Original Article

Comparison of intra-articular analgesics in arthroscopic anterior cruciate ligament reconstruction surgeries: A randomized controlled trial

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Abstract

Background and Aims: Arthroscopic anterior cruciate ligament reconstruction (ACLR) is one of the most common knee surgeries done worldwide today. It involves immense pain at sites of graft harvest, tibial, and femoral tunnels, thereby delaying recovery and increased patient morbidity, and delayed rehabilitation. Various drugs and combination of drugs administered intra-articularly have been studied for analgesic efficacy. Our study gives an insight if there is any added advantage of additives morphine or clonidine to bupivacaine when compared to administering bupivacaine alone.

Material and Methods: After obtaining the Institute Ethics Committee approval, ninety American Society of Anesthesiology I-II patients undergoing arthroscopic ACLR under spinal anesthesia were randomly assigned to one of three groups (Group B – bupivacaine alone 0.25%, Group BM – bupivacaine 0.25% with morphine 5 mg, Group BC – bupivacaine 0.25% with clonidine 150 mcg). At the end of procedure, 20 mL of the respective drug was administered intra-articularly and postoperative time duration to rescue analgesia, 24 h analgesic requirement, visual analog scale (VAS) score findings at rest and on movement were observed.

Results: The mean duration of time to request for first rescue analgesia in minutes was significantly longer in Group BC 341.55 (103.66 SD) with $P < 0.001$. The VAS scores at that time point were least in Group BM 6.1 (1.7 SD), but not statistically significant. The 24 h analgesic consumption was least in Group B 2.24 (0.79 SD), but not statistically significant.

Conclusion: Combination of bupivacaine and clonidine administered intra-articularly provided a longer duration of analgesia though the quality of analgesia was comparable between the three groups.

Keywords: Arthroscopic anterior cruciate ligament reconstruction, bupivacaine, clonidine, intra-articular analgesics, morphine

Introduction

Anterior cruciate ligament (ACL) injury, which is common in young individuals and athletes, has a very poor healing capacity by means of primary repair, with a failure rate of about 40%–100%. Arthroscopic ACL reconstruction (ACLR) is the gold standard for ACL injuries, decreasing the occurrence of posttraumatic osteoarthritis, and restoring joint stability.[1] It is one of the most frequently injured ligaments of the knee. Free nerve endings present intra-articularly are capable of sensing painful stimuli and produce very severe pain, delaying rehabilitation, and early return to work. Pain is the primary cause of such a delayed rehabilitation leading to delayed strength recovery, prolonged knee stiffness, and anterior knee pain.[2] Arthroscopic ACLR has evolved as a day care procedure over a period.

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Hence, diligent planning of postprocedural pain management protocol in arthroscopic ACLR is one of the emphasizing prerogatives for early recovery and lesser morbidity, thereby not only decreasing the overall hospital resources and improved patient satisfaction but also early return to routine activity.

The hamstring tendon graft for ACLR is associated with immense perioperative pain at sites of graft harvest (medial aspect of tibia) and also due to tibial and femoral tunneling for graft placement. An intra-articular analgesic injection should effectively diminish these responses, due to effect on the pain receptors present intra-articularly. Intra-articular analgesia administration under spinal anesthesia may be more beneficial than under general anesthesia as it prevents establishment of central sensitization and thereby prevents amplification of postoperative pain.[2]

Various studies have been done previously to study analgesic efficacy of intra-articular local anesthetics,[3] morphine,[4,5] clonidine,[6,7] dexmedetomidine,[8,9] etc., with varying results.

We had hypothesized that the addition of morphine or clonidine to bupivacaine would have an added analgesic benefit in terms of duration and quality of analgesia as compared to administration of bupivacaine alone.

Material and Methods

After obtaining Institute Ethics Committee approval, and written informed consent from patients, 93 American Society of Anesthesiology I-II patients between 21 and 60 years undergoing arthroscopic ACL tear reconstruction under spinal anesthesia, were included in a prospective double-blinded randomized-controlled trial. Patients who were allergic to any of the drugs used had been excluded from the study.

