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Original Article

Anaesthesia Section

Postoperative Analgesic Efficacy of Transdermal Fentanyl Patch in Patients Undergoing Total Laparoscopic Hysterectomy: A Randomised Controlled Trial

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ABSTRACT

Introduction: Total Laparoscopic Hysterectomy (TLH) is associated with significant postoperative pain, necessitating effective analgesia to enhance recovery. Transdermal Fentanyl Patches (TFP) provide a non-invasive, sustained-release opioid delivery system; however, their efficacy in TLH remains underexplored.

Aim: To evaluate the postoperative analgesic efficacy of preoperative TFP (25 mcg/hr) compared to placebo in patients undergoing TLH.

Materials and Methods: In the present double-blinded, randomised controlled trial, 60 female patients (aged 40-65 years, American Society of Anesthesiologists (ASA) I-II) undergoing elective TLH were randomised to receive either a 25 mcg/hr TFP (n=30) or a placebo patch (n=30) applied 10-12 hours preoperatively. Pain intensity was assessed using the Numeric Rating Scale (NRS) at 2, 4, 6, 8, 10, 12 and 24 hours postoperatively. Secondary outcomes included ambulation scores (0-3), Ramsay Sedation Scores (RSS) (1-6) and incidence of Nausea and Vomiting (N/V, 0-3). Data were analysed using t-tests, chi-square tests and general linear models, with statistical significance set at $p<0.05$.

Results: Baseline characteristics (age, Body Mass Index (BMI), ASA grade and duration of anaesthesia) were comparable between groups ($p>0.05$). The fentanyl group demonstrated significantly lower pain scores at all time points (e.g., 2 hours: 3.87±0.434 vs. 6.83±0.461; 24 hours: 1.53±0.629 vs. 3.30±0.651; $p<0.001$). Ambulation scores were higher in the fentanyl group (e.g., 12 hours: 3.00±0.170 vs. 1.70±0.450; $p<0.001$), indicating better mobility. Sedation scores were lower in the fentanyl group at most time points (e.g., 24 hours: 0.13±0.346 vs. 0.77±0.430; $p<0.001$). The incidence of nausea and vomiting was significantly reduced in the fentanyl group (e.g., 2 hours: 0.23±0.305 vs. 2.93±0.254.

Conclusion: Preoperative application of TFP (25 mcg/hr) significantly reduces postoperative pain, enhances ambulation, minimises sedation and decreases nausea and vomiting in patients undergoing TLH. These findings support the inclusion of TFP as an effective component of multimodal analgesia for gynecologic surgery and warrant further studies to assess long-term outcomes and comparative efficacy.

Keywords: Ambulation, Analgesia, Nausea, Pain, Postoperative period, Transdermal patch, Vomiting

INTRODUCTION

Total Laparoscopic Hysterectomy (TLH) is widely accepted as a standard surgical technique for managing various benign and malignant gynaecological disorders. Compared to open hysterectomy, it offers advantages such as smaller incisions, reduced blood loss and faster recovery [1]. Nevertheless, patients frequently experience considerable postoperative discomfort, particularly visceral pain, which is often difficult to control. Poorly managed pain not only increases patient distress but may also delay ambulation, prolong hospital stay and contribute to the development of persistent postsurgical pain [2].

Consequently, effective analgesia is a cornerstone of Enhanced Recovery After Surgery (ERAS) pathways, aiming to optimise functional recovery, minimise opioid use and improve overall surgical outcomes [1]. Opioids remain the mainstay for managing postoperative pain because of their strong efficacy against visceral nociception [3,4]. However, conventional administration routes such as Intravenous (IV) or epidural delivery have notable limitations. Intravenous opioids can lead to fluctuating plasma concentrations, resulting in periods of inadequate pain relief or excessive side effects including nausea, vomiting, constipation and respiratory depression [5]. Epidural techniques, although highly effective, are invasive and may be associated with complications such as hematoma, nerve injury, or catheter-related problems [5]. These challenges have generated interest in alternative methods that can provide stable and sustained analgesia with fewer adverse effects.

