นิพนธ์ต้นฉบับ ▪ Original Article

การศึกษาย้อนหลังสิบปีในผู้ป่วยเด็กที่ได้รับการปลูกถ่ายไตจากผู้บริจาคสมองตายในภาคตะวันออกเฉียงเหนือ

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Deceased Donor Kidney Transplantation in Pediatric Recipients: A Decade Results in Northeast Thailand

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Received: 6 December 2019
Accepted: 12 February 2020

หลักการและวัตถุประสงค์: การปลูกถ่ายไตเป็นการรักษาที่ดีที่สุดสำหรับผู้ป่วยเด็กโรคไตวายระยะสุดท้าย โรงพยาบาลศรีนครินทร์ได้ทำการปลูกถ่ายไตส่วนใหญ่จากผู้บริจาคสมองตายเนื่องจากระยะเวลารอไตไม่นาน ในอดีตมีการให้ยากดภูมิคุ้มกันชนิด interleukin 2 receptor antagonist (IL2-RA) ก่อนทำการผ่าตัดอย่างจำกัดเนื่องจากยามีราคาแพง การศึกษานี้จึงศึกษาผลของการปลูกถ่ายไตในเด็กจากผู้บริจาคสมองตายและไม่ได้รับยากดภูมิคุ้มกันชนิด IL2-RA

วิธีการศึกษา: การศึกษาผลการปลูกถ่ายไตแบบย้อนหลังสิบปีในผู้ป่วยเด็กที่ได้รับการปลูกถ่ายไตจากผู้บริจาคสมองตายตั้งแต่ปี พ.ศ. 2546 ถึง 2557 โดยผู้ป่วยทุกรายได้รับยากดภูมิคุ้มกันเหมือนกันทุกราย ยกเว้นยากดภูมิคุ้มกันชนิด IL2-RA ก่อนทำการผ่าตัดปลูกถ่ายไต และศึกษาผลของการปลูกถ่ายไตเทียบกลุ่มที่ได้รับยา IL2- RA และไม่ได้รับ

ผลการศึกษา: มีผู้ป่วยเด็กที่ได้รับการปลูกถ่ายไตทั้งหมดจำนวน 48 ราย อายุเฉลี่ยคือ 12.8 ปีและอายุเฉลี่ยของผู้บริจาคสมองตายคือ 30.3 ปี ผู้ป่วยเด็กที่ได้รับการปลูกถ่ายไตทุกรายได้รับการตรวจการเข้ากันได้ของเนื้อเยื่อกับผู้บริจาค จากจำนวนทั้งหมดมีผู้ป่วยเพียง 14 รายที่ได้รับยากดภูมิคุ้มกันชนิด IL2-RA ก่อนทำการผ่าตัดร่วมกับยาสเตียรอยด์ และกลุ่มที่ได้รับยาสเตียรอยด์อย่างเดียว พบว่าการเกิดภาวะปฏิเสธไตและการติดเชื้อของผู้ป่วยทั้งสองกลุ่ม ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ อัตราการรอดของไตที่ได้รับการปลูกถ่ายที่ 1, 3 และ 5 ปีหลังการปลูกถ่ายไต คือร้อยละ 93.7, 83.9, และ 74.8 ตามลำดับ นอกจากนี้พบว่าอัตราการรอดของไตระหว่างกลุ่มที่ได้รับยา IL2-RA และไม่ได้รับนั้น ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติเช่นกัน โดยมีอัตราการตายร้อยละ 16.7

สรุป: การปลูกถ่ายไตในเด็กจากผู้บริจาคสมองตายโดยไม่ได้รับยา IL2-RA ก่อนการผ่าตัดปลูกถ่ายไตนั้นได้ผลดี อย่างไรก็ตาม

Background and objective: Kidney transplantation (KT) is the best modality treatment in children with end-stage renal disease. Our center has performed KT mostly from deceased donors due to short waiting time. The induction therapy by interleukin 2 receptor antagonist (IL2-RA) was limited use due to financial issue. Therefore, this study aimed to report our experience in pediatric deceased donor KT with restricted use of induction therapy.

