Original Article

Comparison of different routes of administration of clonidine for analgesia following anterior cruciate ligament repair

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Abstract

Background and Aims: A high percentage of patients undergoing arthroscopic repairs on day care basis complain of inadequate postoperative pain relief. Clonidine was evaluated for the best route as an adjuvant in regional anesthesia in anterior cruciate ligament (ACL) repair to prolong analgesia.

Material and Methods: A prospective randomized double-blinded study was planned in a tertiary care hospital in North India in which 85 American Society of Anesthesiologists I and II patients undergoing ACL repair were enrolled. All groups received 0.5% hyperbaric bupivacaine intrathecally as in control group C. Group IT received intrathecal 1 μg/kg of clonidine along with hyperbaric bupivacaine, group IA received 0.25% bupivacaine and 1 μg/kg clonidine intra-articularly, and group NB received 0.25% bupivacaine and 1 μg/kg clonidine in femoro-sciatic nerve block (FSNB). Postoperative pain free interval and block characteristics were the primary outcomes studied.

Results: Pain-free duration was 546.90 (±93.66) min in group NB ($P < 0.001$) in comparison to 234.90 (±20.99), 367.80 (±47.40) and 172.20 (±54.82) min in groups IA, IT and C, respectively. Sensory block and motor blockade in NB were 474.90 (±43.80) and 267.40 (±34.59) min, respectively, and were significantly prolonged ($P > 0.001$) in comparison to other groups. The mean rescue analgesic requirement and cumulative frequency of rescue analgesia were least in group NB, followed by groups IT, IA and C.

Conclusion: Clonidine is safe and effective adjuvant with bupivacaine in prolonging analgesia through various routes employed for post knee surgery pain. The maximum prolongation of analgesia is achieved through FSNB with a risk of prolonging postanesthesia care unit stay.

Key words: Anterior cruciate ligament, clonidine, postoperative pain

Introduction

Increased performance of arthroscopic knee repairs on day care basis necessitates adequate postoperative analgesia for successful home discharge.[1] Regional anesthetic techniques with adjuvants are commonly utilized to extend the analgesic effect into the postoperative period. Clonidine has been studied in knee surgery as an adjuvant to local anesthetics in intra-articular, incisional, intrathecal routes and in peripheral nerve blocks individually.[2-5] Although the studies employing clonidine show a prolongation in the analgesic duration, different times and dosages have been used with no comparison between the efficacies when used through different routes in similar doses in a single type of surgery. The present study was planned to explore whether clonidine could be used as the ideal adjuvant, which could permit a single administration in ensuring adequate analgesia postoperatively through different routes. Primary outcome of interest were analgesic duration and block characteristics while the secondary outcomes were hemodynamic and sedation scores.

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Material and Methods

After approval from institutional ethics committee and written informed consent, 88 American Society of Anesthesiologists I and II patients of either sex undergoing arthroscopic anterior cruciate ligament (ACL) repair were included in this prospective randomized double-blinded study. No narcotics were used in premedication. Any patients with contraindications to spinal anesthesia like spinal deformities,

neurological disease, coagulation abnormalities, any local infections at the site of injection, and refusal to give consent were excluded from the study. Patients with a history of drug allergy or contraindications to nonsteroidal anti-inflammatory drugs were also excluded from the study.

Randomization was done by computer generated random number table and sealed envelope technique. Patients were educated about the 11 point verbal rating score (VRS) where 0 as no pain and 10 as worst imaginable pain. A single anesthesiologist blinded to study drug performed spinal anesthesia and nerve block by ultrasound (US) guidance combined with nerve stimulator technique (Stimuplex® – DIG, B Braun, Melsuengen, GMBH, Germany) and recorded intraoperative and postoperative observations. The level of spinal anesthesia was ensured to be above the T11 dermatome after the performance of nerve block. With an initial current of 1 mA and frequency of 1 Hz, the needle was introduced with US guidance till the motor response was present at currents below 0.5 mA, following which local anesthetic mixture was administered. A single surgeon performed all arthroscopic ACL repair with the administration of test drug intra-articularly at the end of surgery before tourniquet release. All drugs were prepared by another anesthesiologist blinded to patient data and intraoperative recordings.

