NHS England

# Evidence Review:

## Total pancreatectomy with islet autotransplantation for chronic pancreatitis

**September 2015**

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## Contents

# 1. Introduction

Total pancreatectomy with islet autotransplantation (TP-IAT) is an established treatment for chronic pancreatitis. The operation was first performed in 1977, and in the UK, the Leicester group has performed TP IAT on more than 60 patients since 1996.

The primary goal of surgery is to control pain resistant to other therapies; islet autotransplantation is intended to prevent or lessen the diabetes mellitus which is an inevitable result of total pancreatectomy.

TP IAT is a complex procedure, so reports from low volume, inexperienced centres will not reflect the experience of established programmes. Also, surgical techniques for pancreatectomy, islet isolation techniques and patient selection, have improved over time so publications from the early era of TP IAT will be misleading. Ideally, the evidence reviewed should be limited to reports from high volume centres in the modern era.

## 2. Research Questions

The research question is the effectiveness of total pancreatectomy with islet autotransplantation in the treatment of chronic pancreatitis in adults at experienced centres in the recent era.

Population: adult patients with chronic pancreatitis

Intervention: total pancreatectomy with islet autotransplantation

Comparator: total pancreatectomy without islet autotransplant, or total pancreatectomy alone, or no surgical treatment

Outcome: mortality, quality of life, insulin independence, pain control, adverse events

## 3. Methodology

PubMed was searched for articles published since 2010 using the following string:

> (total[All Fields] AND ("pancreatectomy"[MeSH Terms] OR "pancreatectomy"[All Fields]) AND islet[All Fields] AND ("transplantation, autologous"[MeSH Terms] OR ("transplantation"[All Fields] AND "autologous"[All Fields]) OR "autologous transplantation"[All Fields] OR "autotransplantation"[All Fields])) AND ("2010/08/30"[PDat] : "2015/08/28"[PDat] AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])

## Table 1: Scottish Intercollegiate Guideline Network (SIGN) levels of evidence

| Level of evidence | Type of evidence |
|---|---|
| 1++ | High quality meta-analyses, systematic reviews of RCTs (including cluster RCTs), or RCTs with a very low risk of bias |
| 1+ | Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1–* | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| 2++ | High quality systematic reviews of, or individual high quality non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a very low risk of confounding, bias or chance |
| 2+ | Well conducted, non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a low risk of confounding, bias or chance |
| 2–* | Non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a high risk of confounding, bias or chance |
| 3 | Non-analytical studies (eg case reports, case series) |
| 4 | Expert opinion, formal consensus |
| *Studies with a level of evidence (–) should not be used as basis for making recommendations.<br>*Source*: adapted from SIGN (2001). | |

**Table 2: Scottish Intercollegiate Guideline Network (SIGN) Grades of Evidence**

| **Grades of recommendations** |
|---|
| ***Grade 'A'*** <br><br> At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population ***or*** <br><br> A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results. |
| ***Grade 'B'*** <br><br> A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results ***or*** <br><br> Extrapolated evidence from studies rated as 1++ or 1+ |
| ***Grade 'C'*** <br><br> A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results ***or*** <br><br> Extrapolated evidence from studies rated as 2++ |
| ***Grade 'D'*** <br><br> Evidence level 3 or 4 ***or*** <br><br> Extrapolated evidence from studies rated as 2+ |

*Source: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 2001*

## 4. Results

The search retrieved 49 papers. Abstracts were reviewed and papers which did not contain primary data (e.g. reviews), did not report patient outcomes, or reported case series of 10 patients or fewer, were excluded, leaving 11 papers for analysis. Two were systematic reviews, and the remainder case series with pre / post operation comparisons.

The first systematic review [1] identified 15 observational studies. Meta analysis was used to estimated the rate of insulin independence (4.62 per 100 patient years for lasting independence) and mortality (1.38 per 100 person years). The other systematic review [2] identified five studies published between 1983 and 2009, and reported insulin independence and opioid reduction. The rate of insulin independence ranged from 46 per cent of patients at 5 years' mean follow-up to 10 per cent at 8 years; two studies reported reduction in opioid use.

