Original Research Article

Intraarticular fentanyl compared with morphine for pain relief following arthroscopic surgery of knee

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Abstract

Background and Aims: We sought to compare the analgesic effect of intra-articular administration of morphine, fentanyl and placebo following arthroscopic surgery of knee. **Methods**: A prospective, randomised, placebo controlled, double blind comparative study conducted in 60 patients of either sex, who underwent arthroscopic surgery of knee, between the age group of 18 and 65 years and of ASA class II physical status and I were included in the study. Patients were randomly assigned equally to one of the 3 groups of 20 each by a sealed envelope method. The groups were Group A- Patients receiving IA Fentanyl 50mcg in 20 ml normal saline. Group B - Patients receiving IA Morphine 3mg in 20 ml normal saline. Group C-Patients receiving IA 20 ml normal saline as placebo. Parameters monitored were degree of analgesia along with hemodynamic parameters and side effects. Data were analysed using student's t-test for continous variables and Chi-Square test was used to find out the association between categorical variables. **Results:** Pain scores at one, two, four and eight hours were greater at all times in placebo group. Pain scores for fentanyl and morphine were similar at one hour, but thereafter less ($p < 0.001$) for IA-Fentanyl group. **Conclusion:** Intra-articular 50-mcg fentanyl provided better post-operative analgesia than 3mg morphine.

Key Words: Intraarticular, Analgesia, Opioids, Arthroscopy.

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INTRODUCTION

Pain is a common human experience, a symptom frequently encountered in clinical practice that is usually associated with actual or impending tissue damage. "Failure to relieve pain is morally and ethically unacceptable." Adequate pain relief could be considered a basic human right. Pain is not a straightforward sensory "perception". It is an "experience" as the physiological sensation is inseparable from the associated emotional distress. Pain after orthopaedic surgery depends on the site and extent of surgery. Arthroscopic procedures are routinely performed on outpatient basis and have spared patients large incisions and decreased morbidity compared with open incisions but has not eliminated pain. At present, several techniques are available to treat pain following arthroscopic surgeries; these include the use of opioids (either providing peripherally or centrally mediated analgesia), local anaesthetics, non-steroidal anti-inflammatory drugs, corticosteroids, clonidine and cryotherapy. The evidence of synovial opioid receptors supports the use of intra-articular (IA) opioids to achieve a peripheral opiate receptor-mediated analgesia. A number of such studies have demonstrated effective and prolonged analgesia from small intraarticnlar (LA) doses of morphine.[1-8] In contrast, other investigators have failed to demonstrate an analgesic effect of IA morphine.[9-15] Morphine is the most frequently used opioid analgesic. Better postoperative analgesia was reported with intra-articular fentanyl when compared to morphine. Various direct and indirect measures had evaluated the effects of intra-articular application of opioids on postoperative pain relief. Here we sought to compare the analgesic

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efficacy of intra-articular administration of morphine and fentanyl following arthroscopic surgery of knee.

MATERIAL AND METHODS

The study designed was a prospective, randomised, placebo controlled, double blind comparative study conducted at Amrita Institute of Medical Sciences and Research centre, Kochi. 60 patients of either sex, who underwent arthroscopic surgery of knee; between the age group of 18 and 65 years and of ASA class, I and II physical status were included in the study. Patients of ASA III and IV physical status and patients on chronic medications were excluded from the study. After approval from the hospital ethics committee, 60 patients were randomly assigned equally to one of the three groups of 20 each by a sealed envelope method.

Group A: Patients receiving IA Fentanyl 50mcg in 20 ml normal saline.

Group B: Patients receiving IA Morphine 3mg in 20 ml normal saline.

Group C: Patients receiving IA 20 ml normal saline as placebo.

The randomized assignment was sealed in an envelope and handed over to a senior anaesthesia technician, who would verify the group on the day of surgery and prepared the bolus solution of drug with 20ml 0.9% Normal saline under aseptic precautions. This was injected intra-articularly at the end of the arthroscopic surgery by the operating surgeon. The patient, the operating surgeon, the anaesthesiologist conducting the case and the nursing staff who assessed the pain and delivered rescue medication were blinded regarding the drug used.

