and 0.3% at all times. ** $P < 0.05$ 0.1% vs saline at 4 and 21 hours, * $P < 0.01$ 0.1% vs 0.3% at the eight hour measurement.

FIGURE 5 Motor blockade measured using Bromage scores, values are means $\pm$ SD. * $P < 0.05$ saline vs 0.3% at all times, * $P < 0.05$ 0.2% vs 0.3% at 4 and 8 hours, * $P < 0.05$ 0.1% vs 0.3% at eight hours, ** $P < 0.05$ 0.2% vs saline at 4 and 21 hr.

blockade is shown in Figure 5. The ropivacaine 0.2% and 0.3% groups had a higher degree of block than saline at the times shown ($P < 0.05$). The ropivacaine 0.3% group also had a higher block than 0.2% at 4 and eight hours ($P < 0.05$), and higher than 0.1% at eight hours ($P < 0.05$). There was no difference among the groups for any side effects (Table III). Similarly, there was no difference in the quality of treatment scores or pulmonary function tests at any of the measurement times.

Discussion

This dose-finding study investigated the use of continuous epidural infusions of varying concentrations of a new amide local anaesthetic, ropivacaine, for postoperative analgesia in patients undergoing major orthopaedic

TABLE III Incidence of side effects experienced during the 21 hour epidural infusion

	Saline	0.1%	0.2%	0.3%
Hypotension	5(45)	4(33)	2(18)	6(54)
Bradycardia	3(27)	4(33)	3(27)	2(18)
Urinary retention	3(27)	8(67)	6(54)	5(45)
Nausea	7(64)	7(58)	4(36)	7(64)
Vomiting	2(18)	3(25)	5(45)	6(54)

Values are number (%). NS differences among groups.

surgery. We showed that the epidural use of ropivacaine 0.1%, 0.2%, and 0.3% infused at $10 \text{ ml} \cdot \text{hr}^{-1}$ for 21 hr both improved postoperative analgesia and decreased morphine requirements when compared with saline. These findings are similar to those by Raj *et al.*,¹⁰ who, utilizing bupivacaine 0.25% in a similar group of orthopaedic patients, produced similar results. There was, however, no dose response effect in terms of analgesia or morphine requirements. This was most likely due to the intraoperative epidural use of ropivacaine 0.5% in our study, as there was sufficient power to detect differences in morphine utilization and moderate power with respect to pain scores. Similar amounts of epidural ropivacaine when used without a postoperative infusion produce sensory anaesthesia of 4–6 hours duration.^{8,9} All three ropivacaine concentrations infused at $10 \text{ ml} \cdot \text{hr}^{-1}$ were able to maintain this effective block, as shown by the lack of difference in sensory anaesthesia to pinprick, and therefore make it extremely difficult to separate pain scores or opioid use among them. The intraoperative use of ropivacaine 0.5% would also explain the persistent median level of sensory block of L₂–L₄ in the saline group up to eight hours.

Unlike the findings regarding sensory level of anaesthesia, the 0.1% and 0.2% concentrations of ropivacaine produced less motor block than did the 0.3% concentration. These results are consistent with those recently reported in volunteers, where epidural infusions of ropivacaine 0.1%, 0.2% and 0.3% at $10 \text{ ml} \cdot \text{hr}^{-1}$ preceded by a 10 ml bolus resulted in the 0.2% concentration producing similar sensory anaesthesia but with less motor blockade than the 0.3% concentration.¹⁵ In this study by Zaric *et al.*, the 0.1% concentration yielded insufficient sensory anaesthesia and likely differed from our results because as noted above, we utilized ropivacaine 0.5% for intraoperative anaesthesia. These findings are also similar to those reported with the epidural use of bupivacaine combined with fentanyl for postoperative analgesia, where the use of bupivacaine 0.125% produced less motor blockade than did a concentration of 0.25%.¹⁶ Since early ambulation is one of the goals of postoperative pain management, the use of the two lower concen-

trations of ropivacaine would therefore seem more appropriate.

Though we were able to show both improved analgesia and decreased opioid requirements with the epidural use of ropivacaine when compared with the use of saline, we were unable to show any difference in the incidence of side effects or quality of treatment scores. This may have been due to the fact that during the 8–21 hr period there was no difference in the number of patients using PCA morphine. Since many of these side effects can also occur from the use of PCA morphine, any differences among epidural groups would therefore be difficult to detect. Similar results have occurred in studies of continuous infusions of intravenous ketorolac involving identical orthopaedic patients, whereby the group receiving the ketorolac infusion had improved analgesia and decreased opioid requirements, but no difference in side effect profile.¹⁷ With regards to our study, there was no increased incidence of hypotension and bradycardia, side effects related to epidural local anaesthetics, in the three ropivacaine groups compared with saline.

As noted, the ropivacaine groups utilized less PCA morphine during the entire study period, however, there was no difference among the four groups in the number of patients utilizing the PCA machine during the 8–21 hr period. This indicates that the use of $10 \text{ ml} \cdot \text{hr}^{-1}$ of epidural ropivacaine 0.1%–0.3% as a postoperative infusion was insufficient as the sole analgesic in orthopaedic patients. Clinically, one could increase the infusion rate to overcome this. However, when rates greater than $10 \text{ ml} \cdot \text{hr}^{-1}$ of ropivacaine 0.2% were utilized in patients undergoing lower abdominal surgery this resulted in an increase in the incidence of motor blockade which itself is undesirable.¹⁸ Therefore, the use of epidural ropivacaine for postoperative analgesia following orthopaedic surgery will most likely require its combination with an opioid as has been reported with epidural bupivacaine.^{19,20}

In conclusion, we have demonstrated that epidural infusions of ropivacaine 0.1%, 0.2% and 0.3% at $10 \text{ ml} \cdot \text{hr}^{-1}$ were safe, improved postoperative analgesia, and decreased PCA morphine requirements in patients undergoing major orthopaedic surgery. The 0.1% and 0.2% concentrations produced similar sensory anaesthesia with less motor blockade when compared with 0.3% and warrant further investigation.

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