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Comparitive Study of the Anti- Nociceptive Effects of Oral Methadone and Oral Tramadol in Patients Suffering from Cancer Pain

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ABSTRACT

Background: Cancer-related neuropathic pain is a major cause of suffering in cancer patients and significantly impairs quality of life, physical functioning, and psychological well-being. Opioids remain the mainstay of treatment, but comparative evidence regarding the efficacy and safety of oral methadone and tramadol in neuropathic cancer pain is limited. Therefore, the present study was conducted to compare the analgesic efficacy, adverse effects, and impact on quality of life of oral methadone and oral tramadol in cancer patients with neuropathic pain. **Aim & Objectives:** To compare the anti-nociceptive efficacy of oral methadone and oral tramadol in cancer patients with neuropathic pain, evaluate adverse effects, assess quality of life improvement, and establish equianalgesic oral doses. **Methodology:** This hospital-based prospective observational study was conducted in the Department of Anesthesiology and Critical Care, Muzaffarnagar Medical College & Hospital over 18 months. A total of 60 opioid-naïve adult cancer patients with neuropathic pain were randomly allocated into two groups. Group A received oral methadone 2.5 mg twice daily, while Group B received oral tramadol 50 mg twice daily. Pain severity was assessed using the Numerical Rating Scale (NRS), and quality of life was evaluated using the EORTC QLQ-C30 questionnaire. Patients were followed every 15 days for 3 months. Statistical analysis was performed using SPSS version 30, and $p < 0.05$ was considered significant. **Results:** Baseline demographic characteristics were comparable between both groups. Group A showed significantly greater reduction in pain scores compared to Group B from 15 days onward, with highly significant differences at later follow-ups ($p < 0.0001$). Methadone achieved effective blood concentration earlier and remained in the body longer than tramadol ($p < 0.0001$). Patient satisfaction and quality of life improvement were significantly better in Group A ($p < 0.0001$ and $p = 0.0006$, respectively). Adverse effects in both groups were generally mild, although Group A demonstrated better tolerability. **Conclusion:** Oral methadone was superior to oral tramadol in the management of cancer-related neuropathic pain, providing better pain relief, improved quality of life, higher patient satisfaction, and acceptable tolerability.

Keywords*: Cancer pain, Neuropathic pain, Methadone, Tramadol, Opioid analgesics, Quality of life, Pain management.*

INTRODUCTION

Pain is one of the most common and burdensome symptoms associated with cancer, affecting up to three of four people with cancer and adversely affecting their quality of life. [1,2] Causes of cancer pain are complex and varied but typically

arise from a verifiable lesion that produces pain through direct tissue injury, metastatic disease, and/or cancer-related inflammatory processes. [3]

The World Health Organization‘s (WHO‘s) sequential three-step analgesic ladder, which was developed over 30 years ago for cancer pain treatment, begins with non- opioid analgesics, such as acetaminophen/ paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) (step 1); and progresses to opioids for mild/moderate pain, including codeine, hydrocodone, or tramadol (step 2); then to opioids for moderate/severe pain, including morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, and oxymorphone (step 3). [4,5] The WHO list of essential medicines includes morphine, methadone, and fentanyl patches for the treatment of cancer pain. [4,6]

Tramadol is 2-(dimethylamino)-methyl)-1-(3′-methoxyphenyl) cyclo- hexanol hydrochloride. [7] Tramadol is mainly used in the treatment of muscle pain, joint pain and wound pain. Its use is not recommended for children below 16 years. Patients with medical history of drug addiction, alcoholism, seizure, epilepsy, head injury and metabolic disorders have more possibility of seizures when treated with tramadol. Its use is not practiced in patients with kidney disease, liver disease, stomach disorder, mental illness, depression and suicidal ideation as it can worsen the patient‘s condition. Its usage is restricted in pregnant women as well as breast feeding mothers as it may cause birth defects and harm the foetus and to the nursing babies. Tramadol is rated as Category C in the pregnancy risk drug by American Food and Drug Administration. Due to these effects, physician should avoid prescribing tramadol to pregnant women and nursing mothers. [8]