Methods: This retrospective descriptive study, review the results of KT over 10 years. Medical records of all pediatric KT recipients who were transplanted from 2003 to 2014 were reviewed. All patients received the same maintenance immunosuppressive drugs except the induction therapy by IL2-RA. We also reviewed the results of KT between two groups in a different period.

Results: Forty-eight pediatric KT recipients were included in this study. The mean age of the recipients was 12.8 years and the mean age of the deceased donor was 30.3 years. All recipients were non-sensitized patients and compatible crossmatch. Fourteen patients (29%) received induction therapy with IL2-RA and methylprednisolone, the rest received only methylprednisolone (non-induction group). The rate of rejection and infection between the induction and non-induction groups did not differ significantly. The graft survival rates at 1, 3, and 5 years after KT were 93.7%, 83.9%, and 74.8%, respectively. The graft

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ยังต้องการการศึกษาในจำนวนผู้ป่วยที่มากขึ้นเพื่อยืนยันผลการศึกษาดังกล่าว

คำสำคัญ: การปลูกถ่ายไต, ผู้ป่วยเด็ก, ผู้บริจาคสมองตาย

survival rates between induction and non-induction groups were not significantly different. The mortality rate of this study was 16.7%.

Conclusion: The standard-risk pediatric deceased donor kidney transplantation in limited resources for induction therapy had satisfying results. However, the future study requires a greater data to support this outcome.

Keyword: Kidney transplantation, Pediatrics, Deceased donor

ศรีนครินทร์เวชสาร 2563; 35(2): 224-229. ● Srinagarind Med J 2020; 35(2): 224-229.

Introduction

Kidney transplantation (KT) is the best modality treatment in children with end-stage renal disease. At the time of the first pediatric KT in the 1950s, patients and graft survival in children worsen than in adult[1]. However, over the last several decades the outcome of KT in children has improved[2,3]. The advancement of surgical techniques and immuno-suppressive drugs ameliorated both graft and patient survival rates. From previous studies, five years of graft survival in pediatric patients were 44-95% and 23-95% at 10 years[2,4–8]. Since 1996, the first pediatric KT in Thailand was successfully done[9]. The 15-years data from the National Transplant Registry of Thailand reported the graft survival at 1, 3, and 5 years post-transplant were 95%, 88%, and 76%, respectively[10]. Even though the survival rate in Thailand did not differ from other countries, transplantation in limited resources is a challenge. Our center has performed KT only from deceased donors in the large, low-income area. Therefore, this study aimed to report our experience in pediatric KT with restricted use of induction therapy and the results of transplantation from a deceased donor.

Patients and Methods

The first pediatric kidney transplant recipient was transplanted successfully at Srinagarind hospital, Khon Kaen university, Thailand in 2003. This retrospective descriptive study aimed to review the results of KT over 10 years period. Medical records of all pediatric kidney transplant recipients who received the kidney from the deceased donor from 2003 to 2014 were reviewed.

Donors' and recipients' characteristics were gathered including sex, age at transplantation, underlying diseases, HLA mismatching, immunological status, immunosuppressive regimens, rejection, and infection. Graft and patient survival were also recorded.

From 2003, the recipients received intravenous methylprednisolone at the time of transplantation as induction therapy. Only one patient received a lymphocyte-depleting agent for the second kidney transplant. Besides methylprednisolone and lymphocyte-depleting agent, all patients received the same triple immunosuppressive therapy with calcineurin inhibitors (tacrolimus or cyclosporin), mycophenolate mofetil or mycophenolic acid or azathioprine, and prednisolone with the same standard protocol for KT. After the KDIGO Clinical practice guideline for the care of kidney transplant recipients was published in 2009[11], all pediatric transplant recipients who were transplanted from 2009 to the present, have received Interleukin 2 receptor antagonist (IL2-RA) and methylprednisolone for induction therapy. This study also reviewed the results of transplantation between those who received only methylprednisolone (non-induction group) and those who received IL2-RA and methylprednisolone (induction group) in a different period.

