

Methadone for intractable pain associated with the neoplastic brachial plexopathy: a retrospective analysis of 23 patients

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Abstract

[Purpose] Neoplastic brachial plexopathy (NBP) sometimes presents with severe neuropathic and somatic pain. The efficacy of methadone for intractable pain associated with NBP has not been established. This study aimed to investigate the efficacy and safety of methadone for intractable pain associated with NBP.

[Methods] A retrospective analysis was conducted using electronic medical records for all patients who received methadone at our institution for pain associated with NBP between April 2016 and July 2025.

[Results] A total of 23 patients with a male-to-female ratio of 13:10 and an average age of 64.7 ± 10.5 years (47–82 years) were included. The primary sites of malignancy were lung (8 patients), breast (4), esophagus and malignant lymphoma (2 each), unknown (3), and others (4). The median daily oral morphine equivalent dose of prior opioids, including rescue doses, was 120 mg/day (IQR, 65.2–202.5). The initial, maximum, and final doses of methadone were a median (IQR) of 15 (5–20), 20 (10–45), and 20 (10–25) mg/day, respectively, with a total duration of 32.0 (11.0–93.5) days. Seven days after methadone initiation, median minimum pain intensity (Numeral Rating Scale, 1–10) decreased from 4.0 (IQR, 2.0–5.0) to 2.0 (IQR, 1.0–3.0; $p = 0.001$), and maximum pain intensity also decreased from 7.0 (IQR, 7.0–8.3) to 5.0 (IQR, 3.0–6.0; $p = 0.0005$). Methadone administration was ceased in only one patient due to drowsiness.

[Conclusion] This study suggests that methadone is an effective and safe treatment option for intractable pain caused by NBP.

Introduction

Neoplastic brachial plexopathy (NBP) caused by malignant tumors can result in neuropathic pain in the brachial plexus in addition to local somatic pain, causing severe pain and numbness in the affected shoulder and upper limb^{1–12}. Surgical options for the causative tumor are limited, and while radiation therapy and chemotherapy may be used to control the tumor, many cases show poor responses to these treatments. Therefore, appropriate drug therapy for pain relief is essential for maintaining and improving the patient's quality of life.

The synthetic opioid methadone possesses μ -opioid receptor agonism, as well as N-methyl-D-aspartate (NMDA) receptor antagonism and norepinephrine-serotonin reuptake inhibition, and has been applied to various types of intractable cancer pain^{13–23}. However, clinical evidence for its use in NBP is limited to a small number of case reports²⁴. Due to its unique pharmacological effects, it is considered a drug that should be handled by healthcare professionals familiar with opioids, and it remains underutilized. Furthermore, the efficacy and side effects of methadone for NBP-related intractable pain have not been clarified yet. This study evaluates its clinical value and safety in managing this severe condition.

Methods

1. Study Design

A retrospective analysis was performed based on clinical information from the electronic medical records.

2. Patients

Included in this study were all patients who received initial methadone therapy from the palliative care team or unit between April 2016 and July 2025, and who presented with intractable pain associated with NBP.

3. Administration Method and Dosage Adjustment

Methadone was initiated using distinct two strategies: (1) Stop-and-go initiation: Complete discontinuation of the preceding opioid prior to the first dose of methadone. (2) Concomitant initiation: Continuation of the preceding opioid regimen alongside the introduction of low-dose methadone (either 5 mg/day or 10 mg/day).

In the general wards, the Palliative Care Team (PCT) shared information regarding patient conditions with the ward staff on a daily basis. They examined the patients, and determined the dosage of each analgesic including methadone after mutual consultation with the team members and the ward staff. For the patients who transferred to the Palliative Care Unit (PCU), the attending palliative care specialist collaborated with the ward staff to adjust drug dosages. Although some exceptions occurred, the methadone dosage was held constant for at least 7 days following initiation or subsequent adjustment, in accordance with the manufacturer's prescribing information. Dosage increases were capped at 50% of the total daily dose, and the single doses were restricted to 5 mg.

Electrocardiograms (ECG) were routinely performed before methadone initiation, and 5 to 7 days following initiation or dosage increments. Furthermore, when a new drug with strong cytochrome P450 (CYP) inhibitory or inducing effects was administered, ECG tests were conducted as required.

