

Multimodal analgesia versus patient-controlled analgesia in the management of acute postoperative spinal pain: systematic review and meta-analysis

Analgesia multimodal versus analgesia controlada pelo paciente no tratamento da dor aguda pós-operatória da coluna: revisão sistemática e meta-análise

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ABSTRACT

BACKGROUND AND OBJECTIVES: Spine diseases have a high annual prevalence and are the main causes of years lived with disability and chronic pain. Among the postoperative analgesic control options, patient-controlled analgesia (PCA) and multimodal analgesia (MMA) have shown good clinical results. This meta-analysis seeks new evidence to help in the treatment of acute postoperative pain in patients undergoing spinal surgery.

CONTENTS: The following databases were used: Cochrane Central Register of Controlled Trials, Medline and Embase. Studies that compared two post-surgical analgesic interventions were included; MMA and PCA. The parameters evaluated were: analgesic effect; opioid consumption; length of hospital stay; and adverse effects. Registration of the systematic review protocol: (PROSPERO CRD42023446627). There was no statistical difference when assessing analgesic improvement comparing MMA to PCA (MD -0.12 [-0.41, 0.17] 95%CI with p=0.69). There was a statistical difference, with lower opioid consumption in

MMA compared to PCA (MD -3.04 [-3.69, -2.39] 95%CI with p=0.0002). Statistically significant difference regarding length of hospital stay in favor of MMA (MD -13.17 [-16.98, -9.36] 95%CI with p=0.00001), and significantly lower incidence of nausea and vomiting in patients undergoing MMA in compared to PCA (OR 0.26 [0.11, -0.64] 95%CI with p=0.003).

CONCLUSION: MMA was equivalent to PCA in the treatment of acute postoperative spinal pain, with the significant clinical advantage and safety of lower amounts of infused opioids, shorter hospital stay and lower incidence of adverse effects.

Keywords: Acute pain, Analgesia, Combined modality therapy, Low back pain, Modality therapy, Neck pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: As doenças da coluna apresentam alta prevalência anual e são as principais causas de anos vividos com incapacidade e de cronificação da dor. Dentre as opções de controle analgésico pós-operatória, a analgesia controlada pelo paciente (ACP) e a analgesia multimodal (AMM) apresentam bons resultados clínicos. O objetivo deste estudo foi buscar novas evidências que auxiliem no tratamento da dor aguda no pós-operatório do paciente submetido à cirurgia da coluna.

CONTEÚDO: As bases de dados utilizadas: *Cochrane Central Register of Controlled Trials*, Medline e Embase. Foram incluídos estudos que compararam duas intervenções analgésicas pós cirúrgicas; AMM e ACP. Os parâmetros avaliados foram: efeito analgésico; consumo de opioide; tempo de internação hospitalar e efeitos adversos. Registro do protocolo de revisão sistemática: (PROSPERO CRD42023446627). Não houve diferença estatística quando avaliadas a melhora analgésica comparando a AMM à ACP (MD -0,12 [-0,41, 0,17] 95%CI com p=0,69). Houve diferença estatística, com menor consumo de opioide na AMM em comparação à ACP (MD -3,04 [-3,69, -2,39] 95%IC com p=0,0002). Diferença estatística significativa com relação ao tempo de permanência hospitalar a favor da AMM (MD -13,17 [-16,98, -9,36] 95%IC com p=0,00001), e incidência significativamente menor de náuseas e vômitos nos pacientes submetidos a AMM em comparação a ACP (OR 0,26 [0,11, -0,64] 95%IC com p=0,003).

CONCLUSÃO: A AMM foi equivalente à ACP no tratamento da dor aguda pós-operatória da coluna, com a significativa vantagem clínica e a segurança de menores quantidades de opioides

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HIGHLIGHTS

- Multimodal analgesia presents lower rates of opioid consumption than patient-controlled analgesia.
- Multimodal analgesia presents a shorter hospital stay and lower rates of adverse effects than patient-controlled analgesia.
- Clinical efficacy and safety of multimodal analgesia compared to patient-controlled analgesia.

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infundidos, menor tempo de internação hospitalar e menor incidência de efeitos adversos.

Descritores: Analgesia controlada pelo paciente, Cervicalgia, Dor Aguda, Dor lombar, Terapia combinada.

