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No advantage of adrenaline in the local infiltration analgesia mixture during total knee arthroplasty

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Abstract
Purpose Local infiltration analgesia (LIA) is widely applied in patients undergoing total knee arthroplasty (TKA). In daily practice, adrenaline is added to the LIA mixture to achieve vasoconstriction. However, adrenaline has some possible negative side effects (e.g. tissue necrosis). This trial investigated whether ropivacaine alone is at least as effective for postoperative pain relief after LIA.
Methods Fifty patients scheduled for primary TKA were included in this prospective randomized, double-blind, controlled pilot study receiving high-volume (150 mL) single-shot intra-capsular LIA with ropivacaine (2 %) with (Ropi+) or without (Ropi−) adrenaline (0.01 %). All patients received the same pre-, peri- and postoperative care with multimodal oral pain protocol. Postoperative pain was assessed before and after the first mobilization and during the first 48 h postoperative using the visual analogue scale (VAS). Secondary outcomes were rescue medication use, early mobilization, length of hospital stay, adverse events (AE's) and readmission rates. Patient reported outcomes measures (PROMS); Oxford Knee Score and WOMAC, were obtained preoperative and 3 months postoperative.
Results VAS scores were not significantly different before (n.s.) and after the first mobilization (n.s.), neither over the first 48 h postoperative (n.s.). Patients who needed rescue medication (n.s.), who mobilized <6 h postoperative (n.s.), who were discharged before postoperative day 3 (n.s.), AE's and readmission rate (n.s.) were comparable between both groups. At 3-month follow-up, PROMS significantly improved within both groups.
Conclusion To prevent possible negative side effects (e.g. tissue necrosis), adrenaline should be omitted from the LIA mixture. Single-shot LIA with ropivacaine alone results in clinical acceptable adequate pain control and can be used in daily TKA practice.
Level of evidence Randomized, double-blind, prospective clinical trial, Level I.

Keywords Adrenaline · Epinephrine · Local infiltration analgesia · Pain management · Total knee arthroplasty · Early mobilization · Early discharge · Fast track

Introduction

Early mobilization after TKA can be delayed due to severe high intense pain 3 to 6 h postoperative [6, 11]. Recent literature supports the use of LIA to challenge with direct postoperative pain after TKA [17]. LIA with ropivacaine in joint replacement surgery was first described in 2003 after which the technique was further developed [4, 19, 31]. The literature shows progressive results in terms of pain control, early mobilization and discharge from hospital and reduced opiate use [1, 3, 11, 30, 31]. Several results are attributable to different analgesic infusion techniques after TKA, all with positive and negative side effects [11, 30]. This technique involves intra-operative infiltration of an analgesic mixture. The combination of ropivacaine with adrenaline is most common used and described in the literature

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to deal with postoperative pain [17]. During surgery, the use of locally administered adrenaline reduces potentially toxic blood concentrations of ropivacaine [4, 6, 17, 22, 24], decreases the clearance and distribution processes into the blood flow [29], and it may also reduce the risk of bleeding into the knee [7]. However, there are also some potential local and systemic adverse effects such as tissue necrosis and increased risk of infections [12, 21, 22, 29, 30]. The data are limited to support the role of adrenaline during intra-operative single-shot LIA in combination with ropivacaine in patients undergoing TKA [17, 18, 23, 27, 28, 30, 34]. The theoretical advantage of adrenaline is the vasoconstrictive effect. On the other hand, ropivacaine itself is a long-acting analgesic with vasoconstrictive properties to reduce local absorption [4, 5, 22, 24]. There are no data to support the effect of ropivacaine alone for single-shot LIA on postoperative pain relief after TKA compared with LIA, consisting a ropivacaine and adrenaline mixture.

This study hypothesized that LIA with only ropivacaine is at least as effective in short terms as the widely used current method, LIA procedure with mixture of ropivacaine and adrenaline. This prospective, randomized, double-blind controlled trial examines the effect of adrenaline in the LIA mixture in patients undergoing TKA.

