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SCIENTIFIC ARTICLE

Comparison of postoperative analgesia with methadone versus morphine in cardiac surgery[☆]



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KEYWORDS

Methadone;
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Abstract

Background and objectives: Pain is an aggravating factor of postoperative morbidity and mortality. The aim of this study was to compare the effects of methadone versus morphine using the numerical rating scale of pain and postoperative on-demand analgesia in patients undergoing myocardial revascularization.

Method: A randomized, double-blind, parallel clinical trial was performed with patients undergoing coronary artery bypass grafting. The subjects were randomly divided into two groups: morphine group and methadone group. At the end of cardiac surgery, 0.1 mg.kg⁻¹ adjusted body weight of methadone or morphine was administered intravenously. Patients were referred to the ICU, where the following was assessed: extubation time, time to first analgesic request, number of analgesic and antiemetic drug doses within 36 h, numerical pain scale at 12, 24, and 36 h postoperatively, and occurrence of adverse effects.

Results: Each group comprised 50 patients. Methadone showed 22% higher efficacy than morphine as it yielded a number-needed-to-treat score of 6 and number-needed-to-harm score of 16. The methadone group showed a mean score of 1.9 ± 2.2 according to the numerical pain scale at 24 h after surgery, whereas as the morphine group showed a mean score of 2.9 ± 2.6 ($p=0.029$). The methadone group required less morphine (29%) than the morphine group (43%) ($p=0.002$). However, the time to first analgesic request in the postoperative period was 145.9 ± 178.5 min in the methadone group, and 269.4 ± 252.9 in the morphine group ($p=0.005$).

[☆] Study conducted at Hospital Nossa Senhora da Conceição (HNSC), Tubarão, SC, Brazil.

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Conclusions: Methadone was effective for analgesia in patients undergoing coronary artery bypass grafting without extracorporeal circulation.

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PALAVRAS-CHAVE

Metadona;
Morfina;
Dor pós-operatória;
Cirurgia cardíaca

Comparação da analgesia pós-operatória com uso de metadona versus morfina em cirurgia cardíaca

Resumo

Justificativa e objetivos: A dor é fator agravante da morbidade e mortalidade pós-operatória. O objetivo foi comparar o efeito da metadona versus morfina quanto à dor e demanda de analgesia pós-operatória em pacientes submetidos à revascularização do miocárdio.

Método: Ensaio clínico randomizado, duplo-cego, em paralelo. Pacientes submetidos à cirurgia de revascularização do miocárdio foram randomizados por blocos em dois grupos: Grupo Morfina (Gmo) e Grupo Metadona (Gme). No fim da cirurgia cardíaca, 0,1 mg.kg⁻¹ peso corrigido de metadona ou morfina foi administrado por via venosa. Os pacientes foram levados à UTI, onde foram avaliados o tempo até a extubação e a necessidade do primeiro analgésico, o número de doses necessárias de analgésicos e antieméticos em 36 horas, a escala numérica de dor em 12, 24 e 36 horas após a cirurgia e a ocorrência de efeitos adversos.

Resultados: Foram incluídos 50 pacientes em cada grupo. A metadona apresentou eficácia 22% maior do que a morfina com *Number Needed to Treat* (NNT) de 6 e *Number Needed to Harm* (NNH) de 16. Gme apresentou média de dor pela escala numérica em 24 horas após o procedimento de 1,9 ± 2,2 em comparação com o Gmo, cuja média foi de 2,9 ± 2,6 ($p=0,029$). O Gme necessitou de menos morfina de resgate 29% do que o grupo Gmo 43% ($p=0,002$). Entretanto, o tempo até a necessidade de analgésico no pós-operatório foi de 145,9 ± 178,5 minutos no Grupo Gme e de 269,4 ± 252,9 no Gmo ($p=0,005$).

Conclusões: A metadona mostrou-se eficiente para a analgesia em cirurgias cardíacas de revascularização do miocárdio sem circulação extracorpórea.