Anaesthetic technique and performance

All patients were premedicated with H-2 blocker (Ranitidine 150 mg) and benzodiazepine (Alprazolam 0.5mg). Postoperative pain intensity was assessed by visual analogue scale which is a "0 to 10" cm Scale, with score 0 as "No Pain", upto 3 mild bearable pain, "3 to 5" as "Moderate Pain", greater than "5" as "Severe Pain" and "10" as "Worst Pain". All patients were explained about VAS before surgery and written informed consent was obtained. After shifting the patient to operation theatre, an 18G intravenous cannula was secured and connected to intravenous fluid. Pre-induction monitoring included pulse-oximeter, non-invasive blood pressure monitoring and continuous electrocardiography. Injection midazolam 1mg and injection glycopyrrolate 0.01mg/kg was administered intravenously. After pre-oxygenation for 3 minutes with 100% oxygen, anaesthesia was induced with injection fentanyl 2mcg/kg and injection propofol 2mg/kg intravenously. After loss of consciousness and eyelash reflex, appropriate size laryngeal mask airway (LMA) was placed. After confirming proper placement of LMA, patient's ventilation was assisted or left breathing spontaneously if found satisfactory with continuous capnography monitoring. Oxygen, nitrous-oxide combination was administered in 1:2 ratios with isoflurane 0.6% to 2% concentration throughout the procedure. No further analgesics or sedative medications were given for the duration of the procedure. At the end of the surgical procedure, before tourniquet was released the surgeon injected study drug intra-articularly and patient was extubated.

Pain Assessment and Data Collection

Post operative pain intensity scores and hemodynamic data (heart rate and blood pressure) were recorded 15 min after extubation and noted as the score at 0 hour, further pain scores were recorded at 1, 2, 4 and 8 hours by the bedside nursing staff who was explained about visual analogue scale and rescue analgesia. Any VAS>3 were given injection tramadol 50mg intravenously as rescue analgesia. The staff recorded the time of first rescue analgesia and total dose of rescue analgesia during 8 hours. Side effects like nausea, vomiting, pruritis, urinary retention and respiratory depression were specifically looked for during the observation period.

Statistical Methodology

The study sample size was determined to be at least 18 patients in each of the 3 groups studied, which would provide 80% power for detecting a significant difference in analgesic effect. The student t – test was used both to assess homogeneity and to compare the main results and to find difference between the groups for continuous variables. Data were analyzed using SPSS 11.0 software. A descriptive statistical tool such as mean was used to represent the continuous data. Differences within the groups were analyzed using analysis of variance and Post Hoc test was used to test the difference between individual groups. Chi-Square test was used to find out the association between categorical variables. In all cases, the level of statistical significance (P value) was less than 0.05.

OBSERVATIONS AND RESULTS

During the period of August 2006 and November 2007, 60 patients in age group of 18-65 years were studied. Distribution of patients in each of the three groups was similar with respect to demographics, diagnosis and operative procedures.

Age and Sex Distribution

The mean age in the study population was 35 years. The age comparison was done by student t test, which demonstrated no significant difference in its distribution among 3 groups.

Table 1: Age distribution among 3 groups

	GROUP (mean + /std deviation)		
	A (Fentanyl)	B(Morphine)	C(Placebo)
AGE (years)	33.3+/-10.5	36.8+-12.0	34.0+/-10.4

Table 2: Sex distribution among 3 groups

	GROUP		
SEX	A (Fentanyl)	B(Morphine)	C(Placebo)
F	3	5	3
M	17	15	17

49 male and 11 female patients were enrolled in this study. The group comparison was done by student t test, which demonstrated no significant difference in its distribution among 3 groups with regard to distribution of sex and also there was no difference between groups in terms of ASA (p – 0.951). The group comparison was done by student t test, which demonstrated no significant difference in its distribution among 3 groups with regard ASA physical status.