4. Combination Therapy

We investigated the use of non-opioid analgesics and adjuvant analgesics co-administered with methadone, as well as the utilization of chemotherapy, radiotherapy, and nerve block therapy. Radiotherapy and chemotherapy were, in principle, administered at the discretion of the oncology or radiation oncology departments.

5. Data Collection

We investigated patient attributes, clinical pain mechanisms, types and dosages of preceding opioids, methadone dosage and duration of administration, concomitant medications, combination therapies such as chemotherapy, radiotherapy, and nerve block therapy, changes in pain intensity and rescue medication use, as well as side effects.

6. Statistical Analysis

Changes in pain intensity and rescue medication use frequency before and after methadone administration were statistically analyzed using the Wilcoxon signed rank-sum test with BellCurve® for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan) statistical software, and a *p*-value of < 0.05 was considered statistically significant.

7. Ethical Considerations

This clinical study was conducted with the approval of the Institutional Review Board at the Shizuoka Cancer Center (Ethics approval number: J2025-106-2025-1-3), and with full consideration given to protecting patients' personal information.

Results

1. Patient Characteristics

The number of patients extracted was 23, representing 4.4% of the 518 patients who received methadone managed by the PCT during the study period. The male-to-female ratio of the patients was 13:10, and the average age (mean $\pm$ standard deviation) was 64.7 ± 10.5 years. Methadone was initiated in 19 patients (82.6%) in the inpatient setting and 4 patients in the outpatient clinic. The primary diseases were lung cancer, breast cancer, cancer of unknown primary origin in 8, 4, and 3 patients, respectively; esophageal cancer, malignant lymphoma in 2 each; laryngopharyngeal cancer, gastric cancer, cervical cancer, and rectal cancer in 1 each.

2. Causes and Symptoms of Brachial Plexus Dysfunction

The causes of brachial plexus dysfunction were: cervical lymph node enlargement (*n* = 5), supraclavicular lymph node enlargement (*n* = 12), Pancoast tumor (*n* = 7), axillary lymph node enlargement (*n* = 4), axillary tumor (*n* = 2), and brachial plexus tumor (*n* = 1), including overlapping etiologies (Fig. 1).

The locations of pain and numbness varied by laterality. On the right side, symptoms occurred in the upper limb (*n* = 10; including 4 restricted to the ulnar side), shoulder (*n* = 8), axilla (*n* = 5), neck (*n* = 3), and

scapular region ($n = 3$). On the left side, the shoulder ($n = 6$), upper limb ($n = 5$; including 1 restricted to the upper arm and 1 to the ulnar side), neck ($n = 4$), scapular region ($n = 3$), and axilla ($n = 2$).

3. Prior Opioids

The median opioid dose (oral morphine equivalent, OMED) was 120.0 (interquartile range, 65.2-202.5) mg/day including rescue doses provided immediately preceding methadone administration. Four patients received an OMED of < 60 mg/day, 10 received 60–159 mg/day, 7 received 160–389 mg/day, and 2 received ≥ 390 mg/day (Fig. 2).

The list below shows the prior opioids administered immediately before the start of methadone administration:

- Hydromorphone extended-release (ER) and tapentadol ER tablets ($n = 2$)
- Oxycodone ER tablets ($n = 2$)
- Oxycodone ER and tapentadol ER tablets ($n = 5$)
- Oxycodone ER and tramadol ER tablets ($n = 2$)
- Tapentadol ER tablets ($n = 4$)
- Tapentadol ER and tramadol ER tablets ($n = 1$)
- Transdermal fentanyl patches and tapentadol ER tablets ($n = 2$)
- Morphine and tramadol injections ($n = 1$)
- Hydromorphone and tramadol injection ($n = 2$)
- Oxycodone injection ($n = 2$)
- Fentanyl and tramadol injections ($n = 1$)

4. Dosage and Duration of Methadone Administration

The initial, maximum, and final daily doses of methadone were 15.0mg(IQR: 5.0–20.0; range 5–40), 20.0mg(IQR: 10.0–45.0; range 5–100), and 20.0mg(IQR: 10.0–25.0; range 5–80), respectively (Fig. 3). Low doses of either 5 mg/day or 10 mg/day were administered 10 patients initially, 7 patients at maximum, and 10 patients finally. The median duration of methadone administration was 32.0 days(IQR: 11.0–93.5; range 4–769).

