

Clinical Effectiveness of Transdermal Buprenorphine compared to Oral Morphine in Advanced Cancer Pain

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ABSTRACT

Background: Inadequate management of moderate-to-severe cancer pain remains a significant challenge in oncology. Oral morphine is traditionally considered the standard WHO Step 3 opioid; however, its long-term use is often hindered by gastrointestinal side effects and frequent dosing demands. This study evaluated the comparative efficacy, titration requirements, and safety profile of transdermal buprenorphine versus oral morphine in patients with chronic advanced cancer pain.

Methodology: In a prospective, randomized, comparative trial, 50 patients with solid tumors and chronic cancer pain (VAS > 40) were randomized into two equal arms (n = 25 per group). Group A received transdermal buprenorphine patches starting at 20 µg/h, replaced weekly, while Group B received immediate-release oral morphine 10 mg every 4 hours, both titrated as needed. Pain intensity was monitored weekly using the Visual Analog Scale (VAS) over four weeks, and treatment-emergent adverse effects were recorded.

Results: Baseline demographic and clinical parameters were comparable between the two arms (p > 0.05). Both treatments yielded marked, progressive reductions in mean pain intensity with no statistically significant differences in VAS scores at any time point (p > 0.05): baseline (80.21 ± 16.35 vs. 81.27 ± 13.82; p = 0.806), Week 1 (67.34 ± 21.36 vs. 69.36 ± 16.62; p = 0.711), Week 2 (22.32 ± 16.06 vs. 29.32 ± 17.36; p = 0.145), and Week 3 (4.62 ± 5.87 vs. 6.16 ± 8.04; p = 0.443). By Week 2, 92% (n = 23) of Group A patients achieved stable pain control. Transdermal buprenorphine demonstrated a markedly lower incidence of gastrointestinal side effects compared to oral morphine: nausea/vomiting occurred in 16.0% (n = 4) vs. 80.0% (n = 20) and constipation in 32.0% (n = 8) vs. 76.0% (n = 19), respectively. Adverse events were clinically manageable, with no study dropouts.

Conclusion: Transdermal buprenorphine provides analgesic efficacy equivalent to oral morphine in managing advanced cancer pain while offering a significantly superior gastrointestinal safety profile and patient convenience. It serves as a highly effective and better-tolerated Step 3 opioid option in palliative oncology.

Keywords: Cancer Pain, Transdermal Buprenorphine, Oral Morphine, Visual Analog Scale, Palliative Care.

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INTRODUCTION

Cancer-related pain remains one of the most distressing and disabling symptoms experienced by patients with advanced malignancies. Pain associated with cancer can arise due to tumor invasion, treatment-related complications, or associated inflammatory and neuropathic mechanisms, frequently leading to deterioration in functional capacity, psychological well-being, and overall quality of life. Despite significant advances in oncological treatment and supportive care, adequate pain control continues to be a major clinical challenge.¹

Opioids remain the cornerstone of management for moderate to severe malignant pain, particularly in patients with advanced disease. Morphine has traditionally been considered the reference opioid for cancer pain management because of its well-established analgesic efficacy, extensive clinical experience, and cost-effectiveness. However, prolonged oral morphine therapy may be associated with several limitations, including gastrointestinal adverse effects such as nausea, vomiting, and constipation, fluctuating plasma concentrations, frequent dosing requirements, and difficulties in administration among patients with poor oral intake or advanced illness.^{2,3} These challenges have encouraged the evaluation of alternative opioid formulations that can

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provide sustained analgesia with improved tolerability and patient convenience.