Table 3: Surgeries among 3 groups

	GROUP		
SURGERY	A(Fentanyl)	B(Morphine)	C(Placebo)
ACL Reconstruction	11	10	13
Menisectomy	4	3	5
Partial Menisectomy	0	2	0
Synovectomy	5	5	2

There is no difference between groups in terms of surgeries (p –0.846).

Comparison Of Analgesia: Visual analogue scores assessed at 0, 1, 2, 4, and 8 hours were compared with chi-square test for statistical difference among the groups.

Visual Analogue Score with respect to groups at 0 hour;

Table 4: Vas at 0 hour

	Group		
VAS	A(Fentanyl)	B(Morphine)	C (Placebo)
0	20	20	0
3	0	0	2
4	0	0	9
5	0	0	6
6	0	0	3

Table 5: Comparison of analgesia at 0 hour

	Group		
	A (Fentanyl)	B (Morphine)	C (Placebo)
VAS <3	20	20	0
VAS >3	0	0	20

VAS<3 - Adequate analgesia. VAS >3 - Inadequate analgesia.

Mean visual analogue scores analysed during the 0 hour were lower (VAS-0) in A and B groups, when compared to group (C) (Table 5). There was statistically significant difference among 3 groups with respect to VAS at 0 hour (p- 0.000). Pain intensity scores were higher in-group (C) when compared with other 2 groups. However, there was no statistical difference among A and B groups (p-0.944). All Placebo group patients received rescue analgesia during 0 hour (VAS > 3) which indicated inadequate analgesia (Table 6), while none in other 2 groups.

Visual Analogue Score with respect to groups at 1 hour;

Table 6: Vas at 1 hour

	GROUP		
VAS	A (Fentanyl)	B (Morphine)	C (Placebo)
0	20	20	0
3	0	0	0
5	0	0	5
6	0	0	10
7	0	0	5

Table 7: Comparison of analgesia at 1 hour

	GROUP		
	A (Fentanyl)	B (Morphine)	C (Placebo)
VAS <3	20	20	0
VAS >3	0	0	20

Visual analogue scores compared at 1 hour (table 6) had high scores in placebo in comparison with A and B groups. There was significant difference (p- 0.000) between placebo and the drug groups. However, there was no significant difference (p-0.944) between the two drug groups.

Visual Analogue Score with respect to groups at 2 hours;

Table 8: Vas at 2 hours

	GROUP		
VAS	A (Fentanyl)	B (Morphine)	C (Placebo)
0	20	8	0
1	0	7	0
2	0	5	0
3	0	0	0
4	0	0	1
5	0	0	5
6	0	0	10
7	0	0	4

Table 9: Comparison of analgesia at 2 hours

	GROUP		
	A (Fentanyl)	B (Morphine)	C (Placebo)
VAS <3	20	20	0
VAS >3	0	0	20

At 2nd hour VAS score (Table 8) showed significant difference between placebo and other two groups (p-0.000). Pain intensity scores was significantly different (p-0.002) between group A and B. Even though morphine had significant p values when compared to fentanyl, none of the patients received rescue analgesia (Table 9).

Visual Analogue Score with respect to groups at 4 hours;

Table 10: Visual analogue score at 4 hours

	Group		
VAS	A (Fentanyl)	B (Morphine)	C (Placebo)
0	11	2	0
1	6	2	0
2	3	10	0
3	0	6	1
4	0	0	7
5	0	0	7
6	0	0	1
7	0	0	3
8	0	0	1

Table 11: Comparison of analgesia at 4 hours

	GROUP		
	A (Fentanyl)	B(Morphine)	C(Placebo)
VAS <3	20	14	0
VAS >3	0	6	20

At 4 hours, there was significant difference with respect to VAS score among all 3 groups (Table 10). Placebo had high scores (p-0.000). A and B groups differed significantly as 6 patients (morphine) (p-0.04), had inadequate analgesia with VAS>3. **Visual Analogue Score with respect to groups at 8 hours;**

