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A Clinical Comparative Study between Transdermal Patches of Fentanyl and Buprenorphine for Post-Operative Pain Relief Following Lower Limb Surgeries

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Abstract:
Introduction*: Opioid is generally regarded as an important part of multimodal perioperative analgesia, especially for moderate to severe pain. A transdermal drug delivery system provides steady and continuous drug delivery.*
Aim*: To evaluate the efficacy of transdermal buprenorphine and fentanyl patch in postoperative acute pain management for lower limb surgeries.*
Materials and methods: *60 patients undergoing lower limb surgeries under spinal anesthesia were randomly divided into two groups (n=30). Group B received buprenorphine 10micrograms per hour patch and group F received fentanyl 25microgram per hour patch. All patients received patch 12 hours prior to surgery.*
Results*: Base line and demographic variables were comparable in both the groups. The mean level of VAS score at the end of 24 hours of post operative period in group F was 2.4 ± 0.51, and in group B it was 4.6 ± 0.28 ($p < 0.001$). On 2nd and 3rd postoperative period the VAS score in group F was 3.7 ±0.6 and 3.5 ± 0.5 respectively whereas in group B the values were 3.5 ± 0.37 and 3.6 ± 0.91 respectively. The mean level of VAS score was significantly lower in group F when compared to group B on first 72hrs of postoperative period ($p < 0.0001$).The mean level of sedation score was significantly lower in group F when compared to group B which was statistically significant ($p < 0.001$). The mean time required for rescue analgesia in group B was 3.15 hours of postoperative period whereas in group F it was 5.20 hours, which was statistically significant ($p <0.05$).*
Conclusion: *buprenorphine and fentanyl TDS were effective in controlling postsurgical pain. However, on considering cost effectiveness, buprenorphine TDS is better as it is cheaper and can be used for 7 days.buprenorphine is more cost effective and of longer duration and should be preffered. However, if greater analgesia is required then fentanyl TDS is better.*

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I. Introduction

Transdermal drug delivery system has the advantage of providing steady and constant drug delivery resulting in constant plasma concentrations. Its non-invasive dosing, avoidance of gastrointestinal tract, and lack of first pass metabolism and maintenance of sustained blood level of the drug.(3) Opioids are commonly used for chronic pain management in different routes. Buprenorphine is a partial agonist with a very high affinity for opioid receptors for which it has got a long duration of action.

Buprenorphine is a highly lipophilic and semi synthetic derivative of thebaine, a morphine alkaloid (1), being a potent and safe analgesic (75 to 100 times greater than that of morphine), at 5-10% receptors occupancy, causing less respiratory depression. It acts as a partial agonist on the μ opioid receptors, antagonist on the k opioid receptors, agonist on δ opioid receptors, partial agonist on opioid receptors like (ORL1) receptors. ORL 1 receptors are similar in structure to opioid receptors and may be involved in central modulation of pain (2).The transdermal delivery system has been used in clinical practice, they overcome the pharmacokinetic problems of oral and parenteral routes (5).

Fentanyl is a pure agonist and is more potent than morphine (4). Fentanyl does not appear to have any active metabolites and is therefore suitable for patients with renal dysfunction, although dose reduction should

be considered. The study was designed to evaluate the efficacy of transdermal fentanyl and buprenorphine patches for postoperative pain relief in terms of analgesia, complications and side effects.

II. Materials and Methods

This study was a prospective, randomized, double-blinded study conducted after obtaining Institutional Ethical Committee clearance and patients' consent. The study was conducted at Guntur medical college attached to government general hospital, Guntur during the period from January 2019 to August 2019. We recruited 60 patients with American Society of Anesthesiologist (ASA) physical status 1-3, aged between 18 and 70 years undergoing lower limb surgeries.

Exclusion criteria: Patients with hepatic failure, alcohol abuse, opioid abuse, with any neurological impairment like head injury, stroke, epilepsy, psychiatric disease, compromised cardio respiratory function, pregnancy and history of known allergy to the studied drug were excluded from this study.

