INDONESIAN JOURNAL OF ANESTHESIOLOGY AND REANIMATION
Volume 7 (1), January 2025 : 22-29

Original Research Article

A COMPARISON OF POSTOPERATIVE ANALGESIC EFFECT OF INTRAVENOUS TRAMADOL VERSUS TRANSDERMAL BUPRENORPHINE PATCH IN PATIENTS UNDERGOING AORTOFEMORAL GRAFT SURGERY

Reema Meena[1], Ashish Sharma[1], Namita Garg Prajapati[1a], Ramgopal Yadav[1]
[1] Sawai Man Singh Medical College and Attached Hospitals, Jaipur, India
[a] **Corresponding author:** culnamita@gmail.com

ABSTRACT

Introduction: The popularity of the transdermal buprenorphine patch (TDB) is currently increasing for chronic pain management because of its ease of use, non-invasive nature, sustained drug delivery, and avoidance of side effects associated with oral or parenteral routes. However, its role in postoperative pain management for aortofemoral bypass surgery is poorly established. The study was designed to compare the postoperative analgesic effect of intravenous tramadol versus transdermal buprenorphine patch in patients undergoing aortofemoral graft surgery. **Objective**: To compare the efficacy between a buprenorphine patch versus intravenous tramadol for postoperative analgesia in patients undergoing aortofemoral bypass surgeries. **Methods:** This is a hospital-based, prospective, randomized, and interventional study. This study was conducted in the cardiac surgery Operation Theatre (OT). A total of 60 patients of either sex belonging to ASA 2 or 3 in the age group of 30-60 years and BMI ≤ 40 kg/m2 scheduled for aortofemoral bypass surgery were enrolled in this study. These 60 patients were divided into two groups; the intravenous tramadol and the transdermal buprenorphine patch group using a randomization table. **Results:** The two groups were comparable in terms of demographical data, duration of surgery, and time for extubation. The analysis of variance showed that the VAS score was higher in the buprenorphine group as compared to the tramadol group for the first 3 hours post operatively but after that, the VAS score was significantly less in the buprenorphine group at various study intervals. A greater number of patients complained of pain for the first 3 hours postoperatively, but after that the patients had better pain relief for the rest of the study period. **Conclusion**: Transdermal buprenorphine applied preoperatively is a safe and effective option for postoperative pain management as it offers superior pain control and reduces the need for rescue analgesia, thereby decreasing potential side effects as compared to intravenous tramadol.

Keywords: Aortofemoral Surgery; Postoperative analgesia; Rescue Analgesia; Transdermal Buprenorphine; VAS Score

ABSTRAK

Pendahuluan: Popularitas *Patch Buprenorfin Transdermal* (TDB) saat ini meningkat untuk manajemen nyeri kronis karena mudah digunakan, sifatnya yang non-invasif, pemberian obat yang berkelanjutan, dan pengurangan efek samping yang terkait dengan rute oral atau parenteral. Namun, perannya dalam manajemen nyeri pascaoperasi untuk operasi bypass aortofemoral belum ditetapkan dengan baik. Penelitian ini dirancang untuk membandingkan efek analgesik pascaoperasi tramadol intravena versus *patch buprenorfin transdermal* pada pasien yang menjalani operasi *bypass* aortofemoral. **Tujuan:** Untuk membandingkan efektivitas antara penggunaan *buprenorphine patch* versus tramadol intravena untuk analgesia pascaoperasi pada pasien yang menjalani operasi *bypass* aortofemoral. **Metode**: Studi ini merupakan studi intervensi acak berbasis rumah sakit. Studi prospektif ini dilakukan di ruang operasi bedah jantung. Sebanyak 60 pasien dari kedua jenis kelamin yang termasuk dalam ASA 2 atau 3 dalam kelompok usia 30-60 tahun dan BMI ≤ 40 kg/m2 yang dijadwalkan untuk operasi bypass aortofemoral didaftarkan dalam studi acak prospektif ini. Ke-60 pasien ini dibagi menjadi dua kelompok yaitu tramadol intravena dan kelompok patch buprenorfin transdermal menggunakan tabel pengacakan. **Hasil**: Kedua kelompok sebanding dalam hal data demografi, durasi operasi, waktu ekstubasi. Analisis varians menunjukkan bahwa skor VAS lebih tinggi pada kelompok buprenorfin dibandingkan dengan kelompok tramadol selama 3 jam pertama pasca operasi tetapi setelah itu, skor VAS secara signifikan lebih rendah pada kelompok buprenorfin pada berbagai interval penelitian. Lebih banyak pasien mengeluhkan nyeri selama 3 jam pertama pasca operasi tetapi setelah itu