Table 12: Vas at 8 hours

VAS	GROUP		
	A (Fentanyl)	B(Morphine)	C (Placebo)
0	10	0	0
1	1	0	0
2	8	0	0
3	1	4	0
4	0	10	3
5	0	5	8
6	0	1	7
7	0	0	2

Table 13: Comparison of analgesia at 8 hours

	Group		
	A (Fentanyl)	B (Morphine)	C(Placebo)
VAS<3	19	0	0
VAS>3	1	20	0

At 8 hours, P values were significantly different among 3 groups. Placebo was significantly different (p-0.000) from A and B groups, in terms of VAS score (Table 12). However, the number of patients with inadequate analgesia (VAS>3) was same in morphine and placebo group (Table 13). VAS score in morphine group showed significant difference when compared to fentanyl. (Table 13). **Heart Rate with respect to groups from 0 to 8 hour**

Table 14: Comparison of heart rate from 0 to 8 hour

	Heart Rate bpm(mean +/-std deviation)		
Time	A(Fentanyl)	B (Morphine)	C(Placebo)
Hour-0	70.7+/-10.6	75.15+/-7.3	80.05+/-5.9
Hour-1	69.85+/-8.9	72.25+/-4.8	86.55+/-4.6
Hour-2	71.2+/-9.0	75.5+/-4.7	88.45+/-4.2
Hour-4	71.15+/-9.1	78.75+/-5.2	83.25+/-5.0
Hour-8	74.75+/-7.6	84.6+/-5.6	84.65+/-4.0

Mean arterial pressure with respect to groups from 0 to 8 hours.

Table 15: Comparison of mean arterial pressure from 0 to 8 hour

	MAP mm Hg (mean +/- std deviation)		
Time	A(Fentanyl)	B(Morphine)	C (Placebo)
Hour-0	90.3+/-6.3	90.4+/-5.5	94.1+/-5.7
Hour-1	87..6+/-6.3	86.8+/-3.9	98.6+/-3.7
Hour-2	88.6+/-4.2	85.2+/-4.0	101.8+/-4.4
Hour-4	89.6+/-4.6	86.3+/-3.4	96.8+/-5.1
Hour-8	89.7+/-3.9	87.2+/-4.2	98.4+/-3.1

Heart rate and MAP was higher in the placebo group when compared to A and B group (Table 15) through out observation period and was statistically significant (p-0.01). Nevertheless, there was no significant difference between the other 2 drug groups (p-0.00).

Table 16: Time of first rescue analgesia

	No. of Patients								
DURATION (hour)	0	1	2	3	4	5	6	7	8
Fentanyl	0	0	0	0	0	0	0	0	1
Morphine	0	0	0	0	6	7	5	2	0
Placebo	20	0	0	0	0	0	0	0	0

Table 17: Total dose of analgesic received in 8 hours

	No. of Patients	Total dose of Tramadol in mg.
Fentanyl	1	50
Morphine	20	1000
Placebo	20	2050

Patients in Placebo group had highest dose of rescue analgesia followed by morphine group, while fentanyl group had none or least respectively. None of the patients in any of the group had any of these side effects during the observation period.

DISCUSSION

The knee is a joint in which arthroscopy has the greatest IA surgical application. There is rich innervation to articular capsule, tendons, ligaments, synovium and periosteum via a mixture of free nerve endings and

