Original Article

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# Comparative Evaluation of Analgesic Efficacy of Intra-Articular Vs Intrathecal Clonidine in Arthroscopic Anterior Cruciate Ligament Repair: A Randomised, Double Blind Prospective Study

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## Abstract

**Background**: The purpose of this study was to compare the analgesic effects of Clonidine as an adjuvant through different routes for ACL repair surgeries. **Subjects and Methods:** Ninety adult patients of ASA grade I and II, both sex, age 18-60 years scheduled for ACL repair under Sub-arachnoid block (SAB) were randomly allocated into three groups. All patients received 0.5% bupivacaine intrathecally as in control group. Group IT received 1 $\mu$g/kg of clonidine in saline intrathecally with hyperbaric bupivacaine. Group IA received Clonidine 1$\mu$g/kg with 30 ml saline injected intra-articularly at the end of surgery. The duration of analgesia and block characteristics were the primary outcomes studied. **Results :** Statistical analysis was done by Statistical Package for Social Sciences (SPSS version 20.0) and epi info 7 (CDC Atlanta). The mean duration of Analgesia in Group IA(5.9$\pm$ 1.02h) was significantly (p=0.01) longer than that of Group IT(5.2$\pm$0.85h) and Group C (4.0 $\pm$ 0.78h) and the requirement of total number of rescue analgesics in 24 hr period was lesser in Group IA(1.1 $\pm$ 0.33) and Group IT (1.3 $\pm$ 0.50) than Group C (3.4 $\pm$ 0.69). The mean duration of sensory and motor block in Group IT was (4.5 $\pm$ 0.88 h) and (3.8 $\pm$ 0.78 h) respectively which was significantly longer than other groups. **Conclusion:** Clonidine is a useful adjuvant in prolonging analgesia through various routes for ACL repair surgeries arthroscopically. Intra-articularly administered clonidine provided most effective postoperative analgesia with least hemodynamic changes and complications.

**Keywords:** Clonidine, anterior cruciate ligament repair, arthroscopy, post operative analgesia

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## Introduction

Arthroscopic knee surgery is a minimally invasive procedure associated with postoperative pain because of the irritation of free nerve endings present in the intra-articular structures of the knee.[1] Patients with anterior cruciate ligament tear present with complaints of pain and swelling, and are at increased risk for postoperative complications like prolonged knee stiffness, delay in strength recovery and anterior knee pain.[2–4] Sub-arachnoid block (SAB) has been the safest choice in these patients but as it produces transient analgesia, adjuvants are added to maximize postoperative analgesia.

Due to paucity of studies showing comparison between efficacy of clonidine used in similar dosages through intrathecal and intrarticular routes to prolong analgesia in a single type of surgery the present study was planned with an aim to compare the analgesic effects of Clonidine as an adjuvant through intrathecal and intra-articular routes for ACL repair surgeries. We hypothesized that inta-articular and intrathecal clonidine would provide better analgesia than the control group. Our primary objective was to compare the duration of analgesia and secondary objective was to study the block characteristics and hemodynamic parameters.

## Subjects and Methods

After approval from Institutional Ethics Committee (Regd.No-ECR/635/INST/GJ 2014) during the year Sep 2016 to Oct 2018 in a tertiary care hospital we conducted a prospective randomized double blinded study including ninety adult patients of ASA (American Society of Anaesthesiologists) grade I and II patients of either sex, age 18-60 years, height between 140

to 185 cm and weight between 40 to 80 kg scheduled for ACL repair surgeries under SAB. Patients with contraindications to SAB like major neurological, cardiovascular or respiratory diseases, coagulation abnormalities, any local infections at the site of injection, refusal to give consent, history of drug allergy or contraindications to non-steroidal anti-inflammatory drugs were excluded from the study.

All patients were kept nil per oral for minimum 6 hours. A written informed consent and a 10 cm Visual Analogue Scale (VAS) was explained in the preoperative visit. An intravenous line was secured with an intravenous cannula (18G) in the upper limb and preloaded with Ringer's lactate 15ml/kg over 10 min. Pulse oximeter, non-invasive blood pressure cuff and ECG electrodes were applied and baseline pulse rate, blood pressure was recorded.

Patients were randomly allocated into three groups using computer-generated random numbers and concealed by sealed opaque envelopes. Blinding was done by consultant not directly involved in the study. Coding and decoding was also done by him/her. Patients were allocated one of the three study groups:

**Group C (control group)** received 2.5 ml of 0.5% hyperbaric bupivacaine and 0.5 ml of saline intrathecally (total volume 3ml). 30 ml saline was administered through the intra-articular route by the surgeon blinded to the study design at the end of surgery.

