

KIDNEY TRANSPLANTATION FROM DECEASED DONORS WITH HIGH TERMINAL SERUM CREATININE

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The ever increasing number of possible recipients of kidney transplantation and the relatively unchanged number of organ donors has led to consideration of alternative strategies and expansion of deceased donor criteria in order to expand donor pool. Previously, kidneys from expanded criteria donors were underestimated strongly because of the conventional opinion suggesting these kidneys to have a higher rate of preservation injury, delayed graft function, rejection and non-function. Reducing the difference between graft outcome from patients transplanted with expanded criteria donor (ECD) and standard criteria donor (SCD) is one of the goals of many respectable kidney transplantation centers. This includes strong concern about reduction of cold ischemia time, recipient selection, novel and adapted immunosuppressive regimens, increased nephron mass by dual kidney transplantation, and using histologic criteria for marginal donor graft selection. There are not many reports about the outcome of transplanted kidneys from donors with acute renal failure and high terminal creatinine. In this review, we have tried to show the exact definition of marginal donor, especially donors with acute renal failure. Management of such grafts during preimplantation and implantation period, outcomes and care after transplantation pose a great challenge to transplantation teams. Recipients of such grafts have to be well informed about the possibilities and potential complications, and give their consent accordingly. Some respectable studies have shown that under certain, highly controlled conditions, these kidneys can be used safely, with excellent short- and longterm outcomes.

Key words: renal transplantation, expanded criteria donor, outcome

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INTRODUCTION

Kidney transplantation is the treatment of choice for all patients with end stage renal disease (ESRD) without contraindications for immunosuppressive treatment, while offering better quality of life and survival when compared with dialysis^(1,2). The increasing number of potential renal transplant recipients on waiting lists has not been accompanied by appropriate rise in the number of deceased donors. This discrepancy challenges transplantation centers to consider other opportunities for making more organs available for transplantation. In order to expand donor pool, many centers have started us-

ing kidneys from elderly and expanded criteria donors. Until 2002, transplant centers used intuition to discriminate organs that were supposed to have less than optimal function⁽³⁾. Based on the "clinical feeling" of transplantation teams, most of the kidneys supposed to have poor graft outcome were discarded. Thus, donors with advanced age, impaired hemodynamics and prolonged ischemia time, as well as donors with elevated serum creatinine level prior to transplantation were refused. In 2002, Port *et al.* defined expanded criteria donor (ECD) as a deceased donor aged ≥ 60 or donor aged 50-59 with minimum 2 factors: history of hypertension, serum creatinine level greater than 1.5 mg/dL (132.6 mmol/L) and cerebrovascular cause of death. The risk of

graft failure in these transplantations was much higher than of grafts from standard criteria donors (SCD). Using Cox regression models, Port *et al.* revealed a 70% higher risk of graft failure compared to ideal kidneys (relative risk greater than 1.7). According to their study, grafts from older donors with diabetes, hypertension or renal impairment have a higher risk of failure but are good enough to be transplanted⁽⁴⁾. However, based on the ECD graft definition, first assumption is an increased risk of less favorable outcome compared to SCD graft. In this way, refusals of ECD kidneys are frequent, cold ischemia time is prolonged, leading to organ discarding⁽⁵⁾. Massie *et al.* found that many transplant centers expressed their willingness to accept ECD transplants, but finally refused organs when they were offered, thus creating delays resulting in organ discarding⁽⁶⁾.

As there is no unique definition of adequate kidney graft, transplantation centers differ according to the criteria for refusal or acceptance of grafts considered to be marginal. The most common reason for refusal is hemodynamically unstable donor and high terminal serum creatinine. Nevertheless, the use of ECD has led to an increased number of transplanted patients with better survival compared to patients on dialysis⁽²⁾. A new target of modern kidney transplantation is to reduce difference in outcomes between the recipients of allografts from marginal donors and those transplanted from optimal donors.

In the present paper, we discuss the issue of ECD and define strategies to improve outcome of kidneys obtained from these donors.

DONOR WITH ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is rapid deterioration of kidney function that occurs in approximately 5% of all hospitalized patients. It is one of the most common complications in the intensive care units (ICU) affecting 36% of these patients⁽⁷⁾. In more than 50% of AKI in ICU, the cause of kidney injury is septic shock or sepsis.

