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Traditional laxatives in preventing opioid-induced constipation in adult patients with cancer: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Opioid-induced constipation (OIC) affects up to 90% of patients with cancer receiving long-term opioid-related analgesic therapy, resulting in various potential complications, compromised pain management and decreased quality of life. Laxatives stimulate or facilitate bowel evacuation. Traditional laxatives, such as polyethylene glycol and lactulose, are widely used because of their low cost, easy accessibility and tolerability. OIC prophylaxis with laxatives is recommended for patients receiving opioid therapy. However, systematic reviews that support this practice are lacking. They have primarily focused on patients with existing constipation and the effectiveness of other pharmacological therapies. Thus, we are conducting a systematic review to evaluate the efficacy and safety of traditional laxatives in preventing OIC in adult patients with cancer.

Methods and analysis The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement was used to guide the reporting of this protocol. Database searches will be performed in PubMed, Embase, Web of Science, Cochrane Library and EBSCO from inception to a date within 6 months of the submission of the full systematic review (estimated 31 December 2024). Reference lists will also be accessed for additional studies, including Google Scholar, for the inclusion of grey literature. A combination of Medical Subject Headings/Emtree and free-text terms will be used when searching the core concepts of 'OIC', 'laxative' and 'cancer.' The eligibility criteria will be defined by the type of population (patients with cancer receiving opioid therapy), type of intervention (traditional laxatives) and type of study (randomised controlled trials and quasi-experimental trials). Two reviewers will independently select eligible studies, extract data and assess the methodological risk of bias. A third reviewer will be invited to reach a consensus if necessary. Subgroup and sensitivity analyses will be conducted to explore sources of heterogeneity.

Ethics and dissemination Ethical approval is not required, as patients will not be included in systematic reviews and meta-analyses. We will publish this study in a peer-reviewed journal and communicate the results at open conferences.

PROSPERO registration number CRD42024507127.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The literature search process is guided by the Joanna Briggs Institute approach.
⇒ Cochrane tools will be used to assess the quality of the included studies.
⇒ Sensitivity and subgroup analyses will be conducted to investigate potential sources of heterogeneity.
⇒ Only studies published in English databases will be included.

INTRODUCTION

Cancer is a major threat to public health. In patients with cancer, pain is reported to be one of the most distressing and burdensome symptoms. With the implementation of new pain management guidelines, drugs and treatment strategies, there has been a decline in the prevalence and severity of pain. A recent systematic review (SR) and meta-analysis showed that, compared with observations in previous studies, the overall prevalence of cancer-related pain was 44.5%, and 30.6% of the patients with cancer experienced moderate to severe pain.[1]

According to the WHO analgesic ladder and other published guidelines, opioid agonists, such as morphine and oxycodone, are the mainstay therapies for treating moderate-to-severe pain. Along with pain relief, patients on chronic opioid use may also experience various side effects, such as sedation, respiratory depression and opioid-induced bowel dysfunction, with opioid-induced constipation (OIC) being the most common,[2] affecting up to 90% of patients receiving opioid therapy for cancer-related pain.[3] By binding to μ-opioid receptors in the gastrointestinal tract, opioids increase circular muscle contraction, reduce coordinated peristalsis and decrease fluid and electrolytes secretion, leading to prolonged transit time and dry,

hard stools.[4] OIC is defined by the Rome IV criteria as new or worsening symptoms of constipation when initiating, changing or increasing opioid therapy, and it must include two or more of the following symptoms: straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction/blockage, manual manoeuvres with the same frequency cut-off (25%) and fewer than three spontaneous bowel movements per week.[5]

OIC has a series of negative effects on patients receiving opioid therapy. In addition to serious complications, such as faecal impaction, bowel perforation, anal fissures and rectal bleeding, OIC also causes impaired quality of life, compromised pain management and increased healthcare and economic burdens. The quality-of-life scores of patients with OIC have been reported to be significantly lower.[6] To alleviate OIC, one-third of patients reduce opioid use; however, almost all of them report worsening pain.[7] In the first year of opioid therapy, patients with OIC are more likely to experience all-cause hospitalisation (OR=2.47), or pain-related hospitalisation (OR=2.15), and the mean unadjusted overall healthcare costs postindex in the USA were $21 629 higher than for those without constipation.[8]