Methadone is a synthetic opioid, structurally belonging to diphenyl propylamine class, developed way back in 1937 in Germany. [9] In India, methadone was introduced as a substitution therapy medication for opioid dependence treatment in the year 2012. It became commercially available for pain management in 2014. In 2015, the Government of India listed methadone as an ―Essential Narcotic Drug for medical and scientific use under the modified NDPS Act 2015. [10] Methadone has been found to be twice as powerful as an analgesic as morphine; therefore, it is important to monitor opiate-naïve patients for respiratory depression and overdose. [11] Tapering off methadone must be done slowly to avoid withdrawal symptoms such as insomnia, nausea, mood changes, diaphoresis, and muscle cramps. [12]

Cancer-related pain significantly impairs quality of life and remains difficult to manage, particularly when neuropathic components are present. Oral opioids such as methadone and tramadol are commonly used, but comparative evidence regarding their efficacy and safety is limited. This study aims to compare oral methadone and tramadol in cancer pain management with respect to analgesic efficacy, side-effect profile, and patient outcomes. The findings may help in developing evidence-based and individualized pain management strategies.

AIM & OBJECTIVES

1. To compare the efficacy of anti-nociceptive effects of methadone alone vs tramadol administered orally, in treatment of different types of cancer patients with neuropathic pain & evaluate adverse effects.
2. To assess effect of drugs on patient quality of life [QoL]
3. To establish equianalgesic oral doses of methadone and tramadol in cancer patients with neuropathic pain.

MATERIAL AND METHODS

The present study entitled was conducted as a hospital-based prospective comparative observational study in the Department of Anesthesiology and Critical Care at Muzaffarnagar Medical College & Hospital over a period of 18 months, including 12 months for data collection and 6 months for data compilation and analysis. A total of 60 opioid-naïve adult cancer patients suffering from neuropathic pain were enrolled using purposive sampling technique and randomly allocated into two groups through a computer-generated randomization table. Group A patients received oral Methadone 2.5 mg twice daily, while Group B patients received oral Tramadol 50 mg twice daily. Baseline evaluation included detailed medical history, physical examination, DN4 assessment for confirmation of neuropathic pain, baseline vital parameters, Numerical Rating Scale (NRS) pain assessment, and quality of life evaluation using the EORTC QLQ-C30 questionnaire. Patients were followed up every 15 days for a duration of 3 months and treatment response was assessed based on percentage reduction in pain scores. Statistical analysis was performed using SPSS version 30. Quantitative and qualitative variables were analyzed using Student’s t-test, paired t-test, independent t-test, and Chi-square test as appropriate. A p-value of <0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrolment in the study.

Inclusion criteria: Patients fulfilling the following criteria were included:

- Clinically diagnosed cancer patients with neuropathic pain
- Opioid-naïve patients
- Patients able to take medications by oral route
- Age ≥18 years

- Patients able to communicate effectively to complete EORTC QLQ-C30 questionnaire
- Patients who provided informed consent to participate in the study.

Exclusion criteria: Patients were excluded if they had:

- Patients not willing for procedure.
- Age <18 years
- Known hypersensitivity to methadone or tramadol
- Psychiatric illness
- Inability to take oral drugs due to oral malignancy

RESULTS

In **Table 1**, the demographic characteristics of participants were comparable between Group A and Group B. The mean age was 58.33 ± 6.21 years in Group A and 56.97 ± 5.82 years in Group B, with no significant difference ($p = 0.32$). Gender distribution was equal in both groups, with 16 males and 14 females each ($p = 1.00$). Mean height and weight were also similar between the groups, with statistically non-significant differences ($p > 0.05$).

Comparison of mean pain scores on the NRS scale showed that both groups had similar baseline pain severity, with a mean score of 7.37 ± 0.96 in both groups ($p = 1.00$). However, follow-up assessments demonstrated a significantly greater reduction in pain in Group A compared to Group B. After 15 days, the mean pain score was significantly lower in Group A (5.33 ± 0.96) than Group B (6.37 ± 0.96) ($p = 0.0002$). This difference further increased over time, with Group A showing progressive reduction in pain scores at 1 month, 45 days, 2 months, 75 days, and 3 months compared to Group B, and all differences were highly statistically significant ($p < 0.0001$). These findings indicate superior pain relief in Group A throughout the follow-up period. (**Table 2**)

Table 3 shows comparison between the two groups showed significant differences in the time required to achieve minimum effective concentration in blood and the time taken for the drug to completely leave the body. Group A achieved effective blood concentration earlier than Group B (49.9 ± 7.29 vs 93.93 ± 9.54). However, the drug stayed in the body for a longer duration in Group A compared to Group B (27.8 ± 4.16 vs 6.7 ± 1.24). These differences were statistically highly significant ($p < 0.0001$).

