Brunei International Medical Journal

OFFICIAL PUBLICATION OF
THE MINISTRY OF HEALTH
AND
UNIVERSITI BRUNEI DARUSSALAM

Volume 18 1 August 2022 (3 Muharram 1444H)

KIDNEY TRANSPLANTATION IN BRUNEI DARUSSALAM – PAST, PRESENT AND FUTURE.

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ABSTRACT

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Keywords: Brunei Darussalam, Dialysis, Kidney Failure, Kidney Transplantation, Wawasan 2035.

Brunei Int Med J. *2022;18:129-138*

ISSN 1560 5876 Print
ISSN 2079 3146 Online

Online version of the journal is available at www.bimjonline.com

Brunei International Medical Journal (BIMJ)
Official Publication of
The Ministry of Health
and
Universiti Brunei Darussalam

ISSN 1560-5876 Print
ISSN 2079-3146 Online

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Acknowledgements

Only persons who have made substantial contributions but who do not fulfill the authorship criteria should be acknowledged.

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ABSTRACT

Kidney transplantation is the treatment of choice for the majority of patients with Kidney Failure in an ideal world and is preferred over dialysis on the basis of evidence that demonstrate improvement in health-related quality of life and prolongation of life expectancy. However, shortage of suitable organs remains a limiting factor for program expansion. In Brunei Darussalam, despite having conducted over 16 cases of successful living related donor-recipient kidney transplantation over a period of 8 years, the program is still considered at its infancy state. This review article discusses the evolution of our program and the problems associated with setting up such a nationwide kidney transplantation program and elaborate our plans to increase the scope of services in the future, towards 'Wawasan 2035'.

Keywords: Brunei Darussalam, Dialysis, Kidney Failure, Kidney Transplantation, Wawasan 2035.

BACKGROUND

Kidney transplantation (KT) is the treatment of choice for the majority of patients with Kidney Failure (KF).[1] KT is usually preferred over dialysis on the basis of evidence that demonstrate improvement in health-related quality of life (HRQOL) and prolongation of life expectancy.[2] In the long-term, KT is the most cost-effective Kidney Failure Replacement Therapy (KFRT), with respect to expenditure on hospital admissions and associated medical complications; but immunosuppressed patients will require careful long-term follow up due to susceptibility to infection, malignancy and cardiovascular disease.[3]

KT was first performed in 1954 in Boston, Massachusetts with a set of identical twins, negating the use of any immunosuppressive medications.[4] Following that groundbreaking endeavor, KT had proceeded to shift paradigm on treatment for KF leading to rapid expansion of international transplant programs over the subsequent decades. This was achieved not only within the realms of nephrology but also through paving the way for

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other solid organ transplantations.[5] Regionally, Singapore performed their first kidney transplant in 1970, through a deceased kidney transplant donor.[6] Malaysia followed suit in 1975 with a living-related KT, followed by a cadaveric KT program in 1976.[7] Brunei commenced a living-related KT program in 2013, but continues to send complex cases to Singapore and Malaysia for transplantations under government sponsorship, through a partnership that has lasted for over 20 years.[8] However, KT penetration rates (defined as KT numbers/ total KFRT numbers x 100%) within the South East Asian region (Singapore 18%, Brunei 5% and Malaysia 4%) remains low compared to developed Western countries (UK 56%, Australia 48%, USA 29%)[9], likely due to socio-cultural barriers and poor public awareness on organ donation.[10] As a result of organ shortages and supply discrepancy, the region has become an active hub for trafficking of human beings for the purpose of organ removal, particularly in countries with lower socio-economic status.[11]

The prevalence and incidence of KF has increased over the past decade in Brunei, but penetration of KT as a KFRT modality remains static (Table I). Given the disproportionate provision of KFRT services in the country, there is a need to consolidate and galvanize the KT program in the country to ensure that patients have easier access to KT. This article focuses on archiving historical transplantation activities, describing the current transplant program and forecasting future service directions in the country.

