

Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery²

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Background. As continuous wound instillation with local anaesthetic has not been evaluated after hip/knee arthroplasties, our study was designed to determine whether this technique could enhance analgesia and improve patient outcome after joint replacement surgery.

Methods. Thirty-seven patients undergoing elective hip/knee arthroplasties under spinal block were randomly assigned to two analgesia groups. Group M received continuous i.v. infusion of morphine plus ketorolac for 24 h. Then, a multi-hole 16 G catheter was placed subcutaneously and infusion of saline was maintained for 55 h. Group R received i.v. saline. Thereafter the wound was infiltrated with a solution of ropivacaine 0.5% 40 ml, then a multi-hole 16 G catheter was placed subcutaneously and an infusion of ropivacaine 0.2% 5 ml h⁻¹ was maintained for 55 h. Visual analogue scale scores were assessed at rest and on passive mobilization by nurses blinded to analgesic treatment. Total plasma ropivacaine concentration was measured.

Results. Group R showed a significant reduction in postoperative pain at rest and on mobilization, while rescue medication requirements were greater in Group M. Total ropivacaine plasma concentration remained below toxic concentrations and no adverse effects occurred. Length of hospital stay was shorter in Group R.

Conclusion. Infiltration and wound instillation with ropivacaine 0.2% is more effective in controlling postoperative pain than systemic analgesia after major joint replacement surgery.

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Postoperative pain after major joint replacement surgery of the lower limb is most often reported by patients to be at its worst on the first and second postoperative days.¹ In the following days, pain intensity at rest usually decreases significantly. However, after mobilization, pain triggered by

spasm of the femoral quadriceps² is still present and interferes with the patients' general activity and walking

ability. Several studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing either early postoperative pain after orthopaedic surgery or

the opioid requirement.^{3,5} However, these drugs are not always effective on early mobilization pain and have well-documented potential side-effects.⁶ In addition, some authors have reported that NSAIDs decrease the rate of fracture healing.⁷

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Thus, alternative strategies for postoperative pain relief have been studied. In particular, the treatment of postoperative pain by topical administration of local anaesthetics in the surgical area has recently proved effective in reducing postoperative pain after various surgical procedures.^{8,17} One of the most important limitations on the widespread use of this method is the potential toxicity of local anaesthetics¹⁸ resulting from their excessive plasma concentrations. Systemic absorption may be increased by large surgical incisions and soft-tissue dissection, which occur typically during major orthopaedic surgery.

Ropivacaine has vasoconstrictive properties¹⁹ and less cardiotoxicity compared with bupivacaine.^{20,21} These properties become particularly useful in the case of major surgical procedures. To the best of our knowledge, no studies have been performed concerning the pharmacokinetics and clinical effectiveness of large doses of ropivacaine infiltration and continuous perfusion in the surgical wound after major joint replacement surgery. The present randomized study was designed to evaluate the safety and effectiveness of continuous ropivacaine wound perfusion on postoperative pain levels compared with systemic analgesia in a sample of patients undergoing hip and knee arthroplasty.

Patients and methods

The Medical Ethics Committee of the S. Anna Hospital of Ferrara approved the study protocol. After written informed consent had been obtained, patients (age 38 ± 8 yr, weight 48 ± 90 kg, ASA I-II) undergoing elective hip or knee arthroplasty were enrolled in the study. Exclusion criteria included known local allergy to anaesthetics or NSAIDs, renal or liver failure, coagulation abnormalities, pathological obesity (body mass index $>35\%$), wound infection, non-compensated cardiopathy or pneumopathy, severe diabetes, and a history of peptic ulcer. Patients with significant alcohol, drug or medication abuse were also excluded.

All the patients received spinal anaesthesia using 0.5% plain bupivacaine (15 mg, 3 ml; Marcaina^a 0.5; AstraZeneca, Basiglio, Italy) and fentanyl 15 mg at the L3-L4 interspace with Whitacre 27 spinal needles. The same surgeon performed all the operations. A direct lateral approach was used for hip replacement and a median parapatellar approach for knee arthroplasties.