INTRODUCTION

Neck pain and low back pain have an annual prevalence of 14.4%¹ and 30%² respectively and are among the clinical conditions with the highest rates of years lived with disability^{3,4}. Low back pain is the main cause of chronic pain, accounting for 35% of all cases⁵, and is responsible for a large part of the socio-economic loss due to absenteeism and premature retirement in the world⁶.

US estimates show that in 2016, the cost of diagnosing and treating spinal diseases was 134 billion dollars⁷. Of the total 313 million surgeries performed worldwide each year, the United States of America was responsible for carrying out approximately 500,000 procedures related to lumbar diseases alone⁸.

The incidence of acute pain (AP) after spinal surgery can reach 80%⁹. Of these patients, 86% reported moderate, severe or extreme pain^{10,11}, and 40% had persistent pain⁸. Ineffective control of pain is the main risk factor for its chronification, so much so that a 10% increase in the intensity of postoperative pain was associated with a 30% increase in the prevalence of chronic pain^{12,13}.

Inadequate post-operative analgesic control can increase the length of hospital stay, cause greater immobilization and consequent personal dissatisfaction¹⁴. The costs related to chronic pain control are 50% higher, added to the increased risk of medical complications due to prolonged use of non-steroidal anti-inflammatory drugs and opioids⁸.

Among the various analgesic options available, patient-controlled analgesia (PCA) has been shown to be a safe and effective method in post-surgery, in the control of moderate and severe pain^{15,16}. The drug is infused intravenously or epidural, continuously or in boluses, to improve pain control without abrupt fluctuations in plasma levels^{17,18}.

With the development of PCA in the 1970s, rapid and effective control of postoperative AP was observed. However, some authors have noted an increase in the incidence of adverse effects, especially nausea and vomiting related to the excessive use of opioids¹⁹. In this scenario, the improvement of multimodal analgesia (MMA) in the treatment of postoperative pain has become a viable option to PCA²⁰.

MMA aims to relieve pain using multiple mechanisms of action, through an additive or even synergistic effect between different classes of drugs and non-pharmacological interventions, acting on both the peripheral and the central nervous systems²¹. Its aim is to reduce the individual doses of drugs and consequently the incidence of their adverse effects^{21,22}.

Pain assessment and control are essential but remain a challenge in postoperative clinical management²³. This study seeks new evidence to help in the treatment of AP, since there is no similar study in the literature comparing the clinical outcomes of MMA and PCA in the postoperative period of patients undergoing spinal surgery.

The aim of this study was to compare the effects of two interventions, MMA and PCA, on post-surgical spinal disorders, with the following parameters being evaluated: analgesic effect, opioid consumption, length of hospital stay and adverse effects.

CONTENTS

The search for relevant studies was carried out in March 2023 in a single phase. The search results were limited to studies published in English from 2000 onward and no publication restrictions were applied. The databases used in the search were the Cochrane Central Register of Controlled Trials (CENTRAL), Medline and Embase. The search strategies can be found in table 1.

Table 1. Database search strategy

Cochrane	Multimodal analgesia in Title Abstract Keyword AND patient controlled analgesia in Title Abstract Keyword AND spine surgery in Title Abstract Keyword - (Word variations have been searched)
Medline	(((((multimodal analgesia[Title/Abstract]) OR (Multimodal Treatment[Title/Abstract]) OR (Therapy, Combined Modality[Title/Abstract])) AND (Patient Controlled Analgesia[Title/Abstract]) AND (spine[Title/Abstract]) OR (Vertebral Column[Title/Abstract]) OR (Spinal Column[Title/Abstract]) OR (lumbar[Title/Abstract]) OR (low back[Title/Abstract]) OR (neck[Title/Abstract]) OR (cervical[Title/Abstract]))
Embase	('analgesia multimodal' OR (('analgesia'/exp OR analgesia) AND multimodal)) AND 'patient-controlled analgesia'

Controlled clinical trials, randomized or not, and observational studies carried out in adults comparing the two interventions; multimodal analgesia and PCA, in postoperative pain from spinal diseases were included. Studies involving children were excluded, even if the data was separated or the proportion of children was small and/or balanced between the intervention groups, pharmacological trials, studies in animals or with biological interventions and acupuncture and its variants, as well as traditional Chinese medicine.

The focus was on short-term outcomes, preferably assessed during the postoperative hospitalization period.

