ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 11 | November - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARISON OF INTRA-ARTICULAR INJECTION OF MORPHINE VERSUS DEXMEDETOMIDINE AS AN ADJUVANT TO BUPIVACAINE IN ARTHROSCOPIC KNEE SURGERIES FOR POST-OPERATIVE ANALGESIA: A RANDOMISED DOUBLE BLINDED STUDY

Anaesthesiology

Niharika Thakur* MD, Senior Resident, Department of Anaesthesiology, Bharati Vidyapeeth Medical College and Hospital, Pune *Corresponding Author

Varshali Keniya DNB, Professor, Department of Anaesthesiology, Bharati Vidyapeeth Medical College and Hospital, Pune

Mridul Panditrao DA, MD, Professor, Department of Anaesthesiology, Bharati Vidyapeeth Medical College and Hospital, Pune

ABSTRACT

Objective Despite its proven pain-relieving properties, the analgesic effect of intra-articular bupivacaine when administered without adjuvants remains short-lived. The aim of this study was to compare intra-articular injection of Morphine versus Dexmedetomidine as an adjuvant to bupivacaine in arthroscopic knee surgeries for post-operative analgesia **Methods** A randomized double blinded study was conducted in 60 adults of American Society of Anaesthesiologists (ASA) I & II undergoing elective arthroscopic knee surgery. Patients were randomized to receive morphine 5mg (group M) or dexmedetomidine 1microgram/kg (group D) in combination with bupivacaine 0.25% 19cc. Vitals, Ramsay sedation score and VAS were monitored. Diclofenac Sodium (75mg) was administered intravenously as rescue analgesic at VAS >3. Time to first request of analgesic and dosage of total analgesic consumption in 24 hours were recorded. Adverse effects, if any were noted. **Results** Cases in group M had adequate analgesia for 16.20 ± 3.75 hours which was significantly higher (p value <0.001) than those in group D, that lasted for 9.47 ± 1.36 hours. Total number of analgesic injections required were higher in Group D than in group M (p value <0.001). In group M, none had any side effects while 2 out of 30 in group D had hypotension and urinary retention respectively. **Conclusion** Combination of intra-articular morphine with bupivacaine provides better analgesia than with dexmedetomidine with prolongation of time required to use rescue analgesic in post-arthroscopic knee surgery.

KEYWORDS

analgesia; morphine; dexmedetomidine; intra-articular

INTRODUCTION

Knee arthroscopy is a well-acknowledged minimally invasive procedure in a modern orthopaedic set up, offering the advantage of being comparatively less traumatic than open technique. However, inadequately controlled pain can neutralize the various beneficial effects offered by this newer technique resulting in prolonged hospital stay and patient discomfort.[1]

The postoperative hypersensitivity state ("spinal wind-up") is responsible for reduction in pain threshold, both at the surgical site (primary hyperalgesia) and in the surrounding uninvolved tissue (secondary hyperalgesia). Occurring due to a synergy of peripheral as well as central sensitization, afferent pain signals and associated inflammatory response facilitate it. In research for the best modality of postoperative pain relief, various approaches (systemic, neuraxial, peripheral, intra-articular) are being studied.[2]

Evidence demonstrates that a single local anaesthetic injected intra-articularly provides sufficient analgesia post knee arthroscopy without potential adverse effects.[2,3] Several intra-articular agents (local anaesthetics, opioids, ketamine, NSAIDS, alpha-2 adrenergic agonists) have been investigated for control of pain after knee surgeries.[1,2,4] Likewise, Bupivacaine, has been instilled intra-articularly, yet when administered without adjuvants, the effects remain short-lived extending only to a few hours.[2,4]

