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Total pancreatectomy and islet autotransplantation for chronic pancreatitis (Protocol)

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[Intervention Protocol]

Total pancreatectomy and islet autotransplantation for chronic pancreatitis

Abigail E Vallance[1], Colin H Wilson[1], Ashley Dennison[2], Derek M Manas[1], Steven A White[3]

[1]Institute of Transplantation, The Freeman Hospital, Newcastle upon Tyne, UK. [2]Department of Hepatobiliary Surgery, Leicester General Hospital, Leicester, UK. [3]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

Contact address: Colin H Wilson, Institute of Transplantation, The Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN, UK. Colin.Wilson@nuth.nhs.uk, colinwilson2206@gmail.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess and compare the effectiveness of TP/IAT with that of alternative treatments for the management of individuals with CP.

BACKGROUND

Description of the condition

Chronic pancreatitis (CP) is a condition characterised by fibrosis and inflammation of the pancreatic parenchyma resulting in progressive and irreversible damage (Blondet 2007). Cases of CP appear to be increasing and, although the exact prevalence is unknown, in Western Europe there are estimated to be around 26 cases per 100,000 population (Dite 2001; Levy 2006; Spanier 2008). Chronic alcohol use accounts for the majority of the cases of CP in Western countries; however, other factors including genetic mutations, pancreatic duct obstruction, hypertriglyceridaemia, hypercalcaemia and autoimmune disorders are also implicated (Etemad 2001; Witt 2007). Recurrent abdominal pain is experienced by 95% of individuals with CP (Walsh 2012), which is in turn associated with poor quality of life and depression (Ohayon 2010). Destruction of exocrine and endocrine cells of the pancreas can result in diabetes and malabsorption (Witt 2007). The chronic inflammation involved in chronic pancreatitis has also been proposed as an independent risk factor for the development of pancreatic cancer (Malka 2002).

Description of the intervention

The primary goal of managing CP is to achieve long-term pain relief while reducing associated complications. An ideal intervention would not only relieve pain but also reduce chronic opioid use, maximise endocrine and exocrine function, improve quality of life and reduce complications such as pancreatic cancer, pseudocyst and duodenal stenosis (Raimondi 2010).

There are multiple hypotheses for the pathophysiology of pain in CP, which are reflected in the diverse and numerous management options available. Increased intraductal pressure has been implicated as a possible cause of pain; however, around 30% of individuals treated with decompressive surgery will still experience recurrent attacks of pain (Beger 1999).

Surgical procedures available for the management of CP may be subdivided into drainage procedures, procedures involving resection and those combining the two. Resection procedures for the treatment of CP include pancreaticoduodenectomy (Whipple procedure), pylorus-preserving pancreaticoduodenectomy, duodenal-preserving pancreatic head resection (Beger procedure), distal pancreatectomy and total pancreatectomy (TP). Drainage procedures include Puestows (side-to-side longitudinal pancreaticojejunostomy) and combination procedures include Izbicki (longitudinal V-shaped excision of the ventral pancreas) and Frey's (local resection of the pancreatic head with extended longitudinal pancreaticojejunostomy) (Shrikhande 2006).

Endoscopy, which is inherently less invasive, can also be used to treat pain in CP via endoscopic retrograde cholangiopancreatography (ERCP) procedures. Drainage can be provided by the insertion of a pancreatic stent, sphincterotomy or dilation of the pancreatic duct (Wilcox 2009).

Other treatment modalities for CP include the endoscopic or thoracoscopic denervation of sympathetic pain afferents (Puli 2009; Shrikhande 2006).

Conservative methods involve centrally acting analgesic drugs and pancreatic enzyme supplementation.

As can be seen there is a wide range of treatment options, each of which have a differing risk-benefit profile. At one end of the spectrum, minimal intervention (simple analgesia) may provide very little pain relief, whereas TP will leave individuals liable to the complication of brittle diabetes (Berney 2000).

To combat this, TP with islet cell autotransplantation (IAT) (TP/IAT) has gained popularity over the past 40 years. This procedure was first performed in 1977 by Sutherland and colleagues at the University of Minnesota in the USA, and was a unprecedented success. The first individual who underwent this procedure remained pain free and insulin independent until her death from an unrelated cause 6 years later (Sutherland 1980). Since then other centres have struggled to realise this early success, with the notable exception being the Leicester Hepato-Pancreato-Billiary Unit in the UK (White 2001). Recently. the procedure has received more interest, particularly in the USA, and is regaining popularity with improved islet isolation and reimplantation techniques.

