Bampton Tristan (Orcid ID: 0000-0001-7326-286X)

Australian Experience with Total Pancreatectomy with Auto Islet Cell Transplant (TP-IAT) to treat chronic pancreatitis

Bampton T.J.[1,2], Holmes-Walker D.J.[3, 10,] Drogemuller C.J.[2], , Radford T.[2], Anderson P.[10], Etherton C.[2], Russell C.H.[2], Khurana S.[4], Torpy D.J.[2], Couper J.J.[4], Couper R.L.T..[4], Macintyre P.[2], Neo E.L.[5], Benitez-Aguirre P[9], Thomas, G.[6], Loudovaris T.[7], Thomas H.E[7]., Lyle J. Palmer.[8], Wu Denghao[1], Rogers N.M. [10,11], Williams L.[10], Hawthorne W.J[10,11,12], O'Connell P.J. [10,11], Kay T.W[7]., Pleass H[9, 10,11,12], Chen J.W.[2,4], Coates P.T.[1,2]

On behalf of the Australian Islet Consortium

Affiliations

[1] The University of Adelaide

[2] Royal Adelaide Hospital, Adelaide , South Australia

[3] Department Endocrinology Westmead Hospital, Westmead Sydney

[4] Women's and Children's Hospital, Adelaide, South Australia

[5] Flinders Medical Centre, Bedford Park, South Australia

[6] Westmead Children's Hospital, Westmead, New South Wales

[7] St Vincent's Institute, Fitzroy, Victoria

[8] School of Public Health, University of Adelaide, Adelaide, South Australia.

[9] Sydney Medical School, University of Sydney

[10] Westmead Millennium Research Institute

[11] Department Renal Medicine Westmead Hospital

[12] Department of Surgery Westmead Hospital

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ans.16853

Correspondence to:

Dr Tristan Bampton

The University of Adelaide

4 North Terrace, Adelaide, South Australia 5000

Phone: +61 407 797 465

Email: Tristan.bampton@sa.gov.au

ETHICS

This was study was approved by the Central Adelaide Local Health Network (CALHN) human research ethics committee reference HREC/19/CALHN/217. Included are results from patient outcomes reported in the Collaborative Islet Transplant Registry (CITR) https://citregistry.org/, and the Australian and New Zealand Islet and Pancreas Transplant Registry ANZIPTR http://anziptr.org/

ABSTRACT

Aims: To describe the clinical outcomes of Total Pancreatectomy with Islet Auto Transplantation (TP-IAT) in Australia.

Methods: Individuals selected for TP-IAT surgery according to Minnesota Criteria without evidence of diabetes were evaluated including time to transplantation from pancreatectomy, islet numbers infused, and post transplantation HbA1c, C-peptide, total daily insulin, and analgesic requirement.

Results: Sixteen individuals underwent TP-IAT from Australia and New Zealand between 2010 and 2020. Two recipients are deceased. The median Islet Equivalents (IEQ) /kg infused was 4244 [IQR = 2290 – 7300] Median C-peptide one month post TPIAT 384 [IQR = 210 – 579] pmol/L and at median 29.5 [IQR = 14.5 – 46.5] months from transplant was 395 [IQR = 139 – 862] pmol/L. Insulin independence was achieved in 8/15 (53.3%) of surviving recipients. A higher IEQ transplanted was most strongly associated with the likelihood of insulin independence ($P<0.05$). 14 of 15 surviving recipients demonstrated substantial reduction in analgesic requirement.

Conclusion: The TP-IAT program in Australia has been a successful new therapy for the management of individuals with chronic pancreatitis including hereditary forms refractory to medical treatment to improve pain management with 50% insulin independence rates.

Key words: Auto-Islet transplantation, hereditary pancreatitis, chronic pancreatitis

Word count of abstract: 185

Word count of text: 2,946

Tables and figures: 4

Introduction

Total pancreatectomy with islet autotransplantation (TP-IAT) was first performed as a treatment for chronic pancreatitis in 1977 at the University of Minnesota School of Medicine[1]. The primary indication for TP-IAT is relief from intractable pain. The procedure involves surgical removal of the chronically inflamed pancreas with subsequent islet cell isolation and re-infusion into the liver. Auto-transplantation of islet cells allows the recipient the potential for insulin independence or, where insulin independence is not achieved, to reduce risk of severe hypoglycemia and improve glycaemic control[2]. TP-IAT was first performed in Australia in 2010 at Westmead Hospital in Sydney. Since then, a total of 16 TP-IAT procedures have been performed by the Australian Islet Transplant Consortium, with islets isolated at Westmead Hospital for New South Wales (NSW) cases, and at St Vincent's Hospital Melbourne via pancreas shipping for South Australian (SA) cases[3].