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Introduction

Longitudinal median sternotomy is the most commonly used incision for cardiac surgeries. Associated with the use of retractors, it is the best method for exposing the anatomical region.¹ However, the described method associated with an extended surgery time, places chest muscles under great tension and stress causing great pain to the patient in the postoperative period, which hinders deep breathing and reduces the elimination of secretions from respiratory tract that may trigger atelectasis and respiratory infections.²

Despite the advances in analgesic drugs, different routes of administration, and non-pharmacological techniques for pain relief, this is still considered an important postoperative problem and, to date, there is no standardized protocol in several hospitals. Among the options for postoperative management of cardiac surgeries are opioid analgesics and supportive measures.³

Currently, many institutions use intravenous opioids with high clearance and relatively short half-lives, such as morphine, that produce important fluctuations in serum opioid levels, ranging from inadequate analgesia to toxic values.⁴ The option, in this case, would be intravenous infusion of

analgesics, either on-demand or continuous infusion. Both methods, however, require high-cost apparatus.³ Thus, an optional method that promotes continuous analgesia without the problems associated with infusion techniques would be the use of an agent with long half-life and low clearance applied intraoperatively, such as methadone. Methadone is a synthetic opioid of long duration and latency, used for several years in the treatment of drug addiction⁵ and rediscovered as an analgesic for treating chronic pain,⁶ cancer pain,⁷ and also for postoperative analgesia, both in adults⁸ and children.^{9,10}

Methadone has an interindividual variation in pharmacokinetics as well as the potential to cause late toxicity due to its elimination half-life, which ranges from 8 to 59 h, making it difficult to handle that may be a problem, particularly in minor surgeries.¹¹ However, other studies have used methadone to control acute postoperative pain in short-duration surgical procedures, such as cholecystectomies.¹² Its multimodal profile contributes to postoperative pain management. The R(–) isomer of methadone has β -agonist activity, while its S(+) isomer is almost inactive at that receptor. However, this isomer has NMDA receptor antagonist activity. Consequently, there is synergism between the

R(–) and S(+) isomers of methadone in promoting antinociceptive effect.¹³

The aim of this study was to compare the repercussions on postoperative analgesia and the occurrence of its adverse effects (nausea, vomiting, and respiratory depression) in the first 36 postoperative hours of myocardial revascularization surgeries provided by a dose of methadone or morphine administered at the end of surgery.

Methods

This study was approved by the Research Ethics Committee of the *Universidade do Sul de Santa Catarina*, through registration No. 1.049.850, on May 5, 2015. It was also registered in the *Registro Brasileiro de Ensaio Clínicos* No. RBR-8spkx9.

A randomized, double-blind, phase IV parallel trial was conducted. Patients of both sexes, older than 18 years, with physical status classification by the American Society of Anesthesiologists – ASA III or IV, who underwent coronary artery bypass grafting without cardiopulmonary bypass were selected. Participants gave written informed consent during the preanesthetic visit.

For sample size calculation, we consider the percentage of non-exposed positives; that is, satisfactory analgesia in 50% of the patients receiving morphine (Control Group) and 80% among the exposed positives; (Intervention Group) with a 95% confidence level and study power of 80%, and we obtained a minimum sample necessary for the study of 80 patients (40 in each group). Patients taken illicit drugs, those with a history of allergies to any of the medications used in the study, and those who had to remain intubated postoperatively for more than 12 h were excluded.

Patient randomization was performed by blocks with a sequence of four participants. Patients were allocated randomly by blocks into two groups: MeG (methadone) and MoG (morphine). The blocks were drawn by the research team and passed on to the head of anesthesiology to determine the drug used. Both the investigators and research assistants, responsible for data collection, and the patients were blind to the allocated groups, ensuring study blindness. In the operating room, all patients were monitored with invasive blood pressure, cardioscopy, pulse oximetry, capnography, temperature, diuresis, and central venous pressure. Induction of anesthesia was performed with sufentanil ($0.5 \mu\text{g}\cdot\text{kg}^{-1}$) and a $10 \mu\text{g}$ bolus as needed, etomidate ($0.2 \text{ mg}\cdot\text{kg}^{-1}$), and rocuronium ($0.1 \text{ mg}\cdot\text{kg}^{-1}$).

Anesthesia was maintained with sufentanil ($0.25\text{--}0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$); sevoflurane (0.5–1 MAC). At the end of anesthesia, MeG received methadone ($0.1 \text{ mg}\cdot\text{kg}^{-1}$ corrected weight) or MoG received morphine ($0.1 \text{ mg}\cdot\text{kg}^{-1}$ corrected weight).

