INPLASY PROTOCOL

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Corresponding author:
Sophie Hooke

sophie.hooke@auckland.ac.nz

Author Affiliation:
The University of Auckland.

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None declared.

Postoperative prevalence of pancreatic enzyme replacement therapy (PERT) prescription in patients post-pancreaticoduodenectomy: protocol for a systematic review

Hooke, S[1]; Russell, K[2]; Windsor, JA[3].

Review question / Objective: **The aim of this systematic review is to document the prescribing patterns of PERT in patients following PD to determine the level of compliance with current guidelines/recommendations. To this end, the proposed systematic review will answer the following questions: 1. What is the prevalence of PERT prescription in patients post-PD? 2. What are the indications for commencement of PERT prescription in patients post-PD? 3. What additional factors are associated with variation in rates of PERT prescription?**
Condition being studied: **Given PERT has been shown to not only improve quality of life but also improve survival however, there is evidence that not all patients with PEI receive adequate PERT (19). Understanding the prescribing and monitoring patterns of PERT internationally is a critical first step to understanding the barriers to improving care for this group of patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 September 2022 and was last updated on 15 September 2022 (registration number INPLASY202290064).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to document the prescribing patterns of PERT in patients following PD to determine the level of compliance with current guidelines/recommendations. To this end, the proposed systematic review will answer the following questions: 1. What is the prevalence of PERT prescription in patients post-PD? 2. What are the indications for commencement of PERT prescription in patients post-PD? 3. What additional factors are associated with variation in rates of PERT prescription?**

Rationale: Pancreatic exocrine insufficiency (PEI) is characterized by inadequate production, insufficient secretion, and/or inactivation of pancreatic enzymes, resulting in maldigestion (1). A recent review of international studies found that the prevalence of PEI following PD ranged from 15 to 42% of patients (2). Another review found a wider range of PEI prevalence of 23-80% post-PD and 46-100% of patients with resectable pancreatic and ampullary cancers (3). A prospective observational cohort study published in 2022 revealed that at three months post-PD, 93% (27/29) of patients had developed PEI and after 6 months, 100% of patients were diagnosed with PEI (4).

A recent Australian study found a significantly high rate of PEI after PD (89%) (5). Patients who underwent pancreatoduodenectomy were particularly at risk of malnutrition, with close to 50% of patients assessed as malnourished (5). Despite the wide range of PEI prevalence, international studies report low rates of PERT prescribing in pancreatic cancer, even though guidelines recommend PERT as an integral part of treatment (6) (7).

Data published last year revealed that approximately 50% of long-term PD survivors report ongoing gastrointestinal symptoms, suggestive of PEI, using a pancreas cancer-specific quality of life tool (EORTC QLQ-PAN26) (8). This is disappointing as the efficacy of PERT to reduce these symptoms and as the mainstay of treatment for PEI is well established (9). Treating PEI with PERT increases survival, particularly in those experiencing significant weight loss (10). Despite this efficacy and improvement in symptoms, PEI remains undertreated (11-13)

There have been several recent reviews on this topic as summarized below:

1. Thogari et al. 2019. Aimed to determine the incidence of PEI following PD.
2. Chaudhary et al. 2020. Aimed to analyse the prevalence and pathophysiology of PEI after pancreaticoduodenectomy, gastrectomy and pancreatojejunostomy and examine the use of PERT for effectively managing PEI.
3. Moore et al. 2021. Aimed to determine the incidence and diagnostic criteria for PEI after PD, distal pancreatectomy (DP) or central pancreatectomy (CP) for pancreatic cancer.
4. Pathanki et al. 2020. Aimed to ascertain the incidence of PEI, and its consequences and management in the setting of PD for indications other than chronic pancreatitis.

Previous reviews, whilst similar to the present, differ as their primary outcome was PEI incidence, rather than PERT prescription prevalence.

Furthermore, some have confused the issue by defining PEI solely by whether the patient was on PERT. If they do discuss PERT, they focus on the effects of PERT and ways to optimise PERT administration rather than directly reporting the prevalence of PERT prescription.

However, the rate of PERT prescription itself is important because there is no highly sensitive test for early PEI. Diagnostic tests, such as fecal-elastase-1, do not detect PEI until it has reached an advanced stage. Deterioration of up to 90-95% of pancreatic exocrine function may be needed before clinical signs of PEI develop (3). Therefore, clinicians often rely on the development of symptoms such as steatorrhea and weight loss.

