POSTOPERATIVE ANALGESIA FOR ARTHROSCOPIC KNEE SURGERY: A COMPARISON BETWEEN INTRA-ARTICULAR BUPIVACAINE ALONE OR IN COMBINATION WITH MAGNESIUM SULPHATE OR CLONIDINE

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Summary

Various medications have been administered intra-articularly to provide postoperative analgesia after arthroscopic knee surgery. Among the potentially efficient substances, magnesium sulphate and clonidine are of particular interest.

Ninety patients undergoing elective knee arthroscopy were randomly assigned to one of the following groups (n=30) in a double blind manner. A total of 20 ml of medications were given intra articularly in each group. Group B received 19 ml of 0.25% bupivacaine and 1 ml of isotonic saline, Group M received 500 mg (1 ml) of magnesium sulphate added to 19 ml of 0.25% bupivacaine intra-articularly, Group C received 150 µg (1 ml) of clonidine added to 19 ml of 0.25% bupivacaine. Analgesic effect was evaluated by measuring pain intensity (VAS score) and duration of analgesia.

A longer delay was observed between intra-articular injection of study medication and first requirement of supplementary analgesic in group M (12.32±2.8 hours) and group C (10.16±2.4 hours) compared to group B (5.14±1.2 hours). Total consumption of fentanyl citrate in postoperative period was significantly less in group M and group C. No significant side effects were noted.

Both magnesium sulphate and clonidine, added as adjuncts to bupivacaine in patients undergoing arthroscopic knee surgery, improve the quality and duration of post operative analgesia.

Key words: Magnesium sulphate, Clonidine, Bupivacaine, Arthroscopic knee surgery, Intra articular Injection.

Introduction

Pain relief after surgery is one of the fundamental responsibilities of the anesthesiologist. There has always been a search for a simple method for providing postoperative analgesia in patients who undergo knee arthroscopy. Intra-articular administration of various drugs provide satisfactory analgesia in immediate postoperative period. Lidocaine[1], bupivacaine[2], morphine[3], clonidine[4] and more recently, magnesium sulphate[5] have all been administered intra-articularly alone or in combination to provide effective postoperative analgesia.

Clonidine is an imidazoline derivative with alpha$_2$ agonistic activity. It has been shown that the mechanism of peripheral analgesic effects of clonidine results from its inhibition of noradrenline release at terminal nerve fiber endings[4].

N-methyl-D-aspartate (NMDA) receptors play a major role in central nociceptive transmission, modulation and sensitization of acute pain state. In addition to this central location, NMDA receptors are found in skin, muscle, knee joint and they play a role in sensory transmission of noxious signals[5]. Both systemic and intra thecally administered magnesium sulphate produce postoperative analgesia through its voltage dependent block of NMDA receptors[6]. Magnesium sulphate, when administered intra-articularly, has also been shown to provide effective analgesia due to its action on peripheral NMDA receptors present in the peripheral terminal of articular primary afferent fibers in the knee joint and on cellular elements in the joint[5].

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

Methods

The study protocol was approved by the ethical committee of Calcutta National Medical College, Kolkata and informed consent was obtained from every patient. Ninety 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 thirty patients each. Surgical procedures consisted of meniscectomy and ligament repair. Patients having history of cardiovascular, cerebrovascular, respiratory diseases, pregnancy, receiving chronic pain treatment or beta blocking agents, converting enzyme inhibitors, calcium channel blockers, α_2 – adrenergic agonists, drugs known to have interaction with NMDAs and undergoing surgical procedures requiring intra-articular drainage were excluded from the study. On preoperative rounds, patients were explained of the type of procedure and were also taught to interpret the visual analogue scale (VAS) (graded from 0 = no pain to 10 = maximum pain).

All patients were kept fasting after midnight and received diazepam 10 mg orally as premedication. 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(SpO_2) were recorded. An intravenous line was secured.

After pre oxygenation for 3 minutes, induction of anesthesia 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. Anesthesia was maintained 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 $EtCO_2$ between 35 - 40 mm Hg. At the end of surgical procedure, residual neuromuscular paralysis was adequately reversed using intravenous glycopyrrolate and neostigmine and subsequently extubated.

