Original Article

Comparative evaluation of analgesic efficacy of buprenorphine transdermal patch and fentanyl patch in management of postoperative pain after arthroscopic lower limb surgery: A randomized controlled trial

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Abstract

Background and Aims: Transdermal opioids are newer modality in use for the control of postoperative pain, because of its noninvasiveness, longer duration of action, sustained blood levels, and with minimal side effects. The study was aimed to evaluate the efficacy of analgesia of buprenorphine patch 10, 20 $\mu g \cdot h^{-1}$ and fentanyl patch 25 $\mu g \cdot h^{-1}$ for relief of pain in the postoperative period in patients undergoing arthroscopic lower limb surgeries.

Materials and Methods: It was a randomized, double-blinded, prospective study in which adult patients undergoing lower limb arthroscopic surgery were randomly segregated into three groups. In Group 1 (fentanyl patch 25 $\mu g \cdot h^{-1}$), Group 2 (buprenorphine patch 10 $\mu g \cdot h^{-1}$), and Group 3 (buprenorphine patch 20 $\mu g \cdot h^{-1}$), transdermal patches were applied 12 h prior to surgery. Mean NRS score, total rescue analgesic requirement, drug-related adverse effects, and hemodynamic status were evaluated till 72 h in the postoperative period.

Results: Out of 175 screened patients, 150 patients were finally analyzed. Baseline characteristics were the same among all the three groups. Median NRS score was lowest in Group 3 [*P* value < 0.05 at 2, 4, 8, 12, and 24 h after surgery (Kruskal Wallis test). The total consumption of postoperative rescue analgesic diclofenac was the lowest in Group 3 as compared to other groups without any significant increase in adverse events.

Conclusions: In arthroscopic lower limb surgery, buprenorphine patch (20 $\mu g \cdot h^{-1}$) applied 12 h prior to surgery is an effective postoperative analgesic and it is not associated with any significant adverse effects.

Keywords: Acute pain, buprenorphine patch, fentanyl patch, pain management, postoperative analgesia

Introduction

Postoperative pain management is an ever-unfolding subject and still remain a challenging issue. Studies have proved that about 50–80% of patients do not get adequate pain control after surgery, and this leads to delayed rehabilitation, hemodynamic instability, inadequate respiratory effort, and other psychological problems which if untreated in time may lead to persistent postsurgical pain.[1,2]

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New evidences of benefits of drugs used for chronic pain and re-emergence of older analgesics in acute pain management has enhanced postoperative recovery.[3,4] Modalities like Transdermal drug delivery system (TDS), which have a proven role in managing chronic pain, are used now in acute pain management with good results.[5]

TDS is a simple, reliable, non-invasive convenient method of analgesic delivery for pain relief. Drugs like fentanyl, buprenorphine, diclofenac, etc., can be used through transdermal route. The role of transdermal opioid patches in chronic pain is well known. The emerging advantages of using TDS for acute postoperative pain are that they eliminate the pharmacokinetic side effects of parenteral and oral routes of drugs. Though they are an expensive alternative to parenteral and oral drugs, they avoid the additive doses of opioids given in the postoperative period. Drug is released in small doses with constant and sustained blood level of the drug for sufficient period.[6]

Buprenorphine and fentanyl patches have been used safely and effectively for acute pain management in a number of studies.[7,8] To the best of our knowledge, no study has been done to compare the different strengths of transdermal patch of buprenorphine (10, 20 μg·h^{-1}) and fentanyl patch (25 μg·h^{-1}).

The primary aim of the study is to compare the efficacy of fentanyl patch (25 μg·h^{-1}) and buprenorphine patch (10 μg·h^{-1}) and 20 μg·h^{-1} in managing acute postoperative pains in arthroscopic lower limb surgeries up to 72 h. Secondary aim is to note hemodynamic variability and adverse effects of fentanyl and buprenorphine patches.

Materials and Methods

This is a randomized, controlled, parallel armed double-blind study started after getting clearance from Institutional Ethical Committee (Ref no: SGRR/IEC/17/18) of the tertiary care hospital where this study was done. This study was done over a period of 10 months from 1/2/2019 to 1/11/2019 as per the Helsinki declaration after taking written informed consent from the patients for their voluntary participation in the study. This study is reported as per the consolidated standards of reporting trial (CONSORT standards).

