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ORIGINAL ARTICLE

Methadone patient-controlled analgesia for postoperative pain: a randomized, controlled, double-blind study

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Abstract
Purpose Postoperative pain is an important health-care issue. Patient-controlled analgesia (PCA) is considered the gold standard for systemic postoperative pain treatment. Methadone PCA is used for patients with chronic pain and those in the palliative care setting. However, its efficacy as a first-line drug for acute postoperative pain is unknown. This study evaluated the use of postoperative methadone PCA after total hip arthroplasty (THA) compared with morphine PCA.
Methods This was a randomized, double-blind, controlled, parallel-group study. Patients were randomized into two groups: group methadone—methadone PCA, and group morphine—morphine PCA, for postoperative analgesia. Drugs were delivered through PCA pumps throughout the first 24 h after surgery (T1:6, T2:12, T3:18, T4:24 h).
Results Opioid consumption in 24 h was significantly lower for group methadone than for group morphine. Group methadone patients experienced significantly less pain than group morphine at rest. Pain after movement was significantly lower in group methadone at T1 and T3 and marginally lower at T2 and T4. Adverse events more frequently reported were sleepiness, nausea, and vomiting, but no statistical difference between groups was found.
Conclusion This study demonstrated that methadone PCA prompted less opioid consumption and lower pain scores at rest and at motion in comparison with morphine PCA as postoperative analgesia after THA.

Keywords Postoperative pain management · Patient-controlled analgesia · Methadone · Morphine

Introduction

Postoperative pain is an important health-care issue. Many advances have been made in our understanding of the process of nociception and innovations in both analgesic agents and techniques for providing better postoperative analgesia [1]. Despite all this progress and the positive contribution of postoperative analgesia, acute postoperative pain is still inadequately treated, and a substantial proportion of patients report moderate to severe pain [2, 3].

Pain associated with major surgical procedures is usually severe by the first day, and >35 % of patients report scores >7 on the visual analog scale (VAS) [1]. Inappropriate postoperative pain treatment induces pathophysiological responses that can result in increased morbidity [1–4].

Intravenously administered patient-controlled analgesia (PCA) is considered the gold standard by which systemic opioids are delivered for postoperative pain management. PCA provides more effective pain relief and greater patient satisfaction compared with the conventional method of titrated bolus injection IV for postoperative pain relief [4, 5]. Methadone is a synthetic opioid that has the same potency of morphine when given intravenously, and its

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analgesic properties go beyond the activation of opioid receptors. Methadone's elimination half-life ranges from 8 to 90 h, with wide variability among individuals. As it has a long duration of action (4–8 h), along with a high lipophilic property, methadone carries the risk of accumulating during the titration phase. Despite potential benefit of its long-lasting analgesic effects, it is not commonly used for postoperative pain [6].

The use of methadone PCA IV is widely used for patients with chronic pain and those in the palliative care setting. Its use is more challenging than other opioids because of its pharmacological characteristics and drug interaction risk, but it has been safely employed for opioid rotation [6, 7]. Its efficacy as a first-line drug for acute pain is unknown. This study evaluated the use of methadone PCA with morphine PCA for postoperative analgesia after total hip arthroplasty (THA).

Methods

This was a randomized, double-blind, controlled, parallel-group study designed, conducted, and adhering to the Consort Statement [8]. The study was approved by the Ethics Committee on Research of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, registered under the number 0011.0.015.000-10 at SISNEP (National System of Information on Ethics in Research Involving Human Subjects of the Ministry of Health of Brazil)—http://portal2.saude.gov.br/sisnep/extrato_projeto.cfm?CODIGO=311875. Written informed consent was obtained from patients scheduled for elective THA. Although Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [9] recommendations were designed for chronic pain studies, we followed the recommendations suitable for acute pain studies.

Surgery was done by the same surgical team using similar surgical approaches; prostheses were comparable. All procedures were performed under spinal anesthesia, preferably at L3–L4, using 15–20 mg of hyperbaric bupivacaine using 27-gauge Whitacre needles. No opioid was added to local anesthetic; patients were sedated with midazolam with incremental doses to achieve sedation.

Exclusion criteria were patient's refusal to participate; American Society of Anesthesiologists (ASA) physical status IV and V; psychiatric illness; chronic use of opioids; known allergy to tested drugs or use of concurrent drugs that affect methadone metabolism; electrocardiogram (ECG) evidence of QT interval >440 ms; low plasmatic levels of potassium and magnesium; evidence of renal failure, sleep apnea, chronic obstructive pulmonary disease, morbid obesity; or any surgical complication requiring conversion to general anesthesia during the procedure.