PAST PRACTICE

The first recorded Bruneian patient to undergo KT was a 16 years old girl, who was sent by the Brunei Government to the United Kingdom in the late 1970s.[12] The recipient, with chronic glomerulonephritis, received a kidney donation from her sister. However, transplant activities involving Bruneian patients in the 1980s and 1990s were limited, and patients who managed to be transplanted were those who made personal arrangements with foreign institutions. Due to the logistic and organisational difficulties of foreign-performed KT, not many patients were able to be transplanted because of long overseas stay and financial repercussions. Furthermore, the public perception and acceptance of KT were tepid and lukewarm, particularly through religious and cultural viewpoints. Tentative efforts to establish a national transplant center in Brunei began in the 1990s, where partnerships were explored with institutions in Malaysia and Singapore; but this did not come to fruition because of financial and technical reasons.

Formal KT arrangements were made with Singapore General Hospital in the early 2000s, when eligible patients were sent under government sponsorship. The criteria for sponsorship depended on recipients being Brunei citizens, having related Bruneian donors and being medically fit. Typically, the recipient and donor (along with two carers) would have to stay abroad for up to six months before being allowed to return to Brunei. Further partnerships were established

Table I: Kidney failure replacement therapy in Brunei Darussalam (2012-2021).

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
All KFRT	620	652	698	698	754	778	783	786	881	893
HD	533	570	606	586	629	656	655	660	752	732
PD	53	46	53	67	78	75	82	80	81	114
Tx	34	36	39	45	47	47	46	46	48	47

Abbreviations: KFRT-Kidney Failure Replacement Therapy, HD-Haemodialysis, PD-Peritoneal dialysis, Tx-Transplantation.

Table II: Types of kidney transplants (1993-current).

Period of year	Local	Foreign-government sponsored	Foreign Non-government sponsored	Total
1993-2000	0	4	9	13
2001-2005	0	6	5	11
2006-2010	0	13	5	18
2011-2015	3	6	3	12
2016-2020	10	4	3	17
2021-current	3	0	0	2
All	16	33	25	74

with the National University Hospital, Singapore and Prince Court Medical Center, Malaysia in the subsequent years, which allowed many patients to be sent at one time and patients to choose their preferred centres. There had been discussions to include institutions in other countries, primarily through ad-hoc patients' requests, but these centers were rejected on the grounds of sub-optimal international repute and poor track record with commercialization.

Reliable and comprehensive data on KT were limited in the 1980s and 1990s, due to incomplete documentation and poor record keeping. Table II shows the number of KT performed on Bruneian patients from 1993 onwards. Prior to the commencement of a local program, up to 40% of KT were done through commercialized channels, mainly in China and India. A previous local study cited unavailability of a national transplant program and the lack of living-related donors being motivations for pursuing commercialization in foreign countries.[13] However, increased awareness of transplant ethics and malignment of illegal commercialization, alongside logistic difficulties in arranging the work-up processes have led to a decline in this practice over the past decade.[14] The renal service in Brunei has always maintained an unswaying stance on discouraging patients from pursuing commercialization, but has embraced a non-judgmental viewpoint in providing long term follow up to patients who have returned from such undertaking.

Data from historical kidney transplants from 1993 to 2013 have shown that patient and graft survival of commercialized and non-commercialised KT had equivalent long-term outcomes with 5- and 10-years graft survival of 91.1% and 81.2% respectively in a study that involved 49 patients.[15] These rates were similar to those achieved within South East Asia and other developed Western countries.[16] KT patients in Brunei also had a superior HRQOL, compared to patients on haemodialysis and peritoneal dialysis for physical health, psychological health, social relationship and environment scores with the World Health Organisation Quality of Life (WHOQOL-BREF) questionnaire.[17,18] Another national study in 2010 involving 300 respondents showed that the majority of respondents (78.7%) were willing to donate their kidneys and 59.7% preferred to have transplantation done locally.[19] Evidence from all these studies have contributed significantly to the development and inauguration of the national KT program.

