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ORIGINAL ARTICLE

Comparing the Efficacy of Intra-Articular Dexmedetomidine in Combination with Fentanyl versus Fentanyl Alone for Post-surgical Analgesia after Knee Arthroscopy

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Abstract

Background: Effective management of post-surgical pain in knee arthroscopy is crucial for early rehabilitation of patients. This study is aimed to analyse the potency of fentanyl when administered intra-articularly alone and in combination with dexmedetomidine for postsurgical analgesia after knee arthroscopy. **Methods:** Prospective double-blinded randomized controlled study included 60 patients of elective knee arthroscopy. The patients were classified in group I (100-mcg fentanyl) and group II (treated with 100-mcg + 50-µg dexmedetomidine). VAS score and time for foremost requirement of analgesia was documented. **Results:** The difference in the VAS scores across the two groups was statistically significant for initial 6 hours. In groups I, 18 (60%), and II, 4 (13.33%) patients requested analgesia within 6 hours, whereas 12(40%) and 26(86.67%) patients requested analgesia after 6 hours, respectively. For the foremost requirement of analgesia within and after 6 hours, the difference between the number of patients in group I was statistically insignificant (P = 0.1967), whereas that in group II was statistically significant (P < 0.001). **Conclusion:** Dexmedetomidine when administered intra-articularly in amalgamation with fentanyl provides > 6-hour-long analgesia, lowers degree of postsurgical pain, and requirement for postsurgical analgesia. Therefore, mentioned combination is highly effective and better analgesic than fentanyl alone.

Key Words

Post-operative analgesia, Arthroscopy, Dexmedetomidine, Fentanyl

Introduction

Knee arthroscopy is a surgical procedure practiced for diagnosis and treatment of synovial, cartilaginous, and meniscal pathologies. [1] Though minimally invasive, it is associated with substantial degree of post operative pain .[2,3] Optimal post operative pain relief will enhance the rehabilitation and minimize hospital stay. Different modalities are practiced for post operative pain management in knee arthroscopy like neuraxial blocks, intra articular injection, systemic analgesics, transdermal patch ect. [2,4] Intra articular injection of local anaesthetic agents, opioids, along with adjuvants are proven to reduce early post operative pain to great extent. [5] Multiple drug combinations of local anaesthetic agents like

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levobupivacaine and ropivacaine, opioids like morphine, tramadol, fentanyl and non- opioids like clonidine, dexmedetomidine have been tried so far. [6-9] However available literature is sparse and inadequate for concluding the efficacy of fentanyl as an intra articular supplementation in clinical use for post operative analgesia after knee arthroscopy.

Addition of dexmedetomidine, a selective alpha2 receptor agonist as an adjuvant, prolongs the time duration of analgesia. [10,11] And substantially alleviate the requirement of post operative analgesic medication. Intra articular administration reportedly mitigates systemic adverse effects of drugs as well.

Material and Methods

This study conducted in D. Y. Patil Medical College and Research Centre Kolhapur is a prospective randomized double-blinded controlled study. The study enrolled total 60 patients, nearly 25-65 years of age, who were admitted for elective knee arthroscopy and willing to participate in the study. The study involved two anaesthesiologists. The first anaesthesiologist was aware of the drug to be administered intra-articularly depending on randomization schedule and helped the surgeon load and inject the drug, whereas the second anaesthesiologist, who assessed the VAS scores postoperatively was blinded in terms of the patient groups and administered drugs. Patients were also not revealed about their group allotment. Prior to initiation, the study was authorized by the Institutional Ethics Committee, and informed consent was obtained in written from all the included patients. Sixty adult patients fulfilling the inclusion criteria (the American Society of Anaesthesiologists grade I and II, posted for primary arthroscopic procedure under spinal anesthesia) were selected for the study. Exclusion criteria included patients categorized under the American Society of Anesthesiologists grade III and IV, those not willing to participate in the study, those not willing to be operated under spinal anesthesia, those with known allergy/ sensitivity to opioids, and those already on beta blockers.

Sample size calculation

Taking power of 0.75 and alpha error of 0.01, sample size was calculated to be 28 in each group. Considering dropouts, the required sample was enhanced to 30(12).