Dexmedetomidine, a potent and highly selective alpha-2 adrenoreceptor agonist, has been used by intra-articular route to augment post knee arthroscopy pain and has shown an increase in time to request for rescue analgesic as well as a reduction in requirement of total postoperative analgesia.[5] At the same time, peripheral administration of opioids is also known to be associated with clinical benefits, morphine being recognized as a potent and long-acting drug with anti-inflammatory as well as anti-nociceptive effects on joints. It has no chondrotoxicity, making it one of the narcotics that may be a feasible alternative for the purpose of intra-articular injection.[6] Though the efficacy of intra-articular dexmedetomidine versus morphine for post-operative analgesia has been evaluated previously, data in adults remains insufficient to effectively conclude on one's superiority over the other. The aim of this study was to evaluate the effect of adding morphine versus dexmedetomidine as an adjuvant to intra-articular bupivacaine for post-operative analgesia after knee arthroscopic surgeries; the primary objective being to assess the time required to request for rescue analgesic and compare the total number of analgesic injections required over a period of 24 hours.

METHODS

The study was conducted in a tertiary care teaching hospital in Pune, Western Maharashtra between October, 2018 and October, 2020. The Institutional Ethics Committee approval was taken. A written informed consent was obtained from all patients. This double-blinded randomized controlled trial was conducted in 60 American Society of Anaesthesiologists (ASA) physical status I and II adults who underwent elective arthroscopic knee surgery under spinal anaesthesia.

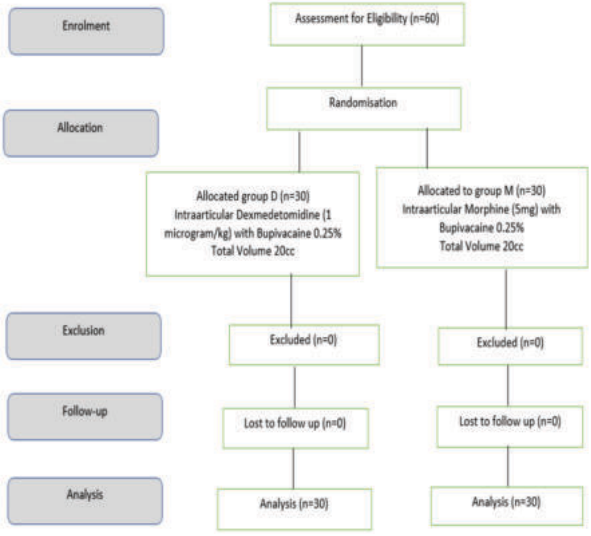
The age group included was between 18 to 60 years.Participants were allocated to receive 19ml of 0.25% plain Bupivacaine + 1ml of 5mg Morphine referred to as group M or 19 ml of 0.25% plain Bupivacaine + 1 ml of Dexmedetomidine (1 micro-gram/kg) called as group D. Group allocation was based on a randomized sequence in which both assessor and patients were blinded to group allocation by an opaque sealed envelope method. The envelope was opened and the test drugs were prepared based on the assigned group by an anaesthesiologist who was not a part of the study. Patients with known allergy to local anaesthetic, known underlying liver or renal disease and those with use of opioid analgesics within the last 24 hours were excluded.

Detailed pre-anaesthetic check-up of all patients posted for surgery was done one day prior to surgery. All the patients were kept nil by mouth for 6 hours prior to surgery. On the day of surgery patients were brought to operation theatre. During the pre-anaesthesia evaluation, 10 cm Visual Analogue Scale (VAS) for pain assessment was explained to each patient with 0 and 10 labelled as "no pain" and "worst pain imaginable" respectively. Before induction of anaesthesia, 3 lead ECG, baseline blood pressure, saturation, heart rate, and respiratory rate was recorded in each patient. Intra-operatively a subarachnoid blockade was performed with the patient in sitting position with 25-gauge Quincke spinal needle at the L3-L4 inter-spinal space using a median approach. Injection Bupivacaine 0.5%, 3.6ml was given to all patients. Standard intraoperative monitoring of pulse rate, systolic and diastolic blood pressure, respiratory rate and saturation was done intra-operatively. Tourniquet inflation time was noted. Subsequently a standard arthroscopic technique was performed through two portals, one antero-lateral and one antero-medial. Towards the end of surgery and 10 minutes before release of tourniquet, the study drug using preloaded unlabelled syringe was injected intra-articularly under strict aseptic precautions through the anterolateral port site itself by means of 23-gauge Quincke spinal needle just before skin closure. The time of injection was taken as the start time for determining time to first request for analgesia. After application of compression bandage for 10

