

Comparison between transdermal buprenorphine and intravenous paracetamol for post-operative analgesia after major plastic reconstructive surgery under general anesthesia – A randomized double-blind controlled trial



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ABSTRACT

Background: Adequate pain management is an essential entity in reconstructive surgery to prevent adverse physiological and psychological outcome. Transdermal buprenorphine has been mostly studied in chronic pain and cancer related pain but hardly studies in acute pain are available. **Aims and Objectives:** The aims of this study were to compare post-operative pain relief achieved by transdermal buprenorphine and IV paracetamol in terms of safety and efficacy. Sedation and adverse effects were also studied. **Materials and Methods:** This is a prospective, parallel group, double-blind, and randomized trial. After ethics, clearance and consent from 46 patients undergoing major reconstructive surgery were allotted into Group B, (n = 23) who received transdermal buprenorphine and Group P (n = 23) who received m IV paracetamol 6 hourly. IV Paracetamol was taken as active control. Standard institutional protocol for general anesthesia was followed. Visual analog scale (VAS) score was measured postoperatively for 48 h. Diclofenac sodium was the rescue analgesic. Sedation was assessed by Ramsay Sedation score. **Results:** Transdermal buprenorphine patch (TDB) gave superior pain relief in comparison to intravenous paracetamol 48 h postoperatively, $P \leq 0.05$ in VAS score. The total amount of rescue analgesic required was high in Group P than Group B ($P = 0.034$). Hemodynamic stability was better maintained with TDB with minimal sedation and side effect. **Conclusion:** TDB (20 $\mu\text{g}/\text{h}$; 20 mg) can be safely used for post-operative analgesia with greater efficacy and minimal side effects when compared to intravenous paracetamol.

Key words: Intravenous paracetamol; Plastic reconstructive surgery; Post-operative pain; Transdermal buprenorphine patch; VAS scores

INTRODUCTION

Anesthesiologists are responsible for proper pain management during the perioperative period and continuing their care for acute post-operative pain services

as well. Provision of effective analgesia is an important component of this multidimensional task.¹

Different studies showed that despite the presence of an acute pain services, 41% of patients had moderate-to-

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severe pain on the day of surgery, which persisted until the 4th post-operative day.⁶ It is estimated that one in four surgical patients with acute post-surgical pain received complete relief.⁷

Plastic reconstructive surgery refers to a highly specialized operation performed to repair, restore, or improve body parts. This prolonged surgical intervention causes moderate-to-severe pain postoperatively. Adverse physiological and psychological changes related to pain, abett the recovery process.¹⁻³ Moreover, pain itself causes vasoconstriction, reducing vascularity at the flap (reconstruction) site, and cause flap necrosis.

Of the most frequently used analgesics for pain in the post-operative period, opioid forms the first-line drug. Buprenorphine, a potent analgesic, is a semisynthetic opioid. It is a partial μ agonist and has k receptor antagonist property and, hence, causes less respiratory depression.^{1,4,5} It has a potent and safe analgesic profile (75–100 times greater than morphine) at 5–10% receptor occupancy.⁵ Buprenorphine is metabolized in liver and is safe in patients with poor renal function.⁶ In 1978, Dr Donald R. Jasinski of the U.S Addiction Research Center described buprenorphine as an analgesic with low abuse potential.⁷ Transdermal patch of buprenorphine (20 μ g/h; 20 mg) is unique and non-invasive method of drug delivery system which releases the drug at the rate of 20 μ g/hr with effective plasma concentration achieved at 12–24 h¹ and gives pain relief for 7 days.^{1,3,8,9} They provide sustained drug release for prolonged periods with higher bioavailability, resulting in steady state plasma concentration, and lesser side effects.¹⁰ They are used to treat a chronic cancer and non-cancer pain.^{11,12} Studies evaluating the effects of buprenorphine patch in the post-operative period are few, and hence, this study was required to evaluate the analgesic efficacy of buprenorphine patch in prolonged surgery comparing the same with a standard active control.

Intravenous paracetamol is a commonly used analgesic and antipyretic agent recommended for the treatment of pain and fever in adults and children. Adverse reactions are very rare with paracetamol.¹³ Paracetamol (acetaminophen), available for intravenous use, is not a NSAID and interferes neither with platelet nor kidney functions nor does it present the unwanted side effects of NSAIDS.

