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Efficacy of opioid combination versus single opioid for adult cancer pain: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Chronic pain is one of the most common and serious symptoms of cancer. Despite the limitations of dose titration using only one type of opioid, the effects of opioid combinations are poorly understood.

Methods and analysis This study will be conducted in accordance with the Cochrane Handbook of Systematic Reviews of Interventions 6.3. We will search the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science databases from their inception to June 2023. This review will consider all clinical trials involving patients aged ≥18 years who received opioids for chronic cancer pain. Two reviewers will independently screen and select relevant studies. The intervention will be a combination of opioids, including both strong and weak, to control cancer pain. The comparator will be set as a single opioid, with or without a placebo. For randomised controlled trials, version 2 of the Cochrane tool will be used to assess the risk of bias. For non-randomised studies, the risk of bias will be assessed using a tool for assessing the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I). The primary outcome will be pain response; if a quantitative synthesis is not appropriate, a synthesis without a meta-analysis will be undertaken. The quality of evidence for each primary outcome will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation guidelines.

Ethics and dissemination Ethical approval was not required for this systematic review and meta-analysis. The findings will be disseminated through peer-reviewed (open-access) journal publications and conference presentations. Given the widespread use of opioid-based cancer pain management in clinical practice, this study is expected to generate significant interest among physicians, many of whom are likely to review and consider the findings in the context of their clinical decision-making.

PROSPERO registration number PROSPERO CRD42023427299.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study aimed to collect all the available published literature by placing no language or study design restrictions on the inclusion criteria.
⇒ This design encompasses both strong and weak opioids, thus minimising the likelihood of missing relevant opioid studies.
⇒ Considering the rarity of clinical studies on this topic, this study includes the broadest possible time period from 1946 to the present.
⇒ The most notable limitation of this study is the heterogeneity among the studies, which occurs because the tools for assessing the pain response and measuring the effectiveness of any intervention vary across studies.

INTRODUCTION

Chronic pain is one of the most common and serious symptoms of cancer. The prevalence of cancer pain is estimated to be 59% among patients receiving active anticancer treatments.[1] Approximately, 64% of patients with advanced metastatic disease or those in the terminal stage suffer from chronic cancer pain. A recently published systematic review revealed that 39.3% of patients after curative treatment, 55.0% during anticancer treatment and 66.4% in advanced, metastatic or terminal stage of disease were in pain, highlighting that this remains a high symptom burden in patients with cancer.[2] Among strong opioids, there is no evidence supporting the superiority of one opioid over another.[3] Clinicians can select weak or strong opioids, typically weak opioids for mild to moderate pain and strong opioids for moderate to severe pain. It is essential to personalise opioid therapy based on each patient's clinical status as well as the clinician's preference or availability of a particular drug. In general, it is recommended to start and titrate the dose using a single type of opioid.[4] According to the current clinical guidelines, if the pain is not well controlled despite dose escalation of a given opioid, further increases

can be attempted based on daily around-the-clock medication and rescue doses.[3–5] If unacceptable toxicity occurs with dose escalation, rotation to another opioid type can be considered. Additionally, a combination of opioids with non-opioid analgesics, such as non-steroidal anti-inflammatory drug (NSAID) or acetaminophen, is a recommended option. However, predicting the most suitable type of opioid for each individual is challenging.[6] It is known that 10–30% of patients respond poorly to a single opioid.[7] When morphine and oxycodone were used as the first-line opioids, the response rates were estimated to be 62% and 67%, respectively, suggesting that certain patients do not benefit from a single opioid.[8] Moreover, 10–20% of patients receiving opioid therapy may need to change treatment because of intolerable side effects and consequent limiting dose titration.[9] Given the limitations of dose titration using only one type of opioid, there is an unmet need to identify new methods other than opioid rotation to increase efficacy and reduce the side effects of opioids. The fact that each opioid acts on a different receptor has been recognised as the reason for opioid combination therapy (OCT).[10 11] For example, morphine is a mu-opioid agonist, and the action of oxycodone is mediated by putative-opioid receptors. However, evidence supporting the use of a combination of different strong opioids to treat cancer pain is scarce. To our knowledge, meta-analyses providing comprehensive guidance on this question are scarce. A systematic review published more than a decade ago exists, but it also concluded that no clear recommendations could be drawn.[12] This outdated review only addressed combinations of strong opioids, excluding weak opioids, and the types of opioids included in the literature search were also limited. Hence, in this systematic review, we aimed to investigate whether OCT is more effective than a single opioid and assess any differences in safety between the two approaches.

