

Kidney transplantation, brief history and Croatian experience

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ABSTRACT:

Kidney transplantation is the treatment of choice for patients with end-stage renal disease. However, it took years and numerous attempts to achieve success, for the kidney to function well and for the patient to survive after the transplantation. Following this breakthrough made by Murray in 1954, the introduction of immunosuppressive therapy and tissue typing has significantly improved this program. Today we have new challenges in maintaining or improving a kidney transplant program, one of which is COVID-19 infection. This review presents the history and current status of kidney transplantation, emphasizing the Croatian Kidney Transplant Program.

KEYWORDS: kidney transplantation, history of transplantation, Croatia, Eurotransplant

SAŽETAK:

TRANSPLANTACIJA BUBREGA, KRATKA POVIJEST I HRVATSKO ISKUSTVO

Transplantacija bubrega je metoda izbora liječenja završnog stadija kronične bubrežne bolesti. Međutim, bilo je potrebno puno godina i pokušaja da bi se napravila uspješna transplantacija bubrega, odnosno da bi bubreg profunkcionirao, a bolesnik preživio transplantaciju. Prvu uspješnu transplantaciju je napravio Murray 1954, a daljnji napredak omogućen je uvođenjem imunosupresivne terapije i tipizacije tkiva. Danas imamo nove izazove u održavanju i napretku programa transplantacije bubrega, a jedna od njih je COVID-19. U ovom radu prikazujemo povijest i sadašnju situaciju s transplantacijom bubrega s naglaskom na program transplantacije bubrega u Republici Hrvatskoj.

KLJUČNE RIJEČI: transplantacija bubrega, povijest transplantacije, Hrvatska, Eurotransplant

The road to a successful kidney transplant took more than half a century and was filled with many obstacles that needed to be addressed. The first important step forward was made by Alexis Carrel, a French surgeon born in 1873 in Sainte-Foy-lès-Lyon. In 1904 he moved to the United States, first to Chicago and then in 1906 to New York, where he became a member of the Rockefeller Institute for Medical Research. He mainly focused on vascular surgery, tissue and organ transplantation, for which he received the Nobel Prize in 1912.¹ His discovery of a successful vascular anastomosis technique that was the basis for transplantation of all solid organs, but also the development of vascular surgery in general, was followed by several decades of kidney transplantations from various animal species, including goats, sheep, pigs and monkeys to humans. The lack of options for prolonging the life of patients with end-stage renal failure led surgeons to these attempts, which, we now know, were doomed to failure in advance.

Yurii Voronoy did the first human allograft kidney transplantation described in medical literature in Kherson in Ukraine. The donor was a 60-year-old male who died of head trauma and the recipient was a 26-years-old female who tried suicide by mercury poisoning. The warm ischemia time was more than 6 hours, and the kidney was transplanted in the right thigh area with its blood vessels anastomosed with the femoral blood vessels and the ureter connected to the skin. The renal function was never regained, and the patient died after 48 hours.² After Voronoy's transplantation, several transplantations were published in medical or newspaper articles, but the results were disappointing. Neither adequate renal function was established, nor did the recipient survive the procedure, i.e., death occurred shortly after transplantation.

It is also important to mention Rene Küss, a French urologist and transplant surgeon born in 1913 in Paris. He described and standardized the techniques which we are using today. In this technique, the kidney was placed in the iliac fossa and the renal vessels were anastomosed with iliac vessels and the ureter was anastomosed with the urinary bladder. The technique was developed, among other things, due to using the organs of prisoners who were guillotined. His role was not only important as a surgeon, but to develop transplantation he also founded several organizations such as "Paris Transplant", "French Transplant" and "French Transplantation Society".³

The first successful kidney transplantation was performed by Joseph E. Murray, an American surgeon born in 1919 in Milford, along with his associates in 1954 in Boston, United States.⁴ The donor and recipient were genetically identical twins, brothers Richard and Ronald, which made it possible to overcome the immunological problems that were the reason for the failure of most previous transplantations. The transplantation lasted about five hours, and Richard (the brother who received the kidney) survived with a functional kidney for eight years. It is an interesting anecdote that he got not only a kidney but also a wife,

because the nurse who took care of him fell in love and became his wife.⁵ In the following years, the development and use of immunosuppressive drugs and tissue typing techniques made a huge contribution to organ transplantation that entered the field of deceased and unrelated living donor transplantations.⁶