receptors. These sensory nerves respond to mechanical stimuli such as stretching of the joint capsule as well as intra-articular surgical instrumental intervention. Many nerve fibers, for example, are non-responsive under normal conditions but react after inflammation, therefore, there is a potential for acute injury or inflammation to sensitize nerves such that they respond even when the original stimuli is removed. Hence, just like any other surgical procedure, the arthroscopic intervention of the knee joint can cause considerable postoperative pain that limits ambulation and combined with a stress induced hypercoaguable state, may contribute to an increased incidence of deep vein thrombosis. Postoperative analgesia following arthroscopic knee surgery can be provided either by systemic administration of narcotic and non narcotic analgesic drugs or IA administration of local anaesthetic drugs,[16] non-narcotic analgesic drugs (ketorolac)[17] and narcotic analgesic drugs (morphine,[18] pethidine and fentanyl). Intermittent systemic analgesic administration cannot keep the patient totally pain free for all times where as IA route requires specialized technique, possible only when patient undergoes surgical procedure. However, IA route provides qualitatively better analgesia without major side effects, e.g. respiratory depression. In our study we sought to evaluate the analgesic efficacy and the need for rescue analgesia with 3mg morphine and 50mcg fentanyl were compared with a placebo (20 ml 0.9% normal saline) when administered intra-articularly following arthroscopic knee surgery. We found that in immediate postoperative period at 0 and 1 hour fentanyl and morphine had good and equal analgesic effect as none of the patients required rescue analgesia. In contrast, all 20 patients in placebo group had moderate to severe pain and all required supplementary analgesics. These results were similar to inferences of Kazemi *et al*[19], Mandal P *et al*[20], Varrassi *et al*[21], and Varkel *et al*[22] studies. Further comparing the analgesic efficacy at 2 hours postoperatively all 20 patients had no pain in fentanyl group indicating good analgesic effect. Even though morphine provided analgesia, 12 patients had mild pain but did not require rescue medication. This was significantly different from fentanyl. This was similar to study by Rosseland *et al*, who concluded that postoperative analgesic effect of IA morphine was found only in subgroup of patients with higher pain intensity in the immediate post anaesthetic period. The possible reasons quoted were lack of inflammation that was prerequisite for peripheral opioid analgesia, lack of expression of opioid receptors and due to weak pain stimulus. At 4 hours, the analgesic efficacy of morphine was wearing off with six patients having moderate pain and requiring analgesics supplementation. Nevertheless, this was better than placebo group, where everyone had moderate pain even after rescue analgesia. In comparison with morphine and fentanyl, fentanyl had good analgesic effect with 9 patients having mild pain, but without requiring analgesics. This was demonstrated by Varkel *et al*[23] with similar doses of morphine and fentanyl as in our study and concluded that postoperative analgesia with IA fentanyl was better when compared with morphine during 8 hours of observation. At 8 hours, morphine did not from that of placebo group as all 20 patients had inadequate analgesia and required supplementary analgesics. This was similar to the conclusion drawn by Heard *et al* who considered IA morphine no better than placebo, except for prolonging the time of first analgesic request and for its systemic effect. Fentanyl was a better analgesic than morphine when administered intra-articularly and differed significantly in terms of pain scores and rescue analgesic requirement in comparison to morphine. This was consistent with study of Mandal P *et al*[21] who inferred 50mcg fentanyl provided longer duration of totally pain free state without any supplementary analgesic therapy and fentanyl was better analgesic than morphine at 8 hours duration. We compared the hemodynamic data in which the placebo group had higher heart rate and mean arterial pressure than the other two drug groups and this was statistically significant. This could be due to pain and anxiety causing sympathetic stimulation. However, no significant difference with hemodynamic data among the two drug groups. We also noted the time of request for first rescue analgesia, with placebo group requiring analgesics in the immediate postoperative period itself. With better early analgesic effect only one patient requiring first rescue analgesia at 8th hour of observation in fentanyl group, while Six patients required first rescue analgesia at 4th hour of observation in morphine group. The total dose of analgesic consumption in 8 hours showed placebo group requiring highest dose (2050 mg of tramadol intravenously for 20 patients), followed by morphine group (1000mg of tramadol) while fentanyl group hardly required any analgesic dose. None, in any of the three drug groups, had significant side effects during 8-hour observation period.

CONCLUSION

Intra-articular fentanyl provided effective post-operative pain relief and reduced rescue analgesic requirement in the first 8 hours following arthroscopic knee procedures. It also revealed that fentanyl is better intra-articular analgesics than morphine. While intra-articular morphine was found to provide good pain relief during early post-operative period, it lacked analgesic efficacy in the later half of our observation period.

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