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**Original research article**

# Comparative Study of Injection Tramadol and Buprenorphine Transdermal Patch For Postoperative Analgesia in Nephrectomy Surgery

**[1]Dr. Gangwani Prakash, [2]Dr. R.C. Gupta, [3]Dr. Birbal Baj, [4]Dr. Praveen Kumar Shekhrajka**

[1] PG resident, Department of Anaesthesiology, Critical Care & Pain management, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

[2] Professor, Department of Anaesthesiology, Critical Care & Pain Management, Medical Superidentent, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

[3] Professor, Department of Organ Transplant Anaesthesia and Critical Care, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

[4] Assistant Professor, Department of Anaesthesiology, Critical Care & Pain Management, Mahatma Gandhi Hospital and Medical College, Jaipur, Rajasthan, India

**Corresponding Author:**

Dr. Praveenkumar Shekhrajka (Email: praveenshekhrajka@gmail.com)

**Abstract**

**Background and Aims:** Open nephrectomies are commonly seen surgeries in renal transplant and renal tumours are associated with moderate to severe pain. These patients need good post-operative analgesics for early rehabilitation and mobilisation. Transdermal buprenorphine which is used in chronic pain management has rarely been studied in acute pain management.

The aim of this study was to compare the efficacy and safety of transdermal buprenorphine patch to injection tramadol for post-operative analgesics following open nephrectomy surgeries.

**Methods**: Sixty adult aged 18-60 years with American Society of Anaesthesiology physical status I/II scheduled for open nephrectomy surgeries under general anaesthesia were divided in two groups. Group A received Transdermal buprenorphine patch 10 mcg/hour applied 12 hours before surgery and Group B received injection tramadol 100 mg just after extubation. Injection Paracetamol 1 gram intravenously was given as rescue analgesia. Pain score at rest, on movement, total doses of rescue analgesia and side effects were compared in both the groups for seven days.

**Results**: There was significant low visual analogue scale (VAS) score in group A compare to group B at rest and on movement ($p<0.001$). The requirement of rescue analgesia was significantly lower in group A (14.3% vs 100%). The side effects like nausea, vomiting, drowsiness was lower in group A compared to group B. Group A has better satisfactory scores compared to Group B.

**Conclusion**: Transdermal buprenorphine patch can be safely used for post-operative analgesia and is more efficacious in reducing post-operative pain with fewer side effects compared to injection tramadol.

**Keywords:** Buprenorphine, Nephrectomy, Post-operative pain, Tramadol, Transdermal patch

## Introduction

Definition given by the international association for the study of pain defined pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." This definition recognizes the interplay between physiological and sensory aspects of pain, objective and its subjective components and emotional and psychological components. Conduction of pain occurs through three neuronal pathways: These pathways transmit noxious stimuli arising from the periphery to the cerebral cortex of brain. Modulation of pain occurs peripherally at the nociceptor, in the spinal cord and in supraspinal structures. [i]

Management of postoperative pain is a challenging issue and an ever unfolding subject. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality.[ii] Evidence suggests that surgery suppresses the immune system and this suppression is proportionate to the invasiveness of the surgery.[iii] Good analgesia can reduce this deleterious effect. Studies done in pain management indicate that afferent neural blockade with local anaesthetics is the most effective technique for analgesia. Next in order of effectiveness are high opioid doses, epidural opioids and clonidine, patient controlled opioid analgesia, and non-steroidal anti-inflammatory drugs (NSAIDS). [iv]

Post-operative pain is very common in laparotomy cases. Patient undergoing major surgery has main concerns for that. These patients require adequate post-operative analgesia. By virtue of their efficacy, opioid analgesics have been used for the treatment of both acute and chronic pain since long. Many techniques and drugs have been used for management of post-operative pain management with variable success results. Every technique and drugs have its own advantages and disadvantages. Transdermal drug

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delivery systems are simple, non-invasive and compliant method of delivery which provides sustained drug release for prolonged period. They are available for analgesics like opioid (fentanyl and buprenorphine), non-steroid anti-inflammatory drugs (NSAIDS) such as diclofenac, antihypertensive like nitroglycerine (NTG), hormones (estrogen, testosterone), anticholinergic (scopolamine), clonidine, rivastigmine, monoamine oxidase inhibitor (MAOI) selegiline, methylphenidate, cyanocobalamine, nicotine etc.[v]

