

# Continuous Wound Infiltration with Ropivacaine Reduces Pain and Analgesic Requirement After Shoulder Surgery

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After achieving a reduction of pain scores for 10 h with a single dose wound infiltration after shoulder surgery, we examined in a prospective, placebo-controlled and double-blinded study the analgesic effects of continuous wound infiltration with different concentrations of ropivacaine. Forty-five patients undergoing shoulder surgery were randomly assigned into three groups to receive single dose wound infiltration with 30 mL saline (group S) or ropivacaine 7.5 mg/mL (groups R2 and R3.75) after skin closure. Postoperatively, patients received a continuous wound infiltration with saline (group S), ropivacaine 2 mg/mL (group R2) or ropivacaine 3.75 mg/mL (group R3.75) for 48 h. Supplemental pain relief was provided by IV patient-controlled analgesia with the opioid piritramide. At 1, 2, 3, 4, 24, and 48 h postoperatively visual analogue scale (VAS) values (0–100 mm), piritramide requirements and side effects

were registered. Plasma levels of ropivacaine were measured preoperatively and at 24 h and 48 h after surgery. Until 48 h VAS values were smaller in group R3.75 compared with group S (group R3.75,  $8 \pm 9$  mm; group S,  $31 \pm 14$  mm;  $P < 0.005$ ), whereas 4 h and 48 h postoperatively VAS values were even smaller in group R3.75 compared with group R2 ( $P < 0.05$ ). Cumulative piritramide consumption was always smaller in groups R2 and R3.75 compared with group S (1–24 h,  $P < 0.005$ ; 48 h,  $P < 0.05$ ). Plasma ropivacaine levels remained less than the toxic threshold. We conclude that continuous postoperative wound infiltration with ropivacaine, especially using 3.75 mg/mL, provides smaller VAS values and opioid requirement in comparison with saline after shoulder surgery.

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**M**any efforts have been made to improve postoperative analgesia after shoulder surgery because this kind of surgery is always associated with high postoperative pain scores (1). The application of IV or oral opioids are the most frequently used therapies for postoperative pain relief after shoulder surgery, but it very often results in insufficient pain control and side effects such as respiratory depression, nausea and vomiting.

An alternative pain treatment, apart from the increasing use of interscalene brachial plexus blocks, is

postoperative wound infiltration with long-lasting local anesthetics. In a previous study we were able to show that wound infiltration and lavage with 30 mL ropivacaine 7.5 mg/mL resulted in low pain scores and reduced opioid requirement until 10 h postoperatively in patients undergoing major shoulder surgery while the mean unbound ropivacaine plasma concentrations remained less than the toxic threshold of 0.6  $\mu\text{g}/\text{mL}$  (2). However, analgesia was limited to 10 h postoperatively in this study.

Therefore, we designed this prospective, randomized, double-blinded study to compare the effects of continuous wound infiltration for 48 h postoperatively using a newly designed infusion pump with two different concentrations of ropivacaine in a comparable population of patients.

## Methods

After approval of the local ethics committee and written informed consent, 45 adult patients undergoing

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orthopedic shoulder surgery were included in the study within 9 mo. Surgical procedures included rotator cuff repair and anterior shoulder stabilization. Patients with total shoulder replacement or any other kind of implantation, revision surgery, or arthroscopic procedures were not included in the study. Further exclusion criteria consisted of ASA physical status >II, pain symptoms apart from preexisting shoulder pain, and preoperative use of opioids.