How the intervention might work

TP/IAT can relieve the severe pain associated with CP whilst preventing or minimising the occurrence of brittle diabetes (Bramis 2012). TP/IAT is performed in a single operation. There are several techniques used for islet cell isolation. with the modified Ricordi method being the most common (Ricordi 1988). In brief, following excision of the pancreas gland, the pancreatic duct is cannulated and enzymes used to digest the pancreas. Islet cells are then prepared intraoperatively whilst an enteroenterostomy and choledochojejunostomy are performed (White 2001). Islet cells are then infused through the portal vein or one of its tributaries (although islets may be infused into the spleen, peritoneum, renal capsule, omentum and skeletal muscles) where some will remain viable and functional (Blondet 2007; Bramis 2012).

There is no clear evidence regarding the optimal timing of TP/IAT in the course of CP, although the advantages of early TP/IAT include a higher yield of islet cells at the time of transplantation (Sutherland 2008) and a reduced risk of the chronic opioid dependency that often manifests later in the course of CP (Bramis 2012).

Although alternative treatments are available for CP most result in only transient symptomatic relief, with the best results confined to individuals with early-stage disease without opioid dependence (White 2001). TP is usually offered to individuals when conservative treatments, such as opioid analgesia, and minimally invasive procedures, such as coeliac plexus blocks, are no longer effective.

As well as an absence of insulin, individuals who have undergone TP will experience both glucagon and pancreatic polypeptide (PP) deficiency, rendering them vulnerable to episodes of severe hypoglycaemia and resistant to ketosis (Jethwa 2006; Karmann 1987). PP deficiency may also contribute to increased hepatic insulin resistance resulting in challenges in maintaining control of diabetes (Jethwa 2006; Slezak 2001). Although many individuals continue to require some basal insulin following TP/IAT, IAT may reduce the incidence of complications such as hypoglycaemia and ketoacidosis.

Why it is important to do this review

Health-related quality of life is significantly worse in individuals with CP than in the gender- and age-adjusted general population, and the effective treatment of this condition remains a challenge

(Berney 2000). Although a recent systematic review has compared the endoscopic and surgical management of painful CP (Ahmed Ali 2012), the use of TP in conjunction with IAT has not been systematically compared with the more traditional alternatives available for the management of this difficult disease.

A glossary of terms is provided in Appendix 1.

OBJECTIVES

To assess and compare the effectiveness of TP/IAT with that of alternative treatments for the management of individuals with CP.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing TP/IAT with alternative surgical, endoscopic or other minimally invasive techniques for the management of pain in CP. We will include studies reported as full text, those published in abstract form only and unpublished data.

Types of participants

We will include adults (≥18 years) with a confirmed diagnosis of CP.

Types of interventions

We will include studies comparing:

- TP/IAT and any other treatment
- TP/IAT and surgical intervention
- TP/IAT and ERCP
- TP/IAT and minimally invasive techniques, conservative treatment (nerve block, analgesia, nutritional support) or both

Types of outcome measures

Primary outcomes

- Mortality
- Number of participants with major postinterventional complications. These will include intra-abdominal abscess, ileus necessitating surgery, pancreatitis flare-up, significant bleeding, anastomotic leakage, sepsis, abdominal fascial dehiscence and myocardial infarction
- Quality of life improvement (physical/mental health) according to the 36-item Short-Form Health Survey, the EQ-5D or other validated scale
- Number of participants experiencing a reduction in pain. This will be assessed according to a visual analogue scale or change in opiate requirements (mg)

Secondary outcomes

- Further procedures related to the treatment of CP (treatment failure)
- Number of participants with minor postinterventional complications. These will include wound infections, pneumonia, cholecystitis, prolonged ileus (not necessitating intervention), urinary tract infections, urinary retention and deep venous thrombosis
- Change in nutritional status (body weight or body mass index (BMI)) after intervention
- Number of participants with improved glycaemic control. This may be measured in a variety of ways including days insulin independent, a comparison of insulin requirements, glycosylated haemoglobin levels, C-peptide levels and new-onset endocrine insufficiency
- Hospital admissions for exacerbation of abdominal pain

We will not consider the reporting of any of the outcomes listed here an inclusion criterion for the review. If outcomes are described at a number of time points, we will use the measurement closest to one year post-intervention.