The causes of AKI in hospitalized patients without previous kidney disease can be prerenal, renal and postrenal. In 60%-70% of cases, the cause is prerenal, which includes dehydration, hypoperfusion, ischemia due to blood loss, sepsis, surgery, severe burn and injury, liver or heart failure. Renal damage is the most complicated cause of AKI which affects filtering function or blood supply within the kidney, or kidney tissue responsible for salt and water balance. Infections cause glomerulonephritis. A common cause of acute interstitial nephritis are nephrotoxic agents, including drug abuse such as heroin and cocaine, crush injuries leading to myoglobinuria, drugs frequently used in ICU in inappropriate doses such as antibiotics, anti-inflammatory drugs and diuretics. Acute interstitial nephritis is usually reversible if kidney

damage is not severe. Acute tubular necrosis is usually the final result of other causes of renal damage accounting for 90% of cases of primary renal AKI. Postrenal failure is a rare cause of acute kidney failure in ICU^(8,9). In ICU patients with AKI considered as potential kidney donors, we are searching for correctable causes of AKI in order to optimize kidney function and prepare them for potential grafting. Interpretation of a kidney injury is a problem when evaluating potential donors. In some patients admitted to ICU, AKI is nothing but acutization of chronic renal failure. Some patients admitted with good kidney function experience rapid deterioration of kidney function due to numerous reasons. As mentioned earlier, common reasons of renal failure in ICU are prerenal and renal. Radiocontrast induced kidney injury is usually a reversible form of AKI, defined as an increase in serum creatinine level by more than 25% or its absolute increase of 0.5 mg/dL early after radiographic examination using radiocontrast agent. A frequent question is how to quantify damage in donors to discriminate potential grafts with good outcome. A potential problem is that most studies investigating outcome of kidney transplantation from donors with high terminal creatinine are based on the last serum creatinine level rather than on its change during intensive care management.

Serum creatinine is a widely used parameter for calculating glomerular filtration rate (GFR) in everyday practice, but its sensitivity and specificity in predicting AKI are lacking. As a sole parameter, serum creatinine is a poor predictor of kidney damage because of rapidly changing levels in critically ill patients with AKI and its dependence on muscle mass. In recent studies, there is a question of predicting reversibility of kidney damage and impact of AKI on long-term graft survival, graft function and rejection. Some studies have shown that high serum creatinine solely cannot be a measure to discard kidney for transplantation. Serum creatinine level reduction in donors is not a sign of insult recovery, although high serum creatinine level does not represent irreversible injury⁽¹⁰⁾.

The RIFLE (risk, injury, failure, loss and end stage renal disease) criteria are the internationally accepted classification of kidney damage in AKI in hospitalized patients. In 2010, Rodrigo *et al.* first reported the use of RIFLE criteria to evaluate AKI in deceased donors. The idea of the study was to standardize and quantify renal injury in donors and its possible influence on graft outcome. Risk was defined when creatinine increased x1.5, injury x2, and failure when the last creatinine level increased x3 with respect to its value on the day of admission. The authors concluded that RIFLE criteria were feasible in the diagnosis of AKI in kidney donors but further studies including a larger number of patients need to confirm this hypothesis⁽¹¹⁾. However, this classification cannot be used as isolated criteria for discarding donated kidney.

In 2006, Kumar *et al.* reported three-year results of successful kidney transplantation from deceased donor with AKI, but the authors did not use RIFLE criteria to classify AKI. This study reported comparable three-year kidney function between kidneys transplanted from selected deceased donors with acute renal failure without previous positive medical history and chronic histologic lesions, and kidneys from SCD⁽¹²⁾.

QUALITY OF KIDNEY GRAFTS – OBJECTIVE MEASURES AND DONOR SELECTION

In 2006, Remuzzi *et al.* assessed outcome of renal transplantation from elderly donors. It was well known from clinical practice that long-term survival of renal grafts obtained from elderly donors was inferior to survival of grafts from younger donors. However, the authors wanted to prove that selection of older kidneys according to histologic characteristics before transplantation could influence graft outcome. The international group of pathologists presented a scoring system for kidneys from donors older than 60, based on biopsy findings. The intention was assessment of kidneys with enough viable nephrons, available for transplantation by thorough analysis of tubuli, vessels, glomeruli and internal changes. Scores ranged from 0 (absence of lesions) to maximum of 12 (marked changes in renal parenchyma). Kidneys with scores 3 or lower were supposed to be used as single transplants. Kidneys with scores 4, 5 or 6 could be used as dual transplants (only if the total number of viable nephrons in two kidneys approached the number in one ideal kidney). Discarded were kidneys with score 7 or higher. Graft survival rate of histologically evaluated marginal kidneys did not differ from kidneys of donors aged <60, but it was better than in recipients whose grafts from donors older than 60 were not evaluated histologically. Remuzzi *et al.* concluded that histologic criteria had a critical role in the evaluation of marginal donors, as they improved graft outcomes and thus may have expanded the pool of donors. Nowadays, many transplantation centers have implemented preimplantation kidney biopsy as a routine procedure in order to identify usable grafts⁽¹³⁾.