In **Table 4**, comparison of regular drug intake between the two groups showed that most participants in both groups were compliant with treatment. Regular intake of the drug was observed in 93.33% participants in Group A and 83.33% participants in Group B, while irregular intake was seen in 6.67% and 16.67% participants, respectively. However, the difference between the groups was statistically non-significant ($p = 0.42$), indicating comparable treatment compliance in both groups.

Table 5 shows the comparison of patient satisfaction between the two groups showed a statistically highly significant difference ($p < 0.0001$). In Group A, the majority of participants reported higher satisfaction levels, with 40% participants giving a satisfaction score of 4 and 43.33% giving a score of 5. In contrast, most participants in Group B reported lower satisfaction levels, with 16.67% participants giving a score of 1 and 53.33% giving a score of 2. Very few participants in Group B reported higher satisfaction scores of 4 or 5. Overall, patient satisfaction was markedly better in Group A compared to Group B.

Table 6 shows the comparison of improvement in patients' quality of life between the two groups showed a statistically significant difference ($p = 0.0006$). In Group A, most participants reported greater improvement in quality of life, with 36.67% participants each reporting scores of 4 and 5. Lower improvement scores were observed only in a few participants. In contrast, participants in Group B mainly reported lower improvement scores, with 40% participants reporting a score of 2 and 26.67% reporting a score of 3. Very few participants in Group B reported higher scores of 4 or 5. Overall, improvement in quality of life was better among participants in Group A compared to Group B.

Figure 1 shows the distribution of participants according to provisional diagnosis showed variation between the two groups. In Group A, breast carcinoma and esophageal carcinoma were the most common diagnoses (20% each), followed by colorectal carcinoma and gall bladder carcinoma (16.7% each). Cervical carcinoma and prostate carcinoma accounted for 13.3% and 10% cases, respectively, while gastric carcinoma was least common (3.3%). In Group B, cervical carcinoma was the most common diagnosis (26.6%), followed by breast carcinoma, prostate carcinoma, and gall bladder carcinoma (16.7% each). Colorectal carcinoma accounted for 13.3% cases, while esophageal carcinoma was seen in 10% participants. No case of gastric carcinoma was observed in Group B.

Figure 2 shows the comparison of participants in both groups according to neuropathic pain. In both Group A and Group B, 56.67% participants had neuropathic pain, while 43.33% participants did not have neuropathic pain. The distribution was identical in both groups, indicating comparable baseline characteristics regarding neuropathic pain.

Figure 3 shows the comparison of participants in both groups according to adverse effects. In Group A, mild constipation (23.53%) was the most common adverse effect, followed by mild nausea (14.71%), dry mouth (11.76%), dizziness (11.76%), and initial drowsiness (11.76%). No participant in Group A reported headache, vomiting, or sweating. In Group B, mild nausea (23.26%) was the most common adverse effect, followed by dizziness (16.27%), vomiting (13.95%), mild constipation (11.63%), and sweating (6.98%). No participant in Group B reported dry mouth. A higher proportion of participants in Group A reported no adverse effects (26.48%) compared to Group B (11.63%).

Table 1: Demographic profile of Study Participants: (N = 60)

	Group A	**Group B**	**p value**
Age (years)	58.33 ± 6.21	56.97 ± 5.82	0.32
Gender (M/F)	16/14	16/14	1.00
Height (cm)	167.07 ± 7.54	166.13 ± 7.56	0.62
Weight (kg)	71.77 ± 8.47	70.7 ± 8.53	0.61

Table 2- Comparison of mean Pain on NRS Scale on different days between two groups:

Pain on NRS Scale	**Group A**		**Group B**		**p value**
	Mean	**Std Dev.**	**Mean**	**Std Dev.**	
Initially	7.37	0.96	7.37	0.96	1
After 15 days	5.33	0.96	6.37	0.96	0.0002
After 1 month	4.03	0.89	6.37	0.96	**<0.0001**
After 45 days	3	0.83	5.37	0.96	**<0.0001**
After 2 months	2.23	0.63	5.37	0.96	**<0.0001**
After 75 days	1.97	0.76	4.6	0.72	**<0.0001**
After 3 months	1.5	0.57	4.37	0.96	**<0.0001**

Table 3: Comparison of participants in both groups according to duration to achieve min. effective concentration in blood and time taken to completely leave body: (N=60)