Patients were randomized into two groups for postoperative analgesia: the first group received methadone (group methadone) and the second received morphine (group morphine). Drugs were delivered through PCA pumps throughout the first 24 h after surgery. Analgesia started before transfer of patients to the Post Anesthesia Care Unit (PACU). Randomization was done using a manually generated random allocation sequence, and group membership was concealed by placing the assignment code in an opaque envelope that was not opened until informed consent was obtained. During PCA preparation, only personnel not involved in postoperative evaluation had access to the medication; they had no access to the assignment code.

Drugs were delivered in 1-mg/ml solution. PCA parameters were bolus 1 mg, lockout interval 6 min, 4-h limit 20 mg. Continuous infusion of 1 mg/h was used. The investigator was allowed to alter PCA bolus to achieve analgesia when the Numerical Rating Scale (NRS) score was >4. All patients received 750 mg paracetamol every 6 h during the postoperative period, and no medication that could increase the risk of cardiac events was associated.

Patients were evaluated before surgery when demographic data, associated diseases, risk factors for arrhythmia, and preoperative pain were registered. During the postoperative period, patients were assessed five times to collect data regarding pain intensity, medication side effects, and analgesic consumption. Visits were scheduled so that the first occurred at arrival in PACU (T0) and within 6 h (T1), 12 h (T2), 18 h (T3), and 24 h (T4) after PCA installation; data acquirement started at T1. Pain intensity was assessed through the NRS for pain (0–10; 0 = no pain; 10 = worst pain imaginable) [10, 11].

Adverse effects (nausea, vomiting, sleepiness, itching, constipation, urine retention, respiratory depression) were evaluated during interviews. All patients had ECG recorded during preoperative evaluation. In the postoperative period, an ECG recorder was available in the ward to exclude ventricular arrhythmia if any cardiac event took place. After 24 h, total medication consumption was recorded and the study protocol was stopped.

The primary outcome of the study was opioid consumption during the first 24 h after surgery. A ratio of 1:1 between morphine and methadone analgesic potencies was used to convert the total methadone dose to morphine in order to compare opioid consumption between groups. The ratio is used for individuals receiving opioid for the first time, when methadone has the same analgesic potency as morphine [6, 12]. Secondary outcomes assessed were pain intensity during follow-up evaluations and incidence of

adverse effects related to drug infusion. Ordinal and interval data were compared using the Student *t* test or Mann–Whitney test, and nominal data were compared using Fisher's exact test. Side effects and gender were compared using the chi-square test. Data was tabulated and analyzed using BIO STAT 4.0 (Instituto de Desenvolvimento Sustentável Mamirauá, PA, Brazil) software [13]. Literature is scarce on the use of methadone for postoperative analgesia, especially using the PCA technique; to calculate the sample size, we used data from another clinical trial comparing opioid consumption in the postoperative period [14]. The sample size for this study was calculated to achieve 80 % power and a type1 error of 0.05 ($\alpha = 5$ %) to detect a mean difference of 15 mg between groups in opioid consumption with a standard deviation (SD) of 19; 18 patients per group were necessary.

Results

Fifty patients were assessed for eligibility: six did not consent to participate and ten were not eligible. General anesthesia was planned for eight patients and two other patients had chronic renal failure. Thus, 34 patients gave informed consent to participate in the study; however, two patients were excluded from group morphine because their anesthetic plan was changed to general anesthesia after consent form was signed. Thirty-two patients were athus evaluated for the 24-h study period (Fig. 1).

During study period, became clear that some patients reported less pain and consumed less opioid. Therefore, the decision was made to stop the study protocol in order to favor the group that presented better analgesia and to perform statistical analysis. Preoperative subject characteristics were similar in both groups (Table 1). Group morphine had 64 % women and 36 % men; group methadone had 44 % women and 56 % men. The most frequent reason for surgery was osteoarthritis (group methadone 93 %; group morphine 83 %).

Preoperative pain was similar between groups during rest and knee flexion, when 57 % of patients from group methadone reported intense pain versus 56 % from group morphine. Group methadone patients experienced significantly less pain at rest than group morphine at T1, T2, T3, and T4 (Fig. 2a). Pain after movement (knee flexion) was significantly lower in group methadone at T1 and T3 and marginally lower at T2 and T4 (Fig. 2b).

Opioid consumption in 24 h was significantly lower in group methadone than in group morphine: 37 mg (median) vs 55 mg (median), respectively (Table 2).

