Comparison of the effects of intra-articular sole ropivacaine and combined ketorolac and ropivacaine for pain control after knee arthroscopy surgery

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Abstract

Introduction: Effective pain relief is important after arthroscopic knee surgery to permit initiation of daily activities of life. This study is performed in order to investigate the effect of multi-model therapy for pain control after surgery. This clinical, randomized and double-blind trial is conducted on patients who get knee arthroscopy surgery.

Methods: Of these patients, 40 were divided into two groups by Block Randomization method: 1 – sole ropivacaine group (150 mg); 2 – combined ketorolac (30 mg); and ropivacaine (150 mg) group. These drugs were injected intra-articularly at the end of knee arthroscopic surgery. The first consequence including measurement of pain severity after entrance to recovery room and 2, 4, 8, 12, 18 and 24 hours after surgery were evaluated according to the visual analogue pain score. The second consequence, including nausea, vomiting and sedation, was assessed by expert nurses in the recovery room and surgery part according to nausea and vomiting scale and Ramsay sedation scale, respectively.

Results: All groups had excellent analgesia at 0 and 4 hours, postoperatively. Group-combined ketorolac and ropivacaine had significantly lower visual analogue pain score as well as higher sedative scale at 8, 12, 18 and 24 hours after surgery at rest and during movement compared with the other group ($p < 0.05$). Moreover, there was no statistical difference between groups in regard of nausea and vomiting.

Conclusion: Addition of ketorolac to ropivacaine intra-articularly in arthroscopic knee surgery enhances analgesic efficacy of local anaesthetics and cause more sedation after surgery.

Keywords

Ropivacaine, ketorolac, pain, arthroscopic knee surgery, sedation, nausea and vomiting, intra-articular

Introduction

Diagnostic and minor therapeutic knee arthroscopy is a common and novel procedure that has accuracy and efficacy of the management because of sound diagnosis and lower interventions during the surgery.¹ It seems that arthroscopic surgery of the knee is preferred by the majority of properly selected and well-informed patients² that can be performed under general or local anaesthesia.³ It is found that the postoperative stay after knee arthroscopy was significantly shorter in subjects receiving local anaesthesia compared with general anaesthesia, and they recommended local anaesthesia

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for most outpatient knee arthroscopies.⁴ Still, many orthopaedic surgeons are reluctant to use local anaesthesia for fear of having to convert to general anaesthesia because of inadequate pain control.^{4,5} It has been reported that a significant number of patients have moderate to severe pain 24 hours after ambulatory surgery in general and knee arthroscopy in particular,^{2,6} and sometimes, this pain would become worst and affect the sleep and patient's activity level;⁷ this pain may impede early recovery of many patients, thereby increasing the total cost of such procedures.⁸

Intra-articular analgesia is useful in reducing patients' postoperative disability. It anticipates and prevents the onset of pain, and helps avoid the need for additional drugs. Usually it is possible to reach good analgesia in the immediate postoperative period by the administration of analgesic drugs. However, such substances do not always reach the aim because they are not site-specific, and can be burdened by side effects, such as acute gastric lesions. Recently, intra-articular administration of different anaesthetic substances with a local action (e.g. bupivacaine, morphine) has been introduced in clinical practice.^{8,9} The aim of the administration of these substances should not be the reduction of postoperative pain, but its prevention. This kind of analgesia can ease the management of the outpatient who needs complete pain control in a nonhospital setting. To reach this goal, the therapy must be long lasting with rapid onset, easily administered.⁸ In an effort to provide an effective, safe and long-lasting postarthroscopy analgesia, several studies using different drugs and regimes have been published during the last two decades. Intra-articular administration of local anaesthetics has been widely used, but some studies have questioned their efficacy.^{2,8,10}