5. Concomitant Opioids

Of the 23 patients, 17 received concomitant around-the-clock (ATC) opioids during methadone administration. Because some patients received overlapping drugs, the breakdown of concomitant scheduled opioids were as follows: oral tapentadol ($n = 6$), oral hydromorphone ($n = 3$), oral tramadol ($n =$

3), oral morphine ($n = 1$), transdermal fentanyl ($n = 1$) and a combination of hydromorphone and tramadol injections ($n = 1$).

Concomitant rescue medications during methadone administration included immediate-release oxycodone powder ($n = 12$), immediate-release hydromorphone tablets ($n = 11$), oral morphine solution ($n = 3$), a combination of hydromorphone and tramadol injections ($n = 2$), and morphine injection ($n = 1$). Several patients received overlapping rescue regimens.

6. Combination Therapies

Concomitant therapies administered during methadone administration included both pharmacological and non-pharmacological interventions. Several patients received non-opioid analgesics, including oral diclofenac sodium ($n = 8$), transdermal diclofenac sodium ($n = 5$), oral acetaminophen ($n = 2$), and oral naproxen ($n = 1$); 9 patients who did not receive non-opioid analgesics. Concomitant adjuvant analgesics included mirogabalin ($n = 18$), dexamethasone ($n = 10$), pregabalin ($n = 8$), duloxetine ($n = 5$), mirtazapine ($n = 5$), clonazepam ($n = 3$), lidocaine injection ($n = 2$), carbamazepine ($n = 1$), and betamethasone ($n = 1$); 1 patient did not receive any adjuvant analgesics (Table). In addition, 6 patients (26.1%) underwent chemotherapy and 9 patients (39.1%) received radiotherapy as concomitant non-pharmacological pain relief therapies.

8. Administration of Opioids and Ketamine After Discontinuation of Methadone

Methadone administration was discontinued in 22 of 23 patients due to oral intake difficulties, and in 1 patient due to the inability to secure a prescription at the receiving hospital. No therapy discontinuation occurred as a result of adverse events, inadequate analgesia, or patient request.

Upon methadone discontinuation, patients transitioned to the following opioid regimens and ketamine therapies (with some overlap):

- Hydromorphone and tramadol injections ($n = 15$)
- Ketamine injections (concomitant use; $n = 6$)
- Morphine injection ($n = 2$)
- Morphine and tramadol injections ($n = 2$)
- Hydromorphone injection ($n = 1$)
- Oxycodone injection ($n = 1$)
- Oxycodone and tramadol injections ($n = 1$)
- Transdermal fentanyl ($n = 1$)

9. Patient Prognosis

By the end of the study period, all 23 patients had died due to exacerbation of their underlying disease. Of these, 14 died in the general ward, 8 in the palliative care ward, and 1 after transitioning to home care. The median survival time from the last dose of methadone to death was 23.0 days (IQR: 6.0–27.5; range 0–136) days.

Discussion

NBP can cause severe localized somatic pain in the affected shoulder, upper arm, and axilla, as well as intractable neuropathic pain due to brachial plexus damage characterized by severe numbness or electric shock-like sensations in the upper limb^{1–12}). In such cases, achieving symptom relief with standard drug therapy can be challenging. Research on the efficacy and safety of methadone for NBP-associated neuropathic pain has been limited to a single case report involving only 3 patients²⁴); thus, its clinical effects remain to be clearly established. Therefore, the objective of this study was to investigate the clinical usefulness of methadone for NBP by evaluating a larger patient cohort.

The initiation of methadone significantly reduced both minimum and maximum daily pain intensity. Although there was no statistically significant difference in the frequency of rescue medication use, a decreasing trend was observed. Methadone is presumed to possess N-methyl-D-aspartate (NMDA) receptor antagonism^{25–30}) and norepinephrine/serotonin reuptake inhibition effects^{13–23, 31–33}) in addition to its potent agonist effect on μ -opioid receptors. These unique pharmacological effects—not found in other strong opioids—likely acted on intractable NBP-induced somatic and neuropathic pain, resulting in a favorable analgesic effect.