PRESENT PRACTICE

Brunei Darussalam commenced a living-related KT program in 2013.[8] The program was pioneered on the premises of equity, quality, sustainability and morality. Equity means that all residents and citizens in the country will have access to the local transplant program, without necessitating government sponsorship or spending considerable time abroad. Quality indicates the governance and academic measures that are put in place

to ensure parity with and adherence to the best international practice. Sustainability refers to the concerted efforts to ensure that the program prioritizes the leadership of local spearheads and development of succession planning. Morality alludes to the adherence to strong ethical principles in deterring commercialization and exploitation of vulnerable individuals, consistent with the principles of the Istanbul Declaration on organ trafficking and transplant tourism.[20]

Preliminary outcomes from the program have shaped the nephrology landscape in the country, with increment in transplant rates of 36% since its inception, whilst yielding a transplant output of 8 per million population in 2019, on par with most developed Asian countries.[21] Most importantly, the transplant team has also acquired self-sufficiency and self-proficiency in running the program, without the need for external expertise from overseas.[22] To date, the team has successfully completed 15 kidney transplantations in RIPAS Hospital in the past 8 years, despite a 2-year moratorium on transplant activities during the COVID-19 pandemic. Complicated transplant cases continue to be sent abroad- particularly those with complex medical conditions and high-risk cross-match- due to the lack of resources to deal with long hospital stays and diagnose rare complications. Since the advent of the local transplant program, only 5 cases needed to be sent overseas, which has resulted in significant cost-savings for the government (Table II).

Table III shows the demographics, operative and hospital stay details of all the 16 local transplant recipients. There was a 2:1 male preponderance for recipients, but a slight female preponderance for donors. The median age of recipients was 28 years. Only 6 out of 16 recipients had definitive histological diagnosis of glomerulonephritis, whilst the rest were never biopsied due to late presentations of kidney diseases. 6 out of 16 patients were considered high risk with pre-sensitization through donor specific antibodies, but typically with mean fluorescence intensity (MFI) of less than 2000. The median HLA-ABDR mismatch was 2, particularly at the DRB3 and DR52 loci. The HLA-incompatible cases were all inducted with anti-thymocyte globulin (ATG), whilst the non-sensitized cases received anti-interleukin-2 receptor antibodies (Basiliximab). Warm and cold ischaemic times were relatively short due to different retrieval and implantation teams coordinating and operating side-by-side in adjoining theatres. The median hospital stay for recipient was 13 days (including the three pre-operative days).

Table IV shows the follow-up details of all the 16 local transplant recipients. The median creatinine at discharge, one year and two years were 96, 109 and 125 mmol/l respectively. One patient had an antibody-mediated rejection and recurrence of primary glomerulonephritis and subsequently lost her graft at 31 months. Transplant-related medical complications included acute rejection (n=2), CMV disease / infection (n=2), BK nephritis (n=4) and mycobacterium infection (n=1). One patient required a surgical evacuation of infected haematoma during the post-operative phase of the admission.

Table V shows the demographic data for the prevalent patients (n=48) in the program (2021 Renal Transplantation registry). The mean patient age and graft age were 38.61 ± 10.20 and 8.34 ± 5.90 years respectively. There was a 69% male preponderance, with 27% of operations being done in Brunei. 25% of the prevalent population had commercialized KT from China, India. Philippines, Indonesia and Cambodia; with an unknown proportion from cadaveric transplantation. There are more female (n= 23; wife, mother, daughter and sister) than male donors (n=17; husband, father, son and brother).

Table III: Demographics and admission details of all kidney transplantation cases (n=16) done in Brunei.

Case number	Gender	Relationship with donor	Age at transplant	Year of operation	ESKD Diagnosis	Blood group	Presence and type of Donor Specific Antibody	HLA mismatch	Panel Reactive Antibody (%)	Warm Ischaemia time (minutes)	Hospital stay (days)
1	F	Daughter	21	2013	HSP	O	Yes	1	<3	150	12
2	M	Son	29	2014	UK	AB	No	2	47	90	14
3	M	Husband	45	2015	UK	B	No	5	<3	90	16
4	F	Sister	28	2016	UK	B	DR52	0	<3	75	15
5	F	Daughter	26	2017	UK	AB	No	2	<3	153	13
6	F	Wife	29	2018	MCGN	A	DQ6	5	Class 1-11 Class 2- < 3	105	15
7	M	Brother	47	2018	MCGN	A	No	0	Class 1- 4 Class 2 -10	120	16
8	F	Sister	23	2019	UK	B	DRB3	3	< 3	141	13
9	M	Brother	36	2019	UK	O	No	0	Class 1- < 3 Class 2- 38	73	23
10	M	Brother	21	2019	FSGS	A	No	2	< 3	132	13
11	M	Brother	36	2020	UK	O	No	2	<3	105	12
12	M	Husband	38	2020	UK	B	DR52	0	<3	29	12
13	M	Son	25	2020	UK	A	DRB3	3	<3	46	13
14	M	Son	20	2021	FSGS	A	No	2	<3	95	10
15	M	Brother	31	2022	FSGS	0	No	0	<3	80	11
16	M	Brother	22	2022	CAKUT	O	No	0	<3	70	13

