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Immunosuppressive drug assaying: A challenge for renal transplantation in the Northern Territory, Australia

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RESEARCH

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ABSTRACT

Background
Renal transplant patients of the Northern Territory (NT) of Australia, suffer poor transplant outcomes including graft rejection, infection and increased mortality, therefore requiring stringent immunosuppressive drug assay monitoring. Best practice dictates that drug assay results should be received within 24 hours and at the most no later than 48 hours post blood collection. Assays from the Royal Darwin Hospital (RDH) are processed at an interstate laboratory, therefore prolonging the time to dosage adjustment.

Aims
To assess the time delay that exists between blood sample collection at the Royal Darwin Hospital (RDH) and the faxing of results from an interstate laboratory to RDH.

Methods
We conducted a retrospective audit of immunosuppressive drug assay samples and results between the 4th of January 2013 and the 22nd April 2014. Time delay was divided into intervals: T1: Total time between collections to faxing of results back to RDH, T2: Time between blood collection, sending of samples and reporting at an interstate laboratory, T3: Time between results reporting and the faxing of results back to RDH.

Results
A total of 389 drug assays from 49 renal transplant patients were analysed. Median times in hours (interquartile ranges) were T1=53.48 (31.68-78.55), T2=47.18 (28.80-76.18), T3=2.70 (1.87-3.90). 13.3 per cent of the results led to the requirement for dosage changes with the potential risk of under-dosing or overdosing.

Conclusion
The long median time delay between sample collection and receiving of results illustrates the challenges of immunosuppression in this setting and the need for on-site immunosuppressive drug assaying.

Key Words
Renal transplantation, immunosuppression, drug assaying

What this study adds:

1. What is known about this subject?
Immunosuppressive drug assaying in renal transplants patients is required to balance the risk of rejection versus the risk of infections and other complications.

2. What new information is offered in this study?
Remote-regional areas provide significant challenges to managing renal transplantation, as interstate laboratory drug assaying leads to the risk of increased time to dosage adjustment.

3. What are the implications for research, policy, or practice?

Provisions should be made for on-site immunosuppressive drug assaying for remote and regional areas such as Darwin in Northern Australia.

Background

The Northern Territory (NT) bears much of the brunt of Chronic Kidney Disease (CKD) in Australia. Among its Indigenous population, CKD is 4-10 times higher when compared to non-Indigenous Australians. This is principally attributed to higher rates of diabetes mellitus, hypertension, smoking, infections, glomerular disease and low nephron endowment.[1]

Complicating the burden of CKD in the territory is the remoteness of its sufferers. Compared to other states and territories, 45 per cent of the NT's population live remotely. 75 per cent of its Indigenous population live in areas defined as remote and very remote.[2]

Renal replacement treatments (RRT) including peritoneal dialysis, home haemodialysis and community health centre dialysis, is offered, thus diminishing the need to relocate to greater centres for treatment for those who can use these modalities of treatment. Unfortunately, however, due to the many challenges of living remotely and the large burden of co-morbidities among Indigenous people, these alternatives are offered to a minority of patients. This therefore leaves most patients accepting haemodialysis in bigger centres in Darwin, Katherine and Alice Springs, often at the cost of being separated from their homeland, cultural responsibilities, children and spouses.

In a bid to improve both patient outcomes, there has been a recent increase in the number of successful renal transplantation in the NT. Unpublished data suggests that over the last 6 years renal transplants have almost doubled, therefore increasing the use of services involved in routine transplant care.

Renal transplantation among most patients with end stage renal failure (ESRF) is the most effective form of renal replacement therapy. It offers improved quality of life, reduced morbidity, mortality and economic benefits in most patient populations when compared to dialysis.[3-6]

Specifically, renal transplantation compared to haemodialysis, is associated with improved patient survival[3]. However, when paralleled to non-Indigenous transplant patients, Indigenous renal transplant recipients suffer higher rates of renal allograft loss and mortality.[4-6] Data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry published by McDonald et al. in 2004, analysed both graft survival and patient survival at 5 years post transplantation, between Indigenous and Non Indigenous patients. At 5 years post transplantation, graft survival of Indigenous transplant recipients was 47.8 per cent compared to 80 per cent in non-Indigenous recipients. Similarly, at 5 years post transplantation, patient survival among Indigenous patients was 61.7 per cent compared to 88.7 per cent among non-Indigenous patients.[5] Various factors such as increased rates of infection, septicaemia, increased plasma cell infiltrates in grafts (thus increasing susceptibility to post transplant infection rates due to increased immunosuppression burden). Greater rates of human leukocyte antigen (HLA) mismatches and increased rate of sensitisation prior to transplant among Indigenous recipients with increased rates of rejection, were attributed to the disparities.[1,4,5]

Additionally, poor outcomes in the NT were also attributed to the absence of on-sight renal pathologists and of specific interest to this report, the absence of on-site immunosuppressive drug assay processing.[7,4]

At RDH, immunosuppressive drug assays from patients are currently done in interstate laboratories. Patient blood samples are collected by pathology at RDH prior to morning dose administration. Multiple samples are then sent collectively to an interstate laboratory by aeroplane for analysis. Once reported at the interstate laboratory, these reports are finally faxed back to RDH, for clinicians to review.