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

pasien mengalami pereda nyeri yang lebih baik selama sisa periode penelitian. **Kesimpulan:** Buprenorfin transdermal yang diberikan sebelum operasi merupakan pilihan yang aman dan efektif untuk manajemen nyeri pascaoperasi karena menawarkan pengendalian nyeri yang lebih baik, mengurangi kebutuhan akan analgesik penyelamatan, sehingga mengurangi potensi efek samping dibandingkan dengan tramadol intravena.

Kata kunci: Operasi Aortofemoral; Analgesia Post-operatif; *Rescue Analgesia*; Transdermal buprenorphine; Skor VAS

Article info: Received: August 3, 2024; Received: December 12, 2024; Accepted: January 10, 2025; Published: January 30, 2025

INTRODUCTION

Post-operative pain management has always been a challenging issue despite our knowledge in the physiology of acute pain. Various methods of pain management exist including opioid and non-opioid analgesics, systemic and local delivery methods, and regional and minimally invasive techniques (1).

Many drugs and routes have been studied earlier. Transdermal drug delivery system plays a vital role in managing chronic as well as acute pain as they are easy to use, provide a constant rate of drug delivery, and maintain sustained blood levels for pain management. They can eliminate the need for parenteral or oral routes of drug administration, which can have side effects (2).

The buprenorphine patch is an example of a transdermal drug delivery system (TDDS) which is simple, easy to use, compliant, relatively safer, and provides sustained drug delivery. To be able to use it as a patch, buprenorphine is incorporated into an adhesive polymer matrix (acrylate vinyl acetate), which allows it to be released continuously over 7 days. The patches are available in three strengths of 5, 10 and 20 mg with drug release rates of 5, 10 and 20 mg/hour respectively (1,3).

The buprenorphine patch has been compared with oral tramadol, but till now we could not find the comparison between the buprenorphine patch and intravenous tramadol for postoperative analgesia. This study was designed with the primary aim to compare the efficacy of buprenorphine patches to intravenous tramadol for postoperative analgesia in patients undergoing aortofemoral bypass surgeries. Also, to determine the difference in time to first rescue analgesia and the total dose of rescue analgesic required in the first 72 hours postoperatively.

METHODS

This is a prospective and randomized study, that has received ethical approval from the institutional ethics committee (Ref no. 720/MC/EC/2020). The study was registered with the Clinical Trial Registry of India (CTRI) with trial number CTRI/2021/09/036226. Written informed consent was obtained from 60 patients aged 30-60 years of either sex belonging to ASA 2 or 3 with a BMI ≤ 40 kg/m2, and undergoing aortofemoral bypass surgery. There had to be 30 cases in each group to get a 95% confidence level and 80% power to confirm the expected difference of 34% in the number of cases in each group that needed rescue analgesia within 7 days, as mentioned in the seed article (4). The sample size calculation was based on the formula:

$$N = \frac{Z^2.P(1-P)}{d^2}$$

N: the sample size
Z: the level of confidence
P: the expected prevalence or proportion
d: the precision

Patients who were taking medications that may interact with tramadol or buprenorphine, alcoholics or drug abusers, and

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

those who with known drug allergies were excluded from the study. The patients were divided into 2 groups either the intravenous tramadol group (Group 1) or the transdermal buprenorphine (TDB) patch group (Group 2) using a randomization table. The patients were aware of the group they belonged to (by looking at the buprenorphine patch or IV tramadol); however, the physician assessing pain and satisfaction score was unaware of the group the patient belonged to. Hence it was a single-blinded study.

