PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

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

Authors

Maeng, Chi Hoon; Hui, David; Kang, Ji-Yeon; Kim, Soo Young; Kwon, Jung Hye

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Lu, Yuhan**
Affiliation department	**Peking University Cancer Hospital & Institute, Nursing**
Date	**27-Feb-2024**
COI	**No conflict of interest**

This study will be helpful in clarifying the role of combination therapy in prescribing analgesics.

Reviewer	**2**
Name	**Espinoza Suarez, Nataly R**
Affiliation	**Laval University, Laval University**
Date	**27-Feb-2024**
COI	**NO**

Thanks very much for inviting me to review this relevant protocol.

this is a very important subject and it needs attention. Here are some minor commentaries:

It is necessary also to see the inclusion and exclusion criteria. It can be presented in a table or a box or narratively in the text.

Also please report a section of knowledge dissemination plan and an ethics section separated from the previous one, and a section mentioning the strengths and limitations of

your study in the discussion section. You can see models of protocols from other BMJOpen publications.

Reviewer	**3**
Name	**Dupoiron, Denis**
Affiliation	**Institut de Cancerologie de l'Ouest Angers, Anesthesiology and Pain medicine**
Date	**05-Mar-2024**
COI	**no**

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great protocol

no concerns about the topic methodology and the methodology

Reviewer	**4**
Name	**Kim, Kun Hyung**
Affiliation	**Pusan National University School of Korean Medicine**
Date	**05-Apr-2024**
COI	**none to declare**

This is a protocol of systematic review and meta-analysis which aims to assess the quality of evidence on opioid combination therapy versus a single opioid therapy for adult cancer pain. The research aim is valid and clinically relevant, and the standard methodology of systematic review is well illustrated. I would like to provide a few minor comments to help authors revise the manuscript as follows:

#1. Title:

My suggestion is to explicitly describe comparison of combination versus single opioid therapy in the title as is often recommended in Cochrane Handbook and other standard review methodology, because the specific comparison of interest in the manuscript is “combined opioid therapy versus a single opioid therapy”.

#2. Research aim:

Authors may explicitly include “assessing safety” of two types of opioid therapies (combined versus single) in the research aim description (p7, line 101).

#3. Methods-eligible study design:

Please specify which types of “observational studies” are eligible, such as cross-sectional, historical/prospective cohort studies or case-control studies. This is a recommended research practice to avoid any confusion in search process and selective inclusion of the searched studies during analysis. (Cochrane Handbook and other standard systematic review methodology).

#4. Methods - population:

I assume what is meany by “cancer pain” in the manuscript can fall into the “cancer-related pain” category by the International Association for the Study of Pain (IASP) classification for ICD-11, as the terminology of “chronic cancer-related pain” includes pain caused by the primary cancer itself or metastases or its treatment.(Bennet 2019) (Although authors have not clarified chronicity of pain in the manuscript, I assume that authors’ interest was on the chronic cancer-related pain.) For the sake of clarity, please consider to specify authors’ scope of cancer pain and its chronicity (acute, chronic or both). It will also help search and study selection process.

#5. Interventions / comparisons

Please consider to specify the types of the drug administration routes (e.g., oral, intravenous, intramuscular, epidural, transdermal or other types of parenteral) are of interest in the manuscript. Authors may refer to the TIDieR guideline to comprehensively address the components of the interventions in the manuscript both in the design and reporting stage. (https://www.equator-network.org/reporting-guidelines/tidier/)

#6. Primary outcomes:

Please specify the primary timepoint when outcomes were reported in multiple times. For instance, a study may report pain outcomes at week 4, 8 and 12 from baseline. If the primary timepoint for analysis is not pre-specified, it poses risk of selective inclusion of the most favourable outcomes in the review results. Authors do not necessarily discard outcomes data measured at non-primary time points, and can analyse them as secondary outcomes.

#7. Data collection process

Please move the sensitivity analysis section to the paragraph entitled as “subgroup and sensitivity analysis” subheadings.