Opioids are most commonly used analgesics for postoperative pain and their transdermal patches provide sustained blood levels of the drug for sufficient period. Buprenorphine is a semisynthetic opioid with a μ-agonistic and κ-antagonistic receptor-binding profile. Studies over the past two decades have demonstrated that buprenorphine has complex and unique pharmacological profile having enhanced therapeutic benefits combined with a favourable safety profile. Having been underused in past, the development of a new transdermal drug delivery system for buprenorphine has increased interest in this area. Transdermal buprenorphine provides a non-invasive method of rate-controlled drug release ensuring constant and predictable serum buprenorphine levels over a prolonged period. It has been shown to be advantageous for long-term treatment of chronic pain patients providing reliable pain control. Tramadol releases serotonin, inhibits reuptake of norepinephrine and it is a weak μ-opioid receptor agonist. Tramadol is metabolized to O-desmethyltramadol which is significantly more potent μ-opioid agonist. Tramadol and its major metabolite(s) are distinguished from other more potent opioid agonists by relative selectivity for μ-opioid receptor. [vi]

While opioids are very effective analgesics, opioids also carry with them many undesirable side effects like sedation, respiratory depression, nausea and vomiting, hypotension and bradycardia, pruritus, and inhibition of bowel function. The treatment of some complications such as pruritus may include the administration of antihistamines, which have an additive effect on sedation and respiratory depression. Respiratory depression is a major life-threatening complication of opioids. The incidence of severe respiratory depression with patient-controlled analgesia pumps has been described to be as high as 1 per 10,000 patients. These events may be usually associated with an error in management.

In our institute, open nephrectomies are performed on regular basis for Renal Transplant and other renal diseases, that is why we have selected nephrectomy patients for our study.

In this study we compare analgesic effects of injection tramadol & transdermal buprenorphine patch in postoperative period after open nephrectomy surgery.

**Methods**

After approval from the institutional research and ethical committee (MGMCH/IEC/JPR/2021/1277; CTRI/2022/08/044612), this prospective, single blinded, randomised controlled trial was conducted from March 2021 to February 2022 at a tertiary care hospital. After taking written informed consent, American Society of Anaesthesiologists (ASA) physical status I and II patients, aged between 18 and 60 years, undergoing open nephrectomy surgeries were included. Patients with ASA grade III or more, known allergy to study drug, lack of consent, known chronic use of analgesics and sedatives, psychiatric disorders were excluded. A sample size of sixty patients was divided in two groups. Group A received Transdermal buprenorphine patch 10 mcg/hour applied 12 hours before surgery and Group B received injection tramadol 100 mg just after extubation. Injection Paracetamol 1 gram intravenously was given as rescue analgesia. Pain score at rest, on movement, total doses of rescue analgesia and side effects if any were compared in both the groups for seven days. Patients were randomly assigned through 1:1 allocation to Buprenorphine or Tramadol groups. Randomization was performed using a computer-generated list, which was concealed from the first author before the randomized allocation. The patients were aware of the group they belonged to (by looking at buprenorphine patch or tramadol injection they needed to take). However, the person assessing pain and satisfaction score was unaware of the group the patient belonged. Hence, this was a single-blinded study.

The patients were explained about the study drugs, post-operative pain treatment options and pain score assessment, a day before the surgery. For the patients in the Group A, a transdermal buprenorphine patch of 10 mcg/hour was applied to the upper outer arm, 12 hours before the surgery (effective serum concentration for transdermal buprenorphine patch is achieved after 12 hours). The group B of patients received Injection Tramadol 100 mg just after extubation.

The patients were pre-oxygenated and pre-medicated with intravenous fentanyl 2 μg/kg and midazolam 30 μg/kg IV, induced by administering injection propofol (till loss of verbal command) and injection cis-atracurium 0.15 mg/kg as muscle relaxant. The patient was intubated and maintenance of anaesthesia was done with isoflurane and nitrous oxide in both groups. At the end of surgery residual neuromuscular block was antagonised with neostigmine (50 μg/kg) and glycopyrrolate (20 μg/kg). The patient was extubated once appropriate extubation criteria were met. Injection Paracetamol 1 gram intravenous for rescue analgesia was given when visual analogue scale (VAS) score was 4 or higher. Post-operatively, vitals were measured and pain was assessed using visual analogue scale scores (0–10), at rest and with movement at the following time periods: 30 minuts, 1 hour, 2 hour, 4 hour, 8 hour, 16 hour, 24 hour and up to 7 days.