Buprenorphine, a semi-synthetic opioid derivative, possesses unique pharmacological properties that differentiate it from conventional full μ -opioid receptor agonists. It acts as a partial agonist at μ -opioid receptors and demonstrates high receptor affinity, slow dissociation kinetics, and prolonged analgesic activity. These characteristics contribute to effective pain relief with a potentially favourable safety profile, particularly concerning respiratory depression and tolerance development.⁴ The development of transdermal delivery systems has further expanded the clinical utility of buprenorphine by providing continuous drug administration, maintaining stable plasma concentrations, and reducing the need for frequent oral dosing.⁵

Transdermal buprenorphine has been investigated extensively in patients with chronic cancer and non-cancer pain. Sittl reported that transdermal buprenorphine provides effective and sustained analgesia in chronic pain conditions, with advantages including ease of administration, improved compliance, and predictable drug delivery.⁶ In patients with malignant pain, Pace et al. demonstrated the effectiveness of buprenorphine in long-term cancer pain control, supporting its role as an alternative opioid option for patients requiring prolonged analgesic therapy.² Furthermore, comparative pharmacological studies have suggested that transdermal buprenorphine provides analgesic potency comparable to other strong opioids, including morphine and fentanyl, when appropriate dose conversion strategies are applied.⁷

Earlier comparative investigations have demonstrated that buprenorphine provides analgesic efficacy comparable to morphine derivatives in various acute pain scenarios.^{4,8} However, evidence directly comparing transdermal buprenorphine with oral morphine specifically in patients with chronic malignant pain remains limited, particularly in terms of analgesic effectiveness, adverse effect profile, and patient tolerability.

Dose equivalence between transdermal buprenorphine and conventional opioids remains an important consideration during opioid rotation. Studies evaluating equipotent dosing between transdermal buprenorphine and transdermal fentanyl have attempted to establish clinically applicable conversion strategies, although variations exist due to differences in opioid pharmacodynamics and patient-related factors.^{7,9} Appropriate opioid selection should therefore consider not only analgesic efficacy but also safety, tolerability, route of administration, and impact on quality of life.

Considering the increasing emphasis on individualized cancer pain management, identifying opioid formulations that provide effective analgesia with improved tolerability is clinically important. Therefore, the present study was undertaken to compare the efficacy and safety of transdermal buprenorphine with oral morphine in patients suffering from chronic pain of malignant origin.

MATERIALS AND METHODS

Study Design and Participants

This prospective, randomized, comparative clinical study was conducted in the Department of Radiation Oncology from July 2024 to January 2026. The study included patients with solid tumor malignancies presenting with chronic moderate-to-severe cancer pain. Ethical approval was obtained from the Institutional Ethics Committee, and written informed consent was taken from all participants.

A total of 50 patients fulfilling the eligibility criteria were enrolled and randomized into two groups (1:1 allocation) using a computer-generated randomization method, with 25 patients in each group.

Inclusion and Exclusion Criteria

Patients aged 18–70 years, with confirmed solid malignancy, chronic pain duration >3 months, VAS pain score >40, life expectancy >2 months, and ability to understand and respond to pain assessment were included. Patients who had received opioid analgesics within the preceding 3 months, had significant neurological deficits, cognitive impairment, severe hepatic/renal dysfunction, opioid hypersensitivity, or unwillingness to participate were excluded.

Treatment Protocol

Patients in Group A (Transdermal Buprenorphine group) received transdermal buprenorphine patches at a dose of 20 μ g/hour, replaced every 7 days. Dose escalation by 20 μ g/hour weekly was permitted in patients with inadequate pain control (VAS >40).

Patients in Group B (Oral Morphine group) received immediate-release oral morphine 10 mg every 4 hours. Dose modification was performed weekly, with an increase of 30 mg/day in patients with persistent inadequate pain relief.

Concomitant medications including paracetamol, NSAIDs, pregabalin, amitriptyline, dexamethasone, and lorazepam were permitted according to clinical requirements.

Outcome Assessment

Patients were evaluated weekly for a minimum of four follow-up visits. Pain intensity was assessed using the Visual Analog Scale (VAS). The primary outcome was reduction in pain score from baseline. Secondary outcomes included opioid dose requirement, time to achieve pain control, and treatment-related adverse effects.

