

Intraoperative administration of methadone reduced postoperative pain and opioid consumption following cadaveric renal transplantation: a randomized controlled trial

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Abstract: **Objective:** In this randomized clinical trial study, the impact of prophylactic administration of methadone during surgery on postoperative pain and analgesic requirement following cadaveric renal transplantation was assessed.

Methods: Ninety patients were randomized to receive either methadone 0.15 mg/kg or 0.15mg/kg morphine after tracheal intubation. Both groups were treated with acetaminophen 1 gr before extubation. Protocol of anesthesia was the same in both groups and the anesthetist was blinded to the study groups. The primary outcome was defined as total opioid consumption during recovery and first day after surgery. Secondary outcomes were pain scores and level of patients' sedation during the recovery period and first postoperative day as well as opioid-related complications.

Results: Data of eighty-five eligible patients were analyzed. The mean pain and sedation scores were lower in the methadone group compared to the morphine group during recovery and the first 24 hours after surgery. The time of first rescue analgesic requirement was later in the methadone group (10.4 vs 6.3 hours). Also, postoperative morphine consumption was significantly less in the methadone group compared to patients receiving morphine (3.5 vs. 6.9 mg; $P < 0.001$).

Conclusion: Intraoperative administration of methadone decreased postoperative pain scores, reduced opioid consumption after surgery and improved level of sedation during the first 24 hours after surgery.

Keywords: Kidney Transplantation; Methadone; Morphine; Postoperative Pain; Pain Management

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1. Introduction

Acute postoperative pain is a crucial condition with significant impact on escalation of hospital stay as well as morbidity and mortality rates. This condition is usually moderate to severe in intensity involving up to 70% of patients (1).

Unfortunately, the reluctance of medical staff to administer sufficient doses of analgesics in postoperative pain management leads to incomplete or inadequate control of acute postoperative pain with deleterious consequences such as painful recovery, higher cardiovascular/respiratory morbidity and mortality (2, 3). Opioids are the most common agents used to control severe pain after surgery (4). However, complications such as hypoventilation, hypoxemia, nausea and vomiting may negatively influence their usage (5).

Administration of analgesics such as opioids in the postoperative phase of renal transplantation surgery is a matter of

challenge due to the expected reduction in the clearance and consequent accumulation of active medication metabolites (6).

Methadone is a μ -opioid receptor agonist that also antagonizes N-methyl-D-aspartate (NMDA) receptors and inhibits the reuptake of serotonin and noradrenaline in the central nervous system (7). Methadone has a long duration of action from 13 to 50 hours which makes it a drug of choice in acute pain management compared to the other opioid agents (8). Many studies have advocated the use of intravenous methadone intraoperatively to reduce acute postoperative pain and analgesic requirements (9, 10). In addition, the combined or multimodal therapy has significantly reduced the use of postoperative analgesics and side effects of opioids (11, 12). This study was designed to assess the clinical effectiveness and safety of intraoperative administration of methadone in postoperative pain management of patients

undergoing renal transplantation surgery.

2. Methods

2.1. Study design and setting

This double-blinded randomized clinical trial was conducted from April 10, 2021 to March 10, 2022 at Sina Hospital, Tehran, Iran. Patients were taken informed consent before enrollment in the study. Study was conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects.

After approval by the Research Ethics Committee of Sina Hospital affiliated to Tehran University of Medical Sciences (IR.TUMS.SINAHOSPITAL.REC.1400.013), the study protocol was registered at www.irct.ir (IRCT20130304012695N9) then patients' enrolment was commenced.

2.2. Study population

All patients aged 20 to 60 years with a history of end-stage renal disease who met the criteria for receiving renal transplantation from a cadaver donor were included in the study. All patients with history of drug addiction, methadone maintenance therapy, consumption of psychiatric medications, prolonged QT interval on EKG and elevated liver enzymes were excluded from study. All patients were on the waiting list for kidney transplantation and had already undergone the required consultations and examinations for kidney transplantation surgery. The transplantation team and patients were usually informed about the surgery 8-10 hours before operation.