Materials and methods

Fifty patients with a painful and disabled knee joint resulting from osteoarthritis, a high need to obtain pain relief and improve function, able and willing to follow instructions were included after informed consent. Patients with a general or an active knee infection, failure of previous joint replacement of the knee to be operated on, pregnancy, contraindication for ropivacaine and/or adrenaline, and patients who were not able to understand and complete the procedure due to cognitive dysfunction or language barrier were not included in this pilot study.

Multidisciplinary enhanced clinical pathway

The following pathway applies to both groups. A personal coach was involved as much as possible to inspire, correct and support the patient while in hospital and directly after discharge. In addition, the coach also indirectly reduces the workload on the nursery in terms of helping with all-day activities. All patients received preoperative education and exercise training, to become familiar with walking (stairs) with crutches and transfers from bed to a chair and vice versa, information about the in- and outpatient process and home-based rehabilitation. The first mobilization was attempted <6 h postoperative including transfer from a bed to a chair and vice versa following walking with a walker if possible under supervision of a physiotherapist and nurse. All patients were familiar with the overall discharge criteria: mobilize and transfer into and out of bed individual and safe, able to get into and up from a chair, walk independently with crutches and if necessary walking stairs with crutches. After discharge, physiotherapy in their home environment was started 14 days postoperative. All patients were seen at the outpatient clinic at 2, 6 and 12 weeks postoperative.

Table 1 Multimodal opioid sparing pain protocol was provided

	Preoperative	Postoperative			
	2 h	4 h	8 h	First day	Day 2–14
Arcoxia (mg)	90			90	90
Paracetamol (g)	1	1	1	1[a]	1[a]
Gabapentin (mg)	600		300	300	
Omeprazol (mg)	40			40	40

[a] Paracetamol (1 g) was given four times daily on fixed intervals throughout the day

Randomization and blinding

To make sure LIA medication was blinded to the patients, orthopaedic surgeon, investigator and other persons direct and indirect involved in the study, randomization and preparation of the syringes for both ropivacaine with (Ropi+) and without adrenaline (Ropi−), were performed by the hospital pharmacist (HK). Randomization was performed using computer, web-based generated randomized numbers (www.random.org). Three syringes (50 ml each) were numbered from one to three, whereas syringe one and two contained ropivacaine (2 %) with or without adrenaline (0.01 %) and the third syringe was always without adrenaline. Randomization was unblinded after study completion or in case of a suspected unexpected serious adverse reaction (SUSAR).

Operative and analgesia treatment

According to a standardized pain protocol (Table 1), patients received premedication 2 h before operation. Patients were operated under spinal or general anaesthetic treatment by a single experienced knee arthroplasty surgeon (NK) with the use of patient-specific positioning instruments (Signature™, Biomet, Warsaw IN) for TKA. All patients received a cemented Vanguard™ Complete Knee System. (Biomet, Inc, Warsaw, IN) A pneumatic tourniquet was positioned on the thigh before surgery and inflated to 350 mmHg during cementing. Single-shot LIA was injected by the orthopaedic surgeon (NK), intra-operatively according to Kerr and Kohan [19]. Mean operation

time (incision to closure in minutes) and mean blood loss (total volume of blood in the suction device prior to rinsing the knee with pulse lavage system in millilitres) were recorded in the patients' operative records. Patients did not receive an intra-articular catheter, nor postoperative injections with analgesia nor a drain or urinary catheter. Urinary retention was tested with the use of a bladder scan (Verathon®, BVI 9400). Pre- and postoperative patients received a multimodal opioid sparing pain protocol (Table 1). Daily thromboprophylaxis (Fondaparinux) was administered subcutaneously once each evening for 35 days, starting on the day of surgery. Compression bandage was removed <24 h. On day one postoperative patients received analgesics in the morning (Table 1) and daily four times paracetamol (1 g). If analgesics were ineffective on the day of surgery or the first or second day postoperative, rescue analgesia (Tramadol, 100 mg) once daily was provided on demand. From day two till day 14 postoperative, patients received analgesics according to a multimodal opioid sparing pain protocol (Table 1).

