A randomised controlled trial for the effectiveness of intra-articular Ropivacaine and Bupivacaine on pain after knee arthroscopy: the DUPRA (DUtch Pain Relief after Arthroscopy)-trial

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Abstract

Purpose In this double-blinded, randomised clinical trial, the aim was to compare the analgesic effects of low doses of intra-articular Bupivacaine and Ropivacaine against placebo after knee arthroscopy performed under general anaesthesia.

Methods A total of 282 patients were randomised to 10 cc NaCl 0.9%, 10 cc Bupivacaine 0.5% or 10 cc Ropivacaine 0.75%. Patients received the assigned therapy by intra-articular injection after closure of the portal. Pain and satisfaction were measured at one, 4 h and 5–7 days after arthroscopy with Numerical Rating Scale (NRS) -scores. NSAID consumption was also recorded.

Results One-h NRS-scores at rest were higher in the NaCl group compared with the Bupivacaine group ($P < 0.01$), 1 h NRS-scores in flexion were higher in the NaCl group compared with the Bupivacaine ($P < 0.01$) and Ropivacaine ($P < 0.01$) groups. NRS-satisfaction at 4 h was higher for the Bupivacaine group compared with the NaCl group ($P = 0.01$). Differences in NRS-scores were significant but low in magnitude. NSAID consumption was lower in the Bupivacaine group compared with the NaCl group ($P < 0.01$).

Conclusions The results of this randomised clinical trial demonstrate improved analgesia after administration of low doses of intra-articular Bupivacaine and Ropivacaine after arthroscopy of the knee. Considering reports of Bupivacaine and Ropivacaine being chondrotoxic agents and the relatively small improvement on patient comfort found in this trial, it is advised to use systemic anaesthetic instead of intra-articular Bupivacaine or Ropivacaine for pain relief after knee arthroscopy.

Level of evidence I.

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Introduction

In 1931, Burman posted the knee as being a joint suitable for arthroscopy [1]. Over time, more indications for arthroscopy have been posted. Momentarily approximately 150.000-day care knee arthroscopies are performed a year in The Netherlands.

Pain control in day care arthroscopy is essential for patient comfort and early hospital discharge. Intra-articular administration of single-dose local anaesthetic solutions is used to provide better analgesia after knee arthroscopy and reduce consumption and possible side effects of oral and intravenous anaesthetic.

Although Bupivacaine and in some countries Ropivacaine are still commonly used in low doses as an intra-articular anaesthetic after knee arthroscopy, evidence from literature does not provide definite level I evidence to

advocate the use of an intra-articular anaesthetic [6, 12–15, 17, 19, 22].

If the effect of the intra-articular anaesthetic is proven not clinically relevant this would be a definite argument to stop the administration of these agents.

This study was designed to investigate the superiority of single-low dose 10 cc Bupivacaine 0.5% and 10 cc Ropivacaine 0.75% compared to physiologic saline after knee arthroscopy performed under general anaesthesia. It was hypothesised that intra-articular injection with Bupivacaine or Ropivacaine was significantly more effective than intra-articular injection with saline.

Materials and methods

This study was a prospective, placebo controlled, randomised double-blind clinical trial. The study protocol was approved by the Medical Ethical Committee of the University of Utrecht, The Netherlands and was executed in the Tergooi Hospitals, Hilversum, The Netherlands.

Inclusion criteria were the following: Patients scheduled for knee arthroscopy under general anaesthesia without concomitant ligament or meniscal reconstruction, cartilage transplantation or cartilage procedure, American Society of Anaesthesiologists (ASA) classification I and II, and age over 18 years. Exclusion criteria were the following: A history of adverse reactions to study medication, physical or mental handicaps not allowing the regular rehabilitation or communication, and the use of 'drugs' or anaesthetic for prolonged episodes. From 2005 until 2010, a total of 282 patients were included, randomised and analysed.

Patients were randomised into three groups: The Control group was injected with 10 cc NaCl 0.9%; group Bupi was injected with 10 cc Bupivacaine 0.5% (50 mg); and group Ropi was injected with 10 cc Ropivacaine 0.75% (75 mg). A total of 96 patients were allocated to the Control group. Ninety-four patients were allocated to group Bupi, and 92 patients were allocated to group Ropi. All patients received the allocated treatment. One patient in group Bupi was excluded from analysis because the arthroscopy was performed while this patient had total knee prosthesis in situ. A total of 96 patients were analysed in the Control group, 90 patients in group Bupi and 90 patients in group Ropi (Fig. 1).