Transdermal systems offer a non-invasive approach to drug administration, characterised by gradual and consistent release into the systemic circulation [6,7]. Fentanyl, a potent and lipophilic opioid, is particularly well-suited for this route of delivery [8]. When applied as a transdermal patch, it bypasses first-pass metabolism and maintains therapeutic plasma levels for up to 72 hours [9]. This avoids the peak-trough fluctuations associated with intermittent dosing and may reduce the incidence of dose-related side effects while ensuring reliable pain relief [7].

The TFP have been evaluated in various surgical contexts, showing favourable outcomes. Several studies have demonstrated that TFP reduces pain scores and the need for rescue opioids after major abdominal procedures [10], total knee arthroplasty [11] and forefoot surgery [12]. Despite these promising results, there is limited evidence regarding their use in gynaecological laparoscopy. While a few trials have examined TFP following abdominal gynaecologic surgery [13] or open hysterectomy [14], data specifically related to TLH remain scarce. Most available literature focuses on abdominal [10,15] and orthopedic surgeries [11,16], which differ in both pain mechanisms and patient populations.

Moreover, TLH is associated with distinctive features such as visceral pain and shoulder-tip discomfort related to pneumoperitoneum, further emphasising the need for targeted evaluation [14]. Therefore, this study was undertaken to address this gap by assessing the

postoperative analgesic efficacy of a preoperatively applied TFP (25 mcg/hr) compared with placebo in women undergoing TLH.

The primary outcome of this study was postoperative pain intensity, measured using the NRS (0-10) at 2, 4, 6, 8, 10, 12 and 24 hours after surgery. The secondary outcomes included ambulation scores (0-3), sedation levels assessed by the RSS (1-6) and the incidence and severity of nausea and vomiting (N/V score, 0-3).

MATERIALS AND METHODS

The present randomised controlled study was a double-blinded, randomised controlled trial conducted in the Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, BG Nagara, Karnataka, India, from November 18, 2024 to February 18, 2025. A total of 60 female patients were enrolled. The study was approved by the Institutional Ethics Committee (Approval No: AIMS/IEC/198/2024) and written informed consent was obtained from all participants prior to enrollment.

Sample size calculation: The sample size was calculated based on the expected difference in mean postoperative pain scores between the fentanyl and placebo groups, using the following formula:

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{d^2}$$

Where:

σ = pooled Standard Deviation (SD) of pain scores from previous studies (≈33)

d = minimum clinically significant difference in mean pain scores considered relevant (25)

Z(1-α/2) = 1.96 for α = 0.05

Z(1-β) = 0.84 for 80% power

$$n = 2(1.96 + 0.84)^2 (33)^2 / (25)^2$$

$$n = 15.68 \times 1089/625$$

$$n = 17,066.5/625 \approx 28$$

Using these assumptions, the required sample size was calculated to be 28 patients per group. To compensate for possible dropouts, 30 patients were recruited in each group, making the final sample size 60 patients.

Inclusion criteria: The study included female patients aged between 40 and 65 years, classified as ASA physical status I or II, who were scheduled to undergo elective TLH. Only normotensive, clinically stable patients with a Mallampati airway grade of I or II were considered eligible.

Exclusion criteria: Patients were excluded if they were younger than 40 years or older than 65 years, had a BMI of 35 kg/m² or higher, or had a history of obstructive sleep apnea, severe hepatic or renal dysfunction. Individuals with known hypersensitivity to fentanyl or other opioids, those receiving chronic pain medications, or patients who declined to provide consent were also excluded.

