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Original Article

Intraoperative methadone for postoperative pain management - systematic review protocol

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Abstract: Methadone is a long acting opioid initially used to treat opioid withdrawal symptoms. It has been suggested that methadone, when given as a single bolus while under anesthesia, provides good postoperative analgesia and is associated with minimal risk of opioid adverse events. Several small studies have investigated the use of methadone for postoperative analgesia with some promising results. Here we describe our protocol for a meta-analysis to investigate the postoperative analgesic effect of methadone.

Keywords: Methadone, postoperative pain, opioids

Introduction

Despite the advances in perioperative care, pain remains a common adverse event in the postoperative period. Postoperative pain is distressing for the patients, limits mobilization after major surgeries, increases the risk of atelectasis and infection; it is also associated with delayed recovery and impaired long-term function [1]. The current best practice for managing postoperative pain involves multimodal analgesia, with appropriate use of regional anesthesia, regular non-opioid regime, with judicious use of opioids [2]. While regional anesthesia can provide reliable and long-lasting postoperative analgesia, it is often limited by the availability of skilled practitioners and is contraindicated by several patient and surgical factors. On the other hand, interval dosing of systemic analgesia opioid and non-opioid tend to result in fluctuating plasma concentration, therefore varying analgesic efficacy [3].

Methadone is a long acting opioid initially used to treat opioid withdrawal. It is a full agonist of the μ-opioid receptor, however with lower affinity to the receptor when compared to morphine [4]. In addition, methadone is also a weak N-methyl-D-aspartate (NMDA) receptor antagonist [5], which has been suggested to reduce opioid induced hyperalgesia and ameliorate neuropathic pain [6, 7]. When administered intravenously, methadone is estimated to reach peak effector site concentration in 8 minutes, with an elimination half-life of 24-36 hours [8].

In the past few years, methadone has attracted significant attention as a potential postoperative analgesic agent. When given intraoperatively (IV), it would in theory reach peak effector site concentration and therefore peak respiratory depressant effect while the patient is under anesthesia, and subsequently provide sustained analgesic effect due to its long half-life. This eliminates the 'peak and trough' effect associated with interval dosing, and minimizes the risk of inadequate analgesia as well as over-sedation. Several recent trials have reported that intraoperative IV methadone is associated with significantly better postoperative analgesia. However, such studies are generally limited by the relatively small sample sizes. Following the guideline proposed by Cochrane collaboration [9], we propose this meta-analysis in order to summarize the findings of the relevant studies and attempt to aggregate the results the postoperative analgesic efficacy of methadone.

Methods

Study objectives

Primary objective: To determine the analgesic efficacy of intraoperative methadone in patient undergoing major surgical procedures, measured by 24-hour opioid requirement postoperatively.

Secondary objectives: To determine the effect of intraoperative methadone on other pain related outcomes: pain score measured at different time intervals (on emergence, 1-6 hours, 7-12 hours, 13-18 hours and 19-24 hours postoperatively) and time to rescue analgesia.

To determine the risk of opioid related adverse events such as PONV and respiratory depression associated with intraoperative methadone.

To determine the effect of intraoperative methadone on patient satisfaction.

Study design

This is a protocol for a systematic review and meta-analysis of relevant randomized control trials. The protocol is registered on PROSPERO, CRD42019130872. The manuscript reporting the findings of the meta-analysis will be prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [10].

Eligibility criteria and study selection

Study design: Randomized control trials (RCT) published in English. Conferences abstracts without a clear description of the randomization process will be excluded.

Type of participants: Adult patients (>18 years old) undergoing any major surgical procedures, under general anesthesia, with expected hospital stay of longer than one day.

Intervention: Studies must compare the use of single dose, intraoperative methadone to standard practice or to other shorter acting opioids (such as morphine or fentanyl). Studies with the following characteristics will be excluded: studies without a valid comparator, studies which administers multiple dose or continuous infusion of methadone, studies where methadone is given by routes other than intravenously. We will also exclude any studies which administers regional anesthesia from the meta-analyses, but will report the relevant findings descriptively.

Outcomes of interest: Studies will need to report at least one of the outcomes below to be included in the meta-analysis.

Our primary outcome is the total opioid requirement for the first 24 hours after surgery, this includes any systemic (oral, intravenous, intramuscular and subcutaneous) opioids administered during the 24 hours from the end of the surgery, and will be converted into equivalent IV morphine dose. Our secondary outcomes include time to rescue analgesia, defined as the time elapsed in minutes, between emergence from general anesthesia, or completion of surgery, till the first dose of opioid analgesia given postoperatively; pain score up to 24 hours postoperatively; the incidence of PONV; other opioid related adverse events as well as patient satisfaction.

For our secondary outcomes, quantitative pain score such as the numerical rating scale (NRS) scores will be collated for the following time period: on emergence, at 1-6 hours, 7-12 hours, 13-18 hours and 19-24 hours postoperatively, this includes pain score at rest and on mobilization. For the purpose of PONV incidence, we will include any episodes of nausea or vomiting reported up to 24 hours after the operation. Opioid related respiratory adverse events include any signs of respiratory compromise which is not attributed to an alternative cause by the author of the studies. If there is sufficient number of studies, the above outcomes will be analyzed quantitatively according to the statistical analyses protocol outlined below, otherwise the results will be summarized qualitatively. In addition, patient satisfaction will be reported qualitatively due to the inherent heterogeneity in how it is measured.