Fifty percent of patients from group methadone and 33 % from group morphine did not report adverse effects. Adverse events more frequently reported were sleepiness,

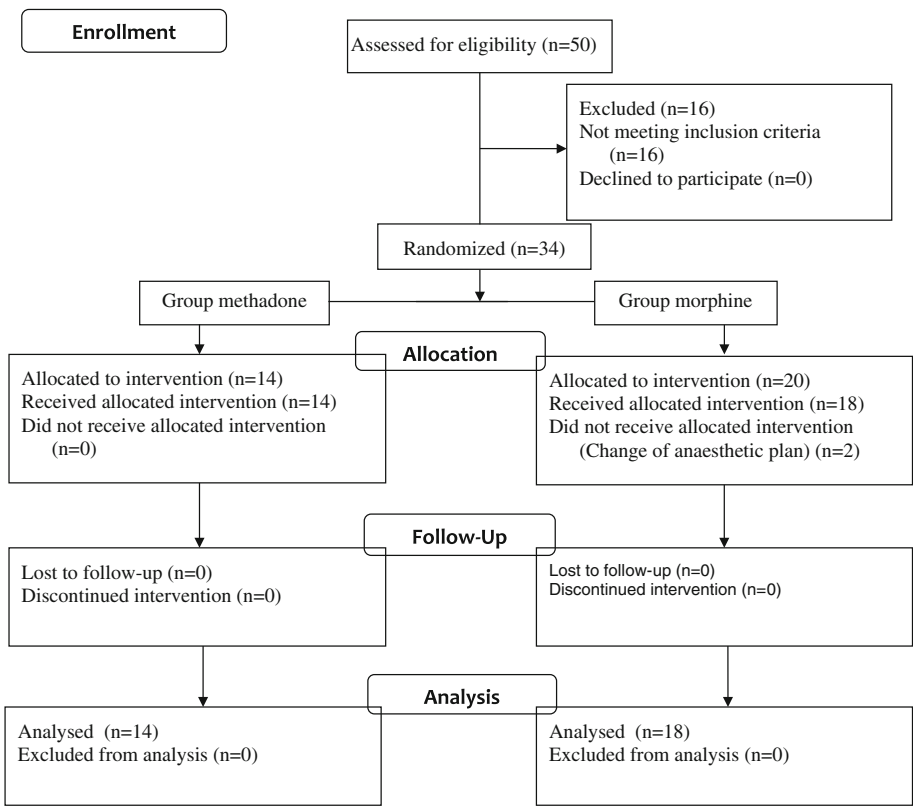

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram

Table 1 Demographic data of patients included and followed in the study

Variables	Group methadone ($n = 14$)	Group morphine ($n = 18$)	P value
Age (years)	50.5 (±17.6797)	50.6 (±14.6574)	0.497
Weight (kg)	78.7 (±12.7)	77.6 (±15.2)	0.409
Height (cm)	156 (±41.3)	166 (±8.11)	0.477
Gender (M/F)	5/9	10/8	0.448

Mean ± standard deviation

* Significant ($p < 0.05$)

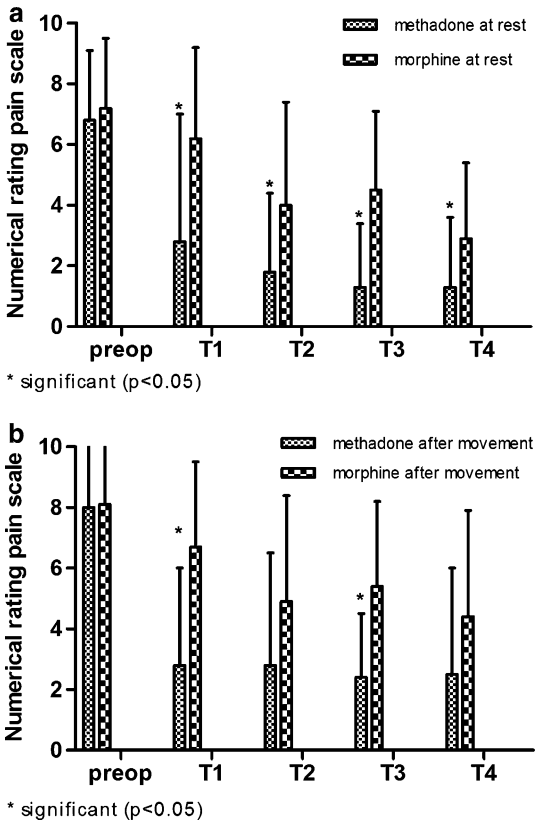

Fig. 2 Pain scores before and after surgery: **a** at rest; **b** after movement (mean ± standard deviation)

nausea, and vomiting, but no statistical difference between groups was found ($p = 0.632$) (Table 3).