In the broadest sense, laxatives include all agents that induce defecation. Among them, traditional laxatives, distinct from recently developed agents,[9] such as osmotic and stimulant agents, are most commonly used for constipation management in clinical settings because of their low cost, easy accessibility and tolerability. They act in different ways to counter the bowel responses to μ-opioid receptor activation, either by drawing water into the intestine and softening stools or by irritating sensory nerve endings to stimulate bowel movements.[9] Laxatives have been recommended as first-line OIC treatment according to international guidelines.[10 11] However, this recommendation is based on limited evidence and SRs involving patients with chronic idiopathic constipation, which differs from OIC in terms of pathophysiological mechanisms.[5 9 12–14] Therefore, these results must be interpreted with caution when extrapolating to patients with OIC. An SR of this population is urgently needed to support this practice.

An updated Cochrane review, published in 2015, aimed to determine the effectiveness and differential efficacy of laxative administration among palliative care patients with constipation and found no differences in effectiveness between different laxatives.[15] In such a palliative care setting, constipation becomes a more complex and challenging problem, occurring as a combined result of the medications used for pain control, disease, diet and mobility factors. Another recent network meta-analysis summarised the effectiveness of the pharmacological therapies in patients with cancer and advanced illness, confirming the significant benefits of methylnatrexone and naldemedine use.[16] Given the available information, previous SRs mainly focused on the treatment, not the prevention, of OIC; they addressed patients diagnosed with OIC but not those at great risk of developing symptoms. However, a consensus has been reached that once OIC occurs, it is much harder to reverse the process; thus, prevention is the best approach.[16] In patients receiving opioid therapy, laxatives are recommended to be coprescribed as OIC prophylaxis.[17]

To the best of our knowledge, there is a paucity of SRs on OIC prophylaxis in adult patients with cancer using traditional laxatives.[18] Since more attention has been drawn to evaluating the efficacy and safety of traditional laxatives for prophylactic use,[19–23] it is now the right time to summarise the current evidence on the use of inexpensive, accessible and well-tolerated traditional laxatives to address the often unrecognised and poorly managed OIC from a preventive perspective. Therefore, this SR aims to evaluate the efficacy and safety of traditional laxatives in preventing OIC in adult patients with cancer-initiating, changing or increasing opioid therapy and to describe the characteristics of OIC prophylaxis based on traditional laxatives.

METHODS AND ANALYSIS

Study design and registration

This SR and meta-analysis protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.[24] This protocol has been registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under registration ID CRD42024507127.

Eligibility criteria for study selection

Types of participants

Patients with cancer, aged ≥18 years, given traditional laxative(s) for prophylactic purposes when initiating, changing or increasing opioid therapy will be included, irrespective of the stage and type of cancer, the priority of cancer care (curative or palliative care) and the care setting (outpatient, inpatient, integrated care facilities or home care).

Types of studies

Randomised controlled trials and quasi-experimental studies written in English will be included. Data from ongoing studies will be followed by the authors. Duplicate publications reporting the same parameters will be excluded.

Types of interventions

All traditional laxatives will be considered, regardless of the type of agent (osmotic, stimulant, bulk-forming or lubricant), form of administration (pills, tablets, capsules, patches or suppositories) and doses administered.

Types of controls

These may include placebo controls, usual care controls or controls comparing different laxatives or their combinations.

Outcome measures

Eligible studies should report the primary outcomes, including defecation frequency and stool consistency, assessed with validated instruments, such as the Bristol Stool Form Scale,[17] straining, and the sensation of incomplete evacuation, measured with validated tools, such as the clinician-administered Bowel Function Index questionnaire,[17] and the frequency of rescue therapies, including enemas and manual manoeuvres to facilitate bowel movements. Secondary outcomes are expected to include laxative-related adverse events (nausea/vomiting, abdominal pain, flatulence, diarrhoea and faecal incontinence),[15] costs and patient preference for laxatives.