The complete process about the study drugs, post-operative pain treatment options, and pain score assessment was explained to patients a day before surgery. Patients in the buprenorphine group received a buprenorphine patch of 10 mcg/h, 18 hours before the surgery (effective serum concentration is achieved after 12-24h) which was applied to the upper outer arm (4). A dosage of alprazolam 0.25 mg was given to all patients the night before surgery to allay anxiety. On the day of surgery, all the baseline parameters (heart rate [HR], blood pressure [BP], oxygen saturation [SpO2]) were recorded, and the intravenous (IV) line was secured. Before induction of anesthesia, IV glycopyrrolate (0.2 mg) and midazolam 0.15 mg/kg were administered to all patients. After preoxygenation, anesthesia was induced with IV midazolam 0.05 mg/kg, fentanyl 2 mcg/kg, etomidate 0.3 mg/kg, and rocuronium 0.9mg/kg to attempt intubation. Anesthesia was maintained with 60% of N_20 and 40% of O_2, isoflurane 1-1.5%, and atracurium 0.5 mg/kg loading dose followed by 0.1 mg/kg maintenance dose. The bispectral index score was maintained between 40-60 throughout the surgery by varying the concentration of isoflurane and 1mcg/kg fentanyl. End-tidal CO2 was kept between 35 and 40 mmHg by adjusting ventilation.

The patients in the buprenorphine group were not given any other analgesic apart from their routine buprenorphine patch, whereas patients in the tramadol group did receive 100 mg tramadol at the time of skin closure, followed by 50 mg every 6 hours till 72 hours. Postoperatively, pain (using visual analogue scores 0-10), sedation score, and hemodynamic parameters were assessed at 1, 3, 6, 12, 24, 36, 48, 60, 72 hours.

Rescue analgesia in the form of 1 gram Paracetamol up to 3 times a day was given to patients whose VAS score went 4 or higher. If in any patient, pain persisted within 6 hours of giving paracetamol then diclofenac (75 mg IM) was given as a secondary rescue analgesic. Recordable side effects were lightheadedness, postoperative nausea and vomiting, and constipation.

A chi-square test or Fisher test was used to analyze categorical or nominal variables (summarized as numbers and percentages). The Fischer exact test was used when at least one of the cells in the 2x2 contingency table had an expected frequency <5. Continuous variables were summarized as mean and standard deviation, for which an independent T-test and Mann-Whitney U test was used to analyze the results with the p-value ≤ 0.05 was taken as statistically significant. All statistical analysis was done using EPI INFO version 7.2.1.0 statistical software.

RESULTS AND DISCUSSION

The study was conducted on 60 patients. The two groups were comparable in terms of demographical data, duration of surgery, and time for extubation. There were no significant differences between 2 groups based on the age ($p = 0.947$), gender ($p = 0.789$), weight ($p = 0.892$), duration of surgery ($p= 0.289$), and time for extubation ($p = 0.279$) (Table 1).

