Original Article

Post-operative Analgesia in Arthroscopic knee surgery: A comparison between Intra-Articular Clonidine and Dexmedetomidine

Chaitali Biswas[1], Amrita Roy[2], Dhurjoti Prosad Bhattacharjee[3], Suhrita Paul[4]

From, [1] Associate Professor, [2] PG Student, [3]Professor, Department of Anesthesia, Calcutta National Medical College, Kolkata, West Bengal, 4 Professor & M.S.V.P, Murshidabad Medical College, Beharampur, West Bengal, India.

Correspondence to: Dr. Chaitali Biswas, 15C/15, Anupama Housing Complex, VIP Road, Kolkata-700052, India. Email: drchaitali.b9@gmail.com

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ABSTRACT

Background: Arthroscopic surgery is associated with variable amount of postoperative pain and sometimes the pain is considerable. To provide postoperative analgesia after arthroscopic knee surgery, various medications have been administered intra-articularly. **Aim**: To compare the postoperative analgesic effects of intra-articular clonidine and dexmedetomidine administered as adjuvants with local anesthetic levobupivacaine in patients undergoing arthroscopic knee surgery. **Methods**: Sixty patients undergoing elective knee arthroscopy were randomly assigned to one of the following groups containing 20 patients each. Group L patients received 19 ml of 0.25% levobupivacaine and 1 ml of isotonic saline (20 ml in total) intra-articularly. Group C patients received 150µg [1ml] of clonidine added to 19 ml of 0.25% levobupivacaine intra-articularly (total volume 20 ml). Group D patients received 100 µg (1 ml) of dexmedetomidine added to 19 ml of 0.25% levobupivacaine intra-articularly (total volume 20 ml). Analgesic effect was evaluated by measuring pain intensity (VAS score) and duration of analgesia. **Results**: A longer delay was observed between intra-articular injection of study medication and first requirement of supplementary analgesic in group C (10.44 ± 4.6 hours) and in group D (10.72 ± 5.6 hours) compared to group L (6.18 ± 1.8 hours). Total consumption of diclofenac sodium in first 24 hours in postoperative period was significantly less in group C and D. No significant side effects were noted. **Conclusion**: Both clonidine and dexmedetomidine, added as adjuncts to levobupivacaine in patients undergoing arthroscopic knee surgery, improve the quality and duration of post operative analgesia.

Key words: *Clonidine, Dexmedetomidine, levobupivacaine, Arthroscopic knee surgery, Intra-articular Injection.*

Arthroscopic surgery is associated with variable amount of postoperative pain and sometimes the pain is considerable. Postoperative pain relief is essential for early rehabilitation after arthroscopic knee surgery. There has always been a search for a simple method for providing postoperative analgesia in these patients. Intra-articular administration of various drugs provides satisfactory analgesia in immediate postoperative period. Local anaesthetics like lido-caine [1] and bupivacaine [2], opioids like morphine [3], alpha2 adrenoceptor agonists like clonidine [4] and magnesium sulphate [5] have all been tried intra-articularly alone or in combination to provide effective postoperative analgesia.

Clonidine is an imidazoline derivative with alpha2 agonistic activity. It has been shown that the mechanism of peripheral analgesic effects of clonidine results from its inhibition of noradrenaline release at terminal nerve fibre endings [4]. Dexmedetomidine is a highly selective alpha2 adrenergic agonist with sedative, anxiolytic, and analgesic, sympatholytic and antihy-pertensive effects [6]. Activation of receptors in the brain and spinal cord level inhibits

neuronal firing, thereby causing hypotension, bradycardia, sedation and analgesia [7]. Dexmede-tomidine has been used intravenously before initiation of regional anaesthesia and it has shown to provide some analgesic effect after arthroscopic knee surgery [8]. But there were some adverse haemodynamic effects [8]. Intra-articular administration of dexmedetomidine may be useful to avoid the adverse haemodynamic effects of intravenous administration while still providing the postoperative analgesia.