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A proper approach to acute postoperative pain management must include an appropriate assessment tool. A 10-point pain assessment scale-Visual Analogue Scale (VAS), where 1 is no pain and 10 is the worst possible pain imaginable, has been nationally accepted. The goal of pain management must be determined with each patient. The goal may not be a score of 1; the patient may be satisfied and functional with a score of 3, preferring to manage some pain and thereby avoid unpleasant side effects of therapy, such as sedation, nausea, or pruritus. The key is to reassess the patient and determine if he or she is satisfied with the outcome. A satisfaction score should be obtained together with a pain score. This combination will help ensure that unrelieved, unwanted pain does not go unnoticed. Responsive analgesia management with good patient communication is the key to a successful program.
Data were entered in Microsoft excel 2019 and statistical analysis was performed using SPSS (Statistical package for Social Science Chicago, IL, USA) version 21 for windows. The categorical data were presented as numbers and percentage and were compared using Chi square test. The Quantative data were presented as mean and SD or Median and IQR and were compared using t test or Mann Whitney U test. Probability was considered significant if p value < 0.05.

**Results**

Both groups had comparable demographic and baseline clinical profiles. There is no statistically significant difference in heart rate, blood pressure and respiratory rate between both the groups. There was significant low visual analogue scale (VAS) score in transdermal buprenorphine patch group compare to injection tramadol group at rest and on movement (p<0.001).

**Table 1:** Post-operative comparison of Visual Analogue Scale (VAS) score on resting between transdermal buprenorphine patch and injection tramadol group (n=60)

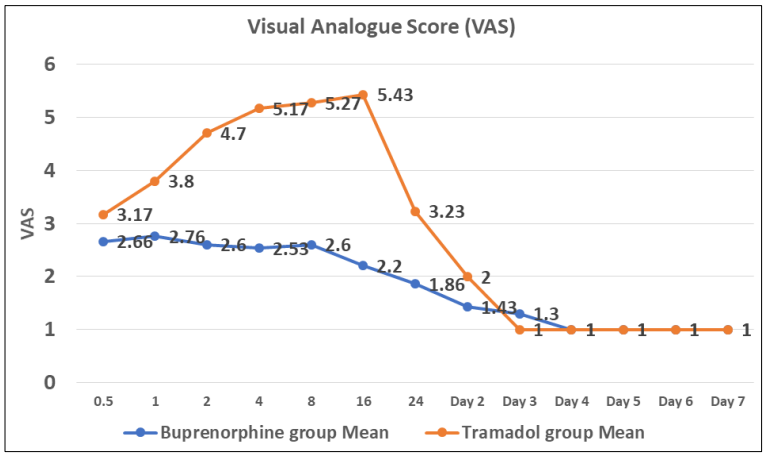
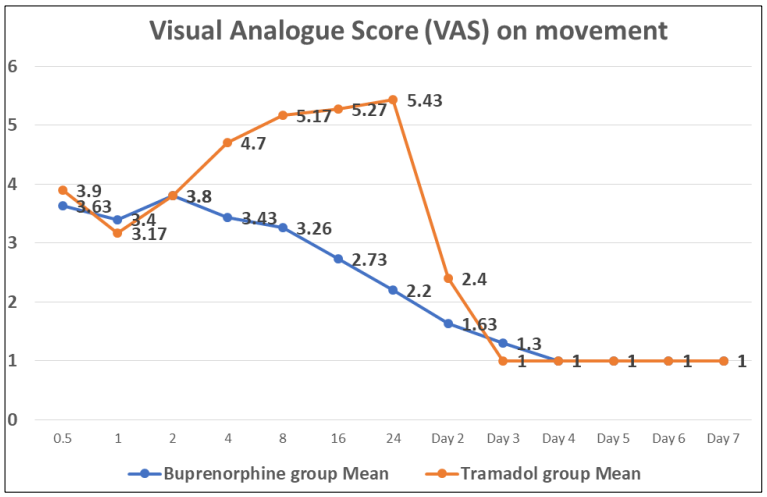



**Table 2:** Post-operative comparison of Visual Analogue Scale (VAS) score on movement between transdermal buprenorphine patch and tramadol group (n=60)




The requirement of rescue analgesia was significantly lower in transdermal buprenorphine patch group as compared to injection tramadol group (14.3% vs 100%).

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**Table 3:** Comparison of requirement of rescue analgesia between transdermal buprenorphine patch group and injection tramadol group (n=60)

| Rescue analgesia requirement | Buprenorphine group (n=30) | | Tramadol group (n=30) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Yes | 5 | 14.3 | 30 | 100 |
| No | 25 | 85.7 | 0 | 0 |
| $\chi^2$ =42.85, df=1, p value < 0.01 | | | | |

The side effects like nausea, vomiting, drowsiness was lower in transdermal buprenorphine group compared to injection tramadol group (26.7% vs 36.7%). Transdermal buprenorphine patch group has better satisfactory scores compared to injection tramadol group (89.96% vs 83.03%).