Study endpoints

Experienced pain was measured with a visual analogue scale (VAS; 0 to 100, 100 being 'worst pain'). Pain was measured before and after the first mobilization and during the first 48 h postoperative on fixed time points (direct postoperative, and daily 8:00, 16:00 and on 22:00 h). *Rescue medication* use was evaluated, the amount of patients who used postoperative Tramadol were registered. *Early mobilization* (minutes) was recorded as time between the start of anaesthesia until the first mobilization. *Length of hospital stay* (days) was evaluated as time between hospital admission and discharge. Adverse events (AE's) were classified as patient related [e.g. postoperative nausea and vomiting (PONV)], thromboembolic events and wound disorders (e.g. persistent wound leakage), surgical related (e.g. infection) and/or prosthesis related (e.g. loosening). Pain, PONV and discharge criteria were evaluated daily on fixed time points (8:00, 16:00 and on 22:00 h). Besides the difference of the LIA mixture, pre-, peri- and postoperative procedures and pain protocol were identical in both groups as well as the completed operative and clinical case report forms. *PROMS* were obtained preoperative and 3 months postoperative including the Oxford Knee Score (OKS; 12 to 60, 12 being the best outcome) [13] and Western Ontario and McMaster Universities Arthritis Index (WOMAC; 0 to 100, 100 being the best outcome) [25].

This prospective, randomized, double-blind pilot study was performed in compliance with the Helsinki Declaration of 1975, as revised in 2000 and was studied and approved by the IRB (METC Atrium-Orbis Zuyd, Heerlen, the Netherlands, IRB Nr. 13T112) and registered online at the European Clinical Trials Database (EudraCT, Nr. NL 20140403), the Dutch Trial Register (www.trialregister.nl, Nr. NTR4769) and conducted in accordance with the guidelines for Good Clinical Practice (GCP).

Statistical analysis

Sample size and power calculations were made based on our expectations. We assumed that both LIA with (Ropi+) or without (Ropi−) adrenaline significantly improves the mean VAS pain score by 20 mm postoperative with a standard deviation of 15 mm on a VAS pain score of 100 mm. With an alpha of 0.05 and 1-beta error of 0.8, we needed 21 patients: 25 taking into account 10 % lost of follow-up. This study included 50 consecutive patients, 25 in each arm. The Shapiro–Wilk test showed that the data were not normal distributed. Statistically significant differences between both groups were analysed with nonparametric Mann–Whitney *U* test (e.g. VAS pain score, early mobilization, early discharge and PROMS), and Chi-square tests were used for categorical variables (e.g. rescue medication use and AE's). *P* value was considered to be statistically significant at $P \leq 0.05$ for all analysis. All statistical analyses were performed with use of SPSS version 17.0 for windows (Inc., Chicago, IL). Results are presented as either with frequencies (%), mean (SD), or median (range).

Results

Fifty randomized patients completed this study. None of the patients were lost to follow-up. Randomization was unblinded after study completion no SUSAR's occurred. Baseline demographics and OR data were not significant different (Table 2).

VAS pain scores were not significantly different (Fig. 1). Thirteen patients (52 %) in the Ropi− group used rescue medication on postoperative day one compared to 7 patients (28 %) in the Ropi+ group (n.s.). One patient

Table 2 Baseline demographics and OR data presented as mean (SD) or absolute number between the groups

Variables	Ropi+	Ropi−
Age (years) at index surgery	62.8 (6.1)	66.3 (9.8)
Gender m/f	14/11	10/15
BMI kg/m^2	27.6 (5.7)	29.6 (3.8)
ASA classification I/II/III	7/17/1	6/19/0
Operative data		
General/Spinal	2/23	6/19
Blood loss ml	251.1 (97.7)	235.4 (96.1)
OR time min	62.4 (12.1)	63.0 (15.1)