minutes, tourniquet was removed. Post operatively the pulse rate, respiratory rate, systolic and diastolic blood pressure and saturation along with Ramsay sedation score and VAS score were recorded at rest, at two hourly intervals for the first 8 hours (O, 2, 4, 6, 8 hrs) and thereafter at 4 hourly intervals for the next 24 hours. Diclofenac Sodium (75mg) was administered intravenously as rescue analgesic in case the patient had VAS score >3. The time to the first request of analgesic and dosage of total analgesic consumption in 24-hour period were recorded.

Calculation of the sample size was based on previous comparative studies on use of intra-articular analgesics post arthroscopic knee surgeries.[3,10,14] Using a proposed non-inferiority design and considering the mean difference in first rescue analgesia and power of previous studies, a total of 30 patients were allotted to each group. Data was analysed using Statistical Package for the Social Sciences (SPSS) version 23.0 computer software. The data were presented as mean ± SD or median [interquartile range (IQR)]. Time to first rescue analgesic was expressed as mean ± SD. A *P* value of <0.05 was considered statistically significant.

RESULTS



The study included 60 patients in all with 30 in each group. There were no drop outs from either group. Baseline characteristics of the two groups were comparable as seen in Table 1.

Age, body weight, ASA grades of cases studied did not differ significantly between two study groups (Table 1). Inter-group comparisons of HR, BP, SpO2, RSS did not differ significantly between the two study groups (P-value>0.05 for all). (Table 1)

Pain score (VAS):

The mean pain score (VAS) at 2-Hrs, 4-Hrs and 20-Hrs among the cases studied did not differ significantly between two study groups (P-value>0.05 for all). The mean pain score (VAS) at 6-Hrs, 8-Hrs, 12-Hrs, 16-Hrs and 24-Hrs among the cases studied was significantly higher in Group D compared to Group M (P-value<0.05 for all).

Hours of analgesia

The mean ± SD of number of hours of analgesia among the cases studied in group M and group D was 16.20 ± 3.75 Hrs and 9.47 ± 1.36 hours respectively. The minimum – maximum range of number of hours of analgesia in group M and group D was 10 – 24 hours and 7 – 12 hours respectively. The mean number of hours of analgesia among the cases studied was significantly higher in Group M compared to Group D (P-value<0.001).

Total number of analgesic injections

The mean ± SD of total number of analgesic injections among the cases studied in group M and group D was 1.50 ± 0.77 and 2.63 ± 0.49 respectively. The minimum – maximum range of total number of analgesic injections required in group M and group D was 0 – 3 and 2 – 3 respectively. The mean total number of analgesic injections required among the cases studied was significantly higher in group D compared to group M (P-value<0.001).

Adverse effects of analgesia

Of 30 cases studied in group M, none had any adverse effects. Of 30 cases studied in group D, 28 (93.4%) did not have any side effects, 1 (3.3%) had hypotension and 1 (3.3%) had urinary retention, the incidence of which did not reach statistical significance (P-value>0.05).

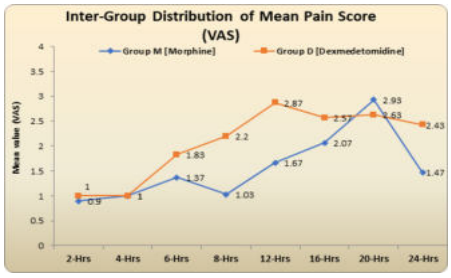


Figure 1) Inter-group comparison of mean pan score (VAS).

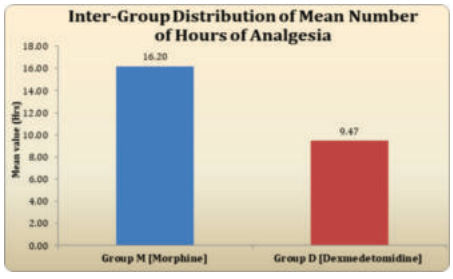


Figure 2) Inter-group comparison of mean number of hours of analgesia.