In the majority of the previous reports, intra-articular postoperative analgesia was provided by the administration of morphine or bupivacaine or both.^{8,9,11} Morphine reduces the excitability of the nociceptive peripheral terminal and inhibits the production of substance P. The action of intra-articular morphine in low doses on peripheral opioid receptors produces significant but delayed postoperative analgesia, starting after 4–6 hours.¹² Bupivacaine is a local anaesthetic that has an exclusive action on peripheral afferents and blocks them. It has an immediate action on pain.¹³ The ideal analgesic drug must cover the whole postoperative period. To provide better pain control of the entire postoperative period (24 hours), these two drugs (i.e. morphine, bupivacaine) and their association have been studied with controversial results.^{14,15}

One of the most important properties of a long-acting local anaesthetic is to reversibly inhibit the nerve impulses, thus causing a prolonged sensory or motor blockade appropriate for anaesthesia in different types

of surgeries.¹⁶ Bupivacaine is a well-established long-acting regional anaesthetic, which like all amide anaesthetics has been associated with cardiotoxicity when used in high concentration.¹⁷ Ropivacaine is a new local amidic anaesthetic that blocks peripheral afferents from acting on voltage-dependent Na channels. It has the same pharmacodynamics as bupivacaine but differs because of its more extended action, due to its greater molecular weight. The chance to use this drug in high concentrations provides higher clinical efficacy^{18,19} and for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles.¹⁷

Although analgesic opioids are used widespread to control moderate and severe postoperative pain, these drugs do not alleviate patient's discomfort and cause side effects which are dose-dependent.^{20,21} Opioid-sparing techniques using different analgesic mechanisms of action and minimizing opioid-related side effects is recognized as an important component strategy for postoperative pain management.²² There are reports that ketorolac as a non-steroidal anti-inflammatory drug (NSAID) is effective in the treatment of mild to severe pain observed after a variety of surgical procedures, showing an analgesic effect similar to that observed with opioid drugs, but of longer duration.^{23,24} Moreover, ketorolac has the advantage over narcotic analgesics in that it does not depress the respiratory and central nervous systems, and hence exhibits a more favourable safety profile.²³ Notwithstanding, ketorolac is not free of side effects. As do other NSAIDs, it can produce gastrointestinal damage, inhibition of platelet aggregation, and impairment of renal function.²⁴

However, studies on intra-articular local anaesthetics and NSAIDs have found opposing results.²⁵ Moiniche et al.²⁶ found that intra-articular local anaesthetics (LA) alone may have only minor effects on postoperative pain relief of short duration (4 hours). NSAIDs such as ketorolac have been shown to provide good postoperative pain relief when administered intra-articularly.²⁷

Multimodal pain therapy (balanced analgesia) is recommended for treatment of postoperative pain.²⁸ The rationale for this therapy is to achieve sufficient analgesia because of additive or synergistic effects between different analgesics, with concomitant reduction of side effects because of lower doses of analgesics used.²⁵ Therefore, a combination of intra-articular ketorolac, morphine and LA given postoperatively may prolong the duration of pain relief and minimize the side effects of each drug.

The goal of this study was to determine whether ropivacaine alone or in combination with ketorolac is superior for pain relief following arthroscopy performed with local anaesthesia.

Methods

The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IRCT2013073014218N1), and all the patients were given prior explanations about the research. All patients who freely agreed to participate in the study signed a free and informed consent statement. In all, 40 patients (American Society of Anesthesiologists I to II) in the age group of 15–60 years scheduled for knee arthroscopy surgery under local anaesthesia in Rasul and Firuzgar Hospital were interviewed between 23 August 2013 and 5 February 2014. Exclusion criteria included the history of using analgesics 24 hours before surgery, the history of bleeding or coagulation problems during the last month before surgery, renal and liver failure, severe cardiopulmonary disease, coagulopathy, morbid obesity (body mass index $> 30 \text{ kg/m}^2$), the history of nausea and vomiting after surgery, the history of migraine, history of anaesthetic complications, known allergy, sensitivity and contraindication about the use of opioid and non-opioid analgesics, pregnancy and lactation, the history of drug and alcohol abuse, being not too satisfied for participating in this study.