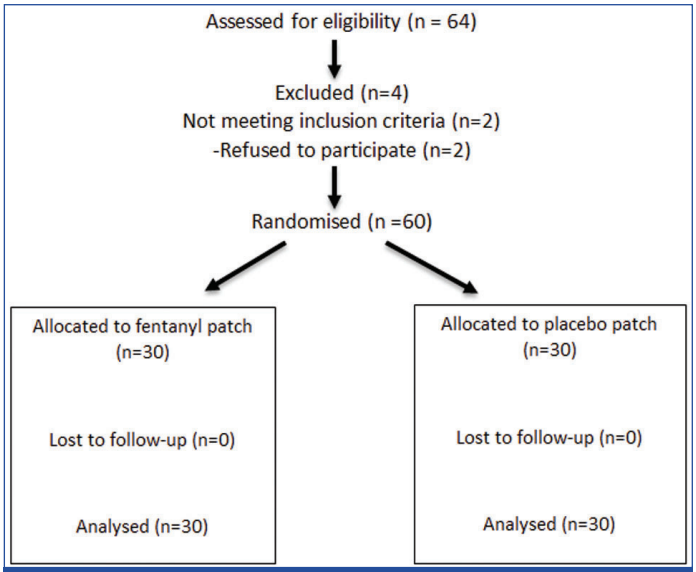
Out of the 64 patients screened, all were randomised. Four patients were excluded post-randomisation due to protocol deviation or withdrawal of consent and data from 60 patients were analysed.

Study Procedure

Randomisation was performed using a computer-generated random number sequence [Table/Fig-1], with allocation concealment ensured by sealed opaque envelopes. Blinding was maintained for patients, anaesthesiologists administering the intervention and outcome assessors.

Group F (Fentanyl patch group): Received a 25 mcg/hr TFP, applied to the anterior chest wall 10-12 hours before surgery and kept in situ for 24 hours postoperatively [10].

Group P (Placebo group): Received an identical-looking placebo patch, applied in the same manner.



[Table/Fig-1]: CONSORT flow diagram.

Anaesthesia protocol: A standardised anaesthesia protocol was followed. Patients were kept nil per oral for eight hours preoperatively and received oral ranitidine (150 mg) and alprazolam (0.5 mg) the night before surgery. In the operating room, an 18G IV cannula was inserted and patients were preloaded with Ringer's lactate (10-15 mL/kg). Induction was achieved using midazolam (0.01 mg/kg IV), fentanyl (2 µg/kg IV), propofol (2 mg/kg IV) and atracurium (0.5 mg/kg IV). Vital signs were continuously monitored throughout the procedure.

Postoperative management: Patients were monitored in the Post-Anaesthesia Care Unit (PACU) for two hours before being transferred to the postoperative ward. The study protocol was strictly followed.

Patients in Group P received IV Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Patients in Group F received rescue analgesia (IV tramadol 100 mg) only if their NRS score exceeded 4 within two hours after surgery.

A total of four patients were excluded from the study due to failure to meet the inclusion criteria or refusal of consent.

Parameters studied:

Postoperative pain intensity: Measured using the NRS (0-10) at 2, 4, 6, 8, 10, 12 and 24 hours after surgery [9].

Ambulation scores: Rated on a scale of 0-3 [16].

Sedation levels: Assessed using the RSS (1-6) [8].

Incidence and severity of nausea and vomiting (N/V): Rated on a scale of 0-3 [17].

STATISTICAL ANALYSIS

All data were analysed using Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean±SD and analysed using the independent t-test for between-group comparisons and the paired t-test for within-group analysis. Qualitative variables were expressed as frequency and percentage and compared using the Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

The demographic characteristics, including age, BMI, ASA physical status and duration of anaesthesia, were comparable between the two groups, with no statistically significant differences (p>0.05, [Table/Fig-2]). This ensured that the study groups were homogenous and suitable for comparison.

Pain, ambulation and sedation scores over time: Pain, ambulation and sedation scores were assessed at multiple time points. The

following table and accompanying text summarise the key findings, including mean and SD values [Table/Fig-3].

Variables	Fentanyl patch (n=30)	Placebo (n=30)	p-value
Age(years) (Mean±SD)	49.27±6.26	48.40±5.39	0.541
BMI (kg/m^2) (Mean±SD)	25.41±4.27	25.18±3.75	0.826
ASA Grade I (n (%))	11 (36.7%)	12 (40.0%)	0.791
ASA Grade II (n (%))	19 (63.3%)	18 (60.0%)	0.791
Mallampatti grade I(n%)	14(46.7)	13(43.3)	0.795
Mallapatti grade II(n%)	16(53.3)	17(56.7)	0.795
Duration of Anaesthesia (hours) (Mean±SD)	2.02±0.45	1.96±0.36	0.79

[Table/Fig-2]: Baseline characteristics of patients in fentanyl and placebo groups.