Patients were enrolled in the study after assessing the inclusion and exclusion criteria. The patients of age 18–60 years, American Society of Anesthesiologists (ASA) physical status grade I–III, of each sex, scheduled for operative arthroscopic surgeries of lower limb (hip, knee, and ankle) were included. Patients undergoing diagnostic arthroscopies, having known allergy to the test drugs, having hepatic disease, renal disease, chronic alcoholic, or suffering from any other chronic pain syndrome were excluded. Patients taking opioids, NSAIDS, or any pain medication for more than 3 months, on antiepileptics or antidepressants, were also excluded from the study. Patients undergoing emergency operation, having malignancy, or pregnancy were excluded from the study.

Patients were randomly allocated into three groups using the computer-generated random table sampling method before surgery. Group allotment concealment (by serially numbered opaque sealed envelope) and patch application were done by nurses who received the patient in the preoperative period but were not part of the study. Patients and physicians (part of the study) were unaware of the group allotment and intervention received.

All patients were enrolled 1 day before surgery and their previous analgesics were stopped. Acetaminophen 325 mg was advised for any breakthrough pain before surgery. Study protocol, side effects of patches like gastritis and nausea/vomiting and the 11-point Numerical Rating Scale (NRS) were explained to the patient selected for the study. Patches were applied on the hairless areas of the right upper arm, 12–16 h before surgery. After application, patches were pressed firmly for 30 s, and the patient was monitored for any skin irritation and episodes of respiratory depression and hypoxia by pulse oximetry overnight. The patches were covered with soft cotton and adhesive tape to hide their appearance from the clinician collecting data.

Group 1 received fentanyl patch (25 μg·h^{-1}); Group 2 received buprenorphine patch (10 μg·h^{-1}) and Group 3 received buprenorphine patch (20 μg·h^{-1}). The fentanyl patches used in our study was manufactured by Dr. Reddy Laboratories marketed as Finrid and buprenorphine patch was manufactured by Modi Mundipharma marketed as Buvalor in India. Patients were taken for surgery in the prelunch slot between 9 am and 1 pm. All patients received subarachnoid block in sitting or lateral position using 0.5% bupivacaine heavy without any adjunct. Intraoperative monitoring and fluids were given as per the ASA protocol to maintain heart rate and mean arterial pressure within ± 20% of baseline.

All patients were analyzed for postoperative pain (using NRS), mean arterial pressure (MAP), and heart rate (HR) after surgery in postoperative room at 1, 2, 4, 8 and 12 h. After 12 h, the patients were assessed at 12 hourly intervals up to 72 h. The patients who had NRS >4, were given diclofenac 75 mg (slow intravenous) as rescue analgesia. If the pain persisted or NRS >4 within 6 h of last dose of diclofenac, then the patients were given tramadol 50 mg intravenous. Ondansetron 4 mg intravenous was given to the patients who

complained of nausea or vomiting. Severe pruritus was treated with injection chlorpheniramine maleate.

Primary outcomes measured and compared were pain scores. Secondary outcomes measured were total rescue analgesia consumed, hemodynamic variability and side effects like pruritus, respiratory depression (SpO_2 less than 90% or respiratory rate <8), sedation (as per Ramsay Sedation Scale score of >5 or >6; Table 1), and postoperative nausea vomiting. Both outcomes were noted and analyzed at different timelines for 72 h.

Statistical analysis

We assumed that in lower limb arthroscopic surgeries, using either buprenorphine patch (20 μg·h^{-1}) or buprenorphine patch (10 μg·h^{-1}) as compared to fentanyl patch (25 μg·h^{-1}) will provide better postoperative analgesia by corresponding effect size of 0.40 (large effect) and 0.25 (medium effect). For three groups and enrolling a much large sample size, we used an effect size of 0.25 rather than 0.40, α error probability 0.05 and power of study 80%. Total 159 patients (53 patients in each group) will be required to prove significance clinical and statistical difference. To compensate for attrition of 10%, we decided to enrol 175 patients in the study [Figure 1].

