

BMJ Open Efficacy of long-acting release octreotide for preventing chemotherapy-induced diarrhoea: protocol for a systematic review

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ABSTRACT

Introduction Diarrhoea is a common adverse effect induced by chemotherapy that can reduce the dose of chemotherapeutic drugs or interrupt the chemotherapy schedule. The current treatment strategies have various limitations. It has been shown that long-acting release octreotide (octreotide LAR) can decrease the occurrence and severity of diarrhoea, yet the efficacy of octreotide LAR in preventing chemotherapy-induced diarrhoea (CID) remains to be assessed. The main objective of this paper was to draw up a protocol for systematic review to evaluate the protective effects of octreotide LAR on CID. **Methods and analysis** We searched Medline, EMBASE, the Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang Data and the VIP Database without language restrictions from inception until 1 September 2016. The references of relevant studies were also manually searched. Two investigators independently accessed the selected studies, extracted data and assessed the reliability of the studies. Any discrepancies were resolved by a third investigator. The effect size of the selected studies was assessed by different measures based on the type of data. The selected studies were descriptively analysed. We then chose a fixed-effect model or a random-effect model based on statistical homogeneity, and pooled data from the studies for meta-analysis, if possible. The primary outcome was the incidence of diarrhoea. The secondary outcomes were the duration of diarrhoea, incidence of diarrhoea-associated symptoms, physical function and quality of life. All statistical analyses were performed by Review Manager V.5.3. **Ethics and dissemination** This systematic review did not require ethics approval, because it included aggregated published data, and not individual patient data. The review was published in a peer-reviewed journal. **Trial registration** This systematic review protocol was registered with PROSPERO (registration number: CRD 42016048573).

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INTRODUCTION

Diarrhoea is a common adverse reaction for patients with cancer undergoing various chemotherapy treatments, especially those containing 5-fluorouracil (5-FU), irinotecan and capecitabine.¹ The incidence of

Strengths and limitations of this study

- This was an objective and normative systematic review that focused on octreotide long-acting release as a potential prophylaxis, not as a treatment of chemotherapy-induced diarrhoea (CID).
- The results of this study addressed previous discrepancies, and generated an evidence-based intervention for CID.
- The participants were those undergoing chemotherapy for the first time and those already undergoing chemotherapy. The results might be biased by the different types of participants.
- The risk of heterogeneity inevitably existed due to types of diarrhoea and chemotherapy in selected studies. Therefore, subgroup analyses were implemented.

chemotherapy-induced diarrhoea (CID) has been reported to be 50%–80%,² with one-third of patients experiencing severe diarrhoea (grade 3/4).³ The occurrence of diarrhoea affects the benefits of chemotherapy by reducing the dose or delaying the schedule and also decreases the quality of life of patients. It can even increase the life-threatening risk of dehydration.^{1 2 4} In spite of the prevalence and severity of CID, it is often not recognised by clinicians and poorly managed.⁵

A consensus among experts and guidelines for the treatment of CID recommend prescribing loperamide and octreotide.^{6 7} Loperamide is only used for mild diarrhoea (grade 1/2), and it is mostly ineffective for severe diarrhoea. With worsening diarrhoea and increasing dose and frequency of the drug, the risk of cardiac arrhythmias increases.^{8 9} On the other hand, octreotide, a potent synthetic somatostatin analogue that has been used to treat CID for decades,¹⁰ is recommended for grade 3/4 diarrhoea or grade 1/2 CID accompanied with risk factors (nausea, vomiting,

fever and neutropaenia). In addition, it often requires hospitalisation to replenish fluids and electrolytes during dehydration, which increases the medical expenses of patients. The benefits of other drugs, such as budesonide,¹¹ probiotics,¹² antibiotics,¹³ activated charcoal¹⁴ and traditional Chinese medicine,^{15 16} are still uncertain, and clinical trials are warranted in the future. Thus, a vigilant and more aggressive prophylaxis for CID is beneficial to patients with cancer in reducing morbidity and medical expenses,¹⁷ especially for those with high-risk factors.