	Duration to achieve min. effective concentration in blood (Mean & S.D.)	**Time taken to completely leave body (Mean & S.D.)**	**p value**
Group A	49.9 ± 7.29	27.8 ± 4.16	**<0.0001**
Group B	93.93 ± 9.54	6.7 ± 1.24	

Table 4: Comparison in both groups according to regular intake of drug (N=60)

Regular intake of drug	**Group A (%)**	**Group B (%)**	**p value**
Yes	28 (93.33%)	25 (83.33%)	0.42
No	02 (6.67%)	05 (16.67%)	
Total	**30**	**30**	

Table 5: Comparison in both groups according to patient's satisfaction (N=60)

Patient satisfaction	**Group A (%)**	**Group B (%)**	**p value**
1	02 (6.67%)	05 (16.67%)	**<0.0001**
2	02 (6.67%)	16 (53.33%)	
3	01 (3.33%)	05 (16.67%)	
4	12 (40%)	02 (6.67%)	
5	13 (43.33%)	02 (6.66%)	

Table 6: Comparison in both groups according to improvement in patient's quality of life (N=60)

Patient's quality of life improvement	**Group A (%)**	**Group B (%)**	**p value**
1	02 (6.66%)	05 (16.67%)	**0.0006**
2	03 (10%)	12 (40%)	
3	03 (10%)	08 (26.67%)	
4	11 (36.67%)	03 (10%)	
5	11 (36.67%)	02 (6.67%)	

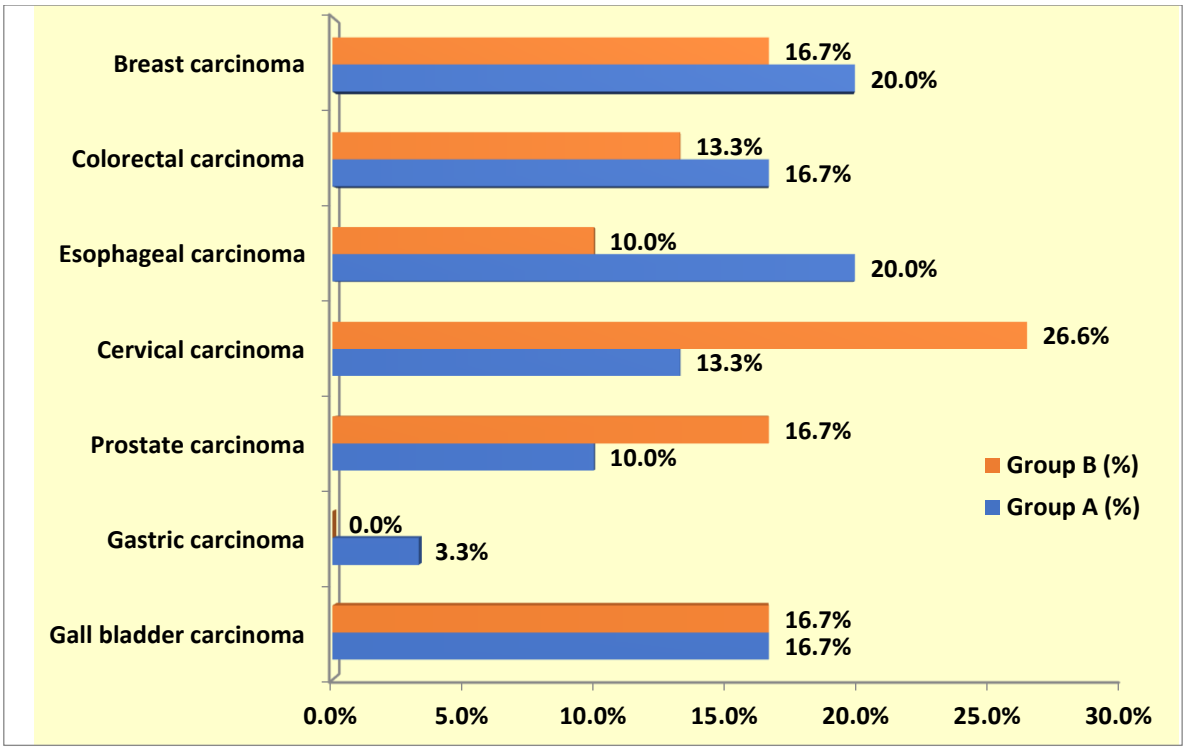

Figure 1: Distribution of participants in both groups according to provisional diagnosis