All data collected was entered in Microsoft Excel worksheet, and graphs were formed using the same (Microsoft Redmond, WA). Shapiro-Wilk test was used to check for normal distribution of data. The quantitative variables (MAP, HR, and diclofenac consumption) were expressed in terms of mean and standard deviation. The categorical variables (proportions of patients experiencing side effects) were expressed in terms of frequency and percentages. Median and interquartile range were calculated for nonparametric data (NRS score). SPSS statistics version 23 (IBM Corp., Armonk, NY) was used for comparing results. One-way ANOVA test was used to compare mean and Chi-square test was used to compare proportions across the three groups. Kruskal Wallis test was used for comparison of median data across the three groups. The *P* value <0.05 was considered as statistically significant for this study.

Table 1: Ramsay Sedation Score: patient having score of >5 or 6 are considered as significantly sedated

Sedation Score	
1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response

Results

Total 175 patients were enrolled in the study. Sixteen patients were excluded from the study before randomization (six were chronic alcoholics, two with deranged hepatic function, two were chronic opioid user, two were on chronic alternative form of pain medicine, one patient is on antiepileptics, and three patient's refusal to enroll later). Four patients discontinued intervention due to erythema (mild) and rashes (around patch application site only), and five patients later got lost to follow up [Figure 2].

Patients' baseline characteristics like weight, age, and sex were comparable among the three groups, and no significant difference was found among the groups regarding duration of anesthesia as well as surgery [Table 2].

The mean value of NRS was found significantly lower in Group 3 in comparison to Group 1 and Group 2 for 24 h postoperatively, and there was no significant change in NRS score thereafter between the groups [Table 3].

The total consumption of rescue analgesic diclofenac used postoperatively was lowest in Group 3 as compared to other two groups and it was found statistically significant [Table 4].

The values of mean blood pressure and heart rate were found significantly higher in Group 1 and Group 2 for first 24 h postoperatively as compared to Group 3 but no significant change was found thereafter. There was no significant change found in mean blood pressure and heart rate between Group 1 and Group 2 in the present study [Figures 3 and 4].

No significant change in respiratory rate or breathing pattern or any respiratory depression was observed in any of the three

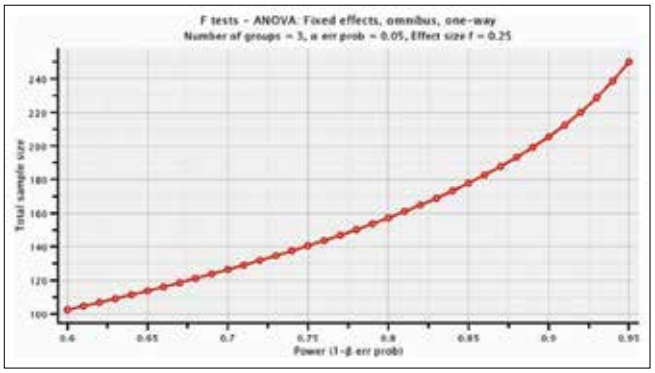

Figure 1: Sample size estimation: on *Y*-axis is total sample size and on X axis is Power (1-β err prob). Effect size d = 0.25; Number of groups = 3, and α err prob = 0.05