Randomization and Intervention

The patients were differentiated in two interventional groups, namely group I and group II, using computer-generated randomization schedule for double-blind randomization of 30 patients in groups I and II each. At the end of the surgery, patients included in group I were treated with intra-articular fentanyl (100 mcg) diluted to 20 ml using normal saline, and those included in group II were treated with intra-articular fentanyl (100 mcg) + dexmedetomidine (50 µg) diluted to 20 ml using normal saline.

Procedure

All patients were evaluated preoperatively and necessary investigations, such as complete blood count, random blood sugar level, blood urea, serum creatinine evaluation, chest X-ray, and electrocardiography, were performed. Each patient was introduced to Visual Analogue Scale (VAS) prior to the surgery.

Arthroscopy was performed using spinal anaesthesia using 3-ml bupivacaine (0.5% heavy). As an intraoperative sedative, 2-mg midazolam was intravenously injected. Intra-articular analgesic solution was instilled right before completing the surgery during suturing phase. Tourniquet was kept inflated for at least for 15 min after injection for allowing the drug to fix to synovial membrane.

VAS scores were documented every hour post-surgery after intra-articularly administering the analgesic for up to 14 hours. The patients were given analgesic medication when VAS score of >4 was seen. The first-choice analgesic medication was 75-mg diclofenac injected intramuscularly. In case of insufficient analgesia after 45 minutes of the diclofenac injection, 100-mg tramadol was given intravenously over 20 minutes.

Outcome

The outcome of the study regarding the VAS scores and time for the foremost requirement of analgesia was noted for 14 hrs post operative

Statistical analysis

Data was analysed using statistical software R version 4.0.1 and MS Excel. Categorical variables were represented by frequency (%). Continuous variables were represented by Mean ± SD form. Chi-square test was

Table 1. Frequency Distribution of Age, Sex, and Weight among Study Population

Variables	Sub-category	Group I	Group II	Total	P value
Age (years)	<30	15 (50%)	18 (60%)	33 (55%)	0.4953[MC]
	30–60	10 (33.33%)	10 (33.33%)	20 (33.33%)	
	>60	5 (16.67%)	2 (6.67%)	7 (11.67%)	
	Mean ± SD	37.5 ± 17.35	32.4 ± 13.97	34.95 ± 15.83	0.2149[t]
	Median (Min, Max)	30.5 (18, 68)	26.5 (18, 67)	28 (18, 68)	
Weight (Kgs)	=50	7 (23.33%)	4 (13.33%)	10 (16.67%)	0.1659[C]
	>50	23 (76.67%)	26 (86.67%)	50 (83.33%)	
	Mean ± SD	61.27 ± 10.77	62.13 ± 9.69	61.7 ± 10.17	0.7444[t]
	Median (Min, Max)	62.5 (42, 87)	62 (45, 86)	62 (42,87)	
Gender	Female	12 (40%)	7 (23.33%)	19 (31.67%)	0.1652[C]
	Male	18 (60%)	23 (76.67%)	41 (68.33%)	

Table 2. Classification of Patients Requiring Postsurgical Analgesia Based on VAS Scores

Time for VAS score evaluation	Group I		Group II		P value
	N	VAS scores (Mean ± SD)	N	VAS scores (Mean ± SD)	
1 Hour	30	4.4 ± 1.28	30	2.73 ± 0.94	<0.001[MW]*
2 Hours	30	4.7 ± 1.39	30	3.2 ± 1	<0.001[MW]*
3 Hours	28	5.11 ± 1.34	30	3.6 ± 1.07	<0.001[MW]*
4 Hours	28	6.07 ± 1.54	30	4.4 ± 1.38	<0.001[MW]*
5 Hours	21	6.52 ± 1.57	28	4.71 ± 1.51	<0.001[MW]*
6 Hours	17	6.76 ± 1.6	27	5.19 ± 1.73	<0.001[MW]*
7 Hours	8	6.88 ± 1.46	25	5.48 ± 1.96	0.077[MW]
8 Hours	2	6 ± 1.41	16	6 ± 2.03	-
10 Hours	1	5	10	5.3 ± 1.83	-
12 Hours	1	5	6	5.17 ± 2.79	-
14 Hours	1	5	2	4.5 ± 3.54	-