In Japan, the electronic package insert recommends an initial methadone dose of 15–45 mg/day for patients receiving an oral morphine equivalent of 60 mg/day or more. However, leveraging the diverse pharmacological properties of methadone as an adjuvant analgesic, adding it at a low dose to other previously administered opioids can also be highly useful^{34–43}). In 10 out of the 23 cases (43.5%) in this study, methadone was added to previously administered opioids at a low dose of 5 or 10 mg/day. Compared with complete opioid rotation, this method of administration offers advantages such as a lower likelihood of introducing significant pharmacological discrepancies, and the ability to safely initiate therapy in an outpatient setting. This may be a method of administration that should be promoted further in the future to lower the hurdles for methadone use. Furthermore, one of the factors behind the early introduction of methadone was the discontinuation of the tapentadol supply in Japan. Tapentadol is a dual-action analgesic that possesses both μ -opioid receptor agonism and norepinephrine reuptake inhibition, and it has been used for intractable cancer pain accompanied by neuropathic pain^{44–55}). However, following its discontinuation, our institution has seen an increase in opportunities to introduce methadone early in cases of intractable cancer pain with a strong neuropathic component, such as NBP, where tapentadol administration would normally have been considered.

The limitations of this study include: (a) its retrospective, single-center design and small sample size; (b) the lack of a standardized definition for intractable pain, which implies potential selection bias because methadone initiation was determined by the clinical judgment of the PCT members; (c) the inability to consistently evaluate pain intensity using standardized tools like numerical scales the NRS (Numeric Rating Scale), compounded by missing data in the medical records; and (d) the absence of established protocols for the concomitant use, dose reduction, or discontinuation of non-opioid and adjuvant analgesics, which made it difficult to exclude the confounding effects of therapies managed by individual clinical judgment.

To address these limitations, several factors and future directions must be considered. Regarding (a), multi-center prospective clinical studies are required in the future in order to establish higher-quality evidence. Regarding (b), the risk of selection bias was reduced by expertise of the first author—a PCT member and a pain clinic specialist with over 30 years of clinical experience—who evaluated methadone indication on a case-by-case basis accounting for both the etiology of pain and patient prognosis. Furthermore, prior to methadone initiation, the PCT evaluated the efficacy of the concomitant administration μ -opioid receptor (MOR) agonist and either tramadol or tapentadol to partially infer the potential response to methadone. Consequently, methadone was introduced while prior opioid doses were relatively low, which likely minimized pharmacological discrepancies at baseline and prevented severe adverse effects. Regarding (c), future prospective studies should incorporate patient-friendly, low burden evaluation methods, as we observed that some patients struggled to comprehend the NRS or found numerical rating of severe pain to be highly stressful. Finally, regarding (d), establishing standardized criteria for managing concomitant medications is essential for objective evaluation in future prospective studies.

Conclusion

Our findings suggest that methadone is a promising treatment option for intractable pain associated with neoplastic brachial plexopathy.

Declarations

Competing interests:

The authors have no relevant financial or non-financial interests to disclose.

Authorship and Contributions of Each Author

Tetsumi Sato conceptualized the research, drafted the paper, and served as the research director.

Shigeki Ohno, Taiichi Kawamura, Akira Fukutomi, Yoshiko Kamo, Akane Wakabayashi, Takamori Miyaguchi, Tetsu Sato, Ryo Taguch, and Rei Tanaka supported to collect data and critically reviewed the paper.

Ethics approval:

This study was approved by the Institutional Review Board for Clinical Researches of the Shizuoka Cancer Center (#J2025-106-2025-1-3) and was conducted with the consents of the patients or their families. After an IRB review, it was determined that consents to participate in the research would be approved by opting out, and that it was not necessary to obtain written informed consents from all subjects. In addition, this research was conducted in accordance with the Declaration of Helsinki.

Consent to participate:

Informed consent was obtained from all individual participants included in this study.

Consent to publish:

The authors affirm that human research participants provided informed consent for publication of the clinical data shown in the text and the figures.

