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Evaluation and comparison of intra-articular Ropivacaine, Clonidine and Fentanyl on postoperative analgesia following arthroscopic knee surgery

Kavita Udaykumar Adate[1,*], Kalyani Nilesh Patil[2], Prashant Vilas Bhandari[3]

[1]Associate Professor, [2]Assistant Professor, Dept. of Anaesthesiology, [3]Assistant Professor, Dept. of Orthopedics, Smt. Kashibai Navale Medical College & General Hospital, Pune, Maharashtra

***Corresponding Author:**
Email: kadate@rediffmail.com

Abstract

Background and Aims: Arthroscopic knee surgery is the commonest orthopaedic day care procedure. It is associated with variable amount of pain. Various drugs and routes have been tried till date for the postoperative analgesia. The aim of our study is to evaluate and compare the efficacy as well as safety of intra-articular (IA) Ropivacaine, Clonidine and Fentanyl on postoperative analgesia following arthroscopic surgery on the knee.

Methods: In this prospective, double blind study, 75 patients were enrolled. Therapeutic knee arthroscopy was performed under spinal anaesthesia. At the end of procedure patients were randomly assigned into one of the three groups to receive intra-articular study drug. Group C (n=25) received injection clonidine 1µg/kg in 20 ml normal saline, Group F (n=25) received injection fentanyl 1µg/kg in 20 ml normal saline and Group R (n=25) received 0.2% ropivacaine 20ml. Analgesic efficacy of IA study drug was measured by the pain intensity quantified using VAS score at the 2nd, 4th, 6th, 8th, 12th and 24th hour after spinal anaesthesia. Intramuscular injection diclofenac sodium 75 mg was given as rescue analgesic if the VAS≥4. Time of first rescue analgesia and total rescue analgesics consumption in first 24 hrs in postoperative period were calculated.

Result: Postoperative VAS scores were significantly lower in group R. Time to first analgesic requirement was significantly greater in Group R (20±2.82) than in Group C (6.96±1.94) and Group F(10.32±2.21)hours, p□0.001. Also, the total dose of analgesic used in Group R (0.08±0.27) was significantly lower compared to study population in Group C (1.96±0.61) and Group F (1.44±0.5), p□0.001.

Conclusion: In comparison with intraarticular fentanyl and clonidine, 0.2% ropivacaine improves the quality and prolongs duration of postoperative analgesia in arthroscopic knee surgery under spinal anaesthesia, without any complications.

Keywords: Arthroscopy, Clonidine, Fentanyl, Intraarticular, Postoperative, Ropivacaine.

Introduction

Arthroscopic knee surgery is the commonest day care procedure. It however causes significant amount of post-operative pain which may delay the rehabilitation and discharge. Various drugs have been tried till now, by different routes, for post-operative analgesia. However none is free from limitations. In previous studies several drugs for e.g. Local anaesthetics, opioids, α2 agonists, ketorolac, magnesium sulphate and dexamethasone were used intra-articularly (IA) to provide postoperative analgesia following knee arthroscopy either as a sole agent or in combinations.[1-6] Due to slower rate of systemic absorption through a relatively avascular surface, intra-articularly administered drugs provide prolonged local analgesia and exhibit less systemic side effects.

Ropivacaine is the s-enantiomer amino-amide local anaesthetic. It blocks the peripheral afferents acting on voltage dependent Na+ channels. It has a lower potential for systemic toxicity as compared to buivacaine. It also has differential blocking effect on motor and sensory nerve fibres.[7,8]

Clonidine is a α2-adrenergic agonist, with peripheral analgesic effects due to facilitation of C-fibre blockade. IA clonidine has been shown to provide effective postoperative analgesia following knee arthroscopy.[9]

Fentanyl is the synthetic opioid, used commonly now a days. IA fentanyl elicits analgesia by acting on peripheral opioid receptors. IA fentanyl has been shown to be more effective than IA morphine.[10,11]

The ideal analgesic agent should be active upon cessation of surgery, should provide prolonged pain relief without associated motor blockade, be easy to administer, should allow pain-free physiotherapy and be without serious side-effects.[1]

In view of finding out the ideal IA agent for post-operative analgesia after knee arthroscopy, we have designed this prospective randomized double blind study. We hypothesized that a more painful arthroscopic surgical procedure could have elicited a difference in analgesic efficacy between clonidine, fentanyl and ropivacaine. Primary aim of our study is to assess and compare the analgesic efficacy of IA clonidine, fentanyl and ropivacaine following knee arthroscopy surgery. The secondary aim is to assess their side effect profile.