**Table 4:** Comparison of side effects between transdermal buprenorphine group and injection tramadol group (n=60)

| Side effects | Buprenorphine group (n=30) | | Tramadol group (n=30) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Yes | 08 | 26.7 | 11 | 36.7 |
| No | 22 | 73.3 | 19 | 63.3 |
| $\chi^2$ =0.69, df=1, p value = 0.4 | | | | |
| Types of side effects | | | | |
| Drowsiness | 05 | 16.7 | 00 | 00 |
| Nausea / Vomiting | 03 | 10 | 11 | 36.7 |

**Table 5:** Comparison of satisfaction score of patients between buprenorphine and tramadol group (n=60)

| Buprenorphine group (n=30) | | Tramadol group (n=30) | |
|---|---|---|---|
| Mean (95% CI) | SD | Mean | SD |
| 89.96 (88.28-91.64) | 4.49 | 83.03 (81.95-84.11) | 2.89 |
| Independent t test<br>t value= 7.09, p value<0.01 | | | |

**Discussion**

In this study, we have compared transdermal buphrenorphine patch (10mcg/hr) with injection tramadol for post operative analgesia in nephrectomy surgeries. It was observed that patients who recevied transdermal buprenorphine patch had lower pain score on rest as well as on movement and had lower side effects like nausea, vomiting, drowsiness and tolerated well when compared with injection tramadol, also the required of resue analgia( injection paracetamol 1gm) was lower in transdermal buprenorphine group.

Buprenorphine is a derivative of the opium alkaloid thebaine and is more potent and longer lasting analgesic than morphine. Its dissociation from opiod receptor binding site is slow. This leads to its longer duration of action. Its lack of delta receptor agonist activity is responsible for its less likely dependence on chronic use [7]. It is used clinically for the treatment of moderate-to-severe pain, including perioperative analgesia. Its formulation as a transdermal patch has been introduced into the Indian market [8], although expensive, this mode of delivery has several potential benefits over oral and parenteral administration. These include non-invasive dosing, better absorption, lack of first-pass metabolism, and steady plasma concentration [9]. The patch releases the analgesic steadily over 7 days and has been successfully used to treat a variety of chronic pain conditions [7]. However, there is limited clinical experience of its utility in postoperative pain [8]. There is limited clinical experience of its utility in postoperative pain. It does not require dose adjustments for those with impaired renal function or for the elderly [15].

Achieving adequate pain control is important to limit the negative effects of persistent postoperative pain, but inappropriate use of strong opioids to manage pain is associated with a risk of tolerance and abuse and, in the elderly, delirium and cognitive decline [7]. Long-term opioid management of chronic non cancer pain suggest that many patients discontinue treatment due to adverse events or insufficient pain relief [11].

It is difficult to quantify postoperative pain as parameters such as time to recovery to normal activities, length of hospital stay or return to work, but is certainly one of the aspects of live kidney donation that the donor experiences most dramatically and recalls most vividly even many months or years later. There it is considerable value to assess early postoperative pain objectively [17].

VAS (visual analogue scale) score has proved to be a valid tool for quantifying subjective pain intensity. In past, pain level was measured with a standard categorical scale (e.g. no pain, mild pain, moderate pain and severe pain). However, the VAS score provides measurement of continuum which produces more sensitive pain estimation than the discrete points of the categorical scale [18].

Transdermal opioid delivery is very effective for alleviation of chronic pain, the slow acting characteristic makes it inappropriate for acute pain management. However, the present results

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demonstrated that transdermal buprenorphine was superior in alleviating postoperative pain following nephrectomy than tramadol injection [19].

In our study, the patch was applied 12 hours before nephrectomy in the present study, because efficacy of the buprenorphine transdermal patch was dose dependent, and the peak-effect was achieved after 12 hours. Therefore, initial postoperative pain from time zero to 3 days was managed by transdermal buprenorphine. Because postoperative pain decreases at 3 days after surgery, the buprenorphine TDS could successfully control postoperative pain following nephrectomy in our study.

The assessment of pain by the VAS scale has certain limitations: One needs to recognize that the pain the patient reports may not be the pain he actually feels: whether or not and at which intensity pain is reported is influenced by many factors, such as a wish to attract the nurse's sympathy and attention or conversely the wish to deny the presence of seriousness. In very few cases where recipient of kidney developed any contraindication for surgery, it could lead to wastage of buprenorphine patch [20].

**Conclusion**

From our study, we can conclude that transdermal buprenorphine had better satisfaction score when compared to injection tramadol when used for post-operative analgesia in open nephrectomy patients. Patients with transdermal buprenorphine could achieve normal vitals i.e. heart rate, blood pressure and respiratory rate earlier than injection tramadol in post-operative period. On visual analogue score, transdermal buprenorphine had better performance than injection tramadol with fewer side effects.

**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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