

Could the Perioperative Use of Opioids Influence Cancer Outcomes After Surgery? A Scoping Review Protocol

Marco Cascella (✉ m.cascella@istitutotumori.na.it)

Istituto Nazionale per lo Studio e la Cura dei Tumori: Fondazione IRCCS Istituto Nazionale dei Tumori

<https://orcid.org/0000-0002-5236-3132>

Arturo Cuomo

Istituto Nazionale Tumori IRCCS Fondazione Pascale

Francesca Bifulco

Istituto Nazionale Tumori IRCCS Fondazione Pascale

Barbara Di Caprio

Istituto Nazionale Tumori IRCCS Fondazione Pascale

Rosanna Accardo

Istituto Nazionale Tumori IRCCS Fondazione Pascale

Cira Antonietta Forte

Istituto Nazionale Tumori IRCCS Fondazione Pascale

Gennaro Esposito

Istituto Nazionale Tumori IRCCS Fondazione Pascale

Marco Fiore

Università degli Studi della Campania Luigi Vanvitelli

Protocol

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Abstract

Background

Opioids are commonly used for the treatment of cancer and non-cancer pain, and during and after general anesthesia. Because preclinical studies underlined a potential opioid-mediated immunosuppression, it was postulated that the perioperative administration of opioids could influence cancer outcomes after surgery. Nevertheless, clinical data have been extrapolated mainly from retrospective analyses. Thus, the precise link between perioperative opioids use and cancer recurrence/metastasis or cancer-related mortality/morbidity remains unresolved.

Methods/design

This scoping review is planned following the Joanna Briggs Institute recommendations. The authors will conduct a literature review through the PRISMA statement using PubMed and EMBASE databases; the Grey literature will be explored using Google Scholar, Conference Proceedings Citation Index (via Web of Science) and Open Grey. The search strategy will be limited to articles published in the English language and to human studies. The database searches are planned from the inception to November 2020. Two reviewers will independently screen titles and abstracts, followed by a full-text screening of potentially relevant articles with standardized data extraction. Any disagreement for the inclusion between the two reviewers will be discussed with a third reviewer.

Discussion

The review aim to map the available literature focusing on a possible association between the perioperative opioids use and cancer outcomes in patients undergoing surgery. The proposed approach will allow to identify and analyze the knowledge gap in the field and, serving as a prerequisite for future research including systematic reviews and clinical studies.

Scoping review registration

Open Science Framework <https://osf.io/ng57c/> DOI 10.17605/OSF.IO/NG57C

Background

Opioids are a class of drugs commonly used for the treatment of cancer and non-cancer pain, and the control of analgesia during and after general anesthesia. Since the end of the last century, several preclinical investigations focused on the opioid-mediated immunosuppression phenomenon, emphasizing impact of these agents on both the innate and adaptive immune systems [1]. These findings, however, are not conclusive as many factors such as the type of opioid, the dose, the timing of administration, and the animal strain used, can influence the data. Later on, the repercussions of morphine on the immune system have been studied in individuals with a history of opioid abuse [2] whereas an association between opioid use and higher risk of infections was found in patients treated for

chronic non cancer pain [3]. Despite this body of studies, the evidence is not strong enough to establish a clear link between chronic opioid use and immunosuppression [4]. This also raised doubts regarding the impact of opioid administration for a limited period such as the surgical phase and a short postoperative period on immunity. Interestingly, intraoperative opioids can increase expression of opioid receptor in cancer tissues without influencing the expression of immune cell markers [5].

In the context of the intraoperative phase, anesthesia strategies focused on low-dose opioid use or opioid-avoiding paths (i.e., opioid-free anesthesia, OFA) are rapidly growing, even in cancer surgery [6]. The motivations underlying this phenomenon are multiple. Synthetic short-acting opioids, for instance, can increase postoperative pain through opioid-induced hyperalgesia mechanisms. Again, the use of opioids during and after surgery can lead to a delay in patient mobilization, a slowing of intestinal peristalsis, and an increase in postoperative nausea and vomiting (PONV). Finally, the concern of a potential postoperative opioids over prescriptions is another serious reason that tends to direct the anesthetic choices towards an opioid-free approach. Beyond the scientific validity underlying these reasons [7], the OFA strategy is based on the concept of multimodal anesthesia which combines different drugs and/or techniques. Regional anesthesia techniques are pivotal components of this multimodal pain management in the whole perioperative setting. These methods could influence the long-term outcome of cancer surgery mostly by attenuating the immunosuppression effects due to surgery [8].