Patients were allocated to one of the four study groups. Patients in group C (control group) received 20 ml saline in each of femoro-sciatic nerve block (FSNB), followed by 2 ml of 0.5% hyperbaric bupivacaine and 0.5 ml of saline intrathecally. Saline in a volume of 30 ml was administered through the intra-articular route by the surgeon blinded to the study design at the end of surgery. Patients in Group IT (intrathecal clonidine group) received saline in FSNB as in control group C, followed by 2 ml of 0.5% hyperbaric bupivacaine along with 1 μg/kg of clonidine intrathecally and saline in intra-articular route as in group C. Group IA patients (intra-articular clonidine group) received FSNB and spinal anesthesia, as mentioned in group C. Clonidine with plain bupivacaine in a volume of 30 ml of 0.25% bupivacaine +1 μg/kg clonidine, was injected intra-articularly at the end of surgery. Group NB (clonidine in nerve block group) patients received FSNB with 20 ml of 0.25% plain bupivacaine along with 0.5 μg/kg clonidine in each of the femoral and sciatic nerve block, followed by spinal anesthesia as mentioned in group C and at the end of the surgery, 30 ml of saline was injected intra-articularly as in group C.

For the purpose of blinding while studying block characteristics, return of sensation around the knee joint and return of motor power at the knee joint was tested at 15 min interval in the postoperative period. The duration of sensory block was defined from injection of the drug till return of sensation around the knee joint (L4 dermatome). Modified Bromage scale was used to measure motor block.[6]

1	Complete block; unable to move feet or knees
2	Almost complete block; able to move feet only
3	Partial block; just able to move knees
4	full flexion of knees with a detectable weakness of hip flexion while supine
5	No detectable weakness of hip flexion while supine

The duration of motor block was defined from injection of the test drug up to the ability to flex knee joint (modified Bromage score 4). Hemodynamic and respiratory parameters included heart rate, blood pressure, respiratory rate and oxygen saturation and were measured at 5 min interval till the end of surgery and at 15 min intervals for first 6 h postoperatively. Pain score was recorded at rest and at movement of the leg using 11 point VRS (between 0 and 10) at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h interval. First rescue analgesia included intravenous (IV) diclofenac 75 mg when VRS score was more than 3. If the VRS after 30 min of administration of IV diclofenac was greater than 3, another dose of IV diclofenac was administered till a total of 3 doses in 24 h. If the pain score at any time in the 24 h was more than 3 even after 3 doses of first rescue analgesia, a second rescue analgesic of IV fentanyl of 1 μg/kg was administered. Time interval between test drug administration up to the requirement of the first rescue analgesic drug was taken as the pain-free period. The total rescue analgesic consumption and the cumulative frequency of analgesic requirement in the 24 h in each group were noted. Sedation was assessed with Ramsay sedation scores both intra- and post-operatively at 5 and 15 min intervals respectively till sedation scores achieved baseline values. All patients were shifted to the wards for 24 h observation once they met the postanesthesia care unit (PACU) discharge criteria.

Statistical analysis

Sample size estimation was based on the increase in sensory blockade (in min). An assumption of difference of 1 (±0.8) on a VRS scale of 0-10 between the test and control groups was taken as significant. A total of 18 patients per group were required to ensure an increase in the duration of sensory block by 50% with an α of 0.05 and β of 0.01. Therefore, we ensured at least 22 patients in each group to adjust for any potential dropouts. Parametric data were compared and analyzed by Kruskal-Wallis test whereas nonparametric data such as VRS, rescue analgesics, and satisfaction scores were analyzed by Mann-Whitney U-test and Chi-square test. Time for first rescue analgesic medication was analyzed using survival analysis and Cox-regression analysis and represented

by Kaplan-Meier survival plot. A value of $P < 0.05$ is considered significant.

Results

A total of 88 cases were enrolled, of which 85 patients completed the study. Three cases were excluded which included one patient in groups C due to inadequate level of spinal blockade, one patient in group IA due to failure to elicit motor response during nerve block and one patient in group NB due to failure to perform spinal anesthesia, necessitating administration of general anesthesia. All groups were comparable regarding age, gender, weight or duration of surgery although, more number of males were studied in each group [Table 1].