- Continuous outcomes: Visual Analog Scale (VAS) from zero to 10, amount of opioids administered and length of postoperative hospital stay (in hours).

- Dichotomous outcomes: adverse effects (nausea and vomiting).

Two of the authors independently examined the search results and assessed the studies potentially eligible for inclusion. In the event of disagreement, a third author made the tie-breaker. Initial decisions on study eligibility were based on the abstracts. Journal titles, authors' names or supporting institutions were not masked at any stage. The final inclusion in the study was by consensus after evaluation of the full article.

All methodological details of the studies, participants, interventions and results were assessed. Data management and the application of Review Manager 2014 were carried out by one of

the authors. The risk of bias was assessed independently by the authors, without masking the source and authorship of the studies. Disagreements were resolved through discussion. The tool described in the Cochrane Handbook for Systematic Reviews of Interventions²⁴ was used to assess the methods of randomization, blinding, data integrity and selection of results.

Mean differences (MD) and odds ratios (OR) with their respective 95% confidence intervals (CI) and statistical probabilities (p) were calculated for each selected study. The interpretation²⁴ of the Cochrane Handbook for Systematic Reviews of Interventions²⁴ was used to assess the heterogeneity of the studies: degrees of heterogeneity (I^2) of 0% to 40% may not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity.

The results were grouped into comparable subgroups using continuous effects and dichotomous effects models. The selection of the presentation model was determined by considering the extent of clinical heterogeneity. Two analyses were established, the first being: analgesic effect, opioid consumption, and length of hospital stay; and the second: incidence of adverse effects.

The protocol for this systematic review was registered in the International prospective register of systematic review (PROSPE-

RO)²⁵, in accordance with the PRISMA-P guideline (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols)²⁶, under registration number CRD42023446627.

RESULTS

The systematic search of the databases retrieved 927 articles. Thirty-seven duplicate studies were excluded and the titles of the remaining 890 were analyzed, with 17 articles selected for their relevance. When they were read in full and the inclusion and exclusion criteria were assessed, 13 articles were excluded. The remaining four articles²⁷⁻³⁰ were included and systematically reviewed (Figure 1). All tests were level 3 evidence according to the Oxford Center for Evidence - based Medicine criteria³¹.

The total number of participants evaluated in the study was 679, 324 were men (47.8%) and 355 were women (52.2%), 229 participants underwent MMA (33.7%), and the remaining 450 underwent PCA (66.3%). The studies covered various surgical modalities in different regions of the spine. The interventions for treating post-operative pain were also different between the articles. Their individual characteristics are listed in the table below (Table 2).

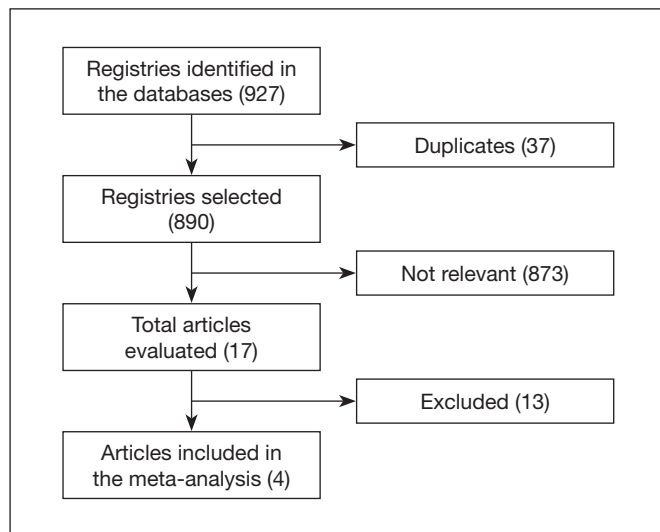


Figure 1. Article selection flow chart.

Analgesic effect

The four articles²⁷⁻³⁰ compared the analgesic response using VAS. In all of them, regardless of the analgesic protocol used, there was a significant improvement in the VAS score when comparing pre- and post-operative pain. However, there was no statistical difference when the analgesic improvement was compared to MMA and PCA (MD -0.12 [-0.41, 0.17] 95%CI with p=0.42). The degree of heterogeneity between the articles was substantial ($I^2=65%$) (Figure 2).