The anesthetic dosage calculation for induction and maintenance of anesthesia had as reference the ideal weight (IW) for rocuronium and corrected weight (CW) for etomidate in which $\text{IW} = \text{height} - 100 \text{ cm}$ for men and $\text{height} - 105 \text{ cm}$ for women and $\text{CW} = \text{IW} + [0.4 \times (\text{real weight}) - \text{IW}]$. At the end of procedure the patient was immediately taken to the ICU, intubated, where the postoperative follow-up was performed. The ICU professionals were blind to which of the groups the patients were assigned

to and according to the ICU medical and nursing team criteria received intravenous dipyrone (1 g) every 6 h continuously (IV). And if there was a complaint of moderate or severe pain, intravenous morphine ($0.03 \text{ mg}\cdot\text{kg}^{-1}$) was given, with a limit of $0.1 \text{ mg}\cdot\text{kg}^{-1}$ in 4 h. In case of nausea or vomiting, metoclopramide hydrochloride (10 mg IV) was given.

Duration of anesthesia in minutes, number of doses, and type of analgesic and antiemetics required during the postoperative period were recorded, as well as the occurrence of possible adverse reactions, such as nausea, vomiting, and respiratory depression. These reactions were observed by the nurses and/or research team during ICU admission. Respiratory depression was considered when there were eight respiratory movements or less per minute and/or need for reintubation. The research team with the help of trained anesthesiology nurses and residents applied the numerical scale of pain at 12, 24, and 36 h post-operatively. Time to first analgesic administration and extubation time were also recorded, in agreement with the ICU's on-call staff medical records. All measurements were made by blinded researchers.

The numerical pain scale ranges from 0 to 10, in which 0 = no pain and 10 = the worst pain possible.¹⁴ In addition, categorically 0–3 is considered mild pain, 4–7 moderate pain, and 8–10 severe pain.¹⁵

For sample size calculation, the OpenEpi program, version 2.3.1, was used. Data collected were registered in a database created using the public domain software Epi-data, version 3.1 (EpiData Association, Odense, Denmark). Statistical analysis was performed using Statistical Product for Service Solutions software (SPSS for Windows v20 Chicago, IL, USA). Descriptive epidemiology was used to present the data; qualitative variables were presented as proportions and quantitative variables as measures of central tendency and dispersion. For analysis of quantitative variables, Kolmogorov–Smirnov test was used for normally distributed data. Student's *t*-test was used to compare means, using parametric statistic. In cases of non-normal distribution, non-parametric statistics were used applying Wilcoxon–Mann–Whitney *U* test. In order to verify the association between the variables of interest, Pearson chi-square test was used for categorical variables.

As a measure of effect, the relative risk reduction or efficacy of methadone compared to the control group was calculated. For this, satisfactory analgesia was considered when the patient presented results below 3 in the three pain scale measurements. In addition, number needed to treat (NNT) and number needed to harm (NNH) regarding the use of methadone were calculated, considering satisfactory analgesia and occurrence of adverse drug reactions. Data analysis was performed on an intention to treat. The level of significance was 95%.

Results

A total of 100 patients submitted to coronary artery bypass surgery, from June 2015 to March 2016, were evaluated; 63% were men and there was no proportional difference between groups regarding sex (p -value = 0.534). Fig. 1 shows the flowchart for selection of study participants.

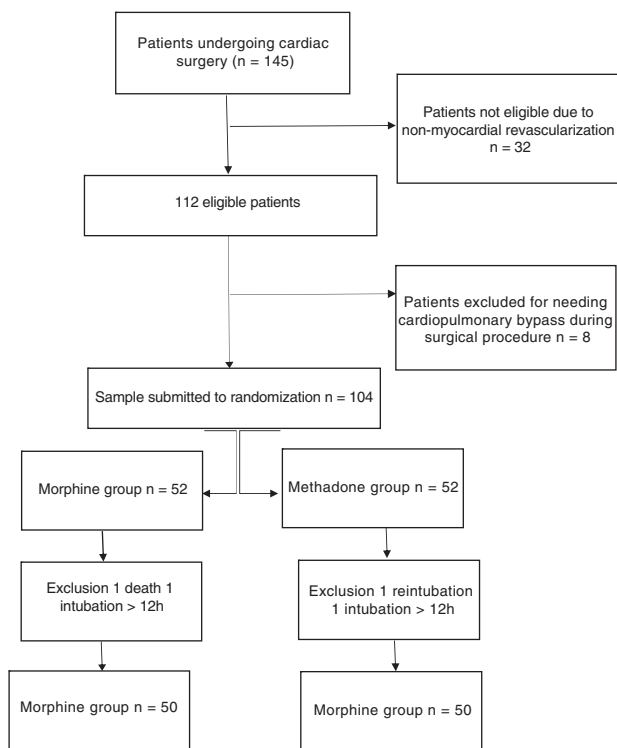


Figure 1 Flowchart of selection of study participants.