Methods and analysis

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42023427299). The Cochrane Handbook of Systematic Reviews of Interventions (version 6.3) will guide this systematic review.[13] We report this protocol in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).[14] The study is scheduled to be completed over a period of 1 year, from June 2023 to June 2024.

Aim

The review question for this research was whether combination opioid therapy is more effective than a single opioid for pain control in adult patients with cancer. Therefore, we aimed to summarise clinical studies that have investigated the combination of opioids to control cancer pain and explore their level of evidence. We will also investigate whether OCT affects safety.

Eligible criteria

Study design

Studies comparing OCT with a single opioid will be searched (eg, randomised trials, non-randomised cohort studies and observational studies with control groups, including prospective and retrospective cohort studies, case–control studies, cross-sectional studies and before-and-after studies) in human participants. No restrictions will be imposed on the types of studies eligible for inclusion in the review to allow for a comprehensive analysis. Additionally, no restrictions will be imposed on the language in which they were written.

Population

This review will consider all clinical trials involving patients aged ≥18 years who received opioids for chronic cancer pain. Both opioid-naïve and opioid-tolerant patients may be included in this study. Patients with any stage of cancer, including those who survived, are eligible. Opioid tolerance was defined as at least 30 mg of oral oxycodone daily, 60 mg of morphine daily, 8 mg of hydromorphone daily or an equivalent dose of another opioid for 7 days or longer.[15]

Interventions

OCT is defined as a combination of any opioids, including both strong and weak opioids, for control of cancer pain. Strong opioids include but are not limited to the following: morphine, oxycodone, oxycodone/naloxone, fentanyl, tapentadol, buprenorphine, hydromorphone, oxymorphone, numorphan, methadone, butorphanol, nalbuphine and pentazocine. Weak opioids include but are not limited to the following: tramadol, codeine, dihydrocodeine and hydrocodone. Combination refers to the simultaneous use of two or more of the above opioids. This can be a combination with two or more strong opioids, or a combination of weak and strong opioids. No restrictions will be imposed on the route of drug administration for opioid therapies. This review will consider all administration routes, including oral, intravenous, intramuscular, epidural, transdermal and other parenteral methods, to ensure a comprehensive evaluation of the available evidence on OCT for cancer pain.

Comparators

The comparator will be set as a single opioid, with or without a placebo. Similar to the intervention, no restrictions will be placed on the routes of drug administration.

Outcomes

Primary outcomes

The primary outcome is efficacy (ie, pain response). Changes in the pain scale scores from baseline to a predefined follow-up period after the intervention were measured using a pain assessment tool. There is no established standard method for measuring the severity of cancer pain. Therefore, there is no restriction on the type of pain measurement tool used by the researchers. The Numeric Rating Scale (NRS) is one of the most commonly

used pain scales in studies and daily practice. Additionally, the Brief Pain Inventory (BPI), Faces Pain Rating Scale-Revised (FPRS-R), Categorical Scale and Visual Analogue Scale (VAS) can be used.[16–19] The NRS uses a scale ranging from 0 to 10. A score of 0 indicates no pain and 10 indicates the most severe pain. The BPI evaluates pain severity and functional deterioration using the NRS. The FPRS-R uses facial images representing different degrees of pain to determine the pain severity. The categorical scale discriminates pain intensity as none, mild, moderate or severe. Numeric ratings of 0 correspond to none, 1–3 to mild, 4–7 to moderate and 7–10 to severe pain, respectively.[20] VAS scores are calculated based on patient-recorded marks placed at one point along a 0–100 mm line. It represents a continuous degree between the two ends of the scale, with no pain at the left end (0 cm) and the worst pain at the right end (100 mm). The following scales used for clinical trials may also be used: the McGill Pain Questionnaire and the Patient-Reported Outcomes Measurement Information System-Pain Interference.[19 21] No gold standard exists for evaluating the degree of pain after an intervention. In general, pain assessment is performed 1–4 weeks after the start of an intervention to evaluate changes in pain severity.[22] However, the time interval between the intervention and pain reassessment can be shorter than 24 hours to assess the immediate effect. In this review, time points will be categorised into two main groups: immediate (≤24 hours) and delayed (>24 hours to ≤1 week, 1–4 weeks and >4 weeks), all measured from baseline.