In the outpatient clinic, a nurse handed out patient-information when the patient got scheduled for surgery. Written informed consent was obtained on the day of surgery, after the patients were enabled to have read the information. Randomisation was performed by a blinded research assistant who randomly picked a closed opaque envelope containing a treatment regimen. Patients were randomised without stratification. After inclusion, patients received a study-diary in which study data were recorded.

Primary outcome measure was the 0–10 Numerical Rating Scale (NRS) for pain at rest and in flexion at 5–7 days after arthroscopy. The 0–10 NRS is an 11-point scale with at the end points the extremes 0 (no pain) and 10 (worst pain). Patients were instructed to circle the numerical value that best represented their pain level at that moment. This scale is commonly used in clinical orthopaedic practice and is a reliable and valid outcome measure for pain, with test–retest reliability coefficients (ICC) ranging from 0.77 to 0.94 [11].

Secondary outcomes were NRS for pain at rest and in flexion 1 and 4 h after arthroscopy, NRS for satisfaction, and consumption of analgesics.

Assessments were performed preoperative, 1 h postoperative, 4 h postoperative and 5–7 days after surgery. Before first NRS-scores were obtained, patients were informed how to use NRS-scores. NRS for satisfaction was scored by having the patient rate their satisfaction with 0 being completely dissatisfied and 10 being completely satisfied. All data were collected by a blinded research assistant.

The arthroscopic procedures were performed by a group of 4 orthopaedic surgeons and a changing number of residents. Surgery was performed using a standard 2-portal arthroscopy technique. The leg to be treated was positioned in a leg clamp, and a tourniquet was inflated tot 350 mm Hg. After surgery, a standard size bandage was applied.
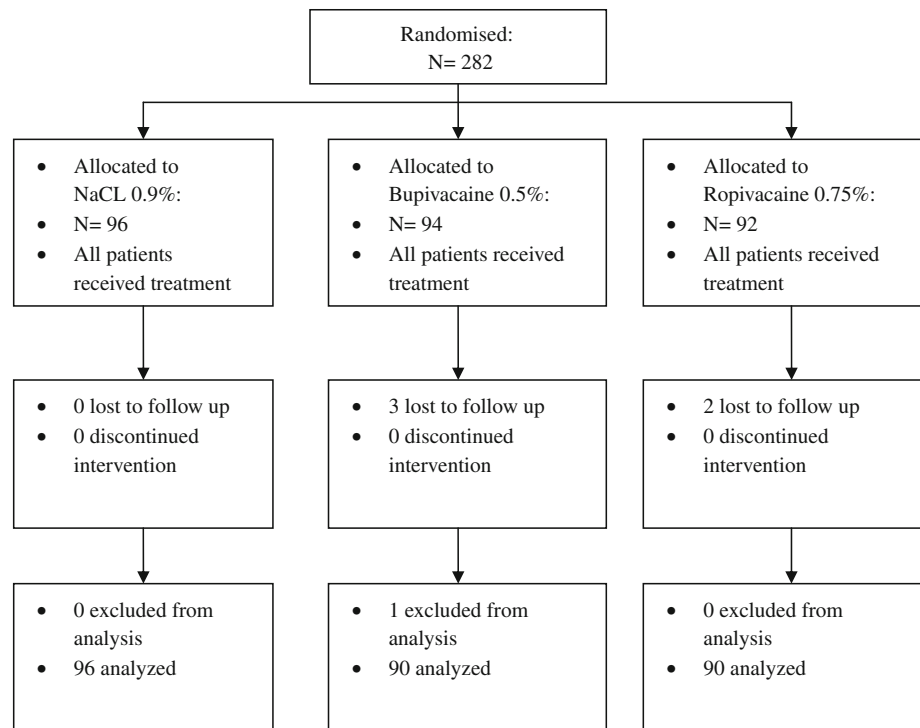
All patients received standardised general anaesthesia with propofol, sevoflurane and sufentanil during surgery. The allocated sealed envelope was opened on the operating room (OR) by OR-personnel. Ten cc of Bupivacaine 0.5%, Ropivacaine 0.75% or NaCl 0.9% was than prepared by OR-personnel in a syringe with a 40 mm needle. Allocated treatment was injected by the surgeon through the portal after closure of the portals with a suture for each portal, and before the tourniquet was released and the patient woke up. The surgeon was unblinded during injection of the study drug for safety reasons, for example allergies or systemic reactions.

After surgery, all patients were transferred to the recovery room where the research-assistant collected 1 h data. Before discharge, the 4 h data were collected.

Patients were given rescue medication at their own wish. First rescue medication was oral or rectal NSAID, second was a morfine analogist. All administered medication was recorded in the patient's diary.