Methods

After obtaining clearance from institutional ethical committee and written informed consent from each patient, 75 patients were included in the study. Sample size was estimated using dose of rescue analgesic required in 24 hours. At 5% level of significance and

80% power the computed sample size was 24 in each group. So we included 25 patients in each group.

Patients of either sex, aged between 18-60 years, of physical status ASA I or II scheduled for therapeutic knee arthroscopy procedure under spinal anaesthesia were included in the study. Surgeries included were synovectomy, ligament reconstruction, and articular cartilage procedure. Patient with ASA status III or more, those having spinal deformity or any contraindication to regional anaesthesia, allergy to local anaesthetics, pregnancy, lactation, and psychiatric illness were excluded from the study.

Our study was designed in a prospective, randomized and double blind manner. During pre-operative visit, history, clinical examination and investigations were noted. Patient were also taught to interpret visual analog scale (VAS) (graded from 0 = no pain to 10=maximum pain) for post-operative pain assessment.

All the patients received tablet diazepam 10 mg orally the night before surgery. In the operation room standard intraoperative monitors like ECG, pulse oximeter, NIBP were attached and baseline parameters were recorded. A wide bore intravenous line was secured and patients were prehydrated with 500 ml ringer lactate solution.

The anaesthesia technique was standardized for all patients. Subarachnoid block was given in L3-L4 intervertebral space by midline approach with 26 Gauge Whitacre needle 0.5% hyperbaric bupivacaine 3ml (15 mg) was given in the subarachnoid space and then patient placed in supine position immediately. After confirming adequate level of sensory blockade (T10), arthroscopic procedure was allowed to start. During procedure if any patient required further dose of analgesia that patient was excluded from the study. All the surgeries were performed by the same orthopedic surgeon. At the end of the surgery, the participants were administered intra-articular study drug assigned as per computer generated randomization.

Group C- Clonidine 1µg/kg diluted to 20 ml normal saline.

Group F- Fentanyl 1µg/kg diluted to 20 ml normal saline.

Group R- 0.2% Ropivacaine 20ml.

At the end of the surgery, the study drug was administered through the port site in the intra-articular space by the surgeon who was unaware of the medication type used. Tourniquet was kept inflated for another 20 minutes. The drain was clamped from before administration of the study drug till 20 minutes after the drug administration.

Post-operatively HR, MAP, pain by VAS and sedation score (Ramsay sedation scale) were recorded at 2nd, 4th, 6th, 8th and 24th hour after spinal block. Scoring was done by the anaesthesia resident (an observer) blinded to patient group assignment (the patient was also unaware of the injected IA drug). Injection diclofenac sodium 75 mg (3ml), intramuscularly was given as a rescue analgesics if the pain VAS ≥4. First post-operative analgesia request time from the spinal block was recorded as duration of analgesia. And total diclofenac sodium consumption in first 24 hrs was also recorded. Vitals were monitored peri-operatively. Decrease in mean arterial pressure 25% from baseline was defined as hypotension and was treated with intravenous fluid and ephedrine. While decrease in mean heart rate 45 beats/ min was defined as bradycardia and treated with atropine.

The occurrence of side effects such as nausea, vomiting, pruritis, cardiac or respiratory depression, sedation and urinary retention were recorded.

Patients were also followed up for next six month by orthopedic surgeon (co-investigator) for any local complaints or limitations to joint movement.

Statistical analysis: Raw data were entered into a MS Excel spreadsheet and analysed using statistical software Epi-Info version 7.2 (CDC Atlant). Discrete variables were analysed using the Pearson's Chi Square test. Normally distributed continuous variables were analysed using the one-way ANOVA followed by post hoc analysis with Barlett's Chi Square test and Kruskal Wallis Test. p value 0.05 was considered statistically significant.