One day before surgery patients were examined with respect to preexisting shoulder pain and hemodynamic variables. On the day of surgery, patients were premedicated with 7.5 mg oral midazolam (Dormicum<sup>®</sup>, Hoffmann LaRoche, Mannheim, Germany). A venous line was inserted in the opposite forearm and infusion of 500 mL lactated Ringer's solution was started. Anesthesia was induced with remifentanyl 0.5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (Ultiva<sup>®</sup>, GlaxoSmithKline, Munich, Germany) and 2 mg/kg propofol (Disoprivan<sup>®</sup>, AstraZeneca, Wedel, Germany). Endotracheal intubation was performed after relaxation with rocuronium bromide 0.5 mg  $\text{kg}^{-1}$  (Esmeron<sup>®</sup>, Organon, Oberschleissheim, Germany). Maintenance of anesthesia was performed with 0.3  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  remifentanyl and 8 mg  $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  propofol. Normothermia was maintained with forced air. At the end of surgery and before skin closure, a 9-hole catheter was inserted through the intact skin 2 cm from one end of the skin incision and placed subcutaneously in the wound through a special needle. After skin closure a single dose wound infiltration was performed by the orthopedist, who was blinded to the applied drug solution. Patients were randomly assigned to receive a total volume of 30 mL of saline (group S) or 30 mL of ropivacaine 7.5 mg/mL (groups R2 and R3.75). Twenty mL of the respective study solution was injected after closure of the skin into the wound using the wound drain, which was then clamped for 20 min. An additional 10 mL was injected subcutaneously at both sides of the wound. Directly afterwards the end of the inserted catheter was connected to an elastomeric infusion pump (Pain Buster<sup>®</sup>, Rüschi, Kern, Germany). The Pain Buster<sup>®</sup> pump contained 300 mL of saline (group S), ropivacaine 2 mg/mL (group R2), or ropivacaine 3.75 mg/mL (group R3.75). The pump was filled under aseptic conditions in the operation theater by an anesthesiologist who was not involved in anesthesia of the patient nor in the study. After surgical disinfection of the hands the anesthesiologist, wearing a mask and a cap, used sterile gloves and gown. Filling of the pump was performed on a sterile table. A constant infusion rate at 5 mL/h was performed until 48 h after surgery. Small dose remifentanyl infusion 0.05  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  was maintained during tracheal extubation and until 15 min after extubation in the postanesthesia care unit (PACU) to ensure that the patient was able to use the IV patient-controlled

analgesia (PCA), which provided additional pain relief on request. The PCA medication consisted of a bolus of 1.5 mg of the  $\mu$  receptor agonist piritramide (15 mg of piritramide is equivalent to 10 mg of morphine) (3). No lockout time was used until the patient left the PACU. After 120 min in the PACU patients were discharged and sent to the ward with a lockout time of 5 min after a single bolus and a 4-h maximum of 22.5 mg piritramide for safety reasons.

At 1, 2, 3, 4, 24, and 48 h after surgery patients were examined with respect to visual analogue scale (VAS) values (0–100 mm), cumulative piritramide consumption, hemodynamic variables such as heart rate, blood pressure, and oxygen saturation (pulse oximetry) and side effects, including a sedation score (1 = patient awake, 2 = patient is easy to awake, 3 = patient difficult to awake, 4 = patient is somnolent, 5 = patient is impossible to awake). Whereas VAS values were examined only at rest until 3 h after surgery, pain was assessed at rest and during mobilization at 4, 24, and 48 h postoperatively (via spontaneous rotation of the operated shoulder and the forearm). Every day the wound was inspected for symptoms of infection such as hyperemia or purulent secretions. The anesthesiologist who performed these examinations was blinded to the study medication.

Venous blood was sampled for measurement of total and unbound ropivacaine plasma concentrations before induction of anesthesia, and at 24 h and 48 h after surgery. Blood was immediately centrifuged for 10 min at 2000 rpm. The resulting plasma samples were frozen at  $-20^{\circ}\text{C}$ . Ropivacaine plasma concentrations were evaluated by high performance liquid chromatography with ultraviolet detection as described previously (4). The accuracy of the assay is nearly 95% and the confidence interval is  $\pm 1.25\%$ .

After the study period of 48 h catheters were removed and analgesia was continued with IV PCA if necessary.