Statistical analysis

Sample size calculation for this study was based on NRS for pain. A clinically relevant difference between the

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                    │   Randomised:       │
                    │   N= 282            │
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- Allocated to NaCL 0.9%:
- N= 96
- All patients received treatment

- Allocated to Bupivacaine 0.5%:
- N= 94
- All patients received treatment

- Allocated to Ropivacaine 0.75%:
- N= 92
- All patients received treatment

- 0 lost to follow up
- 0 discontinued intervention

- 3 lost to follow up
- 0 discontinued intervention

- 2 lost to follow up
- 0 discontinued intervention

- 0 excluded from analysis
- 96 analyzed

- 1 excluded from analysis
- 90 analyzed

- 0 excluded from analysis
- 90 analyzed

treatment groups was defined as 1 point. With an assumed standard deviation of 2 points and an α level of 0.05, 86 patients in each group were required to obtain a power of 90%. In order to incorporate an expected dropout rate of 10%, a total of 282 patients were required.

Analysis was performed with PASW 18.0 software (IBM Company, Illinois, Chicago) and was based on the intention-to-treat principle. Normality of the data was checked by use of the Kolmogorov–Smirnov tests. Analysis of variance (ANOVA) tests was performed for the comparison of age. Kruskall–Wallis (KW) tests were used to compare other continuous data (with skewed distributions), such as surgery time and NRS-scores for pain and satisfaction. When KW tests showed significant differences between the intervention groups, post hoc pairwise comparisons were performed by use of Mann–Whitney U tests with adjustment of the significance level for multiple testing (Bonferroni). Categorical variables were analysed with a Chi-square test or Fisher exact test. A P value <0.05 was considered as statistically significant.

Results

Randomisation revealed three comparable cohorts, mean age of the study population was 50.1 years (SD 14.6), and male/female ratio was 135 (48%):147 (52%) (Table 1), and median duration of surgery was 17 min (range 4–55). Duration of surgery did significantly differ between

residents and staff members performing the surgery ($P < 0.01$). Median duration of surgery by a staff member was 13 min (range 4–37) and for a resident 18 min (range 7–55).

At 1 h postoperative, significant differences between the treatment groups were observed for pain at rest and flexion ($P = 0.01$ and $P < 0.01$, respectively) and 4 h postoperative for satisfaction ($P = 0.02$). (Figs. 2, 3)

Post hoc analysis with Bonferroni correction (significance level was adjusted to 0.017) for NRS at rest at 1 h postoperative showed a significant difference between the Control and the Bupi group ($P < 0.01$) and not between the Control and Ropi group or Ropi and Bupi group. NRS at flexion 1 h postoperative showed significant differences between the Control and Bupi group as well as the Control and Ropi group ($P < 0.01$ and $P < 0.01$, respectively) (Fig. 3). Satisfaction at 4 h postoperative was only significantly different between the Control and Bupi group ($P = 0.01$) (Fig. 4).

One h postoperative, NSAID consumption was reported by 64 (67%) patients in the Control group, 42 (47%) patients in the Bupi group and 38 (42%) patients in the Ropi group. Significantly, more patients in the Control group used NSAID's compared with the Bupi group ($P < 0.01$). No significant differences were found comparing the Control group to the Ropi group or the Ropi group to the Bupi group. At 4 h postoperative, no significant differences in escape medication were observed. No adverse reactions were noted in all study groups.

Table 1 Baseline characteristics and surgical data

	NaCl 0.9% (n = 96)	Bupivacaine 0.5% (n = 94)	Ropivacaine 0.75% (n = 92)	All (n = 282)
Mean age, years (SD)	50.1 (16.3)	50.2 (12.8)	49.6 (14.8)	50.1 (14.6)
Male (%)	40 (42%)	45 (48%)	50 (54%)	135 (48%)
Female (%)	56 (58%)	49 (52%)	42 (46%)	147 (52%)
Med meniscus lesion (%)	43 (45%)	45 (48%)	47 (51%)	135 (48%)
Lat meniscus lesion (%)	8 (8%)	11 (12%)	8 (9%)	27 (10%)
ACL rupture (%)	7 (7%)	3 (3%)	6 (6%)	16 (6%)
Degenerative changes (%)	28 (29%)	18 (19%)	15 (16%)	61 (22%)
Other diagnosis (%) (e.g. loose bodies, plica synovialis)	10 (11%)	17 (18%)	16 (18%)	43 (15%)
Median NRS rest (range)	1 (0–10)	2 (0–9)	1 (0–8)	1 (0–10)
Median NRS flexion (range)	5 (0–10)	4.5 (0–10)	5 (0–10)	5 (0–10)
Surgery by resident (%)	68 (71%)	59 (63%)	65 (71%)	192 (68%)
Surgery by staff (%)	28 (29%)	35 (37%)	27 (29%)	90 (32%)
Duration of surgery, min (range)	16 (4–36)	17 (8–40)	17 (4–55)	17 (4–55)