In the current report we detail the clinical outcomes of all recipients of TP-IAT for chronic and hereditary pancreatitis in Australia from 2010 to 2020.

Methods

In both centres, a multi-disciplinary team assessed the suitability of TP-IAT candidates. The team comprised hepato-biliary surgeons, gastroenterologists, endocrinologists, transplant physicians, dietitians and pain specialists. Guidelines for selection were in accordance with the University of Minnesota criteria[4] and recommendations from PancreasFest in 2014[5] for all but the first recipient. All either underwent a mixed-meal test to assess pancreatic function and insulin secretion in response to a standardized glucose challenge[6] or undertook a standard two-hour oral glucose tolerance test (GTT) with insulin and C-peptide. As of September 2020, 16

individuals had undergone TP-IAT in Australia, five at Westmead (WCH) and Westmead Children's Hospital (CHW) and eleven at the Royal Adelaide Hospital (RAH) (6 cases) and the Women's and Children's Hospital, Adelaide (WCH) (5 cases).

Each recipient underwent pancreatectomy/cholecystectomy and islet infusion on the same day. At Westmead Hospital, islet isolation was performed on site, with the operating team taking a short break while the recipient remained fully anaesthetized/ventilated. Islets were then infused as an open procedure into the portal vein. In Adelaide, the excised pancreas was cold perfused with University of Wisconsin solution[7] prior to commercial air transport to St Vincent's Institute in Melbourne for isolation of islet cells. Once isolated, the cells were subsequently flown back for same day infusion via a percutaneous trans-hepatic approach[8].

Statistical analysis was performed using the Minitab v18 statistical software package[9]. The study population was described using standard metrics[10]. The associations of median levels of IEQ/kg transfused, C-peptide at 1 month and recent, age, sex, diagnosis, HbA1c and insulin independence were investigated using the Mann Whitney U test and Spearman's rank correlation co-efficient. Data are reported as median and interquartile range [Q1 – Q3].

Results

TP-IAT recipients were aged from 4 to 50 years (median = 22 years [15 – 36]) [table 1]. 11 of 16 had a diagnosis of hereditary pancreatitis (PRSS-1 gene mutation, SPINK-1 gene mutation), 6 (54.5%) of whom self-identified as Aboriginal or Torres Strait Islander.

Of the 16 TP-IAT recipients, 7 underwent splenectomy. One recipient had previously undergone splenectomy prior to TP-IAT operation. Of those who underwent

splenectomy with TP-IAT, 3 RAH paediatric cases had the spleen implanted into the omentum. The child aged 4 operated at the CHW had the spleen preserved. A further two required laparotomy for postoperative complications relating to bleeding or bowel obstruction. Blood loss was not measured routinely during operations, with four recipients (25%) requiring blood transfusion in the post-operative period. Typical ICU time was approximately two nights until the completion of IV heparin infusion. Average operative commencement to pancreas removal time was approximately 3.5 hours.

There were two deaths (12.5%). One, aged 50, died three days after TP-IAT surgery from a myocardial infarction as a consequence of post-operative blood loss and refused blood transfusion. The other, aged 36, died 7 years after TP-IAT of multiple complications including chronic malabsorption on long term total parenteral nutrition, opioid dependence and recurrent sepsis as a consequence of multiple laparotomies and small bowel resections following catastrophic peptic ulcer haemorrhage. This was the first TP-IAT recipient in Australia, and would not have qualified for TP-IAT under the current selection criteria.

All remaining living TP-IAT recipients are currently on no or reduced analgesia compared with preoperatively. Prior to TP-IAT, all were treated with regular high-dose opioid medication or other regular analgesics to control pain [table 3]. Two had ongoing significant chronic pain post-TP-IAT which in one was successfully managed with re-do laparotomy to resect retained tissue two years after TP-IAT.