Morgan [3] reported her experience of 177 TP IAT in a 2015 publication. Patients showed improvement after operation on both physical and psychological quality of life. The percentage with psychological improvement increased from the first year of follow up to the third. Thus the percentages of patients evidencing at least a 3-point improvement in physQOL at 1 year, 2 years, and 3 years post surgery were 65%, 60%, and 61%, respectively. The percentages of patients evidencing at least a 3-point improvement in psychQOL at 1 year, 2 years, and 3 years post surgery were 49%, 58%, and 66%, respectively.

Wilson [4] reported 73% narcotic independence and 27% insulin independence in a series of 112 patients at five years or more post TP IAT.

Dorlon [5] reported SF12 scores at two years in a series of 74 patients: physical component scores increased from 26 before TP IAT to 36 at two year follow up; the mental health component scores averaged increased from 36 to 41 at two years. Dorlon also found no correlation between physical and mental component scores.

Sutherland's case series [7] is the largest in the literature, reporting on 407 patients operated between 1977 and 2011. Actuarial patient survival post TP-IAT in adults was 89% at 5 years. At 3 years, 25% of adults were insulin independent. All patients had pain before TP-IAT and nearly all were on daily narcotics. After TP-IAT, 85% had pain improvement. By 2 years, 59% had ceased narcotics. Significant improvement was seen in all dimensions of SF36.

The Leicester series [11] of 60 consecutive TP IAT patients were compared with 37 patients who had received TP alone over the same period. Median survival in the TP IAT group was 16.6 years compared to 12.9 years in the TP alone group. TP IAT was associated with significant reduction in opiate use, frequency of hospital admissions, and length of stay as well as visual analog scale scores for pain. 21.6% of patients with TP IAT were insulin-independent, and those requiring insulin have reduced daily requirements compared with those having TP alone (22 vs 35 IU).

Walsh [6] , Morgan [8] and Sutton [9] all reported improvements in pain control and other measures in small case series (20, 33 and 16 patients respectively). Morgan's case series [8] probably includes the same patients as reported in her more comprehensive recent paper mentioned above [3].

Bhayani et al [10] examined short term morbidity as reported in the US National Surgical Quality Improvement Programme from 2005 to 2011. Patients in the TP IAT group were younger and had fewer comorbidities than those in the TP group. Major morbidity was more

frequent after TP IAT than after TP (41% versus 29%). Transfusions were more common after TP IAT (20% versus 7%), as was longer hospitalization (13 days versus 9 days). There was no difference in mortality.

The strongest evidence for safety of the procedure in NHS practice is the Leicester case series [11]. Using the Clavien grading of complications, there were Grade III complications (required an intervention) in a 13.3% of the TP IAT and 5.4 % of the TP group; no Grade IV compliations (life threatening) were reported in either group; and Grade V complications (death) in 1.7% of the TP IAT and 5.4% of the TP group.

The Leicester group [11] estimated that TP IAT was cost saving over 16 years in their cohort of patients (16 years was the median survival in the TP IAT group). Cost in the absence of TP IAT was estimated from costs incurred in the 5 years (extrapolated to 16 years) before operation in patients receiving either TP IAT or TP alone. Costs included were the procedure costs, analgesia, and hospital admissions over the 16 year period. The cost of TP IAT over the 16-year survival period was £101 608 compared with £110 445 estimated 16-year costs if no TP + IAT was undertaken.