#8. Data synthesis

If authors include observation studies using effect measures of odds ratio, odds ratios can be one of measures for quantitative synthesis (i.e., meta-analysis). The model selection between fixed and random effects should be pre-specified before analysis and should not depend on the observed heterogeneity (Borenstein 2021 and the Cochrane Handbook). Authors should pre-specify whether randomised trials and non-randomised/observational

studies would be combined or separately analysed in a meta-analysis (latter is recommended due to different level of selection bias).

#9. Subgroup/sensitivity analysis

Please specify criteria for dividing subgroups (e..g, strong versus weak opioids for 'types of opioids' subgroup analysis, or authors' own categorisation). For the sensitivity analysis, please specify authors' missingness of interest (e.g., missing reports in the allocation concealment process, missing values in the pain measurement or variances of data, etc) which are deemed the likely source of serious bias in the primary analysis.

Reviewer **5**

Name **Ji, Ya-Jie**

Affiliation **Shanghai University of Traditional Chinese Medicine, breaset surgery department**

Date **13-Apr-2024**

COI **No.**

The focus of this article is to evaluate the efficacy of opioid combination therapy for adult cancer pain and to provide a protocol for systematic review and meta-analysis. The aim of the article is to assess the efficacy of opioid combination therapy for adult cancer pain by collecting and analyzing data from relevant studies. For the benefit of the reader, however, several points need clarifying and certain statements require further justification. The revision suggestions for the article include the following points.

Major comments:

1.There is no explicit mention of existing relevant research in the introduction, lacking a review and summary of existing research on the topic. Particularly, the current clinical practice of using opioid combination therapy is not mentioned.

2.In the assessment of the credibility of cumulative evidence section, there is no specific explanation of the methods used for evaluation.

3.The incidence of cancer pain during chemotherapy is extremely high, and the severity of pain is closely related to tumor type, choice of chemotherapy drugs, and treatment duration. Subgroup analysis should be more comprehensive to minimize heterogeneity.

4.Current clinical studies often use other treatment modalities such as acupuncture, meditation, and psychological interventions in conjunction with opioid therapy for cancer pain. Will you include such articles in your literature search? If so, how will you ensure the efficacy of opioid analgesia?

Minor comments:

1.Language in the article needs polishing.

2.The novelty and highlights of the research are insufficient and need further enhancement.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Yuhan Lu, Peking University Cancer Hospital & Institute

Comments to the Author:

This study will be helpful in clarifying the role of combination therapy in prescribing analgesics.

[Author response]

We sincerely appreciate your time and effort in reviewing our manuscript, and we are grateful for your positive comment.

Reviewer: 2

Ms. Nataly R Espinoza Suarez, Laval University

Comments to the Author:

Thanks very much for inviting me to review this relevant protocol.

this is a very important subject and it needs attention. Here are some minor commentaries:

It is necessary also to see the inclusion and exclusion criteria. It can be presented in a table or a box or narratively in the text.

[Author response]

Thank you very much for your positive comments and for highlighting this important aspect of the protocol. We sincerely appreciate your careful attention to detail.

Regarding the inclusion and exclusion criteria you mentioned, we have outlined these in the

"Eligible Criteria" section of the Methods, as follows:

"*Studies comparing OCT with a single opioid will be searched (e.g., randomized trials, non-randomized cohort studies, and observational studies with control groups) only in human subjects. Otherwise, no restrictions will be imposed on the types of studies eligible for inclusion in the review. There are no restrictions on the language in which they were written*."

Additionally, specific details regarding the participants or conditions of interest, which are relevant for study selection, are provided immediately after this in the PICO section.

Also please report a section of knowledge dissemination plan and an ethics section separated from the previous one, and a section mentioning the strengths and limitations of your study in the discussion section. You can see models of protocols from other BMJOpen publications.

[Author response]

Ethics and dissemination section was revised and updated in Line 311-318.