Eight recipients (50%) remain insulin independent after a median of 24 [14 - 45] months since transplant [table 2]. Median random c-peptide on most recent blood test in this group was 589 [346 – 914] pmol/L, and was 139 [90 – 530] pmol/L in those requiring insulin ($p < 0.05$). Median insulin dose/kg in those requiring insulin was 0.4

[0.15-0.55] IU/kg In this case series, TP-IAT recipients achieving insulin independence received a larger quantity of islets (IEQ/kg. p <0.05), with a median 6650 [4660 – 10500] IEQ/kg compared to a median of 3500 [1930 – 4240] IEQ/kg in those requiring exogenous insulin. Insulin independent TP-IAT recipients also had a lower median HbA1c of 34 [30 – 42] mmol/mol than those requiring insulin 78 [75-86] mmol/mol (p <0.05).

Although age was not significantly associated with achieving insulin independence, younger recipients (<=18) tended to have a higher IEQ/kg (P=0.07) [figure 1]. On linear regression analysis, older age was associated with an increased HbA1c (p <0.05).

Sex, diagnosis and C-peptide at 1-month post operation were not significant predictors of insulin independence in this series.

Discussion

In this report we summarise the clinical outcomes of 16 recipients of TP-IAT in Australia, of which 50% have achieved sustained insulin independence, with a median HbA1c of 34 [30 – 42] mmol/mol. Of the 50% who did not achieve insulin independence, median insulin requirements were 0.4 [0.15-0.55] IU/kg, however HbA1c outcomes were suboptimal with a median HbA1c of 78 [75 – 86] mmol/mol.

The proportion of individuals transplanted through the Australian Islet Consortium who achieved insulin independence (50%) is better than results reported from other international centres performing the procedure at similar time points post transplant[11,12]. This may be biased by the relatively recent status of most transplants, and less insulin independence may be seen over time given the published experience in other centres[11,12].

A study of 112 TP-IAT recipients demonstrated 27% being independent of insulin at 5 years[11]. Bellin et al.[2] demonstrated insulin independence rates of 27% in 215 TP-IAT recipients at 1-year post TP-IAT, with a further 44% having at least partial graft function at 1 year as defined by the presence of C-peptide >0.6 ng/dl (approximately 200 pmol/L). Sutherland et al.[12] demonstrated similar results, with total insulin independence at one year of 26%, with a further 58% having 'partial' graft function. Early results for the program in Australia appear promising, likely reflecting careful case selection and small case numbers.

Insulin independence results are consistent with prior studies showing that infusion of >5000 IEQ/kg is a strong predictive factor for insulin independence in TP-IAT recipients, with >2500 IEQ/kg associated with achieving at least satisfactory glycaemic control[13]. In the current study, IEQ/kg infused was the strongest positive indicator of insulin independence ($P<0.05$). These data provide an interesting comparison to islet allotransplantation as practiced in the Australian Islet Consortium. In an as yet unpublished in full data, insulin independence rates are similarly 50% at 5 years but require significantly greater islet mass and often multiple infusions to achieve independence (>10,000 IEQ/kg) [14] , likely due to the impact of chronic rejection and toxicity of immunosuppression, which is not a concern in auto-transplantation.

Despite the longer cold ischaemic time of the SA TP-IAT recipient group given the requirement for the pancreas to be flown to St Vincent's Hospital in Melbourne, this group did not have a significant reduction in islet yield, nor were they at higher risk of future insulin dependence.

In this series, children tended to achieve higher auto-islet yield IEQ/kg ($p = 0.07$) [figure 1], with a median of 6650 [4660 – 10500] IEQ/kg as compared to 3,500

[1930 – 4240] IEQ/kg in the adult group. This is likely because intervention early in the disease process is crucial to harvesting sufficient islet cells.

Importantly, the current study provides clear evidence of the analgesic benefit of the TP-IAT procedure (Table 3), consistent with results from other centres. Wilson et al.[11] demonstrated a narcotic independence rate of 73% at five years post procedure. Another US based study of TP-IAT demonstrated narcotic use for any reason at 1-year post-surgery was 54%, reduced from 100% prior to operation, with 77% of recipients reporting significant pain relief at 1 year as compared to pre-surgery[2].

The proportion of hereditary pancreatitis TP-IAT recipients identifying as Aboriginal or Torres Strait Islander (54.5%) suggests that this diagnosis may be more common in this ethnic group. A case report[15] of hereditary pancreatitis in a family of Aboriginal descent emphasized the importance of taking a full family history in episodes of recurrent acute pancreatitis, and considering this diagnosis in individuals with Aboriginal and Torres Strait Islander background who present with pancreatitis.