Time (hrs)	Pain score (F/P) (Mean±SD)	p-value	Ambulation score (F/P) (Mean±SD)	p-value	Sedation score (F/P) (Mean±SD)	p-value
2	3.87±0.434 / 6.83±0.461	<0.001	1.97±0.183 / 1.27±0.450	<0.001	1.80±0.407 / 2.07±0.365	0.010
4	3.80±0.677 / 6.77±0.528	<0.001	2.07±0.143 / 1.43±0.395	<0.001	1.97±0.213 / 2.13±0.434	0.057
6	3.90±0.670 / 6.70±0.505	<0.001	2.07±0.127 / 1.27±0.450	<0.001	1.80±0.407 / 2.10±0.449	0.002
8	3.23±0.568 / 6.23±0.430	<0.001	2.27±1.33 / 1.33±1.87	<0.001	1.33±0.479 / 1.13±0.346	<0.001
10	3.23±0.467 / 4.67±0.485	<0.001	2.27±1.70 / 1.33±1.13	<0.001	1.33±0.479 / 1.13±0.346	0.069
12	1.97±0.183 / 4.67±0.450	<0.001	3.00±0.170 / 1.70±0.450	<0.001	0.90±0.300 / 1.13±0.400	0.007
24	1.53±0.629 / 3.30±0.651	<0.001	3.00±0.213 / 2.13±0.434	<0.001	0.13±0.143 / 0.77±0.300	<0.001

[Table/Fig-3]: Comparison of mean pain, ambulation and sedation scores over Time.

Pain scores measured using the NRS were significantly lower in Group F compared to Group P at all time intervals (p<0.001). For example, at two hours postoperatively, the mean pain score was 3.87±0.434 in Group F versus 6.83±0.461 in Group P and at 24 hours, it was 1.53±0.629 versus 3.30±0.651, respectively.

Ambulation scores were consistently higher in Group F, indicating earlier mobilisation, while sedation scores were generally lower in the fentanyl group, reflecting a reduced need for rescue analgesics.

The incidence of postoperative Nausea and Vomiting (N/V) was markedly lower in Group F compared to Group P at all time points (p<0.001). For instance, at two hours postoperatively, the mean N/V score was 0.23±0.305 in Group F versus 2.93±0.254 in Group P. At 24 hours, the scores were 0.03±0.098 in Group F and 0.90±0.300 in Group P. These findings demonstrate a significant reduction in opioid-related side effects in the fentanyl group [Table/Fig-4].

Time (hrs)	N/V Score (F/P) (Mean±SD)	p-value
2	0.23±0.305 / 2.93±0.254	<0.001
4	0.23±0.305 / 2.73±0.327	<0.001
6	0.30±0.464 / 2.90±0.300	<0.001
8	0.20±0.259 / 2.33±0.480	<0.001
10	0.20±0.259 / 1.30±0.464	<0.001
12	0.20±0.259 / 1.30±0.464	<0.001
24	0.03±0.098 / 0.90±0.300	<0.001

[Table/Fig-4]: Incidence of Nausea & Vomiting (N/V) over time.

DISCUSSION

The present randomised, double-blind trial found that preoperative application of a TFP at a dose of 25 µg/hr significantly reduced postoperative pain scores compared to placebo in patients undergoing TLH. This analgesic benefit was consistent across all observed intervals (2-24 hours, p<0.001).

The findings are consistent with earlier randomised studies in abdominal and gynaecological surgeries, which demonstrated that transdermal fentanyl lowers postoperative pain and reduces the need for rescue opioids [10,12,15,17]. The pharmacokinetic advantage of the patch, delivering stable plasma concentrations for 24-72 hours [7,9], likely explains the prolonged analgesia observed in this study. Comparable effects have also been documented in trials involving abdominal, orthopaedic and forefoot surgeries [4,11,18], where transdermal delivery avoided the plasma fluctuations associated with systemic opioids and ensured more consistent pain relief.