Patients were randomized with a computer-generated sequence and assigned to one of the following two postoperative options after opening a sealed envelope. (1) A loading dose of i.v. morphine 10 mg was given to both groups at the end of surgery. Group M (19 patients) then received a standard baseline i.v. infusion of morphine at 0.5 mg $h_{\pm 1}$ plus ketorolac 3.6 mg $h_{\pm 1}$ for 24 h through an elastomeric pump at a flow rate of 2 ml $h_{\pm 1}$. (2) In Group R (18 patients) a normal saline solution was given i.v. at the same rate for 24 h. In Group R

at the end of surgery, after the closure of the fascia, the surgeon infiltrated all surgical strata, in equal proportions for the whole length of the wound, with 40 ml of a solution of ropivacaine 0.5%, 200 mg (Naropine^a; AstraZeneca). In both groups of patients, under direct visualization a multi-hole 16 G peridural catheter was placed between the muscle fascia and the subcutaneous tissues, with the catheter tip sited at the point that demarcated 50% of the length of the surgical wound. Thereafter, the catheter was stitched to the skin and the wound was closed in the usual way. A suction drain was usually placed near the arthroplasty and under the fascia at a distance from the indwelling catheter. The catheter was immediately connected to a bacterial filter through which an elastomeric infusion pump device delivered ropivacaine 0.2% at 5 ml $h_{\pm 1}$ of (Group R) or saline solution (Group M) for the following 55 h. The catheter was removed at the end of infusion with an aseptic technique and the tip was subjected to microbiological analysis.

In Group R, peripheral venous blood samples (4 ml) were collected before the start of ropivacaine administration, 15, 30, 90, 180, 360 and 720 min after ropivacaine infiltration and on the first, second and third postoperative days. All plasma samples were frozen within 1 h after collection and stored at $\pm 20^{\circ}$ C until assayed. Total plasma ropivacaine concentration was measured with a high-performance liquid chromatography method with ultraviolet detection at 210 nm.²² The system consisted of a solvent module pump (model 125; Beckman Coulter, Fullerton, CA, USA) connected to a Triathlon autoinjector and a UV detector (166 model). The column was a Lichrospher 5 μ m (K5RBP12M; 125X4).

On regression of the sensory block, trained nurses, blinded to the analgesic technique used, instructed the patients on how to express their hip or knee pain at rest and on passive mobilization by knee-hip flexion using a 100-mm visual analogue scale (VAS; 0 mm=no pain, 100 mm=worst imaginable pain). Pain assessments were made 2, 4, 8, 12, 24, 48 and 72 h after surgery.

During the entire postoperative period of observation, the nurses administered rescue analgesia according to this standard protocol: if VAS was <50 the patients was to receive i.m. diclofenac 75 mg; if the VAS score was >50 mm or if satisfactory pain relief was not achieved with diclofenac, an i.v. dose of 100 mg of tramadol was given (and repeated if necessary) until a pain score of <30 mm was recorded.

There were no restrictions on the frequency of drug administration or the overall daily dose in both groups. The amount of drugs needed for rescue analgesia was recorded and considered as a measure of ropivacaine efficacy. We recorded (i) local and systemic adverse events, such as postoperative bradycardia, hypotension, nausea, vomiting, headache, fever, agitation, drowsiness and confusion, (ii) liver and kidney function and (iii) the length of the

Table 1 Patient characteristics. Mean (SD or range). No significant differences (Student t-test)

	Group M (n=19)	Group R (n=18)
Sex (M/F)	4/15	3/15
Age (yr)	66 (35±81)	64 (38±80)
Weight (kg)	70 (8)	69 (9)
Height (cm)	162 (11)	163 (11)
Type of surgery (hip/knee)	15/4	14/4
Duration of surgery (min)	132 (21)	157 (19)
Length of incision	23.4 (0.9)	22.4 (0.8)

wound incision. Other adverse events were recorded when observed by the physician or reported spontaneously by the patient. Patients were observed carefully for any symptoms of central nervous system toxicity, such as tinnitus, metallic taste, numbness of the tongue, dizziness or visual disturbances, muscular stiffness or twitching, dysarthria or haemodynamic changes, so that ropivacaine infusion could be stopped immediately.