Search methods for identification of studies

Electronic searches

We will conduct a literature search to identify all published and unpublished RCTs. The literature search will identify potential studies in all languages. We will translate non-English language papers and fully assess them for potential inclusion in the review, as necessary.

We will search the following electronic databases in order to identify potential studies:

- Cochrane Central Register of Controlled Trials (CENTRAL) (for search strategy, see Appendix 2)
- MEDLINE (1966 to present) (for search strategy, see Appendix 3)
- EMBASE (1988 to present) (for search strategy, see Appendix 4)
- CINAHL (1982 to present).

We will also conduct a search of ClinicalTrials.gov.

Searching other resources

We will check the reference lists of all primary studies and review articles identified for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies. We will also contact manufacturers and experts in the field.

We will search for errata or retractions for eligible trials on http://www.ncbi.nlm.nih.gov/pubmed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (AEV and CHW) will independently screen the titles and abstracts of identified studies for inclusion. We will code all the potential studies we identify as a result of the search as either 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publications and two review authors (AEV and CHW) will independently screen the full text and identify studies for inclusion, and identify and record reasons for the exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult the senior author (SAW).

Data extraction and management

We will use a standard data collection form that has been piloted on at least one study in the review to collate study characteristics and outcome data. Two review authors (AEV and CHW) will extract the following study characteristics from included studies.

1. Methods: study design, total duration study and run in, number of study centres and location, study setting, withdrawals, date of study
2. Participants: number of participants (N), mean age, age range, gender, BMI, diagnostic criteria, type of pain (A or B according to the Ammann classification (Ammann 1999)), inclusion criteria, exclusion criteria
3. Interventions: intervention, comparison, surgical/endoscopic experience of surgeon/centre, islet cell yield
4. Outcomes: primary and secondary outcomes specified and collected, time points reported
5. Notes: funding for trial, notable conflicts of interest of trial authors

We will resolve disagreements by consensus or by involving the senior author (SAW).

Assessment of risk of bias in included studies

AEV and CHW will independently assess the risk of bias in each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will grade each potential source of bias as high, low or unclear. We will resolve any disagreements by discussion or by involving a third assessor (SAW). We will assess the risk of bias according to five domains.

- ***Random sequence generation***
  - Low risk - if the investigators describe a random component in the sequence-generation process such as the use of a computer or a random number table
  - Unclear - if the trial was described as randomised, but the method used for generation of the allocation sequence was not described
  - High risk - if the investigators state that a non-random component in the sequence-generation process (e.g. a system involving dates, names or hospital record numbers) was used for the allocation of participants
- ***Allocation concealment***
  - Low risk - if the allocation of participants involved central allocation or sequentially numbered, opaque, sealed envelopes
  - Unclear - if there is insufficient information to permit a judgement of 'low risk' or 'high risk'
  - High risk - if participants or investigators enrolling participants could possibly foresee assignments (e.g. if the allocation was based on the use of an open random allocation schedule, such as a

list of random numbers, or assignment envelopes without appropriate safeguards)

- ***Blinding***
  * Low risk - if blinding of participants or assessors is ensured and the method described (although blinding of participants may often have not been possible due to the nature of the interventions evaluated)
  * Unclear - if there is insufficient information to permit a judgement of ‘low risk’ or ‘high risk'
  * High risk - if there is no blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding
- ***Incomplete outcome data***
  * Low risk - if there are no missing outcome data, the reasons for missing outcome data are unlikely to be related to the true outcome, missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; the proportion of missing outcomes compared with observed event risk is not sufficient to have a clinically relevant impact on the intervention effect estimate; or missing data have been imputed using appropriate methods
  * Unclear - if there is insufficient reporting of attrition/ exclusions to permit a judgement of ‘low risk’ or ‘high risk’ (e.g. number randomised not stated or no reasons for missing data provided)
  * High risk - if reasons for missing outcome data are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups; the proportion of missing outcomes compared with observed event risk is sufficient to induce a clinically relevant bias in the intervention effect estimate; per-protocol analysis is carried out with substantial departure of the intervention received from that assigned at randomisation; or there has been a potentially inappropriate application of a simple imputation
- ***Selective reporting***
  * Low risk - if the published reports include all expected outcomes, including those that were prespecified
  * Unclear - if there is insufficient information to permit a judgement of 'low risk' or 'high risk'
  * High risk - if not all of the study’s prespecified primary outcomes have been reported; if one or more primary outcomes is reported using measurements, analysis methods or subsets of the data that were not prespecified; if one or more reported primary outcomes were not prespecified; if one or more outcomes of interest were reported incompletely; or if the study report failed to include results for a key outcome that would be expected to have been reported for such a study

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios and continuous data as mean differences or standardised mean differences. We will ensure that higher scores for continuous outcomes have the same meaning for each particular outcome, explain the direction to the reader and report where the directions were reversed if this was necessary.