Table 1 shows the clinical and procedural characteristics and comparison of groups: morphine (MoG, control group) and methadone (MeG, intervention group).

Table 2 shows the postoperative distribution of variables. If we consider the numerical scale of pain in which 0 = no pain and 10 = the worst pain possible, the range was between 0 and 10 in 36 h.

Of the interviewees, 3% were sedated and could not respond to the pain scale. In this case, prolonged extubation time was considered an adverse effect. Table 3 shows the distribution of groups regarding efficacy and safety of analgesics used. For definition of efficacy, analgesia equal to or less than three (considered as mild pain) was used as the cut-off point on the numerical pain scale through the follow-up time (36 h).

Taken Table 3 data into consideration, the methadone efficacy as a postoperative analgesic effect, calculated by

relative risk reduction, was 22%. The NNT for a favorable event of satisfactory analgesia in the first 36 h was six patients and the NNH, that is, an adverse reaction to methadone, was equal to 16 patients.

Discussion

Methadone group had greater analgesia within 24 h after surgical procedure and required less use of morphine in the period. However, the time elapsed between the end of surgery and use of analgesic during ICU stay was lower than that of control group. If we consider satisfactory analgesia equal to or less than three with a 36-h pain scale and consider mild pain as 'no pain', the methadone efficacy was 22% higher than morphine.

Opioids are traditionally used for pain control from the first to the third day after cardiac surgery; it should be noted that the intermittent administration of short-acting opioids, such as morphine, results in fluctuations in plasma concentrations, which may explain the relatively elevated pain levels in this patient population. This study revealed the interest of using intraoperative methadone in cardiac surgeries, since the number of opioid doses required was significantly lower in methadone group at the end of anesthesia.

The use of methadone at the end of anesthesia allowed for more effective analgesia, so that during the first 36 postoperative hours the number of patients requiring analgesia was lower with methadone. In addition, patient satisfaction with the quality of analgesia in this group resulted in a pain score also lower than that of morphine group and, even so, the time required for extubation was not prolonged.

The results of the present study are similar to those reported by Murphy et al.¹⁶ that concluded that methadone (0.3 mg.kg⁻¹) used in induction of anesthesia for cardiac surgery resulted in a significant reduction of postoperative analgesic requirement; better pain scores, better pain perception by the patient, and improved pain management for 72 h after tracheal extubation, in addition to the non-observation of adverse events related to methadone administration.

However, Gottschalk et al.¹⁷ reported less opioid use postoperatively only after 48 h of methadone administration. The lower need for opioids in the postoperative period by those who received methadone may justify the lower incidence of nausea and vomiting in this group, which is quite

Table 1 Patient demographics and anesthesia/surgery data.

| Variable | MoG (n = 50) | MeG (n = 50) | p-Value ^a |
|---------------------------|---------------|----------------|----------------------|
| Age (years) | 62.4 ± 9.0 | 63.0 ± 10.2 | 0.756 ^b |
| Weight (kg) | 69.4 ± 11.7 | 71.78 ± 12.1 | 0.314 ^b |
| Height (m) | 1.63 ± 0.08 | 1.65 ± 0.08 | 0.309 |
| Sufentanil dose (µg) | 150.8 ± 42.9 | 160.12 ± 38.1 | 0.285 |
| Duration of surgery (min) | 187.2 ± 46.6 | 201.1 ± 52.4 | 0.104 |
| Extubation time (min) | 226.8 ± 153.2 | 247.96 ± 213.5 | 0.327 |

Data presented as mean and standard deviation.

MeG, methadone group; MoG, morphine group; kg, kilograms; m, meters; µg, micrograms; min, minutes.

^a Wilcoxon-Mann-Whitney U test.

^b Student's t-test.