The routine practice in the kidney transplantation department was administration of 8 to 10 mg of morphine in the first postoperative day for acute pain control. Considering the hypothesis that intraoperative methadone administration can reduce postoperative morphine consumption by 50%, the sample size of 90 patients was calculated for detection of 50% difference in the postoperative morphine consumption between two groups, with a standard deviation of 5%, a test power of 80%, and level of significance of less than 0.05.

2.3. Randomization

The randomization was done by a computer-generated randomization table and the patients were assigned to equal methadone or morphine groups. A nurse anesthetist who was not a member of the research team controlled the randomization process and prepared the study drugs. Both drugs were provided in transparent form by 5-ml syringes according to the study groups by the nurse anesthetist. The patients' names and drug codes were recorded. All patients and care providers were blinded to the study groups during all the steps of the project.

2.4. Intervention

Anesthesia induction was performed under standard monitoring protocol including blood pressure measurement, pulse oximeter, capnography and bispectral index. Anesthetic drugs were the same in both groups. After laryngoscopy and tracheal intubation, patients were assigned to receive either morphine 0.15mg/kg or methadone 0.15 mg/kg based on the study groups.

Anesthesia was maintained during the surgery by administration of 1-1.5% isoflurane and remifentanyl 0.1 μ g/kg/min to achieve a bispectral index value within 40 to 60. The patients' systolic blood pressure was kept at 120-140 mmHg during the surgery, before completion of the renal artery anastomosis and de-clamping the external iliac artery. After de-clamping the artery supplying the kidney, systolic blood pressure was maintained higher by 15-20%. Patients received ondansetron 4mg and intravenous acetaminophen 1gr at the end of surgery.

2.5. Outcome measurement

After tracheal extubation, the patients were monitored and evaluated in the recovery room. Intensity of pain score was assessed on arrival to the recovery room by resident of anesthesia every 15min based on visual and verbal analog scale (VAS; 0 = no pain to 10 = worst pain). The postoperative level of patients' sedation was graded on a 0 to 3 scale (0 = awake; 1 = drowsy and awaken with sound; 2 = often drowsy and awaken by shaking; and 3 = deep sedated, and difficult to awaken). During the first 24 hours of ward admission, pain and sedation levels were assessed every 6 hours and rescue analgesics (2-4 mg titrated morphine) was administered in patients with VAS score >3. Simultaneously, after each injection of morphine, patients were evaluated for the opioid complications including hypoxemia, nausea and vomiting. The primary outcome was total analgesic consumption in the recovery room and first postoperative day in the ward. Opioid-related complications were also recorded. The secondary outcomes included pain score and level of sedation during the PACU and first postoperative day.

2.6. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 16 (IBM Corp., Armonk, N.Y., USA). Quantitative variables were presented as mean \pm standard deviation (SD). Categorical parameters were reported in the form of absolute frequencies and percentages. Categorical and quantitative variables were compared using chi-square and t-student tests, respectively. Repeated measures ANOVA test was also used to compare the effectiveness of methadone and morphine intervention on pain intensity and sedation of patients during the postoperative period. Statistical significance threshold was considered as 0.05 and less.