Result

Seventy five patients (25 in each group) were enrolled in this study. None was excluded. Demographic parameters such as mean age, weight of the patients, duration of surgery and tourniquet time were comparable among three study groups[Table 1].

Table 1: Patient demographic and surgical data

Parameter	Group C Mean ±SD (n=25)	Group F Mean ±SD (n=25)	Group R Mean ±SD (n=25)	P value
Age (years)	34.44±7.46	31.36±9.60	32.56±8.44	0.44
Sex (M/F)	14/11	14/11	11/14	0.61
Weight(kg)	60.52±5.62	62.88±7.46	62.8±8.53	0.43
Duration of Surgery (min)	89.0±11.06	89.66±11.33	94.52±12.04	0.18

Tourniquet Duration (min)	111.48±10.33	112.40±10.96	116.8±11.95	0.2

The type of therapeutic arthroscopic procedures performed in all three groups were comparable. The anterior cruciate ligament reconstruction being performed in 13, 12 and 13 patients and meniscectomy was performed in 12, 13, and 12 patients in group C, F and R respectively.

There were no significant difference among three study groups in peri-operative mean HR and mean MAP[Fig. 1 and 2].

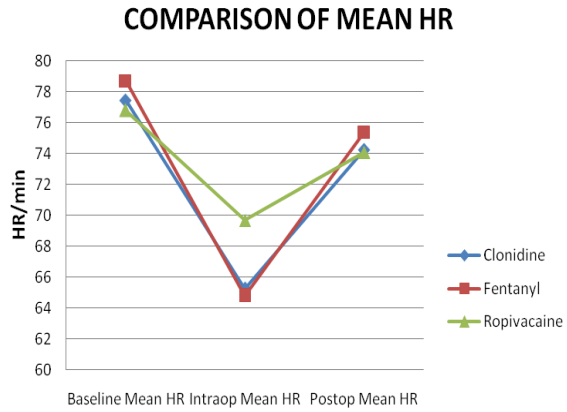

Fig. 1: Comparison of Mean HR/min between three groups

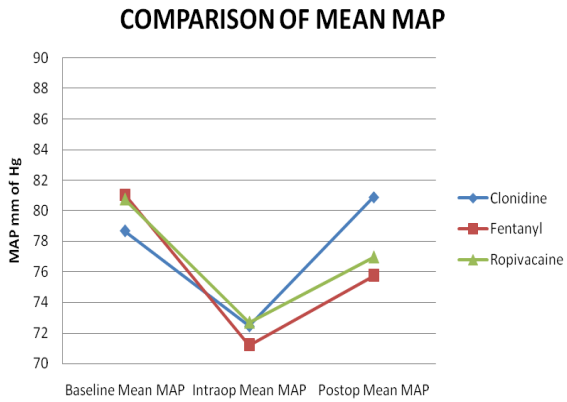

Fig. 2: Comparison of Mean MAP (mm Hg) between three groups

The mean post-operative sedation, as assessed by Ramsay Sedation Score was also comparable among the three groups.(p 0.45) [Fig. 3].

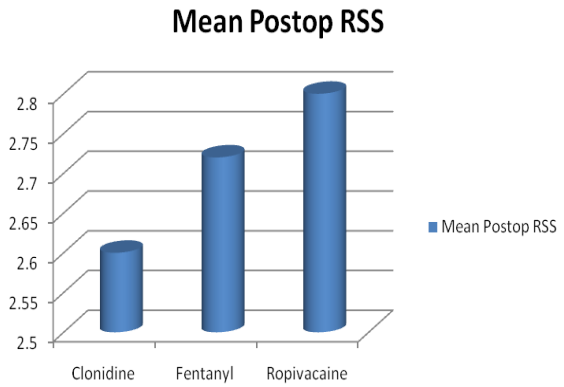

Fig. 3: Comparison of mean RSS among three groups

VAS score of 0 in all the groups at 2nd postoperative hour was due to residual effect of spinal anaesthesia (p 0.37). Fig. 4 shows the difference between VAS score in three study groups at 2nd, 4th, 6th, 8th, 12th and 24th post-operative hour. VAS was significantly lower in Group R compared with Group F and Group C from 4th hour onwards (p 0.00).

