Original article

Efficacy and safety of morphine versus methadone for patient-controlled analgesia: A randomized clinical trial

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BACKGROUND: The aim of the study was to evaluate the efficacy and safety of intravenous patient-controlled analgesia (PCA) morphine versus intravenous PCA with methadone for postoperative pain management. **METHODS:** In a randomized controlled clinical trial, 400 patients were randomly allocated to receive either morphine or methadone delivered via intravenous PCA after surgery. Patients were followed for 24 hours after surgery. Pain and patient satisfaction was assessed via numeric rating scale as well as sedation score. Data on the incidence of nausea and vomiting, severe sedation and pruritus were also collected. **RESULTS**: Pain scores at 1 and 3 hours postoperatively in the morphine group was significantly higher than methadone group ($p < 0.050$), but the trend of pain score, sedation score and the incidence of nausea and vomiting during the 24 hours follow-up were not significantly different between groups. Patients in the methadone group had higher ratings of satisfaction than the morphine group ($p = 0.001$). Incidence of pruritus in morphine group were higher than the methadone group ($p = 0.006$). **CONCLUSIONS**: PCA with methadone might be more effective than PCA with morphine in reducing postoperative pain during the first hours after surgery with less frequency of pruritus.

KEYWORDS: Patient-controlled Analgesia, Morphine, Methadone, Pain Management

BACKGROUND

Early and high quality recovery needs a planned postoperative pain management.[1] Patient-controlled analgesia (PCA) is a well-established method for postoperative pain control.[2,3] PCA allows the patient to self-administer small doses of opioids such as morphine, methadone or fentanyl as needed to manage pain.[4] PCA is used to maintain a mild level of pain rather than total pain relief, allowing the patient to self-administer enough drugs to achieve a comfortable balance between analgesia and adverse effects.[5-8]

In the United States, more than 60 percent of the patients who experienced moderate to severe postoperative complications attributed to opioids had received morphine as the postoperative pain therapy.[9] Though morphine is often the basic analgesic for intravenous PCA, other opioids, including fentanyl or methadone are also administered for postoperative pain management. Morphine and its active metabolites can be accumulated in situations such as patients with renal impairment and have toxic effects.[10] However, morphine manufacturing is simple, but the immediate-release morphine preparation can be prohibitively expensive in developing countries.[11] On the other hand, methadone has a number of advantages compared to morphine. It does not have any recognized active metabolites and does not undergo significant renal elimination. It is synthetic and simply manufactured and could be a good opioid option in the setting of limited resources.[12] To our knowledge, no earlier study has compared intravenous PCA with morphine and with methadone for postoperative pain management. The present study was conducted to compare the efficacy as well as complications of morphine with methadone in intravenous PCA for postoperative pain management.

METHODS

The study was a randomized controlled trial and performed over a six-month period (from September to March 2010). Four hundred patients being scheduled for elective surgery in Sadi hospital, Isfahan, Iran, were randomly assigned to receive either intravenous PCA with morphine (n = 200) or methadone (n = 200). Block randomization wasperformed using a random table allocation. Pa tients were eligible if they did not have ability to

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use the PCA device, known allergy to any of the study medications, diabetes mellitus or history of drug abuse. All patients were informed on the purpose of the study and written consent was obtained from all of them.

The anesthesia protocol was the same in all patients. They received 100 μg of fentanyl intravenously as premedication. Anesthesia was induced with IV propofol (2 mg/kg) and atracurium (0.5 mg/kg). Anesthesia was maintained with IV propofol (proportionate to the patients' hemodynamic status), inhalational N_2O (50%) and O_2 (50%) as well as atracurium as 10 mg bolus doses when required.

Patients received intravenous PCA when they were admitted to the postanesthesia care unit and were awake, being able to answer questions and follow commands. The continuous intravenous PCA regimens consisted of a 100 CC solution of morphine or 100 CC solution of methadone with a 1 CC bolus and 15 min lockout. All pumps were established to deliver a basal infusion of morphine 0.5 mg/h and methadone 0.25 mg/h.

The primary outcomes of the study were self-reported pain and satisfaction scores measured using numeric rating scales (NRS) from 0 to 10 (no pain to worst possible pain and no satisfaction to fully satisfied, respectively). We also evaluated sedation score using a 6 point scale (0 = awake to 5 = nonresponsive to painful stimuli), the incidence of nausea and vomiting and pruritus. When the patients were admitted to the ward time 0 was assigned for the purpose of assessments. End points were assessed at 0, 1, 3, 5, 9 and 24 hours after discharge from recovery.

Comparison of two means formula was used to sample size calculation with type I error (α) equal to 0.05 and power 80%. Data are presented as means ± SD, median [IQR] or number (percent) as appropriate. Independent samples Student's t-test and Mann-Whitney U test were used to compare the pain score, satisfaction and sedation score during 24 hours follow-up. Repeated measures analysis of variance (ANOVA) was used to compare trend of pain score. The proportion of patients experienced side effects was analyses with chi-square test. Probability values under 0.05 were considered statistically significant. Data analyses were conducted using SPSS for Windows (version 18; SPSS Inc., Chicago, IL, USA).