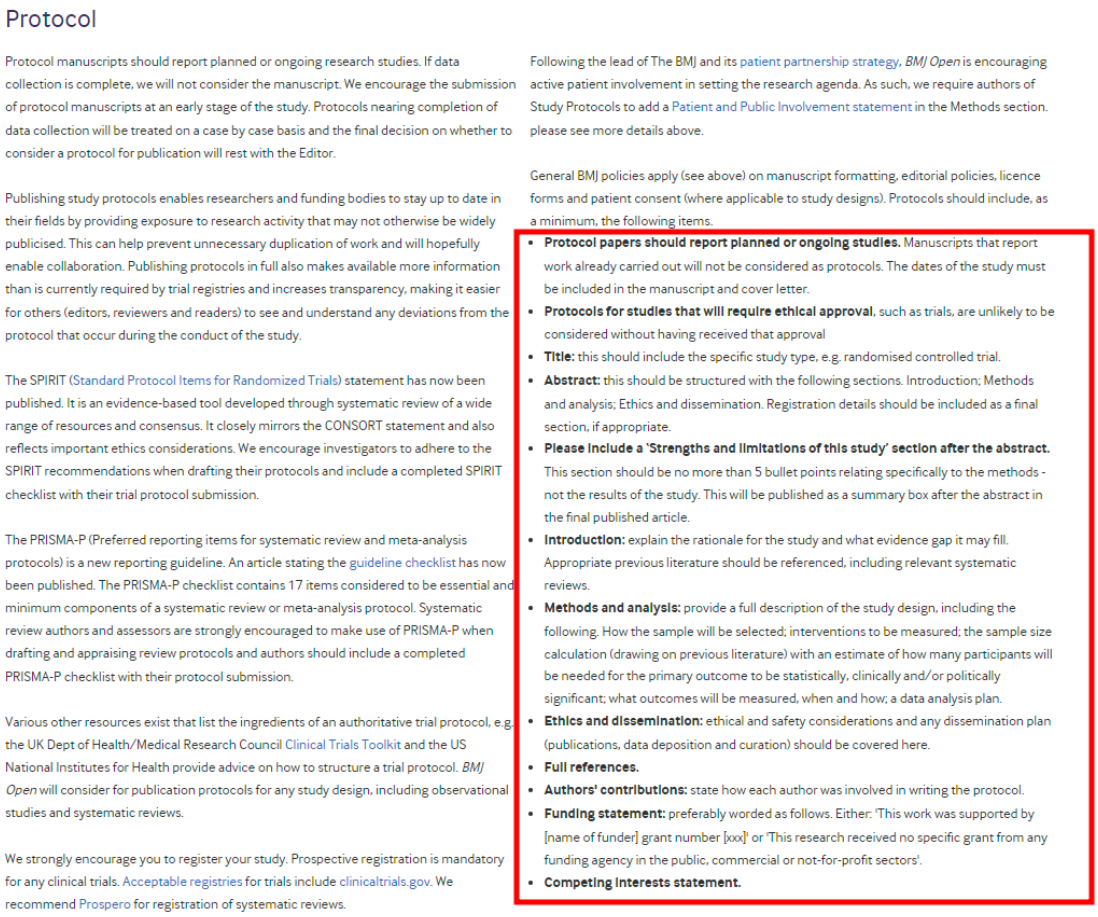
Ethical approval was not required for this study. This systematic review and meta-analysis extracts data from the previously published literature using publicly available bibliographic databases. It does not collect or record personally identifiable information and does not involve direct contact or 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.

According to the author instructions of BMJ Open, it appears that protocol papers do not typically include a Discussion section. Please refer to the captured image below. However, your comment is of great importance and cannot be overlooked. Additionally, as per your recommendation, we reviewed other BMJ Open publications (BMJ Open 2021;11: e047190. doi:10.1136/bmjopen-2020-047190) and confirmed that a Discussion section is indeed included in that article. Therefore, following your valuable suggestion, we have added a

Discussion section in lines 319-335.

Thank you once again for your valuable feedback.



Protocol

Protocol manuscripts should report planned or ongoing research studies. If data collection is complete, we will not consider the manuscript. We encourage the submission of protocol manuscripts at an early stage of the study. Protocols nearing completion of data collection will be treated on a case by case basis and the final decision on whether to consider a protocol for publication will rest with the Editor.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The SPIRIT (Standard Protocol Items for Randomized Trials) statement has now been published. It is an evidence-based tool developed through systematic review of a wide range of resources and consensus. It closely mirrors the CONSORT statement and also reflects important ethics considerations. We encourage investigators to adhere to the SPIRIT recommendations when drafting their protocols and include a completed SPIRIT checklist with their trial protocol submission.