All kidney grafts, either from old or young, marginal or standard criteria donor, can suffer harm with some events just before donation or previously, even before the donor was admitted to ICU (chronic lesions). Some potential donors may have high serum creatinine at the time of admission to ICU, as they have chronic renal insufficiency. Serum creatinine level may rise a few days before donation because of several reasons related to stay or treatment in ICU. Understandably, only grafts with acute but correctable renal dysfunction are considered for transplantation. Biopsy is necessary to distinguish cases of high entrance serum creatinine due to chronic renal disease and high creatinine due to some

acute injury⁽³⁾. Specific evaluation and allocation is necessary for marginal grafts with possible chronic lesions before considering for transplantation.

In 2001, a consensus meeting of the American Society of Transplantation and American Society of Transplant Surgeons was held in Crystal City, Virginia. The goal of the meeting was development of guidelines for improving recovery and transplantation of organs from deceased donor. Kidney Work Group discussed how to increase the use of elderly donor kidneys, decrease cold ischemia time and delay graft function. In this way, patient outcome could be improved, as it could decrease the length and cost of hospital stay⁽¹⁴⁾.

In order not to discard kidneys from ECD but improve their allocation and graft survival, Nyberg *et al.* developed a scoring system for these kidneys. Deceased donor score (DDS) includes scores for donor's age, hypertension, creatinine clearance, HLA mismatch and cause of death. If the score is higher than 20, 6-year graft survival is lower than 70%; if DDS is lower than 20, 6-year graft survival is higher than 80%⁽¹⁵⁾.

DUAL KIDNEY TRANSPLANTATION

Transplantation of dual ECD kidneys is one of the possible ways to reduce the number of discarded kidneys and increase nephron mass of 'marginal' kidneys. It may be a good approach in expanding donor pool. Still, there are no determined criteria for single or dual transplantation in a recipient of ECD kidney.

One of the first reports of dual kidney transplantations from elderly donors showed that these recipients had a decreased incidence of delayed graft function, better graft function and survival than recipients of single kidney from similar age donors⁽¹⁶⁾. Some studies praise the strategy of dual kidney transplantation in expanding donor pool, but found a high incidence of primary non-function^(17,18).

In 2003, Bunnapradist *et al.* showed a similar outcome of 403 dual transplantations (mean donor age 60.8 years) with 11033 single kidney transplantations when recipients of single kidney were grafted with donors aged over 55⁽¹⁹⁾. In 1999, Remuzzi *et al.* compared graft survival of single and dual kidney transplants from ECD (donor age >60, history of diabetes or hypertension, urine protein excretion up to 3 g/24 h) based on clinical or preimplantation histologic evaluation. This study showed that graft evaluated histologically before implantation had similar outcome in dual transplant recipients as single grafted recipients from younger donors. These results strongly suggest that histologic criteria should be considered as an important part on choosing between single and dual kidney transplantation from marginal donor⁽²⁰⁾.

RECIPIENT SELECTION AND IMMUNOSUPPRESSION

It is important to mention that long-term graft and patient survival after transplantation has improved in the last years as a result of factors such as good patient care, enhanced organ preservation and surgical techniques, effective antimicrobial prophylaxis, and availability of potent immunosuppression regimens⁽²¹⁾. One possible additional factor may be proper selection of recipients for certain graft.

Elderly patients make up an increasing percent of the waitlist, as well as of donated and recovered kidneys. Use of elderly donors for kidney transplantation may create obstacles to long-term survival, as older kidneys are associated with inferior outcomes. However, the major risk for dialysis patients is to stay on dialysis, thus elderly patients should be individually evaluated for renal transplantation. 'Physiological' age is much more important than 'chronological' age in this group of patients⁽²²⁾.