Randomization was done as per a computer-generated random number and a sealed-envelope technique was used for allocating each one of them to one of three groups to either receive an intra-articular volume of 20 mL of bupivacaine alone 0.25% (Group B) or bupivacaine 0.25% with morphine 5 mg (Group BM) or bupivacaine 0.25% with clonidine 150 mcg (Group BC) at the end of surgery through the existing anterolateral arthroscopy port just before skin closure.

During the preanesthetic workup, the patient was instructed for usage of visual analog scale (VAS) for postoperative self-assessment of pain. The patient was blinded to the group allotment. A single surgeon had performed all the surgeries so as to standardize the surgical procedure as well as to minimize variability in tissue handling. All patients received spinal anesthetic as per standard institute protocols. After attaching the standard monitors – electrocardiogram, noninvasive blood pressure monitor, and pulse oximetry, all the patients were preloaded with 10 mL/kg of crystalloid and then administered 3 mL of spinal anesthetic bupivacaine 0.5% heavy under strict aseptic precautions in lateral position. Tourniquet was applied after 10 min after achieving the level of about T10 at a pressure of 100 mmHg above systolic blood pressure. The patients then underwent arthroscopic ipsilateral quadruple hamstring tendon graft reconstruction (semitendinosus and gracilis double-folded) using endobutton (Smith and Nephew) for femoral fixation and bioabsorbable interference screw (Smith and Nephew) for tibial graft fixation using standard two portal single incision technique.

At the end of the procedure, a single person (to remove performer bias) who was blinded to the group distribution, administered the three drug combinations using preloaded unlabelled syringes (drug prepared by another person) intra-articularly under strict aseptic precautions through the anterolateral port site itself just before skin closure, by means of a 23-gauge Quincke spinal needle. After 10 min, tourniquet was gradually deflated. Compression bandage was applied along with an additional crepe bandage on top of it. Knee was immobilized with the help of a knee brace.

In the postanesthesia care unit, with standard monitoring in place, a single observer (to remove observer bias), blinded to the group to which the patient belongs, made the observations. The time to first request for analgesic (T-rescue) was noted down (in minutes from the time of administration of study drug) along with the VAS findings (VAS T-rescue) at that time point, at which point the patient was administered injection tramadol 1 mg/kg slow intravenously over 5 min and analgesia continued with injection tramadol 50 mg intramuscularly thrice daily as well as SOS for 24 h from the time of study drug administration. Tourniquet pressure and duration were noted. The demographic parameters, duration of surgery, sensory level at the end of surgery, and total dose of tramadol administered in 24 h were noted. The pain intensity was monitored using VAS (0 = no pain and 10 = worst possible pain) at rest and with straight leg raise at various time points postoperatively at 2, 4, 6, 12, and 24 h. Any side effects such as nausea, vomiting, sedation, pruritus, or urinary retention if present was also noted and treated accordingly. Hemodynamic parameters – blood pressure, heart rate, pulse oximetry saturation, and respiratory rate of the patient were noted down periodically every 15 min for 2 h postoperatively.

We had calculated the sample size based on a pilot study done earlier in our hospital. We had calculated that 30 per group would be sufficient to achieve a power of 80% ($\alpha = 0.05$ and $\beta = 0.2$) for a 40% difference in time to rescue analgesia which would be clinically significant. We had elected to recruit 31 per group to compensate for any data loss.

Statistics

Statistical analysis was done by Statistical Package for the Social Sciences 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY:IBM Corp.). The time to rescue analgesia, the 24 h analgesic requirement, and the VAS at various time points at rest and on movement between groups were analyzed using ANOVA. Data are presented as mean ± standard deviation. A $P < 0.05$ was considered as statistically significant.

Results

Ninety out of 93 patients who have entered randomization have completed the study.

All the three groups were comparable in age, weight, and height [Table 1].

There were more male patients ($n = 76$) as compared to females ($n = 14$). There was no difference among the groups in terms of tourniquet duration, tourniquet pressure, duration of surgery, and level of spinal block endoperatively [Table 2].

The mean duration of analgesia was longest in Group BC 341.6 ± 103.7 min ($P < 0.001$) and the 24 h analgesic consumption was least in Group B 2.2 ± 0.8 mg/kg, but not statistically significant. VAS at the time to rescue analgesic was least in Group BM (6.1 ± 1.7), but not statistically significant [Table 3].