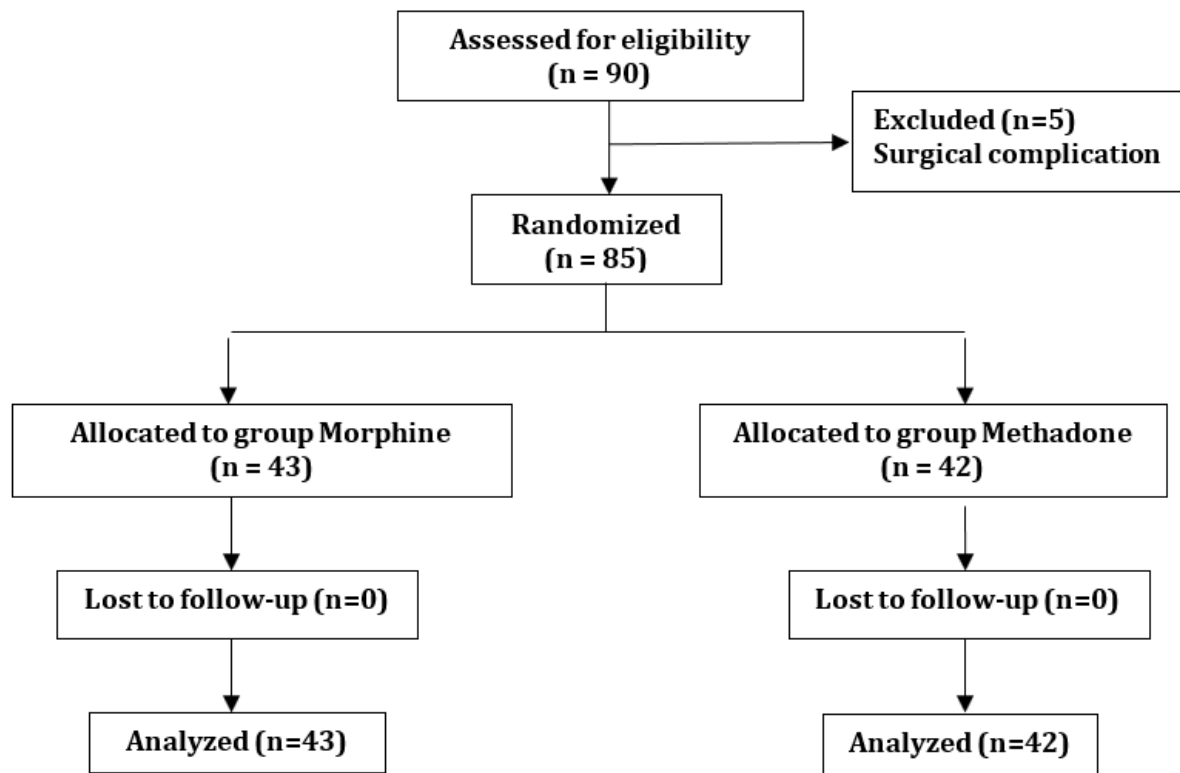


Figure 1 Flow diagram of patients participating in the study

Table 1 Demographic, baseline and surgical parameters in methadone and morphine groups

Variables	Methadone (n=43)	Morphine (n=42)	P
	Mean±SD / number (%)		
Age (yr)	36.23±5.37	38.38±7.67	0.552
Male/Female	27 /16	30/12	0.881
Weight (kg)	72.22±4.5	69.24±6.5	0.553
Hypertension	38 (88.4)	36 (85.7)	0.642
Ejection fraction (%)	51.5 ± 10.8	52.6 ± 11.2	0.547
Diabetes mellitus	3 (7.0)	4 (9.5)	0.875
Duration of surgery (min)	144.82±7.19	139.16±9.28	0.741
Blood loss (ml)	490±35	512±29	0.551

3. Results

90 patients participating in the study were randomly placed in two groups of methadone (n=45) or morphine (n=45) treatments. Five patients were excluded because of post-operative surgical complications. Finally, data of 85 patients were collected and analyzed (figure 1).

The mean age of the patients was 37.12±4.17 years with majority of the study population being males (67%). The mean duration of surgery was 140±6.17 minutes. There was no significant difference in demographic parameters between the two study groups (table 1).

The first dose of rescue analgesic in postoperative period was administered significantly later in patients of the methadone group compared to the morphine group (10.4 vs 6.3 hours). As the primary outcome, the mean total opioid consumption

(morphine) during the first day after surgery in methadone group was significantly lower than morphine group (3.5±1.6 vs. 6.9±2.8 mg; $P < 0.001$).