The PRISMA-P (Preferred reporting items for systematic review and meta-analysis protocols) is a new reporting guideline. An article stating the guideline checklist has now been published. The PRISMA-P checklist contains 17 items considered to be essential and minimum components of a systematic review or meta-analysis protocol. Systematic review authors and assessors are strongly encouraged to make use of PRISMA-P when drafting and appraising review protocols and authors should include a completed PRISMA-P checklist with their protocol submission.

Various other resources exist that list the ingredients of an authoritative trial protocol, e.g. the UK Dept of Health/Medical Research Council Clinical Trials Toolkit and the US National Institutes for Health provide advice on how to structure a trial protocol. *BMJ Open* will consider for publication protocols for any study design, including observational studies and systematic reviews.

We strongly encourage you to register your study. Prospective registration is mandatory for any clinical trials. Acceptable registries for trials include clinicaltrials.gov. We recommend Prospero for registration of systematic reviews.

Following the lead of The BMJ and its patient partnership strategy, *BMJ Open* is encouraging active patient involvement in setting the research agenda. As such, we require authors of Study Protocols to add a Patient and Public Involvement statement in the Methods section. please see more details above.

General BMJ policies apply (see above) on manuscript formatting, editorial policies, licence forms and patient consent (where applicable to study designs). Protocols should include, as a minimum, the following items.

- **Protocol papers should report planned or ongoing studies.** Manuscripts that report work already carried out will not be considered as protocols. The dates of the study must be included in the manuscript and cover letter.
- **Protocols for studies that will require ethical approval**, such as trials, are unlikely to be considered without having received that approval
- **Title:** this should include the specific study type, e.g. randomised controlled trial.
- **Abstract:** this should be structured with the following sections. Introduction; Methods and analysis; Ethics and dissemination. Registration details should be included as a final section, if appropriate.
- **Please include a 'Strengths and limitations of this study' section after the abstract.** This section should be no more than 5 bullet points relating specifically to the methods - not the results of the study. This will be published as a summary box after the abstract in the final published article.
- **Introduction:** explain the rationale for the study and what evidence gap it may fill. Appropriate previous literature should be referenced, including relevant systematic reviews.
- **Methods and analysis:** provide a full description of the study design, including the following. How the sample will be selected; interventions to be measured; the sample size calculation (drawing on previous literature) with an estimate of how many participants will be needed for the primary outcome to be statistically, clinically and/or politically significant; what outcomes will be measured, when and how; a data analysis plan.
- **Ethics and dissemination:** ethical and safety considerations and any dissemination plan (publications, data deposition and curation) should be covered here.
- **Full references.**
- **Authors' contributions:** state how each author was involved in writing the protocol.
- **Funding statement:** preferably worded as follows. Either: 'This work was supported by [name of funder] grant number [xxx]' or 'This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- **Competing interests statement.**

Reviewer: 3

Dr. Denis Dupoiron, Institut de Cancerologie de l'Ouest Angers

Comments to the Author:

great protocol

no concerns about the topic methodology and the methodology

[Author response]

We greatly value the time and effort you dedicated to reviewing our manuscript, and we are thankful for your encouraging feedback.

Reviewer: 4

Prof. Kun Hyung Kim, Pusan National University School of Korean Medicine

Comments to the Author:

This is a protocol of systematic review and meta-analysis which aims to assess the quality of evidence on opioid combination therapy versus a single opioid therapy for adult cancer pain. The research aim is valid and clinically relevant, and the standard methodology of systematic review is well illustrated. I would like to provide a few minor comments to help authors revise the manuscript as follows:

#1. Title:

My suggestion is to explicitly describe comparison of combination versus single opioid therapy in the title as is often recommended in Cochrane Handbook and other standard review methodology, because the specific comparison of interest in the manuscript is "combined opioid therapy versus a single opioid therapy".

[Author response]

Thank you for highlighting multiple important points. We greatly appreciate your kind and insightful comments. Following your recommendation, we have revised the title to more explicitly reflect the comparison between opioid combination therapy and single opioid therapy. The updated title is: "**Efficacy of opioid combination versus single opioid for adult cancer pain: A protocol for systematic review and meta-analysis**"

#2. Research aim:

Authors may explicitly include "assessing safety" of two types of opioid therapies (combined versus single) in the research aim description (p7, line 101).