Table 1: Demographic Characteristics and Outcome Variables

	Group D (n=30)	Group M (n=30)	P
Age (years)	28.70 ± 6.36	27.80 ± 3.65	0.504
Gender (M:F) number (%)	25:5 (83.3:16.7)	23:7 (76.7:23.3)	0.519
Weight (kg)	64.07 ± 4.95	62.93 ± 4.20	0.343
ASA Grade (I:II) number (%)	22:8 (73.3:26.7)	23:7 (76.7:23.3)	0.766
Number of hours of analgesia	9.47 ± 1.36	16.20 ± 3.75	0.001
Total dosages of analgesia	2.63 ± 0.49	1.50 ± 0.77	0.001
Side Effects Hypotension Urinary Retention	0 0	1 1	0.355

DISCUSSION

For the past couple decades, best possible combination of analgesic and local anaesthetic for intra-articular injection is an active topic of research. As seen in our results (Table 1), the baseline characteristics with respect to age, sex and body weight were comparable in both the groups under study. Similarly, the ASA grading of patients chosen for study among the two groups were also comparable.

The exact mechanism of action by which dexmedetomidine causes analgesia by intra-articular route is not understood very clearly, but as suggested by various authors including Dhar et al, it is hypothesised to be similar to clonidine (which acts on alpha-2 adrenergic presynaptic receptors and inhibits release of norepinephrine at peripheral afferent nociceptors).[7] As previously stated by many animal studies, the peripheral action of morphine at intra-articular site is through peripheral opioid receptors (which are inactive under normal circumstances but get activated by injury and inflammation, thus allowing morphine to exert its effects).[8,9]

The mean pain score (VAS) in our study at 6-Hrs, 8-Hrs, 12-Hrs, 16-Hrs and 24-Hrs among the cases studied is significantly higher in group D compared to group M (P-value<0.05 for all) . The mean ± SD of number of hours of analgesia among the cases studied in group M and group D was 16.20 ± 3.75 Hrs (972 ± 225 minutes) and 9.47 ± 1.36 Hrs (584.4 ± 81 minutes) respectively. The minimum – maximum range of number of hours of analgesia in group M and group D was 10-24 hours and 7-12 hours respectively. The number of hours of analgesia was

significantly higher in group M compared to group D (P-value<0.001). Previously there have not been many studies comparing morphine with dexmedetomidine intraarticularly. In a similar study, Agarwal et al in 2017 compared 8mg morphine with 100 microgram dexmedetomidine in combination with 0.25% levobupivacaine 18ml and observed that the mean duration of analgesia was longer in morphine group (9.60±1.11 hours) compared to dexmedetomidine Group (7.68±0.64 hours).[13] Whether analgesic action of morphine is dose dependent or not is a controversy. Likar et al in 1999 studied dose dependent analgesic effect of morphine with regards to postoperative analgesia in arthroscopic knee surgeries. Low doses of morphine (1mg / 2 mg and 4 mg) were compared and it was observed that total hours of supplement free analgesia increased with increased dosage of morphine without significant central adverse effects of morphine.[16] On the contrary, in 2002, Drosos et al compared high dose (15mg) morphine with low dose (5mg) morphine in combination with saline for intra-articular injection and concluded that both had equivocal analgesia.[17] In our study we chose 5 mg morphine as it was observed in previous studies that it produces equivocal analgesia as high dose morphine without the risk of hyperalgesia.[17]

Panigrahi et al in 2015 compared single dose dexmedetomidine (1 µg/kg) versus double dose dexmedetomidine (2 µg/kg) in combination with ropivacaine 0.2% in arthroscopic knee surgeries for postoperative analgesia and observed that with 1 µg/kg dexmedetomidine the duration to request for first post-operative analgesic was 433.2 ± 54.3 min, whereas with 2 µg/kg it was 757.30 ± 207.68 minutes.[10] In our study we chose dexmedetomidine 1 µg/kg to avoid the potential adverse effects such as bradycardia and hypotension and to avoid bias that could occur if double dose dexmedetomidine would be compared with low dose morphine (5mg).