This aim of the study was to compare the safety and efficacy of transdermal buprenorphine patch (TDB) with intravenous paracetamol for managing post-operative pain following major plastic reconstructive surgery.

MATERIALS AND METHODS

After obtaining Institutional Ethics Committee approval, this prospective randomized parallel group double-blind active controlled trial was done.

The study was registered with Clinical Trial Registry of India CTRI no. REF/2019/02/024237

Inclusion and exclusion criteria

Patients between 18 and 65 years with ASA physical status I and II undergoing major plastic reconstructive surgery under general anesthesia were included in the study. Subjects who had pre-existing pain in non-surgical site (polytrauma, any fracture, neurological pain, etc.) were excluded from the study. Significant cardiac, respiratory, hepatic and renal impairments or any other uncontrolled systemic illness, obese (body mass index [BMI] >35), H/O uncontrolled convulsion, pregnancy, lactation, and allergic reaction to study drugs were also excluded from the study. Patients with opioid addiction, infection, and dermatitis at the application site of the patch were excluded from the study.

Sample size calculation and statistical analysis

The study of Desai et al.,¹² safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain was taken as reference in this study. Visual analog scale (VAS) score for post-operative pain at 24 h postoperatively was considered as the primary outcome measure for calculation of sample size. As per this calculation, 16 subjects would be required per group for a difference of 2 cm in the VAS score taking into consideration 80% power and 5% probability of type 1 error. This calculation presumed a standard deviation (SD) of 2 cm in VAS score and two-sided testing. About 20% margins of drop-out was allowed. Twenty subjects were recruited in each group or 40 over-all. Sample size calculation was done using N master 2.0 (Dept. Of Biostatistics, Christian Medical College, Vellore, 2011) software.

Data were summarized by mean and SD for numerical variables with normal distribution, median, and interquartile range for skewed numerical variables and percentages for categorical variables. Student's t-test or Mann–Whitney U-test was used for numerical variables as per their distribution. Fishers exact test was utilized for intergroup comparison of categorical variables. Repeated measure analysis of variance (ANOVA) or Friedmans ANOVA was used where ever appropriate. Two-tailed analysis was done. $P < 0.05$ was considered significant in all comparisons.

Patient allocation

Forty-six patients were divided into two groups, Group B (n=23) and Group P (n=23) using a computer-generated

random number table. Group B was administered buprenorphine through transdermal route (20 µg/h; 20 mg) and in Group P received paracetamol through intravenous route (15 mg/kg 6 h).

Anesthesia and pain management

After pre-anesthetic evaluation, patients were explained regarding surgical intervention and anesthesia with the risks and benefits. Before inclusion, informed consent was obtained. Tab Ranitidine, Metoclopramide, and Alprazolam were given orally as premedication in appropriate doses. Transdermal patch of buprenorphine (20 mg; with releasing the drug @ 20 µg/h) was applied to each patient belonging to Group B and a placebo (sticker, identical to the patch) was also applied to the individual patients belonging to Group P, on the night before surgery (around 10 pm) as onset of action for transdermal buprenorphine is achieved after 12–24 h. The application site (upper outer arm, or chest) was relatively hairless and properly cleaned with a cotton swab. VAS score was demonstrated and explained to all patients.

After receiving the patient in the operation theater, all the baseline hemodynamic parameters such as heart rate and blood pressure was measured. SpO₂ and ECG were also recorded and an IV line was done with 18 G cannula in a large peripheral vein. They were premedicated with Inj. Glycopyrrolate, Inj. Midazolam, and Inj. Fentanyl in appropriate doses as per body weight. After pre-oxygenation for 3 min, the patients were induced intravenously with Inj. Propofol (2 mg/kg). Succinylcholine (1 mg/kg) was given to aid tracheal intubation. Anesthesia was maintained with 60% nitrous oxide and 40% oxygen with isoflurane (0.6–1.4%) and Inj. Iecuronium (0.1 mg/kg loading and 0.05 mg/kg for maintenance). EtCO₂ was kept between 35 and 40 mmHg. Group P received Inj. Paracetamol (15 mg/kg) infusion for

15 min before surgical incision. Group B received (1.5 ml/kg) NS in bottles identical to PCM bottle over 15 min before incision to serve the purpose of blinding. Study drugs were delivered by an anesthesiologist who was not involved in this research work. Residual muscle paralysis was reversed with Inj. Neostigmine and Inj. Glycopyrrolate in required doses.