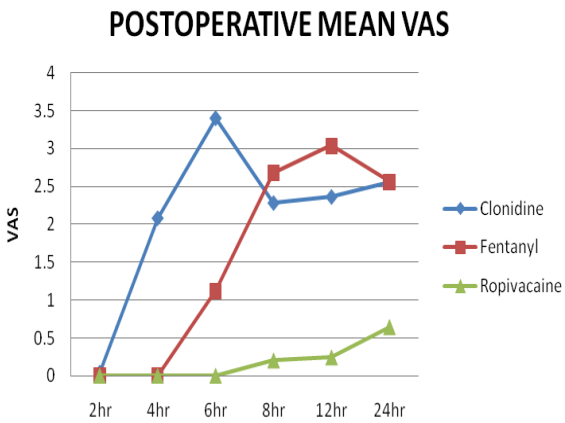

Fig. 4: Trends in post-operative visual analogue scale

Duration of analgesia after IA study drug injection was significantly higher in Group R compared to Group C and Group F (Fig. 5). Patients in Group C and Group F required significantly more rescue analgesic in first 24 hours, as compared to Group R [Table 2] (p 0.00). Only 2 patients in Group R required rescue analgesia while all the patients in Group C and Group F required rescue analgesia in first 24 hrs.

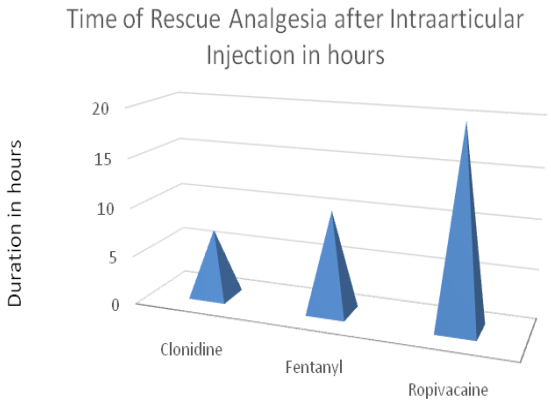

Fig. 5: Comparison of duration of analgesia among three study groups

Table 2: Comparison of post-op analgesia parameters among study groups

Parameter	GroupC (n=25)	GroupF (n=25)	GroupR (n=25)	P value
No. of patients required Rescue Analgesia	25	25	2	0.00
The first analgesic requirement time (Hrs) (mean±SD)	6.96±1.94	10.32±2.21	20±2.82	0.00
Total No. of rescue analgesics required in 24 hours(mean±SD)	1.96±0.61	1.44±0.5	0.08±0.27	0.00

There were no adverse effects (nausea, vomiting, itching, sedation or urinary retention) among the study population.

Discussion

Fast rehabilitation after arthroscopic knee surgery requires the use of effective methods for postoperative pain control. To reduce pain after arthroscopy, we compared individual intra-articular administration of ropivacaine, fentanyl or clonidine. Our result shows that 0.2% IA ropivacaine provides significantly prolonged and superior postoperative analgesia (20±2.82 hrs) than IA clonidine (6.96±1.94 hrs) and IA fentanyl(10.32±2.21 hrs).

Ropivacaine is a commonly used local anaesthetic agent and it is related structurally to bupivacaine and mepivacaine. It is less lipid soluble than bupivacaine but its pharmacokinetic disposition is similar. Ropivacaine seemed to provide similar and effective post arthroscopy analgesia compared to bupivacaine, showing less CNS and cardiac toxicity. Samoldas et. al. proposed that intra -articular ropivacaine is effective to reduce postoperative pain and requirement of systemic analgesics.[12] MB Manuar et. al. In their study used 10 ml of 0.75% IA ropivacaine and shows superior analgesic efficacy when compared to IA fentanyl and dexmedetomidine following arthroscopic knee surgery.[1] In our study we used 20 ml of 0.2% IA ropivacaine and found that duration of analgesia is prolonged than IA clonidine (1ug/kg) and fentanyl (1ug/kg). Thus with the low concentration of ropivacaine we have achieved the desired result.