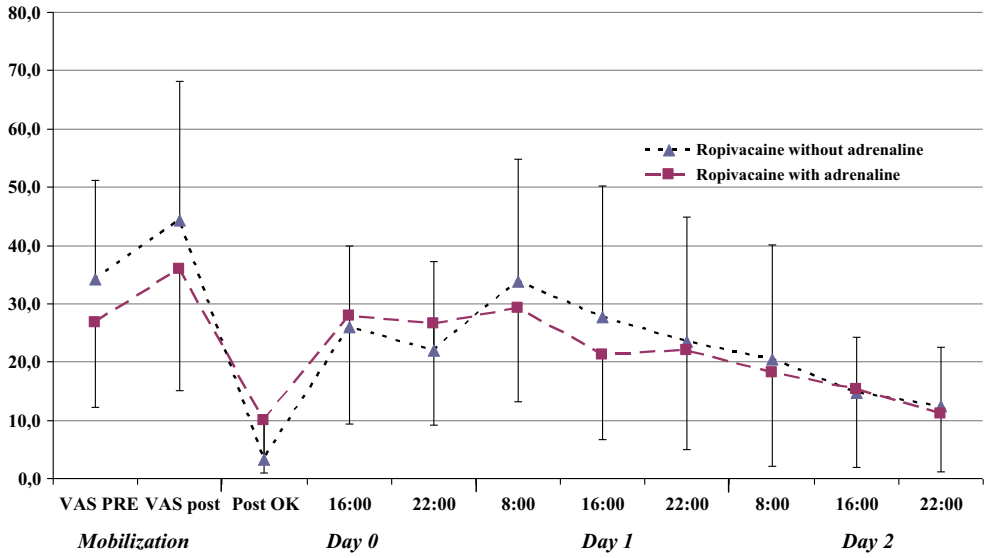

Fig. 1 Mean experienced pain (*vertical axis*) before and after the first mobilization, during the first 48 h, measured direct postoperative (post OR), and daily 8:00, 16:00 and on 22:00 h (*horizontal axis*) with use of a VAS pain score. Standard deviations (SD) are displayed with whiskers

Table 3 The amount of AE's between both groups were not significant different

AE's	Ropi+	Ropi−	Remarks
Patient related	10	6	PONV, vasovagal syncope, electric cardioversion, delirium
Wound disorders	3	0	Major wound leakage
Surgical related	3	1	Loss of sensibility due to delayed recovery from anaesthesia, limited knee flexion[a], superficial wound infection[a]

[a] All adverse events occurred during initial admission except for the readmissions

in both groups used rescue medication on day two. Early mobilization was comparable between both groups (n.s.). Twenty-two patients (88 %) in the Ropi+ group could mobilize within a mean of 336 min (76.0) compared to 21 patients (84 %) who mobilized within a mean of 350 min (68.0) after anaesthesia in the Ropi− group. Length of hospital stay was comparable between both groups (n.s.). Twenty patients (80 %) in the Ropi+ group compared to 15 patients (60 %) in the Ropi− group were discharged before postoperative day 3 (n.s.). AE's are summarized in Table 3. There were no thromboembolic or prosthesis related AE's although one patient in the Ropi+ group underwent electric cardioversion due to atrial fibrillation and was discharged on postoperative day 3. At 3-month follow-up, the mean WOMAC and OKS significantly ($P < 0.00$) improved within each group with a mean of 30.7 (22.6) and 15.5 (10.9) in the Ropi+ group and 23.5 (25.3) and 12.5 (10.8) in the Ropi− group. There were no significant differences between both groups for both PROMS.

Discussion

The most important findings of the present study was that the ropivacaine and adrenaline LIA mixture was not clearly superior to LIA consisting only ropivacaine with respect to experienced pain before and after the first mobilization and during the first 48 h postoperative. In this study, both groups gave improved and comparable pain relief after TKA.