*VAS: Visual analogue scale; MW: Mann-Whitney U test. Valid N refers to the number of patients present in the study at each duration, whereas * indicates statistical significance.*

Table 3. Classification of Patients Based on the Request for Analgesia and Time of the Request (6 hours post-surgery)

	Within 6 Hrs	After 6 hours	Total	P-value
Group I	18 (60%)	12 (40%)	30	0.1967
Group II	4 (13.33%)	26 (86.67%)	30	<0.001*

** indicates statistical significance.*

implemented to check the association between attributes. To compare the mean between two independent groups, two-sample t test and Mann-Whitney U test were used. P <0.05 was considered statistically significant.

Results

Table 4 Classification of patients based on the request for analgesia and time of the request (14 hours post-surgery)

Duration (Within *x* hours)	Group I, N = 30, n (%)	Group II, N = 30, n (%)
3	3	2
5	14	4
6	18	4
7	24	7
8	28	15
14	30	30

The mean age of study cohort (60 patients) was 34.95 ± 15.83 years with male preponderance (68.33%). Patients were distributed in interventional groups I and II. There was no difference in demographic characteristics of both the groups (*Table 1*)

Vas score was more amongst the patients in group, I compared to group II in early post operative period. According to the frequency distribution of VAS scores, *Table 2* presents number of patients needing analgesia during the initial 14 hours post-surgery.

The difference as reported between groups I and II regarding the time of administering rescue medicine was statistically significant (P value <0.001). 18 patients from group I asked for analgesic medication before 6 hrs post operative, and 12 took the medication after 6 hrs (P value 0.1967), while from group II only 4 patients asked for analgesic in first 6 hrs while 26 patients were asked for it after 6 hrs post-operative (P value< 0.001) (*Table 3*) Moreover, any adverse effects, such as pruritis, vomiting, and nausea, were not exhibited by any patient. *Table 4* presents classification of patients in both groups requesting analgesic medication within 14 hours post-surgery. Majority of the patients from group II were pain free compared to group I

Discussion

Successful knee arthroscopy is often attributed to the effective management of postsurgical pain, early rehabilitation and mobilization of patients. [5] Many analgesics have been previously implemented, but the ideal one remains unidentified. Thus, our study compared and analysed the efficacy of dexmedetomidine when used intra-articularly with fentanyl versus fentanyl alone, as a postsurgical pain relief agent after knee arthroscopy. For postsurgical pain management, a plethora of analgesic procedures have been developed, such as systemic administration, intravenous and intramuscular administration, and neuraxial blockades. [10,13-15] Nevertheless, intra-articularly administered anesthetics and analgesics are reportedly highly beneficial with less postsurgical pain. Thus, our study implemented and subsequently endorsed intra-articularly administered analgesics for substantial effect. [5]

Concurrent with the literature, our study proposed that pain occurring after knee arthroscopy is independent of age, weight, and sex of patients. [2] Fentanyl is a synthetic opioid used regularly for clinical aesthetic purposes. Owing to its ability to act on peripheral opioid receptors for eliciting analgesic effects, fentanyl has previously been used several times in clinical studies. In a meta-analysis conducted by J Lu, *et al* (2020) [5] concluded that intra articular fentanyl supplementation does benefit in pain control after knee arthroscopy. They studied 4 RCT in their analysis and found substantial reduction in pain score in 1 st hour and significant reduction in post op pain up to 8 hours. In our study we also found VAS score less than 4 in early post operative phase in both the groups suggesting good degree of analgesia. Fentanyl has advantage of high lipophilic property and no histamine release and hence there is no hyperalgesia. Good efficacy and low incidence of side effects was observed when used intra articularly for post operative pain relief. Nevertheless, small dosages of systemically inactive fentanyl or relevant narcotic drugs when administered intra-articularly helped achieve optimal outcome after performing knee arthroscopy. On an average, 50-µg intra-articular fentanyl was comparatively a more efficient pain-relieving agent than 3-mg intra-articular morphine. [5] Thus, our study implemented 100 mcg of fentanyl for achieving the desired analgesia. Nevertheless, considering the low efficiency of the dose when implemented as the

exclusive source of analgesia, our study suggests using marginally higher doses of fentanyl.