Fentanyl is a synthetic opioid, which acts on peripheral opioid receptors to elicit its analgesic efficacy. P. Mandal et al. compared two different doses of IA fentanyl (25 ug and 50 ug) with a placebo. They found that 50ug is the minimum effective dose to achieve a totally pain free period of 24 hrs and more.[11] In our study we used IA fentanyl 1ug/kg and found that mean duration of analgesia is 10.32±2.21 hrs. Majority of cases included in the P. Mandal study are diagnostic while the patients included in our surgery have undergone therapeutic arthroscopic knee procedure. In a study conducted by MB Manuar et al, with 50ug IA fentanyl, total doses of rescue analgesia required in first 24 hrs in postoperative period were 1.75±0.4 which is similar to the requirement in Group F in the present study (1.44±0.5).[1]

Clonidine is an α2 adrenergic agonist mediates its analgesic effect through supraspinal, spinal and peripheral action. It acts on presynaptic α2 adrenergic receptors and inhibits the release of norepinephrine at peripheral afferent nociceptors. It elicits local anaesthetic effect by inhibiting the conduction of nerve signals through C and A δ fibers and release of encephalin like substance at peripheral site.[9] In a meta-analysis of seven RCTs, Rao Sun et al. concluded that IA clonidine reduced the pain intensity for the first 4hr after surgery, reduced the consumption of rescue analgesics and the incidence of postoperative nausea, but increased the risk of hypotension after surgery. Out

of seven RCTs, six studies have used 150ug IA clonidine while only one has used 1ug/kg IA clonidine.[13] In our study, the mean duration of analgesia calculated is 6.96±1.94hrs. None of the patient had postoperative bradycardia, hypotension or sedation. This could be attributed to the lower dose of IA clonidine (1ug/kg) used in our study.

In a study done by Reuben SS et al, there was no significant difference in analgesic consumption between groups, when one received IA bupivacaine with clonidine 1ug/kg and other received IA clonidine 1ug/kg alone.[14]

We used 20 ml volume of study drug which was same that was used in previous studies. Volume of injected drug increases the intraarticular pressure. Excessive pressure may promote the systemic absorption of the drug once the tourniquet is released.[15]

Tourniquet was kept inflated and drain was also clamped for 20 mins after administration of study drug. It helps to increase the duration of action of study drug at the local site and also delays systemic absorption of the drug from the joint.[16]

The study by Brew et al, showed that bupivacaine, ropivacaine and mepivacaine have toxic effect on cartilage tissue, which directly correlate to the time, concentration and methods of drug administration.[17] We, in our present study, have avoided use of IA drug combinations, so as to avoid any additive toxic effect on the cartilages, as there is limited data available on drug combinations. None of the patient from study population has reported functional limitation of knee movement in next six month after arthroscopic procedure. This concludes the safety of IA study drugs clonidine fentanyl and ropivacaine.

As per the institutional protocols the surgery was performed under subarchnoid block which may be a confounding factor in postoperative pain relief and complications like urinary retention.

Main limitation of the study is limited number of participants, uni-centeric results, lack of laboratory data to measure the plasma concentration and limiting the study to otherwise healthy patient who are more resistant to adverse effect. Multicenteric studies with large number of patients are required so that this regime may be promoted as an important component of multimodal approach of postoperative analgesia.

An important achievement of our study is that all the patients were monitored for next six months and none of them had any local tissue damage in intra-articular space due to study drugs.

To date only limited numbers of studies have evaluated the analgesic effect of IA drug alone in knee arthroscopy. Our study nonetheless has clinically significant results.

Conclusion

0.2% IA ropivacaine is an ideal drug for postoperative analgesia after therapeutic knee arthroscopy. It prolongs the duration of analgesia and also reduces the postoperative analgesic requirement without any complications.

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