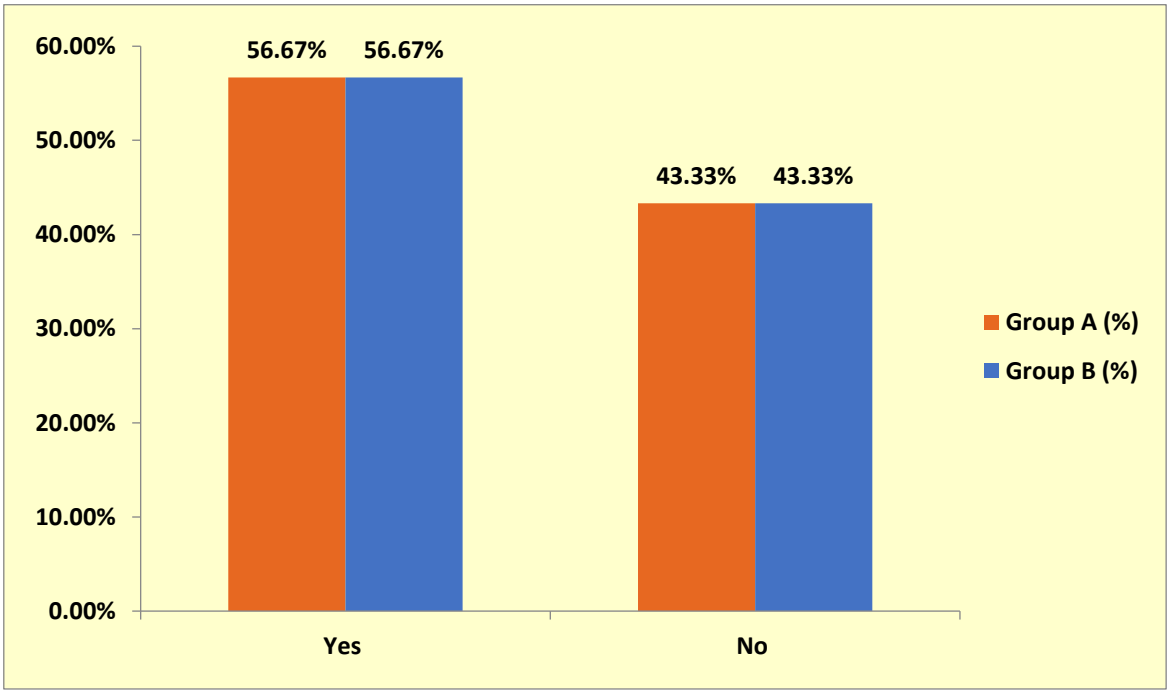

Figure 2: Comparison of participants in both groups according to neuropathic pain (N=60)