According to entrance and exclusion criteria, the patients were selected and their blood pressure and heart rate were determined after connecting non-invasive blood pressure (NIBP) monitoring and pulse-oxygen meter at the operation room. All patients were permitted to eat and drink 8 hours before operation, intravenous access was obtained and the catheter heparinized. The patients were informed about the visual analogue pain score (VAS; 0 = no pain, 10 = worst imaginable pain), and VAS was measured preoperatively at rest and on the movement of the knee to be operated. Thereafter, combination of 0.01 mg/kg of midazolam and 2 µg/kg of fentanyl was used as a pre-medication. Induction of anaesthesia was achieved by 5 mg/kg of thiopental and 0.5 mg/kg of atracurium. Endotracheal intubation was performed and mechanical ventilation was applied. Anaesthesia was maintained by 100 µg/kg of propofol and 0.1 µg/kg of remifentanyl and no other anaesthetic agents were applied during surgery. At conclusion of surgery, muscle relaxant was reversed by neostigmine sulphate 0.05 mg/kg and atropine sulphate 0.02 mg/kg. Then, knee arthroscopic surgery was conducted by orthopaedic surgeons. No other sedatives or analgesics were administered during the procedure.

Computer-generated random numbers were used and inserted into sealed envelopes by a nurse not involved in the study. Inside these envelopes was a number, which informed the nurse of the group to which the patient was allocated. The nurse mixed the drugs according to a protocol and gave two labelled

syringes (total volume 30 mL) to the surgeon at the end of the procedure.

The portals were sealed carefully before the injection of the test drugs and at the end of surgery, one of the following drugs was administered intra-articularly in a double-blind manner via the arthroscope: (1) Group 1 ropivacaine 0.5%, 150 mg (30 mL); (2) Group 2: combination of ropivacaine 0.5% (150 mg) and ketorolac (30 mg) dissolved in saline 0.9% (total volume 30 mL). Neither the surgeon and the anaesthesiologist nor the nurse looking after the patient postoperatively was aware of the randomization sequence.

At the end of the operation, the first consequence, including VAS pain scores at rest and on movement (90° flexion of the knee) after entrance to recovery room and 2, 4, 8, 12, 18 and 24 hours after surgery was recorded. Rescue medication consisted of paracetamol 1 g (maximum three times a day) for all patients when pain was $> \text{VAS } 3$ and if the pain relief was insufficient after 30 minutes, tramadol 50 mg orally (maximum four times a day). The patient was also asked to grade his or her satisfaction with the anaesthesia technique on a 4-point scale (1 = poor, 2 = satisfactory, 3 = good, 4 = excellent), and if he or she would have a similar operation using the same anaesthetic technique. The second consequence, including nausea, vomiting²⁹ and sedation³⁰ was assessed according to nausea and vomiting scale by patient's explaining about his or her symptoms (no nausea and vomiting/nausea/one to two order of nausea and vomiting/nausea and vomiting more than two orders) and Ramsay sedation scale (1 = anxious or restless or both, 2 = cooperative, orientated and tranquil, 3 = responding to commands, 4 = brisk response to stimulus, 5 = sluggish response to stimulus, 6 = no response to stimulus).

Calculation of sample size was based on a minimum difference of 10 mm in the VAS measurement for pain between group means, based on a reported value of minimal clinically important differences in acute pain,³¹ on a standard deviation of 18, with $p = 0.80$ and $\alpha = 0.05$. We obtained a sample size of 18 patients per group. A sample size of 20 patients per group was then chosen to ensure that the calculated number of patients would still be available by the final analysis.³² It should be noted that there was no drop out of patients during this study and the final number of patients was 20 persons.

Statistics

The data at this study were obtained from the information of patients' dossier and their follow up after discharge. Statistical significance was determined using SPSS software version 19 (SPSS Inc, Chicago, IL). All results are presented as mean $\pm$ standard deviation or

median (range) as appropriate. For nonparametric data, the Kruskal–Wallis test was used when appropriate followed by the Mann–Whitney *U* test when a significant difference was found and for parametric data two-way analysis of variance (ANOVA) for multiple comparisons, followed by the post hoc Tukey–Kramer test was used. A significance level of $p < 0.05$ was used in all cases.