In addition to pain control, the study demonstrated significantly better ambulation scores in the fentanyl group. Early mobilisation is a vital component of ERAS protocols, as it lowers the risk of thromboembolic events and accelerates functional recovery. Previous literature has linked improved pain relief with earlier ambulation and studies in abdominal and orthopaedic populations have reported faster rehabilitation and greater tolerance for physiotherapy when patients received transdermal fentanyl [4,14,18]. By reducing the need for additional systemic opioids, the patch may facilitate safe and comfortable mobility and the findings confirm its potential role in enhancing functional outcomes after laparoscopic hysterectomy.

Interestingly, sedation scores in the trial were not elevated in the fentanyl group. On the contrary, Ramsay scores were lower at later time points, reflecting that steady analgesia limited the need for supplementary sedating rescue analgesics. This contrasts with the sedation often observed with systemic opioid boluses. The results are supported by earlier trials reporting that transdermal fentanyl can achieve effective analgesia without excessive sedation when administered at appropriate doses [9,10,17]. Moreover, Intensive Care Unit (ICU) sedation monitoring literature highlights the importance of using validated scales, such as the Ramsay score, to differentiate between adequate analgesia and clinically concerning sedation [8]. Nevertheless, caution remains necessary, as interindividual variation in patch absorption can occasionally result in delayed side effects, particularly in vulnerable patients [5].

Another important secondary finding was the lower incidence of Postoperative Nausea and Vomiting (PONV) in the fentanyl group compared with placebo. Reductions in PONV have also been observed in other studies using transdermal fentanyl for abdominal hysterectomy and orthopaedic procedures [10-12,17]. This effect can be attributed to the avoidance of sharp plasma peaks that occur with IV or oral opioid administration, which are known to trigger emetogenic effects. Clinically, lower PONV translates into improved tolerance for oral intake, greater comfort and higher patient satisfaction-outcomes that are increasingly emphasised in ERAS pathways.

Finally, the study showed that the preoperative application of the patch 10-12 hours before surgery, kept in situ for 24 hours postoperatively, was well tolerated without unexpected complications. Previous pharmacokinetic studies and clinical trials support this practical regimen, though they also stress careful consideration of factors such as BMI, skin condition and comorbidities, which may influence absorption [7,9,12]. While the findings are encouraging, the modest sample size and restriction to ASA I-II, Mallampati I-II patients represent important limitations. Larger multicentre studies are required to confirm these results and explore alternative dosing strategies. Future investigations should also consider direct comparisons of transdermal fentanyl with multimodal analgesia regimens, including regional anaesthesia techniques and non-opioid agents, to determine the safest and most effective strategy for laparoscopic gynaecologic surgery. Furthermore, the cost-effectiveness of transdermal fentanyl, as emphasised in previous work [6], deserves evaluation in resource-limited settings. Finally, integrating patient-reported outcomes, such as satisfaction, quality of recovery and quality of life, would provide a more comprehensive assessment of its clinical value [8].

Limitation(s)

This study has a few limitations. First, it included only female patients undergoing TLH, which may limit the generalisability of the findings. Larger studies are needed to confirm these results across diverse populations. Second, the study did not assess long-term outcomes, such as chronic pain or opioid dependence, which are critical considerations in the context of the opioid epidemic.

CONCLUSION(S)

This study demonstrates that preoperative application of a 25 µg/hr TFP provides consistent and superior analgesia following TLH compared with placebo. Patients receiving the patch experienced significantly lower pain scores, improved mobility, reduced sedation and a lower incidence of nausea and vomiting. The patch was well tolerated, simple to administer and required fewer rescue analgesics, making it a practical tool in perioperative care. By maintaining stable plasma concentrations, transdermal fentanyl overcomes the limitations of systemic opioid dosing and supports smoother recovery. These results highlight its potential integration into multimodal analgesia and ERAS pathways for gynaecologic surgery. Larger multicentre studies are needed to validate these findings and to assess cost-effectiveness and long-term outcomes.

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