On the basis of the previous results we expected a reduction of VAS values of  $\geq 15$  mm in group R3.75 compared with group S 48 h after surgery. The anticipated pooled standard deviation was set at 10 mm of the VAS values. We would permit a type I error of  $\alpha = 0.05$ , and with the alternate hypothesis, the null hypothesis would be retained with a type II error of  $\beta = 0.2$ . This analysis reaches a power of 0.8 and indicated that a sample size of at least 13 patients per group was necessary (Instat, GraphPad, San Diego, CA).

Computerized statistical analysis was performed using SPSS 9.0. Differences among groups were compared with the Mann-Whitney *U*-test. Categorical variables were analyzed using Fisher's exact test. Data are expressed as mean  $\pm$  SD if not otherwise indicated.  $P < 0.05$  was considered to be statistically significant.

## Results

Of the 45 patients included in the study, four had to be excluded from the statistical analysis. In group S one patient had to be excluded because of an incorrect program of the PCA pump. In group R2 one patient was excluded because of dislocation of the IV line during the first postoperative night, which led to termination of the PCA. Two other patients were excluded because of catheter dislocation.

As shown in Table 1, demographic data were comparable among groups with respect to age, sex, weight, height, and duration of surgery. Patients of all groups showed relatively large preoperative VAS values without differences between groups (group S,  $29.2 \pm 16$  mm; group R2,  $35.4 \pm 20$  mm; group R3.75,  $39.6 \pm 21$  mm). Continuous wound infiltration with ropivacaine 3.75 mg/mL resulted in significant ( $P < 0.005$ ) reduction of pain scores at rest in comparison with infiltration with saline during the whole study period and provided smaller VAS values than ropivacaine 2 mg/mL 4 h and 48 h after surgery (Fig. 1). Infiltration with ropivacaine 2 mg/mL showed a reduction in VAS values at rest until 48 h postoperatively except at 3 h and 4 h after surgery when compared with infiltration with saline. During mobilization VAS values in group R3.75 were smaller than in group S ( $P < 0.005$ ) and group R2 ( $P < 0.05$ ) (Fig. 2). Continuous wound infiltration with ropivacaine 2 mg/mL also resulted in lower pain scores compared with group S ( $P < 0.005$ ) over time.

The cumulative piritramide consumption was significantly less in patients with wound infiltration with both ropivacaine 2 mg/mL and ropivacaine 3.75 mg/mL when compared with saline infiltration until 24 h ( $P < 0.005$ ) and 48 h ( $P < 0.05$ ) postoperatively (Fig. 3). No differences in piritramide consumption between groups R2 and R3.75 could be seen over the whole study period.

Hemodynamic variables were comparable among groups. Side effects like nausea and vomiting were infrequent and were not different among groups (Table 2). No patients showed any sign of motor block in the respective shoulder/arm as a result of infiltration with local anesthetics. No clinical symptoms of local anesthetic intoxication were detected. The plasma levels of unbound ropivacaine always remained less than the toxic threshold of  $0.6 \mu\text{g/mL}$  (Fig. 4). No patient showed any sign of local infection or wound healing problems.

## Discussion

In this prospective, randomized and double-blinded study we were able to show significant reduction in VAS values using continuous postoperative wound infiltration with ropivacaine 2 mg/mL and 3.75 mg/mL in comparison with saline. This effect could be shown at

rest and during mobilization. In the treatment groups, the cumulative piritramide consumption was significantly lower within 48 h postoperatively. Infiltration with the smaller concentration of ropivacaine also resulted in a reduction of VAS values and piritramide consumption but was less effective than ropivacaine 3.75 mg/mL 4 h and 48 h postoperatively. In the light of the small concentrations of unbound ropivacaine our data suggest that continuous wound infiltration with ropivacaine 3.75 mg/mL is an effective analgesic technique of pain management that can be administered at a rate of 5 mL/h without significant risk for systemic toxicity after major shoulder surgery.