## Table 3

| Clinical Effectiveness and / or safety | | | | | |
|---|---|---|---|---|---|
| **Level of Evidence** | **Study design & Intervention** | **Outcome measure(s)** | **Results** | **Reference** | **Comments** |
| 1+ | Design: Systematic review<br><br>Intervention: Partial and total pancreatectomy with islet autotransplantation | Insulin independence, mortality | Fifteen observational studies were included.<br>For TP IAT, The II rates for IAT post-TP at last follow-up and transiently during the study were 4·62 per 100 person-years (95% CI: 1·53-7·72) and 8·34 per 100 person-years (95% CI: 3·32-13·37), respectively. In the later group, patients achieved transient II lasting 15·57 months (95% CI: 10·35-20·79). 30-day mortality for IAT post-TP was 5% (95% CI: 2-10%), the long-term mortality was 1·38 per 100 person-years (95% CI: 0·66-2·11) | 1 Dong | Studies published up to January 2011 |
| 1+ | Systematic review<br>Intervention TP IAT | Pain reduction (morphine equivalents), insulin independence | Five studies were included published between 1983 and 2009.<br>TP/IAT was successful in reducing pain in patients with chronic pancreatitis. Comparing morphine requirements before and after the procedure, two studies recorded significant reductions. Concurrent IAT reduced the insulin requirement after TP; the rate of insulin independence ranged from 46 per cent of patients at 5 years' mean follow-up to 10 per cent at 8 years. The impact on quality of life was poorly reported. | 2 Bramis | 173 / 296 patients included were from the Minnesota series of Sutherland et al |

| Clinical Effectiveness and / or safety | | | | | |
|---|---|---|---|---|---|
| **Level of Evidence** | **Study design & Intervention** | **Outcome measure(s)** | **Results** | **Reference** | **Comments** |
| 2+ | Pre / post Case series n=177 | Quality of life (SF12), CES depression, opioid use | The percentages of patients evidencing at least a 3-point improvement in physQOL at 1 year, 2 years, and 3 years post surgery were 65%, 60%, and 61%, respectively. The percentages of patients evidencing at least a 3-point improvement in psychQOL at 1 year, 2 years, and 3 years post surgery were 49%, 58%, and 66%, respectively | 3 Morgan 2015 | Single centre experience (Charleston SC); likely overlap / same patients as reference 8. |
| 2+ | Case series n=112 | Outcomes at 5 years or more for narcotic requirements, glycemic control, islet function, quality of life (QOL), and survival. | Zero operative mortality; 94.6% 5yr survival<br>73% narcotic independence<br>27% insulin independence; all patients stable glycaemic control with median HbAC1 6.9%; two patients required whole organ pancreas transplant<br>There were substantial improvements in all domains of SF36 among 34 patients avaluated at > 5years post operation. | 4 Wilson | |

| Clinical Effectiveness and / or safety | | | | | |
|---|---|---|---|---|---|
| **Level of Evidence** | **Study design & Intervention** | **Outcome measure(s)** | **Results** | **Reference** | **Comments** |
| 2+ | Case series pre / post n=74 | Quality of life (SF12) | Preoperative QOL scores were a mean of 26 for the physical component and 36 for the mental health component. Postoperatively, physical component scores averaged 33 at 6 months ($p < 0.001$), 36 at 12 months, and 36 at 2 years; the mental health component scores averaged 42 at 6 months ($p = 0.007$), 41 at 12 months, and 41 at 2 years. There is no correlation between physical component score or mental component score QOL scores and daily insulin requirements ($r = -0.016$ and $r = 0.039$, respectively) | 5 Dorlon | |
| 2+ | Case series pre/post n=20 | Depression Anxiety Stress Scale, Pain Disability Index, and visual analogue pain scale | All patients reported moderate (45 %) to severe (55 %) pain prior to surgery; 80 % reported no or mild pain after TP IAT. 30 % discontinued narcotics. Improvements in all PDI QOL domains improved from 79 to 90 % ($p = 0.002$).. | 6 Walsh | |