This placebo controlled, double blind, prospective study is designed to assess and compare the postoperative analgesic effects of intra-articular clonidine and dexmedetomidine administered as adjuvant with local anaesthetic levobupivacaine in patients undergoing arthroscopic knee surgery.

METHODS

This prospective study was conducted at a tertiary care centre in Kolkata, India over a period of one year (March 2017- February 2018). The study protocol was approved by the institutional ethical committee and informed consent was obtained from every patient. Sixty ASA I –II patients of either sex, aged 18-65 years, undergoing elective knee arthroscopy, were randomly assigned to one of the three groups, containing twenty patients each. Power calculations suggested that a minimum of 17 subjects per group were required to detect 10% difference in visual analogue scale (VAS) score between groups (a= 0.05, b= 0.80). To accommodate-date the probable drop outs, a number of 20 patients in each group were included.

Surgical procedures consisted of meniscetomies and ligament repair. Patients having history of cardiovascular, cerebrovascular, and respiratory diseases, pregnancy, receiving chronic pain treatment or hypertension treated with α methyl dopa, clonidine or β adrenergic blockers were excluded from the study. On preoperative rounds, patients were explained regarding the procedure and were also taught to interpret the VAS (graded from 0 = no pain to 10 = maxi-mum pain). All the patients were given diazepam 10 mg and ranitidine 150 mg orally (in tablet form) on the night before surgery and tab. ranitidine was repeated on the morning of surgery. On the operation table, routine monitoring (ECG, pulse oximetry, NIBP) were started and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO2) were recorded. An intravenous line was secured.

After preoxygenation for 3 minutes, induction of anaesthesia was done by fentanyl 2µg/kg and propofol 2mg/kg. Patients were intubated with appropriate size endotracheal tube after muscle relaxation with vecuronium bromide in a dose of 0.08mg/kg. Anaesthesia was main-tained with 33% oxygen in nitrous oxide and isoflurane 1%. Muscle relaxation was maintained by intermittent bolus doses of vecuronium bromide. The patients were mechanically ventilated to keep EtCO2 between 35 - 40 mm Hg. Patients received top-up of i.v. fentanyl (1µg/kg) at half- hourly interval. Patients were randomly allocated using a computer generated randomization list into three groups (n=20). Sealed envelopes containing one syringe with levobupivacaine and saline, le-vobupivacaine and clonidine or levobupivacaine and dexmedetomidine were prepared. The anaesthesiologist and surgeon were unaware of the nature of the drug in each syringe. At the end of the surgical procedure, intra-articular solutions were injected into the knee joint through the cannular sheath after withdrawal of camera by the orthopedic surgeon before the arthroscope was removed. In Group L, 19 ml of 0.25% levobupivacaine and 1 ml isotonic saline (total volume 20 ml) [9,10] was administered into the knee joint. In Group C, 19 ml of 0.25% levobupivacaine and 1 ml (150µg) of clonidine (total volume 20 ml) was administered into the knee joint. Similarly, group D patients received 100 µg of dexmedetomidine (1 ml) added to 19ml 0.25% levobupivacaine [again making a volume of 20 ml].

At the end of the operation, ondansetron 4 mg was administered i.v. for prophylaxis against nausea and vomiting. Residual neuromuscular paralysis was reversed using intravenous glycopyrrolate and neostigmine and subsequently extubation was done. All patients were observed postoperatively by resident doctors who were unaware of the study group. Patients were transferred to post-anaesthesia care unit and intensity of pain and vital parameters were assessed after thirty minutes and then an hourly interval for 24 hours. Diclofenac sodium (75 mg) was administered i.v. as analgesic supplement if the recorded VAS pain score was 4 or more and was repeated every 8 hour, if required. Tramadol 100 mg i.v. was used as a rescue analgesic, if the patients continued to have pain after diclofenac administration. The time to the first analgesic requirement and the total diclofenac consumption during first 24 hour after operation were also recorded. The patients were monitored for nausea and vomiting, drowsiness, hypotension (defined as systolic

blood pressure >20% decrease from baseline) and bradycardia (heart rate < 60 beats/min) during this period.