Abbreviations: F=Female, M=Male, CAKUT=congenital abnormality of kidney and urinary tract, FSGS= Focal segmental glomerulosclerosis, HSP= Hneoch schonlein purpura, MCGN= Mesangio capillary glomerulosclerosis, UK= unknown.

Table IV: Follow-up details of Kidney Transplantation cases (n=16) done in Brunei.

Case number	Duration of follow up (months)	Discharge creatinine (mmol/l)	1 year creatinine (mmol/l)	2 years creatinine (mmol/l)	5 years creatinine (mmol/l)	Significant surgical complications	Significant medical complications	Biopsy
1	104	105	104	101	137	-	CMV nephritis and colitis Recurrence of IgAN	yes
2	93	139	133	138	152	-	-	no
3	83	159	152	147	141	-	-	yes
4	75	92	91	64	90	-	Tacrolimus-induced Diabetic Keto-acidosis, New onset Diabetes after transplant (NODAT)	
5	60	120	134	152	124	-	-	yes
6	32	86	83	538	Dialysis	-	Antibody-mediated rejection, Recurrence of MPGN	yes
7	47	82	88	90	-	-	BK Nephritis	no
8	38	75	73	76	-	-	CMV disease	yes
9	38	87	109	89	-	Infected haematoma requiring open surgical drainage	BK Nephritis	
10	33	120	139	125	-	-	Tuberculosis, Acute cellular rejection	yes
11	29	137	199	167	-	-	BK Nephrits	Yes
12	22	96	89	-	-	-	Enterocobacter septicaemia post-transplantation	No
13	19	102	137	-	-	-	BK viremia	No
14	16	114	99	-	-	-	-	no
15	2	95	-	-	-	-	Valganciclovir-induced hepatitis	no
16	1 week	88	-	-	-	-	-	-

The present program has its limitations. More experience and resources are needed to attempt more complex operations that require sophisticated in-house laboratory tests for cross-matching (complement-dependent cytotoxicity, flow cytometry, Luminex studies with single bead antigen assay), viral assay (BK virus and cytomegalovirus polymerase chain reaction), immunosuppressant assay (m-tor inhibitor, mycophenolic acid and leflunomide) and blood group titers (anti-A and anti-B). Engagement and co-operation of hospital staff are needed to ensure multi-specialty co-ordination to provide manpower, ward and operating theater facilities. A recent national study also showed that lack of donor, inadequate information, unwillingness to take risk and financial problems were the main deterrents for dialysis patients to consider KT.[13]

FUTURE PRACTICE

Tolerance is the Achilles' heel of transplantation. The future of transplantation will hinge delicately on advances in immunogenic science to improve graft survival and to prevent rejection. The efficacy of newer immunosuppressive regimens in achieving tolerance will have to be weighed up against the potential complications of rendering patients susceptible to infective, neoplastic and metabolic insults. As such, the future direction of the local program must be underpinned by the continuing success of transplanting low immunogenic patients with a high tolerance thresh-

Table V: Renal Transplant Registry 2021— Demographic details of all prevalent Kidney Transplantation cases (n=48) in Brunei.

Variables	Mean (SD)	Median	N (%)
Current age (years)	38.61 (10.20)	39	48 (100)
Graft age (years)	8.34 (5.90)	8	48 (100)
Gender			
Male			33 (69)
Female			15 (31)
Race			
Malay			36 (75)
Chinese			8 (17)
Others			4 (8)
Place of tx			
Brunei			13 (27)
Singapore			22 (46)
Philippines			3 (6)
China			3 (6)
India			2 (4)
Others			5 (10)
Sponsorship			
Government			36 (75)
Self			12 (25)
Donor			
Husband			4 (6)
Wife			11 (23)
Son			2 (4)
Daughter			1 (2)
Father			3 (6)
Mother			3 (6)
Brother			8 (17)
Sister			8 (17)
Other			1 (2)
Unknown			7 (15)

old. This delicate balance can be optimized through meticulous selection of appropriate KT candidates; to circumvent pitfalls and challenges that might lead to poor outcomes and to promote public confidence.