Discussion

Although considered a safe and efficacious drug to obtain analgesia, methadone is not normally used as the opioid of choice in the postoperative setting [4, 6]. We showed in this study that methadone PCA provided better analgesia than morphine PCA for THA. Methadone was associated with lower pain scores and less opioid consumption in the first 24 h of analgesia both at rest and after movement. Report of side effects was similar between groups. PCA parameters were established based on morphine delivered IV; both drugs had the same potency (1:1) [6, 12]. Methadone PCA patients received significantly less opioid than morphine PCA patients and consistently reported less pain during most of the follow-up period at rest and in movement.

Table 2 Opioid consumption in the first 24 h after surgery

Variables	Group methadone ($n = 14$)	Group morphine ($n = 18$)	P value
Total consumption (mg)	37 (±1.34)	55.6 (±1.57)	0.0204*

Median ± Interquartile range

* Significant ($p < 0.05$)

Opioid analgesics are the basis of pharmacological management of postoperative pain, especially morphine for moderate to severe pain [15]. Methadone has been used mainly for malignant and nonmalignant chronic pain. In the 2012 updated Practice Guidelines for Acute Pain Management in the Perioperative Setting, the ASA stimulated the use of PCA with opioids IV during the postoperative period [16]. When compared with as-needed treatment, this technique improved analgesia and decreased the risk of pulmonary complications [16–18]. IV PCA allows the patient to administer a predetermined dose of opioid within the limits of a lockout period, resulting in less variability in drug blood levels, thereby enabling titration of the drug to effect [19]. Patients after THR usually experience moderate to severe pain. In our institution, the protocol for postoperative pain care of these patients includes opioid PCA and basal infusion. Methadone acts on pain pathways through more than one mechanism: μ-opioid receptor activation, *N*-methyl-D-aspartate (NMDA) receptor blockade, and inhibition of norepinephrine and serotonin reuptake in the central nervous system [6]. These three mechanisms of action could explain the better analgesic effect of methadone compared with morphine. In our study, we used racemic methadone, which is composed of R-methadone enantiomer, responsible for opioid effect; and S-methadone enantiomer, responsible for NMDA blockade and serotonin and norepinephrine reuptake inhibition [6]. Methadone has been used occasionally for PCA, especially in nonresponders to morphine PCA, in cancer-related pain, and in palliative care patients [20, 21]. Concern about the long duration of action of methadone was taken into consideration in our study, and patients were evaluated every 6 h for signs of side effects related to accumulation.

Table 3 Adverse effects observed in the first 24 h after surgery

	Nausea *n* (%)	Vomiting *n* (%)	Sleepiness *n* (%)	Constipation *n* (%)	Urinary retention *n* (%)	None *n* (%)
Morphine ($n = 18$)	5 (27)	5 (27)	6 (33)	0 (0)	0 (0)	6 (33)
Methadone ($n = 14$)	4 (28)	4 (28)	4 (28)	0 (0)	0 (0)	7 (57)

Significant ($p < 0.05$)

All patients allocated to receive study medications had an ECG recorded during preoperative evaluation. This measure was prompted by the risk of methadone inducing prolonged QT interval. Drug-induced prolongation of the QTc interval is related to blockade of the cardiac potassium channel, which leads to longer repolarization period, which is represented on a surface ECG as a prolonged QT interval. The prolonged interval may increase the risk of ventricular arrhythmia, particularly torsade de pointes (TdP) [6, 22, 23]. The risk of TdP is directly proportional to QT interval duration and is particularly high if this is >500 ms [24]. In our study, cutoff QT interval of 440 ms was used to improve safety, and an ECG recorder was available in the ward. However, systematic assessment was not performed. There were no cardiac symptoms during the follow-up period that prompted an ECG. Evidence does not support the use of routine ECG screening in patients without risk factors [24]. Notably, marked QT interval >500 ms is uncommon, being evident in 0.7 % of patients [24]. Side effects in our study did not achieve statistical difference between groups, but there was a tendency favoring group methadone: 50 % of the methadone group did not report side effects, whereas 33 % of the morphine group did. In a study comparing morphine, methadone, and fentanyl, there was no difference in the side-effect profile [25].

Our study is limited by its short evaluation time. A 24-h period, as opposed to 48 h, was chosen to improve safety, as methadone's behavior after continuous infusion in the postoperative setting is not known. This choice might nonetheless have imposed a limitation to our study, because side effects in the methadone group may appear after a longer infusion period.

In conclusion, this study presents data that favors the use of methadone for treating postoperative pain after major surgeries. A better understanding of its pharmacological behavior when given for short periods is still needed. Nevertheless, methadone PCA could appear as a suitable candidate in postoperative pain management. This study demonstrated that methadone PCA prompted less opioid consumption and lower pain scores at rest and at motion in comparison with morphine PCA after THA.

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Conflict of interest None.

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