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ORIGINAL ARTICLE

Comparative Study of Analgesic Effects of Intraarticular Administration of Equipotent Dose of Morphine and Fentanyl with Bupivacaine and Bupivacaine alone in Arthroscopic ACL Reconstruction

[1]Somnath Mandal, [2]Dipasri Bhattacharya, [3]Sandip Roy, [4]Anjana Bose, [5]Mohan C Mandal, [6]Gautam Choudhury

ABSTRACT

Intraarticular (IA) local anesthetics and opioids are often used for the management and prevention of pain after arthroscopic anterior cruciate ligament (ACL) reconstruction. In this study, analgesic efficacy of IA administration of equipotent dose of morphine and fentanyl with bupivacaine and bupivacaine alone in arthroscopic ACL reconstruction under spinal anesthesia has been compared. Forty-five patients, aged between 15 and 55 years, of American Society of Anesthesiologists (ASA) grade I and II were assigned into three equal groups (n = 15) in a randomized double-blind protocol. Group B received 20 mL of 0.25% bupivacaine and 1 mL normal saline (NS); group BF received 20 mL of 0.25% bupivacaine and 50 μg (1 mL) fentanyl; and group BM received 20 mL of 0.25% bupivacaine and 5 mg (0.5 mL) morphine and 0.5 mL NS through IA route at the end of the procedure. Postoperative analgesia was assessed by visual analogue scale (VAS) score. The VAS score in BM group was less during all the time in the postoperative period compared with the other two groups. This group also experienced longer duration of postoperative analgesia and lesser rescue analgesic. Intraarticular administration of morphine and bupivacaine is safe and provides prolonged analgesia with minimal side effects compared with bupivacaine and fentanyl and bupivacaine alone.

Keywords: Anterior cruciate ligament reconstruction, Bupivacaine, Fentanyl, Intra-articular administration, Morphine, Visual analogue scale score.

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[1]Postgraduate Trainee, [2]Professor and Head, [3,6]Professor [4]Assistant Professor, [5]Associate Professor

[1,2]Department of Anesthesiology, Critical Care and Pain, RGK Medical College, Kolkata, West Bengal, India

[3]Department of Orthopedics, RGK Medical College and Hospital, Kolkata, West Bengal, India

[5]Department of Anesthesiology, North Bengal Medical College Kolkata, West Bengal, India

[6]Department of Anesthesiology, Critical Care and Pain, RGK Medical College, Kolkata, West Bengal, India

Corresponding Author: Dipasri Bhattacharya, Abhyudoy Housing, Kolkata, West Bengal, India, Phone: +919433396306 e-mail: dipasribhattacharya123@gmail.com

INTRODUCTION

Arthroscopic anterior cruciate ligament (ACL) reconstruction is one of the most common surgical procedures done all over the world. Pain is one of the important causes of this surgery preventing patients' rehabilitation.[1] The pain is caused by irritation of free nerve endings of synovial tissue, anterior pad of fat, and joint capsule during surgical excision and resection.[2] Adequate control of postoperative pain helps the patients to begin early physiotherapeutic rehabilitation, enable early hospital discharge, and reduce hospitalization costs. It also prevents arthrofibrosis, improves tonus and muscle trophism, and allows better motor control over the limb.[3,4] A variety of types of postoperative analgesia are frequently used. An ideal drug should provide adequate analgesia and should be safe with low incidence of complications and side effects. Intra-articular (IA) use of drugs can avoid systemic action (intravenous or oral) and their side effects.[5] This is, therefore, an attractive method used in clinical practice. Several drugs have been proposed and tested for IA use, including nonsteroidal anti-inflammatory drugs,[6] opioids,[7] and local anesthetics.[8] Intraarticular approach acts on the peripheral receptors for prevention of postoperative pain. Intra-articular route of drug administration is a good example for management of pain after joint surgery utilizing the peripheral receptors. It provides analgesia locally with minimal systemic side effects.[9,10] Current evidence shows that the use of single administration of IA bupivacaine is effective for postoperative pain management in patients undergoing arthroscopic knee surgery, with satisfactory short-term safety.[11] Combination of local anesthetic with opioid prolongs the duration of analgesia.[12]