[Author response]

Thank you for your valuable suggestion. Following your recommendation, we have revised the sentence in Lines 105-107 as follows:

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.

#3. Methods-eligible study design:

Please specify which types of "observational studies" are eligible, such as cross-sectional, historical/prospective cohort studies or case-control studies. This is a recommended research practice to avoid any confusion in search process and selective inclusion of the searched studies during analysis. (Cochrane Handbook and other standard systematic review methodology).

[Author response]

We totally understand and agree that. Based on your comments, the paragraph has been replaced as follows in Line 123-128.

Studies comparing OCT with a single opioid will be searched (e.g., randomized trials, non-randomized 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.

#4. Methods - population:

I assume what is meany by "cancer pain" in the manuscript can fall into the "cancer-related pain" category by the International Association for the Study of Pain (IASP)

classification for ICD-11, as the terminology of "chronic cancer-related pain" includes pain caused by the primary cancer itself or metastases or its treatment.(Bennet 2019) (Although authors have not clarified chronicity of pain in the manuscript, I assume that authors' interest was on the chronic cancer-related pain.) For the sake of clarity, please consider to specify authors' scope of cancer pain and its chronicity (acute, chronic or both). It will also help search and study selection process.

[Author response]

We appreciate your accurate and scientific comment. In the **Methods > Eligibility Criteria > Population** section, we had already mentioned chronicity as follows:

Population

"This review will consider all clinical trials involving patients aged ≥ 18 years who received opioids for ***chronic*** cancer pain."

We believe that this mention of "chronic cancer pain" addresses your comment, as we deemed it unnecessary to repeatedly use the term "chronic" before every instance of cancer (or cancer-related) pain thereafter in the manuscript.

Additionally, while your suggestion to specify "cancer-related pain" to encompass all types of pain directly or indirectly associated with cancer, including pain caused by the cancer itself or by cancer treatments, is valid, it is more common in the fields of palliative care and clinical oncology to use the broader term "cancer pain" without distinguishing further. Therefore, we have opted to retain the expression "cancer pain" and hope for your understanding.

#5. Interventions / comparisons

Please consider to specify the types of the drug administration routes (e.g., oral, intravenous, intramuscular, epidural, transdermal or other types of parenteral) are of interest in the manuscript. Authors may refer to the TIDieR guideline to comprehensively address the components of the interventions in the manuscript both in the design and reporting stage. (https://www.equator-network.org/reporting-guidelines/tidier/)

[Author response]

Thank you for your insightful suggestion. In line with the comprehensive nature of our review, we have not restricted the routes of drug administration (e.g., oral, intravenous, intramuscular, epidural, transdermal, or other parenteral routes). We believe that including all available administration routes will allow for a more inclusive and thorough analysis of the interventions. The added sentence has been included in Lines 144-147 and Lines 149-150.

Interventions

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 opioid combination therapy 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.

We appreciate your reference to the TIDieR guideline and will ensure that all relevant components of the interventions are comprehensively addressed in both the design and reporting stages.

#6. Primary outcomes:

Please specify the primary timepoint when outcomes were reported in multiple times. For instance, a study may report pain outcomes at week 4, 8 and 12 from baseline. If the primary timepoint for analysis is not pre-specified, it poses risk of selective inclusion of the most favourable outcomes in the review results. Authors do not necessarily discard outcomes data measured at non-primary time points, and can analyse them as secondary outcomes.

[Author response]

Thank you for your precise and scientific comment. We fully acknowledge the importance of pre-specifying timepoints to avoid selective reporting. In our analysis, we plan to categorize the timepoints based on the clinical characteristics of cancer pain patients receiving opioid therapy. Specifically, we will assess immediate outcomes (within 24 hours) following the intervention, as well as *delayed* outcomes: within 24 hours to 1 week, 1-4 weeks, and beyond 4 weeks. This approach will allow us to capture both immediate and longer-term effects, ensuring a comprehensive analysis across various timeframes. Therefore, we added the following sentences in Line 175-177:

In this review, time points will be categorized into two main groups: immediate (≤ 24 hours) and delayed (>24 hours to ≤ 1 week, 1-4 weeks, and > 4 weeks), all measured from baseline.