Adverse events including nausea, vomiting, constipation, dizziness, sedation, and other opioid-related toxicities were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Data was analysed using SPSS version 26. Continuous variables was expressed as mean $\pm$ standard deviation. Categorical variables was compared using Chi-

square/Fisher exact test. A p-value <0.05 was considered statistically significant.

Results

A total of 50 patients were evaluated and analyzed in the study, allocated equally to Group A (n = 25) and Group B (n = 25). Baseline demographic variables, functional performance, and clinical profiles were comparable

between the two arms with no statistically significant differences ($p > 0.05$ across all parameters) [Table 1]. The most common primary malignancy sites were head and neck (36.0% in Group A vs. 24.0% in Group B) and breast (24.0% in both groups) ($p = 0.912$). The majority of participants in both cohorts presented with Stage III disease (64.0% in Group A vs. 60.0% in Group B; $p = 0.884$).

Table 1. Baseline profile comparison between the two study groups

Baseline profiles	Group A (n = 25)	Group B (n = 25)	p-value
Age (years) Mean $\pm$ SD	49.5 $\pm$ 12.1	50.2 $\pm$ 11.5	0.742
Gender, n (%) Females Males	12 (48.0%) 13 (52.0%)	10 (40.0%) 15 (60.0%)	0.569
ECOG performance status, n (%) 2 3 4	 9 (36.0%) 11 (44.0%) 5 (20.0%)	 6 (24.0%) 12 (48.0%) 7 (28.0%)	0.521
Primary tumor site, n (%) Breast Cervix Head and neck cancer Lung Others	6 (24.0%) 2 (8.0%) 9 (36.0%) 5 (20.0%) 3 (12.0%)	6 (24.0%) 3 (12.0%) 6 (24.0%) 7 (28.0%) 3 (12.0%)	0.912
TNM staging, n (%) II III IV	3 (12.0%) 16 (64.0%) 6 (24.0%)	4 (16.0%) 15 (60.0%) 6 (24.0%)	0.884

Analgesic Titration and Dose Requirements

Group A (Transdermal Buprenorphine): At the end of the first week, 11 patients achieved adequate pain control (VAS ≤ 40 mm), while the remaining 14 required a dose titration by 20 $\mu\text{g/h}$. By the second week, 12 patients attained pain relief on a total dosage of 40 $\mu\text{g/h}$. Overall, 2 patients ultimately required escalation to the maximum dose of 60 $\mu\text{g/h}$ to achieve target pain control.

Group B (Oral Morphine): Within Arm B, initial pain relief was reported by 3 patients receiving 30 mg/day of oral morphine at 1 week. Subsequent stabilization was achieved in 12 patients on 60 mg/day by Week 2, 7 patients on 90 mg/day by Week 3, and 3 patients on 120 mg/day by Week 4.

Table 2. Changes in Visual Analog Scale Score over time

Time Point	Group A (n = 25)	Group B (n = 25)	p-value
Baseline	80.21 $\pm$ 16.35	81.27 $\pm$ 13.82	0.806
1st Week	67.34 $\pm$ 21.36	69.36 $\pm$ 16.62	0.711
2nd Week	22.32 $\pm$ 16.06	29.32 $\pm$ 17.36	0.145
3rd Week	4.62 $\pm$ 5.87	6.16 $\pm$ 8.04	0.443

Pain Score Trajectory (Visual Analog Scale): Baseline Visual Analog Scale (VAS) scores were comparable between Group A (80.21 $\pm$ 16.35) and Group B (81.27 $\pm$ 13.82; $p=0.806$) [Table 2]. Both groups demonstrated progressive, marked reductions in mean VAS scores over the study period. At Week 1, mean VAS scores decreased to 67.34 $\pm$ 21.36 in Group A and 69.36 $\pm$ 16.62 in Group B ($p=0.711$). By Week 2, scores further declined to 22.32 $\pm$ 16.06 and 29.32 $\pm$ 17.36, respectively ($p=0.145$). By Week 3, mean VAS scores reached minimal levels (4.62 $\pm$ 5.87 in Group A vs.