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Author Contribution

T.S. conceptualized the research, drafted the paper, and served as the research director. S.O., T.K., A.F., Y.K., A.W., T.M., T.S., R.T., and R.T. supported to collect data and critically reviewed the paper.

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Data availability:

No datasets were generated during the current study will be available upon reasonable request.

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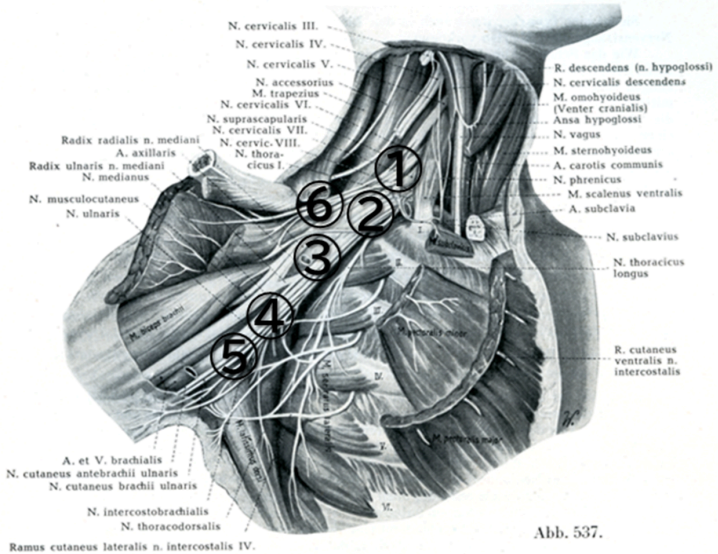
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Figures

Figure 1

①Cervical LN	5
②Supraclavicular LN	12
③Pancoast tumor	7
④Brachial LN	4
⑤Brachial tumor	2
⑥Brachial plexus tumor	1



Lehrbuch Der Anatomie Des Menschen Vol. 6
by Rauber AA and Kopsch F

Figure 1

Areas of damage to the brachial plexus ($n=23$ including some overlapping cases)

The anatomical illustration is taken from Lehrbuch Der Anatomie Des Menschen Vol. 6.

Figure 2

(Patients)