#7. Data collection process

Please move the sensitivity analysis section to the paragraph entitled as "subgroup and sensitivity analysis" subheadings.

[Author response]

Thank you for your valuable suggestion. The mention of sensitivity analysis in the 'Data Collection Process' section was not intended to detail the methodology of sensitivity analysis itself, but rather to outline how we plan to address issues like missing data during the data collection process. For this reason, we have decided to retain it in its current form.

However, in line with your recommendation, we have also added a description of the sensitivity analysis plan in the 'Subgroup and Sensitivity Analysis' section (Lines 286-293). Since the two revised paragraphs would not be easily distinguishable if marked in the same color, I used slightly different shades of blue to make the distinction clear as follows:

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 (e.g., fixed-effect vs. 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.

#8. Data synthesis

If authors include observation studies using effect measures of odds ratio, odds ratios can be one of measures for quantitative synthesis (i.e., meta-analysis). The model selection between fixed and random effects should be pre-specified before analysis and should not depend on the observed heterogeneity (Borenstein 2021 and the Cochrane Handbook). Authors should pre-specify whether randomised trials and non-randomised/observational studies would be combined or separately analysed in a meta-analysis (latter is recommended due to different level of selection bias).

[Author response]

Thank you for your valuable comment. We confirm that we will use a random-effects model for the meta-analysis. Additionally, randomized and non-randomized/observational studies will be analyzed separately, as recommended, to account for the different levels of selection bias. Accordingly following sentences were added in Line 251-252, and 257-259, respectively.

A random-effects model will used for all meta-analyses.

Randomized trials and non-randomized studies, including observational designs, will be analyzed separately to account for different levels of selection bias.

#9. Subgroup/sensitivity analysis

Please specify criteria for dividing subgroups (e.g, strong versus weak opioids for 'types of opioids' subgroup analysis, or authors' own categorisation). For the sensitivity analysis, please specify authors' missingness of interest (e.g., missing reports in the allocation concealment process, missing values in the pain measurement or variances of data, etc) which are deemed the likely source of serious bias in the primary analysis.

[Author response]

Thank you for your precise feedback. The subcategories for pain severity (by NRS) and pain type (breakthrough, nociceptive, neuropathic) were already defined in the original text. For the type of opioid, we have now clarified and explicitly specified the categories for the subgroup analysis in parentheses on Lines 281-282, as follows: (strong plus strong vs. single opioid, strong plus weak opioid vs. single opioid).

Additionally, in response to another reviewer's comment, we have expanded and provided further detail on this section, resulting in a newly revised paragraph.

In the sensitivity analysis section, as described above (in your comment #7), we have added a description of the sensitivity analysis plan in the 'Subgroup and Sensitivity Analysis' section (Lines 286-293) as follows:

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 (e.g., fixed-effect vs. 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.

Reviewer: 5

Dr. Ya-Jie Ji, Shanghai University of Traditional Chinese Medicine

Comments to the Author:

The focus of this article is to evaluate the efficacy of opioid combination therapy for adult cancer pain and to provide a protocol for systematic review and meta-analysis. The aim of the article is to assess the efficacy of opioid combination therapy for adult cancer pain by collecting and analyzing data from relevant studies. For the benefit of the reader, however, several points need clarifying and certain statements require further justification. The revision suggestions for the article include the following points.

Major comments:

1. There is no explicit mention of existing relevant research in the introduction, lacking a review and summary of existing research on the topic. Particularly, the current clinical practice of using opioid combination therapy is not mentioned.

[Author response]

Thank you for taking the time to review our manuscript and for providing valuable feedback that has helped improve its quality.

We agree with your comments. However, we would like to point out that in the Introduction section, we had already included a paragraph addressing the lack of existing evidence regarding current clinical practice and opioid combination therapy, as shown below:

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 personalize 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

However, evidence supporting the use of a combination of different strong opioids to treat cancer pain is scarce.

The strategy of strong opioids in combination with weak opioids, such as tramadol, also has little clinical evidence, especially in patients with cancer.