Intra-articular opioids like morphine[12] and fentanyl[13] have been shown to reduce postoperative pain and supplemental analgesic consumption for arthroscopic knee surgery. But there is no such study where comparison of analgesic efficacy of IA administration of equipotent dose of morphine and fentanyl has been performed. Therefore, the purpose of this clinical investigation was to compare the analgesic efficacy of IA administration of equipotent dose of morphine and fentanyl with bupivacaine and bupivacaine alone in arthroscopic ACL reconstruction.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee and informed written consent from the patients the study was performed. A total of 45 adult patients were randomly allocated into three equal groups (n = 15 in each group) using computer-generated random number list in a double-blind protocol. All the patients of American Society of Anesthesiologists (ASA) I and II physical status, aged between 15 and 55 years of both sexes with body weight of 50 to 70 kg undergoing elective arthroscopic ACL reconstruction under spinal anesthesia were included in this study. Patients of ASA III or more physical status or those having any spinal deformity with comorbidities like hypertension, diabetes, ischemic heart disease, any contraindication to regional anesthesia, allergy to local anesthetic, preexisting neurological deficit, pregnancy, lactation, and psychiatric illness were excluded from the study.

Group B: Received 20 mL of 0.25% bupivacaine + 1 mL normal saline (NS).

Group BF: Received 20 mL of 0.25% bupivacaine with 50 µg (1 mL) fentanyl.

Group BM: Received 20 mL of 0.25% bupivacaine with 5 mg (0.5 mL) morphine + 0.5 mL NS.

Total volume of drug of each group was 21 mL. This study was conducted in the orthopedic operation theater of R.G. Kar Medical College and Hospital, Kolkata, for 6 months.

All patients were clinically examined in the preoperative period, when the whole procedure was explained. Visual analogue scale (VAS) of 10 cm (0, no pain and 10, worst possible pain) was also explained to each patient during the preoperative visit.

The laboratory investigations, such as blood for hemoglobin, total count, differential count, erythrocyte sedimentation rate, urea, creatinine, and fasting blood sugar/postprandial blood sugar were advised during preanesthetic checkup for all patients. A 12-lead electrocardiography (ECG) and chest X-ray were also advised. Routine monitoring in the form of noninvasive blood pressure, ECG, and pulse oximetry was used perioperatively. The anesthetic technique was standardized for all patients. Lumbar puncture was done in a sitting position at L3 and L4 intervertebral space in midline approach with 26 gauge spinal needle; 3 mL of 0.5% (15 mg) hyperbaric bupivacaine was administered in the subarachnoid space and then the patients were placed in supine position immediately. After 5 minutes of subarachnoid injection confirming the sensory blockade height (T10), arthroscopic procedure was allowed to start. During the procedure if any patient needed further dose of analgesia, that patient was excluded from the study. At the end of the surgery before the skin closure, the study drug was administered through the port site in the IA space by the surgeon who was unaware of group allocation. All the patients were sent to postanesthesia care unit (PACU) after surgery. All the patients were assessed in the postoperative period by the PACU nurse who was completely blind to the study drug and group allocation. Noninvasive blood pressure, SPO_2, pulse, and heart rate were recorded immediately after anesthesia and thereafter at every 5 minutes interval for intraoperative assessment. Intensity of pain was assessed by VAS score in the immediate postoperative period and thereafter at the 1st, 4th, 8th, 12th, 16th, 20th, and 24th postoperative periods, which was explained to the patient preoperatively. Rescue analgesic was given when VAS score ≥3 or on patient demand. Injection diclofenac sodium (75 mg intramuscular) was used as rescue analgesic. Our study ended at the time of discharge of the patient. First postoperative analgesia request time and total diclofenac used in the first 24 hours were recorded. Sedation was assessed by Ramsay Sedation Score (RSS) for first 4 hours.

SAMPLE SIZE CALCULATION

Sample size was calculated based on a previous study by Ei-Hamamsy and Dorgham[13] in arthroscopic knee surgery comparing IA bupivacaine and fentanyl. According to this study, the time to first postoperative analgesic required for bupivacaine was 230 ± 85 minutes and for fentanyl it was 465 ± 90 minutes.

Considering 90-minute difference in first analgesic dose as minimally clinical significant difference and using the formula given below, the sample size was calculated:

$$n = (Z\alpha + Z\beta)^2 (S_1^2 + S_2^2)/d^2$$

where $Z\alpha = 1.96$ (considering 95% confidence level)

$Z\beta = 0.84$ (assuming 80% power of the test)

S_1 and S_2 = expected standard deviation in duration of analgesia in minutes in groups II and BF, and d = minimum clinically important difference which was 90 minutes.