Search strategy

The literature search will be guided by the Joanna Briggs Institute approach.[25] Minor adjustments may be necessary to finalise the search strategy.

Electronic data

Starting with the PubMed database, subject terms and synonyms of the core concepts 'opioid', 'constipation', 'prevention', 'laxatives' and 'cancer' will be analysed during the preliminary search. Following this, searches will be conducted in Embase, Web of Science, Cochrane Library and Elton B. Stephens Company (EBSCO). A comprehensive retrieval strategy will be formulated for eligible articles published from database inception to a date within 6 months of the submission of the full SR (estimated 31 December 2024). Medical Subject Headings and free-text terms will be used together. Online supplemental material S1 shows the detailed search strategy for the databases.

Search for other resources

There are several other methods to broaden the literature search. The reference lists of included studies will be inspected for additional relevant studies. Google Scholar will also be accessed to include grey literature in the first 10 pages. Leaders in OIC management, clinicians and researchers will be contacted to identify other studies. Moreover, as sponsors of traditional laxatives, the manufacturers of the agents can be contacted for potential data when necessary.

Study selection

Two PhD nursing students will independently select the studies. EndNote will be used to deduplicate the retrieved studies. A pilot test will be conducted at the beginning of the selection process to ensure a high level of consistency within the review team. We will refine and clarify the eligibility criteria mentioned previously and then rank the importance of the criteria as 'constipation', 'opioid', 'traditional laxatives' and 'age≥18 years'. Based on this, we will screen titles and abstracts to focus more closely on this study. Full texts of the included articles will be downloaded for further assessment. If there is any disagreement between the authors, we will first discuss it ourselves to reach an agreement; if not, a third researcher will be invited to make a decision.

Data extraction

The data will be extracted and recorded independently by two students. An Excel spreadsheet will be created and piloted to collect information on the key features and results of the included studies. The items will include the first author, year of publication, region, study design, participants (number, age, sex and dropouts/withdrawals), laxative(s) (type, dose(s), route of delivery and control used), outcome data (laxation response and assessment method, tolerance and adverse effects, cost and participants' preferences), findings and duration of follow-up.

Dealing with missing data

Various potential sources of missing data, such as unpublished studies and unanalysed or unreported outcomes, may introduce bias into an SR.[26] Therefore, as much data as possible will be obtained from unpublished articles. For full texts or any data from relevant studies that are not available, the original investigators will be contacted at least once via email to request missing data, in order to minimise potential bias. Sensitivity analyses will be performed to assess how sensitive the results are to reasonable changes in the assumptions made. In addition, we will elucidate the potential impact of missing data on the final findings of the review in the Discussion section.

Risk-of-bias appraisal

The Cochrane Collaboration Tools,[27] ROB-2.0 (The Cochrane Risk of Bias Tool, V.2 for randomised trials, updated in 2011) and ROBSIN-I (Risk Of Bias in Non-randomised Studies of Interventions, 2017 version) for randomised controlled trials and non-randomised studies, respectively, will be used to methodologically appraise the risk of bias in the included studies. The main sources of systematic bias will be assessed in this SR, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data and selective reporting. Two PhD students will independently conduct the assessments. For each domain, 'low risk' will be assigned if the defined criteria are met, 'high risk' if they are not and 'unclear' for insufficient information. A third review author will be consulted in cases of persistent disagreement.

Data synthesis and statistical analysis

Data synthesis

RevMan software will be used for data synthesis. For the primary outcome, the frequency of defecation or scale scores, standardised mean difference (SMD) and corresponding 95% CI will be calculated for continuous variables. An SMD of zero means that there is no difference between the groups, and a negative SMD means that the experimental group had a lower mean score than that of the control group, and vice versa. SMD values of 0.2

to 0.5 are considered a small effect, values of 0.5 to 0.8 a moderate effect and values >0.8 a large effect. Because SMD is not intuitive to interpret, the findings may be translated into units of one or more specific measurement instruments.[27] For dichotomous variables, the risk ratio and corresponding 95% CI will be analysed. Statistical significance will be set at p<0.05. Forest plots will be used for the analysis.