Duration of sensory and motor block was significantly higher ($P < 0.001$) in group NB in comparison to groups C, IT, and IA. On further analysis, duration of sensory and motor blockade in group IT was also higher than groups C and IA ($P > 0.05$) [Table 2]. Pain scores at rest [Figure 1a] and movement [Figure 1b] were lower in groups NB at all times in comparison to other groups till 24 h postoperatively [Table 2]. The mean postoperative pain-free period was highest in group NB in comparison to other groups. Kaplan–Meier survival plot for postoperative pain-free period also showed least survival times in group C, followed by groups IA, IT and NB [Figure 2].

The rescue analgesic requirement was significantly less in patients receiving clonidine compared to control group and was highest in group IA and least in NB group as shown by cumulative rescue analgesic requirement and their frequency [Figure 3]. On intergroup comparison, analgesic requirement at 6 and 24 h were comparable in groups C and IA and significantly lesser in groups IT and NB. The need for second rescue analgesia with fentanyl was seen in 23 patients in group C and 5 patients in group IA while none of the patients in group IT and NB required a second rescue analgesic [Table 2].

No, statistically significant differences in hemodynamic and respiratory parameters were found between the groups in either

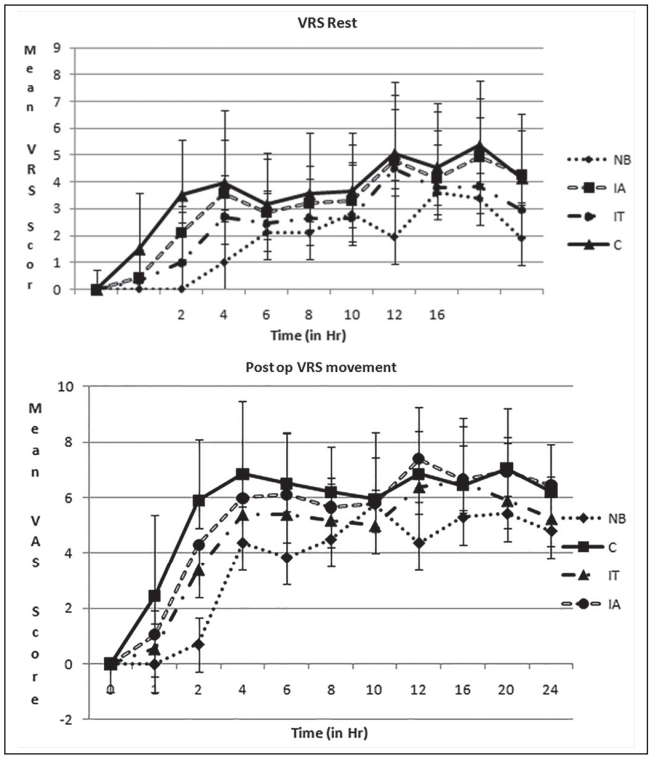

Figure 1: Pain scores (verbal rating score) at (a) rest and (b) movement showing a lower pain scores in group NB followed by groups IT, IA and C

Table 1: Demographic data

Patient characteristic	Group C	Group IT	Group IA	Group NB	*P*
Age (in years)	27.15 (±5.67)	29.60 (±9.64)	29.35 (±8.28)	30.30 (±9.61)	0.67
Sex (male/female)	17/3	16/4	16/4	18/2	0.72
Weight (in kg)	67.35 (±9.77)	67.80 (±10.70)	69.10 (±8.23)	69.45 (±9.81)	0.88
ASA status (1/2)	20/0	19/1	18/2	19/1	0.55
Duration of surgery (min)	96.25 (±10.9)	94.25 (±7.48)	95.25 (±11.50)	102.25 (±16.20)	0.27
PACU stay (min)	115 (±2.5)	131 (±2.8)	119 (±2.6)	186 (±5.2)	0.02