Often drug assay results take a considerable amount of time to return. In some instances local clinicians report reviewing patients in transplant clinics 2-3 days post blood sampling, without being able to comment on dosage regimes due to pending drugs assay results. Best practice dictates that immunosuppressive drug assays should be received within 24 hours and no later than 48 hours post blood collection, for the optimum management of renal transplant care.

This audit aimed to assess the time delay that exists between blood sample collection at RDH, drug assay reporting and the faxing of results from an interstate laboratory back to RDH.

Method

This was a retrospective audit of immunosuppressive drug

assay results between the 4th January 2013 and 22nd April 2014. The audit was registered with the ethics committee of the Northern Territory Department of Health and Menzies School of Health Research. HREC Reference number: QAAR 2014-2234.

A renal transplant patient information database and medical files were used to extract immunosuppressive drug assay results and demographic data.

The following de-identified data was extracted; the dates and times blood samples were collected at RDH, the dates and times blood drug assays were reported at an interstate laboratory, the dates and times drug assay reports were faxed back to RDH and finally drug assays whose reports were signed by doctors noting the need for dosage changes.

Data analysis occurred by dividing time into the following intervals: T1: The total number of hours between collection and faxing results back to Darwin, T2: The number of hours between blood sample collection in Darwin, sending of samples and result reporting at an interstate laboratory and T3: The total number of hours between results reporting at an interstate laboratory and the faxing of results to Darwin.

Descriptive and exploratory analyses were performed for each length of time summarising the data as means and their standard deviations (SD) for continuous normally distributed variables and medians and interpercentile ranges (IR) for data, which was not normally distributed. An analysis was performed to assess the association between time variables and requirement for dosage changes using chi-squared test and fisher's exact test as appropriate for categorical variables and t-test and Wilcoxon-Mann-Whitney test for continuous data as appropriate. A two-tailed p-value of $p<0.05$ was significant. All analyses were performed using Stata Version 13.1 (StataCorp, College Station, Texas, US) and Microsoft Excel © 2010 Microsoft.

Results

A total of 389 immunosuppressive drug assay results from 49 renal transplant patients were audited from the 4th of January 2013 to the 22nd of April 2014. The patients belonged to 5 different ethnic backgrounds (Table 1). The majority of the patients were Indigenous (Aboriginal and Torres Strait Islander) and Caucasian, 42.9 per cent and 40.8 per cent respectively. The mean (SD) age in years was 49.0 (14.3). Indigenous patients were older than Caucasians with mean (SD) ages in years of 48.3 (12.7) and 43.7 (10.5) respectively.

The median (IR) number of hours among time intervals were T1=53.48 (31.68-78.55), T2=47.18 (28.80-76.18) and T3=2.70 (1.87-3.90) (Table 2). The longest time delay was between sample collection and analysis in the interstate laboratory. This was predominantly contributed to by the time taken to transport the samples.

Among the 389 assay results, 13.3 per cent (n=52) required dosage changes. The median (IR) number of hours for the drug assay results requiring dosage changes were different from those who did not require dosage changes but the differences were not statistically significant (Table 3); T1=42.43(31.53-79.82) versus T1=53.57 (31.68-78.28) p=0.938, T2=30.53 (28.82-77.22) versus T2=48.08 (28.80-75.93), p=0.712 and T3=2.48 (1.83-3.67) versus T3=2.75 (1.92-3.93), p=0.522. There was no difference in time delay by ethnicity.

Discussion

Best practice for monitoring stable renal transplant patients in remote and regional locations such as the NT, would require that immunosuppressive drug assay results be received within 24 hours and at most no later than 48 hours post blood collection. Previous cohort and registry data analyses have shown that both patient and graft survival among Indigenous renal transplant patients in the NT of Australia are poor compared to Non-Indigenous patients from the same region.[1,4-6] The main causes of death and graft loss were infections and rejection.[4,5] This underlines the need for comprehensive monitoring of patients' immunosuppression. Maintenance of an appropriate balance between the risk of rejection and over-immunosuppression depends on immunosuppressive drug assay screening, in order to avoid graft rejection or infections. Receiving results with time delays create delays in clinical decision-making.