The patients were randomized equally into two groups F and B using computer generated random sequence of numbers. Allocation concealment was ensured using sequentially numbered opaque, sealed envelopes. Group B received buprenorphine 10micrograms per hour patch and group F received fentanyl 25microgram per hour patch. All patients received patch 12 hours prior to surgery. All the patients were kept fasting for 6 hours for solids and 2 hours for clear fluids before surgery.

Pre anesthetic checkup was done for all patients the day before surgery. Routine laboratory investigation like hemoglobin concentration, differential leucocyte count, bleeding time and clotting time, fasting blood sugar, serum urea and creatinine, serum sodium and potassium, liver function test and cardiological evaluation was done.

Patients were explained about "visual analogue scale" (VAS) which is a 10 cm scale. 1- Indicating no pain, 2- probably no pain, 3- mild discomfort, 4- mild pain, 5- mild to moderate pain, 6- moderate pain,7- increased moderate pain, 8- moderate to severe pain, 9- severe pain, 10- severe to excruciating pain.

All patients received premedication with oral alprazolam 0.5mg and oral ranitidine 150mg on the night before surgery. On the day of surgery, when patients were brought into operation theater IV line was secured with 18G cannula and basal vital parameters like pulse rate, blood pressure, respiratory rate were checked. All patches were covered and all patients were given subarachnoid block with 0.5% bupivacaine 2.5ml. Intraoperatively heart rate, noninvasive blood pressure, ECG, SPO2 were monitored at every 15mins interval.

Post operatively, the degree of analgesia was assessed by using "visual analogue score" and sedation was assessed by "Ramsay sedation score" (1 – awake, 2- drowsy, 3- sleepy but arousable to verbal commands, 4- sleepy but arousable to moderate stimulus, 5- unconscious) for next 3 days 12 hourly. Hemodynamic parameters and any adverse effects were also noted. Injdiclofenac (75mg IV) was used as a rescue analgesic in patients complaining of inadequate pain relief. Other side effects of opioids like nausea, vomiting and pruritus were recorded.

Results of the data are subjected to statistical analysis by using unpaired student t test. P value <0.05 was taken as significant and p value <0.001 were taken as highly significant.

III. Results

Table 1: demographic data

There was no significant difference between two groups in demographic data (age, gender, body weight) ($p > 0.05$). Distribution of ASA status was also comparable ($p > 0.05$).

	Group F Mean ± S.D	Group B Mean ± S.D	P value
Age (years)	45.86±18.2	46.2±17.8	>0.05
Sex (male/female)	15/15	21/9	>0.05
Body weight (kgs)	52.04±7.4	49.46±7.8	>0.05
ASA I/II	18/12	17/13	>0.05