Search strategy

We will search PubMed, Central, EMBASE, CINAHL, Google Scholar, Web of Science citation index and clinicaltrials.gov using search terms “methadone” AND (surgery OR intraoperative OR postoperative OR anesthesia). Where applicable, we will also adapt the search term to Medical Subject Headings (MeSH) terms. We also will hand search the bibliography of the included studies as well as major anesthesiology conferences from the last 3

years. We will include all studies published before the final search date, and there will be no restrictions in terms of language. The literature search, as well as subsequent assessment for inclusion will be done independently by two authors.

Data extraction

Literature search will be done by two authors independently and studies will be screened according to title and abstract; subsequently through review of full text. The result will then be compared, and discrepancies discussed. Any disagreement which could not be resolved will be decided by a third author (JL).

Data extraction will be done using a standardized pro forma on Microsoft Excel. The data will then be checked by a second author. Extracted data will include bibliographical information (author, year, PubMed ID or article URL); study design (description of control and intervention, type of surgery, number of participants); pain related outcomes (NRS score and opioid requirement at the time points outlined above, time to first rescue analgesia); other outcomes (PONV, other complications).

Risk of bias assessment

We will assess each included study using the Cochrane risk-of-bias tool for randomized trials [11], which consists of six assessment criteria: Random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data and selective reporting. Grades (low risk, high risk or unclear risk) are assigned to each criterion for all the included studies. Risk of bias assessment will be done by two authors independently and disagreements will be settled by a third author (JL).

Statistical analyses

Data synthesis: The statistical analyses will be conducted using Review Manager Version 5.3 (RevMan, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Continuous variables such as time to rescue analgesia and opioid requirement will be analyzed quantitatively using the inverse-variance meta-analysis method, and presented as mean difference (MD) ± standard deviation (SD). NRS score will be analyzed as follows: if it is reported as median and interquartile range, we will estimate the mean and standard deviation assuming normal distribution using methods described by Cochrane [9]. However, if there is evidence of significant skewing of the data (such as SD range crosses zero) in more than a half of the studies, quantitative analysis will be abandoned and the findings will only be reported descriptively.

If the spread of the data is not reported, we will attempt to contact the author of the paper. Should there be no response, we will substitute the SD with the pooled SD of the other studies within the same comparison by: [square root] ([n-ary summation](N SD2)/[n-ary summation] N).

PONV and other opioid related adverse events will be analysed quantitatively using the Mantel-Haenszel method if the outcome was described consistently in a majority of the studies. If only a small proportion of the studies reported the particular adverse event, it will be reported descriptively.

Heterogeneity assessment: Heterogeneity will be described using the I^2 statistic, which describe the percentage of the variability attributable to inconsistency rather than sampling error. I^2 greater than 50% will be considered as significant heterogeneity, and will be addressed according to the following approach. We will attempt subgroup analysis in order to identify potential sources of heterogeneity, according to the dose of methadone, the total dose of intraoperative opioid administered and the type of surgery. If any other heterogeneities in the study characteristics are identified during the data extraction, we will also attempt subgroup analysis according to those factors, and will discuss the findings as post hoc analysis. If there are no identifiable factors which contribute towards the heterogeneity, we will use the random effects model and discuss the reliability of the evidence.

Publication bias: Publication bias will be assessed using Egger's regression using methods described by Suurmond et al. [12]. *P*-values less than 0.05 will be considered significant.

Overall quality of evidence: We will use the GRADEpro Guideline Development Tool (GRADEpro GDT, McMaster University, 2015) to assess the quality of the meta-analysis findings. For the purposes of a meta-analysis based on RCTs, the quality of evidence is assigned a 'high' grade a priori, this is then down-

graded if it fulfills the following criteria: risk of bias, inconsistency, indirectness of evidence, imprecision and publication bias.

Discussion

Administration of systemic opioid require very little time and practitioner skill, but the analgesic efficacy of systemic opioid tend to demonstrate peak-and-trough fluctuation associated with interval dosing. On the other hand, continuous opioid administration (such as background infusion on patient controlled analgesia regime) is associated with the risk of over-sedation [13]. Due to its longer duration of action, methadone should theoretically provide sustained analgesia for longer period of time. When given intraoperatively, the peak respiratory depressant effect should in theory occurs while the patient is still in the operating room or the PACU, with anesthesia practitioners experienced in managing respiratory compromise, therefore providing safe and consistent postoperative analgesia. In addition, while the efficacy of NMDA antagonists in postoperative analgesia is not well studied, there are some evidence that NMDA antagonists may work in synergy with opioid analgesia [14]. Intraoperative methadone may be useful in providing postoperative analgesia in institutions with insufficient resources to provide regional anesthesia services. We hope that our proposed meta-analysis could clarify the role of methadone in providing multimodal postoperative analgesia.

Disclosure of conflict of interest

None.

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