Opioid consumption

All the articles selected²⁷⁻³⁰ compared opioid consumption in postoperative pain. The volume of opioids in one of the articles was standardized, using a bioavailability ratio of 3:1. Statistical differences in opioid consumption were observed in all of them, and it was significantly lower in MMA compared to PCA (MD -3.04 [-3.69, -2.39] 95%CI with p<0.0001). The degree of heterogeneity between the articles was moderate ($I^2=60%$).

Table 2. Characteristics of the selected studies

Authors	Surgical procedure	Group	Number of patients	Type of intervention
Bohl et al. ³⁰	Anterior cervical decompression and arthrodesis	MMA	55	Tramadol, codeine with paracetamol, cyclobenzaprine, pregabalin and oxycodone
		PCA	184	Fentanyl citrate, cyclobenzaprine and morphine
Choi et al. ²⁷	1- or 2-level lumbar arthrodesis	MMA	34	Celecoxib, acetaminophen, pregabalin oxycodone with naloxone
		PCA	66	Fentanyl, nefopan, propacetamol
Rajpal et al. ²⁸	Multiple spine surgeries	MMA	100	Oxycodone, gabapentin, acetaminophen
		PCA	100	Morphine or hydromorphone
Singh et al. ²⁹	Minimally invasive transforaminal arthrodesis	MMA	39	Oxycodone, pregabalin, cyclobenzaprine, codeine and paraceramol and tramadol
		PCA	100	Morphine, cyclobenzaprine and fentanyl

PCA = patient-controlled analgesia; MMA = multimodal analgesia.