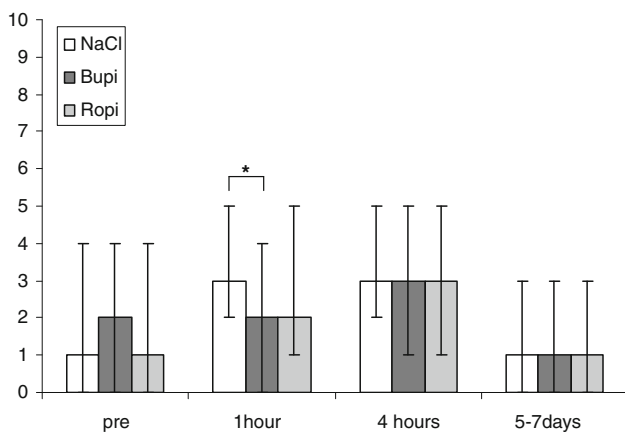No statistical differences were observed between the treatment groups

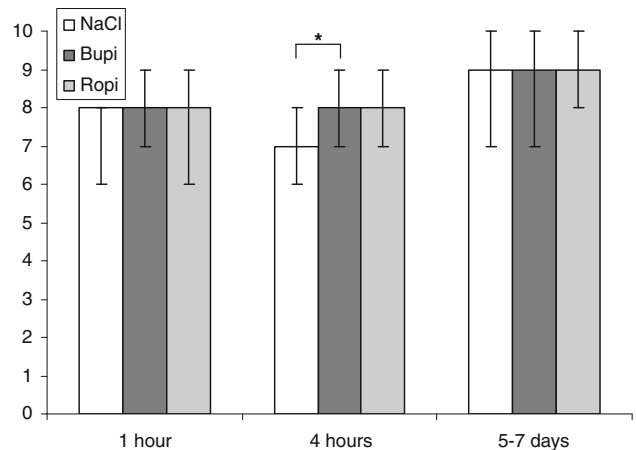**Fig. 2** Median NRS (with interquartile ranges) for pain at rest. *$P < 0.01$

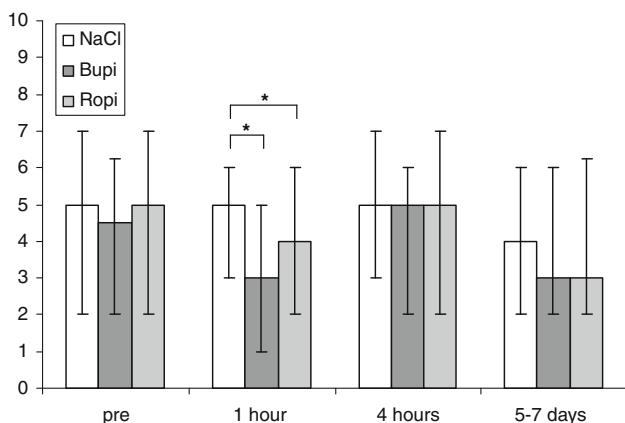**Fig. 4** Median NRS (with interquartile range) for satisfaction. *$P = 0.01$

Fig. 3 Median NRS (with interquartile ranges) for pain during flexion. *$P < 0.01$

Discussion

The most important finding of this study is that both intra-articular 10 cc Bupivacaine 0.5% and 10 cc Ropivacaine 0.75% reduce pain in the first postoperative period after arthroscopy of the knee. Ropivacaine was less effective than Bupivacaine for pain at rest at 1 h postoperative, although NSAID consumption was not different between Bupivacaine and Ropivacaine groups.

Though significant, the analgesic effects were relatively small and lasted for a short period of time; 4 h after surgery, no difference in pain scores could be recorded anymore between the groups. Patient satisfaction, however, did differ 4 h after surgery. This can be the result of better analgesia the hours before this measurement, which is supported by the lower NRS-scores at 1 h postoperative. The small and relatively short lasting effects as well as the,

though being significant at 1 h postoperative at rest, small differences between Bupivacaine and Ropivacaine can also be the cause of the nonsignificant difference in NSAID consumption between Bupivacaine and Ropivacaine groups.