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

Table 1. Demographic Variables, Surgery, and Anaesthetic Data

Parameters	Group 1 Tramadol; (N = 30)	Group 2 Buprenorphine; (N = 30)	p-value
Age (Years) [mean ± SD]	47.6 ± 8.23	46.9 ± 8.31	0.947*
Gender Male Female	18 (60) 12 (40)	20 (66.7) 10 (33.3)	0.789**
Weight (kg) [mean ± SD]	58.1 ± 5.53	58.3 ± 5.78	0.892*
Duration of Surgery (min) [mean ± SD]	98.37 ± 12.64	101.53 ± 10.14	0.289*
Time for extubation (min) [mean ± SD]	123.17 ± 12.53	126.4 ± 10.28	0.279*

*Based on the independent T-test, significant if p-value ≤ 0.05
**Based on the chi-square rest, significant if p-value ≤ 0.05

The analysis of variance showed that VAS scores were initially higher in the buprenorphine group for the first 3 hours postoperatively (i.e., till 24 hours of applying the buprenorphine patch) but after that, the buprenorphine group consistently had lower pain scores throughout the study period (Figure 1).

We observed that patients of the buprenorphine group initially had higher pain scores than the tramadol group for the first 3 hours post-operatively but after that throughout the study period, the VAS was less in the buprenorphine group. This was so because though we applied the buprenorphine patch 18 hours before the start of the surgery but its analgesic effect started only 22-24 hours after application as has been seen in many previous studies (5,6), while subjects in the tramadol group received 100mg IV tramadol loading following skin closure so had better pain relief for the first 2-3 hours only but after the initial 3-4 hours post operatively, the VAS was less in the buprenorphine group throughout the study period, though 50mg tramadol was given 6 hourly.