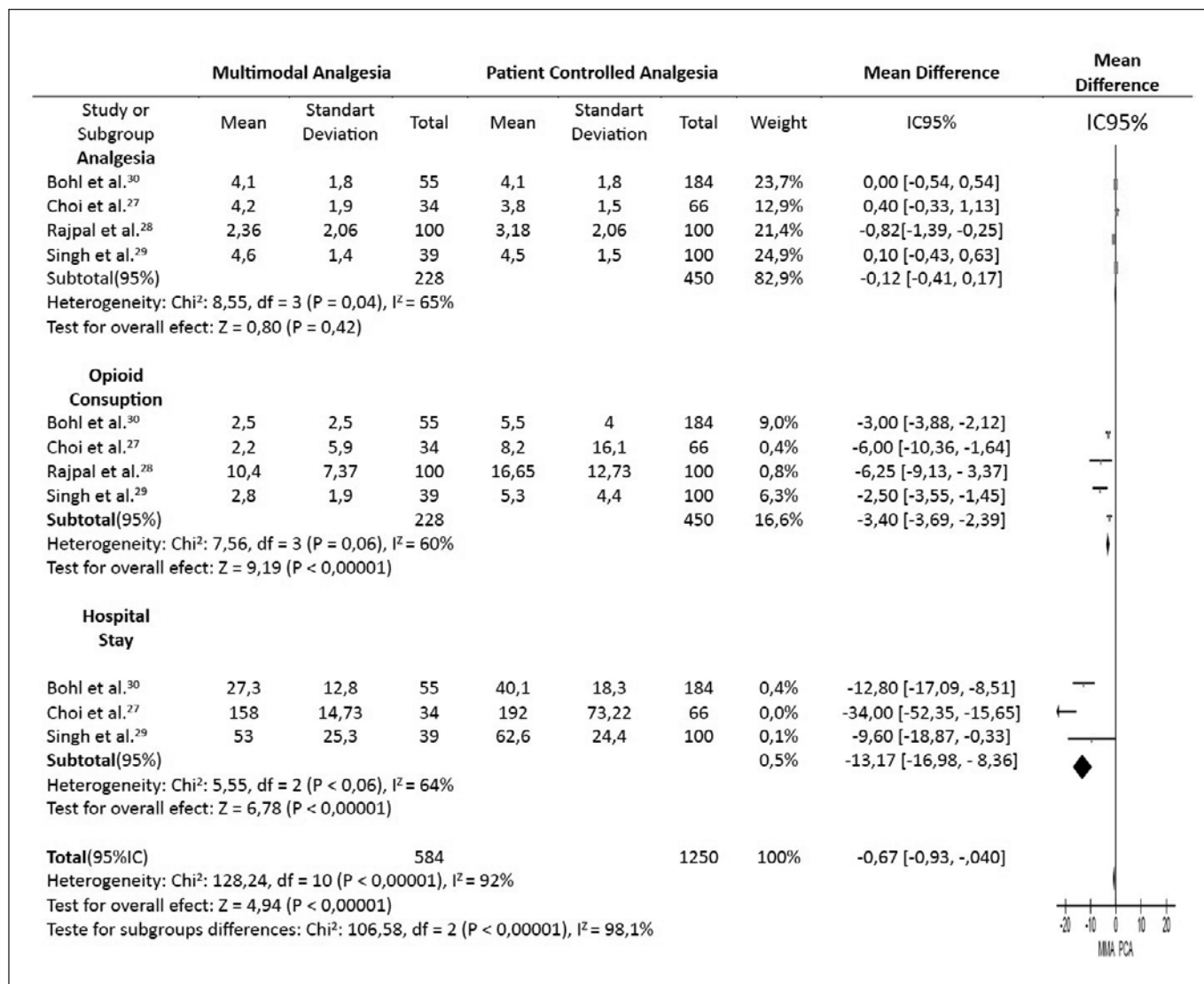


Figure 2. Forest plots: Comparison between multimodal analgesia and patient-controlled analgesia

Length of hospital stay

Three of the four articles^{27,29,30} assessed the length of hospital stay, comparing patients undergoing MMA with those undergoing PCA. In one of them, the length of stay was given in days, which, for standardization reasons, was converted to hours. All the articles showed statistically significant differences in favor of MMA when comparing to PCA (MD -13.17 [-16.98, -9.36] 95%CI with p<0.00001). The degree of heterogeneity between the articles was substantial (I²=64%).

Adverse events

Of the four articles, three^{27,29,30} compared the incidence of adverse effects. For reasons of standardization, only the most prevalent were assessed, in this case nausea and vomiting. The statistical analysis showed a significant difference, with lower incidence rates of nausea and vomiting in patients undergoing MMA compared to PCA (RR0.26 [0.11, -0.64] 95%CI with p=0.003). The degree of heterogeneity between the articles was substantial (I²=62%) (Figure 3).

Evaluation of heterogeneity

The Chi-square test used to assess the significance of heterogeneity in the results indicated a value of I²=92% for continuous results and 62% for dichotomous results, showing considerable heterogeneity between the studies. Sensitivity and meta-regression analysis was not possible due to the small number of studies available, four eligible studies, for the composing of the systematic review.

Assessment of risk of bias

All the studies included in this review were assessed according to the Cochrane Handbook for Systematic Reviews of Interventions²⁴. The four articles were classified as having a moderate risk of bias, with agreement between the reviewers. The risk of bias assessments are represented in figure 4, showing each included study and how strong it is in several quality criteria for that specific type of study.

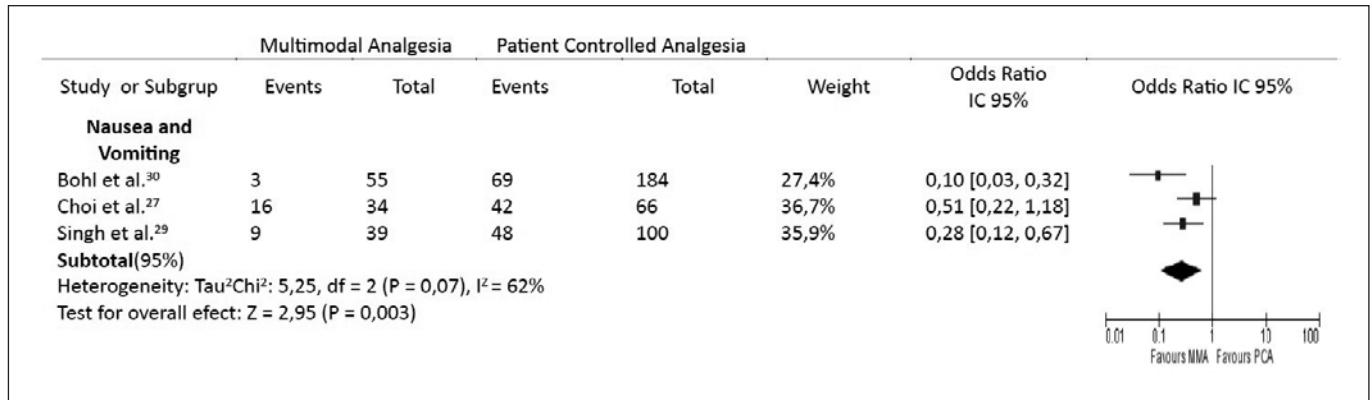


Figure 3. Forest plot: Comparison between multimodal analgesia and patient-controlled analgesia, dichotomous variable; incidence of nausea and vomiting.