Secondary outcomes

Any reported side effects related to OCT will be secondary outcomes. Adverse events can be described according to the Common Terminology Criteria for Adverse Events. The number of rescue medications required and the reduction in the dose of opioids required to obtain an equivalent level of analgesia are also considered secondary outcomes.

Search strategy

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE via PubMed), Embase (via Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science databases from inception to June 2023. The search will be conducted by a medical librarian who is an experienced bibliographical expert (J-YK) in medical journals, based on a thorough discussion with all authors. To identify relevant studies, we will use Medical Subject Headings (MeSH) and relevant text words related to opioid combinations. Thereafter, to adapt the search terms to several databases, a combination of MeSH and relevant keywords found in the titles and abstracts of relevant literature will be used. The full search strategies for each of the databases to be used are provided in online supplemental file 1.

Data collection and analysis

Selection of studies

After finalising the search results, all records will be collected into an EndNote library to remove duplicates. The data will be then exported to a Microsoft Excel sheet (Microsoft Corp.) or Covidence (Veritas Health Innovation, Melbourne, Victoria, Australia). The principles for removing duplicate records will be as follows: (1) the author, title and year of publication are the same and (2) the same author and title have been published in the same journal. Decisions to select the retrieved literature for assessment will be made based on the eligibility criteria. Two independent reviewers (CHM and JHK) will screen the titles and abstracts. If the title and abstract meet the inclusion and exclusion criteria, the full text will be retrieved. In this step, if the opinions of the two independent reviewers conflict, a third reviewer (SYK) will be involved. All excluded records will provide reasons for exclusion, and the selection process will be documented in a PRISMA flow diagram.

Data collection process

Two reviewers will independently extract the data using a prespecified standardised data extraction form. First, the reviewer extracts data from several retrieved articles to build a pilot form. Subsequently, this form will be tested in other studies, and the final data extraction form will be created in Excel (Microsoft Corp.) or Covidence with appropriate revisions. Cross-checking of the data will be conducted independently by the reviewers following data extraction. The following data will be extracted from each study: study design, population type, including inclusion and exclusion criteria, the gender ratio of participants, mean and/or median age (range, SD), cancer type (eg, gastric cancer) and status (eg, metastatic or locally advanced), the country where the clinical trial was conducted or the nationality of the subjects, the language used in the published literature, interventions and comparison used, outcome measures, including the definition of pain response, sample size (under or over preplanned), pain response as a primary or secondary outcome, pain score changes/effect size, pain scale or assessment tool, the time interval between baseline and the assessment following an intervention, and side effects, sources of study funding and authors' declarations of interests. In case of significant missing data, the paper's corresponding author will be contacted to obtain accurate information. When this is unavailable, and the missing data pose a serious risk of bias, we will explore the impact of including these studies in the overall assessment of the results using a sensitivity analysis.

Risk of bias assessment

For randomised controlled trials, version 2 of the Cochrane tool will be used to assess the risk of bias in randomised trials, which includes the following bias domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias

due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the reported result and the overall risk of bias judgement.[23] For non-randomised studies, we will assess the risk of bias using a tool for assessing the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I).[24] Two reviewers will independently assess the risk of bias in individual studies, as recommended in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.[25] The risk of bias within and across the included studies will be presented using a risk of bias graph and summary.

Data synthesis

Quantitative analysis

Risk ratios and pooled variance measures will be synthesised using Mantel–Haenszel random effects meta-analysis for dichotomous data. We will extract the means and SD for continuous outcome data and use them to estimate the weighted mean difference. If outcomes were not measured on the same scale across studies, the standardised mean difference between treatments and the 95% CI will be used. A random-effects model will used for all meta-analyses. If the included studies do not provide raw data but only effect estimates and their SEs, we will use the generic inverse variance random-effects model to input these data into Review Manager (RevMan). I^2 and Q-statistics will be used to evaluate the heterogeneity of treatment effects across the studies. An I^2 value >50% will be considered an indication of substantial heterogeneity.[26] Funnel plots will be used to assess publication bias if more than 10 studies were included in the analysis. Randomised trials and non-randomised studies, including observational designs, will be analysed separately to account for different levels of selection bias. We will review these data to determine whether it is possible to conduct a meta-analysis.[27]