The two main indications for TP-IAT are (a) severe chronic pancreatitis refractory to medical treatment[16], and (b) hereditary pancreatitis associated with chronic pain. First recognized in 1952[17], hereditary pancreatitis has an estimated frequency of 0.3-0.6/100,000 in European-ancestry populations and a mean of age onset at 10 years[18]. Any onset of pancreatitis prior the age of 20 has a strong association with genetic causes, with the most common genetic mutations being in the cationic trypsinogen pathway PRSS1 and SPINK1 genes[19]. Mutations in the cationic trypsinogen pathway cause a cascade of digestive enzymes in the pancreas, leading to auto digestion and therefore pancreatitis. The cardinal symptom in children is recurring, acute episodes epigastric pain often without elevation of lipase for all episodes. Other clinical features include nausea, vomiting, and steatorrhoea/malabsorption and failure

to thrive[20]. Given the chronic inflammation, hereditary pancreatitis is also associated with an increased risk of pancreatic ductal adenocarcinoma. Estimates of the magnitude of this risk vary from 7% to 40% by age 70 years[21, 22].

Precaution should be taken when considering patients with previous surgical intervention, as this reduces the likelihood of successful islet cell transplantation[12].

Prior to TP-IAT, surgical options for chronic pancreatitis were limited to partial or total pancreatectomy (removal of part or all of the pancreas). This procedure allowed relief from pain, but was associated with significant morbidity, including inevitable, difficult to control 'type 3c' or pancreatogenic diabetes[23]. Classically, this type of post-pancreatectomy diabetes was termed 'brittle' diabetes due to increased glycemic lability with the loss of not only insulin but also glucagon secretion[24], leading to a cycle of hypo and rebound hyperglycaemia.

Pancreatectomy is associated with considerable mortality[25], although existing data may have bias as pancreatectomy has traditionally been primarily performed for pancreatic malignancy. A recent study demonstrated a 90-day mortality of 14% for total pancreatectomy patients[26]. The operative mortality in this cohort at 90 days was 1/16 or 6.15%. A 10-year outcome study of 742 TP-IAT recipients demonstrated an actuarial survival rate of 72% at 10 years, with 95% survival at 1-year post operation[2] with a BMI of >30kg/m^2 the strongest predictor of mortality.

Conclusion

The TP-IAT program in Australia has been a successful addition to the therapeutic armamentarium for the management of individuals with chronic pancreatitis. In conjunction with reduction of pain and reduced reliance on analgesia, early results demonstrate the benefit of this operation when performed early in the disease process.

The timely identification and referral of potential candidates is crucial to the success of the procedure. We recommend the establishment of a coordinated national TP-IAT program with the intention to provide comprehensive assessment and TPIAT for Australians and New Zealanders with hereditary pancreatitis.

Acknowledgements

Australian Islet Consortium

Islet isolations undertaken in Adelaide were funded by an unrestricted grant from The Hospital Research Foundation (HRF).

The Royal Adelaide Hospital team would like to thank Professor Ashley Dennison, Dr. Greg Szot and Professor Balamurugan N. Appakalai for their assistance in the establishment of Islet Auto-Isolation in the Adelaide/Melbourne program.

Disclosure statement

The authors have no conflicts of interest to declare.

Author contribution statement

All listed authors contributed to the development, delivery and review of the TP-IAT program in Australia. All listed authors contributed to the manuscript through either data contribution, review, writing or editing.

REFERENCES

1. Sutherland DE, Matas AJ, Najarian JS. Pancreatic islet cell transplantation. *Surg Clin North Am*. 1978; **58**: 365-82.
2. Bellin M, Beilman G, Sutherland D, et al. (2019). How Durable Is Total Pancreatectomy and Intraportal islet Cell Transplantation for Chronic Pancreatitis? *J Am Coll Surg.* 2019; **228**: 329-339.
3. Geyer MC, Coates PT, Khurana S, et al. First Report of Successful Total Pancreatectomy and Islet Autotransplant in Australia. *Pancreas* 2017; **46**: e18-e20.
4. Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Quality of life improves for pediatric patients after total pancreatectomy and islet autotransplant for chronic pancreatitis. *Clin Gastroenterol Hepatol.* 2011; **9**: 793–799.
5. Bellin MD, Freeman ML, Gelrud A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology*. 2014; **14**: 27-35.
6. Lundberg, R., Beilman, G., Dunn, T., et al. Metabolic Assessment Prior to Total Pancreatectomy and Islet Autotransplant: Utility, Limitations and Potential. *American Journal of Transplantation* 2013; **13**: 2664-2671.
7. Southard, J. and Belzer, F. The University of Wisconsin organ preservation solution: Components, comparisons, and modifications. *Transplantation Reviews* 1993; **7**: 176-190.
8. Marathe CS, Drogemuller CJ, Marathe JA et al. Islet cell transplantation in Australia: screening, remote transplantation, and incretin hormone secretion in insulin independent patients. *Horm Metab Res.* 2015: **47**:16-23
9. Minitab 18 Statistical Software [Computer software]. State College, PA: 2017: Minitab, Inc. (www.minitab.com)
10. Rosner B. Fundamental of biostatistics. Fifth ed. Boston: PWS-Kent; 2000.
11. Wilson GC, Sutton JM, Abbott DE, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation?. *Ann Surg*. 2014; **260**: 659-667.