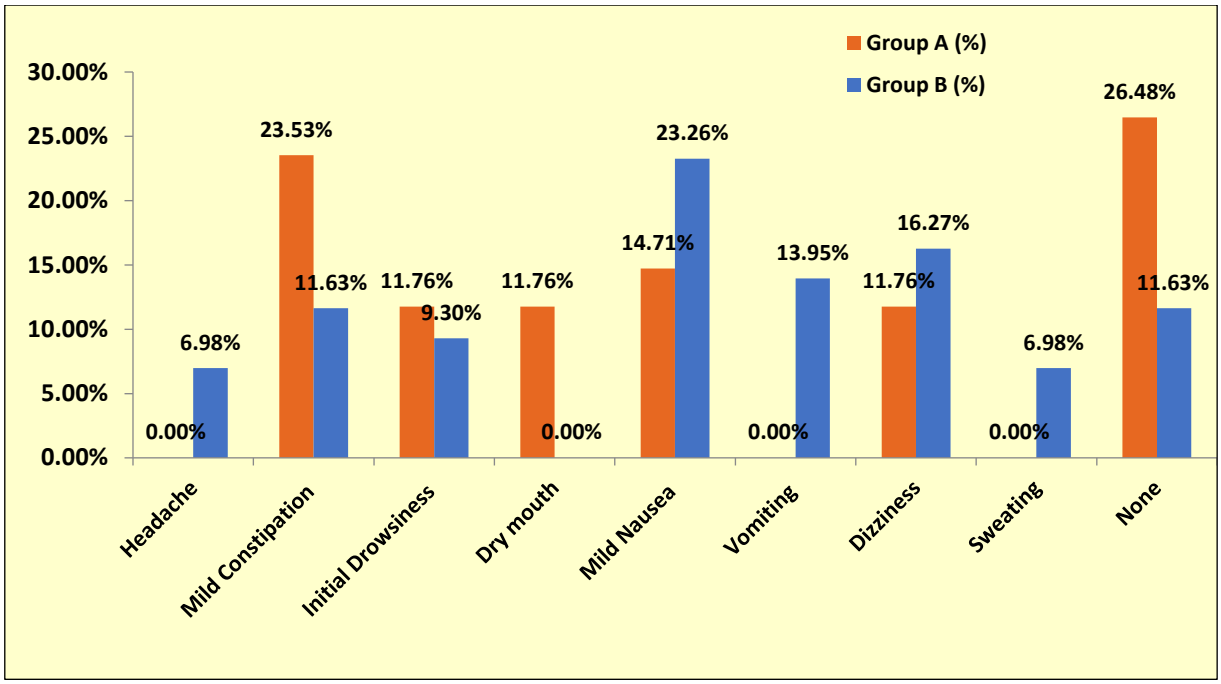

Figure 3: Comparison of participants in both groups according to any adverse effect (N=60)

DISCUSSION

In the present study, most patients in both Group A (methadone) and Group B (tramadol) belonged to the 55–60 years age group (30% each), followed by 60–65 years (26.67% each). **Abdel Shaheed C et al. (2024)** reported that more than 60–70% of cancer pain cases occur in patients above 50 years, particularly in gastrointestinal, breast, gynaecological and genitourinary malignancies. Cancer pain prevalence in these age groups ranges from 44% to >80%, depending on tumour type. [13] **Mercadante et al. (2022)** studied methadone as first-line opioid in advanced cancer patients with a mean age close to 60 years, very similar to the mean age in the present study (58.33 and 56.97 years). [14] This concordance shows that the age distribution in the present study reflects real-world cancer pain populations globally and in India.

Gall bladder carcinoma accounted for 16.67% in both groups. Cervical carcinoma was more frequent in Group B (26.66% vs 13.33%), while esophageal carcinoma was higher in Group A (20% vs 10%). Breast carcinoma was similar (20% vs 16.67%), and colorectal carcinoma was 16.68% vs 13.33%. Overall, there was no significant difference ($p = 0.64$). **Abdel Shaheed C et al. (2024)** reported that pain prevalence is extremely high in GI, breast and gynecological cancers (40–90%), which dominate the present cohort. [13] The balanced cancer distribution ensures similar pain biology in both groups. **Mercadante S e al (2018)** emphasized that methadone is particularly useful in cancers with mixed nociceptive–neuropathic pain, which is typical of esophageal, cervical, and colorectal cancers present in our cohort. The balanced cancer distribution ($p = 0.64$) therefore allowed methadone's unique pharmacology to be fairly tested against tramadol. [14]

Exactly 17 patients (56.67%) in each group had neuropathic pain. This is clinically crucial because tramadol is weaker in neuropathic pain, while methadone blocks NMDA receptors and inhibits serotonin-norepinephrine reuptake. The Indian RCT by **Adumala et al. (2023)** showed that methadone reduced DN4 scores from 6.05 to 0 compared to morphine, confirming strong efficacy in neuropathic cancer pain. [15]

Both groups started with identical severe pain (7.37 ± 0.96). After 15 days, methadone reduced pain to 5.33 ± 0.96 vs 6.37 ± 0.96 with tramadol ($p = 0.0002$). By 3 months, methadone reduced pain to 1.5 ± 0.57, whereas tramadol remained at 4.37 ± 0.96 ($p < 0.0001$). **Mercadante S et al. (2022)** showed similar sustained pain reduction with methadone due to minimal tolerance and NMDA blockade. [14] Methadone reached effective blood levels in 49.9 ± 7.29 min, while tramadol took 93.93 ± 9.54 min ($p < 0.0001$). **Marcianò G et al. (2023)** explained this by methadone's high oral bioavailability and direct μ-receptor action, whereas tramadol requires metabolic activation. [16]