Figure 1: post-operative VAS score

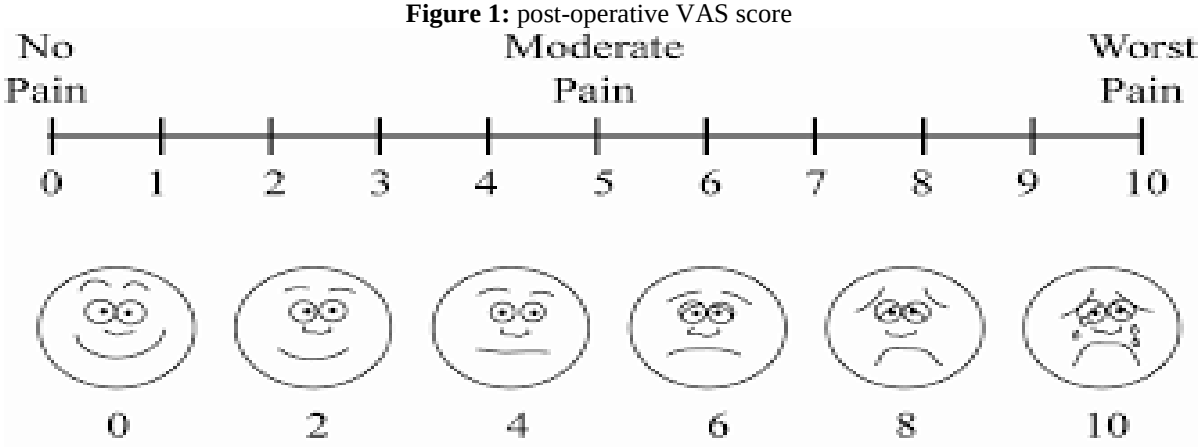
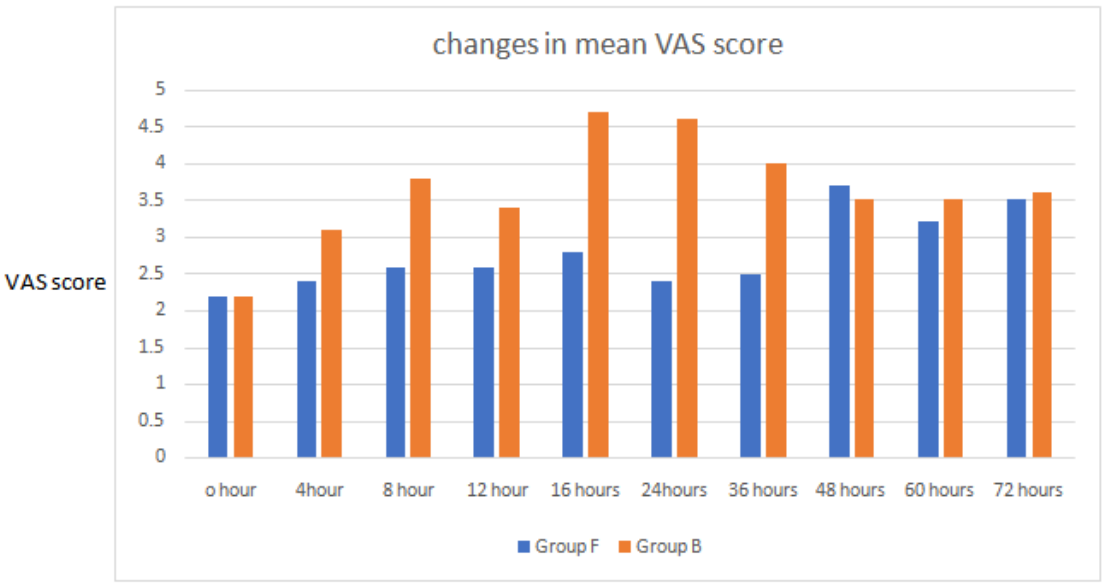