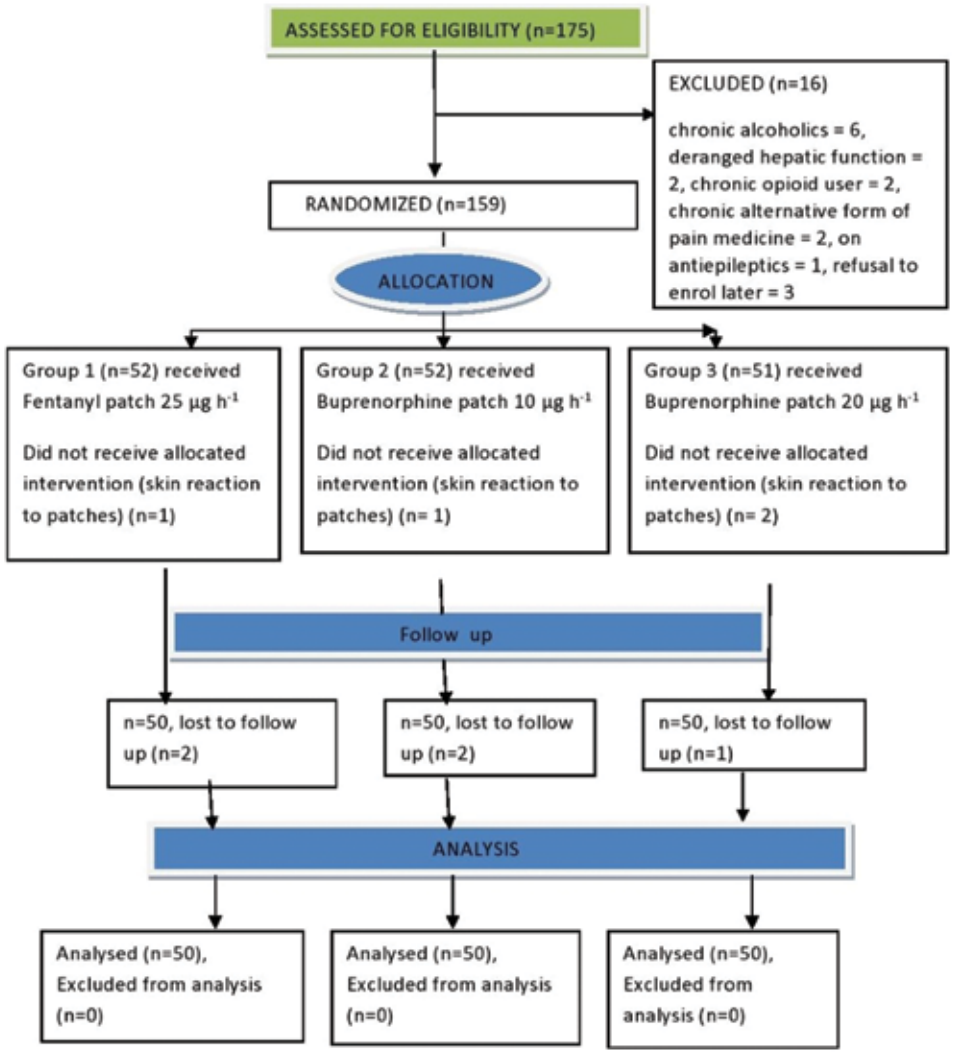

Figure 2: Consort Flow Diagram showing flow of patients in the study

Table 2: Baseline Characteristics

Characteristics	Group 1	Group 2	Group 3	*P*
Age in years, Mean±SD	46±8.6	43±7.8	45±9.2	0.21
Male: Female *n*:	34:16	32:18	35:15	0.81
Weight, Mean±SD	66±7.4	64±8.2	68±8.7	0.05
ASA Physical Status I: II: III; Number of persons	20: 20: 10	22: 18: 10	18: 20: 12	0.94
Duration of surgery, (min) Mean±SD	116±18.4	110±16.8	112±17.2	0.22

Values are Mean±SD or the number of patients, "n" = Number of patients ASA - American Society of Anaesthesiologists; SD - Standard deviation; P value<0.05 is clinically significant. One-way ANOVA test is applied for parametric distribution and Chi square test for proportions

groups. The oxygen saturation was maintained above 95% in all patients in three groups throughout the study.

Pruritus was more common in fentanyl group which was statistically significant as compared to the buprenorphine group. Pruritus was seen in eight patients in the Fentanyl group but only two patients in Group 2 and four patients in Group 3. Group 3 showed more incidence of nausea/vomiting as well as more requirement of antiemetic as compared to other two groups, but it was not statistically significant. Five patients in Group 1, three patients in Group 2 and seven patients in Group 3 reported nausea and vomiting. Sedation was seen only in one patient in Group 1 and Group 2 and in two patients in Group 3 [Table 5].

Discussion

Different methods of administration of analgesics are used by anesthesiologists in the management of postoperative pain. All modalities have their own benefits and adverse effects. The intravenous and oral routes though very effective in the early postoperative period, have their adverse effects. For acute or postoperative pain, use of transdermal patches is becoming popular in hip surgeries, knee arthroplasties, and abdominal

Table 3: Comparison of Median NRS at different time intervals in Groups 1-3

Time (h)	Median (IQR) NRS of Group 1	Median (IQR) NRS of Group 2	Median (IQR) NRS of Group 3	*P*
1	2 (1.75-3)	1 (1-2)	1 (1-2)	0.06
2	5 (4-5)	3 (3-3.25)	2 (2-3)	0.00
4	5 (4-5)	3 (3-4)	3 (2-3)	0.00
8	3 (2.74-4)	3 (2-3)	2 (2-3)	0.03
12	3 (3-4)	3 (3-4)	3 (3-3)	0.04
24	3 (3-4)	3 (3-4)	3 (2-3)	0.00
36	3 (2-3)	2 (2-3)	2 (2-3)	0.44
48	2 (2-2)	2 (2-3)	2 (2-2)	0.21
60	2 (2-2)	2 (2-2)	2 (2-2)	0.07
72	1 (1-2)	1.5 (1-2)	1 (1-2)	0.21