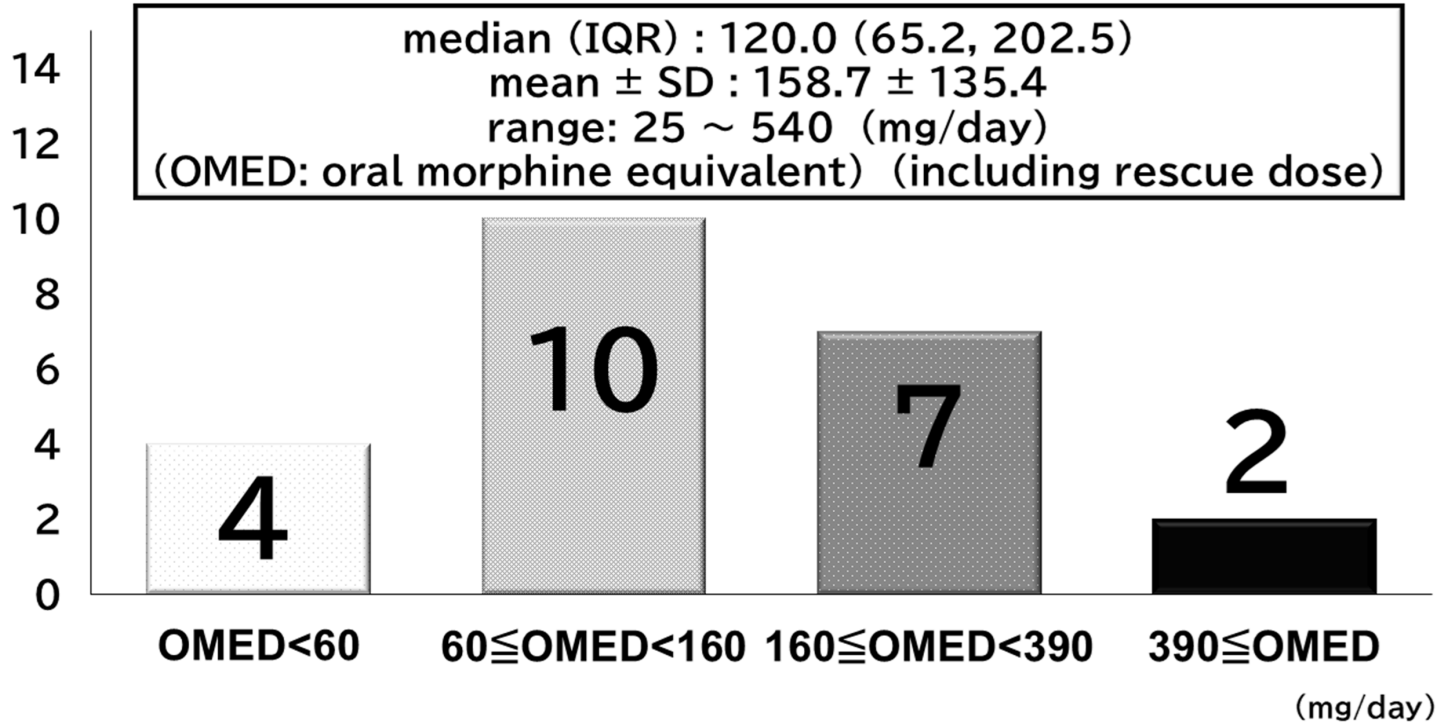


Figure 2

Prior opioid doses immediately before methadone initiation (n=23)

Figure 3

(mg/day)

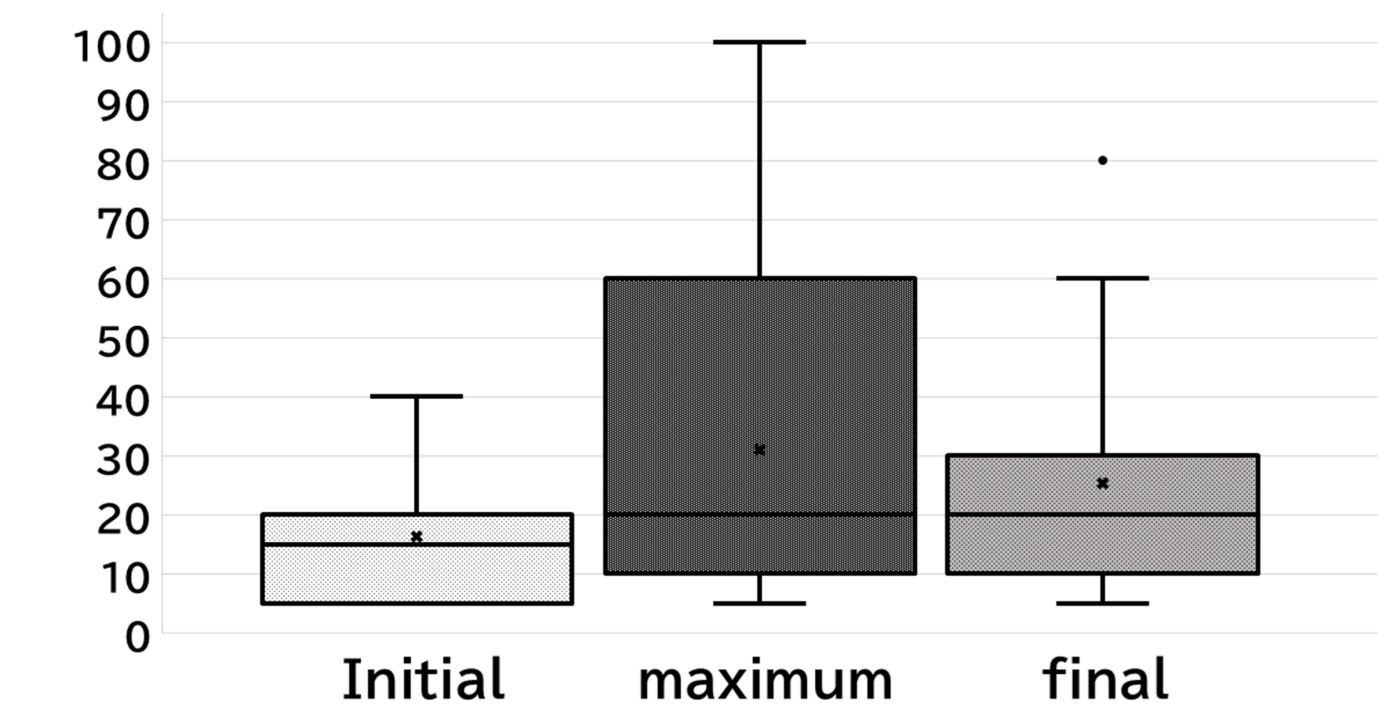


Figure 3

The initial, maximum, and final doses of methadone (n=23)