The numerical data obtained from the study were expressed as Mean ± SD. Comparison be-tween groups were performed with Kruskal-Wallis one-way analysis of varience (ANOVA) by ranks or Fisher's exact test for small samples with a 5% risk. Mann-Whitney- Wilcoxon tests were performed when normality tests failed. Statistical software SPSS version 20 has been used for the analysis.

RESULTS

The three groups were comparable with regard to age, sex, body weight and duration of surgery (table 1). The three groups were comparable with regard to types of surgical procedures (table 2).

Table 1 - Patients Characteristics

Variables/ Group	Group L (n=20)	Group C (n=20)	Group D (n=20)	P
Age (Year)	38.2±9.64	39.4 ±11.6	38.4± 9.6	0.47
Sex (M/F)	12/8	11/9	11/9	
Weight (kg)	54.35±8.86	56.32±11.48	54.62±9.42	0.67
Duration of surgery (min)	75.36±16.4	74.24±26.56	76.36±26.4	0.62

Table 2 - Types of surgical procedures undergone by three groups

Surgical procedure	Group L	Group C	Group D
Lateral meniscetomy	4	5	6
Medial meniscetomy	2	2	3
Medial Collateral lig repair	4	3	2
Lateral Collateral lig repair	3	3	4
Anterior cruciate lig repair	3	4	2
Posterior cruciate lig repair	4	3	3

Intensity of pain was significantly less in group C and group D compared to group L at 1 hour (P<0.01), 2 hour (P<0.05) and 6 hour (P<0.05) following surgery. However from 10 hour, intensity of pain was comparable in both groups (table 3). On comparing patients in group C and group D, no significant difference regarding intensity of pain was found at any time interval. The mean duration of analgesia (delay between the intra-articular injection and the first postoperative analgesic demand) was longer in group C and D compared to group L (table 3). Diclofenac consumption in first 24 hours was significantly less in group C and D compared to group L (P<0.01) (Table 4).

Table 3 - Intensity of Pain in Postoperative Period

Post-Operative Period	Group L (Mean±SD)	Group C (Mean±SD)	Group D (Mean±SD)
1 hour	2.7±0.62	1.94±0.62*	1.9±0.67*
2 hour	3.03±0.72	2.4±0.67*	2.28±0.65*
6 hour	3.92±1.16	3.33±0.88*	3.22±0.92*
10 hour	3.62±1.02	3.64±1.8	3.72±1.04
14 hour	3.38±0.92	3.36±1.02	3.46±1.06
18 hour	3.48±1.02	3.36±1.04	3.4±.0.96
24 hour	3.54±1.04	3.48±1.06	3.58±.0.98

*Significant difference between groups (P<0.05)

Table 4 - Duration of analgesia and diclofenac consumption in the postoperative period

Duration in hours	Group L (Mean±SD)	Group C (Mean±SD)	Group D (Mean±SD)	P value
Analgesia	6.18 ± 1.8	10.44 ± 4.6*	10.72 ± 5.6*	<0.05
Diclofenac	165.8±44.32	94.34±26.24*	89.27±28.32*	<0.05

*Significant difference between groups (P<0.05); [P value was determined by comparing Levobupivacaine (L) clonidine(C) and dexmedetomidine (D) groups.]

On comparing patients in group C and group D, no significant difference regarding duration of analgesia and diclofenac consumption was found. Regarding adverse effects, there is no significant difference among the incidences of adverse effects in both groups (table 5).