After 72 h, we recorded patient satisfaction with the analgesia provided using a scale of 'poor', 'satisfactory' and 'excellent'. Length of hospital stay was also recorded. Discharge was decided by the surgeons, who were blinded to the randomization, according to the following discharge criteria: (i) satisfactory pain control for self-mobility; (ii) uncomplicated wound-healing process; (iii) uncomplicated clinical and radiographic outcome; (iv) no evidence of deep vein thrombosis; and (v) no impairments in haemoglobin or liver±kidney function.

Statistical analysis

Data are expressed as mean (SEM) or mean and confidence interval. The results were analysed using the non-parametric Mann-Whitney test, Student's t-test or the χ^2 -test, as reported in the table and figure legends. A P-value of <0.05 was considered to be statistically significant.

Sample size calculation was based on an expected difference of 20 mm in the VAS measurement for pain between group means, based on a reported value of minimal clinically important differences in acute pain,²³ on a standard deviation of 16, obtained from previous studies, with $P=0.90$ and $\alpha=0.05$. A sample size of 14 patients per group was obtained. For the same variables, an expected difference in patient satisfaction of 50% between the two groups generated a similar sample size. A conservative sample size of at least 18 patients/group was then chosen to ensure that the calculated number would be maintained for the final analysis.

Microsoft Excel for Windows and SAS for Windows were used for data entry and analysis.

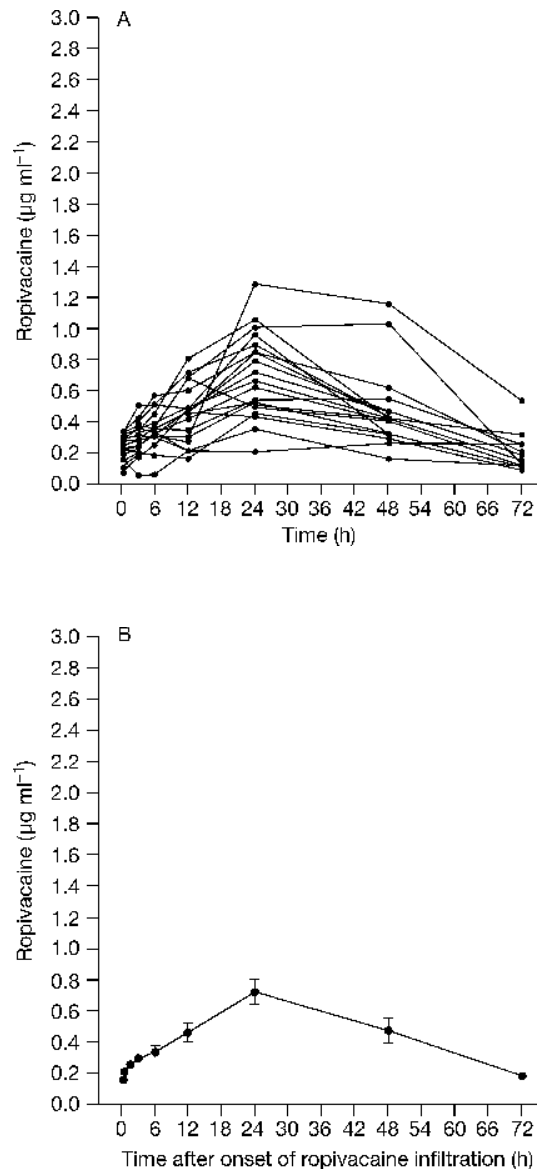


Fig 1 Individual (A) and mean (B) total plasma concentrations of ropivacaine in patients receiving infiltration and long-term wound perfusion of the drug (for details see Patients and methods). The total plasma ropivacaine concentration was determined from peripheral venous sample taken 15, 30, 90, 180 and 360 min and 12, 24, 48 and 72 h after the onset of drug infiltration.

Results

All patients enrolled in the study completed the study protocol: 19 in Group M and 18 in Group R. Patient characteristics are presented in Table 1. There were no significant differences.