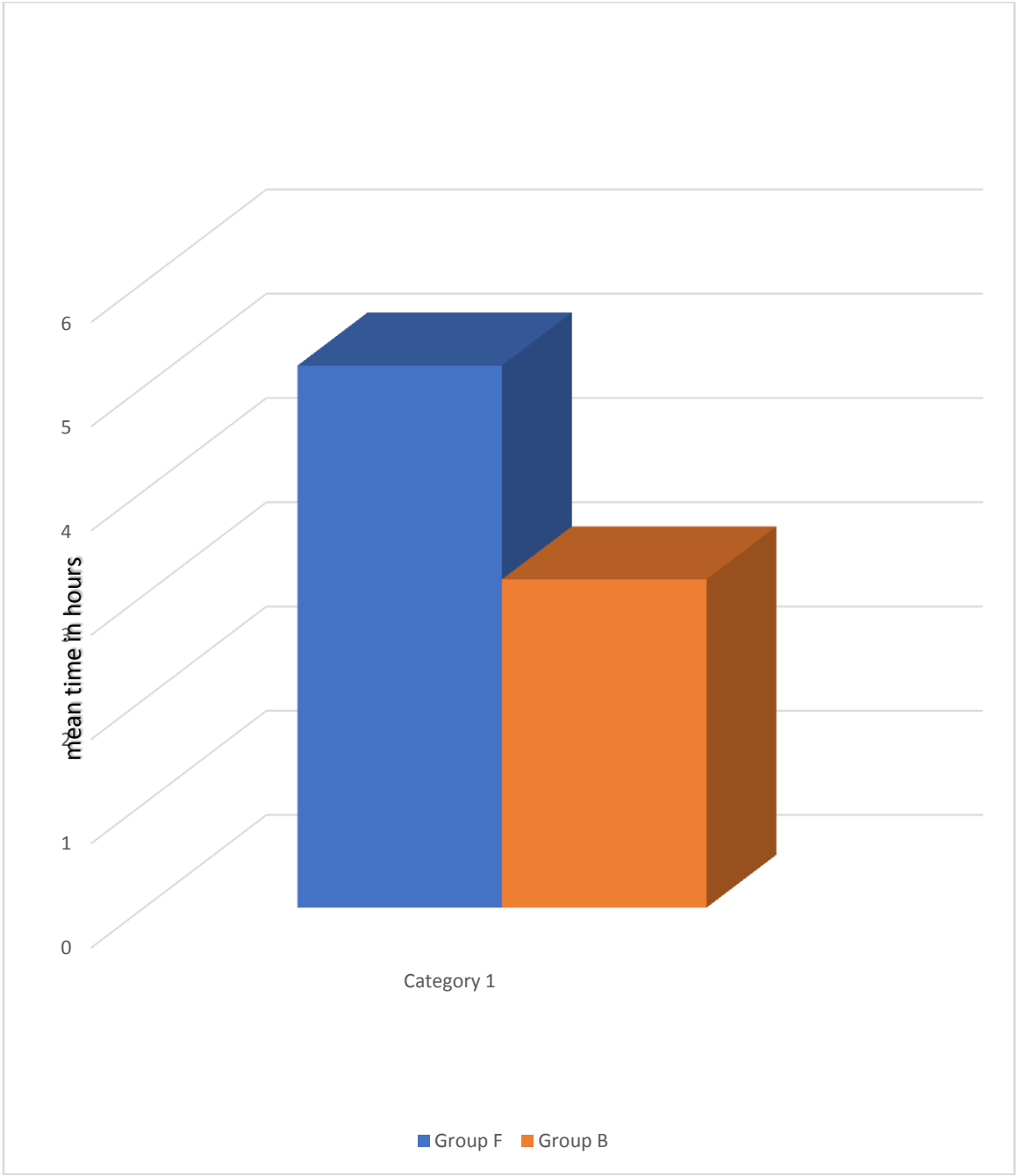
Table 1: post operative VAS score

Table 1 shows the mean values of VAS score from 1st to 3rd post operative period in both groups. The mean level of VAS score at the end of 24 hours of post operative period in group F was 2.4 ± 0.51, and in group B it was 4.6 ± 0.28 ($p < 0.001$). on 2nd and 3rd postoperative period the VAS score in group F was 3.7 ±0.6 and 3.5 ± 0.5 respectively whereas in group B the values were 3.5 ± 0.37 and 3.6 ± 0.91 respectively. The mean level of VAS score was significantly lower in group F when compared to group B on first 72hrs of postoperative period ($p < 0.0001$).



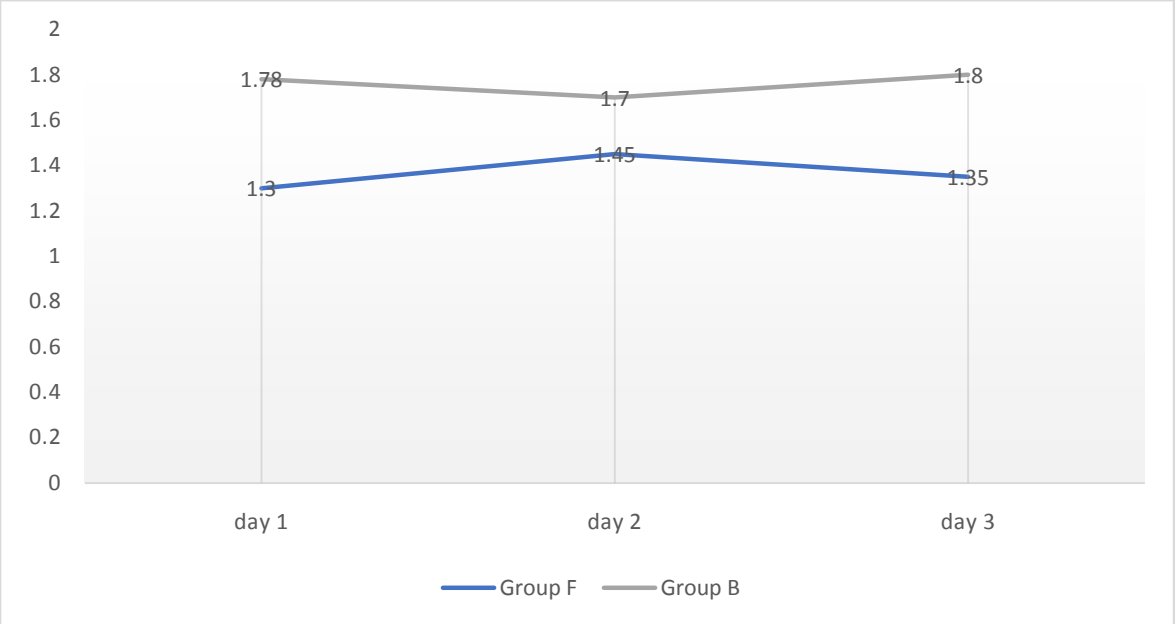
Graph 2: Time for post-operative analgesic requirement in hours