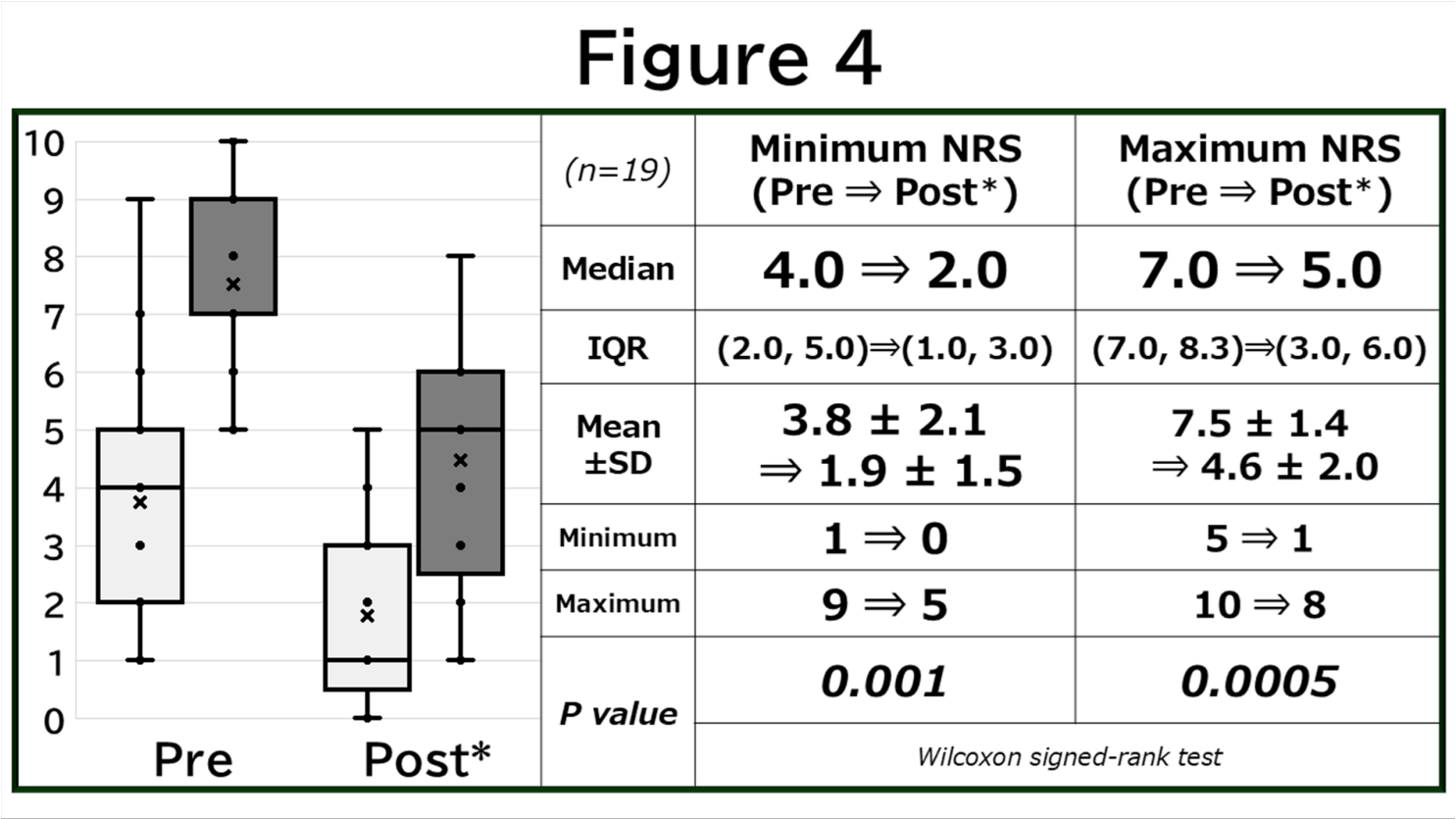


Figure 4

Changes in pain intensity the day before and 7 days after the initiation of methadone administration (n=19)

Note: If the methadone administration period was less than 7 days, the data presented correspond to the 24 hours prior to the final methadone dose.