Long-acting release octreotide (octreotide LAR), a long-acting formulation of octreotide, is just as effective and tolerable as octreotide.¹⁸ It has been reported that somatostatin, and its analogue octreotide, can reduce the loss of water and electrolytes,¹⁹ suppress intestinal motility²⁰ and protect the intestinal barrier.²¹ Octreotide LAR has similar actions. Compared with the conventional formulation, octreotide LAR has advantages of slow release, a steady plasma concentration and convenient application.¹⁸ In particular, the pharmacokinetic profile of octreotide LAR indicates that it may be a good agent to prevent diarrhoea.

Octreotide LAR has been shown to effectively prevent CID in preliminary studies. In several patients who developed refractory CID towards conventional therapy, octreotide LAR sped up the resolution of CID and limited further episodes of diarrhoea during subsequent cycles of chemotherapy.²² Another study indicated that octreotide LAR can be used as a secondary preventive approach in patients experiencing grade 2–4 CID, and monthly injections reduced the incidence of diarrhoea while the chemotherapeutic regimen was completed.²³ However, inconsistent results were also reported. In patients with colorectal cancer, for example, most of whom received 5-FU and/or oxaliplatin, there was no benefit from octreotide LAR in terms of the incidence of diarrhoea or quality of life.²⁴ Another study showed that the prophylactic use of octreotide LAR was similar to placebo in the incidence of grade 2–4 acute diarrhoea.²⁵

A recent meta-analysis has shown that octreotide was more beneficial as a therapeutic rather than a prophylactic agent against diarrhoea,²⁶ although the existence of heterogeneity, such as the type of intervention (short-acting and long-acting octreotide) and the cause of diarrhoea (chemotherapy and radiotherapy), may have affected the conclusion. Thus, the protective effects of octreotide LAR for CID require additional studies.

The aim of this study was to systematically review clinical studies and to evaluate the protective effects of octreotide LAR on CID in patients with cancer. This study provided a protocol for the systematic review, and the protocol was performed by the PRISMA-P checklist (<http://www.prisma-statement.org/Extensions/Protocols.aspx>),²⁷ which is supplied in online supplementary Appendix 1.

METHODS AND ANALYSES

Inclusion criteria for study selection

Types of studies

We included randomised controlled trials (RCTs) and excluded case reports, case series, commentaries, quasi-RCTs and non-randomised controlled studies.

Types of participants

Patients with cancer (aged >18 years) undergoing chemotherapy with irinotecan, 5-FU and/or capecitabine, with active or prior CID, were included. Patients with any other condition such as a primary disease (eg, infective enteritis or inflammatory bowel disease), radiation enteritis or laxative agent use that causes diarrhoea were excluded.

Types of interventions

For the experimental intervention, octreotide LAR at 20–30 mg was administered intramuscularly every 4 weeks. Octreotide LAR combined with other treatments was included, while control group had the same treatment besides comparative interventions.

Comparative interventions included placebo, no treatment or conventional drugs. We included data on antidiarrhoea and supplementary therapy for patients experiencing diarrhoea during or after chemotherapy received in both arms.

Types of outcome measures

Primary outcomes

The primary outcome was the incidence of diarrhoea after chemotherapy, including the total of all grades of diarrhoea and the different grades of diarrhoea. The definition and grading of diarrhoea was according to the Common Terminology Criteria Adverse Events V.4.0.

Secondary outcomes

The secondary outcomes were as follows:

- i. the duration of diarrhoea;
- ii. the incidence of diarrhoea-associated symptoms (abdominal cramps, frank bleeding);
- iii. the physical function and quality of life. These outcomes were assessed by common scales for patients with cancer, such as the Performance Status, Eastern Cooperative Oncology Group, Karnofsky Performance Score and Quality of Life Questionnaire-Core.