It was observed that none of the patients required rescue analgesia in the first three hours of post-operative period. The mean time required for rescue analgesia in group B was 3.15 hours of postoperative period whereas in group F it was 5.20 hours, which was statistically significant ($p < 0.05$)

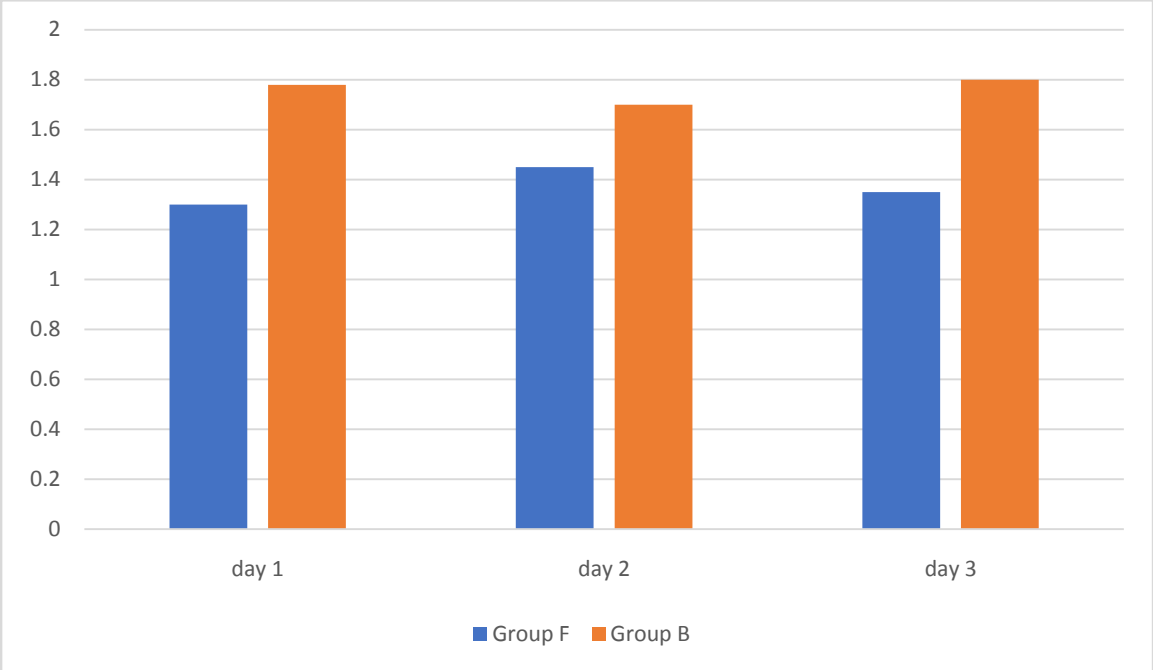


Graph 3: post-operative sedation score

Graph 3 depicts the mean value of sedation score for initial 72 hours post operatively in both groups
The value of sedation score in day 1 for group F was 1.3 ± 0.42 and in group B 1.78±0.44 which was statistically highly significant (p <0.0001) and on 2nd post-operative day it was 1.45 ± 0.42 for group F and it was 1.7 ± 0.3 for group B (p < 0.0001). On 3rd post-operative day the sedation score for group F was 1.35 ± 0.1 and for group B it was 1.8 ± 0.3 (p - <0.0001)
The mean level of sedation score was significantly lower in group F when compared to group B which was statistically significant (p <0.001)