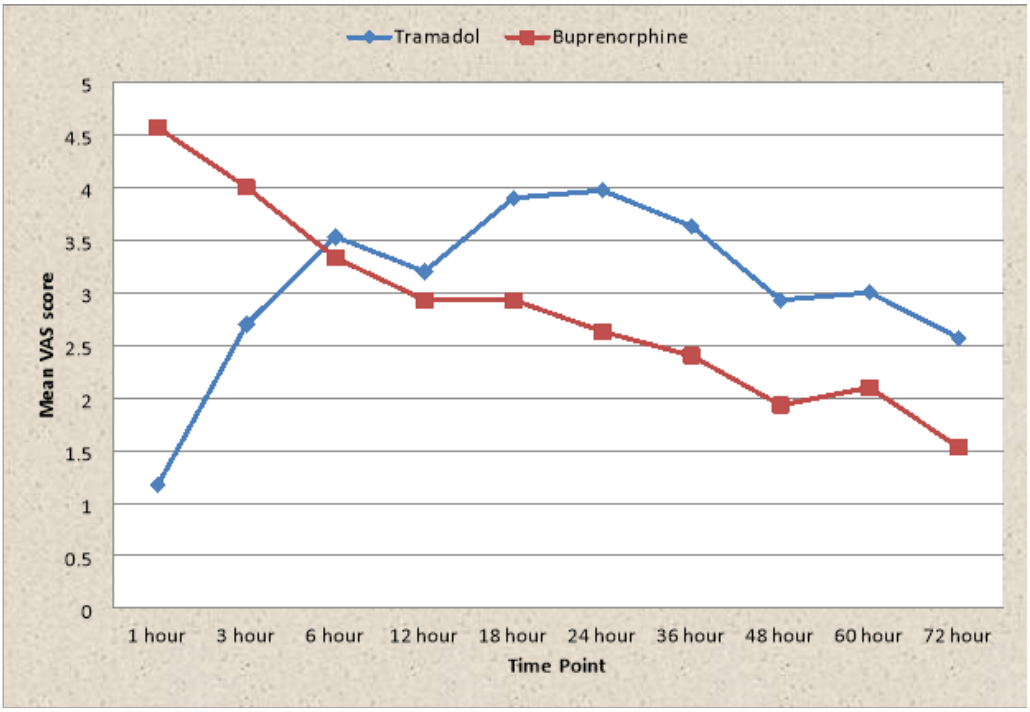

Figure 1. Postoperative Visual Analogue Score 0-10

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

This may be because IV bolus drug administration may cause excessive therapeutic plasma concentration soon after administration, and later the drug levels drop to a subtherapeutic level causing pain while transdermal administration provides a steady state plasma concentration of the desired drug. However, as drug absorption from transdermal patch is delayed, it has to be applied preoperatively and use of it as a pre-emptive analgesic could lead to the development of adverse effects in the absence of painful stimuli in the preoperative period (2). Aortofemoral bypass surgery is a procedure utilized commonly for the treatment of aorto iliac occlusive disease. Patients with this disease often experience moderate to severe rest pain of the lower extremities and also need good postoperative pain management after aortofemoral bypass surgery. Thus, use of transdermal buprenorphine patches in these patients may be of great use. Also, these patients with peripheral vascular disease have an incidence of 37.9% associated renal dysfunction and buprenorphine which is metabolized in the liver has a potential safety in patients with renal dysfunction (7). No literature now is available about the use of transdermal buprenorphine patches in these aorto-occlusive disease patients.

Table 2. Comparison of Time to First Rescue Analgesic Given between the Both of Groups

Variable	Group 1 Tramadol (N = 30)	Group II Buprenorphine (N = 30)	p-value
Time to first rescue analgesia (hours) [mean ± SD]	14.46 ± 10.46	2.03 ± 1.9	< **0.001***

*Based on the independent T-test, significant if p ≤ 0.05

The first rescue analgesia requirement was earlier in the buprenorphine group (2.03 ± 1.9) hours than in the tramadol group (14.46 ± 10.46) hours. Based on the statistical test, there is a significant difference between Group I and Group II based on the time for first rescue analgesia with the p-value < 0.001 (Table 2).

However, with the passage of time, the buprenorphine group required a lower number of rescue analgesia than the tramadol group (Table 3). The buprenorphine group also received fewer rescue medicine (paracetamol) dose as compared to the tramadol group (Table 4).

Table 3. Comparison of Number of Rescue Analgesia at Different Time Intervals between Both the Study Group

Time Point	Group 1 Tramadol (N = 30)	Group 2 Buprenorphine (N = 30)	p-value
1 hour	1	22	< 0.001
3 hours	14	20	0.193
6 hours	16	9	0.116
12 hours	14	6	0.055
18 hours	19	5	< 0.001
24 hours	18	6	0.001
36 hours	18	5	0.001
48 hours	12	3	0.017
60 hours	10	3	0.060
72 hours	10	1	0.008

*Based on the Fischer exact test, significant if p ≤ 0.05

Table 4. Comparison of Paracetamol Dose Received between the Both of Groups

Variable	Group I Tramadol (N = 30)	Group II Buprenorphine (N = 30)	p-value
Dosage of paracetamol injection (gram) [mean ± SD]	4.2 ± 1.35	2.23 ± 0.84	0.001

*Based on the Mann-Whitney test, significant if p ≤ 0.05

Rescue analgesic doses accounted for a total of 132 in the tramadol group, out of which 126 doses were of Paracetamol (1 gram) and 6

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

doses were of diclofenac (75 mg IM) while in the buprenorphine group total number of rescue analgesic doses was only 80, which included 67 doses of paracetamol and 13 doses of diclofenac ($p < 0.001$).

Desai et al., (8) observed that an average number of diclofenac tablets consumed in 7 postoperative days in transdermal buprenorphine (10 mg) patch group was 2.4 ± 2.2 and in oral tramadol (50 mg TID) group was 6.6 ± 3.0, and an average number of paracetamol tablets consumed in 7 postoperative days in transdermal buprenorphine group was 0.68 ± 2.2 and in oral tramadol group was 1.9 ± 3.7, subjects in buprenorphine group needed less rescue analgesic then in tramadol group similar to our study.

Table 5. Side effect profile between the both of groups

Side effects	Group I Tramadol (N = 30) [N (%)]	Group II Buprenorphine (N = 30) [N (%)]
Nausea or vomiting	6 (20)	1 (3.3)
Constipation	2 (6.7)	1 (3.3)
No side effect	22 (73.3)	28 (93.33)

The incidence of postoperative nausea and vomiting was significantly lower in the buprenorphine group (3.3%) compared to the tramadol group (20%). Respiratory depression was not noticed in any of the group. Skin rash was not reported in any patient of the buprenorphine group (Table 5).