In line with your recommendation, we have added a summary of current practices by citing guidelines from ASCO and ESMO. Additionally, we have expanded on the need for further research on this topic, based on existing literature reviews, by adding two sections in the manuscript: Lines 83-87 and Lines 99-104.
We have deleted some sentences to reduce redundancy.

According to the current clinical guidelines, if 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.

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 was also limited.

2.In the assessment of the credibility of cumulative evidence section, there is no specific explanation of the methods used for evaluation.

[Author response]

Thank you for your insightful comment. We agree with your observation. We would like to point out that the GRADE approach for assessing the quality of evidence was already included in the 'Quality of Evidence' section.

However, in line with your recommendation, we have added a sentence at the end of this section to make the intended meaning more explicit in Line 307-308:

This approach will be used to assess the credibility of the cumulative evidence for each primary outcome.

This adjustment clarifies how the GRADE methodology will be applied to evaluate the cumulative evidence.

3.The incidence of cancer pain during chemotherapy is extremely high, and the severity of pain is closely related to tumor type, choice of chemotherapy drugs, and treatment duration. Subgroup analysis should be more comprehensive to minimize heterogeneity.

[Author response]

Thank you for your thoughtful suggestion. We fully agree with your perspective. However, since we have already registered the subgroup categories in PROSPERO as originally outlined in the manuscript (type of opioid, pain severity, and cancer status), we have chosen not to add additional subcategories at this stage. Instead, as per your recommendation, we have provided more detailed explanations of the existing categories.

In the revised manuscript, we expanded the brief descriptions previously mentioned in parentheses and made an effort to include additional details within the existing categories, such as addressing both solid and hematologic cancers in addition to the previously specified metastatic versus cured states (Line 278-286). Thank you for your understanding.

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 vs. single opioid, and strong plus weak opioid vs. single opioid) and the inclusion or exclusion of non-opioid analgesics (e.g., 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, tumor type and disease status will be categorized as solid tumors and hematologic malignancies, in addition to metastatic and cancer survivor.

4.Current clinical studies often use other treatment modalities such as acupuncture, meditation, and psychological interventions in conjunction with opioid therapy for cancer pain. Will you include such articles in your literature search? If so, how will you ensure the efficacy of opioid analgesia?

[Author response]

Thank you for providing such an interesting perspective and valuable insights. As you mentioned, there is a growing number of studies exploring the effects of complementary and alternative medicine (CAM) on cancer pain. Investigating the analgesic effects of the modalities you referenced, along with body-manipulative procedures, is also of personal

interest to me, and I am currently preparing a separate systematic review on this topic (see CRD42024553067). However, in this systematic review, we will not be covering such interventions, as our focus is solely on the effects (and side effects) of opioid combinations. Thank you again for your input.

Minor comments:

1. Language in the article needs polishing.

[Author response]

In the initial submission, the final manuscript was reviewed and edited by a native English-speaking professional editor. However, it seems there were still some minor grammatical and linguistic issues. Since this revision contains many newly added sentences and paragraphs, I have once again sought the assistance of a native English proofreading expert to ensure the accuracy of the language. I will submit the proofreading certificate as a separate file when uploading the revised manuscript.

2.The novelty and highlights of the research are insufficient and need further enhancement.

[Author response]

In response to the major revision point 1 you raised, we have revised the manuscript to further elaborate on why this study is necessary in comparison to current practice and why it addresses an unmet need for clinicians. To summarize, there is currently no comprehensive, systematic evidence on the synergy or safety of combining two (or more) opioids, beyond the scattered individual studies that exist. Notably, major guidelines such as those from ASCO or ESMO do not address this topic. Within our research team, we discussed the possibility of conducting a prospective clinical trial on opioid combination therapy and agreed that the first step should be to systematically review the current published evidence and perform a meta-analysis based on the available data. We sincerely hope you will understand the rationale behind this study and kindly consider the manuscript for publication.

VERSION 2 - REVIEW

Reviewer	**4**
Name	**Kim, Kun Hyung**
Affiliation	**Pusan National University School of Korean Medicine**
Date	**09-Oct-2024**
COI	

The manuscript is well revised and I have no further comments.