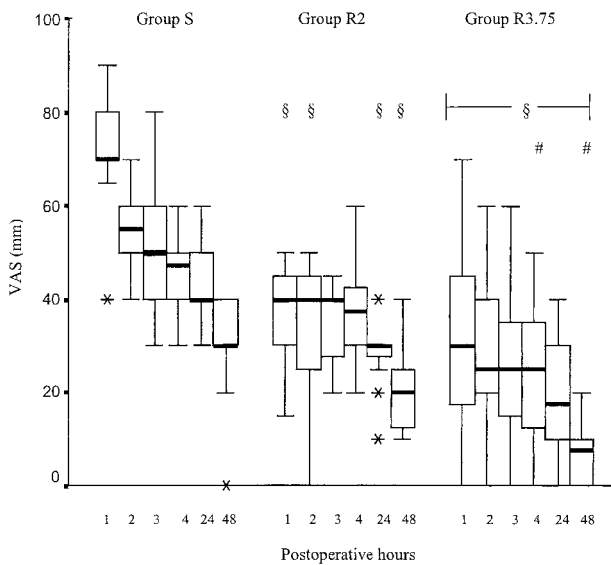
Apart from using interscalene plexus block for postoperative pain management, different efforts have been made treating postoperative pain after shoulder surgery. Rodola et al. (5) compared intraarticular bupivacaine and ropivacaine after arthroscopic shoulder surgery. Intraarticular injection of ropivacaine resulted in significantly better postoperative pain relief 6–24 hours after arthroscopy. In another study including patients after outpatient arthroscopic shoulder surgery Barber and Herbert (6) administered bupivacaine 0.5% via a continuous infusion pump. Using an insertion needle the catheters were placed in the subacromial space after subacromial and rotator cuff surgery and in the glenohumeral joint after glenohumeral surgery. Using an infusion rate of 2 mL/h mean pain scores were significantly lower during 7 postoperative days (except on days 2 and 3) in the treatment group. Catheters were removed 48 hours after surgery. In another trial Savoie et al. (7) used an indwelling infusion catheter placed into the subacromial area after arthroscopic shoulder surgery. Infusion for 48 hours was performed with bupivacaine 0.25% and resulted in reduced pain scores until postoperative day 5. Muittari and Kirvela (8) compared the analgesic effects of single dose injection in the subacromial bursa of 10 mL of bupivacaine 0.5% or 5 mg oxycodone and bupivacaine 0.5% with interscalene brachial plexus block. Additional use of IV fentanyl was comparable between interscalene block and injection of oxycodone/bupivacaine but was larger in the group with injection of bupivacaine. However, the lowest pain scores were seen in patients receiving interscalene plexus block (8).

In contrast to the studies of Rodola et al., Barber and Herbert, and Savoie et al., patients in our study underwent open shoulder surgery rather than an arthroscopic procedure. Muittari and Kirvela only used a single dose injection of the respective study solutions. We used an intraoperatively placed catheter for a continuous postoperative infusion with different concentrations of ropivacaine than have been described before. The infusion pump we used in our study has been previously used to perform continuous interscalene brachial plexus block in patients after open shoulder cuff repair (9).

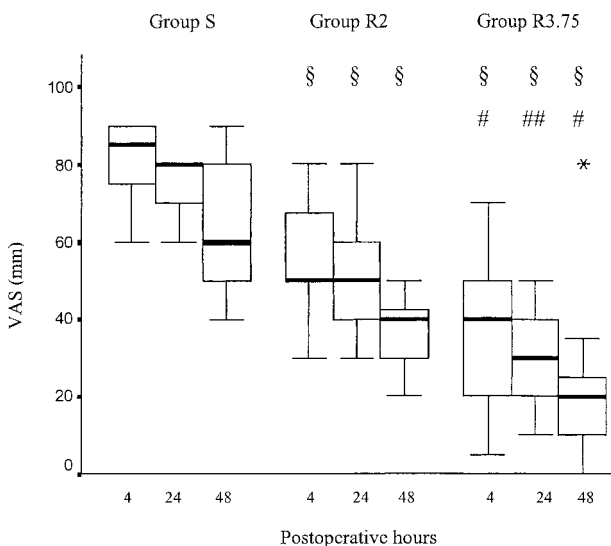
**Table 1.** Demographic Data and Duration of Surgery