In addition to the effects on the early postoperative, a debate is underway on possible opioid-induced long-term effects in the setting of cancer patients. To date, most of the scientific evidence in favor of this thesis comes from preclinical studies while clinical data have been extrapolated mainly from retrospective analyses [9]. For instance, a retrospective study on patients who underwent prostatectomy for cancer showed that patients treated through epidural analgesia had a significant reduction in cancer recurrence compared to those managed with opioids [10]. On the other hand, a recent controlled investigation demonstrated that regional anesthesia-analgesia approaches did not reduce breast cancer recurrence compared with standard opioid-based anesthesia [11]. Recently, a systematic review that included 13 studies on perioperative opioids and colorectal cancer recurrence found no conclusive results. Furthermore, the authors decided to not perform the meta-analysis because the low quality of the primary studies [12]. Thus, the precise link between perioperative opioids and cancer recurrence or metastasis as well as survival remains unresolved.

Importance of this review

Although opioids are commonly used during the whole perioperative period, the opioid-induced immunosuppression could negatively influence recurrence or metastasis. It is important to establish whether eliminating the use of opioids in the perioperative period and favoring opioid-free multimodal approaches can result in improved oncological outcomes. These favorable effects could be added to the immediate positive outcomes such as rapid mobilization and reduced incidence of PONV.

Methods

Protocol design

The protocol was registered prospectively with the Open Science Framework on 6 October 2020 [13]. It has been planned, according the JBI Scoping Review Methodology Group [14], following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) [15].

Patient and public involvement

Patients and public were not involved in the preparation of this protocol

Research questions

This review is planned to answer the following research question:

Could the perioperative use of opioids influence cancer outcomes after surgery?

The research sub-questions include:

1. Is it possible to find possible differences according to the type of opioid used?
2. Is there a correlation between chronic opioid use and variation in outcomes in cancer patients?
3. Are there any differences related to the type of multimodal analgesia applied?

Eligibility criteria

Primary studies of any design will be included. No restrictions on publication year will be adopted. We will exclude unpublished works as a full-text, abstract, conference meetings, studies published in not peer-review journals, uncontrolled studies as case series or case reports, reviews, and studies published not in English.

Manuscripts will be excluded if they do not match the assumed framework of the study, centered on opioids administration and cancer recurrence or metastasis after surgery (Table 1).

Table 1
Eligibility criteria

	Inclusion	Exclusion
Study design	Primary studies of any design	Systematic reviews, meta-analysis, narrative reviews, letter to editor, case reports, case series, animal studies, in vitro investigations, studies on human volunteers
Population	Patients who underwent surgery for cancer disease	n/a
Intervention/exposure	Administration of opioids for treatment of pain/anesthesia	n/a
Comparator	Methods of opioid-free anesthesia	No opioids should be administered in the whole perioperative
Outcomes	Disease-free survival and/or overall survival	Those other than the chosen outcomes
Language	English	Those other than in English
Publication status	Published in peer review journals, full-length articles	Published in not peer-review journals, unpublished works as a full-text, abstract, conference meetings
Others	All study dates, length of follow-up, setting	n/a

Search Strategy

The search strategy will be defined following the PICO strategy. The population will be patients who underwent surgery for cancer disease, and the Intervention will be the administration of opioids alone or in combination with other drugs for the treatment of pain perioperatively and anesthesia management. The comparator will be any method of opioid-free anesthesia regional anesthesia-analgesia approaches for the perioperative management of pain. The outcomes will be the time of disease-free survival, and the overall survival. The search strings follow the evidence-based guideline for Peer Review of Electronic Search Strategies (PRESS) for systematic reviews, health technology assessments, and other evidence syntheses developed by McGowan and colleagues [16]. A proposed search string for Medline, via Ovid, is detailed in Table 2; the search strategies for the other databases will be comparable in structure with similar search terms and synonyms.

A consequent search using keywords and index terms will be performed using several computer-assisted databases, including PubMed, EMBASE, and for the grey literature: Google Scholar, Conference Proceedings Citation Index (via Web of Science) and Open Grey. The search strategy will be limited to articles published in English language and to human studies.

Table 2
Scoping Review Search Strategy Ovid Medline Search Strategy
(October 27, 2020).

Searches	Results
1. cancer.mp.	1777313
2. oncolog*.mp.	174974
3. 1 or 2	1852442
4. exp managment/ or exp treatment/	4630647
5. pain.mp.	730950
6. opioid.mp.	113051
7. 4 and 5 and 6	21928
8. monitor*.mp.	985970
9. 7 and 8	1350
10. 3 and 9	231

Study selection

Articles will be selected by the authors by evaluating titles and abstracts to identify potentially eligible studies; subsequently, the full text of eligible studies will be reviewed by the authors to exclude irrelevant studies or methodologies that are not usable for future analysis.

Data charting

The reviewers will record key information from included articles in a Microsoft Excel data extraction form. Two reviewers (FB and RA) will independently extract data to minimize errors. Each study will be extracted with the following information: title, year of publication, first author, the country where the study was conducted, type of study, lying cancer disease for which the surgery was required, anesthesia method, type and dose of the opioid(s), type of multimodal analgesia (regional techniques, drugs), and outcomes including type of recurrence or metastasis, time elapsed since surgery, and overall survival.