Descriptive statistics including frequency, mean and standard deviation, were analyzed for patients' characteristics and outcomes for the normal distributed data. The Kaplan-Meier curves were applied for graft and patient survival analysis. A p-value less than 0.05 was considered statistically significant. Stata version 10.1 was used as statistical software for data analysis. This study was approved by Khon Kaen university Ethics Committee for Human Research, Khon Kaen university, Thailand. (Reference No. HE571273)

Results

Forty-eight pediatric kidney transplant recipients were included in this study. There were 27 males (56%) and the ages at transplantation were between 4.9 - 17.6 years. The most common cause of end-stage renal disease in the recipients was renal hypoplasia (58.3%) especially in young children and the other causes were shown in Table 1. All recipients received kidneys from deceased donors which mostly death from an accident without the underlying disease (91.7%). The mean age of deceased donor was 30.3 years (range 3-53 years) and the mean cold ischemia time was 19.4 ± 5.7 hours (range 6-35 hours). All donors and recipients had immunity for cytomegalovirus. All recipients were non-sensitized patients (zero percent of panel reactive antibody) and compatible crossmatch. Fourteen patients (29%) received induction therapy with IL2-RA and methylprednisolone, the rest received only methylprednisolone. All patients also received the triple immunosuppressive medications with prednisolone, calcineurin inhibitors, and mycophenolate mofetil or mycophenolic acid or azathioprine. The majority of patients (73%) received tacrolimus and the dose was adjusted by tough whole blood levels 4 to 7 ng/mL.

All patients were performed the blood test for the human leukocyte antigen (HLA) before transplantation. The rate of rejection in patients with one or two HLA-B mismatches was 33.3%, whereas 25.7% in the patients with HLA-DR mismatches and 26.6% in patients with both HLA-B and HLA-DR mismatches. Delayed graft function was found in 14 patients, the rate of delayed graft function was high in patients who received IL2-RA for induction therapy (42.8% compared with 23.5% in the non-induction group, Table 2).

Table 1 Recipient demographic data

Characteristics	Number of patients, N=48 (%)
Male	27 (56.2)
Underlying diseases	
- Renal hypoplasia	28 (58.3)
- Glomerulonephritis	8 (16.7)
- Focal segmental glomerulosclerosis	4 (8.3)
- Reflux nephropathy	3 (6.2)
- Multicystic dysplastic kidney	1 (2.1)
- Alport syndrome	1 (2.1)
- Drug-induced nephropathy	1 (2.1)
- Hemolytic uremic syndrome	1 (2.1)
- A ruptured kidney from trauma	1 (2.1)

Thirty-nine patients (81%) had at least one episode of infection after transplantation and the most common cause of infection was urinary tract infection. One-third of the patients had acute rejection (33%). The rate of rejection between the induction and non-induction groups did not differ significantly (35.7 vs. 32.4%). Moreover, the prevalence of infection between the two groups did not differ as well (57% vs. 73.5%) as shown in Table 2. The mean estimated glomerular filtration rate (eGFR) in the induction group was 33 ± 19.3 mL/min/1.73 m^2 and 32.4 ± 19.9 mL/min/1.73m2 in the non-induction group, measured from the latest visit for this study.

Mean creatinine at 1, 3 and 5 year after transplantation were 1.30 ± 0.68, 1.37 ± 0.68, 1.49 ± 0.61 mg/dl, respectively. Mean eGFR at 1, 3 and 5 years after transplantation were 52.8 ± 18.4, 52.2 ± 18.5, 46.6 ± 16.7 mL/min/1.73m2, respectively. Male recipients had higher serum creatinine than females in all 1, 3, and 5 years after KT.

The graft survival rates at 1, 3, and 5 years after KT were 93.7%, 83.9%, and 74.8%, respectively. The patient survival rates at 1, 3 and 5 years after KT were 97.8%, 92.7%, and 87.4%, respectively. The Kaplan-Meier curve of graft and patient survival were shown in Figures 1 and 2. However, when we compare the graft survival between induction and non-induction groups, graft survival was not significantly different (Figure 3). Furthermore, patient survival did not differ between the two groups (Figure 4).