Now, putting all the values we get a sample size of 15 (approximately) in each group. So, the number of people required in each group was 15.

Statistical Analysis

Statistical data were collected and analyzed using appropriate statistical tool. Statistical Package for the Social Sciences (SPSS) v20 was used. Analysis of variance test and chi-square test were used. A value of $p < 0.05$ was considered to be significant.

Table 1: Comparison of demographic data between the three study groups

Parameter	Group B Bupivacaine (n = 15)	Group BF Bupivacaine and fentanyl (n = 15)	Group BM Bupivacaine and morphine (n = 15)	p-value
Age (years)	31.00 ± 9.06	29.93 ± 8.94	33.20 ± 8.71	0.951
Sex (male:female)	13:2	8:7	12:3	0.092
Height (cm)	165.33 ± 7.28	161.40 ± 9.25	164.73 ± 6.78	0.065
Body weight (kg)	55.07 ± 7.40	56.67 ± 5.602	55.80 ± 5.116	0.234
ASA physical status (I:II)	13:2	7:8	11:4	0.055

Table 2: Duration of postoperative analgesia in hours

Parameter	Groups	n	Mean	Std deviation	Std error mean	p-value
Duration of analgesia [Time of first analgesic request (hours) postoperatively]	B	15	4.00	0.000	0.000	0.015
	BF	15	6.00	0.000	0.000	
	BM	15	10.07	0.258	0.067	

Table 3: Rescue analgesic required in 24 hours in milligrams

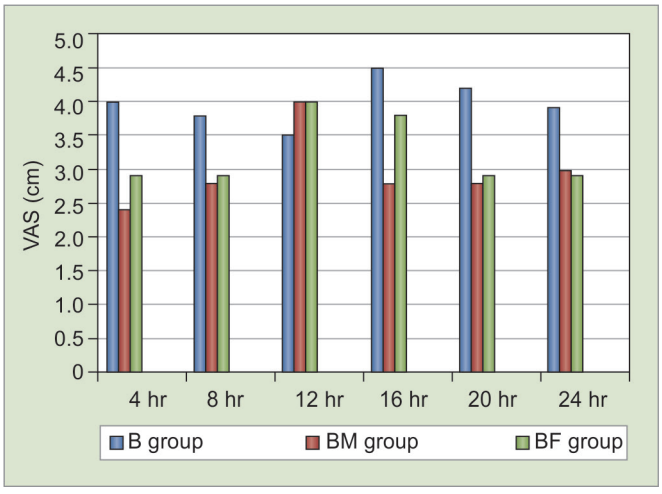
Parameter	Groups	n	Mean	Std deviation	Std error mean	p-value
Total amount of diclofenac sodium (mg) as rescue analgesic	B	15	260	38.73	10.00	0.004
	BF	15	140	26.39	6.81	
	BM	15	90	31.05	8.01	

RESULTS

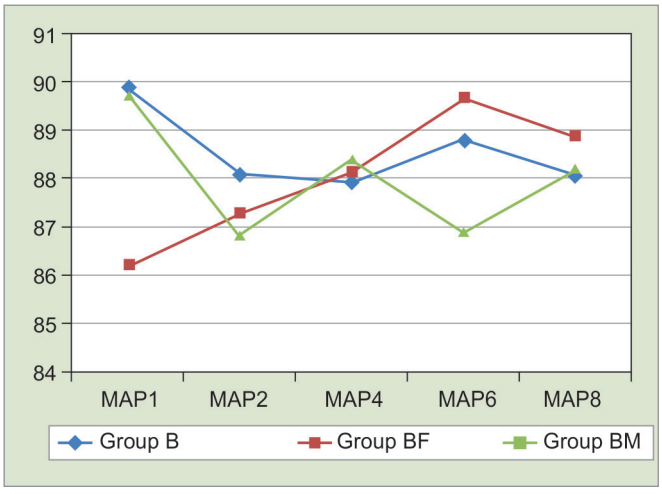
There were no significant differences between the two groups with regard to demographic data, such as age, sex, weight, and height (Table 1). Time for the request of first postoperative rescue analgesia in group BM [(10.07 ± 0.258) hours] was longer compared with group BF [(6.00 ± 0.000) hours ($p < 0.05$)] and group II [(4.00 ± 0.000) hours ($p < 0.05$)] (Table 2). Total amount of rescue analgesia requirement in the first 24 hours in the postoperative period was significantly less in group BM [(90.00 ± 31.05) mg ($p < 0.05$)] compared with group BF [(140.00 ± 26.39) mg ($p < 0.05$)] and group II [(260.00 ± 38.73) mg ($p < 0.05$)] (Table 3). The VAS score in bupivacaine and morphine group was less all the time in the postoperative period compared with the other two groups (Graph 1). Ramsay Sedation Score at 1st, 2nd, 3rd, and 4th hours was the same (RSS = 1) for all three groups (Graph 2). No incidence of adverse effects, such as nausea, vomiting, urinary retention, and itching was observed in anyone in the study population.