Different modalities of pain management have been utilized for the management of postoperative pain which has their benefits and side effects. Buprenorphine is a partial agonist at mu receptors with low oral bioavailability, increased lipid solubility, and low molecular weight which offers sustained pain relief through transdermal delivery (9,10).

Tramadol is a centrally acting analgesic with weak opioid agonist properties and low dependence. Therefore, clinically relevant respiratory depression and abuse potential is not seen making it a suitable drug for use in post-operative analgesia (11,12). However. incidence of postoperative nausea and vomiting is quite high and it tends to accumulate in patients with renal failure. Therefore, it warrants caution in such high-risk patients (13). In the past a comparison has been done between transdermal buprenorphine and tramadol for non-cancer chronic pain in which buprenorphine has been found superior but only a few studies are there considering the use of transdermal buprenorphine for post-operative pain management (14). No study could be found of comparison of transdermal buprenorphine with IV tramadol for post-operative analgesia.

In this study, a transdermal buprenorphine patch of 10 mcg/hr was used for the management of post-operative pain in patients operated on aorto-iliac occlusive disease and compared with IV tramadol.

Desai et al., (8) compared transdermal buprenorphine 10mcg/h (which was applied 24 hours before surgery) with oral tramadol and observed that patients of the buprenorphine group had lower pain scores, less requirement of rescue analgesic and had decreased incidence of vomiting but VAS was more than 4 till 24 hours after surgery after which it started decreasing gradually lowest being 2.5 at 7th day. They concluded that transdermal Buprenorphine was more effective in decreasing post-operative pain after approximately 48 hours of applying the patch but in our study, the effect could be seen after 24 hours of the application of the Buprenorphine patch.

Prerana et al., (15) who studied a transdermal patch of Buprenorphine (20µg/hr),

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

observed that patients belonging to the buprenorphine group were composed, comfortable, and easily roused throughout the study period, with mean sedation score being 1.93 ± 0.25. Z Arshad et al., (16) also concluded in their study that transdermal buprenorphine 10mcg/h is safe and efficacious for the management of post-operative pain.

We noted very few drug-related adverse effects in both the groups which were not statistically significant. The limitations of our study include the use of 10mcg/hr transdermal buprenorphine patch only for post operative pain management in patients with aortofemoral bypass surgery. Therefore, more studies are required to evaluate the efficacy of higher concentrations of buprenorphine transdermal patches in these surgeries.

CONCLUSION

Transdermal buprenorphine (10 microgram/hr) applied preoperatively is a safe and effective option for postoperative pain management in patients undergoing aortofemoral bypass surgery. It offers superior pain control, and reduces the need for rescue analgesia, thereby decreasing potential side effects as compared to intravenous tramadol.

Acknowledgement

None. The authors thank the surgical and nursing staff of cardiothoracic and vascular surgery, at Sawai Man Singh Medical College.

Conflict of Interest

None

Funding

None

Authors' Contributions

All the authors were actively involved in study planning, study design, execution, writing of the articles, and arranging all the necessary materials required.