There are elaborate plans to increase the scope of services of the local program in the future. Current guidelines- in accordance with the Istanbul declaration of organ transplantation- limits transplantation amongst individuals that are immediately related to the donors (spouse, siblings, offspring and parents), to ensure that the intention for donation is driven by true family altruism. With the rudimentary transplant infrastructure and framework within the country, it is difficult to ascertain genuine intentions of donors beyond the defined criteria and this has not been helped by the absence of a law-enforcing National Transplant Act. All donors are interviewed individually by independent healthcare workers that are not involved in their care- psychologists, psychiatrists, medical social workers and medical doctors- to elicit intention to donate and capacity to decide. On top of that, patients are also interviewed by a suitably appointed ethics committee to guide decisions on organ acceptance. It is hoped that with experience and improved capacity, the program will be able to cater for altruistic donations, beyond the realms of immediate family.

Despite the success of the program, there is a growing desire to expand the donor pool. There has been no precedence in decision-making on organ donation after deaths or legislative definition for brain death in Brunei. Amongst Muslim countries, opinions are divided about the legality and suitability of cadaveric donation, particularly with respect to religious belief.[23] The concept of darurah (necessity) and deliberation in the formulation of fatwas (formal ruling by Islamic law) on cadaveric transplantation differs amongst different Muslim countries.[24] Nevertheless, many prominent Islamic countries, especially in the Middle East and South East Asia, have embarked on their own journey of cadaveric kidney transplantation with successful outcomes.[10,25,26] Iran has a hugely successful model for cadaveric kidney transplantation, especially after a fatwa in the early 1980s lifted many religious and legal barriers.[25] Malaysia and Singapore also have cadaveric donor program; albeit on a smaller scale compared to their existing living donor program.[10] Most Middle-Eastern countries also have lim-

ited-scale cadaveric program; which was largely hampered by insufficient public education, lack of approval and support by Islamic scholars, poor government infrastructure and limited financial resources.[27] Public opinion about the feasibility of cadaveric donation is needed, to enable the commencement of a cadaveric transplant program.

Innovative schemes to improve living kidney donations could incorporate exchange programs for donors who are incompatible with their recipient, but can proceed with donation to another similar recipient-donor couple that are not compatibly matched.[28] Another method could involve a domino paired donation where an altruistic donor can begin a string of subsequent donations, with the proviso that the intended donor of an incompatible recipient can reciprocate the donation to another incompatible pair.[29] It is also hoped that with enough experience, the local KT program can extend a goodwill philanthropic service to other KF patients in Borneo. As there is no other transplant center in Borneo, this will be a valuable opportunity to showcase the service on a higher humanitarian pedestal in trailblazing and innovating a service that will benefit and foster regional relationship and well-being.

The success of the local KT program will also augur well for the future of other solid organ transplantations in the country; most notably liver, heart, lungs and pancreas. The technical framework and infrastructure, that has been assembled and developed for KT, can be remodeled to suit the requirements of other specialty services, under the auspices of an overarching national transplant center. The ambitious aspirations stem from the vision that is exemplified by Wawasan 2035 (WB35), which aims to transform Brunei to become a nation that will be recognized for three goals: *highly educated and accomplished local population*, *high quality of life* and *dynamic and sustainable economy*. We believe that our vision is congruent with expectations from WB35; through pushing medical frontiers with academic excellence, transfiguring a platform for medical tourism to invigorate the economy and provision of services that are fundamentally attuned to improve and prolong life.

CONCLUSION

KT will remain the best treatment for patients with KF for the foreseeable future. The national 40-years KT journey has been eventful, but the scope for progress is expansive and exciting. It is hoped that we can capitalize on the success so far, to push the envelope further, for the betterment of patient care.

ACKNOWLEDGEMENTS

The authors would like to thank the anaesthetists, radiologists, operating theatre nurses and staffs of Department of Renal Services for their significant contributions throughout the last 8 years towards the teamwork required for the successful conduct of the 16 cases of renal transplantations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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