Table 2 Postoperative analgesia, use of analgesics, and adverse events.

| Variable | MoG (n = 50) | MeG (n = 50) | p-Value |
|----------------------------------|---------------|---------------|--------------------|
| <i>Pain scale</i> | | | |
| 12 h | 4.7 ± 2.6 | 4.2 ± 2.7 | 0.186 ^a |
| 24 h | 2.9 ± 2.6 | 1.9 ± 2.2 | 0.029 ^a |
| 36 h | 0.5 ± 1.1 | 0.5 ± 1.2 | 0.657 ^a |
| Time to 1st analgesic (min) | 269.4 ± 252.9 | 145.9 ± 178.5 | 0.005 ^a |
| Morphine use ^d | 43% | 29% | 0.002 ^b |
| Metoclopramide use ^d | 27% | 18% | 0.070 ^b |
| Adverse effects ^d | 19% | 16% | 0.529 ^b |
| Nausea ^d | 19% | 15% | 0.457 ^c |
| Vomiting ^d | 3% | 5% | 0.248 ^c |
| Respiratory failure ^d | 1% | 2% | 0.434 ^c |

%, percentage; MeG, methadone group; MoG, morphine group; h, hours; min, minutes.

^a Wilcoxon–Mann–Whitney *U* test.

^b Pearson's chi-square test.

^c Fisher exact test.

^d Relative to percentage of patients.

Table 3 Satisfactory analgesia and occurrence of adverse events in the first 36 postoperative hours.

| | MoG (n = 50) | MeG (n = 50) | p-Value ^a |
|---------------------------|--------------|--------------|----------------------|
| <i>Pain analgesia</i> ≤ 3 | | | |
| Failure | 36 (72%) | 28 (56%) | 0.096 |
| Success | 14 (28%) | 22 (44%) | |
| <i>Adverse reaction</i> | | | |
| Yes | 19 (38%) | 16 (32%) | 0.529 |
| No | 31 (62%) | 34 (68%) | |

%, percentage; MoG, morphine group; MeG, methadone group.

^a Pearson's chi-square test.

interesting in interventions with greater pain potential, such as sternotomy.

Another fact observed was the time to first analgesic administration that was significantly lower in methadone group. This diverges from the results of Udelsmann et al.¹⁸ whose methadone use in the induction of anesthesia for cardiac surgery allowed more prolonged analgesia, so that the first dose of analgesic in patients receiving methadone was only given almost 4 h after that of the morphine group. In another double-blind study comparing methadone and morphine for upper abdominal surgeries, the mean time required for rescue analgesia was significantly longer in patients receiving methadone (21 vs. 6 h).¹⁴ One possible explanation may have been the dose chosen, which interferes with the drug clearance time, and duration of methadone effect, which is influenced by the patient's individual characteristics. In this case, the methadone dose with concentrations higher than 20 mg is recommended, always considering patient's age, surgical procedure, and respiratory rate.^{19,20}

Intravenous morphine shows a peak of analgesic effect at 20 min after its administration and the duration of analgesic action is 4–5 h.²¹ It is also worth noting that, even if there is no statistical difference between groups, on average, the

duration of surgery in methadone group was higher than in morphine group.

Because of its prolonged action, methadone has become an interesting analgesic option in postoperative pain management, particularly in major surgeries with prolonged recovery time, such as cardiac surgeries. However, methadone like other opioids has among the possible side effects nausea, vomiting, pruritus, and dose-dependent respiratory depression, which may delay extubation time and increase institutional costs. Although already used in other countries, it is only recently available for parenteral use in Brazilian institutions.

Methadone efficacy was 22% higher than that of morphine. The NNT result of six (considered a high-impact treatment of less than 25) and NND of 16 reveal that methadone is a good, effective, and safe therapeutic option for postoperative analgesia when administered at the end of surgery. It should be emphasized that the control group in this study is morphine (which was considered the conventional treatment); therefore, these are satisfactory indexes that aid in clinical decision, as they present the risk-benefit of both drugs.

Among the limitations of this study, it should be emphasized that pain is extremely subjective and difficult to measure, despite the option of using a scale already validated for its measurement, but that may influence the results of this study. The variations in pain severity in 24 h, despite presenting a statistically significant difference, are clinically similar and fully satisfactory for postoperative pain in this type of procedure. No standardized measure was used for assessing sleepiness, which may have influenced the perception of pain. Therefore, multicenter studies with a follow-up period of more than 36 h are required to prove this data.

This work contributes to the knowledge of using methadone as a postoperative analgesic option in cardiac surgeries. This drug is poorly used for this purpose by anesthesiologists, although it is an interesting and inexpensive option, effective and safe, compared to other methods used in major surgeries.

Conclusion

Based on data found, methadone was effective for analgesia in patients undergoing coronary artery bypass grafting without cardiopulmonary bypass.

Conflicts of interest

The authors declare no conflicts of interest.

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