The poor diagnostic sensitivity and high incidence of early PEI is why international guidelines recommended routine use of PERT following PD (10,11). Depending on how its defined, many studies are likely to under-report the incidence of PEI because of these issues.

In recent studies, pancreatic surgery for pancreatic adenocarcinoma combined with adjuvant chemotherapy has shown a median and 5-year survival rate of approximately 20 months and 20-30%, respectively (14-16). The development of PEI leads to malnutrition, reduced quality of life, increased hospital stays, poor survival (17)(18). According to an observational study, the degree of PEI measured by faecal elastase-1 (FE-1) was strongly associated with poor survival in patients with advanced pancreatic cancer (18).

Condition being studied: Given PERT has been shown to not only improve quality of life but also improve survival however, there is evidence that not all patients with PEI receive adequate PERT (19). Understanding the prescribing and monitoring patterns of PERT internationally is a critical first step to understanding the barriers to improving care for this group of patients.

METHODS

Search strategy: Literature search strategies will be developed using medical subject heading (MeSH) and text words related to pancreatic enzyme replacement therapy (PERT). We will search MEDLINE (OVID interface, 1948 onwards) and Scopus (1970 onwards). PubMed will not be searched as it is the same database at MEDLINE OVID, but under a different interface. The literature search will be limited to English language and human subjects. To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews identified through the search.

Both qualitative and quantitative studies will be sought. No study design or date limits will be imposed on the search. The specific search strategies will be created by the authors of this review with assistance from a Medical and Health Sciences Librarian with expertise in systematic review searching where needed. The MEDLINE strategy will be developed with input from the project team, then peer reviewed by the librarian. A draft MEDLINE search strategy is included in below.

1. Pancreaticoduodenectomy/
2. Pancreatectomy/
3. "pancreatic resection".mp.
4. pancreatectomy.mp.
5. pancreaticoduodenectomy.mp.
6. 1 or 2 or 3 or 4 or 5
7. Enzyme Replacement Therapy/
8. "enzyme replacement therapy".mp.
9. "pancreatic enzyme replacement therapy".mp.
10. 7 or 8 or 9
11. Exocrine Pancreatic Insufficiency/
12. "pancreatic exocrine insufficiency".mp.
13. 11 or 12
14. 10 or 13
15. 6 and 14

The search strategy was translated into Scopus with the help of a librarian and the use of a systematic review translation assistance tool, The Polyglot Search Translator (48). The final Scopus search is outlined below:

(INDEXTERMS(Pancreaticoduodenectomy) OR INDEXTERMS(Pancreatectomy) OR TITLE-ABS-KEY("pancreatic resection") OR TITLE-ABS-KEY(pancreatectomy) OR TITLE-ABS-KEY(pancreaticoduodenectomy)) AND ((INDEXTERMS("Enzyme Replacement Therapy") OR TITLE-ABS-KEY("enzyme replacement therapy") OR TITLE-ABS-KEY("pancreatic enzyme replacement therapy") OR INDEXTERMS("Exocrine Pancreatic Insufficiency") OR TITLE-ABS-KEY("pancreatic exocrine insufficiency"))

The review authors will independently screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain full reports for all titles that appear to meet the inclusion criteria or where there is any uncertainty. Reviewers will then screen the full text articles and decide whether these meet the inclusion criteria. We will seek additional information from study authors where required to resolve questions about eligibility. We will resolve disagreements or conflicts through discussion. We will record reasons for exclusion via Covidence. Neither of the review authors will be blind to the journal titles or to the study authors or institutions.

Participant or population: Studies of patients >18 years of age who underwent PD or variations (PD with PJ or PG anastomosis, pylorus-preserving PD) for any indication (pancreatic cancer, chronic pancreatitis, etc) will be included. Studies where PERT is used as the intervention will be excluded.

Intervention: N/A.

Comparator: N/A.

Study designs to be included: We will include all English-language, randomized

controlled trials (RCTs), including cluster RCTs, controlled (non-randomized) clinical trials (CCTs), controlled before-after (CBA) studies, prospective and retrospective comparative cohort studies, case-control or nested case-control studies, and cross-sectional studies. We will exclude case series, reviews, patents, guidelines and meta-analyses.