Results

Demographics were not different between groups (Table 1). Postoperatively, pain intensity on a VAS 0–10 cm (rest, movement) over the 24 hours is shown in Figures 1 and 2, respectively. All groups had excellent analgesia at 0 and 4 hours, postoperatively. Group ropivacaine and ketorolac (Group 2) had significantly lower pain score at rest and movement compared with group ropivacaine (Group 1) at 8 and 24 hours ($p < 0.05$).

As shown in Table 2, Patients were more satisfied with the analgesia technique in the ropivacaine and ketorolac group compared with the ropivacaine group ($p < 0.05$). Moreover, there were group differences in respect of rescue medication (Table 2), as the number

of tablets taken by the ropivacaine group was more than the ropivacaine and ketorolac group ($p < 0.05$). Table 2 indicates that the first time of patient request for taking analgesics after surgery in the ropivacaine and ketorolac group is longer than that in the ropivacaine group.

Comparing sedative scale between these two groups showed (Figure 3) that there is no difference during the first 8 hours after surgery according to the Ramsay scale, and there is statistical difference between these two groups at 12, 18 and 24 hours after surgery; as in group ropivacaine and ketorolac (Group 2), there is more sedation than group ropivacaine (Group 1; $p < 0.05$).

No significant differences were recorded between the groups with respect to nausea and vomiting (Figure 4).

Discussion

Our findings show that the combination of ropivacaine 150 mg with ketorolac 30 mg injected intra-articularly at the end of arthroscopic knee surgery enhances analgesic efficacy of local anaesthetics without increasing side effects after arthroscopic knee surgery. Moreover, there was more sedation after arthroscopic knee surgery in the group that received combination of ropivacaine and ketorolac.

The presentation of pain after arthroscopic surgery is dependent on the procedure of surgery and it is said that diagnostic arthroscopy produces minor pain and invasive procedures create moderate to severe pain. At the present study, we used minor arthroscopic surgery and found that the severity of pain seems to be slight, as the pain scores according to VAS was up to 3 during the rest after surgery and this is in accordance with Huey-Ping et al.'s²⁵ results. However, pain during movement was moderate to severe in our study, specifically in Group 1

Table 1. Patients demographics and surgical data.

	Ropivacaine group	Ropivacaine + ketorolac group
Age (years)	42.4 ± 12.2	45.05 ± 13.6
Height (cm)	177.9 ± 6.7	171.8 ± 6.9
Weight (kg)	83.35 ± 10.5	76.45 ± 9.08
ASA (I/II)	15.6	19.2
Sex (male/female)	17 versus 3	14 versus 6
Operation time	38.7 ± 9.7	39.45 ± 9.6

ASA: American Society of Anesthesiologists.

Figure 1. Postoperative pain is shown as VAS at rest during the first 24 hours after arthroscopic surgery. Data are presented as means ± SD. *Group ropivacaine and ketorolac versus group ropivacaine ($p < 0.05$). SD: standard deviation; VAS: visual analogue pain score.

Figure 2. Postoperative pain is shown as VAS at movement during the first 24 hours after arthroscopic surgery. Data are presented as means $\pm$ SD. *Group ropivacaine and ketorolac versus group ropivacaine ($p < 0.05$). SD: standard deviation; VAS: visual analogue pain score.

Table 2. Patient satisfaction, first time of analgesic request and analgesic tablets ingestion.

	Ropivacaine group	Ropivacaine + Ketorolac group
Satisfaction grade of patient with the anaesthesia technique	4.5 $\pm$ 0.82	6.35 $\pm$ 0.93*
First time of patient request for taking analgesic after surgery (minute)	309.8 $\pm$ 64.57	635.75 $\pm$ 89.08*
Paracetamol taken: no. of tablets (1 g)	3	1*
Tramadol taken: no. of tablets (50 mg)	2	0*

*Group ropivacaine and ketorolac versus group ropivacaine ($p < 0.05$).

Figure 3. Postoperative sedative scale is shown according to the Ramsay Sedative Scale during the first 24 hours after arthroscopic surgery. Data are presented as means $\pm$ SD. *Group ropivacaine and ketorolac versus group ropivacaine ($p < 0.05$). SD: standard deviation.