12. Sutherland DE, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg.* 2012; **214**: 409-24.
13. Bottino, R., Bertera, S., Grupillo, M., et al. Isolation of Human Islets for Autologous Islet Transplantation in Children and Adolescents with Chronic Pancreatitis. *Journal of Transplantation*. 2012; **2012:** 1-8.
14. O'Connell, P., Holmes-Walker, D., Goodman, D., et al. 2013. Multicenter Australian Trial of Islet Transplantation: Improving Accessibility and Outcomes. *American Journal of Transplantation* 2013; **13**: 1850-1858.
15. McGaughran, J., Kimble, R., Upton, J. and George, P., 2004. Hereditary pancreatitis in a family of Aboriginal descent. *Journal of Paediatrics and Child Health* 2004; **40**: 487-489.
16. Kleeff J, Whitcomb DC, Shimosegawa T, et al. Chronic pancreatitis. *Nat Rev Dis Primers* 2017; **3**: 17060.
17. Comfort M & Steinberg A. Pedigree of a Family with Hereditary Chronic Relapsing Pancreatitis. *Gastroenterology* 1952; **21:** 54-63.
18. Weiss F (2014). Pancreatic cancer risk in hereditary pancreatitis. *Frontiers in Physiology* 2014; **5**: 70.
19. Giefer M, Lowe M, Werlin S, et al. (2017). Early-Onset Acute Recurrent and Chronic Pancreatitis Is Associated with PRSS1 or CTRC Gene Mutations. *The Journal of Pediatrics* 2017; **186**: 95-100.
20. Otsuki M, Nishimori I, Hayakawa T, Hirota M, Ogawa M & Shimosegawa T/Hereditary Pancreatitis: Clinical Characteristics and Diagnostic Criteria in Japan. *Pancreas* 2004; **28**: 200-206.
21. Shelton C, Umapathy C, Stello K, Yadav D & Whitcomb DC. Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer. *American Journal of Gastroenterology* 2018; **113**: 1376-1384.
22. Charnley R. Hereditary pancreatitis. *World Journal of Gastroenterology* 2003; **9**: 1.
23. Dresler C, Fortner J, McDermott K & Bajorunas D. Metabolic consequences of (regional) total pancreatectomy. *Ann Surg* 1991; **214**: 131-140.
24. Tattersall R. Brittle diabetes. *British Medical Journal* 1985; **291**, 555-557.

25. Parsaik A, Murad M, Sathananthan A, et al. Metabolic and target organ outcomes after total pancreatectomy: Mayo Clinic experience and meta-analysis of the literature. *Clin Endocrinol* 2019; **73**: 723-31.
26. El amrani M, Clément G, Lenne X, et al. Should all pancreatic cancer surgery be centralized regardless of patients' comorbidity? *HPB* 2020; **22**: 1057-1066.

APPENDIX

Minnesota criteria

1. Diagnosis of chronic pancreatitis, based on chronic abdominal pain of >6 months duration

- Pancreatic calcifications on CT scan
- At least two of the following: ≥4/9 criteria on EUS, compatible ductal or parenchymal on secretin MRCP; abnormal endoscopic pancreatic function tests (peak HCO2 <80mM)
- Histopathology confirmed diagnosis of chronic pancreatitis
- Compatible clinical history and documented hereditary pancreatitis (PRSS1 gene mutation)

  OR

- History of recurrent acute pancreatitis (more than one episodes of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase >3 times upper limit of normal)

2. At least one of the following:

- Daily narcotic dependence
- Pain resulting in impaired quality of life, which may include: inability to attend school, recurrent hospitalisations, and inability to participate in usual, age-appropriate activities