Individual and mean total plasma ropivacaine concentration±time curves are shown in Fig. 1. The maximum total plasma concentrations (C_{max}) were between 0.30 and 1.28 mg ml^{-1} (mean 0.71 (0.17) mg ml^{-1}). The maximum peak in the total plasma ropivacaine concentration was reached 24 h after initiation of the infusion.

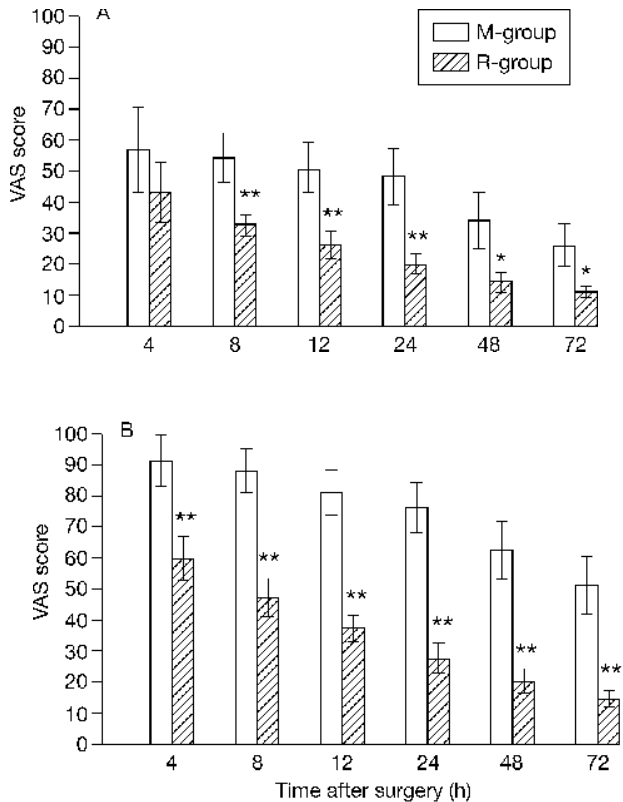


Fig 2 Visual analogue scale scores (100 mm) for pain at rest(A) and during passive mobilization (B) in Groups M and R 4, 8, 12, 24, 48 and 72 h after surgery (abscissa). Data are mean and SEM. Significant differences from control group: *P<0.05; **P<0.01 (non-parametric Mann-Whitney test).

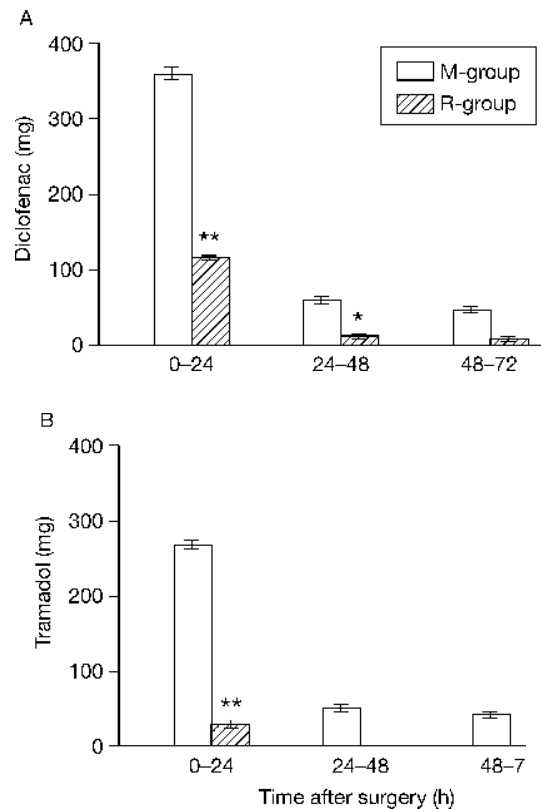


Fig 3 Rescue medication requirements (mg) in Groups M and R. The mean tramadol and diclofenac doses were significantly increased in Group M compared with Group R during the time intervals shown. Data are mean and SEM. Significant differences from control group: *P<0.05; **P<0.01 (non-parametric Mann-Whitney test).