	Group S (n = 14)	Group R2 (n = 12)	Group R3.75 (n = 15)
Age (yr)	47.1 ± 16	48.1 ± 13	55.5 ± 7
Sex (male/female)	9/5	7/5	5/10
Height (cm)	172 ± 11	173 ± 12	166 ± 11
Weight (kg)	80.7 ± 15	85.5 ± 27	74.0 ± 18
Duration of surgery (min)	72.7 ± 27	60.4 ± 32	70.5 ± 29

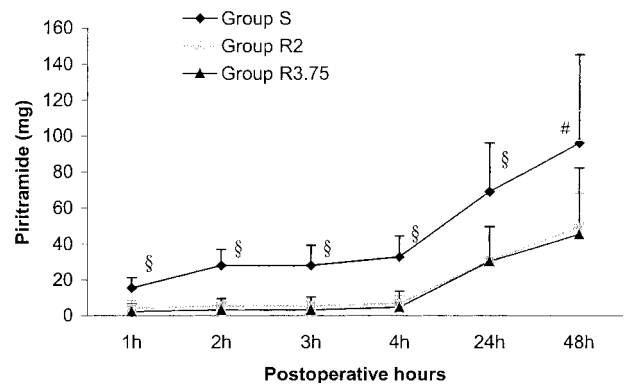
Data presented as mean ± SD.  
Group S received 30 mL saline after skin closure and continuous postoperative wound infiltration with saline. Group R2 received 30 mL ropivacaine 7.5 mg/mL after skin closure and continuous postoperative wound infiltration with ropivacaine 2 mg/mL. Group R3.75 received 30 mL ropivacaine 7.5 mg/mL after skin closure and continuous postoperative wound infiltration with ropivacaine 3.75 mg/mL.  
P = not significant for all data.



**Figure 1.** Visual analogue scale values at rest. Data are presented as median, interquartile range, range, and extreme values (\*>3-times quartile range). §P < 0.005 versus group S, #P < 0.05 versus group R2.



**Figure 2.** Visual analogue scale values during mobilization. Data are presented as median, interquartile range, range, and extreme values (\*>3-times quartile range). §P < 0.005 versus group S, #P < 0.05 versus group R2, ##P < 0.005 versus group R2.



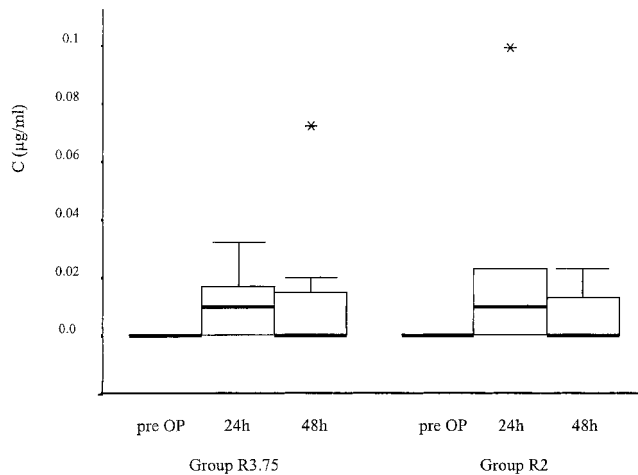
**Figure 3.** Cumulative piritramide consumption. Data are presented as mean ± SD. §P < 0.005 groups R2 and R3.75 versus group S. #P < 0.05 groups R2 and R3.75 versus group S.