Figure 5

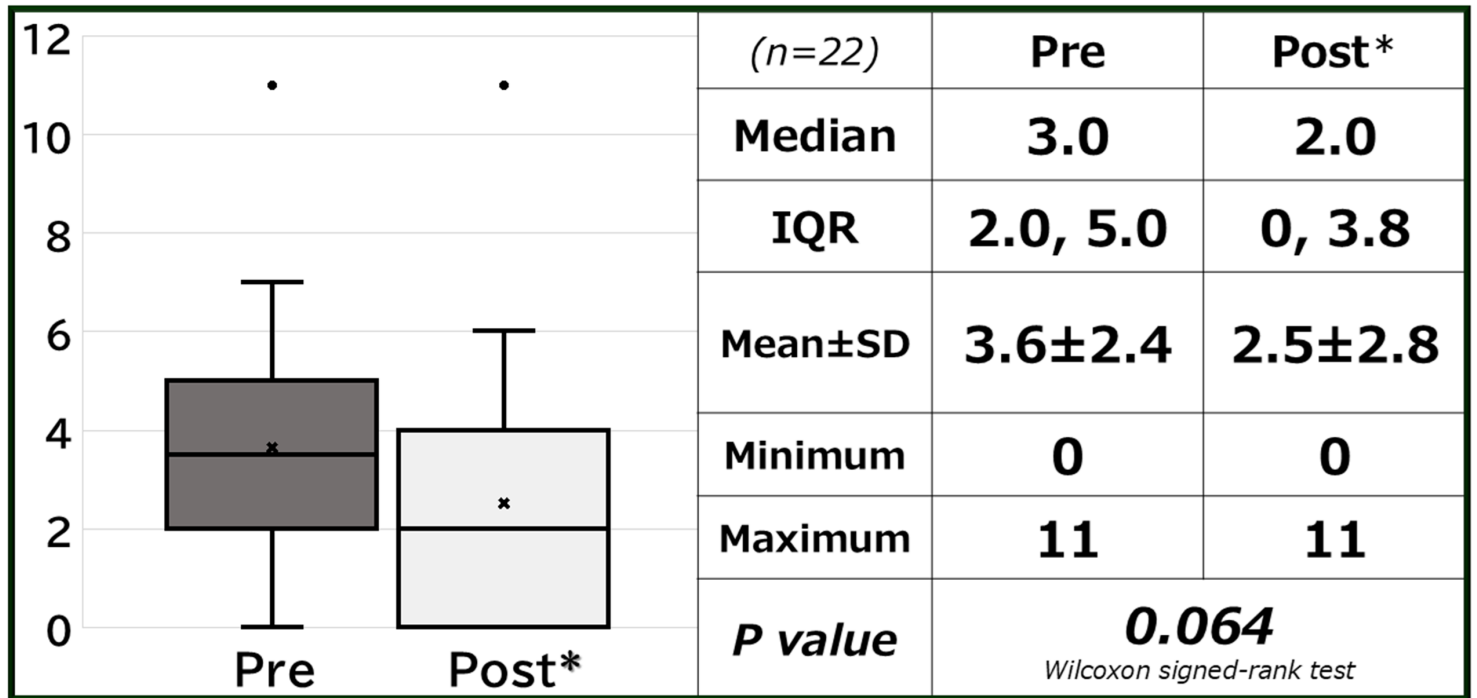


Figure 5

Changes in the frequency of rescue medication usage the day before (pre) and 7 days after (post) the initiation of methadone administration

Note: If the methadone administration period was less than 7 days, the data presented correspond to the 24 hours prior to the final methadone dose.

Supplementary Files

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