Search methods for the identification of studies

Electronic searches

Six electronic databases, including Medline (via PubMed), EMBASE (via embase.com), the Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang Data and the VIP Database, were searched without language restrictions from inception until 1 September 2016. First, the target of retrieval was divided into three parts: (i) octreotide, (ii) chemotherapy and (iii) diarrhoea. Medical subject heading searches were performed for each part. The text word from the other search fields

Table 1 Search strategy used in Medline (via PubMed)

No.	Search items
1	octreotide (mh)
2	octreotide acetate (tiab)
3	long-acting octreotide (tiab)
4	long-acting release octreotide (tiab)
5	long-acting repeatable octreotide (tiab)
6	octreotide LAR (tiab)
7	1 or 2 or 3 or 4 or 5 or 6
8	chemotherapy(mh)
9	irinotecan(mh)
10	CPT-11 (tiab)
11	Campto* (tiab)
12	fluorouracil(mh)
13	5-Fluorouracil(tiab)
14	5-FU(tiab)
15	capecitabine(mh)
16	Xeloda(tiab)
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	Diarrhea (mh)
19	Diarrhoea (tiab)
20	enteritidis (tiab)
21	esoenteritis (tiab)
22	intestinal injury (tiab)
23	adverse reaction (tiab)
24	18 or 19 or 20 or 21 or 22 or 23
25	randomized controlled trial (pt)
26	controlled clinical trial (pt)
27	randomized (tiab)
28	placebo (tiab)
29	clinical trials as topic [mesh: noexp]
30	randomly (tiab)
31	trial (ti)
32	25 or 26 or 27 or 28 or 29 or 30 or 31
33	7 and 17 and 24 and 32

(title and abstract) was then retrieved and combined with the corresponding subject term using 'OR'. Finally, the three parts were combined using 'AND'. The limitation of the article type referred to the high sensitive retrieval strategy for RCT in the Cochrane Handbook for Systematic Reviews of Interventions. The search strategy for Medline (via PubMed) is shown in table 1. The other electronic databases were also be searched using this strategy.

Search of other resources

The references of retrievable studies were manually searched. In addition, the original text and references of other relevant literatures, including conference

proceedings, academic dissertations, reviews, systematic reviews and meta-analyses, were also searched.

Data collection and analysis

Selection of studies

Studies from medical databases and the manual search were imported into EndNote X7. Repetitive studies were excluded. All investigators were required to reach a consensus on the inclusion criteria before screening. Two investigators (CD, BD) then independently screened the titles and abstracts of these studies. Potentially eligible studies were confirmed by evaluating the full text. Any disagreements were arbitrated by a third investigator (HT).

Data extraction and management

Two investigators (CD, BD) independently extracted data from the selected studies and recorded it into the data extraction form.

The extracted data were as follows:

- i. the characteristics of the study (authors, country, year of publication, design, sample size, duration of intervention, follow-up and quality of study);
- ii. the characteristics of the participants (age, gender, race, type of cancer, stage of cancer and chemotherapy regimen);
- iii. the intervention (octreotide LAR and comparators);
- iv. the outcomes (incidence of diarrhoea, duration of diarrhoea, incidence of diarrhoea-associated symptoms, physical function and quality of life).

Assessment of risk of bias in the selected studies

The risk of bias for each selected study was independently assessed by two investigators (CD, BD) with the Cochrane's risk of bias tool, including (i) selection bias (random sequence generation, allocation concealment), (ii) performance bias (blinding of participants and personnel), (iii) detection bias (blinding of outcome assessment), (iv) attrition bias (incomplete outcome data), (v) reporting bias (selective reporting) and (vi) other biases. Each type of bias was classified as low risk, unclear risk or high risk. Two investigators (CD, BD) graded the risk level of these biases, and provided supportive evidence for the judgement in a risk of bias table. Any disagreements were arbitrated by a third investigator (HT).

Measures of the treatment effect

The effect size of the included studies was assessed with different measures based on the type of data. Continuous data were expressed as the weighted mean difference or standardised mean difference (eg, duration of diarrhoea). Dichotomous data were expressed as the relative risk (RR) (eg, incidence of diarrhoea). A 95% CI was used for all data analysis.

Dealing with missing data

In cases of missing data, we contacted the authors of the study. If we failed to obtain the missing data, the study was not included in the data analysis.

Assessment and investigation of heterogeneity

Cochran's Q -test and I^2 statistics were used to evaluate the heterogeneity of the included studies. A Q -test with $p > 0.10$ and an I^2 of no more than 50% indicated that statistical homogeneity was acceptable. Otherwise, we analysed the potential cause of heterogeneity, which included the methodological characteristics of the study and the biological characteristics of the participants. Subgroup analysis and sensitivity analysis were used to account for heterogeneity.