DISCUSSION

Fast rehabilitation after arthroscopic ACL reconstruction surgery requires the use of effective methods for postoperative pain control. A variety of analgesic techniques have been used to manage postoperative pain after arthroscopic knee surgery. Intra-articular administration of drugs is one of them. Several drugs have been proposed and tested for IA use, including nonsteroidal anti-inflammatory drugs,[6] opioids,[7] and local anesthetics.[8] Prolonged postoperative analgesia and decreased



Graph 1: Comparison of VAS score at 1st, 4th, 8th, 12th, 16th, 20th, and 24th postoperative hours



Graph 2: Mean blood pressure over time in groups II, BF, and BM

requirement of rescue analgesia in the IA drug administration may be due to a slower rate of absorption through poorly vascular IA surface.

Bupivacaine is a long-acting local anesthetic agent. It can be used in IA route alone or along with different opioids to reduce postoperative pain in different arthroscopic knee surgeries. No clinically significant ECG abnormalities or serious central nervous system events occur with the dose commonly used. Recent studies have demonstrated dose-dependent chondrotoxic effects of bupivacaine *in vitro* as well as *in vivo*,[14,15] suggesting that lower dose of IA bupivacaine is potentially the least harmful.[16] A dose of 50 mg bupivacaine is considered to be safe.[11]

Fentanyl is a lipophilic opioid that can be added to IA bupivacaine in different arthroscopic knee surgeries like arthroscopic ACL reconstruction. Different studies showed that it improves the quality of postoperative analgesia without producing significant side effects. Mandal and Saudagar[5] in 2002 concluded that although fentanyl is a short-acting narcotic drug, its IA administration provided prolonged postoperative analgesia and the minimum effective dose should be 50 μg.

Morphine is a hydrophilic opioid. It has relatively poor lipid solubility and high degree of ionization at physiologic pH. It can be used in IA route for postoperative analgesia in different arthroscopic knee surgeries. Arti and Mehdinasab[12] in 2011 carried out a study and showed that 5 mg IA morphine was safe and useful and its use with bupivacaine is recommended for pain relief after arthroscopic ACL reconstruction. Fentanyl is about 100 times more potent than morphine.[3] So if the IA dose of morphine is 5 mg then the equipotent dose of fentanyl will be 50 μg. So we used bupivacaine (20 mL of 0.25%, total dose of 50 mg) with morphine (5 mg) or fentanyl (50 μg) for IA administration in our study.

In this study, we have observed the duration of analgesia in bupivacaine and morphine group was longer than bupivacaine and fentanyl and bupivacaine alone groups, which conforms to the study of Danieli et al.[17] The VAS score in bupivacaine and morphine group was less all the time in the postoperative period compared with the other two groups, which was supported by Danieli et al[17] and Koppolu et al.[18] There was no significant difference in the sedation score in morphine group and fentanyl group.

Morphine is an opioid with slow onset of action. It is known that the peripheral tissues have opioid receptors and opioid produces local analgesia in the presence of inflammation (following surgery), but not in the normal tissues.[19]

In our case, all patients received spinal anesthesia, and at the end of operation, they received IA injection of the drug. This not only prolonged analgesia in all cases but also reduced the systemic side effects as was evident by stable hemodynamic with no side effects.[20]

Total dose of rescue analgesic was higher in bupivacaine group compared with the other groups. Limitation of this study is the small sample size. To prove morphine and bupivacaine as better combination for IA administration, more studies with larger sample size are required.

To conclude, IA administration of morphine and bupivacaine is safe and provides prolonged analgesia with minimal side effects in patients undergoing ACL repair under spinal anesthesia compared with bupivacaine and fentanyl and bupivacaine alone.

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