We will undertake meta-analyses only where this is meaningful (i.e. if the treatments, participants and underlying clinical question are similar enough for pooling to make sense).

A common method used by trialists to indicate that data are skewed is the reporting of medians and interquartile ranges. When we encounter this we will note that the data are skewed and consider the implication of this.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) must be entered into the same meta-analysis, we will halve the control group to avoid double counting.

Unit of analysis issues

Non-standard design RCTs may present statistical problems in this review. We anticipate that there will be participants who 'cross-over' from conservative, minimally invasive and endoscopic treatments to surgery and these will be classified as 'treatment failures' (as included in Secondary outcomes). If cluster-randomised trials are found we will analyse the baseline comparability of clusters to ascertain the risk of bias between the baseline characteristics of the groups.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified in abstract form only).

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will explore it through prespecified subgroup analysis.

Assessment of reporting biases

We will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis**.**

If we are able to pool data from > 10 trials, we will create and examine a funnel plot to explore possible publication biases.

Data synthesis

Data will be combined using a random-effects meta-analysis. The following will be analysed:

- TP/IAT versus surgical intervention
- TP/IAT versus endoscopic intervention
- TP/IAT versus conservative treatment (analgesia with or without nutritional support)
- TP/IAT versus minimally invasive techniques, conservative treatment (nerve block, analgesia, nutritional support) or both

'Summary of findings' table

We will create a 'Summary of findings' table including the following outcomes - mortality, health-related quality of life and major complications. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro software. We will justify all decisions to down- or upgrade the quality of studies using footnotes and make comments to aid the reader's understanding of the review where necessary. We will consider whether there is any additional outcome information that we were unable to incorporate into the meta-analyses, note this in the comments and state if it supports or contradicts the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

Depending on the availability of appropriate evidence, we will conduct the following subgroup analyses in this review:

- between small duct and dilated duct CP
- participants on high doses of opiates preintervention
- participants who have had multiple procedures prior to the definitive intervention.

We will restrict these analyses to our primary outcomes (Primary outcomes). We will use the Chi^2 test with a P value of 0.05 to test for subgroup interactions.

Sensitivity analysis

We will perform sensitivity analyses defined *a priori* to assess the robustness of our conclusions. This will involve repeating the analyses in order to explore the influence of the following factors on effect size:

- exclusion of unpublished studies
- exclusion of lower-quality studies (those at high or unclear risk of bias related to randomisation, blinding or attrition)
- exclusion of studies using unpublished criteria or criteria with no established reliability or validity
- use of a fixed-effect model
- exclusion of non-intention-to-treat trials where participants have crossed-over from one arm to another and are not able to be included in the arm to which they were randomised.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies. We will avoid making recommendations for practice and our implications for research will give the reader a clear sense of where the focus of any future research in the area should be and what the remaining uncertainties are.

ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1. Glossary of terms

Anastomotic leak: postsurgical breakdown at the site of closure of hollow organs

Autoimmune: immune response of an organism against its own cells and tissues

Brittle diabetes: very unstable blood sugar levels due to complete lack of insulin

Cholecystitis: inflammation of the gall bladder

Choledochojejunostomy: surgical creation of a passage between the common bile duct and part of the small bowel, the jejunum

Coeliac plexus block: a block of the function of an abdominal nerve transmitting pain from the pancreas

Decompressive surgery: surgery to facilitate drainage of the biliary system

Distal pancreatectomy: excision of the part of the pancreas furthest away from the duodenum

Duodenal-preserving pancreatic head resection: surgical removal of the head of the pancreas whilst leaving the duodenum

Duodenal stenosis: narrowing of the first part of the small intestine

Duodenum: the first part of the small intestine

Endocrine system: hormones directly secreted into the circulatory system

Endoscopic retrograde cholangiopancreatography: the endoscopic visualisation of the biliary system