Assessment of heterogeneity

Heterogeneity among trials will be examined by visual inspection of forest plots and by the χ^2 test for heterogeneity (a p value of 0.10 will be considered statistically significant). The I^2 statistic will be used to measure heterogeneity. The results will be interpreted in accordance with the ranges provided in the Cochrane Handbook for Systematic Reviews of Interventions, V.6.4. When I^2 ranges from 0% to 40%, heterogeneity is not considered significant. Moderate heterogeneity may be possible when the I^2 ranges from 30% to 60%. If it ranges from 50% to 90%, it may represent substantial heterogeneity, and if I^2 is 75%–100%, considerable heterogeneity will be indicated.

Statistical analysis

For the statistical analysis, a meta-analysis will be performed using a fixed-effect model when the parameters are highly homogeneous (I^2 <50%). When I^2 ≥50%, a random-effects model (DerSimonian and Laird method) will be appropriate for analysis, and subgroup and sensitivity analyses will be conducted to investigate potential sources of heterogeneity. If the heterogeneity is considerably high (I^2 >75%), a narrative description will be provided.

Subgroup analysis

If heterogeneity is detected in this meta-analysis (I^2 >50%), subgroup analyses will be performed to investigate possible sources. The different types, doses and routes of administration of opioids and traditional laxatives may introduce clinical heterogeneity.

Sensitivity analysis

If a sufficient number of studies is available, sensitivity analyses will be performed to locate the source of heterogeneity. We will try to exclude studies assessed as having a high risk of bias or unpublished trials and then compare the new results with the original ones.

Publication bias

To avoid publication bias, unpublished studies will be included in the analysis as much as possible during the literature search. Egger's regression test or funnel plots will be used to identify publication bias. Publication bias will not be indicated if the distribution of the plots is symmetrical.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation working group methodology will be used to assess the strength of evidence for the outcomes, based on aspects, such as risk of bias, indirectness, inconsistency, imprecision and publication bias.[28] The quality of the evidence will be judged as high, moderate, low or very low, according to the confidence in the estimate of the effect.

Patient and public involvement

This is a secondary analysis of the available primary data, and no patients were involved in the process.

DISCUSSION

Nurses play a key role in the prevention and management of symptoms, such as constipation, and are eager to seek theoretical and clinical data based on high-quality evidence. OIC has affected a large number of patients with cancer on opioid therapy, posing great challenges to clinical nursing staff. Treatment is much harder than prevention, especially for patients with OIC. All patients initiating opioid therapy should be carefully assessed and educated about the risk of OIC, lifestyle modifications (hydration, physical activity and scheduled toileting) and laxative use.[17] However, studies have mainly focused on the treatment rather than the prevention of OIC. Thus, OIC prophylaxis requires great attention from both patients and healthcare providers. This SR aims to summarise the current evidence on the use of affordable, easy-to-obtain and well-tolerated traditional laxatives for the prevention of OIC in patients receiving opioid therapy. With the findings from this SR, it might be possible for clinical nurses to implement evidence-based practices, decrease patients' suffering from the side effects of opioids, and further improve their quality of life. Moreover, it may provide a reference for non-cancer populations with similar concerns.

Ethics and dissemination

Ethical approval is not required for patients who are not included in SRs and meta-analyses. We will publish this study in a peer-reviewed journal and communicate with scholars at open conferences.

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Contributors YL is the first author and registered the protocol in the PROSPERO database. YL obtained funding, critically revised the protocol and contributed to the

drafting of the final manuscript. YL and HH have been collecting and analysing the data. CX, LT and Y-l L revised and reviewed this article. All authors have read and approved the final manuscript. LL is the guarantor of the study.

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