Considering the findings presented in Table 2 and Table 3, this study highlights the higher efficacy of dexmedetomidine in amalgamation with fentanyl than fentanyl alone. Moreover, when administered intra-articularly, dexmedetomidine offered substantially durable postsurgical pain relief, which lasted for nearly 6 hours, by alleviating the need of patients for analgesic medication. [11] Similar findings were noted in our study.

The analgesic effect induced by alpha2-adrenergic agonists, mainly dexmedetomidine, is suggested to be regulated through peripheral, spinal, and supraspinal mechanisms. In our study, the effective analgesia induced by dexmedetomidine can be attributed to the localized intra-articular route of administering the analgesic, leading to direct local action of the drug. [11] For the patients included in group II, lower postsurgical VAS scores (1-5) ,was reported for nearly 6 hours, whereas for those included in group I, the same was reported for only initial 2-3 hours, after that the patients included in group I reported high scores on VAS, suggesting gradually increasing and severe pain. Moreover, in groups I and II, 18 (60%) and 4 (13.33%) patients requested postsurgical analgesia within 6 hours, respectively. This difference between the two groups highlights the prolonged local analgesic effect or slower absorption of dexmedetomidine and better efficiency compared to that of fentanyl alone. [11]

This study strongly suggested that dexmedetomidine when administered intra-articularly in amalgamation with fentanyl is notably more efficacious and produces more enduring postsurgical analgesic effect than fentanyl alone. This hypothesis is in line with the study conducted by Surana A. B *et al.* (2021)[7] suggesting the addition of adjuvants prolonged the action of local anaesthetic agent significantly and combination of multiple drugs provided better and longer analgesia.

K. Muneer, *et al* (2016)[2] studied the addition of Dexmedetomidine to Ropivacaine. He injected 20 ml of 0.25% Ropivacaine in group I, and 19ml 0.25% of Ropivacaine + 100 mcg of Dexmedetomidine in group II. First rescue analgesic was needed at 5.38±1.4 hr in group I and 10.84±2.6 in group II. Mustafa, G. *et al* (2018) [3] also got the same results with addition of Dexmedetomidine to Bupivacaine. Rescue dose needed was at 3.81±83.7 with only Bupivacaine and 7.63±93.5 with addition of Dexmedetomidine to Bupivacaine. This clearly suggest that addition of dexmedetomidine offered better analgesia and prolonged the duration of action as well. We in our study also found similar results with addition of dexmedetomidine to fentanyl. In the study conducted by Ismail *et al* (2017), comparison of Fentanyl (1 mcg in 10 ml) and Dexmedetomidine (1 mcg in 10 ml) when injected intraarticular Dexmedetomidine found to provide better analgesia than Fentanyl. [10]

Although the degree and duration of analgesia exhibit clear distinction amongst different drugs, their combinations, and doses, the study findings could be enhanced further by conducting more studies enrolling a relatively a greater number of patients. So, studies with a larger sample size and patient follow up for comprehensive evaluation are demanded. Future studies can be conducted to administer the proposed drug combination for alleviating pain occurring after performing knee arthroscopy using different lesser invasive modalities, such as transmucosal (oral or intranasal).

To our knowledge, this study is the first one to analyse the potency of dexmedetomidine when administered intra-articularly in amalgamation with fentanyl for knee arthroscopy. Future research can also strategize a clinically efficient reliable regime and quantify optimal analgesic dosages of dexmedetomidine and fentanyl.

Conclusion

Dexmedetomidine when administered intra-articularly in combination with fentanyl provides more remarkable analgesic effects, lasting for at least 6 hours, as compared to those achieved with fentanyl alone.

The combination yields efficacious analgesia with relatively low postsurgical pain, extended period of pain relief, longer duration to the foremost requirement of analgesia, and decreased necessity for immediate postsurgical analgesia.

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Conflicts of Interest

There are no conflicts of interest.

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