PACU = Postanesthesia care unit, ASA = American Society of Anesthesiologists

Table 2: Block characteristics

Characteristic of block	Group C	Group IT	Group IA	Group NB	*P*
Mean level of spinal block (dermatome) (%)	T10 (56.9)	T9 (62.1)	T10 (60.5)	T10 (58.3)	0.27
Motor blockade (min)	121.50 (±24.38)	201.60 (±34.13)	132.30 (±21.63)	267.40 (±34.59)	0.001
Sensory blockade (min)	164.40 (±29.22)	313.20 (±38.32)	172.50 (±23.10)	474.90 (±43.80)	0.001
Sedation score (6 h)	2.00 (±0.04)	2.55 (±0.51)	2.35 (±0.48)	2.42 (±0.51)	0.001
Pain-free period (h)	172.20 (±54.82)	367.80 (±47.40)	234.90 (±20.99)	546.90 (±93.66)	0.001
24 h rescue analgesic (in mg)	243.75 (±11.25)	105.0 (±15.23)	142.5 (±18.52)	52.5 (±9.48)	0.001
Second rescue analgesic (24 h)	23	0	5	0	0.001

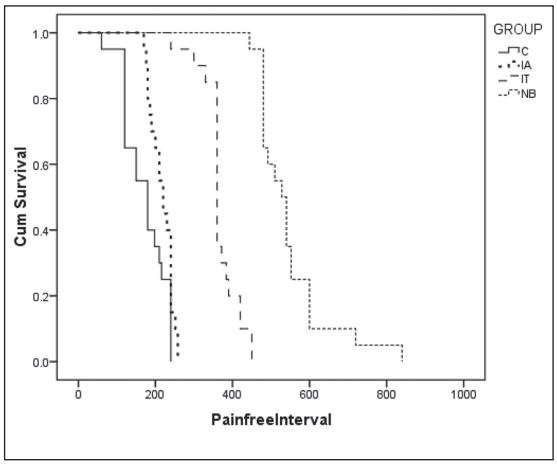

Figure 2: Kaplan-Meier survival plot showing longest survival times in group NB, followed by groups IT, IA and C

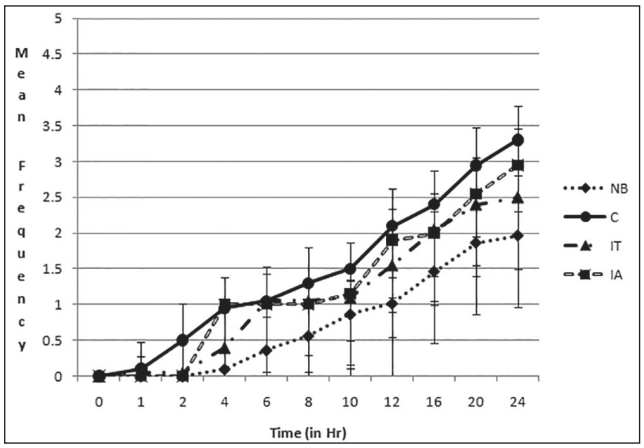

Figure 3: Mean cumulative rescue analgesic frequency in various groups in the postoperative period (24 h) showing least analgesic requirement in group NB, followed by groups IT, IA and C

intra- or post-operative period. An increase in mean sedation scores were noted in groups IT and NB after 15 min of test drug in the first 6 postoperative h ($P < 0.01$) in comparison to group C but was not associated with airway compromise or desaturation [Table 2].

Discussion

Clonidine, when added to bupivacaine in FSNB, showed lowest pain scores, longer pain-free period and lesser total rescue analgesic consumption. Clonidine was used in a dose of 1 μg/kg as this dose has been safely used.[3,7] FSNB employing bupivacaine and clonidine may slightly prolong PACU stay as seen in our study.

Current advances of pain therapy have focused on either improving drug formulations or catheter systems for local infiltrations or improve performance of regional anesthetic techniques. These advances have the potential for side effects from catheter migration after home discharge.[8] An ideal adjuvant, permitting single administration, and not causing systemic side effects, prolonging sensory blockade without increasing motor blockade duration is needed for adequate pain relief. Best route of clonidine administration was sought, which could make it close to ideal adjuvant. Patients receiving clonidine had lower pain scores till 24 h postoperatively. Addition of clonidine to bupivacaine in nerve block resulted in satisfactory prolongation of analgesic duration of 546.90 (±93.66) giving a pain-free duration of about 9-10 h. Although the pain scores, 24 h postoperatively were comparable between groups C and IA, frequency of rescue analgesic requirement was higher in the control group C [Figure 3]. Thus, clonidine may be more suitable adjuvant with local anesthetics for outpatient knee surgeries.