Graph 3: post-operative sedation score



None of the patients complained of pruritus at any point of time during the first three days of post-operative period, which is very well correlated with the study of monuyadav et al studies (12).

IV. Discussion

Inadequate postoperative pain control may cause delay in recovery, prolonged hospital stay, delay in start of physiotherapy, and may even adversely affect the outcome of surgery (7). Patients undergoing elective orthopedic surgery suffers a lot of tissue trauma and intense post-operative pain (6).hence pain relief is of utmost importance in these group of patients. Transdermal drug delivery system (TDS) is a preferable alternative to parenteral and oral drug delivery methods as it avoids painful skin punctures and multiple dosing. It allows continuous drug delivery and maintains sustained plasma levels of the drug. It also decreases the requirement of rescue analgesics by providing sustained pain relief and reducing the incidence of breakthrough

pain. The high efficacy, tolerability and patient compliance of both buprenorphine and fentanyl make both these two opioid valid therapeutic options for the treatment of neuropathic pain in patients with AIDS (8).

In our study we compared two transdermal drug delivery patches (fentanyl 25micrograms per hour and buprenorphine 10micrograms per hour) in first three hours of postoperative period to determine their efficacy. We did not find any adverse hemodynamic events in our study in either group.

VAS score was used to quantify the pain. The mean level of VAS score was significantly lower in group F when compared to group B on first 72hrs of postoperative period ($p < 0.0001$) whichwas very well corelated to the studyby Arshad et al(10). Arshad et al studies the comparision between transdermal buprenorphine and transdermal fentanyl for postoperative pain relief after major abdominal surgeries. They found VAS score for pain significantly decreased in fentanyl group more than buprenorphine group from day 1 to day 3. They concluded that both TDS were effective in controlling postoperative pain.The mean level of sedation score was significantly lower in group F when compared to group B which was statistically significant ($p < 0.001$) (graph 3), but their sedation score was below 2 throughout the treatment period. All the patients were calm, comfortable and easily arousable throughout the study and none of the patient showed excessive sedation or respiratory depression.

Canneti et al.; in his study opioned that both the transdermal fentanyl and buprenorphine are effective in relieving neuropathic pain in AIDS patients (8). Kumar et al in their study concluded that transdermal buprenorphine was effective in relieving postoperative pain after abdominal surgery(9). Setti et al used 17.5,35,52.5 mcg/h of TDB patches to patients undergoing open gynecologic surgeries, providing intravenous morphine and ketorolac as rescue analgesics. They found that the consumption of rescue analgesic was inversely related to the TDB dosage. Increasing TDB doses were not associated with an increased incidence of side effects. They concluded that TDB is a safe and feasible approach to moderate post operative pain management. We used much lower dose of TDB 10mcg/h in our study (11).

In our study the sedation score was significantly higher in group B as compared to group F (graph 3) on statistical analysis, but they were below 2 in first 3 days of post operative period. All patients were calm, comfortable and easily arousable throughout the study and none of the patient showed excessive sedation or respiratory depression. Which are in accordance with the study conducted by Zia arshad, Ravi prakash et al (13).

V. Conclusion

Thus, we can conclude that both buprenorphine and fentanyl TDS were effective in controlling postsurgical pain and fentanyl is better in this regard. Because fentanyl TDS has better analgesia with less sedation. However, on considering cost effectiveness, buprenorphine TDS is better as it is cheaper and can be used for 7 days. So, we recommend both TDS for postoperative analgesia, buprenorphine is more cost effective andof longer duration and should be preffered. However, if greater analgesia is required then fentanyl TDS is better.

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