DISCUSSION

In an attempt to improve the recovery and early rehabilitation after arthroscopic knee surgery, research has been directed towards developing newer techniques for postoperative analgesia. Single IA (intra articular) injection of LA has been suggested to provide adequate pain management after arthroscopy of the knee joint and to reduce consumption and possible adverse effects of systemic analgesics. IA bupivacaine is frequently used because of its extended du-ration of action [11]. The duration of analgesia provided by a single dose of IA bupivacaine is not well defined. In our study, we observed and compared the effects of clonidine and dex-medetomidine used as adjuvants to levobupivacaine administered intra articularly after elective knee arthroscopy. Our study demonstrates a significant increase in postoperative analgesia with clonidine and dexmedeto-

-midine used along with levobupivacaine in comparison to levobupivacaine with saline. Alpha2 adrenergic agonists produce their analgesic effects through supraspinal, spinal and peripheral actions [12].

The analgesic effect of intra-articular dexmedetomidine appears to be mainly due to direct local action. However, a central analgesic effect resulting from systemic absorption cannot be excluded [12]. The mechanism of analgesic effect of in-tra-articular dexmedetomidine might be similar to that of intra-articular clonidine. Clonidine is supposed to produce analgesia mainly through inhibition of the transmission of nociceptive stimulation in the dorsal horn of spinal cord [13]. Clonidine is reported to mimic the effect of nor-adrenaline release by descending inhibitory control pathways [14]. Topical administration of clonidine may reduce pain intensity in patients with sympathetically maintained pain, suggesting a peripheral site of action for this drug [15].

Genteli M and colleagues [16] have used clonidine 150 µg intra-articularly and they observed that clonidine was effective in increasing the duration of postoperative analgesia. Dexmede-tomidine, like clonidine, may provide local anaesthetic effects which inhibit the conduction of nerve signals through C and Aδ fibres [17] and may stimulate the release of enkephalin like substances at peripheral sites [18]. Opioid-analgesic pathway modulation may be an al-ternative explanation for the analgesic effect of dexmedetomidine [19]. A direct inhibition of tetrodotoxin-resistant Na+ channels may contribute to the antinociceptive effects of clonidine and dexmedetomidine (DEX) when used in addition to local anaesthesia [20]. Another study indicated that DEX inhibited neuronal delayed-rectifier potassium currents and sodium cur-rents to produce local anesthetic effects [21]. R.R. Al-Metwalli and colleagues [22] have used dexmedetomidine 100 µg intra-articularly and they observed that dexmedetomidine was effective in increasing the duration of post-operative analgesia.

Shaimaa FM et al [9] demonstrated that duration of analgesia was signif-icantly longer in group bupivacaine-dexmedetomidine (BD) group (458.9 ± 93.5 min) than in the bupivacaine (B) group (229.1 ± 83.7 min) ($p < 0.05$). Postoperative analgesic consumption was lowered in the BD group compared with the B group ($p < 0.05$), which was consistent with our study. In another study by Mohammad Alipour and colleagues [23], intervention group received 1µg/kg dexmedetomidine (D) and isotonic saline. Control group received 25ml isotonic saline (P). The mean of post-operation pain severity in 1, 3, 6,12, and 24 h was significantly lower in the intervention group (D) in comparison with the control group (P). The mean of the total dose of tramadol consumption was significantly lower in the interven-tion group.

Sun R et al [24] studied relevant seven randomized controlled trials (RCTs) and results of the meta-analysis showed that intra-articular clonidine reduced the pain intensity for the first 4 h after surgery, reduced the risk of using rescue analgesics. In another study, Senapati S and colleagues [25] concluded that intra-articular administration of levobupivacaine and clonidine give better post-operative pain relief by increasing duration of analgesia, and decreasing need of rescue analgesic compared to intra-articular ropivacaine and clonidine. The delay between intra-articular injection of levobupivacaine with clonidine and levobupi-vacaine with dexmedetomidine and supplementary analgesic administration was 10.44 ± 4.6 hours and 10.72 ± 5.6 hours respectively in our study. In a study performed by Paul S and colleagues [26], it was found that time period for first analgesic request for intra-articular bu-pivacaine and magnesium sulphate was 12.32±2.8 hours, intra-articular bupivacaine and clo-nidine was 10.16±2.4 hours. In another study by Paul S and colleagues [27], time for first analgesic request for intra-articular dexmedetomidine in combination with ropivacaine was 10.84±2.6 hours. It seems that clonidine and dexmedetomedine administered as adjuvant to levobupivacaine, was able to provide analgesia which was comparable to other intra-articular agents used in previous similar studies.