Stratta *et al.* studied 90 recipients of adult donor kidneys transplanted from 2001 to 2003 (37 from ECDs and 53 from SCDs). Recipient selection for marginal kidney was based on their estimated need for nephron mass by using the criteria of age >40 years, low body mass index (<25 kg/m²) and low immune risk (first transplantation, 0% PRA, HLA matching). They conclude that ECD kidneys should be used for carefully selected patients, employing the "nephron sparing strategy". It means that long-cold ischemia time should be avoided, as well as nephrotoxic immunosuppressive protocols⁽²³⁾. Severe donor-recipient size mismatching should be avoided.

The Eurotransplant Senior Program (ESP) allocates kidneys from elderly donors to recipients older than 65. This program has significantly increased the number of transplantations performed in elderly patients. Croatia introduced its own Senior Program in 2005, based on the ESP but with HLA matching, which has improved outcomes compared to ET results⁽²⁴⁾. Currently, elderly patients wait less than 6 months to receive transplant in Croatia.

As kidneys from ECS have already suffered injury, any further damage should be avoided. Stratta *et al.* presented a management protocol for ECD kidneys. It was based on a number of nephron sparing maneuvers by minimizing cold ischemia time, pulsatile perfusion preservation, immunosuppression with depletion antibodies to minimize preservation injury and risk of rejection, delayed calcineurin administration, and lower tacrolimus levels to maintain balance between effectiveness and toxicity⁽²³⁾.

Nephrotoxic immunosuppressive protocols should be avoided, which means delayed introduction of calcineurin inhibitors under the umbrella of antibodies (either monoclonal in patients with low immune risk, or polyclonal in patients with high immune risk). Based on our experience, these protocols are safe and are not associated with in-

creased incidence of acute rejections. Mammalian target of rapamycin inhibitors (mTOR) seem promising in this setting. Three preliminary reports suggest that CNI-free protocols with costimulation blockade in recipients from ECDs decrease the incidence of delayed graft function, but further studies have to confirm it. Thus, novel immunosuppressive drugs may contribute to less nephrotoxic protocols⁽²⁵⁾. However, current protocols recommend their use at least one month after transplantation to avoid problems with wound healing.

CONCLUSION

Kidney donor pool has evolved over the last few years mainly due to the utilization of ECDs. However, recipients of kidneys from ECD have by definition inferior graft and worse overall survival. Potential recipient has to be well informed about the risks of transplanting grafts from ECD. Such grafts are not for "expanded recipient criteria", but for recipients with low risks and demands. To find the best donor-recipient match, specific allocation policies are required. A challenge is to minimize transplantation outcome differences between the grafts from standard and expanded criteria donors.

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SAŽETAK

TRANSPLANTACIJA BUBREGA OD MOŽDANO MRTVOG DARIVATELJA S VISOKOM KONCENTRACIJOM KREATININA U SERUMU

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Ukupni broj darivatelja organa u posljednje je vrijeme nepromijenjen, a sve veći broj potencijalnih primatelja bubrega na listi čekanja doveo je do razvoja novih strategija i proširenja kriterija kojima se procjenjuje mogući darivatelj organa. Prije se smatralo da su bubrezi darivatelja prema proširenim kriterijima lošiji zbog veće učestalosti oštećenja tijekom prezervacije bubrega, češće odgođene funkcije presatka, odbacivanja i primarne afunkcije organa. Danas je mnogim velikim transplantacijskim centrima cilj smanjenje razlike u ishodu presatka transplantiranog s darivatelja prema proširenim kriterijima i darivatelja prema standardnim kriterijima. Ovaj cilj uključuje strogu kontrolu skraćivanja vremena hladne ishemije, odabira primatelja, prilagođene protokole imunosupresije, povećanja mase nefrona s transplantacijom "dva u jedan" i primjenu histoloških kriterija u odabiru presatka marginalnog darivatelja. Zasad nema mnogo objavljenih radova o ishodu transplantiranog bubrega darivatelja s akutnim zatajenjem bubrega ili visokom zadnjom vrijednosti kreatinina u serumu. Ovim preglednim člankom željeli smo prikazati najnoviju definiciju marginalnog darivatelja i darivatelja s akutnim zatajenjem bubrega. Primatelji bubrega darivatelja prema proširenim kriterijima moraju tijekom prijetransplantacijske obrade biti dobro obaviješteni o svim mogućnostima i komplikacijama takvog postupka te potpisati obaviješteni pristanak. Poznate studije pokazale su da se pod strogo kontroliranim kriterijima bubrezi darivatelja prema proširenim kriterijima mogu sigurno transplantirati odabranim primateljima s dobrim kratkoročnim i dugoročnim ishodom.

Ključne riječi: transplantacija bubrega, darivatelj prema proširenim kriterijima, ishod