There was no significant difference between the groups in terms of VAS at rest and VAS on movement – straight leg raise [Figures 1 and 2]. There was no difference in hemodynamic parameters among the three groups. Postoperative nausea and vomiting (PONV) was present equally in all three groups [Figure 3]. No other side effects were observed in all three groups.

Table 1: Demographic Data

Variable	Group B	Group BM	Group BC	*P*
Age (mean±SD)	30.8±8.7	31.8±8.1	29.6±8.2	0.596
Weight (mean±SD)	68.8±13.2	68.9±12.7	71.7±15.7	0.66
Height (mean±SD)	164.5±7.0	164.5±7.0	168.3±11.0	0.14
Gender (%)				
Male	25 (83.3)	27 (87.1)	24 (82.8)	0.660
Female	5 (16)	4 (12.9)	5 (17.2)	

SD = Standard deviation

Discussion

The aim of this study was to determine which group of analgesic administered intra-articularly would provide a longer duration and a better quality of analgesia in patients undergoing arthroscopic ACLR under spinal anesthesia. Pain in arthroscopic surgeries is mainly explained by surgical tissue handling and resection causing irritation of free nerve endings in the synovial tissue, joint capsule, and anterior pad of fat.[10]

Intra-articular administration of bupivacaine, with or without additives such as morphine,[4,5] clonidine,[6,7] tramadol,[11] and dexmedetomidine[8,9] has proven to have better analgesia as compared to placebo. Hence, our study was designed to find out the additive effect of drugs added to bupivacaine. Femoral nerve block given alone too does not cover the donor site of the hamstring tendons as covered by local infiltration analgesia.[12] In a study investigating the anatomical spread of injectate by local infiltration, it has been found that the solution was concentrated in the popliteal fossa, anterior aspect of femur, and the subcutaneous tissue of the anterior aspect of the knee, which probably explains the analgesic efficacy of this method.[13]

In our study, we have observed a significantly longer duration of analgesia in the bupivacaine with clonidine group similar to other authors.[6,7] Clonidine is an α-2 adrenergic agonist and has local anesthetic effects and selectively blocks the neurotransmission in peripheral sensory Aδ and C fibers, apart from prolonging the duration of local anesthetics.[2] It also helps release endogenous encephalin-like substances, leading to peripheral analgesia.[14] Analgesic effectiveness of clonidine administered intra-articularly is explained by the activation of descending noradrenergic pathway to release acetylcholine in central pain pathways.[15] It prolongs the duration of action of local anesthetics and it may release encephalin-like substances resulting in peripheral analgesia.[2] Sahni *et al.*,[6] in their comparison of different routes of administration of clonidine

Table 2: Confounding Factors

Variables	Mean±SD			*P*
	Group B	Group BM	Group BC	
Tourniquet duration (min)	95.5±17.5	97.6±16.9	93.1±17.5	0.581
Tourniquet pressure (mmHg)	330±30.4	327.4±25.3	322.6±34.7	0.636
Duration of surgery (min)	98.2±22.2	99.0±19.7	94.2±17.5	0.612
Level of spinal block endoperatively	9.6±1.4	10.1±1.6	9.9±1.7	0.404

SD = Standard deviation

Table 3: Primary Obectives

Variables	Mean±SD			*P*
	Group B	Group BM	Group BC	
Time to first request for analgesic (min) (T-rescue)	190.2±72.6	273.4±100.8	341.6±103.7	<0.001
VAS at T-rescue (VAS T-rescue)	6.4±1.5	6.1±1.7	6.7±1.5	0.298
24 h tramadol requirement (mg/kg)	2.2±0.8	2.6±0.8	2.3±0.8	0.209

SD = Standard deviation, VAS = Visual analog scale

in combination with bupivacaine following ACL repair, have found that it was most effective when given in femoral-sciatic nerve block (FSNB) with least pain scores, longer duration, and least analgesic requirement. This may have been due to the intra-articular group receiving lesser dosage of clonidine 1 mcg/kg as compared to their FSNB group who received 2 mcg/kg as well as the absence of preemptive analgesic effect in the intra-articular group as it is given at the end of surgery.

Tran *et al.*[7] in their study have found that clonidine as 2 mcg/kg additive to bupivacaine through the FSNB provided better analgesia with fewer side effects as compared to intra-articular bupivacaine with clonidine 1 mcg/kg and morphine in pediatric ACLR, which once again shows the preemptive analgesic effect when given in a FSNB.