Endoscopic ultrasound: visualisation of the pancreas, duodenum and biliary system via endoscopic ultrasound

Enteroenterostomy: surgical joining of two parts of the small intestine

Exocrine system: hormones and other chemical messengers are secreted through a duct

Fascial dehiscence: the breakdown of a wound in the fascia (layers of fibrous tissue that separate different layers of tissue) in the body

Glucagon: hormone released by the pancreas to raise blood sugar levels

Hypercalcaemia: excess calcium in the body

Hypertriglyceridaemia: excess triglycerides (a type of fat) in the body

Hypoglycaemia: abnormally low blood sugar levels

Ileus: non-mechanical intestinal obstruction

Insulin: hormone released by the pancreas to lower blood sugar levels

Intraductal pressure: pressure within a duct

Islet cell: cell in the pancreas responsible for the secretion of insulin

Islet cell autotransplantation: a procedure to transfer islet cells from an donor into another person

Ketosis: a controlled, insulin regulated process resulting in a mild release of fatty acids and ketone body production in response to low carbohydrate intake, and higher fat consumption

Ketoacidosis: when a lack of insulin in the body leads to a breakdown of fatty acids resulting in a high concentration of ketones

Longitudinal pancreaticojejunostomy: longitudinal incision along the pancreatic duct with over-sewing of the jejunum on the open duct

Myocardial infarction: heart attack

Omentum: a layer of fatty tissue that overlies the abdominal organs

Opioid: narcotic medication such as morphine

Pancreatic polypeptide: a hormone released by the pancreas to self-regulate other secretions

Parenchyma: the functional part of an organ

Pseudocyst: a contained pocket of fluid in or around the pancreas

Pancreaticoduodenectomy: partial excision of the pancreas and duodenum

Peritoneum: the lining of the abdominal cavity and organs

Pylorus: the opening leading from the stomach to the intestine

Sepsis: shock caused by infection

Sphincterotomy: widening of opening of the biliary tree into the duodenum

Stent: a tube inserted into a natural passage of the body

Sympathetic pain afferents: nerves that conduct pain

Total pancreatectomy: complete excision of the pancreas

Ventral: front

Wound dehiscence: the breakdown of a wound usually caused by an infection

Appendix 2. CENTRAL search strategy

1. Pancreatitis, Chronic/

2. (pancrea* adj2 chronic).tw.

3. 1 or 2

4. Pancreatectomy/

5. (pancrea* adj2 resection*).tw.

6. pancreatectom*.tw.

7. or/4-6

8. "Islets of Langerhans Transplantation"/

9. Transplantation, Autologous/

10. (islet adj2 (autologous transplantation* or autotransplantation*)).tw.

11. TPIAT.tw.

12. or/8-11

13. 3 and 7 and 12

Appendix 3. MEDLINE search strategy

1. Pancreatitis, Chronic/

2. (pancrea* adj2 chronic).tw.

3. 1 or 2

4. Pancreatectomy/

5. (pancrea* adj2 resection*).tw.

6. pancreatectom*.tw.

7. or/4-6

8. "Islets of Langerhans Transplantation"/

9. Transplantation, Autologous/

10. (islet adj2 (autologous transplantation* or autotransplantation*)).tw.

11. TPIAT.tw.

12. or/8-11

13. 3 and 7 and 12

Appendix 4. EMBASE search strategy

1. chronic pancreatitis/

2. (pancrea* adj2 chronic).tw.

3. 1 or 2

4. pancreas resection/

5. (pancrea* adj2 resection*).tw.

6. pancreatectom*.tw.

7. or/4-6

8. pancreas islet transplantation/

9. autotransplantation/

10. (islet adj2 (autologous transplantation* or autotransplantation*)).tw.

11. TPIAT.tw.

12. or/8-11

13. 3 and 7 and 12

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: CHW, SAW, AD, DMM

Designing the protocol: AEV, CHW, SAW

Coordinating the protocol: AEV, CHW, SAW

Designing search strategies: AEV, CHW

Writing the protocol: AEV, CHW

Providing general advice on the protocol: CHW, SAW, AD, DMM

Securing funding for the protocol: no funding

Performing previous work that was the foundation of the current study: SAW, AD, DMM

DECLARATIONS OF INTEREST

None known