The limitations of our study were that plasma concentrations and chondrotoxic effects of the drugs were not evaluated. Regarding toxicity, a systematic review and meta-analysis by Sun et al [28] reported the safety of IA bupivacaine during short-term observation. They stated that single- administration IA bupivacaine maximises the safety of postoperative pain relief in the early postoperative period rather than continuous IA infusion of analgesics, which is associated with large effusion of the surgical wound and direct access for infectious agents with catheter placement. In clinical practice also, the toxicity of LAs has mainly been seen with continuous infusions via pain pumps. Akça et al [29] in their study reported no adverse effects of dexmedetomidine on rat knee cartilage but little is known about any effects in hu-mans. In our study, there was no significant difference among the

incidences of adverse effects in patients of all the groups.

CONCLUSION

Both, clonidine and dexmedetomidine, added as adjuncts to levobupivacaine in patients undergoing arthroscopic knee surgery, improves the quality and duration of post operative analgesia and reduces the consumption of diclofenac sodium. There is however, no significant difference between clonidine and dexmedetomidine regarding their ability to provide post-operative analgesia after arthroscopic knee surgery.

REFERENCES

1. Dahl MR, Dasta JF, Zuelzer W, et al. Lidocaine local anesthesia for arthroscopic knee surgery. Anesth Analg. 1990;71: 670 – 4.
2. Chirwaa SS, MacLeod BA, Day B. Intra-articular bupivacaine after arthroscopic menis-cectomy: a randomized double blind controlled study. Arthroscopy. 1989; 5: 33 – 5.
3. Stein C, Comisel K, Haimerl E, et al. Analgesic effect of intra-articular morphine after arthroscopic knee surgery. New Engl J Med. 1991; 325: 1123 – 6.
4. Gentili M, Juhel A, Bonnet F. Peripheral analgesic effect of intra-articular clonidine. Pain. 1996; 64 : 593 – 6.
5. Bondok RS, Abd El-Hady AM. Intra-articular magnesium is effective for postoperative analgesia in arthroscopic knee surgery. Br J Anaesth. 2006; 97(3):389–92.
6. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother. 2007; 41: 245-52.
7. Hayashi Y, Maze M. Alpha2 adrenoceptor agonist and anaesthesia. Br J Anaesth. 1993; 71 : 108-18.
8. Gomez-Vazquez ME, Harnandez-Salazar E, Harnandez-Jimenez A, et al. Clinical anal-gesic efficacy and side effects of dexmedetomidine in the early postoperative period after arthroscopic knee surgery. J Clin Anesth. 2007; 19 :576-82.
9. Shaimaa F Mostafa, Gehan M Eid, Mohammed A Abdullah, et al. Intra-articular dexme-detomidine with bupivacaine versus bupivacaine alone for postoperative analgesia after knee arthroscopy, Southern African Journal of Anaesthesia and Analgesia. 2018; 24(2):54-59, DOI: 10.1080/22201181.2018.1444443.
10. Bajwa SS, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A syste-matic review. J Anaesthesiol Clin Pharmacol. 2013;29:530-9.
11. Wei J, Yang H, Qin J, et al. Single-dose intra-articular bupivacaine after knee arthroscopic surgery: A meta-analysis of randomized placebo controlled studies. Knee Surg Sports Traumatol Arthrosc. 2014;22(7):1517–28. https://doi.org/10.1007/s00167-013-2543-7.Last accessed on 28.06.2018.
12. Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anaesthesiology. 2000; 93: 382-94.