	Bohl et al. ³⁰	Choi et al. ²⁷	Rajpal et al. ²⁸	Singh et al. ²⁹
Randomized sequence generation	-	-	-	-
Concealment of allocation	-	-	-	-
Blinding of participants and professionals	-	-	-	-
Blinding of outcome evaluators	?	?	-	-
Incomplete outcomes	+	+	+	+
Selective outcome report	+	+	+	+
Other sources of bias	+	+	+	+

Figure 4. Summary of the risk of bias according to the assessment of methodological quality.

Adapted from <https://training.cochrane.org/handbook>. Low risk of bias (+), undetermined risk of bias (?), high risk of bias (-).

DISCUSSION

The analgesic effects provided by MMA were shown to be equivalent to PCA in three of the articles evaluated and significantly superior in one of them. The clinical efficacy of MMA in reducing postoperative AP has been previously confirmed^{32,33}, so much so that patients undergoing an MMA protocol in the postoperative period of total hip arthroplasty were able to perform early mobilization and rehabilitation exercises in the immediate postoperative period³⁴.

The results showed that patients who underwent MMA after spinal surgery consumed significantly less opioids during hospitalization than patients treated with PCA. This lower opioid consumption associated with MMA is consistent with observations made by other authors who evaluated patients undergoing invasive spinal procedures³² and total arthroplasty³⁵.

Although the intensity of pain is one of the main causes of prolonged hospital stays, and no difference in analgesia was found between the two interventions, patients undergoing MMA protocols had a significantly shorter hospital stay than patients undergoing PCA^{35,36}. Recent studies have shown that patients undergoing MMA protocols were more likely to

meet discharge requirements in the immediate postoperative period^{32,37}.

The analysis showed that patients undergoing MMA had statistically lower rates of nausea and vomiting during hospitalization than patients treated with PCA. The lower incidence of these effects may be associated with lower opioid consumption during hospitalization^{38,39}. As well as improving the patient experience, the lower rates of adverse effects may also contribute to the difference observed between the lengths of hospital stay.

The significant heterogeneity shown by the I² values for both continuous and dichotomous variables may be associated with the individual characteristics of each study^{40,41}. There were differences in the results, specially regarding the number and socio-demographic data of the participants, and between the surgical interventions in the various regions of the spine, as well as the different analgesic strategies used in MMA and PCA (Table 2). All four studies selected were retrospective, with a lower level of evidence when compared to prospective randomized studies. In these studies, participants are often recruited by convenience sampling and are therefore not representative of the general population, being mainly prone to selection bias, due to failure to allocate between groups, lack of blinding and treatment concealment, as shown in figure 2⁴².

CONCLUSION

The results of this study demonstrate the clinical significance of MMA in the treatment of postoperative AP in spinal surgery. MMA was equivalent to PCA in controlling AP, with lower volumes of opioids administered, shorter hospital stays and lower rates of adverse effects.

However, the quantity and quality of studies available in the literature were low, heterogeneity was significant among the articles selected, and a moderate risk of bias was identified. Further double-blind, multicenter randomized controlled clinical trials could validate the results of this systematic review and meta-analysis, confirming the safety and efficacy of the clinical applicability of MMA in the postoperative period of spinal surgery.

AUTHORS' CONTRIBUTION

Lucas de Melo Castro Deligne

Statistical Analysis, Data Collection, Conceptualization, Project Management, Research, Methodology, Writing – Preparation of the Original, Writing - Review and Editing, Software, Supervision

Guilherme Baldez Pinheiro

Statistical Analysis, Funding Acquisition, Resource Management, Methodology, Writing - Review and Editing, Validation, Visualization

Marcelo de Oliveira Peres

Statistical Analysis, Conceptualization, Resource Management, Project Management, Research, Methodology, Supervision, Validation, Visualization

André Moreira Castilho

Statistical Analysis, Writing - Preparation of the Original, Writing - Review and Editing

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