Group A showed prolonged drug elimination, with a mean elimination time of 27.8 ± 4.16 hours, whereas Group B showed rapid clearance with a mean elimination time of 6.7 ± 1.24 hours. The difference between the groups was highly statistically significant ($p < 0.0001$), indicating markedly slower elimination in Group A. In the **2024 opioid review by Imkamp MSV**, oral methadone is described as having a long and variable half-life (~13–60 hours) with analgesic onset 30–120 minutes after oral dosing and increasing duration with repeated dosing—features that explain prolonged "time to leave the body" in clinical terms. [15] Similarly, **Scarborough B et al** highlights that methadone lacks active metabolites

and has complex pharmacology, so persistence of effect and longer elimination are expected, often requiring specialist experience for titration. [17]

The present study showed that adverse effects were generally mild in both groups, with no statistically significant difference overall (p = 0.21). Group A showed better tolerability, with a higher proportion of participants reporting no adverse effects (26.48% vs 11.63%). Mild constipation was the most common side effect in Group A, whereas Group B showed higher frequencies of nausea, vomiting, dizziness, headache, and sweating. Overall, Group B had more distressing adverse effects, while Group A demonstrated a comparatively better safety and tolerability profile. **Scarborough B et al** found that constipation being relatively prominent in Group A (23.53%) is consistent with opioid-class effects. Cancer pain guidance notes constipation and mild nausea/somnolence are common expected opioid effects and emphasizes proactive prevention, especially stimulant laxatives when starting opioids. [60] Nausea/vomiting being more frequent in Group B (nausea 23.26%, vomiting 13.95%) is supported by evidence that tramadol-containing regimens can show notable nausea/vomiting. [17] In a study by **Koyyalagunta D et al**, tramadol trials reported significant nausea and vomiting and withdrawals due to vomiting in some studies. [18] This supports our observation that Group A had a slightly higher "no adverse effect" fraction (26.48%) but still showed opioid-typical effects such as constipation/ drowsiness/ dry mouth.

Patient satisfaction differed significantly between the two groups (p < 0.0001), with Group A showing markedly higher satisfaction levels. In Group A, most patients (83.33%) reported high satisfaction scores of 4–5, indicating good acceptance and perceived benefit of treatment. In contrast, the majority of patients in Group B (86.67%) reported lower satisfaction scores of 1–3, reflecting poorer treatment experience and lower perceived effectiveness. Overall, Group A provided a superior patient-centered therapeutic outcome compared to Group B. In randomized work comparing methadone with other opioids, methadone-treated patients may experience faster or stronger relief in certain settings; **Adumala A et al** reported significantly greater reduction in NRS pain with methadone vs IR morphine (P < 0.001), supporting the concept that stronger/earlier relief can translate into higher patient-perceived benefit and satisfaction. [19]

Improvement in quality of life showed a statistically significant difference between the two groups (p = 0.0006), favoring Group A. In Group A, most patients (73.34%) reported higher QoL improvement scores of 4–5, indicating marked improvement in daily functioning and overall well-being. In contrast, Group B mainly showed lower scores, with the majority of patients reporting only minimal to moderate improvement. Only 16.67% of patients in Group B achieved high QoL scores (4–5). Overall, Group A demonstrated superior improvement in quality of life and better patient-centered outcomes compared to Group B. This aligns with **Koyyalagunta D et al** study where improved pain relief is consistently associated with improved performance status and QoL metrics. In tramadol trials for cancer-related neuropathic pain, improvements in pain intensity were accompanied by improvements in functional/QoL measures, though nausea/vomiting were notable limitations—paralleling our Group B pattern where GI adverse effects were relatively common. [18] Further, methadone-focused review by **Imkamp MSV et al** emphasized that methadone can be effective and well tolerated in many cancer pain contexts, and its pharmacologic profile may make it helpful in mixed/neuropathic pain—mechanisms that would support improved daily functioning and QoL when pain is brought down sustainably. [15]

CONCLUSION

The present study demonstrated that oral methadone was more effective than oral tramadol in the management of cancer patients with neuropathic pain. Patients receiving methadone showed significantly greater reduction in pain scores throughout the follow-up period, along with higher patient satisfaction and better improvement in quality of life. Methadone also achieved effective blood concentration earlier and had a longer duration of action compared to tramadol. Although both drugs were generally well tolerated, Group A showed a comparatively better safety and tolerability profile, with fewer distressing adverse effects. Overall, the findings suggest that oral methadone provides superior analgesic efficacy and better patient-centered outcomes than oral tramadol in cancer-related neuropathic pain management.

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