The mean pain scores (VAS) of patients were lower in the methadone group compared to the morphine group during recovery and first 24 hours after surgery (table 2). According to table 2, the patients in the methadone group had no remarkable pain while the patients in the morphine group experienced mild pain in recovery room. During the first 24 hours of hospitalization in the ward, the pain intensity of the patients in the morphine group was moderate while the pain in the methadone group had mild intensity.

According to the results of variance analysis of repeated measures, a statistically significant increase in pain score was seen in both treatment groups over time. Also, a statistically significant difference was seen between the two groups in

terms of pain scores during the study (figure 2).

In terms of postoperative opioid complications, no significant episode of nausea, vomiting and hypoventilation had occurred in both study groups.

The level of patients' sedation during postoperative period (especially the first 6 hours after the operation) was deeper in methadone group (table 3). After 12 hours of surgery, the degree of patients' sedation in both groups did not reveal any significant difference.

According to the results of variance analysis of repeated measures, there was a decrease in the sedation score of patients over time in the methadone group while an initial up-trend followed by a down-trend in the sedation of level of patients in the morphine group was detected. Also, in all three time periods, a statistically significant difference was seen between the two groups in terms of the level of sedation (figure 3).

4. Discussion

Patients undergoing renal transplantation surgery usually experience severe pain in the first postoperative 24 hours. Overall, 65% of renal transplant recipients reported moderate to severe intensity of pain after surgery (13).

The use of NSAIDs as analgesic is limited after kidney transplantation due to altered renal function and acetaminophen is not potent enough to overcome severe postoperative pain. Thus, administration of opioids due to their high potency and ease of usage is still the most common strategy in the postoperative pain management (14).

According to the preliminary results of the current study, intravenous administration of methadone 0.15 mg/kg before skin incision led to a significantly more profound decrease in pain score compared to intravenous morphine 0.15 mg/kg in patients undergoing renal transplantation surgery. Patients

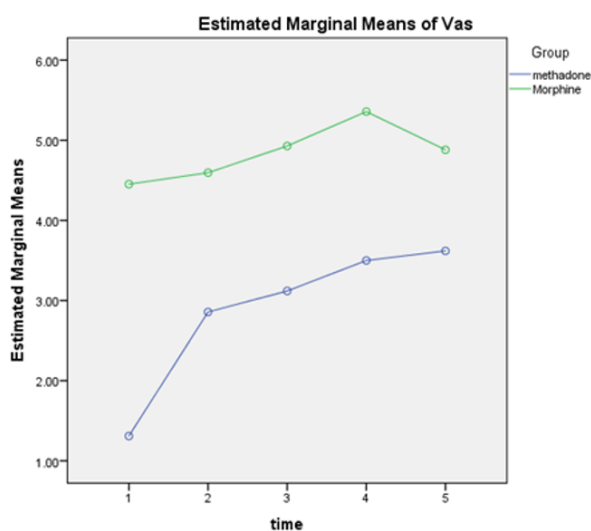


Figure 2 Comparison of pain scores in two groups of patients in the recovery period and 6, 12, 18 and 24 hours after surgery.

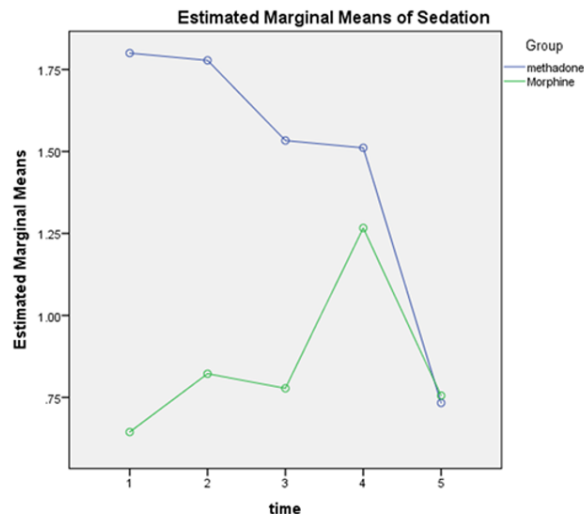


Figure 3 Comparison of sedation scores in two groups of patients in recovery periods and 6, 12, 18 and 24 hours after the operation

in the methadone group had a higher level of sedation score during the first 24 hours after surgery.