Values are shown in Median (IQR); IQR - Interquartile Range. P value<0.05 is clinically significant (Kruskal Wallis test)

Table 4: Comparison of mean total diclofenac consumption up to 72 h in Group 1, Group 2 and Group 3

	Group 1	Group 2	Group 3	*P*
Total diclofenac consumption (mg) Mean±SD	465±47.43	435±47.43	390±59.16	*P*=0.00 F statistics=26.72 Degree of freedom=2

P-value<0.05 is clinically significant. One-way ANOVA test is applied for parametric distribution

Table 5: Comparison of proportion of participants experiencing complications namely nausea/vomiting, pruritus, and sedation at different time intervals in Group 1, Group 2, and Group 3

Group	Postoperative nausea and vomiting episodes		Pruritus		Sedation	
1 (*n*=50)	5	*P*-0.41,	8	*P*-0.11,	1	*P*-0.79
2 (*n*=50)	3	Degree of freedom=2	2	Degree of freedom=2	1	Chi-square=0.48
3 (*n*=50)	7	Chi-square=1.77	4	Chi-square=4.41	2	

P-value<0.05 is clinically significant, applied Chi-square test for proportions

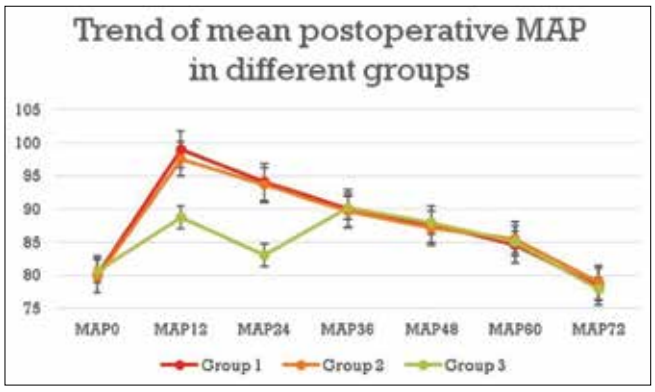

Figure 3: Comparison of mean arterial pressure at different time intervals in Group 1, Group 2, and Group 3; MAP = Mean arterial pressure; MAP0 means MAP at 0 h or on just arrival in Postanesthesia care unit. MAP12, MAP24, MAP36, MAP48, MAP60, and MAP72 represent corresponding mean arterial pressure values at 12, 24, 36, 48, 60 and 72 h. Statistically significant decrease ($P < 0.05$) in MAP was found (One-way ANOV) in Group 3 compared to Group 1 and Group 2 at 12 and 24 h only

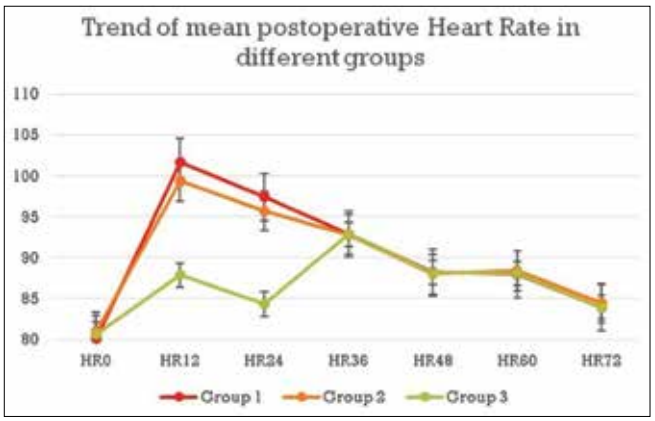

Figure 4: Comparison of heart rate at different time interval in Group 1, Group 2 and Group 3; HR = Heart rate; HR0 means heart rate at 0 h or on just arrival in postanesthesia care unit. HR12, HR24, HR36, HR48, HR60, and HR72 represent corresponding heart rate values at 12, 24, 36, 48, 60, and 72 h. Statistically significant decrease ($P < 0.05$) in HR was found (One-way ANOV) in group 3 compared to group 1 and group 2 at 12 and 24 h only

