The CoURT project

Complications of the Ureter after Renal Transplantation

A Prospective Observational Project

Project Protocol

Version Number	v1.0
Date	23/AUG/2015

Study Documentation – Current Versions

Name	Version Number	Date
Questionnaire	v1.0	23/AUG/2015

Carrel Club

Transplant Research Collaborative

Background

Renal transplantation is the most effective treatment for patients with end-stage renal disease. It leads to a reduction in mortality, a reduction in cardiovascular complications and an improvement in quality of life [1]. During the transplantation operation, the donor ureter is anastomosed to the recipient's bladder. There are a number of different techniques that can be used during this part of the operation, including:

- intra-vesical or extra-vesical anastomosis
- whether to insert a ureteric stent (universally, selectively or never)
- if a stent is inserted, the timing of removal
- administration of prophylactic antibiotics

Urological complications can arise following renal transplantation, including:

- urinary leak
- ureteric obstruction/stenosis
  (together termed major urological complications (MUC)), and
- urinary tract infection (UTI)

The incidence of MUC following renal transplantation is estimated to be approximately 3-6% [2-6] and of UTI to be approximately 20-35% [2, 3, 7-10].

A recent Cochrane Collaboration Intervention Review [2] concluded that the incidence of MUCs was reduced by universal prophylactic stenting, and that UTIs were more common in patients who received a stent unless they were prescribed prophylactic co-trimoxazole. A separate systematic review and meta-analysis [3] concluded that extra-vesical anastomosis of the transplant ureter results in a lower relative risk of ureteric stenosis, urinary leak and haematuria, with no significant difference in the rate of UTI.

Despite the available evidence, there seems to be no definitive consensus on the best surgical management of the transplant ureter within the United Kingdom – at a National Meeting of transplant surgical trainees (Carrel Club Meeting, 28/NOV/2014), discussions on this subject highlighted significant differences in practice between Transplant Centres. The CoURT project has therefore been designed to examine this area in detail.

Aims

1) to describe the incidence of MUCs and UTIs following renal transplantation
2) to identify any current variability of surgical management of the transplant ureter throughout the United Kingdom
3) to identify areas for future investigation

Outcome measures

Primary outcome measures

1) Incidence of urinary leak post-renal transplantation
2) Incidence of ureteric obstruction/stenosis post-renal transplantation
3) Incidence of UTI post-renal transplantation

Secondary outcome measures

The questionnaire and initial pilot study will be used to develop hypotheses and delineate secondary outcome measures to be assessed during the longer prospective study.

Trial Design

The project will be conducted in three phases:

1) *a questionnaire*, submitted to Transplant Surgical Consultants, to summarise the current methods of surgical management of the transplant ureter.

   a prospective audit of a cohort of patients undergoing kidney transplantation. This will comprise:
2) an initial pilot study, with 1 month of recruitment and 3 months post-transplantation follow-up.
   The results of both the questionnaire and the pilot study will then be analysed and a decision taken by the Project Steering Committee whether to refine the methodology and proceed with:
3) a continuing study, with 1 year of recruitment and 1 year post-transplantation follow-up.

Sample size

Questionnaire: All Transplant Surgical Consultants working in the United Kingdom will be invited to participate.

Prospective audit: Between 01/APR/2013 and 31/MAR/2014, a total of 3,256 kidney transplants were performed in the United Kingdom: 1,321 donation after brain death (DBD), 821 donation after circulatory death (DCD) donors and 1,114 living donors [11]. In the same time period, there were a further 246 simultaneous pancreas and kidney (SPK) transplants performed: 203 DBD and 43 DCD [12].

For the initial pilot study, if all Transplant Centres in the UK participate, it is estimated that approximately $1/12^{th}$ of this number of transplants will be performed and therefore eligible for inclusion (i.e. 270 kidney transplants and 20 SPK transplants). For the subsequent study, it is estimated that 1 year of recruitment will result in similar numbers to the recorded year (i.e. 3,256 kidney transplants and 246 SPK transplants).

Definitions

Bacteriuria	the growth of $\geq 10^5$ colony-forming units/mL
UTI	bacteriuria plus the presence of one or more of: - documented pyrexia ≥38.0°C - dysuria - urinary frequency - urinary urgency
Recurrent UTI	≥3 documented episodes of UTI in the 12 months prior to transplantation and/or a recorded formal diagnosis of recurrent UTI during the formal assessment for transplantation

Analysis

The results of the questionnaire and pilot study will be summarised and used to plan the subsequent design and analysis of the longer prospective study.