Morphine reaches its maximum effect 20 minutes after intravenous administration lasting up to 6 hours. Morphine is mainly metabolized in the liver and most of its metabolites are excreted through the kidneys. The elimination half-life of morphine is approximately 2 hours (range 1–8 hours) but in the ESRD patients, the excretion of its metabolites is impaired and prolonged. Morphine-6-glucuronide (M6G) is a potent opioid agonist with analgesic and sedative activity (15). In ESRD patients, the morphine dose should be reduced to less than 25% of the required dose in patients with normal renal function (16).

In terms of pharmacokinetics, methadone is metabolized in the liver with apparently inactive metabolites which are excreted through gut. Therefore, methadone can be safely used in patients suffering from renal diseases (17).

Methadone as a μ -agonist and NMDA receptor antagonist, has analgesic effect on acute and chronic pain. Analgesic effects of methadone appear early after intravenous administration and persist for a long time, which may play an important role in postoperative pain management. Intraoperative administration of methadone blocks NMDA receptors and inhibits reuptake of serotonin and norepinephrine in the central nervous system. As a result, sensitization of the central pain pathway is reduced and provides reliable analgesia with lower opioid requirement in the postoperative period (18).

The administration of high doses of methadone (0.2–0.3mg/kg) at the initiation of procedures such as abdominal, gynecologic, major pediatric, cardiac and spinal surgeries have been proven to reduce pain scores and analgesic requirements in several clinical trials (19, 20, 21).

Patients undergoing renal transplantation surgery are usually uremic with chronic dialysis encephalopathy and associated brain disorders (22); thus, in this study, low doses of

Table 2 The mean pain score based on VAS in methadone and morphine groups during postoperative period

Group	Recovery	Ward			
		6hr	12hr	18hr	24hr
Methadone	1.35 ± 0.72	2.53 ± 0.49	3.17 ± 0.24	3.54 ± 0.51	3.54 ± 0.62
Morphine	3.67 ± 0.64	4.57 ± 0.72	4.52 ± 0.95	5.43 ± 0.33	4.73 ± 0.89
P-value	0.009	0.001	0.001	0.001	0.001

Table 3 The levels of patients' sedation during postoperative period

Group	Recovery	Ward			
		6hr	12hr	18hr	24hr
Methadone	1.73 ± 0.56	2.33 ± 0.79	1.27 ± 0.64	1.54 ± 0.61	0.54 ± 0.61
Morphine	0.84 ± 0.64	0.85 ± 0.72	0.72 ± 0.45	1.13 ± 0.43	0.73 ± 0.83
P-value	0.029	0.054	0.042	0.895	0.995

methadone (0.15mg/kg) were used as a preemptive analgesia in the renal transplantation surgery.

The severity of pain in recovery period in both groups was not high enough to require analgesia, but patients in the morphine group needed more analgesia in the first 24 hours of ward admission.

No serious opioid-related side effects such as respiratory depression, uncontrolled nausea and vomiting were observed in either group.

5. Limitation

There were several limitations in the current study. First, postoperative opioid complications were only assessed for first 24 hours. Second, patient-controlled analgesia pumps were not used to control pain and analgesics were administered to patients as needed. Thus, patients' pain may not have been well-controlled and their actual need for analgesics might exceed what we have reported.

6. Conclusion

In patients undergoing renal transplantation surgery, administration of low dose methadone at the beginning of surgery diminished the postoperative pain score and the need for analgesia in the first 24 hours after surgery significantly compared to the morphine.

7. Declarations

7.1. Acknowledgments

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7.2. Authors' contributions

Study conception and design: MK; data collection: MK, HD and SK; analysis and interpretation of results: HD and AB; draft manuscript preparation: MK and SK. All authors reviewed the results and approved the final version of the manuscript.

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7.4. Conflict of interest

The Authors declare that there is no conflict of interest.

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