RESULTS

All patients in both groups were included in the final analysis (figure 1). The mean age of patients was 36.9 ± 15.5 years (36.7 ± 15.1 years for morphine group versus 37.1 ± 16.0 years for methadone group, p = 0.80). Of 400 patients, 276 (69.0%) subjects were female and 124 (31.0%) were male [134 (48.6%) female in methadone group versus 142 (51.4%) female in morphine group, p = 0.38]. Most of the patients had cesarean section. Type of surgery in two groups was not statistically significant (data not shown).

As shown in table 1, pain scores at 1 and 3 hours after recovery in morphine group were significantly higher than methadone group. Figure 2 shows the result of repeated measures of ANOVA to compare the trend of pain score during 24-hour follow-up, which was not significantly different between groups. Mean sedation scores at 0, 1, 3, 5, 9, and 24 hours after recovery are reported in table 2. Mann-Whitney U test demonstrated that the difference between groups was statistically significant only at 3 hours after recovery.

Table 3 shows the median NRS pain score, satisfaction score, sedation score, the incidence of nausea and vomiting and pruritus during 24 hours postoperatively. Patients in PCA with methadone group recorded higher ratings of satisfaction compared to patients in the morphine group. The reported frequency of pruritus in the morphine group was higher than the methadone group.

Table1. Pain scores in repeated measures in 400 patients who received *patient-controlled analgesia* after surgery

		Time (Hours)					
		0	1	3	5	9	24
PCA morphine	n	198	196	198	194	192	188
	Mean ± SD	4.4 ± 2.6	3.1 ± 2.3	2.1 ± 1.5	1.5 ± 1.4	1.2 ± 1.4	0.3 ± 0.6
PCA methadone	n	199	194	194	196	188	185
	Mean ± SD	4.3 ± 2.7	2.4 ± 2.0	1.7 ± 1.4	1.3 ± 1.4	1.0 ± 1.2	0.3 ± 0.5
P-value*		0.900	0.001	0.018	0.330	0.360	0.340