Eligibility criteria: All selected studies were required to meet the following inclusion criteria: reporting the prevalence of prescription of pancreatic enzyme replacement therapy (PERT); and population (adult patients, aged at least 18 years, who had undergone PD including variations (such as pylorus-preserving PD) for any indication (malignancy, benign disease, chronic pancreatitis, etc.). Articles were excluded if they did not meet the inclusion criteria, were case reports, reviews, patents, guidelines, or meta-analyses, were studies conducted in animals, if PERT was used as the intervention, and if the study investigated outcomes following non-PD surgical procedures alone (such as distal pancreatectomy, total pancreatectomy, or central pancreatectomy). If studies investigated multiple pancreatic surgical procedures, they were included in the review if postoperative outcomes for PD were reported separately.

Information sources: A systematic search will be conducted to identify relevant primary studies that reported on the rates of PERT prescription in patients post-pancreaticoduodenectomy. Endpoints of interest include prevalence, dose and dosage of PERT, indication for pancreatic resection, baseline characteristics of patients and definition of pancreatic exocrine insufficiency (PEI).
Electronic databases (Medline OVID and Scopus) will be searched using a predefined search strategy. PubMed will not be searched as it is the same database as Medline OVID, but under a different interface. The search strategy was developed using medical subject headings (MeSH) and text words related to PERT and pancreatic surgery. Authors consulted a Research Services librarian at the University of Auckland for advice on the initial search strategy. Subsequently, some minor changes were made to ensure literature saturation and retrieval of all relevant articles. MeSH terms were listed on separate lines following by a line of keywords that match the MeSH concept to ensure no articles were overlooked. This was crucial because some publications in Medline aren't indexed with MeSH until a year after publication.

Main outcome(s): The primary outcome is the prevalence of PERT prescription in patients post-PD. For each study, the following data will be extracted, if available: study ID (DOI or PubMed ID), title, lead author contact details, country, study aims, design and dates, statistical methods, sample recruitment criteria and methods, sample size, demographics of patients (sex distribution, mean or median age), data on the surgical procedure performed (procedure, indication for surgery), indication for PERT prescription, definition of PEI, PERT dosage, dose and brand, and the prevalence and frequency of PERT usage. In studies that have multiple study arms, data will be extracted only for the correct surgical procedure group (i.e. pancreaticoduodenectomy). Data will be extracted in all forms (dichotomous, continuous) that are reported in the included studies. Data will be exported from Covidence and entered into a summary table in Microsoft Excel before being cleaned and summarized.

Data management: Search results, including titles, citation, abstracts, and full texts, will be uploaded into an Internet-based systematic review management software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, http://www.covidence.org). This will facilitate collaboration among reviewers during the study selection and data extraction process.

Quality assessment / Risk of bias analysis: Included non-randomised studies may or may not have a control group or the control

used by authors may not be relevant to this topic. To assess the risk of bias within included studies, the methodological quality of potential studies will be assessed by using the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Again, this will be completed by two independent reviewers.
The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE). The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect).

Strategy of data synthesis: The two independent reviewers will extract data using pre-determined and pre-designed forms. Data will be extracted in all forms (dichotomous, continuous) that are reported in the included studies. Data will be exported from Covidence and entered into a summary table in Microsoft Excel before being cleaned and summarized. A systematic narrative synthesis with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies will be constructed. The narrative synthesis will explore the relationship and findings both within and between includes studies.

Subgroup analysis: N/A.

Sensitivity analysis: N/A.

Language restriction: N/A.

Country(ies) involved: New Zealand.

Other relevant information: Please note that this protocol is being registered retrospectively due to initial decision not to register the protocol. Upon further reflection and discussion, the decision was made by authors to register this systematic review with INPLASY therefore formal screening had already commenced at the time of registration.

Keywords: Pancreaticoduodenectomy; pancreatectomy; pancreatic resection; pancreatic exocrine insufficiency; pancreatic enzyme replacement therapy; enzyme replacement therapy; enzyme; Whipple's.

Dissemination plans: This systematic review will be published as part of the corresponding authors Master's thesis at the University of Auckland. Dissemination of findings may be included at professional conferences, events and workshops.

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Contributions of each author:

Author 1 - Sophie Hooke.
Email: sophie.hooke@auckland.ac.nz
Author 2 - Kylie Russell.
Email: kbec@aucklanduni.ac.nz
Author 3 - John A Windsor.
Email: j.windsor@auckland.ac.nz