3. Complete evaluation with no reversible cause of pancreatitis present or untreated

4. Failure to respond to maximal medical and endoscopic therapy

5. Adequate islet cell function (non-diabetic or C-peptide positive)

† = Indicates deceased

Table 1: Pre TP-IAT results

Recipient	Sex	Diagnosis	Centre	Age (years)	Splenectomy	Method of islet infusion (percutaneous vs. open)	Time from cross clamp to beginning islet cell infusion (hours)	IEQ/kg
1 †	F	HP	WM	36	Previous splenectomy	Open	2.6	4,238
2	F	HP	WM	15	Yes	Open	3.6	5,882
3	M	HP	RAH/ WCH/ SVI	7	Yes (implanted)	Percutaneous trans-hepatic	11	1,146
4	F	HP	WM	17	Yes	Open	3.4	1,929
5 †	M	CP	RAH/ SVI	51	Yes (Not implanted)	Percutaneous trans-hepatic	13	2,181
6	F	HP	RAH/ WCH/ SVI	17	No	Percutaneous trans-hepatic	16	7,300
7	M	CP	RAH/ SVI	31	No (Removed later)	Percutaneous trans-hepatic	11	3,500
8	F	HP	RAH/ WCH/ SVI	17	No	Percutaneous trans-hepatic	12	11,600
9	F	CP	RAH/ SVI	41	No	Percutaneous trans-hepatic	12	1,805
10	M	HP	WM	4	No	Open	2.3	7,304
11	F	HP	RAH/ SVI	27	No	Percutaneous trans-hepatic	12.5	2,613
12	F	HP	RAH/ SVI	40	No	Percutaneous trans-hepatic	11	5,999
13	F	HP	RAH/ WCH/ SVI	8	Yes (Implanted)	Percutaneous trans-hepatic	13	11,457
14	F	CP	RAH/ SVI	36	Yes (Not implanted)	Percutaneous trans-hepatic	12.5	4,250
15	F	HP	RAH/ WCH/ SVI	16	Yes (Implanted)	Percutaneous trans-hepatic	13	7,737
16	M	CP	WM	29	No	Open	3.4	3,790

† = Indicates deceased

Table 2: Post TP-IAT results

Recipient	Age (years)	Diagnosis	Time since procedure (months)	Centre	C-Peptide ~1 month post (pmol/L)	C-peptide recent (pmol/L)	Insulin Units/kg	Recent HbA1c (mmol/mol)
1 †	36	HP	122	WM	210	90	0.4	89
2	15	HP	56	WM	540	500	0	44
3	7	HP	59	RAH/WCH/SVI	490	210	0.35	78
4	17	HP	45	WM	370	530	0.55	85
5 †	51	CP	48	RAH/SVI	-	-	-	-
6	17	HP	38	RAH/WCH/SVI	579	1117	0.15	69
7	31	CP	35	RAH/SVI	384	100	0.5	76
8	17	HP	35	RAH/WCH/SVI	404	862	0	37
9	41	CP	21	RAH/SVI	225	272	0	34
10	4	HP	24	WM	360	1600	0	32
11	27	HP	19	RAH/SVI	85	56	0.6	86
12	40	HP	14	RAH/SVI	820	931	0	46
13	8	HP	11	RAH/WCH/SVI	1205	330	0	34
14	36	CP	7	RAH/SVI	686	678	0	26
15	16	HP	6	RAH/WCH/SVI	192	395	0	29
16	29	CP	15	WM	130	139	0.15	75

Table 3: Analgesia

Recipient	**Regular opioid analgesia pre TP-IAT**	**Regular adjunct analgesic medications pre TP-IAT**	**Regular opioid analgesia post TP-IAT**	**Regular adjunct analgesic medications post TP-IAT**
1	Yes	Yes	Yes	Yes
2	Yes	Yes	No	No
3	Yes	Yes	No	No
4	Yes	Yes	Yes	Yes
5	-	Yes	-	-
6	Yes	Yes	No	No
7	Yes	No	No	No
8	Yes	Yes	No	No
9	Yes	No	No	No
10	No	Yes	No	No
11	Yes	No	No	No
12	Yes	Yes	No	No
13	No	Yes	No	No
14	Yes	Yes	No	No
15	Yes	No	No	No
16	Yes	Yes	No	No

Figure 1 – Decreasing IEQ/KG associated with higher age