Selection of Subjects

Inclusion Criteria

Questionnaire: all Transplant Surgical Consultants working at the participating Centres will be invited to complete the questionnaire.

Prospective audit: all adult (aged 18 years or older) patients undergoing kidney transplant alone or kidney transplant as part of SPK transplantation or other multi-organ transplantation at any of the participating Centres.

Many Centres perform transplants on patients who then return to peripheral Nephrology Units for follow-up. For the initial pilot study, all these patients will be included. At the end of the pilot study, an assessment will be made of the ease of collection and completeness of submitted data for those patients who return to peripheral Units, and a decision taken on whether to include similar patients in the subsequent study.

Exclusion Criteria

Questionnaire:	there are no exclusion criteria. (The total number of Consultants who do not take part will be recorded.)
Prospective audit:	age at transplantation <18 years

Organisational Structure of the Project

This project will be undertaken by the Carrel Club Transplant Research Collaborative (CCTRC), the national trainee-led transplant surgical research collaborative. Responsibility for the administration and oversight of the project, as well as writing of abstracts and manuscripts, will lie with the Project Steering Committee (PSC). The members of the PSC are:

Anna Adamusiak	Transplant Registrar Guy's and St Thomas' NHS Foundation Trust	anna.musiak@gstt.nhs.uk
Nicholas Barnett	NIHR Clinical Lecturer in Transplantation Surgery University of Cambridge	nicholas.barnett@nhs.net
Catherine Boffa	Research Fellow in Transplantation Oxford Transplant Centre	catherine.boffa@nhs.net
Simon Knight	Academic Clinical Lecturer Centre for Evidence in Transplantation Nuffield Department of Surgical Sciences	simon.knight@nds.ox.ac.uk
Shruti Mittal	Research Fellow in Transplantation Oxford Transplant Centre	shruti.mittal@gtc.ox.ac.uk
Ismail Mohamed	Specialty Registrar, General Surgery/Transplant London Postgraduate School of Surgery (South East London Rotation)	ismailheyder@yahoo.com
Tahawar Rana	Transplant Fellow University Hospital of Wales, Cardiff	ranatahawar@yahoo.com
David van Dellen	Consultant Transplant Surgeon Central Manchester University Hospitals NHS Foundation Trust	david.vandellen@cmft.nhs.uk

At each Transplant Centre, 1 or 2 surgical trainees will act as Local Investigators, with responsibility for local project approval, data collection and data entry. (In Centres where no suitable surgical trainees are available, other members of staff such as nephrology trainees will be invited to act as Local Investigators.) A Consultant from each Centre will be asked to act as a supervisor, and will be included as an acknowledged collaborator (see Publication Policy section).

Direct Access to Source Data and Documents

The Investigators will permit trial-related monitoring, audits and regulatory inspections by providing direct access to source data and other documents (e.g. patients' case sheets, blood test reports, histology reports etc.).

Ethics and Regulatory Approvals

This project has been assessed to be a clinical audit by the Research and Innovation Division at Central Manchester University Hospitals NHS Foundation Trust. The project will be registered individually with the each participating Centre's Clinical Audit Department.

Data Handling

Questionnaire: All respondents to the questionnaire will be anonymised. A codesheet will be kept, containing the Consultants' names and a separate unique identifier, comprising the letter Q, a single letter (relating to the transplant unit: see Appendix – Centre Identifiers) and a two digit number (e.g. QA01, QF05). The total number of Consultants in each Transplant Unit and the number who did not respond to the questionnaire will be recorded.

Prospective audit: All patient data will be anonymised. Each participating Centre will maintain a codesheet, which will be stored on a password protected NHS computer. This codesheet will contain the unique patient identifiers for each study participant from that Centre (including name, date of birth and hospital number) coupled to an individual participant identifier. This identifier will comprise a single letter (relating to the transplant unit: see Appendix – Centre Identifiers) and a three digit number (e.g. A001, F005). The study number will be the only patient identifier uploaded to the electronic Case Report Form.

Data Management

Electronic Case Report Forms (eCRFs) will be used for both the questionnaire and the prospective audit: data will be collected and managed using REDCap (Research Electronic Data Capture) tools [13] hosted at Guy's and St Thomas' NHS Foundation Trust. (Anna Adamusiak is the REDCap collaborator at this site.) REDCap is a secure, web-based application designed to support data capture for research studies, providing:

1) an intuitive interface for validated data entry
2) audit trails for tracking data manipulation and export procedures
3) automated export procedures for seamless data downloads to common statistical packages
4) procedures for importing data from external sources

Publication Policy

It is intended that the results of the questionnaire and of the prospective project will be reported at national or international conferences and in peer-reviewed scientific journals.