surgeries due to certain advantages and high efficacy.[8-10] There are strong opioids available in transdermal patch form like buprenorphine and fentanyl with advantages like ease of administration, safety profile, and less invasive mode of administration with sustained level of drug in blood.[11,12] Fentanyl is a synthetic opioid having low molecular weight and high lipid solubility, which makes it a very good option for transdermal use in acute pain management.[11] Similarly, buprenorphine is a partial agonist at mu receptors with low oral bioavailability, high lipid solubility, and low molecular weight.

Buprenorphine patches are available in strengths like 5, 10, or 20 μg·h^{-1} for use, where long administration of analgesics is required. Plasma concentration of buprenorphine in 12–24 h reaches its analgesic threshold level of 100 pg·mL^{-1}.[12,13]

The efficacy of both opioid patches is studied and established in the treatment of chronic and acute pain, but very few studies have been carried out to compare them. Furthermore, studies comparing them in acute pain concludes that further prospective randomized studies are required to conclusively find the optimum dose and side effects.[14,15] In the present study, transdermal fentanyl was compared with two doses of transdermal buprenorphine as to evaluate efficacy in providing adequate analgesia for postoperative pain. The incidence of side effects with each drug and their significance in clinical setting were also assessed.

The durations of action for fentanyl and buprenorphine patches are different, approximately 3 and 7 days, respectively, and usually severity of postoperative pain is of moderate to severe grade in first 48–72 h only so we have decided to compare efficacy of fentanyl and buprenorphine patches and their side effects for 72 h postoperatively.[16,17] Keeping in mind the onset of action of opioid patch is 12–24 h, all the patients were given transdermal patch 12 h before surgery. We have used non opioid analgesic (diclofenac) in our study as rescue analgesics as adding intravenous or oral opioid with transdermal fentanyl or buprenorphine will further aggravate the side effects like nausea vomiting and respiratory depression related to opioids.[18]

In our study, we found that buprenorphine patch is more efficient in relieving acute pain after surgery. The total dose of rescue analgesics was decreased with minimal adverse events. The findings of the present study are consistent with systematic review by Machado FC *et al*. They collected data of nine studies with 615 patients in which transdermal buprenorphine was compared with placebo and other analgesics. Most studies concluded that transdermal buprenorphine decreases postoperative analgesic consumption with equivalent postoperative pain scores. Most studies in the systematic review show no increase in adverse drug reactions. However, authors concluded that results of many studies were having high or unclear risk of bias.[19] In the present study, the incidence of nausea/vomiting and pruritus was more common in fentanyl group as compared to buprenorphine group and there was no significant difference found between Group 2 (Buprenorphine patch 10 μg·h^{-1}) and Group 3 (Buprenorphine patch 20 μg·h^{-1}). Walsh *et al.* also observed lesser degree of nausea/vomiting and pruritus in buprenorphine group.[20] In a previous study done by Oliashirazi *et al*., hypotension and bradycardia were observed in some of the patients using fentanyl patch, whereas in the present study, none of the patients of fentanyl group had hemodynamic instability throughout the study.[21] In a study done by Tassinari *et al*., it was found that when buprenorphine was used at higher dose, i.e., 40 μg·h^{-1} there was a significant increase in nausea and vomiting, whereas in the present study with buprenorphine 20 μg·h^{-1}, there was no significant nausea/vomiting and it was less than fentanyl group.[22]

The limitations of our study were that we have evaluated efficacy of transdermal patch in postoperative patients undergoing only lower limb arthroscopic surgeries so more studies are required to see the efficacy of transdermal patch in other major surgeries. Also, dose response curve study was not done for individual drugs. *Post hoc* analysis was not done to calculate the actual power of the study.

Conclusions

In our study, buprenorphine patch 20 μg·h^{-1} was found to be more effective than buprenorphine patch 10 μg·h^{-1} and fentanyl patch 25 μg·h^{-1} for postoperative pain in lower limb arthroscopic surgeries with no increased hemodynamic instability and adverse effects. However, more studies with greater sample size and in different surgical cohorts will be needed to build evidence for further metanalysis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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