After the end of ropivacaine wound instillation, total plasma ropivacaine concentration decreased significantly with time but the local anaesthetic was still detectable in plasma at 72 h.

A significant difference in postoperative pain intensity (VAS) was found in Group R vs Group M both at rest and on mobilization, beginning at 8 h and continuing to 72 h after operation (Fig. 2). These differences increased with time after surgery and became maximal during the following 12±48 h. Before that period (2 and 4 h after surgery) no significant differences between groups were observed.

No significant differences in VAS scores (from 24 to 72 h after surgery) were found in Group R on comparison of pain intensity levels at rest and after mobilization. However, in Group M the pain scores after mobilization were always significantly higher than those measured at rest (P<0.05). In Group R satisfactory pain control was still observed at 72 h, even though ropivacaine infusion had been discontinued for 17 h.

The mean amount of narcotic and non-narcotic rescue medication was significantly lower in Group R than in Group M (Fig. 3). Furthermore, in Group R a significant reduction in the length of hospital stay compared with

group M was observed (6.34 (0.67) and 8.79 (1.39) days respectively; P<0.05).

There was no statistically significant difference in the incidence of adverse events between the two groups (Table 2). The results of catheter tip microbiological analysis were negative in the two groups, no clinical signs of local or systemic infections were observed in any of the patients, and wound healing was considered normal by the surgeon. No major neurological or cardiac complications were observed in Group R. No significant differences in liver or kidney function were observed between the two groups.

As shown in Table 3, more patients in Group R than in Group M described their analgesia as good or excellent.

Discussion

There is clinical evidence that infiltration and instillation with local anaesthetic at operative sites can improve postoperative analgesia and reduce opioid requirement after different surgical procedures.^{8±17} Unlike other operations, the surgical damage after joint replacement involves a large, deep incision area with considerable tissue dissection, muscle and vascular exposure and bone

Table 2 Side-effects. Number of patients (%). No significant differences (χ^2 -test)

Symptoms	Group M (n=19)	Group R (n=18)
Tinnitus	0 (0%)	0 (0%)
Metallic taste	0 (0%)	0 (0%)
Numbness of the tongue	0 (0%)	0 (0%)
Muscular rigidity	0 (0%)	0 (0%)
Muscular twitching	0 (0%)	0 (0%)
Dysarthria	0 (0%)	0 (0%)
Visual and hearing disturbances	0 (0%)	0 (0%)
Nausea and vomiting	10 (53%)	8 (44%)
Dyspnoea	0 (0%)	0 (0%)
Cardiovascular	2 (11%)	0 (0%)
Fever	1(5%)	2(11%)
Headache	1(5%)	1(6%)
Altered state of consciousness	0 (0%)	0 (0%)
Agitation	1(5%)	1(6%)
Seizures	0 (0%)	0 (0%)

Consequently, the clinical and pharmacological impact of local anaesthetic instillation in the wound bed is unpredictable. It has been reported that single-shot wound infiltration and drain lavage with a relatively high concentration of ropivacaine are more effective than i.v. patient-controlled analgesia in reducing postoperative pain after major shoulder surgery, and have a minimal risk of systemic toxicity.⁹

In this randomized clinical study we evaluated the safety and effectiveness of wound infiltration with ropivacaine 0.5% and continuous wound perfusion for 55 h with ropivacaine 0.2% into the surgical area after major joint replacement. Symptoms of systemic toxicity did not occur in the present study and no patient experienced adverse events that may have been related to ropivacaine administration. Accordingly, the total plasma concentration of ropivacaine consistently remained below the central nervous system toxicity threshold. The highest total plasma concentrations (C_{max}) were between 0.30 and 1.28 mg ml⁻¹, with a mean value of 0.71 (0.17) mg ml⁻¹. A possible criticism of this evaluation is that venous rather than arterial plasma ropivacaine concentrations were measured, which may have underestimated the risk of ropivacaine toxicity. However, it is worth noting that the ropivacaine concentrations observed in this study were far below the established toxic threshold. Although previous studies²⁴⁻²⁵ reported mild central nervous system symptoms at venous plasma ropivacaine concentrations ranging from 1 to 2 mg ml⁻¹ after i.v. administration of the drug in non-premedicated volunteers, Wiedermann et al.²⁶ observed that, during long-term epidural infusion of ropivacaine, the total plasma concentration of the anaesthetic increased steadily during infusion from 2.39 to 6.08 mg ml⁻¹ without symptoms of systemic toxicity. In addition, by evaluating the pharmacokinetics of different concentrations of ropivacaine after iliohypogastric block, other authors²⁷ reported a C_{max} of 3.70 mg ml⁻¹ with no adverse reactions. In addition, during 72 h of epidural ropivacaine infusion no signs of