Assessment of reporting biases

Reporting biases or small-study effects were checked by funnel plots generated from data of more than 10 studies.

Data synthesis

The selected clinical studies were descriptively analysed, and summary statistics were presented. The mean difference (MD) was used to assess continuous data, while the relative risk (RR) for dichotomous data, 95% CI were used for all data. If studies were sufficiently homogeneous, data across studies were pooled for meta-analysis using Review Manager V.5.3. If the Q -test indicated $p > 0.10$, we used a fixed-effect model. Otherwise, we used a random-effect model, and the potential cause of heterogeneity was interpreted by subgroup analyses and sensitivity analyses. On the other hand, if meta-analysis was not feasible because of significant statistical heterogeneity, we generated a systematic narrative synthesis to summarise the characteristics and results of the included studies.

Subgroup analysis

Subgroup analysis was performed on at least 10 studies to determine the potential cause of heterogeneity. The different chemotherapeutic and comparative interventions were divided into subgroups for analysis according to the actual conditions.

Sensitivity analysis

To explore the possible sources of heterogeneity, we removed each study one by one, and reanalysed the remaining studies. The before and after results were compared to determine the stability of the integrative results.

Grading the quality of evidence

The quality of evidence for primary outcomes in the review was assessed according to Grading of Recommendations Assessment, Development and Evaluation.²⁸ This classifies the evidence into four grades: high, moderate, low and very low quality.

ETHICS AND DISSEMINATION

This systematic review was performed with aggregated published data and not included primary data, thus ethical approval was not required. The results of the systematic review were disseminated through a peer-reviewed journal.

DISCUSSION

Most patients with cancer require chemotherapy, but various adverse effects limit its widespread application. Thus, appropriate adjuvant therapies are necessary to enhance patients' tolerance to chemotherapy and to achieve suitable treatment schedules. Conventional CID management mostly treats the symptoms after diarrhoea has occurred and ignores the importance of prophylactic interventions.

Most recent studies have reported on the use of octreotide LAR as a preventive approach for CID. Its mechanism of action is similar to that of octreotide, which is recommended for the treatment of severe diarrhoea. Although the efficacy of octreotide LAR is acceptable for chronic refractory CID, its use is limited for acute CID due to its pharmacokinetic profile and limited initial release.²⁹ These findings indicate that octreotide LAR is a better prophylactic agent for CID. In a previous study that involved the injection of octreotide LAR, 10 out of 12 patients with CID grade ≥ 2 had a significant and persistent reduction in the incidence of diarrhoea after receiving an entire dose of chemotherapy.²³ Thus, octreotide LAR reduces the incidence of diarrhoea, especially severe diarrhoea (grade ≥ 2). For patients with refractory CID, octreotide LAR may shorten the duration of diarrhoea, thus improving the quality of life by decreasing abdominal cramping and diarrhoea.²² Based on results from clinical studies, octreotide LAR may be administered as a prophylactic agent prior to chemotherapy or the next cycle of chemotherapy.

It is important not to ignore the discrepancies that have arisen from previous studies because inconsistent results may be due to differences in the characteristics of patients and the types of diarrhoea and chemotherapy. A comprehensive systematic review requires the analysis of results from multiple studies, which in this study will be important to confirm the protective effects of octreotide LAR on CID.

In addition, the different effects of octreotide LAR on diarrhoea induced by various chemotherapy agents²⁴ may be related to the prevalence and severity of diarrhoea. Therefore, it will also be important not to overlook conclusions that may be affected by potential limitations in this protocol. A risk of heterogeneity may exist due to the different types of diarrhoea and chemotherapy, and subgroup analysis will be conducted, if this is shown to be the case. The different types of chemotherapy may also sway the systematic reviews towards bias.

Contributors CD and BD contributed equally to this work. LJ proposed the concept of the study, CD is the drafter of the manuscript protocol. BD, HT and LJ contributed to revise the manuscript. LJ and HT made the search strategy. CD and BD independently screened eligible studies, extracted data, assessed the quality of included studies and entered data into Review Manager for data synthesis, HT arbitrated by discussion if disagreement occurred. All authors participated in the design of the study, and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

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