REFERENCES

1. Khandelwal H, Negi A, Govil N, Singh A, Parag K, Bhardwaj BB. 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. J Anaesthesiol Clin Pharmacol [Internet]. 2021; 37(2). [PubMed] [Webpage]
2. Dave S, Shriyan D, Gujjar P. Newer drug delivery systems in anesthesia. J Anaesthesiol Clin Pharmacol [Internet]. 2017; 33(2). [PubMed]
3. Bajaj S, Whiteman A, Brandner B. Transdermal drug delivery in pain management. Continuing Education in Anaesthesia, Critical Care and Pain [Internet]. 2011 Apr 1; 11(2): 39–43. [Webpage]
4. Yadav M, Mohan CL, Srikanth I, Raj ER, Gopinath R, Chandrasekhar P. Effect of preoperative application of buprenorphine transdermal patch on analgesic requirement in postoperative period in hip and knee replacement surgeries. J Anaesthesiol Clin Pharmacol [Internet]. 2019; 35(1). [PubMed] [Webpage]
5. Sastre JA, Varela G, López M, Muriel C, González-Sarmiento R. Influence of Uridine Diphosphate-Glucuronyltransferase 2B7 (2B7) Variants on Postoperative Buprenorphine Analgesia. Pain Practice [Internet]. 2015 Jan 1; 15(1): 22–30. [PubMed] [Webpage]

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29

6. Kitzmiller JP, Barnett CJ, Steiner NS, Stoicea N, Kamar N, Luzum JA, et al. Buprenorphine: Revisiting the Efficacy of Transdermal Delivery System. Ther Deliv [Internet]. 2015 Apr 1; 6(4): 419–22. [PubMed] [Webpage]
7. Khanna IK, Pillarisetti S. Buprenorphine – An attractive opioid with underutilized potential in treatment of chronic pain. Vol. 8, Journal of Pain Research. Dove Medical Press Ltd.; 2015. p. 859–70. [PubMed]
8. Desai SN, Badiger S V, Tokur SB, Naik PA. Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study. Indian J Anaesth [Internet]. 2017;61(3). [PubMed] [Webpage]
9. Niyogi S, Bhunia P, Nayak J, Santra S, Acharjee A, Chakraborty I. Efficacy of transdermal buprenorphine patch on post-operative pain relief after elective spinal instrumentation surgery. Indian J Anaesth [Internet]. 2017;61(11). [Webpage]
10. Kadapamannil D, Rajan S, Tosh P, Kumar L. Comparison of Efficacy and Safety of Transdermal Buprenorphine Patch Applied 48 Versus 72 Hours Preoperatively in Providing Adequate Postoperative Analgesia Following Major Abdominal Surgeries. Indian Journal of Pain [Internet]. 2018; 32(1). [Webpage]
11. Pradeep Kumar K, Kumar Kulkarni D, Indira, Gopinath. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blinded, placebo-controlled study. J Pain Res. 2013 Jun; 471. [PubMed] [Webpage]
12. Iyer SK, Mohan G, Ramakrishnan S, Theodore S. Comparison of tapentadol with tramadol for analgesia after cardiac surgery. Ann Card Anaesth [Internet]. 2015;18(3). [PubMed] [Webpage]
13. Kumar S, Chaudhary AK, Singh PK, Verma R, Chandra G, Bhatia VK, et al. Transdermal buprenorphine patches for postoperative pain control in abdominal surgery. Journal of Clinical and Diagnostic Research. 2016 Jun 1; 10(6): UC05–8. [PubMed] [Webpage]
14. Machado FC, Neto GC, Paiva LO de, Soares TC, Nakamura RK, Nascimento L de F, et al. Transdermal buprenorphine for acute postoperative pain: a systematic review. Brazilian Journal of Anesthesiology [Internet]. 2020; 70(4): 419–28. [Webpage]
15. Jogdand P. Comparative Study of Transdermal Patch of Fentanyl with that of Buprenorphine for Postoperative Pain Management in Postthoracotomy Surgery Patients. Indian Journal of Anesthesia and Analgesia [Internet]. 2020 Apr 1; 7(2): 459–64. [Webpage]
16. Arshad Z, Prakash R, Gautam S, Kumar S. Comparison between transdermal buprenorphine and transdermal fentanyl for postoperative pain relief after major abdominal surgeries. Journal of Clinical and Diagnostic Research. 2015 Dec 1; 9(12): UC01–4. [PubMed] [Webpage]

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V7I12025.22-29