| Clinical Effectiveness and / or safety | | | | | |
|---|---|---|---|---|---|
| **Level of Evidence** | **Study design & Intervention** | **Outcome measure(s)** | **Results** | **Reference** | **Comments** |
| 2+ | Case series n=409 (of whom 53 aged <19yrs) | Mortality, insulin independence, pain, quality of life (SF36) | Actuarial patient survival post TP-IAT in adults was 89% at 5 years.<br>At 3 years, 25% of adults were insulin independent<br>All patients had pain before TP-IAT and nearly all were on daily narcotics. After TP-IAT, 85% had pain improvement. By 2 years, 59% had ceased narcotics.<br>Significant improvement in all dimensions of SF36 | 7 Sutherland | Single centre experience from 1977 to 2011 |
| 2+ | Case series pre/ post n=33 | Opioid use, quality of life (SF12) | Median follow up 9 months<br>Preoperative QOL scores were a mean 25 for physical component and 32 for mental health component.<br>Postoperatively, physical component scores averaged 33 at 6 months ($p = 0.025$) and 36 at 12 months (mean increase of 11); the mental health component scores averaged 43 at 6 months ($p = 0.007$) and 44 at 12 months (mean increase of 12).<br>Opioid use increased post operatively, 11/17 patients at 12 months required less opioid | 8 Morgan | |

| Clinical Effectiveness and / or safety | | | | | |
|---|---|---|---|---|---|
| **Level of Evidence** | **Study design & Intervention** | **Outcome measure(s)** | **Results** | **Reference** | **Comments** |
| 2+ | Case series n=16 patients with genetic cause of pancreatitis | Narcotic use; insulin use; quality of life (SF36); McGIll pain questionnaire | At a mean follow-up of 22 months, mean insulin requirements decreased to 15 units / day. Seven (44%) patients required 15 or fewer units daily, and 4 (25%) patients were completely insulin-independent. Average daily narcotic usage at most recent follow-up decreased to 70 MEQ (median, 0) with 10 (63%) patients currently narcotic-independent. Analyses of the 36-item short-form health survey and the McGill Pain Questionnaire demonstrated a significant improvement in quality-of-life parameters and pain assessment. | 9 Sutton | Single centre experience (Cincinatti) |
| | Group comparison TP (n=126) vs TP IAT (n=191) | Operative morbidity | Patients in the TP + IAT group were younger and had fewer comorbidities than those in the TP group. Despite this, major morbidity was more frequent after TP + IAT than after TP [n = 79 (41%) versus n = 36 (29%); P = 0.02]. Transfusions were more common after TP + IAT [n = 39 (20%) versus n = 9 (7%); P = 0.001], as was longer hospitalization (13 days versus 9 days; P < 0.0001). There was no difference in mortality. | 10 Bhayani | Multi centre data from 2005-2011 National Surgical Quality Improvement Program |

**Table 4**

| Cost-effectiveness | | | | | |
|---|---|---|---|---|---|
| **Level of Evidence** | **Study design & Intervention** | **Outcome measure(s)** | **Results** | **Reference** | **Comments** |
| | Cost and outcomes in a cohort of TP IAT (n=60) and TP (n=37) patients | Mortality, health service use, health costs | Surgery resulted in significant reduction in opiate use, frequency of hospital admissions, and length of stay as well as visual analog scale scores for pain.<br>TP IAT resulted in longer survival than TP alone (16.6 vs 12.9 years); 21.6% of patients with TP + IAT were insulin-independent, and those requiring insulin have reduced daily requirements compared with those having TP alone (22 vs 35 IU).<br>The cost of TP + IAT with attendant admission and analgesia costs over the 16-year survival period was £110,445 compared with £101,608 estimated 16-year costs if no TP + IAT was undertaken. | 11 | Consecutive case series of all patients treated with TP or TP IAT in Leicester from 1990 to publication date. Indication for surgery was 'chronic abdominal pain refractory to all other treatment modalities; IAT was offered to patients with good endocrine function judged by Glucose Tolerance Test, and willing to have the longer procedure time associated with IAT. Hence this is a pragmatic, retrospective comparison with a high risk of bias. |

## 5. Summary of Evidence

The published literature is limited in some respects, with no randomized controlled trials and few reports of long term outcomes.