Non-quantitative synthesis

We will use alternative synthesis methods, including vote counting based on the effect direction, harvest plots or Albatross plots, if meta-analyses cannot be conducted because of the high heterogeneity caused by the different types of participants and interventions in each clinical study.[28] Vote counting may be employed when statistical test outcomes are accessible in each study. This approach involves tallying the number of studies that reported positive, negative or inconclusive associations, based on a predetermined p-value threshold. To enhance the vote-counting method, harvest plots have been proposed that serve as graphical tools for presenting the findings of each study. In the harvest plot, each study is represented by a bar, and the height and appearance of the bar provide information on the confidence level of the results, such as the risk of bias. The bars are grouped based on whether the study discovered a positive, negative or inconclusive association. Albatross plots will be used when sufficient information is unavailable. The Albatross plot relies on minimal statistical information, which can usually be obtained from each study, especially a specific p value and total sample size, using Stata 16/SE.[29]

Subgroup and sensitivity analysis

Subgroup analyses will be conducted to explore the differences in patient-reported pain according to several factors. First, the types of opioids will be grouped based on opioid combinations (strong plus strong opioid versus single opioid and strong plus weak opioid versus single opioid) and the inclusion or exclusion of non-opioid analgesics (eg, NSAIDs or acetaminophen). Second, pain severity will be classified into mild (NRS 0–3), moderate (NRS 4–6) and severe (NRS ≥7). Third, the types of pain will include breakthrough, nociceptive, neuropathic and bone pain. Finally, tumour type and disease status will be categorised as solid tumours and haematologic malignancies, in addition to metastatic and cancer survivor. A sensitivity analysis will be conducted if missing data significantly impacts the study quality or introduces potential bias and if statistical outliers or specific studies are found to be disproportionately influencing the overall results. This analysis will exclude studies with a high risk of bias, removing outliers or comparing different analytical models (eg, fixed-effect versus random-effect models). By systematically excluding or adjusting for these studies, we will assess the robustness and consistency of the findings, ensuring a single study or methodological choice does not drive the conclusions.

Quality of evidence

The quality of evidence for each primary outcome will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation Guidelines. These guidelines evaluate evidence based on several domains, including risk of bias, publication bias, imprecision, inconsistency and indirectness.[30] The quality of evidence can be categorised into four levels: high, moderate, low and very low. High-quality evidence indicated a high confidence level that the true effect is similar to the estimated effect. Moderate-quality evidence suggests a moderate confidence level in the effect estimate, indicating that the true effect is likely to be close to the estimated effect; however, there is a possibility of substantial differences. Low-quality evidence indicated limited confidence in the effect estimate, with the true effect potentially differing significantly from the estimated effect. Very low-quality evidence signifies very little confidence in the effect estimate, and the true effect is likely to differ substantially from the estimated effect. This approach will be used to assess the credibility of the cumulative evidence for each primary outcome.

PATIENT AND PUBLIC INVOLVEMENT

Patients or the public did not participate in the design, conduct, reporting or dissemination plans of our research.

Ethics and dissemination

Ethical approval was not required for this study. This systematic review and meta-analysis extract data from the

previously published literature using publicly available bibliographic databases. It does not collect or record personally identifiable information and does not involve direct contact or interventions with human participants during the research process. This protocol will be disseminated to researchers and the general public through publication after a peer review. Additionally, the authors will release the study results as stipulated by this protocol in another article. The results will also be disclosed at relevant conferences.

DISCUSSION

The widespread use of OCT for cancer pain management lacks robust evidence supporting its efficacy and safety. This systematic review and meta-analysis aimed to clarify the role of these therapies and address the current reliance on expert opinions in clinical guidelines. One strength of this study is its comprehensive scope, which includes literature without restrictions on language or design, spanning from 1946 to the present. This approach minimises the risk of missing relevant studies and ensures a broad evaluation of both strong and weak opioids. Although the evidence is limited, this study will serve as a foundation for future clinical trials on the efficacy and safety of opioid combinations, contributing to more evidence-based recommendations for cancer pain management. However, the expected heterogeneity among the studies is a significant limitation, particularly in assessing pain response and intervention effectiveness. Unlike more standardised outcomes such as survival rates, pain response and adverse events will likely vary across studies, complicating comparisons and synthesis. In conclusion, despite these limitations, this study will provide valuable insights and inform future research and clinical practice on opioid combination therapies for cancer pain.

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Contributors CHM, DH, JHK and SYK contributed to the study's conceptualisation. CHM drafted the protocol, which was supported by DH, JHK and SYK. The methods were described based on consultations with SYK. J-YK developed a search strategy using contributions from CHM and SYK. JHK and DH supervised this study. JHK contributed to the funding acquisition. All the authors reviewed the final draft of the protocol and agreed to its submission. JHK is the guarantor.

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