**Group IT (intrathecal clonidine group)** received 2.5 ml of 0.5% hyperbaric bupivacaine along with 1 $\mu$g/kg of clonidine in saline intrathecally (total volume 3ml) and 30ml saline in intra-articular route as in group C.

**Group IA patients (intra-articular clonidine group)** received spinal with 2.5 ml of 0.5% hyperbaric bupivacaine and 0.5 ml of saline intrathecally (total volume 3ml). Clonidine 1$\mu$g/kg with 30 ml saline injected intra-articularly at the end of surgery before the release of torniquet with the intra-articular drain clamped after administering the drug for 30min.

Patients were premedicated with Inj.Ondansetron 4 mg and Inj.Ranitidine hydrochloride 50 mg intravenously. A single anesthesiologist blinded to study drug performed the technique of SAB at L3-L4 segmental level with patient in sitting position using 25G Quincke spinal needle under all aseptic precautions. Effect was ensured at least up to T10 dermatome.

The onset time of sensory block was defined as time between intrathecal drug administration and time to achieve sensory level up to L1 dermatomal level. The onset of motor blockade was defined as the time between intrathecal administration of drug and time to achieve Modified Bromage Score 3.[5] Time of maximum sensory level achieved and the time of maximum motor block (Modified Bromage Score 1) achieved was noted.

Hemodynamic and respiratory parameter included heart rate, blood pressure, respiratory rate and oxygen saturation, the baseline value of vital signs were noted before performing the SAB and at 2,5, 15, 30, 60, 120, 180 min after spinal injection and at 30 min interval for 2.5 h postoperatively. For the purpose of our study, hypotension was defined as MAP (Mean arterial pressure) <20% and bradycardia was defined as HR <20% from baseline value. Hypotension treated with i.v. fluid, injection mephentermine 5mg i.v. bolus and repeated when needed. Bradycardia was treated with inj. atropine sulphate 0.6 mg IV. Respiratory depression (RR<10/min) and desaturation (Spo2<90%) if occurred was recorded and was managed with 100% oxygenation.

Duration of sensory block was defined as the time from injection of the drug till return of sensation around the knee joint (L4 dermatome). Duration of motor block was defined as the time from injection of the test drug up to the ability to flex knee joint (Modified Bromage Score 4). Sensory regression time defined as the time taken for sensory block to regress by two dermatomal segments from the highest block achieved. Motor regression time defined as the time elapsed from after administration of SAB up to achievement of Modified Bromage Score5.

Postoperative pain was assessed by VAS score recorded at 4, 6, 8, 10, 12, 16, 20, and 24 h interval. First rescue analgesia was given in the form of intravenous (IV) diclofenac 75 mg when VAS score was more than 3. If the VAS after 30 min of administration of IV diclofenac was still greater than 3, second dose of rescue analgesic if needed was given in the form injection tramadol 0.5mg/kg to 1mg/kg and total number of rescue analgesic given in 24 hours was noted. Total duration of analgesia was defined as the time interval between administration of SAB up to the requirement of the first rescue analgesic drug. Sedation was assessed with Ramsay sedation scores at interval of one hour till it reached baseline values in the recovery ward.[6]

Adverse effects like PDPH, shivering, nausea, vomiting, pruritus, urinary retention and respiratory depression noted and treated accordingly. Parameters and side effect observed at half an hour interval for two hours following surgery, then every hourly for next six hours then six hourly for the 24 hours after surgery.

Based on the previous study,[7] sample size was calculated using mean VAS scores as the primary variable. Assuming a SD of 20 mm, we calculated a sample size of 30 patients in each group to detect a difference of 10 mm on the VAS at an alpha threshold of 0.05 and power of 90%.

We enrolled total 90 patients consisting of 30 patients in each group. The raw data was collected in MS EXCEL sheets and statistical analysis was done by Statistical Package for Social Sciences (SPSS version 20.0) and epi info 7

(by CDC Atlanta). The normally distributed data i.e. onset time, block characteristics, duration of analgesia (DOA) and hemodynamic data (presented as mean± SD) were analyzed by applying one-way ANOVA test and Tukey's honesty significant difference post hoc multicomparision test for intergroup comparison and Chi-square where appropriate. P-value <0.05 was considered as statistically significant.