Several large case series show that patients have reduced morphine requirements and reduced insulin requirement after TP IAT. Thus for example, in Sutherland's series of 409 patients, 25% of adults were insulin independent at 3 years; all patients had pain before TP-IAT and nearly all were on daily narcotics, whereas after TP-IAT, 85% had pain improvement and by two years, 59% had ceased narcotics. There were also significant improvement in all dimensions of SF36. In Morgan's series of 177 patients, 61% of patients showed a clinically important improvement in physical quality of life at three years, and 66% showed a clinically important improvement in psychological quality of life. A report on the Leicester experience compared 60 patients treated with TP IAT with 37 TP alone patients; the TP IAT group fared better on all measures including survival (16.6 versus 12.9 years), pain scores, insulin use and health service use.

One report examined data from the National Surgical Quality Improvement Program in the USA (potentially including both experience and inexperienced centres) and reported higher short term morbidity with TP IAT compared to TP alone with a major complication rate of 41% versus 29%, and length of stay 13 days versus 9 days. In the Leicester series, however, the rate of major complications (Clavien grade III and above) was 15.0% for TP IAT and 10.8% for TP.

All authors emphasise the importance of careful selection of patients.

A single study of cost and effects indicated that the cost surgery, analgesia and inpatient admissions over the median 16-year survival period of patients receiving TP IAT was £101 608 compared with an estimate of £110 445 if no TP + IAT had been undertaken.

The National Institute for Health and Clinical Excellence (NICE) issued full guidance in 2008 to the NHS in England, Wales, Scotland and Northern Ireland on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy.12 The conclusion was as follows: 'The current evidence on autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy shows some short term efficacy, although most patients require insulin therapy in the long term. The reported complications result mainly from the major surgery involved in pancreatectomy (rather than from the islet cell transplantation). The procedure may be used with normal arrangements for clinical governance in units with facilities for islet cell isolation.'

## References


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## Appendices

### Appendix 1 - Search strategy

| **Question(s)** | |
|---|---|
| *Identify all aspects of the topic that need to be explored in order to develop a policy*<br><br>• Is the intervention in tariff?<br>• Is it, or can it be, adequately covered by the appropriate detail in the service specification?<br>• Is it very low volume or does it have a low number of requests, such as less than 10 per year? If it is low volume then it may not merit a clinical commissioning policy or may be deferred to the next round of policy reviews.<br>• Does it appear too difficult to establish an evidence base or find suitable evidence to support a new clinical commissioning policy? If there is such limited evidence that it will not be possible to answer the review question then it will not be possible to generate a clinical commissioning policy.<br>• Is it a clinical area included within the scope? If not, then a clinical commissioning policy may not be suitable for this | |
| **Search strategy** *Indicate all terms used in the search* | |
| P – Patients / Population<br><br>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered? | |
| I – Intervention<br><br>Which intervention, treatment or approach should be used? | |
| C – Comparison<br><br>What is/are the main alternative/s to compare with the intervention being considered? | |
| O – Outcomes<br><br>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use. | *Critical to decision-making:*<br><br>Mortality, quality of life, adverse effects<br><br>*Important to decision-making:* |

| Assumptions / limits applied to search |
| --- |
| None |

## Appendix 2- Version Control Sheet

| Version | Section/Para/Appendix | Version/Description of Amendments | Date | Author/Amended by |
| --- | --- | --- | --- | --- |
| 1 | | | | |
| 2 | Results; discussion | Addition of text to comments column of cost-effectiveness table; Improved description of complication rate in NHS practice; Addition of reference to NICE IPG; | 26 Jan 2016 | E G Jessop |
| 3 | | | | |
| 4 | | | | |
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