Patients were then randomly allocated (using random table assignment) into three groups to receive one of the following intra-articular solutions (prepared by an individual not involved in the study) which were injected into the knee joint through the cannular sheath after withdrawal of camera, by the orthopedic surgeon (who was also unaware of the nature of the study drugs) before the arthroscope was removed.

In Group B, 19 ml of 0.25% bupivacaine and 1 ml isotonic saline (total volume 20 ml) was administered into the knee joint. In Group M, patients received 500 mg (1 ml) magnesium sulphate added to 19 ml 0.25% bupivacaine (total volume 20 ml). Similarly Group C patients received 150µg clonidine (1 ml) added to 19ml 0.25% bupivacaine (again making a volume. of 20 ml).

All patients were observed postoperatively by resident doctors who were unaware of the study drug. Patients were transferred to post anesthesia care unit and intensity of pain and vital parameters were assessed after thirty minutes and then an hourly interval for 24 hours. When pain scores (VAS) were 4 or more, PCA pump was started to deliver boluses (25µg) of fentanyl citrate as per the requirement of the patient the time was recorded as the duration of analgesia. Total requirement of fentanyl citrate in 24 hours was 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..

Statistical Analysis:

Data were analyzed using computer statistical software system Graph Pad Instat Version 3.05 (Graph Pad software, San Diego, CA) and are presented in a tabulated manner. The results were expressed in mean (SD). Comparisons between groups were performed with the Kruskal Wallis one way ANOVA by ranks or Fisher's exact test for small sample with a 5% risk. Mann – Whitney – Wilcoxon tests were performed when normality tests failed.

Results

The three groups were comparable with regard to age, sex, bodyweight and duration of surgery.

Table 1: Patients Characteristics

Variables/Groups	Group B (n=30)	Group M (n=30)	Group C (n=30)	P value
Age (Year)	36.8 ±10.6	37.9 ±11.8	41.5 ±12.3	0.46
Sex (M/F)	21/9	20/10	19/11	
Weight in Kg	52.48 ± 10.76	56.72±10.78	54.88±10.8	0.52
Duration of Surgery (mins)	90 ± 19.6	85.4 ± 18.82	80.22±18.3	0.58

Intensity of pain was significantly less in Group M compared to Group B at 1 hour ($P<0.01$), 2 hour ($P<0.05$) and 6 hour ($P<0.01$) following surgery. Similarly pain score was significantly lower in Group C also in comparison to Group B at 1, 2 and 6 hours ($P<0.05$). However from 10^{th} hour, intensity of pain was comparable in all three groups (Table 2).

Table 2: Intensity of Pain in Postoperative Period (VAS)

Postoperative Period (hours)	Gr. B (Mean ± SD)	Gr. B (Mean ± SD)	Gr. B (Mean ± SD)
1 hour	2.8±0.8	1.8±0.59**	2.3±0.72*
2 hour	2.9±0.86	2.1±0.69*	2.4±0.81*
6 hour	4.02±1.2	2.3±1.01**	3.02±1.01*
10 hour	3.6±1.01	3.31±1.1	3.78±0.92
14 hour	3.4±0.98	3.92±1.3	3.16±1.0
18hour	3.5±1.01	3.66±1.09	3.26±1.02

* = P< 0.05; ** = P< 0.01

The mean duration of analgesia (delay between the intra-articular injection and the first postoperative analgesic demand) was longer in Group M compared to group B (12.32±2.8 hour vs. 5.14±1.2 hour; mean±SD; p<0.001) . The mean duration of analgesia was also longer in group C compared to group B (10.16±2.4 hour vs. 5.14±1.2 hour; mean ± SD, p<0.001). Fentanyl consumption in first 24 hours was significantly less in group M and group C compared to group B (Table 3).

Table 3: Duration of analgesia and opioid consumption in the postoperative period (Mean± SD).

Variables/Groups	Group B (n=30)	Group M (n=30)	Group C (n=30)
Duration of analgesia(hours)	5.14 ±1.2	12.32 ± 2.8 **	10.16±2.4 **
Fentanyl consumption in 24 hours(mg)	290.6±45.24	206.8±31.18*	189.62±25.44*

P value was determined by comparing bupivacaine (B), magnesium sulphate (M) and clonidine (C) groups. * Significant difference within groups * P<0.01; **P<0.001

Regarding adverse effects, no patient in any group experienced nausea and vomiting. One patient from Group M and one from Group C developed hypotension. One patient from Group M and two patients from Group C developed bradycardia. One patient of Group C experienced drowsiness (Table 4) though none of them were statistically significant.