In 1999, Moiniche et al. [15] performed a review on intra-articular Bupivacaine after knee arthroscopy. This study could only provide weak evidence for a beneficial effect of Bupivacaine, especially in lower, 50 mg doses. Reduction in pain scores was short in duration, and a dose-dependent relationship for effectiveness could not be proven. Calmet et al. [2], using 10 cc Bupivacaine 0.25% in patients with arthroscopic partial meniscectomies, proved Bupivacaine to have a longer analgesic effect compared to saline in a small group of patients. Dal et al. [8] showed 20 cc Bupivacaine 0.5% to be more effective for 24 h in a study comparing Bupivacaine to saline in even smaller groups of 15 patients scheduled for arthroscopy. Both these studies, however, lacked a power analysis. More recent work by Marret et al. [13] could not prove 30 cc Bupivacaine 0.5% to be more effective compared to saline in a, however, power analysis based, small sample sized randomised trial. However, 30 cc Ropivacaine 0.75% was proven to be more effective compared with 30 cc saline or 30 cc Bupivacaine 0.5% with the effect lasting between 2 and 6 h for pain at flexion. These results are confirmed by results of Convery et al. [6] demonstrating 20 cc Ropivacaine 0.75% to be superior to 20 cc Bupivacaine 0.5% in a nonplacebo-controlled trial. An also nonplacebo-controlled study performed under local anaesthesia could not prove 30 cc Ropivacaine 0.5% to be more effective compared with 30 cc Bupivacaine 0.5% [17].

Francesci et al. [9] proved 20 cc Ropivacaine 0.375% to be superior to 20 cc saline as placebo for the first 4 h, but these results cannot be confirmed by Santanen et al. in a study performed under spinal anaesthesia using 20 cc Ropivacaine 0.5% compared to placebo.

These previous results are in concordance with the significant, but relatively small and short-lasting effects of 10 cc Bupivacaine 0.5% and 10 cc Ropivacaine 0.75% compared to saline found in this study. However, we could not confirm 10 cc Ropivacaine 0.75% to be superior to 10 cc Bupivacaine 0.5%.

Both Bupivacaine and Ropivacaine have proven to have systemic concentrations below known toxic levels after intra-articular injection of the knee and should, therefore, be safe to use intra-articularly [12, 14, 17, 22].

Despite this, recent reports have shown chondrotoxic effects of both Bupivacaine 0.5 and 0.25% in vitro as well as in vivo [3–5]. Ropivacaine 0.5% also has chondrotoxic effects, although to a less extend than Bupivacaine 0.5% when tested in vitro [10, 18]. Both substances appear to display a dose dependent effect, making a low dose intra-

articular injection strategy possibly the least harmful [10]. Though the evidence for chondrotoxicity is quite strong, the incidence of chondrolysis following intra-articular administration of Bupivacaine in clinical practice seems to be low or possibly underreported. Most reported cases have been after shoulder arthroscopy in combination with continuous infusion of Bupivacaine [20].

A possible limitation of this study design is our randomisation system. Although no differences in demographics were recorded, a computer-block-randomisation system would have been safer. Another possible limitation is the inclusion of a relative large amount of patients with degenerative changes as this possibly results in higher postoperative pain-scores.

The quite low NRS-scores found in this study are the result of the administration of systemic analgesics. Other methods of improving patient comfort should be explored to reduce potential side effects of these systemic analgesics. Locoregional anaesthesia techniques are explored, but the need for a nerve stimulator, the time needed to apply the nerve block and possibility of a failure of the block (10%) make this technique less appropriate for day care surgery. However, when compared to spinal anaesthesia, locoregional anaesthesia provides better postoperative analgesia [7, 16].

Portal anaesthesia combined with general anaesthesia is another possible alternative. Townshend et al. [21] have shown portal anaesthesia with 20 cc Bupivacaine 0.5% (100 mg) to be as effective as intra-articular anaesthesia with 20 cc Bupivacaine 0.5%. Further research should focus on this simple, low cost and probably safe technique to improve patient comfort.

Considering the possible side effects and the, though significant, relatively small and short lasting improvement in already quite low NRS-scores, the administration of intra-articular Bupivacaine or Ropivacaine should be discouraged in favour of systemic anaesthetic until alternative techniques are available.

Conclusion

The analgesic effects of intra-articular Bupivacaine and Ropivacaine after knee arthroscopy are clinically significant when compared to placebo. However, considering the improvement in patient comfort on one side, but the short duration and small amount of this improvement and the risk of chondrotoxicity on the other side, the administration of intra-articular analgesia with Bupivacaine or Ropivacaine cannot be recommended.

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