Patients were extubated and shifted to the recovery room with continuous monitoring of vitals including NIBP, SpO₂, heart rate, and ECG. Patients were assessed at 0, 2, 4, 12, 24, 36, and 48 h postoperatively. Inj. Paracetamol (15 mg/kg iv over 15 min) was infused 6 hourly for 2 consecutive post-operative days to those patients belonging to the Group P and a placebo (15 ml/kg NS, in bottles identical to the PCM infusion) to Group B.

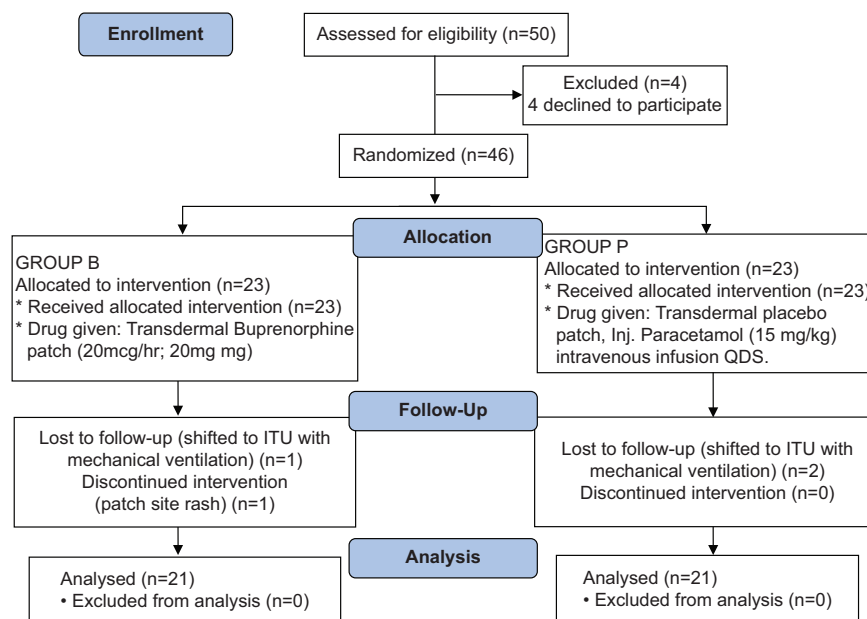
VAS score was assessed at 0, 2, 4, 12, 24, 36, and 48 h interval. Inj Diclofenac sodium 75 mg intravenously was administered as rescue analgesic when VAS score was ≥4.¹⁴

Sedation was assessed by the Ramsay Sedation score (RSS) post-extubation.¹⁵

Complications were noted and managed as per standard protocol. If sedation became significant then the patch was removed and the patient was excluded from the study. Data were recorded and analyzed with mean±SD, and P<0.05 was considered statistically significant. The principal investigator documented all the parameters. He was blinded to the study drugs.

RESULTS

CONSORT flow diagram of the study.



There were no significant differences between the groups with respect to demographic profile, that is, age, sex, ASA grades, height, and body weight (Table 1). BMI was an exception.

Except at 2 h and 4 h postoperatively, at all post-operative time intervals, VAS scores of Group P subjects were significantly higher when compared to subjects in Group (Table 2).

During the post-operative period, mean RSS in Group B (2.71 ± 0.784) was a little higher than Group P (2.29 ± 0.784), but the difference was not significant statistically, with the exception of 36 h postoperatively. No incidence of excessive sedation (RSS>4) or respiratory depression was noted in either group (Table 3).

During the first 48 h following surgery, requirement for rescue analgesic was higher in Group P (1.10 ± 1.136) in comparison to Group B (0.29 ± 0.644) and this was statistically significant.

At all post-operative time intervals, heart rate was significantly higher in Group P subjects than in Group B subjects ($P \leq 0.05$) (Table 4).