The mean ± SD of total number of analgesic injections among the cases studied in group M and group D was 1.50 ± 0.77 and 2.63 ± 0.49 respectively which was statistically significant. Agarwal et al also had similar observations in terms of requirement of rescue analgesia when comparing morphine 8mg versus dexmedetomidine 100µg in combination with levobupivacaine 0.25%. [13]

Comparison of analgesic effects of ropivacaine 0.25% 2mg/kg when administered alone or in combination with dexmedetomidine 1 – 2 microgram/kg intraarticularly for postoperative analgesia has shown a significantly reduced requirement of rescue analgesic in dexmedetomidine group as compared to ropivacaine group.[18] In 2018, Mostafa et al conducted a double-blinded randomised controlled trial where patients were administered either 19ml bupivacaine 0.5% + 1ml normal saline (group B) or 19ml bupivacaine 0.5% + dexmedetomidine 100 µg (1 ml) (group BD) by intra-articular route after which postoperative pain score, duration of analgesia and requirement of rescue analgesics were monitored. It was observed that group BD had significantly lower pain scores and higher duration of analgesia (458.9 ± 93.5 min) when compared to group B (229.1 ± 83.7 min) that showed higher pain scores and lesser duration of analgesia.[1] Gupta et al in a meta-analysis in including 32 randomised placebo-controlled studies for analysing peripheral and intra-articular analgesic effects of morphine and concluded that morphine showed analgesic effects in all phases of post-operative period, however varied results were obtained with regards to total rescue analgesic consumption.[19] We therefore observed that individual studies of morphine and dexmedetomidine showed reduced rescue analgesic requirements but no direct study was available for comparison of two drugs, except study conducted by Agrawal et al whose findings were consistent with ours.

Of 30 cases in group D, 1 (3.3%) had hypotension and 1 (3.3%) had urinary retention while none of the cases in group M had any side effects. This distribution of difference however shows no statistical significance which was in concordance with previous similar studies.[13] Various studies exploring intra-articular administration of dexmedetomidine have not shown any significant adverse effects attributable possibly to the lower dosage as well as relative avascular nature of intra-articular surface.[1,10,18]

CONCLUSION

Even though the best possible combination of local anaesthetic and adjuvant for optimal pain relief and minimal side effects remains a topic of active research, in our study we found that morphine (5mg) provided superior analgesia than dexmedetomidine (1 micro-gram/kg) when combined with bupivacaine 0.25% considering the difference in time to first request for rescue analgesia and the total analgesic consumption in 24 hours post-operatively. Also, morphine showed better safety profile with no hemodynamic changes. No significant adverse effects were noted in either of the group.

However, we also conclude that dexmedetomidine, although less effectively than morphine, prolongs post-op analgesia compared to intra articular bupivacaine without adjuvant. It does so without compromising hemodynamic profile of the patient significantly.

Our study has a few limitations. A larger study group and more comparative studies for intra-articular analgesic effect of dexmedetomidine versus morphine may be warranted as the available research material directly comparing the two is limited. In our study we did not measure plasma concentration of study drugs due to cost effectiveness. It would help to correlate if clinical effects were due to local or systemic action. Despite being more cost effective than dexmedetomidine, easy availability of morphine remains restricted due to its high abuse potential and dependency thus requiring high pharmacovigilance.