*Independent samples Student's t-test
PCA: Patient-controlled analgesia

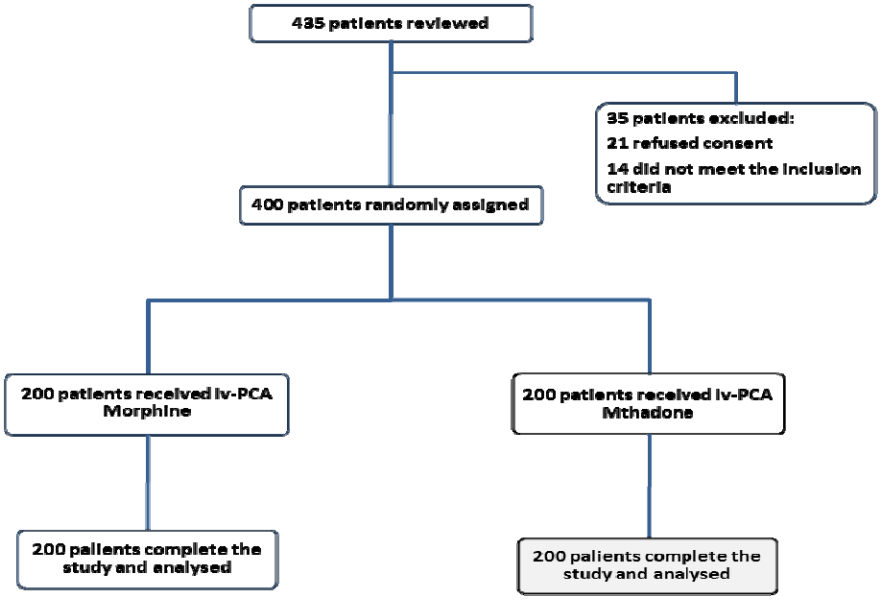

Figure 1. Trial profile

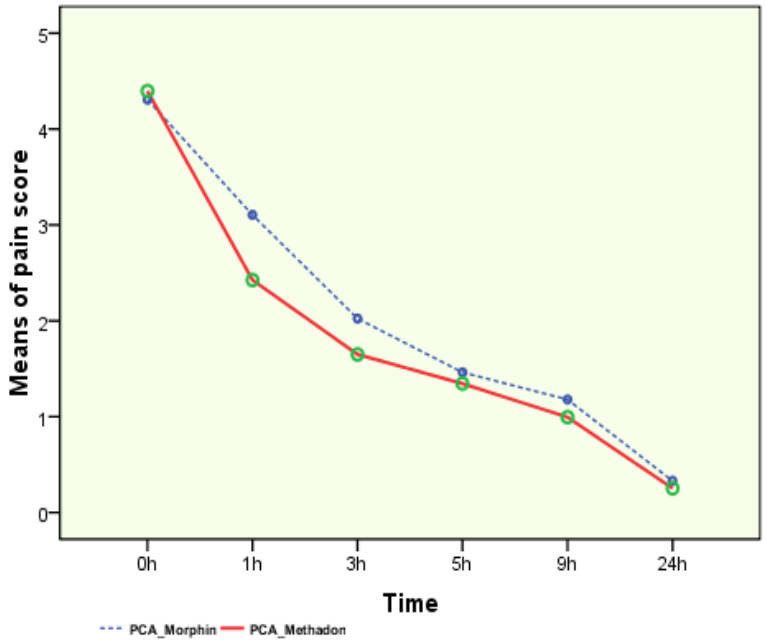

Figure 2. Mean pain intensity scores recorded at 0, 1, 3, 5, 9, and 24 hours for the methadone and morphine intravenous PCA groups (p for trend = 0.08)

Table2. Sedation scores in repeated evaluations

		Time (Hour)					
		0	1	3	5	9	24
PCA morphine	n	198	196	198	194	192	188
	mean±1SD	2.2 ± 1.1	2.0 ± 1.3	1.4 ± 1.2	0.9 ± 1.1	0.6 ± 0.9	0.4 ± 0.0
PCA methadone	n	199	194	194	196	188	185
	mean±1SD	2.1 ± 1.4	1.9 ± 1.4	1.5 ± 1.4	1.3 ± 1.2	0.9 ± 1.1	0.5 ± 0.0
P-value*		0.630	0.370	0.620	0.003	0.080	0.900

*Mann-Whitney U test
PCA: Patient-controlled analgesia

Table3. Overall pain, satisfaction and sedation scores as well as side effects in evaluated patients

	PCA morphine (n = 200)	PCA methadone (n =2 00)	P-value
Pain score (24h)	1.5 [0-2]	1 [0-2]	0.260*
Satisfaction score (24h)	4 [3-5]	5 [3-6]	0.001*
Sedation score (24h)	1.2 [0.8-1.8]	1.4 [0.6-2.1]	0.620*
Nausea &Vomiting (24h)	18 (9.0)	13 (6.5)	0.350†
Pruritus (24h)	12 (6.0)	2 (1.0)	0.006†

Data are presented as median [interquartile range], and number (%).
*Mann-Whitney U test; †chi-square
PCA: Patient-controlled analgesia

DISCUSSION

The aim of postoperative pain management is to supply unbroken effective analgesia that is safe and free from unwanted side effects.[10] PCA is accepted and applied widely as a standard method of postoperative pain management. This method is generally used for evaluation of various drug combinations and multimodal approaches to the pain management.[2-3] Morphine is known as the "gold standard" for intravenous PCA, being the most studied and most frequently used PCA drug in the United States.[13] Findings of this study showed higher pain scores at 1 and 3 hours after recovery for morphine group, but the trend of pain scores during-24-hour follow-up was not significantly different between groups. Sedation score and the incidence of nausea and vomiting were similar in both groups. Patients in the methadone group were more satisfied compared to patients in the other group with less frequency of reported pruritus.

To the best of our knowledge, no previous study has compared intravenous PCA with morphine and with methadone for the treatment of postoperative pain, but several studies had compared morphine with other opioids. One study reported that morphine produced a better quality of analgesia versus nalbuphine with minor incidence of side effects.[14] Viscusi et al.[15] and Hartrick et al.[16] showed that an investigational PCA transdermal system using fentanyl provided postoperative pain control equivalent to that of a standard intravenous morphine regimen delivered by a PCA. One study indicated that PCA tramadol is as effective as PCA morphine for the management of postoperative pain. In addition to the incidences of sedation, nausea or pruritus were the same in both groups.[17] Lak et al.[18] reported that ketamine administration improved pain intensity in contrast to morphine for post-operative analgesia management when its administration was continued for 48 hours postoperatively. In our study, similar to earlier ones,[15-17] both regimens of morphine and methadone PCA showed similar effect on postoperative pain with minor incidence of sedation, nausea and vomiting. However, in contrast to these studies, incidence of pruritus for PCA with morphine regimen was significantly higher than methadone regimen.

The morphine and methadone PCA regimen selected for this study was a fixed dose, being possible to be marked as a limitation of our study, whereas physicians tend to think of PCA regimen as an adjustable item. Another limitation of our study was that we did not gather data about duration of surgery and anesthesia in patients; however, patients were divided into groups by block randomization.

In conclusion, this study demonstrated that both PCA methadone and PCA morphine are equally effective in the management of pain during the first 24 hours after surgery with a similar incidence of nausea and vomiting. However, PCA with methadone might be more effective than PCA with morphine in reducing postoperative pain during the first hours after surgery with less frequency of pruritus.

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