**Table 2.** Cumulative Incidence of Side Effects

	Group S (n = 14)	Group R2 (n = 12)	Group R3.75 (n = 15)
Nausea	4	1	4
Vomiting	1	1	2
Motor block	0	0	0
Paresthesia	3	1	1
Sedation score			
1	6	8	10
2	3	2	4
3	5	2	1
4	0	0	0
5	0	0	0

Group S received 30 mL saline after skin closure and continuous postoperative wound infiltration with saline. Group R2 received 30 mL ropivacaine 7.5 mg/mL after skin closure and continuous postoperative wound infiltration with ropivacaine 2 mg/mL. Group R3.75 received 30 mL ropivacaine 7.5 mg/mL after skin closure and continuous postoperative wound infiltration with ropivacaine 3.75 mg/mL.  
P = not significant for all effects.

The reason for using ropivacaine in our study was mainly based on the pharmacologic aspects of this local anesthetic. The long-acting amide local anesthetic S(+) ropivacaine is chemically related to bupivacaine, which is commonly used as racemate, but the potential for cardiac and central nervous system toxicity appears to be less for ropivacaine than for bupivacaine (10). Ropivacaine binds to the internal entrance



**Figure 4.** Plasma levels of unbound ropivacaine. Data are presented as median, interquartile range, range, and extreme values (\*>3-times quartile range).

of the potassium pore, blocks the channel in an open position, and additionally acts on sodium channels (11). One interesting point, especially for wound infiltration, is that ropivacaine produces cutaneous vasoconstriction and therefore leads to delayed systemic absorption (12). Furthermore, ropivacaine possesses antiinflammatory activity (13). Previous studies indicate that local wound infiltration with ropivacaine is associated with slow absorption into the systemic circulation (14). Because of a large clearance and a short terminal plasma half-life of 1.7 hours and the consecutively small plasma concentration ropivacaine seems to be a suitable local anesthetic for continuous wound infiltration (11,15). Even with quite rapid infusion rates of ropivacaine, plasma levels of unbound ropivacaine always remained less than the toxic threshold of 0.6 µg/mL in our study. The plasma levels of unbound ropivacaine after the single dose infiltration with ropivacaine 7.5 mg/mL had been measured and remained below this potentially toxic threshold (2). These results are comparable with a study recently published by Ekatodramis et al. (16) using infusion rates of 6 mL/h and 9 mL/h of ropivacaine 2 mg/mL for continuous interscalene analgesia after an initial interscalene block with 30 mL of ropivacaine 7.5 mg/mL in patients after major shoulder surgery. In this study plasma levels of unbound ropivacaine also remained less than the toxic threshold.

The continuous wound infiltration with ropivacaine through an intraoperatively placed catheter seems to be a highly effective and safe technique in postoperative pain management even in day-case surgery. According to a recently published review by Rawal (17), incisional and intraarticular local analgesia techniques are of increasing interest in recent years because they are simple, safe, and inexpensive, and provide effective postoperative pain relief. This method excludes

the risk of any nerve or plexus damage, which can be associated with interscalene or other techniques of brachial plexus blockade. One potential risk in performing continuous wound infiltration with local anesthetics is systemic toxicity by inadvertent IV injection or vascular uptake of the local anesthetic. In our study we were able to show that plasma levels of unbound ropivacaine never reached toxic levels with this technique. Another possible complication lies in the infectious potential of an indwelling catheter in a recently operated area. Even after using aseptic conditions filling the infusion pump in the operation theater, strict asepsis has to be performed at any time when manipulating the catheter in the postoperative period to avoid infectious complications.

An indispensable condition for clinical settings where postoperative wound infiltration with local anesthetics is performed is good cooperation and communication with the respective surgeons. The effectiveness of this pain therapy may lead to earlier discharge of patients after surgery. Patients undergoing shoulder surgery could probably be discharged after surgery with a highly effective pain therapy performed via this single use infusion pump. New models of the pump we used in the study exist and include adjustable infusion rates and the possibility of using a patient-controlled bolus application.

In conclusion, our prospective, randomized and double-blinded study demonstrated excellent postoperative analgesia using continuous wound infiltration with ropivacaine 3.75 mg/mL, which led to a significant reduction of VAS values and opioid consumption without severe side effects in patients undergoing major shoulder surgery.

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