Any presentations or publications arising from this work will be listed as being authored by 'The Carrel Club Transplant Research Collaborative'. In addition to the members of the PSC, those involved in data collection and entry at the participating Centres will be listed either as co-authors or cited collaborators (depending on the policy of the conference or journal to which the abstract or manuscript is being submitted). There will be a limit of 2 of these co-authors or cited collaborators from each participating Centre. Each co-author or cited collaborator will be required to submit data from at least 5 patients for the initial pilot study and 15 further patients for the subsequent study, with a minimum submission rate of 90% of the requested data per patient.

Other contributors to the project (such as supervising Consultants or other trainees who provide some help to data collection or entry) will be included as acknowledged collaborators.

The PSC will be responsible for drafting any abstracts and manuscripts arising from this work. The drafts will be sent out to all co-authors/collaborators for final approval prior to submission. For accepted presentations, the PSC will nominate a member of the CCTRC to give the presentation.

References

1. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *American Journal of Transplantation* 2011; 11 (10):2093-2109.
2. Wilson CH, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2013; 6:CD004925.
3. Slagt IK, Klop KW, Ijzermans JN, et al. Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: a systematic review and meta-analysis. *Transplantation* 2012; 94 (12):1179-1184.
4. Saeb-Parsy K, Kosmoliaptsis V, Sharples LD, et al. Donor type does not influence the incidence of major urologic complications after kidney transplantation. *Transplantation* 2010; 90 (10):1085-1090.
5. Gomes G, Nunes P, Castelo D, et al. Ureteric stent in renal transplantation. *Transplantation Proceedings* 2013; 45 (3):1099-1101.
6. Akoh JA, Rana T. Effect of ureteric stents on urological infection and graft function following renal transplantation. *World J Transplant* 2013; 3 (1):1-6.
7. Slagt IK, Dor FJ, Tran TC, et al. A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. *Kidney International* 2014; 85 (2):471-477.
8. Silva M, Jr., Marra AR, Pereira CA, et al. Bloodstream infection after kidney transplantation: epidemiology, microbiology, associated risk factors, and outcome. *Transplantation* 2010; 90 (5):581-587.
9. Lee JR, Bang H, Dadhania D, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: a single-center report of 1166 kidney allograft recipients. *Transplantation* 2013; 96 (8):732-738.
10. Chordia P, Schain D, Kayler L. Effects of ureteral stents on risk of bacteriuria in renal allograft recipients. *Transplant Infectious Disease* 2013; 15 (3):268-275.
11. NHS Blood and Transplant. Transplant Activity in the UK, Activity Report 2013/14, p.30. http://www.organdonation.nhs.uk/statistics/transplant_activity_report/ (accessed 11/JAN/2015).
12. NHS Blood and Transplant. Transplant Activity in the UK, Activity Report 2013/14, p.53. http://www.organdonation.nhs.uk/statistics/transplant_activity_report/ (accessed 28/FEB/2015).
13. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42 (2):377-381.

Appendix – Centre Identifiers

Centre Name	Identifier Letter	Example Consultant Unique Identifier	Example Patient Unique Identifier
Belfast Belfast City Hospital	A	QA01	A001
Birmingham Queen Elizabeth Hospital	B	QB01	B001
Bristol Southmead Hospital	C	QC01	C001
Cambridge Addenbrooke's Hospital	D	QD01	D001
Cardiff University Hospital of Wales	E	QE01	E001
Coventry Walsgrave Hospital	F	QF01	F001
Edinburgh Edinburgh Royal Infirmary	G	QG01	G001
Glasgow Western Infirmary	H	QH01	H001
Leeds St James' University Hospital	J	QJ01	J001
Leicester General Hospital	K	QK01	K001
Liverpool Royal Liverpool University Hospital	L	QL01	L001
London Guy's Hospital	M	QM01	M001
London Hammersmith Hospital	N	QN01	N001
London St George's Hospital	P	QP01	P001
London The Royal Free Hospital	Q	QQ01	Q001
London The Royal London Hospital	R	QR01	R001
Manchester Manchester Royal Infirmary	S	QS01	S001
Newcastle Freeman Hospital	T	QT01	T001
Nottingham City Hospital	U	QU01	U001
Oxford Churchill Hospital	V	QV01	V001
Plymouth Derriford Hospital	W	QW01	W001
Portsmouth Queen Alexandra Hospital	X	QX01	X001
Sheffield Northern General Hospital	Y	QY01	Y001