Data synthesis

The number of studies identified and selected at each stage of the scoping review and the reasons for exclusion will be presented in the PRISMA flow diagram. Results will be recapitulated in a table (Table 3) and exhaustively discussed in narrative way to address the research questions. Results will be assembled conceptually in terms of general study details, study characteristics, participants, interventions/exposures/comparators, instruments used in goal-setting, outcomes, and results. This review will illustrate summaries of these categories, including quantitative measurements of associations (mean differences for scores by validated questionnaires, risk ratios, or odds ratios for dichotomous outcomes), if applicable. Additional groups may be identified during the extraction of results. Authors of papers will be contacted to request missing or additional data for clarification, where required. We will report the results of critical appraisal in narrative form and in one or more tables.

Risk of bias

As this is a scoping review, there will be no risk of bias assessment. This is consistent with relevant guidance [17].

Data dissemination

The results of this scoping review will be disseminated on the authors' web sites. Additional dissemination will occur through presentations at conferences, such as courses and science education conferences, regionally and nationally, and through articles published in peer-reviewed journals. Workshops with health care professionals involved in the management of cancer pain, oncology, and cancer surgery will be planned.

Table 3
Planned variables to be extracted in the scoping review

General study details	Study ID number, lead author, title, journal, year of publication, type of publication, information source
Study characteristics	Study design, study duration, pilot/feasibility study (y/n), number of study arms, covariates (definition and measurement methods)
Participants	1. Total number, setting, inclusion and exclusion criteria 2. Participant characteristics at baseline: for each study, average age (years, mean and standard deviation [SD]), sex (%), country, diagnosis (cancer type, stage), treatment(s), comorbidities
Interventions/exposures and comparators	1. Total number of intervention/exposure [opioid(s) type, doses, opioid administration and surgery (pre-, intra-, postoperatively), time of treatment], and comparison [No opioid use] groups and number of participants in each group 2. For each intervention/exposure and comparison group: intervention/exposure/comparison, duration of intervention/exposure, who and how assessed, and results of assessment
Outcomes	Type of recurrence or metastasis; time elapsed since surgery; overall survival
Results	For each quantitative outcome: sample size, number of missing participants, reasons for loss to follow up, summary data for each group (2 × 2 table for dichotomous data, means and SDs for continuous data), estimate of effect for the difference between groups (or change in baseline and final scores for single-arm studies), confidence intervals, and <i>p</i> value

Discussion

This scoping review aims to describe the link between perioperative opioids and cancer recurrence or metastasis. The subject, however, is particularly complex. The main issue involved in performing the study will be to establish what is the weight of the intervention in the determinism of outcomes. The outcomes considered, indeed, may be dependent on multiple factors such as type of opioid and dose. Literature data are for both variables conflicting [18]. Moreover, it will be important to accurately extract data on the disease (stage, grading). For example, in prostate cancer, a Gleason 4 + 3 = 7 will have a higher probability of developing recurrence or metastasis than a Gleason 3 + 4 = 7. The effect of opioids may vary depending on the stage of the tumor. To this regard, in a retrospective analysis, Cata et al. [19] found that intraoperative opioid was associated with reduced overall survival for patients with early stage non-small cell lung cancer compared to those affected by more advanced disease.

There is also another important challenge that regards the potential immunosuppressive effects among patients receiving preoperatively opioids for the management of chronic cancer pain. Our goal is that the proposed approach will allow to identify and analyze the knowledge gap in the field and, in turn, will serve as a prerequisite for future research including systematic review and clinical studies.

Limitations

Although we will follow an accurate method for this scoping review, several limitations are anticipated. Because of the inclusion of publications written only in the English language, the search may exclude relevant articles in other languages. Furthermore, our broad search strategy might be associated with less accuracy on the aim of the review that may result in a large number of redundant references. Third, the analysis of the results must be interpreted considering that clinical trials of the perioperative opioid-induced effects on cancer are difficult to conduct, as during the perioperative care patients require a combination of anesthetic and no-anesthetic agents. These limitations could lead to serious inconsistency and/or risk of bias, downgrading the outcomes.

Implications

Despite the various limitations, the results of this scoping review may clarify doubts on an extremely important topic. The task is to understand if, in a cancer patient, an approach that limits or eliminates the use of opioids during and after surgery has immediate effects such as the reduction of nausea and vomiting, rapid mobilization, reduced inhibition of peristalsis, or it also results in an improvement of the oncological outcomes.

Abbreviations

OFA: Opioid-free anesthesia

PONV: Postoperative nausea and vomiting

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews

Declarations

Ethics Approval and Consent to participate

This paper does not require ethics approval.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

This study was mainly written by MC, and MF. FB, and RA collected the data. GE and CAF supervised the writing of the paper. AC, and BDC critically revised the paper. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Supplementary Files

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