SBP, DBP, and MAP were found to be significantly higher in Group P in comparison to Group B at all post-operative intervals except at 48 h. Statistically significant difference noted at 2, 4, 12, and 24 h postoperatively.

Post-operative complication was found to be in higher proportion in Group P (98.34%) as compared to Group B (66.67%). However, nausea and vomiting were more frequent in Group B (28.57%) than Group P (4.76%), but the result was not statistically significant (Table 5).

DISCUSSION

Postsurgical pain is a complex response to trauma and surgery that stimulate the central nervous system and cardiovascular system, leading to complications and increase in the cost of medical care.¹⁶

Buprenorphine, a potent, centrally acting opioid has a low molecular weight, along with high lipophilicity. It also has high μ receptor affinity which makes it a appropriate drug for transdermal preparation and delivery. Transdermal preparations which release buprenorphine for 7 days have resulted in re-emergence of the drug.

Transdermal drug delivery system (TDS) provides safe, suitable, and definitive method of drug delivery and it avoids painful skin punctures and multiple dosing.^{1,3}

Table 1: Demographic profile

| Parameters | Group B (Mean±SD) | Group P (Mean±SD) | P-value |
|-----------------------|-------------------|-------------------|---------|
| Age (Mean±SD) | 38.19±11.847 | 37.81±11.188 | 0.915 |
| Body weight (Mean±SD) | 63.90±8.660 | 66.86±6.598 | 0.221 |
| Height (Mean±SD) | 163.10±8.532 | 162.81±8.790 | 0.915 |
| BMI (Mean±SD) | 23.96±2.137 | 25.24±1.743 | 0.039 |
| Sex (prevalence) | | | |
| Female | 10/21 (47.62%) | 10/21 (47.62%) | 1.000 |
| Male | 11/21 (52.38%) | 11/21 (52.38%) | |
| ASA I/II | 12/9 | 6/15 | 0.118 |

BMI: Body mass index

Table 2: Post-operative pain score (VAS) of Group B and Group P at different time points

| Time intervals | Group B (Mean±SD) | Group P (Mean±SD) | P-value |
|--------------------------|-------------------|-------------------|---------|
| Immediate post-operative | 2.05±0.669 | 2.76±1.044 | 0.014** |
| At 2 h post-operative | 2.81±0.928 | 3.24±0.944 | 0.247 |
| At 4 h post-operative | 2.29±0.845 | 2.76±0.831 | 0.113 |
| At 12 h post-operative | 1.86±0.727 | 2.67±1.017 | 0.009** |
| At 24 h post-operative | 1.67±0.913 | 2.62±0.973 | 0.004** |
| At 36 h post-operative | 1.10±0.831 | 2.62±0.921 | 0.000** |
| At 48 h post-operative | 0.67±0.730 | 1.62±0.590 | 0.000** |

**Footnote statistically significant

Table 3: Ramsay Sedation score

| Time Intervals | Group B (Mean±SD) | Group P (Mean±SD) | P-value |
|--------------------------|-------------------|-------------------|---------|
| Immediate post-operative | 2.71±0.784 | 2.29±0.784 | 0.152 |
| At 2 h post-operative | 1.90±0.768 | 1.57±0.676 | 0.182 |
| At 4 h post-operative | 1.67±0.483 | 1.43±0.507 | 0.187 |
| At 12 h post-operative | 1.86±0.359 | 1.52±0.602 | 0.059 |
| At 24 h post-operative | 1.81±0.402 | 1.67±0.483 | 0.428 |
| At 36 h post-operative | 1.95±0.218 | 1.48±0.512 | 0.008** |
| At 48 h post-operative | 1.95±0.218 | 1.81±0.402 | 0.428 |

**Footnote statistically significant

Table 4: Rescue analgesic requirements

| Rescue analgesic requirement | Group B (Mean±SD) | Group P (Mean±SD) | P-value |
|------------------------------|-------------------|-------------------|---------|
| Rescue total | 0.29±0.644 | 1.10±1.136 | 0.034** |