This audit is the first study assessing the challenges of lacking on-site immunosuppressive assay monitoring, in a remote-regional centre in Northern Australia. The results suggest that a greater than 48 hours median time delay exists. A total time from blood sample collection to receiving of faxed results of 53.48 hours has significant implications for outcomes particularly for those requiring treatment of rejection, requiring change of dose or those developing graft dysfunction. The decision to manage these patients will largely end up being empirical whilst waiting for the results, which is not best practice. The data further demonstrated many of these hours (47.18 hours), to be occupied by the hours between blood sample collection in Darwin, sending of samples and results reporting at an

interstate laboratory. Conversely, the hours between results reporting at the interstate laboratory and the faxing of results to Darwin was very short, (2.7 hours) demonstrating the possibility of receiving results within 2 to 4 hours if on-site analysis was established. These results indicate that time is lost in the collection of samples in Darwin, the sending of sample and reporting at an interstate laboratory, and thus provide strong justification for on-sight monitoring. A significant number of changes to collection and transport of samples have already been implemented following the presentation of these results, with the eventual aim of setting up an on-site process for analysis.

Among the 13.3 per cent of drug assays that did require dosage changes, time delays were not statically different from those that did require changes. These results suggest there is a problem across all practice regardless of the urgency of results. Patients and their clinicians waited long times before being able to change to the appropriate and safe immunosuppressive doses, which could have compromised their grafts and outcomes.

Published literature states that immunosuppressive drug assaying is an essential tool in the achievement of the optimum balance between therapeutic effects versus adverse reactions.[7] Pharmacological agents such as tacrolimus, sirolimus, Everolimus, cyclosporine and mycophenolate may exhibit a high degree of ethnic pharmacodynamics and pharmacokinetic variability.[8,9] As these are the drugs used in our transplant patients, it is prudent that the monitoring of their levels occurs in a timely manner.

There are some limitations in this study that should be acknowledged. The main limitation being that time was not correlated to renal function. This would have allowed greater insight into the consequences of delayed dosage changes. However, the aim of this study was to assess the deviation from the time limits for getting the results back and within this limitation the study showed significant findings. The study did not differentiate between new transplant and old transplant recipients, where patients with new transplants are at a time of high risk. Additionally, due to the limited data availability to researchers, total time was only analysed in the three intervals, where some intervals involved multiple steps. Finally, a cost benefit analysis comparing the assaying of samples interstate versus the assaying of samples locally at RDH was not conducted.

Among the 389 immunosuppressive drug assays audited, a greater than 48 hours median delay exists. The greatest delay in time lies in the sending of samples and the processing drug assays at an interstate laboratory. Recommendations from this audit have led to a process of improving blood sample collection and transport to the interstate laboratory whilst a more robust system of on-site monitoring is developed. Further work needs to be done to assess the effect of time delays on graft function, infection episodes, patient outcomes and long term survival of both the renal transplants and the patients.

Conclusion

In order to improve the management of transplant patients this audit supports the commencement of on-site drug assay analysis in the Top End of the Northern Territory.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

The audit was registered with the ethics committee of the Northern Territory Department of Health and Menzies School of Health Research: HREC reference number QAAR 2014-2234.

Table 1: Ethnicity and Gender

	Number	Percentage
Ethnicity		
Asian	3	7.2
Caucasian	20	40.8
Indigenous	21	42.9
Indonesian	2	4.0
Filipino	3	6.1
Gender		
Female	17	34.7
Male	31	65.3
Total	**49**	**100.00**

Table 2: Summary statistics for the time taken from sample collection in Darwin to getting the results from an Interstate Laboratory

Time Variable (In Hours)	Number Of Assays	Median(IR)
T1	389.00	53.48 (31.68-78.55)
T2	389.00	47.18 (28.80-76.18)
T3	389.00	2.70 (1.87-3.90)

Legend:

Time 1 (T1): *Hours between collection of samples in Darwin and results being faxed from Interstate Laboratory,*

Time 2 (T2): *Hours between blood sample collection in Darwin, sending of samples and result reporting Interstate Laboratory,*

Time 3 (T3): *Hours between result reporting in Interstate Laboratory and the faxing of results to Darwin*

Table 3: Summary statistics for the time in hours taken from sample collection to results by whether a dose change was required or not

Dose Change Required	Time	Number Of Assays	Median (IR) (Hours)
No	T1	337.00	53.57 (31.68-78.28)
	T2	337.00	48.08 (28.80-75.93)
	T3	337.00	2.75 (1.92-3.93)
Yes	T1	52.00	42.43 (31.53-79.82)
	T2	52.00	30.53 (28.82-77.22)
	T3	52.00	2.48 (1.83-3.67)
Total	T1	389.00	53.48 (31.68-78.55)
	T2	389.00	47.18 (28.80-76.18)
	T3	389.00	2.70 (1.87-3.90)