Table 4: Distribution of patients according to adverse effects

Variables/Groups	Group B (n=30)	Group M (n=30)	Group C (n=30)
Hypotension	0	1	1
Bradycardia	0	1	2
Nausea & vomiting	0	0	0
Drowsiness	0	0	1

Discussion

In an attempt to improve the recovery from arthroscopic knee surgery, research has been directed towards newer techniques for postoperative analgesia. In our study, we observed the effects of magnesium sulphate and clonidine used as adjuvant to bupivacaine administered intra articularly after elective knee arthroscopy Our study demonstrate a significant increase in postoperative analgesia with both magnesium sulphate and clonidine used along with bupivacaine in comparison to bupivacaine alone.

Magnesium sulphate has been used intravenously and intrathecally to increase the duration of postoperative analgesia. The mechanism is probably the voltage dependent block of NMDA receptors[6, 7]. Lawand NB and Willis WD[8] had shown the existence of NMDA receptors in peripheral terminal of articular primary afferent fibres in the knee joint and on cellular elements in the joint, such as synoviocytes and immune cells; in which their activation were found to play a role in nociception. In our study, we wanted to determine whether magnesium sulphate might improve the quality and duration of postoperative analgesia when administered intra articularly.

Alpha$_2$ adrenergic agonists, like clonidine, are supposed to produce analgesia mainly through inhibition of the transmission of nociceptive stimulation in the dorsal horn of spinal cord[9]. Clonidine is reported to mimic the effect of nor-adrenaline release by descending inhibitory control pathways[10]. Topical administration of clonidine may reduce pain intensity in patients with sympathetically maintained pain, suggesting a peripheral site of action for this drug[11]. In our study, we wanted to determine whether intra-articular administration of clonidine might prolong the postoperative pain relief after arthroscopic knee surgery.

The analgesic effect of intra articular magnesium sulphate is partly due to a local effect as we did not observe the side effects usually seen after systemic administration of magnesium sulphate. Even though, it is still possible that analgesic effect of magnesium sulphate occurs though systemic absorption. Further studies are needed to resolve this matter.

The local analgesic effect of clonidine has been documented in a few patients suffering from sympathetically maintained pain (SMP)[11.] The sympathetic nervous system contributes to the sensitization of nociceptors in experimental arthritis[12], where high doses of adrenaline or clonidine reduce arthritic symptoms through action on alpha$_2$ adrenergic receptors[13]. An alternative explanation could be that a local anesthetic effect mediates the intra-articular analgesic action of clonidine. Clonidine indeed inhibits C-fiber action potential in the isolated, desheathed nerve although this effect is less powerful than that of lidocaine[14,15]. Finally it is conceivable also that clonidine may produce analgesia by releasing enkephalin like substances[16], which have been reported to produce a peripheral analgesic effect[3].

The delay between intra-articular injection of bupivacaine with magnesium sulphate and supplementary analgesic administration by PCA pump was 12.32±2.8 hours in our study whereas in case of intra-articular bupivacaine with clonidine, the delay was 10.16±2.4 hours. When we compare our results with other commonly used intra-articular drugs, Joshi and colleagues[17] found that time period for first analgesic request for intra-articular bupivacaine was 280 minutes, intra-articular morphine was 300 minutes, intra-articular bupivacaine and clonidine was 600 minutes, intra-articular bupivacaine and morphine was 720 minutes and combined intra-articular bupivacaine, clonidine and morphine was 950 minutes. In another study by Dal and colleagues[18], time for first analgesic request for intra-articular neostigmine was 113 minutes and for intra-articular ketamine was 109 minutes. It seems that magnesium sulphate and clonidine administered as adjuvant to bupivacaine are able to provide prolonged analgesia than most other intra-articular agents and first analgesic request is even more delayed in case of intra-articular magnesium sulphate than intra-articular clonidine.

There is no significant difference among the incidences of adverse effects in all the three groups.

In conclusion, both magnesium sulphate and clonidine administered as adjuvant to local anesthetic bupivacaine improves the quality and duration of postoperative analgesia and reduces the consumption of fentanyl citrate. Magnesium sulphate, however, produces a longer duration of analgesia than clonidine.

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