Table 3 Patient satisfaction. Number of patients (%). There was a significant difference between the two groups ($P < 0.01$) (χ^2 -test)

	Control (n=19)	Ropivacaine (n=18)
Excellent	4 (21%)	15 (83%)
Satisfactory	11(58%)	3 (17%)
Poor	4 (21%)	0 (0%)

very high total plasma ropivacaine concentration (7.1 mg ml⁻¹), have been reported.²⁸ Finally, after wound infiltration of ropivacaine (0.75%, 375 mg) for hernia repair surgery, the highest individual maximum plasma concentration was 3.0 mg ml⁻¹, with no evidence of systemic adverse events.¹⁰

Recently, it has been found that patient-controlled wound instillation with ropivacaine decreased post-Caesarean delivery pain and opioid requirements, and good pain relief was found after patient-controlled wound instillation with ropivacaine even in the first hour after cesarean delivery.⁸ In our study, the poor pain control 4 h after surgery could be explained by the inability of ropivacaine to reach periosteum nociceptors under the fascia, which are the main receptors involved in early postoperative pain, while different nociceptive mechanisms cause visceral pain. However, in the following 24±48 h, when postoperative pain is usually considered by the patients to be at its worst, Group R reported significantly better pain relief and fewer differences in pain intensity, both at rest and on mobilization. Interestingly, 72 h after surgery the pain was still reduced in Group R in spite of discontinuation of ropivacaine infusion. This could be explained by a vasoconstrictor action of ropivacaine that reduces its local absorption in relation to the presence of the drug in the plasma, even on the third postoperative day.

The present findings are consistent with previous studies demonstrating that the addition of local infiltration in patients having spinal anaesthesia significantly improves postoperative pain relief.²⁹ It may be suggested that the combination of spinal anaesthesia and local infiltration could prevent central sensitization through an additive or synergistic effect. Unlike the repeated single shot, wound instillation maintains continuous inhibition of the peripheral painful stimulus.

Early mobilization of patients after major joint replacement surgery is one of the most important surgical outcomes for hospital discharge. The optimal mobilization pain control during 48±72 h after surgery in Group R allowed a significant reduction in length of hospital stay with earlier patient rehabilitation, thus improving the patient's quality of life and health-care while reducing hospitalization costs. The higher degree of patient satisfaction compared with systemic analgesia is further evidence in favour of the use of this technique for postoperative pain management.

A possible concern about this technique may be the potential risk of delayed wound healing and infection. Our study revealed no signs of local inflammation in any of the patients. Furthermore, it is worth noting that local anaesthetics have been reported to possess bacteriostatic and antimicrobial effects.³⁰ Although another possible criticism of the present study is that both hip and knee joint replacement patients were included, the fact that both groups had a clear majority of hip replacement patients and an equal number of knee joint replacements should be taken into consideration. We therefore believe that the large and highly statistically significant reduction in rescue analgesia required by Group R constitutes a clinically important finding.

In conclusion, the present data suggest that wound infiltration with ropivacaine 0.5% and wound instillation with ropivacaine 0.2% could be a useful, practical and safe method as a part of a multimodal analgesic regime for the management of postoperative pain after major joint replacement surgery. Further studies in different surgical groups, including evaluation in the long-term rehabilitation setting, may be necessary to confirm the efficacy of this new pain management strategy.

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