Chronic allograft nephropathy (CAN) and chronic allograft dysfunction (CAD) were found in 10 patients (21%). The rate of CAN and CAD was lower in the patients who received IL-2 RA (7% compared with 26.5% in non-induction group). The mortality rate of this study was 16.7%. Three patients died with functioning graft and five patients died with non-functioning graft, mostly death from infection. The rate of graft loss was 25% at the end of the study.

Table 2 Outcome of patients between induction and non-induction groups

Outcome	Induction group n = 14 (%)	Non-induction group n = 34 (%)	p-value
Delayed graft function	6 (42.8)	8 (23.5)	0.294
Rejection	5 (35.7)	11 (32.4)	>0.999
Infection	8 (57)	25 (73.5)	0.315
CAN/CAD*	1 (7)	9 (26.5)	0.242

*CAN: Chronic allograft nephropathy, CAD: Chronic allograft dysfunction

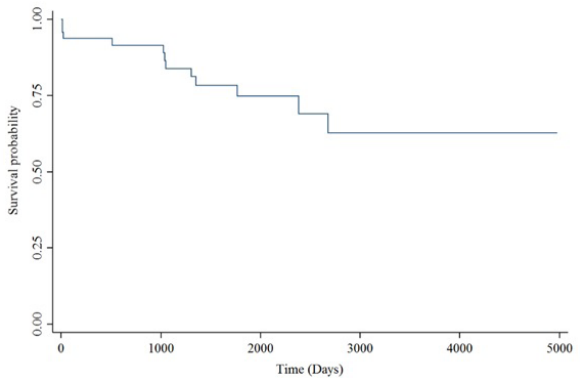

Figure 1 The Kaplan-Meier curve of overall graft survival

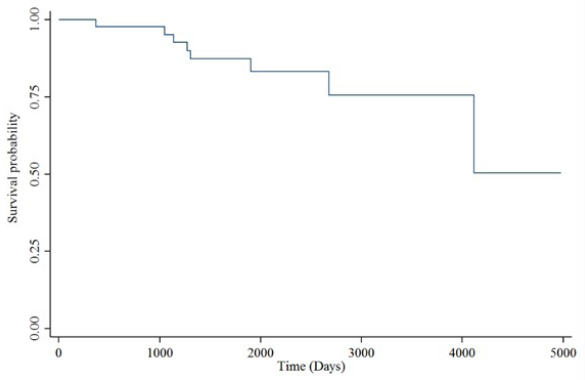

Figure 2 The Kaplan-Meier curve of overall patient survival

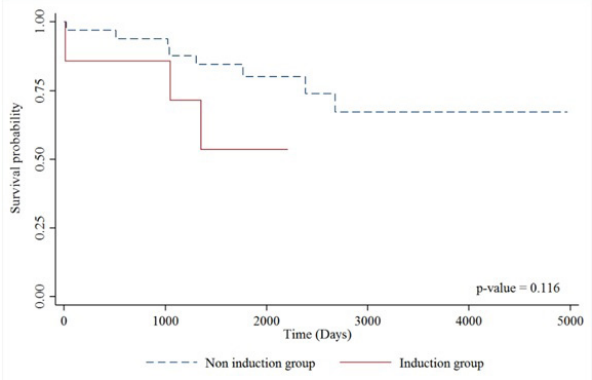

Figure 3 The Kaplan-Meier curve of graft survival in patients who received IL2-RA for induction therapy (induction group) versus the non-induction group

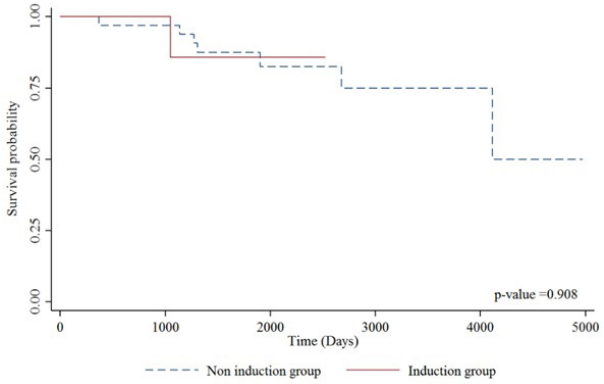

Figure 4 The Kaplan-Meier curve of patient survival in patients who received IL2-RA for induction therapy (induction group) versus the non-induction group