These comparable results on pain relief could be explained by the fact that ropivacaine itself is a long-acting analgesic with vasoconstrictive properties to reduce local absorption [4, 5, 22, 24]. Poorly managed postoperative pain after TKA negatively influences early postoperative recovery [14] and discharge [8, 16, 17]. In this trial none of the patients had a delayed mobilization due to high pain intensity. Most of the delayed mobilization occurred in patients infiltrated with adrenaline including vasovagal syncopes, major wound leakages and one patient did not had any sensibility in both legs due to delayed recovery from

spinal anaesthesia. These patients had a delayed discharge, which was in line with the results of Husted et al. [15, 16] who found a relation between length of hospital stay and early mobilization. In this trial serious side effects were observed in both groups, which resulted in prolonged hospital stay and hospital readmissions.

Many studies have shown the effects of postoperative LIA [3, 8, 34]. Most of these studies focus on analgesic consumption, early mobilization, pain relief and early discharge from hospital [17]. The postoperative pain relief presented in this trial may be comparable to the results from other studies [4, 8, 9, 14]. However, not all results are based on single-shot injections [4]. Many techniques are described in literature, but there is no gold standard in the treatment of pain control after TKA. Most of the studies included single-, continuous [32, 34], intra- or extra-articular infiltrations [3, 7, 26, 30] and with frequent postoperative injections through an intra- [19, 20] or extra-articular catheter [10] Recent published series consist positive results on the LIA technique with ropivacaine and adrenaline infiltrated intra-operatively with single-shot injections [8, 33]. This trial found comparable results in the literature if it becomes to pain, PONV, early mobilization and discharge after single-shot injections of ropivacaine with or without adrenaline. However, also high postoperative pain scores were seen after single-shot injection LIA [34].

One of the limitations in this study, circulating blood levels of ropivacaine were not measured to check for possible considerable chondrotoxicity. Adrenaline reduces potentially toxic blood concentrations of ropivacaine and can extend the effects of the local anaesthetics by keeping it localized to the area of injection, but with possible side effects such as tissue necrosis and increased risk of infections, which was found in one patient per group in our series [12, 21, 22, 29, 30]. Both patients were successfully treated with antibiotics. Other than Andersen et al. [2] reported, a possible risk of considerable chondrotoxicity is clinical relevant in case of performing a TKA without resurfacing the patella.

Secondly, it can be argued that the absent effect of adrenaline may be explained by a continuous effect of the used optimized pain protocol although both groups received the same pre- peri- and postoperative treatment including the same opioid sparing multimodal oral pain protocol. In contrast to other published trials, ketorolac was not added to the LIA mixture. Etoricoxib was part of the multimodal oral pain protocol, administered 2 h pre- and daily up to postoperative day 14.

Thirdly, a comparison with a placebo-controlled group that received LIA with only saline was not made. Given the fact that single-shot LIA is an added value after TKA to cope with postoperative pain relief, LIA should belong to the daily practice during TKA [33]. However, it is unclear which LIA mixture has the most favourable outcome with minimal side effects. Recently, Xu et al. [33] published their meta-analysis of RCT's on single-shot LIA in TKA patients. They concluded that single-shot LIA is effective for postoperative pain management in TKA patients with satisfactory short-term safety without any consensus on the widespread used analgesia. This study found limited evidence to support the role of adrenaline during intra-operative single-shot LIA in combination with ropivacaine in patients undergoing TKA. Further larger RCT's exploring the effect of adrenaline are of interest [10, 17, 27, 28, 30, 33].

Finally, we recommend that LIA with only ropivacaine should be part of daily practice in TKA including a well-established multimodal pain protocol to cope with postoperative pain, without the possible negative side effects of adrenaline.

Conclusion

This randomized, double-blind, prospective clinical trial could not confirm the added value of adrenaline into the ropivacaine solution for LIA, since both groups showed comparable experienced pain during the first 48 h postoperative.

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Authors' contribution MS, HK, JJ and NK designed the study. HK did the randomization. MS collected the data. MS and YB analysed and interpreted the data. MS and YB wrote the manuscript, HK, JJ and NK revised it.

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