Intra-articular analgesia might not be efficient postoperatively as pain originating from extra-articular sites is not adequately controlled[9] as seen in a study comparing continuous epidural infusion, continuous femoral block, and continuous intra-articular infusion.[10] Intra-articular clonidine-local anesthetic mixture provided lesser pain relief than nerve block in ACL reconstruction in children.[11] However, there are methodological differences, their study employed clonidine in dissimilar doses, FSNB group received higher dose (2 μg/kg) compared to intra-articular group (1 μg/kg) where morphine was also added. Although clonidine without local anesthetics has not been tried in nerve blocks, studies on intra-articular opioid and clonidine have also provided comparable analgesia.[12]

Clonidine with intrathecal bupivacaine improves the duration of motor block and analgesic quality without delay in ability to void or readiness for home discharge following knee arthroscopy[11] but central neuraxial techniques themselves prolong home discharge when compared to wound infiltrations or general anesthesia alone.[8] Strebel *et al.*[3] compared 37.5, 75 and 150 μg of intrathecal clonidine and found that intrathecal clonidine produced dose dependent increase in spinal anesthesia and pain relief without any untoward side effect. Cucchiaro and Ganesh[4] reported mean motor block of 9.6 h after addition of clonidine 1 μg/kg to local anesthetic in peripheral nerve block but the assessment of block characteristics might differ from our study due to the retrospective nature of the study and interference from variety of peripheral nerve blocks included. Prolonged motor block may adversely affect hospital discharge as it delays neurological examination. We report an increase in motor blockade duration lesser than those reported by Cucchiaro and Ganesh[4] and hence no significant increases in PACU stay were observed probably due to low concentration of clonidine used (0.5 μg/kg in each block).

Clonidine potentiates the sensory and motor block of intrathecal local anesthetics by 30-50% and is more effective for dynamic

pain control while opioids are effective for pain at rest.[13,14] Hence, clonidine might be effective for permitting early movement especially in the ambulatory setting. Clonidine inhibits the release of substance P in the spinal cord, activates inhibitory G-proteins at spinal and supraspinal sites within the central nervous system and suppresses neurotransmission in peripheral sensory Aδ and C nerve fibers. It activates descending noradrenergic pathway to release acetylcholine in central pain pathways, which may explain the analgesic action of intra-articular clonidine.[15] In nerve blocks, clonidine may also produce local vasoconstriction, resulting in a delayed absorption of local anesthetic and block prolongation apart from directly binding to α_2-adrenergic receptors located on primary afferent terminals, on neurons in the superficial laminae of the spinal cord and several brainstem nuclei implicated in analgesia.[4,15]

Hemodynamic and sedation effects of clonidine are more common in higher doses.[15] Sedative dose of clonidine varies with the route of administration and clonidine has been safely used in doses up to 150 μg intra-articularly.[16] We did not observe clinically significant sedation similar to the study on intrathecal clonidine in doses of 37.5, 75, and 150 μg.[3] In contrast, Kohli *et al*. reported undesirable sedation when using clonidine in a dose of 2 mcg/kg in brachial plexus block although there were no significant hemodynamic alterations.[17] This discrepancy might be due to the use of different endpoints to define sedation. Bupivacaine alone in nerve block shows lower pain scores in the initial 6 h of postoperatively, but a comparable postoperative analgesia with the intrathecal route later.[18] Hence, addition of clonidine in nerve block significantly improved postoperative analgesia and decreased rescue analgesic requirement in comparison to other routes.

A limitation of our study was preemptive analgesic effect of clonidine was possibly present in IT and NB groups but was lost in group IA as clonidine with bupivacaine was administered intra-articularly at the end of the surgery.

Conclusion

Clonidine in a dose of 1 μg/kg with bupivacaine is effective in prolonging postoperative analgesia after arthroscopic ACL repair when administered through various routes. Clonidine was most effective when administered through FSNB and provided longest pain-free period, decreased pain score and least rescue analgesic requirement making it ideal for post knee surgery pain.

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