Discussion

The evolution of pediatric KT has been improved as well as a thorough understanding of immunosuppressive drugs. However, pediatric KT in a developing country has more economic issues than a developed country. Our center has performed pediatric KT since 2003 which started with a deceased donor kidney transplant. From the previous studies, a living donor KT had a better graft survival than deceased donor KT [5,12]. Additionally, living donor transplant also has a benefit for children in term of short waiting time. In our center, the waiting time for a kidney from a deceased donor is shorter than other hospitals due to the high organ donation rate in Northeastern region of Thailand. Mostly donors died from head injury (motorcycle accident) without underlying diseases, and the mean age of donors was in the young adult age group. These were the major reasons that we have performed only deceased donor KT. From the past five years, the living donor transplant rate has been falling in many countries. The data from OPTN/SRTR in 2016, the pediatric recipients receiving a kidney allograft from a living donor KT was 34.2% which was lower than earlier[13,14]. The limitations of a living donor

are the age of the donor, underlying diseases, blood group incompatibility, and financial problem. Deceased donor KT became the first option for pediatric KT in some situations, however, this depended on patient, family and nephrologist's decision.

The graft survival in this study at 1, 3, and 5 years after KT were 93.7%, 83.9%, and 74.8%, respectively. The patient survival at 1, 3, and 5 years after KT were 97.8%, 92.7%, and 87.4%, respectively. Our survival rates were satisfied compared with other studies [4,6–8,14]. The quality of graft either from living or deceased donors may be an important factor to consider. Short duration of cold ischemic time and younger age of donor are possible factors for better survival rates in our study.

Since our first pediatric KT in 2003, our immunosuppressive protocol used intravenous methylprednisolone as induction therapy, except one patient received a lymphocyte-depleting agent for the second kidney transplant. We used the only methylprednisolone because of the limited use of other induction medications for low or standard risk recipients. In 2009, the KDIGO Clinical practice guideline for the care of kidney transplant recipients was published, recommended using an IL2-RA as the first-line induction therapy[11]. All our pediatric transplant recipients who were transplanted from 2009 to the present have received IL2-RA following the guideline in standard-risk patients. On the contrary, using IL2-RA for induction therapy helped to decrease the rejection event, but also increase the risk of infection. Thus, this study also reviewed the outcome of the recipients between the induction group and the non-induction group. Whereas the previous study showed the benefit of Thymoglobulin as induction therapy which could decrease the rate of delayed graft function over IL2-RA[15]. The induction group in this study had a higher rate of delayed graft function than the non-induction group (42.8% vs 23.5%). However, there were a small number of patients in previous and this study to conclude whether IL2-RA could decrease the risk of delayed graft function or not. The rejection rate in both groups was not different, nevertheless, we need a greater number of data to support this evidence. For the infection issue, the non-induction group had a higher rate of infection than the induction group, but the association was not statistically significant due to the small population. In fact, aggressive immunosuppression leads to increase risk of the infection since the patients received the transplant, but our study had the opposite result. This outcome could be from a shorter follow up time in the induction group (2009-2016) compared with the non-induction group (2003-2016). Similarly, we found a lower rate of CAN or CAD in the induction group due to shorter follow up time to detect the chronic changes of graft tissue.

The data about the long-term adverse effect of induction therapy is still deficient. A review study of induction therapy in 2017 mentioned that IL2-RA may not be beneficial in standard-risk KT and may be inferior to Thymoglobulin in high-risk recipients[16]. Further study with a large number of pediatric KT patients and conduct in a randomized controlled study could be necessary to help nephrologists to decide the induction therapy for pediatric patients, especially in the limited resources area.

Conclusion

The standard-risk pediatric deceased donor KT in limited resources for induction therapy had satisfying results. However, the future study requires a greater data to support this outcome.

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