Danieli *et al.*[4] in his study comparing intra-articular saline, bupivacaine, and bupivacaine with morphine after video arthroscopy-assisted ACLR under spinal anesthesia have noted significantly lower VAS values in the bupivacaine and morphine group, with well-controlled pain in the other two groups too, with a greater usage of rescue analgesics in the saline group. These findings were similar to our study though not statistically significant. They have come to a conclusion that this may be due to the preemptive analgesia effect of spinal anesthesia. They suggest that intra-articular usage of these drugs is not useful enough to use regularly despite obtaining a statistically significant analgesia difference between the groups. However, probably their thorough coverage of postoperative analgesia with a multimodal analgesia regimen over and above spinal anesthesia along with only 1 mg morphine added would have lead them to such a conclusion. Their observation of a well-controlled pain in the saline group with larger rescue analgesics probably reiterates the same logic.

Yari *et al.*[5] compared the various doses of intra-articular morphine for analgesia after arthroscopic knee surgery and found that 15 mg morphine group provided a better analgesia as compared to other doses. Drosos *et al.*[16] compared 5 with 15 mg intra-articular morphine in arthroscopic knee surgery and have concluded no additional benefit of adding the morphine dose more than 5 mg. Arti and Mehdinasab[17] had also studied intra-articular effects of various opioids and concluded the efficacy of 5 mg morphine added to local anesthetic after arthroscopic ACLR under general anesthesia. We have also used 5 mg morphine in our study for obtaining a meaningful difference between the groups.

Morphine acts through mu receptors located inside joints mainly but may also release endogenous opioids which in turn influence delta and kappa receptors. In an immunohistochemical analysis of inflamed synovial tissue, it was observed that opioid receptors – mu, delta, and kappa are present in its peripheral nerve endings, which mediate peripheral antinociception.[2] In inflamed tissue, the disruption of perineurium allows better access to neuronal receptors as well as inactive opioid receptors may become active by inflammation.[18] Morphine acts in two prongs. Analgesic effect reduces the excitability of nociceptive input terminal of C-fiber neurons, thereby decreasing the central processing of pain. Anti-inflammatory effect inhibits the pro-inflammatory neuropeptides such as substance P. Morphine's peripheral analgesic effect can be blocked by intra-articular naloxone. The decreased passage into the blood stream of a poorly lipid-soluble morphine across synovial membrane may increase the duration of drug stay intra-articularly.[19]

In their comparison of intra-articular opioids after arthroscopic ACLR under general anesthesia, Hosseini *et al.*[11] have found that intra-articular morphine-bupivacaine combination provides better analgesia as compared to tramadol-bupivacaine. In our study too, the VAS at the T-rescue time point was least, but not significant in Group BM, probably hinting at the early analgesic quality of morphine.

Iqbal *et al.*[20] compared intra-articular administration of morphine 5 mg or clonidine 150 mcg added to normal saline with that of normal saline in arthroscopic ACLR. They have concluded that clonidine as an additive gives a prolonged duration of analgesia as compared to morphine, which was similar to our findings.

In our study, we had observed that the 24 h analgesic consumption, which indicates the quality of analgesia was least, but not statistically significant in Group B. There are various studies in literature with varying results of analgesic effect of intra-articular bupivacaine probably due to interference with other analgesic usage, varying concentrations, and tourniquet

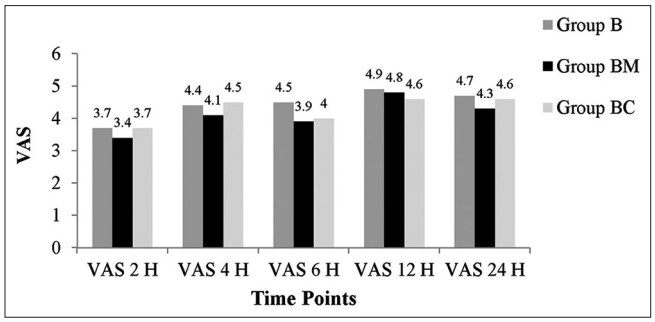

Figure 1: Visual analog scale at rest between groups at various time points over 24 h