REFERENCES

(1) Mostafa SF, Eid GM, Abdullah MA, Elkalla RS. Intra-articular dexmedetomidine with bupivacaine versus bupivacaine alone for postoperative analgesia after knee arthroscopy. Southern African Journal of Anaesthesia and Analgesia. 2018 May 8;24(2):54-9.
(2) Reuben SS, Sklar J. Pain management in patients who undergo outpatient arthroscopic surgery of the knee. JBJS. 2000 Dec 1;82(12):1754.
(3) Al-Metwalli RR, Mowafi HA, Ismail S, et al. Effect of intraarticular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. Br J Anaesth. 2008;101(3):395–9.10.1093/bja/aen184.
(4) Arti H, Arti S. The effects of intraarticular opioids in pain relief after arthroscopic menisectomy: A randomized clinical trial study. Pakistan journal of medical sciences. 2013 Apr;29(2):625.
(5) El-Hamamsy M, Dorgham M. Intra-articular adjuvant analgesics following knee arthroscopy: comparison between dexmedetomidine and fentanyl. Res J Med Med Sci. 2009 Aug;4(2):355-60.
(6) Yari M, Saeb M, Golfam P, Makhloogh Z. Analgesic efficacy of intra-articular morphine after arthroscopic knee surgery in sport injury patients. Journal of Injury and Violence Research. 2013 Jun;5(2):84.
(7) Dhar R, Nayak SP. Intra-articular dexmedetomidine and clonidine for postoperative analgesia in arthroscopic knee surgery. International Journal of Research in Orthopaedics. 2017 Jan;3(1):103.
(8) Stein C, Millan MJ, Shippenberg TS, Peter KL, Herz AL. Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta and kappa receptors. Journal of Pharmacology and Experimental Therapeutics. 1989 Mar 1;248(3):1269-75.
(9) Berg KA, Patwardhan AM, Sanchez TA, Silva YM, Hargreaves KM, Clarke WP. Rapid modulation of μ-opioid receptor signaling in primary sensory neurons. Journal of Pharmacology and Experimental Therapeutics. 2007 Jun 1;321(3):839-47.
(10) Panigrahi R, Roy R, Mahapatra AK, Prasad A, Priyadarshi A, Palo N. Intra.articular Adjuvant Analgesics following Knee Arthroscopy: Comparison between Single and Double Dose Dexmedetomidine and Ropivacaine A Multicenter Prospective Double.blind Trial. Orthopaedic surgery. 2015 Aug;7(3):250-5.
(11) Cepeda MS, Uribe C, Betancourt J, Rugeles J, Carr DB. Pain relief after knee arthroscopy: intra-articular morphine, intra-articular bupivacaine, or subcutaneous morphine?. Regional Anesthesia and Pain Medicine. 1997 Jan 1;22(3):233-8.
(12) Raj N, Sehgal A, Hall JE, Sharma A, Murrin KR, Groves ND. Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. European journal of anaesthesiology. 2004 Dec;21(12):932-7.
(13) Agarwal RK, Payal YS, Chopra G, Agrawal A. Analgesic effect of intra-articular morphine or dexmedetomidine added with levobupivacaine in arthroscopic knee surgeries-A comparative evaluation. Journal of clinical and diagnostic research: JCDR. 2017 Apr;11(4):UC13.
(14) Moeen SM, Ramadan IK, Elkady HA. Dexamethasone and Dexmedetomidine as an Adjuvant to Intraarticular Bupivacaine for Postoperative Pain Relief in Knee Arthroscopic Surgery: A Randomized Trial. Pain physician. 2017 Nov;20(7):671.
(15) Elsharkawy RA, Ramadan TH, Badran MA. Intra-articular versus intravenous administration of dexmedetomidine in arthroscopic knee surgeries under local anesthesia: A prospective randomized study. Egyptian Journal of Anaesthesia. 2018 Jan 1;34(1):15-9.
(16) Likar R, Kapral S, Steinkellner H, Stein C, Schäfer M. Dose-dependency of intra-articular morphine analgesia. British journal of anaesthesia. 1999 Aug 1;83(2):241-4.
(17) Drosos GI, Vlachonikolis IG, Papoutsidakis AN, Gavalas NS, Anthopoulos G. Intra-articular morphine and postoperative analgesia after knee arthroscopy. The knee. 2002 Dec 1;9(4):335-40.
(18) Singh P. Effectiveness of intra-articular dexmedetomidine as postoperative analgesia in arthroscopic knee surgery (A comparative study).
(19) Gupta A, Bodin L, Holmström B, Berggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anesthesia & Analgesia. 2001 Sep 1;93(3):761-70.