## Results

All the groups were comparable in terms of age, sex, weight, height and duration of surgery. [Table 1]

The mean time of sensory onset and maximum sensory block in Group IT was significantly longer than that of Group IA and Group C. The difference was statistically significant between Group C and Group IT. The mean duration of sensory block was significantly longer in Group IT than that in Group IA and Group C. The mean duration of sensory regression in Group IT was also significantly longer than that of Group IA and Group C. On intergroup analysis the results between Group C and Group IA in terms of mean time of sensory onset, maximum sensory block and duration of sensory block were comparable. [Table 2]

The mean duration of maximum motor level reached and duration of motor block was significantly longer in Group IT than Group IA and Group C. The duration of motor block in Group IA was also significantly longer than that of Group C. The mean duration of motor regression was significantly longer in Group IT than that of Group IA and Group C. On intergroup analysis the results between Group C and Group IA in terms of mean duration of maximum motor level reached and mean duration of motor regression were comparable. [Table 3]

The mean VAS score at 2h post intrathecal block was not significant among the three groups. However at 4h post block Group IA (1.8 ± 0.64 h) showed significantly (p=0.00) lower scores than Group C (3.17±0.85h) and Group IT (2.3 ± 0.70h)(p=0.00).Until up to 12h postoperative GroupC showed significantly higher scores compared to GroupIA and GroupIT however there was no significant differences between GroupIA and GroupIT after 4h postoperative. After 12h postoperative there no significant differences amongst the three groups. [Figure 1]

The mean duration of analgesia in Group IA was significantly (p=0.01) longer than that of Group IT and Group C and that of Group IT was significantly longer than Group C. The requirement of total number of rescue analgesics in 24 h period was significantly lower in Group IA and Group IT than Group C. But there was no statistically significant difference between Group IA and Group IT. There was an increase in the mean sedation scores after 1 hr after SAB in Group IT as compared to Group IA and Group C which was statistically significant. At 150min the scores returned to baseline. [Table 4]

In our study the mean intraoperative and post-operative pulse rate changes shows no significant difference amongst the three groups. The mean intraoperative MAP showed significant reduction from 1hr to 2.5h after SAB in Group IT compared to Group IA and Group C. [Figure:3,4]

## Discussion

ACL repair surgeries done arthroscopically involve reconstruction of the anterior cruciate ligament in the knee after it is torn following injury. But it may be associated with significant amount of pain. Good post-operative analgesic management provides advantages like attenuation of the neuro-endocrine stress response, reduction of postoperative pulmonary and cardiac complications, early physiotherapy and early mobilization. Several strategies like systemic medications, intra-thecal adjuvant, peripheral nerve blocks, intra-articular administration of various drugs like opioids, $\alpha 2$ agonist, local anaesthetics, NSAIDS have been used to interrupt the pain pathway, but none is free from drawback such as risk of complications.

Clonidine is an alpha2 adrenergic agonist with some alpha1 agonist properties. It causes anti-nociception by activating the descending noradrenergic inhibitory system and by inhibiting synaptic transmission within the dorsal horn of the spinal cholinergic neurons. Unlike other agents clonidine is not associated with systemic side effects such as pruritis, respiratory depression, nausea, vomiting and is a relatively safe and effective adjuvant.

We found in our study that clonidine when administered intraarticularly produced greater mean duration of analgesia which was clinically relevant and lesser requirement of rescue analgesics in 24 hr period as compared to the control group or when added intrathecally. But there was no statistically significant difference in the total no of rescue analgesic requirement between Group IA and Group IT.

Similar to our findings Mohammad Alipore et al.[8] showed that the analgesic efficacy of intra-articular dexmeditomidine is mainly due to direct local effect, although the central analgesic effect of the drug through systemic absorption cannot be denied which is similar to intra articular clonidine. Neimi L et al.[9] showed that intrathecal clonidine patients needed fewer rescue analgesic doses of oxycodone over the control group.

In our study,patients who received intra-articular clonidine had lower VAS pain scores till 4th postoperative. Gentili M et al.[10] in heir study found that VAS scores were significantly lower in group 2(the patients received 150 $\mu$g of clonidine diluted in 20 ml of isotonic saline injected into the knee joint) compared to groups 1(the patients received 20 ml of

intra-articular isotonic saline) at 1 and 2 h after surgery which proved that Clonidine possess an analgesic effect when injected into the knee joint after arthroscopic surgery which is comparable to our study.

The analgesic effect of intraarticular Clonidine may be due to the activation of descending noradrenergic pathway to release acetylcholine in central pain pathways.[11] In addition to its local anaesthetic effects, clonidine may also produce analgesia by releasing encephalin-like substances resulting in peripheral analgesia.[12]

We also found that Clonidine added intrathecally produced a faster onset and greater height of sensory block as compared to control or intra-articular group which is similar to the study conducted by Amit Tyagi et al.[13]who found that onset time of sensory block was faster in clonidine group(3.73 ± 1.3 min) compared to control group(5.60 ± 1.6 min). They also concluded that median, upper level of sensory block achieved was higher ($T_6$) in clonidine group as compared to control group ($T_8$).