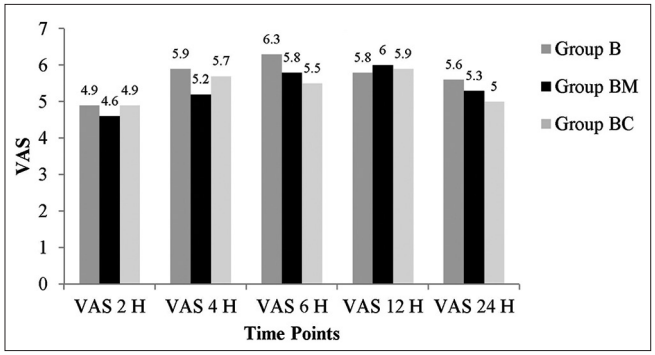

Figure 2: Visual analog scale on movement (straight leg raise) between groups at various time points over 24 h

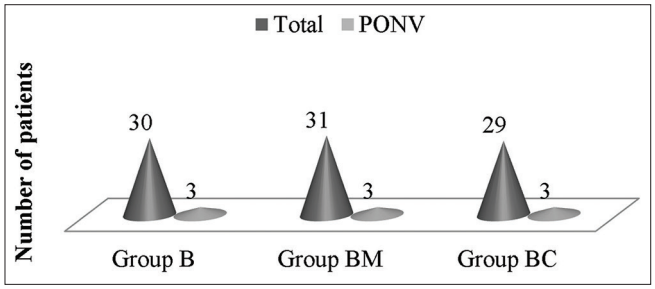

Figure 3: Postoperative nausea and vomiting incidence among groups

factors.[2] Nevertheless, its analgesic efficacy through the intra-articular route has long been proven when compared to placebo.[21] In a systematic review and meta-analysis done by Qi-Bin Sun,[3] single administration of intra-articular bupivacaine was found to be effective in terms of postoperative analgesia.

In terms of PONV, we had observed no significant difference in the three groups. This could have been probably due to a comparable level of 24 h analgesic consumption in all three groups.

We had compared the postoperative analgesia, not in total, but as dose per kg body weight, so as to accurately calculate the requirement even though the groups ultimately did not statistically differ in terms of weight. We preferred to use injection tramadol as the sole drug for postoperative analgesia round-the-clock, so as to avoid multiple drugs and thereby reducing confounding factors. The 24 h analgesic requirement too which denotes the quality of analgesia could be easily calculated if a sole drug is used. Tramadol is widely available in our setup, inexpensive, provides good analgesic effect with minimal side effects.

The other presumably confounding variables such as duration of surgery, spinal anesthesia dermatome level at the end of surgery, tourniquet pressures, and tourniquet duration have all been comparable between the three groups in our study, suggesting that the outcome was less influenced by all these factors.

Tourniquet pressures and duration have been found to have an effect on the perioperative pain. Tourniquet release time was kept uniform in all three groups, so that the drug binding time to intra-articular receptors could be uniform. Contradictory results have been reported in literature[22,23] regarding effect of tourniquet release time on analgesia duration and quality. The preemptive analgesia effect of spinal anesthesia once again has been uniform in all three groups. Spinal anesthesia blunts the neuroendocrine response to surgical trauma, leading to a decrease in inflammatory mediators, which in turn may be the cause of prolonged postoperative analgesic effect along with a preemptive analgesia.[2] This same reasoning may hold good to explain to some extent the inadequate difference in quality of analgesia among the three groups. However, general anesthesia is not required for this procedure unless the patient prefers it.

VAS at rest as well as with straight leg raise has been noted in our study so as to objectively assess the practicality of the analgesia regimen in early clinical recovery so as to plan early rehabilitation and physiotherapy. Recording VAS at rest alone may not be sufficient to assess this aspect.

Conclusion

With these results, we conclude that clonidine added to bupivacaine provides longer duration of postoperative analgesia after arthroscopic ACLR in the Indian population. Nevertheless, the quality of analgesia and PONV incidence was comparable in all three groups, which suggests that even when an additive is not available in a certain setup, bupivacaine *per se* injected intra-articularly would be a safe and effective choice for analgesia with minimal side effects, so as to target and achieve successful early rehabilitation and recovery.

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Conflicts of interest

There are no conflicts of interest.

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