13. Yaksh TL, Reddy SVR. Studies in the primate on analgesic effects associated with intrathecal actions of opiates, alpha2 adrenergic agonists and baclofen. Anaesthesiology. 1981; 54(6):451-67.
14. Yeomans DC, Clark FM, Paice JA, et al. Antinociception induced by electrical stimulation of spinally projecting noradrenergic neurons in the A7 catecholamine cell group of the rat. Brain. 1992;48:449-61.
15. Davis KD, Treede RD, Raja SN, et al. Topical application of cloni-dine relieves hyperalgesia in patients with sympathetically maintained pain. Pain. 1991;47: 309-17.
16. Gentili M, Houssel P, Osman D, et al. Intra-articular morphine and clonidine produce comparable analgesia. Br J Anaesth. 1997; 79 : 660 – 661.
17. Butterworth JFV, Strichartz GR. The alpha2 adrenergic agonists clonidine and gunafa-cine produce tonic and phasic block of conduction in rat sciatic nerve fibres. Anesth Analg. 1993; 76 : 295-30.
18. Nakamura M and Ferreira SH. Peripheral analgesic action of clonidine: mediation by re-lease of endogenous enkephalin like substances. Eur J Pharmacol. 1988;146: 223-28.
19. Post C, Archer T, Minor BG. Evidence for cross tolerance to the analgesic effects between morphine and selective alpha 2-adrenergic agonists. Journal of Neural Transmission. 1988;72:1–9. https://doi.org/10.1007/BF01244627.
20. Oda A, Iida H, Tanahashi S. et al. Effects of alpha2-adrenoceptor agonists on tetrodotoxin-resistant Na+ channels in rat dorsal root ganglion neurons. Eur J Anaesthesiol.2007;24:934–941. .
21. Chen B. S, Peng H, & Wu S. N. Dexmedetomidine, an alpha2-adrenergic agonist, inhibits neuronal delayed-rectifier potassium current and sodium current. Br J Anaesth. 2009;103: 244–254.
22. Al-Metwalli RR, Mowafi HA, Ismail A, et al. Effect of Intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. Br J Anaesth. 2008; 97(3):389 – 92.
23. Mohammad A, Masoomeh T, Reza F, et al. Effect of dexmedetomidine on postoperative pain in knee arthroscopic surgery; A randomized controlled clinical trial. Arch Bone Joint Surg. 2014;2(1):52-56.
24. Sun R, Zhao W, Hao Q, et al. Intra-articular clonidine for post-operative analgesia following arthroscopic knee

surgery: a systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2014 Sep;22(9):2076-84. doi: 10.1007/s00167-013-2615-8.

25. Senapati S, Basu A, Bhattacharya D, et al. Comparison of analgesic effect of intra-articular administration of levobupivacaine and clonidine versus ropivacaine and clonidine in day care knee arthroscopic surgery under spinal anesthesia. Indian J Pain. 2016;30:38-42.
26. Paul S, Bhattacharjee DP, Ghosh S, et al. Postoperative analgesia for arthroscopic knee surgery: A comparison between intra-articular bupivacaine alone or in combination with magnesium sulphate or clonidine. Pharmacologyonline. 2009;3:938 – 943.
27. Pal S, Bhattacharjee DP, Ghosh S, et al. Efficacy of intra-articular dexmeditomidine for postoperative analgesia in arthroscopic knee surgery. Ceylone Medical Journal. 2010; 55:111-15.
28. Sun Q, Liu S, Meng Q, et al. Single administration of intra-articular bupivacaine in arth-roscopic knee surgery: a systematic review and meta-analysis. BMC Musculoskeletal Disorders. 2015;16:151721–31. https://doi.org/10.1186/s12891-015-0477-6.
29. Akça B , Ankay Yilbaş A , Uzumcugil F, et al. Do we cause harm using dexmedetomidine on articular cartilage and synovium in rat knee? Reg Anesth Pain Med. 2017;42:e1–e200.

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