6.16 $\pm$ 8.04 in Group B; $p=0.443$). There were no statistically significant differences in pain reduction between the two treatment arms at any of the evaluation intervals ($p>0.05$).

Common side effects in both the groups were constipation and nausea, higher in group B compared to that of group A (Table 3). However, the side effects were manageable, and no patient was discontinued from the study due to side effects.

Table 3. Adverse effects

Side effect	Group A (n = 25)	Group B (n = 25)
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Nausea/vomiting	4	20
Constipation	8	19

DISCUSSION

Adequate management of moderate-to-severe cancer pain remains a critical challenge in oncology, with literature highlighting a high prevalence of undertreatment globally.¹ Oral morphine has long been regarded as the benchmark WHO Step 3 opioid for severe cancer pain.³ However, non-invasive transdermal drug delivery systems such as transdermal buprenorphine have emerged as valuable alternatives due to their continuous drug release profile, improved compliance, and favorable tolerability.^{2,5,6}

In our study, baseline clinical, demographic, and functional characteristics were comparable between both cohorts, ensuring that observed differences in analgesia and safety profiles were attributable to the intervention. Both transdermal buprenorphine (Group A) and oral morphine (Group B) demonstrated substantial, progressive reductions in mean VAS scores from baseline to Week 3, with no statistically significant differences in pain intensity between the two treatment arms at any measured interval ($p > 0.05$). These findings align with earlier pharmacological and clinical studies establishing buprenorphine as a potent long-acting synthetic analgesic capable of delivering analgesic efficacy comparable to full μ -opioid agonists like morphine.^{4,7}

Transdermal buprenorphine offers unique pharmacological properties that make it particularly suited for chronic cancer pain. As a partial μ -opioid receptor agonist and kappa-opioid receptor antagonist, it exerts potent central analgesia while exhibiting a ceiling effect on respiratory depression, thereby widening its therapeutic window relative to conventional opioids.^{3,8} Clinical evaluations by Pace et al.² and Sittl et al.^{11,13} demonstrated that transdermal buprenorphine provides sustained, long-term pain relief in cancer patients, which is consistent with our observation that 92% ($n = 23$) of Group A participants achieved satisfactory stabilization within two weeks of dose titration. Multiple placebo-controlled and multicenter trials have similarly confirmed the robust efficacy and safety of transdermal buprenorphine in controlling severe cancer-related pain.^{10,12,14,15} Furthermore, conversion and rotation protocols from high-dose oral morphine to transdermal buprenorphine have been validated as safe and effective, highlighting its versatility in palliative care settings.^{9,15}

A major advantage of transdermal buprenorphine over oral morphine observed in our study was its superior gastrointestinal tolerability profile. While both medications successfully controlled pain, the incidence of classic opioid-induced adverse effects was markedly lower in the transdermal buprenorphine arm. Specifically, nausea/vomiting occurred in only 16.0% of Group A patients compared to 80.0% in Group B, and constipation was reported in 32.0% of Group A versus 76.0% in Group B. These findings corroborate prior observational and controlled studies indicating that transdermal delivery

avoids first-pass hepatic metabolism and peak-trough plasma fluctuations, leading to significantly lower rates of constipation and emesis than oral morphine regimens.^{5,6,11,14} Despite these differences in side-effect rates, all adverse events in both groups were clinically manageable, and no patient required treatment discontinuation, reinforcing the viability of both options in clinical practice.

CONCLUSION

Transdermal buprenorphine delivers analgesic efficacy equivalent to oral morphine in managing moderate-to-severe cancer pain, achieving comparable reductions in pain scores. Importantly, it exhibits a superior safety profile with significantly lower rates of gastrointestinal side effects, particularly nausea, vomiting, and constipation. Its non-invasive delivery and improved tolerability make transdermal buprenorphine a compelling alternative to oral morphine for cancer pain management in palliative care.

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