Clonidine added intrathecally prolonged the duration of sensory block which can be explained by the fact that it potentiates or prolongs neuronal blockade of local anaesthetic agent bupivacaine, by reducing vascular uptake and thereby maintaining a higher concentration of local anaesthetic near neuronal tissues for a longer period of time.[14] The prolonged duration of sensory block in Group IA compared to Group C could be attributed to the fact that intra-articular clonidine following arthroscopic knee surgery prolongs the duration of action of local anaesthetics as well as selectively block the conduction of C and A$\delta$ fibres8. In a study conducted by Neeru Sahni et al.[15] found that duration of sensory and motor block was significantly higher ($P< 0.001$) in group NB in comparison to groups C, IT, and IA. Duration of sensory and motor blockade in group IT was also higher than groups C and IA ($P > 0.05$), also in Group IA (172.50 ±23.10) the duration of sensory block was longer than that of Group C (164.40 ±29.22) which compares with our study.

In our study, Clonidine when added intrathecally prolonged the duration of sensory and motor regression as compared to control and intra-articular group. Dobrydnjov et al.[16] intheir study found that two-segment regression, return of S1sensation, and regression of motor block were significantly longer in Group BC30(bupivacaine+ clonidine 30$\mu$g) than in Group BC15(bupivacaine+ clonidine 15$\mu$g) which compares with our study. Kanaze G.E et al.[17] in their study found that the regression time to Bromage 0 was significantly longer in Group C (hyperbaric bupivacaine 12mg+clonidine 30$\mu$g) as compared to Group B (hyperbaric bupivacaine 12mg) which was similar to our study.

In our study, Clonidine added intrathecally resulted in a faster peak motor block as compared to control group and intra-articular group. Sapate M et al.[18] found that the mean peak motor block was earlier in Group A (clonidine group) (6.17±1.20 min) as compared with Group B (control group) (8.63±1.71 min) which compares with our study.

In our study, the mean duration of motor block was significantly longer which was also clinically relevant in Group IT (3.8 ± 0.78 h) than that of Group IA (2.3 ± 0.4h) and Group C (1.8 ± 0.44h). This may be explained by the fact that $\alpha$-2 adrenoceptor agonist action induce a cellular modification in ventral horn of spinal cord (motor neuron hyperpolarisation) and facilitate local anaesthetic action.[19]

Strebel et al.[20] also observed that a significantly larger proportion of patients had intense motor blockade that resolved after 8–10 h in patients who received 150 $\mu$g intrathecal clonidine compared with control group in a dose response study for small dose intrathecal clonidine and isobaric bupivacaine for orthopaedic surgery. Their findings were thus similar to our findings.

In our study, we didn't find a significant change in the mean pulse rate and mean MAP between the intra-articular and the control groups. However, intrathecally added clonidine Group showed a significant fall in the MAP after 1 hr until 2.5 h post SAB. Clonidine causes a post synaptic activation of $\alpha$2 receptors in the CNS and thus inhibits sympathetic activity and enhances parasympathetic activity to cause blood pressure and heart rate changes. Similar to our study Marc de Cock et al.[21] showed that heart rate did not vary among the groups and mean MAP was significantly lower ($P < 0.05$) in patients in groups 3 and 4 (8 mg ropivacaine and 45 and 75 mg clonidine respectively).However, clonidine in lower dosage of 15$\mu$g given intrathecally did not cause systemic side effects like bradycardia and hypotension.

In our study, 2 patients(6.6%) in Group IT experienced bradycardia which was treated with Inj.Atropine. 4 patients(13.3%) in group IT and 2(6.6%)patients in Group C had developed hypotension intra-operatively which was treated with Inj.Mephentramine and 1 patient(3.3%) from Group IT had nausea. Although sedation scores were found to be statistically significant till 1 hr post SAB it was not found to be significant clinically. Marc de Cock et al.[21] showed that 75$\mu$g dose was associated with detectable systemic side effects, such as relative hypotension and sedation. Mobilization and micturition were delayed. These findings were similar to our study.

Limitations of our study were that the pre-emptive analgesic effect of clonidine which was present in Group IT was not present in group IA and C. Also patients were followed up for only 24 hours post surgery for requirement of analgesics. We did not include other arthroscopic procedures like meniscectomy and other articular cartilage procedures. Further research studies should be conducted to compare the efficacy of other $\alpha$2 agonists as an adjuvant through various

routes to find a reliable and clinically efficient regime on a larger study population.

## Conclusion

Clonidine when administered intrathecally had a earlier onset and prolonged duration of sensory and motor blockade, duration of analgesia as compared to the control group. Intra-articularly administered clonidine provided relatively more effective analgesia, decreased requirement of rescue analgesics, least hemodynamic changes and complications making it the preferred route in arthroscopic ACL repair surgeries.

**Key Message**

As per our study intraarticular clonidine was an effective adjuvant for ACL repair surgeries for postoperative analgesia and early recovery. Larger study population with other arthroscopic knee surgeries with various adjuvants can be studied for finding an optimum regime.

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