**Footnote statistically significant

Table 5: Post-operative complications

| Complications | Group B | | Group P | | P-value |
|-----------------------|---------|-------|---------|-------|---------|
| | No. | % | No. | % | |
| Nausea and vomiting | 6/21 | 28.57 | 1/21 | 4.76 | 0.093 |
| Pruritus | 2/21 | 9.52 | 0/21 | 0.00 | 0.488 |
| Application site rash | 2/21 | 9.52 | 0/21 | 0.00 | 0.488 |
| Headache | 0/21 | 0.00 | 0/21 | 0.00 | - |
| Constipation | 0/21 | 0.00 | 0/21 | 0.00 | - |
| No complications | 14/21 | 66.67 | 20/21 | 98.34 | |

TDS avoids first pass metabolism, avoids peaks, and troughs in the plasma level of drugs and breakthrough pain. Due to slow release, it also decreases the incidence of associated adverse effects.³

Kumar et al., in 2016 in a prospective, randomized, double-blind, and controlled trial showed that TDB (20 mg) is effective in decreasing post-operative pain in major abdominal surgery.¹ It requires minimum rescue analgesic and has better hemodynamic stability with fewer side effects.

Arshad et al., in 2015, compared transdermal buprenorphine and transdermal fentanyl for post-operative pain management in major abdominal surgery and found that both were effective in managing post-surgical pain. Fentanyl had a better analgesic profile and had less sedation.³

Setti et al., in 2012, used 17.5, 35, and 52.5 mcg/h of TDB patches to patients undergoing gynecologic surgeries, intravenous morphine, and ketorolac as rescue analgesic. They found that the efficacy was directly proportional to the dosage.¹⁷

In 2008, Privitera and Guzzetta, in two descriptive studies, used 35 mcg/h of TDB for patients undergoing shoulder surgeries and surgeries of the upper femur and noted adequate pain relief 24 h after surgery in 75% patients in addition to a broad margin of safety.^{18,19}

Few studies determined that, with TDB, the requirement of rescue analgesic is reduced, but it is not completely done away with. They concluded that it is due to the long latency in the onset of transdermal delivery, and hence, it is less suitable for post-operative analgesia.²⁰ However, it may be still superior to other conventionally used routes.¹²

In 1994, Walsh et al., observed that nausea, vomiting, euphoria, sedation, delayed gastric emptying, and pupillary constriction were all seen to a lesser degree with buprenorphine due to its high lipophilicity.²¹

Khandelwal et al., very recently in 2021, evaluated the efficacy of analgesia of buprenorphine patch 10, 20 $\mu\text{g}\cdot\text{h}^{-1}$ and fentanyl patch 25 $\mu\text{g}\cdot\text{h}^{-1}$ for relief of pain in the post-operative period in patients undergoing arthroscopic lower limb surgeries and concluded that in arthroscopic lower limb surgery, buprenorphine patch (20 $\mu\text{g}\cdot\text{h}^{-1}$) applied 12 h before surgery is an effective post-operative analgesic and it is not associated with any significant adverse effects.²²

Niyogi et al., in 2017, evaluated the analgesic efficacy of buprenorphine patch for post-operative pain relief in patients undergoing spinal instrumentation surgery. They

found that time to first post-operative rescue analgesic (tramadol) requirement was much delayed and also reduced in patients having TDB. However, intra-and post-operative hemodynamic status was also stable in receiving buprenorphine without any adverse events.²³

TDB has a better analgesic potential than intravenous paracetamol. Hemodynamic stability in the intraoperative and post-operative period is also better with buprenorphine patch.

Side effects of buprenorphine are also minimal. Nausea and vomiting are the common side effects. Thus, buprenorphine patch (20 μg) given 12 h before surgery can safely be used as an effective analgesic in plastic reconstructive surgery.

Limitations of the study

Using pain scale (VAS) which is subjective in nature and a follow-up only for 2 post-operative days are major limitations of our study.

Measuring plasma level of the drugs was desirable for a better insight into the study.

CONCLUSION

Transdermal buprenorphine can be safely and effectively used for post-operative analgesia in plastic reconstructive surgery. Side effects of transdermal buprenorphine are minimal.

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Authors' Contributions:

AM- Concept and design of the study, clinical work, prepared first draft of manuscript; **RB**- Assisted in clinical work, interpreted the results; **SM**- reviewed the literature and manuscript preparation; **SG**- Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript; **SS**- Concept, coordination and revision of the manuscript.

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