Figure 4. Postoperative nausea and vomiting scale is shown according to the Nausea and Vomiting Scale during the first 24 hours after arthroscopic surgery. Data are presented as means $\pm$ SD. *Group ropivacaine and ketorolac versus group ropivacaine ($p < 0.05$).

(group ropivacaine) after 24 hours. Thus, we can say that ropivacaine can cause attenuation of mild pain in the early postoperative period and at rest but is certainly inadequate when used alone during movement. It seems in our study that the efficacy of intra-articular administration of ropivacaine is limited to the first hours after surgery. In this regard, Rautoma et al.¹⁰ showed that 8 hours after arthroscopic knee surgery, there is no difference between patients who received 100 mg ropivacaine intra-articularly and patients who received 200 mg saline intra-articularly. However, Franceschi et al.⁸ found that injection of 75 mg ropivacaine in comparison with injection of 2 mg morphine and saline intra-articularly is more effective for attenuating pain during the first 4 hours after surgery.

NSAIDs have been found to reduce postoperative pain when injected intra-articularly in a number of studies. Both ketorolac and tenoxicam have been used, and most studies have found reduction in VAS pain scores and/or analgesic requirements, postoperatively.²⁵ At this study, we were aimed to use ketorolac in order to reduce the common side effects of narcotics. Moreover, ketorolac has the advantage over narcotic analgesics in that it does not depress the respiratory and central nervous systems, and hence exhibits a more favourable safety profile.³³ Ketorolac has a high affinity with protein; hence, this characteristic causes that the drug exerts from the articular space by delay.³⁴ Moreover, the main effect of ketorolac is to harness the production of prostaglandins.³⁵ It is shown that ropivacaine combined with morphine and ketorolac for pain relief after minor arthroscopic

procedures were found to give a synergistic effect.³⁶ Our present study showed that intra-articular administration of 30 mg ketorolac has the main effect on pain reduction after surgery, so this would confirm the beneficial effects of combining ketorolac and ropivacaine because patients receiving this combination had significantly lower VAS pain scores, specifically on movement up to 24 hours postoperatively compared with ropivacaine alone. So we can state although when administered directly to sites, ketorolac is likely to produce higher local tissue concentrations and to have fewer systemic complications.³⁷

There are different risk factors related to nausea and vomiting after surgery; in this respect, it is said that the type of anaesthesia and the use of narcotics have the main role. There are alternative drugs such as NSAIDs for attenuating the incidence of nausea and vomiting after surgery as compared with opioids.³⁸ In this study, there was no difference about nausea and vomiting between two groups; however, episodes of nausea and vomiting presented at first 4 hours after surgery; it seems ketorolac and ropivacaine are not different with respect to reducing nausea and vomiting after surgery.

Higher sedative score in the group which received ropivacaine and ketorolac simultaneously in comparison with the other group in the present study can be related to the higher plasma concentration of ketorolac during the first 24 hours after surgery. Such sedative effects in relation with ketorolac can reduce the anxiety of surgery and provide better situations after surgery for patient.³⁹

In conclusion, we found that the addition of ketorolac to ropivacaine intra-articularly enhances analgesic efficacy of ropivacaine and cause more sedation after surgery without increasing side effects after arthroscopic knee surgery. Taken together, even relatively minor orthopaedic surgery can be painful (this is supported by the findings presented here) especially pain on movements, better pain management is required. As the use of systemic analgesics is hampered by side effects, local anaesthetic administration is regarded at this study. Even local anaesthetics when given alone are not always sufficient; hence, the combination of these anaesthetics with ketorolac can reduce pain and avoid systemic side effects. Pain reduction with this approach is achieved in this study; however, at the cost of increased sedation. The letter indicated that there might be an element of systemic absorption. However, if and to what extent this is the case would need to be addressed in future research where plasma levels of applied medications might be analysed and after this we would advocate adding ketorolac to ropivacaine for arthroscopies.

Shortcomings of the present study were small sample size, no information about analgesic use during entire hospital stay, plasma levels of locally applied medications and the results must be interpreted with these in mind.

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