CROATIAN KIDNEY TRANSPLANTATION PROGRAM

The first kidney transplantation in Croatia was performed by Vinko Frančišković and his associates in Rijeka in 1971. The donor was a mother who gave her son a kidney and the kidney functioned normally for 14.5 years.⁷ In 1973, the first kidney transplant was performed at the Clinical Hospital Center in Zagreb. The donor was a sister who gave her brother a kidney (Fig. 1.). After these initial transplantations, the kidney transplant program in Croatia has significantly improved both in the number of kidney transplantations (living and deceased donors) and in the number of centers that perform this challenging procedure. Many conditions need to be fulfilled to establish an excellent renal transplant program, especially from deceased donors. One of the most important is the legislation. In Croatia, there is presumed consent, which means that all persons with a brain death are considered potential deceased donors, unless during their lifetime they have objected to organ donation, about which they can declare themselves, i.e. sign a statement with the selected primary care physician or at the Ministry of Health of the Republic of Croatia.⁸ This approach allows for many more potential donors compared to some other countries in which only those who have declared themselves to be so during their lifetime (informed consent) are considered deceased donors.^{9,10} The presumed donors have enabled Croatia to have a high number of deceased donors per million inhabitants for many years. (Fig. 2.).¹¹ Other essential conditions are public and religious support. Despite some differences between religions, more precisely between some isolated groups within different religions, mainly in discouraging deceased, but in some cases even live kidney transplantations, no religion formally forbids one to donate or receive organs or is against transplantation from living or deceased donors.¹² Also important is the cost of transplantation, including hospitalization, treatment, and the cost of diagnostic procedures performed on the donor as well as the cost of hospital coordinators, surgical teams, but also all other physicians and other staff involved in the transplantation. Furthermore, there are costs for possible complications and immunosuppressive medications that patients must take at least while they have a kidney. Although these costs are not small, they are still significantly lower compared to the costs of dialysis, especially if we include the costs of dialysis-related complications, reduced quality of life, but also the survival of patients with end-stage renal disease in general, which is even more pronounced after long-term follow-up.¹³ These findings were recently confirmed in a systematic review by Fu R. et al., although it has been shown



Figure 1. Documents of our first kidney transplant from 1973 (archive of the Department of Urology the Clinical Hospital Center Zagreb).
 a). Newspaper article "Sister's kidney lives in a brother" and "Successfully transplanted kidney".
 b). Angiography showing renal blood vessels.

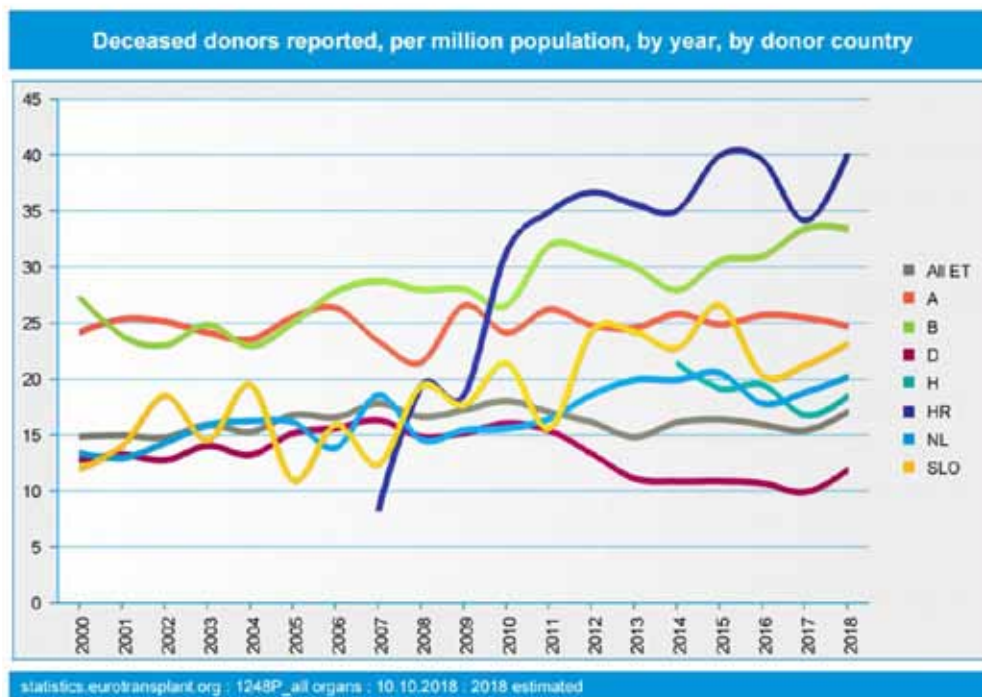


Figure 2. Eurotransplant. Deceased donors per million population, by year, by country.

that they are less prominent for patients with older age, comorbidities, and long wait times.¹⁴ It has also been shown that there are differences inside the kidney transplanted group itself, where living donor kidney transplantation is clearly showing best cost-savings.¹⁵ In our country, these costs outside the hospital limit are covered by the Croatian Health Insurance Fund.

In 2007, Croatia became a member of Eurotransplant, an international organization of 8 countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia). Since then, we have significantly improved our kidney transplant program, liver and heart transplantations and, more recently, lung transplantations. In 2010, we had the largest number of kidney transplantations in our institution (157) since its establishment. Clinical Hospital Center Zagreb is the largest kidney transplant center that has supported and helped other hospitals in Croatia and other hospitals abroad to start and develop their own kidney transplant program. Most of our transplantations are deceased donor kidney transplantations, but we also perform living donor kidney transplantations and transplantations in children. Our patients have the shortest waiting time for the kidney in Eurotransplant (Fig. 3).

Since 2012, we have participated in the national kidney transplant program in Podgorica, Montenegro, significantly decreasing transplant tourism in Montenegro.¹⁶ Urologists, nephrologists, transplant surgeons, anesthesiologists, immunologists and all other medical staff involved in kidney transplantation from various European, but also Asian and African countries visited our department for the purpose of education or to share with us their experiences with kidney transplantation. Although the recent situation with COVID-19 has decreased the number of kidney transplantations in our institution, as well as in other institutions in Europe and the world¹⁷ we continue to carry out kidney transplantation in these challenging times, taking in consideration situation with COVID-19.

In the future, we plan to improve our kidney transplant program not only in the surgical part by improving or introducing new minimally invasive donor nephrectomies, i.e. transplantation using a robotic system, but also further advances in diagnostic methods, immunosuppressive protocols and the introduction of other types of kidney transplantations.

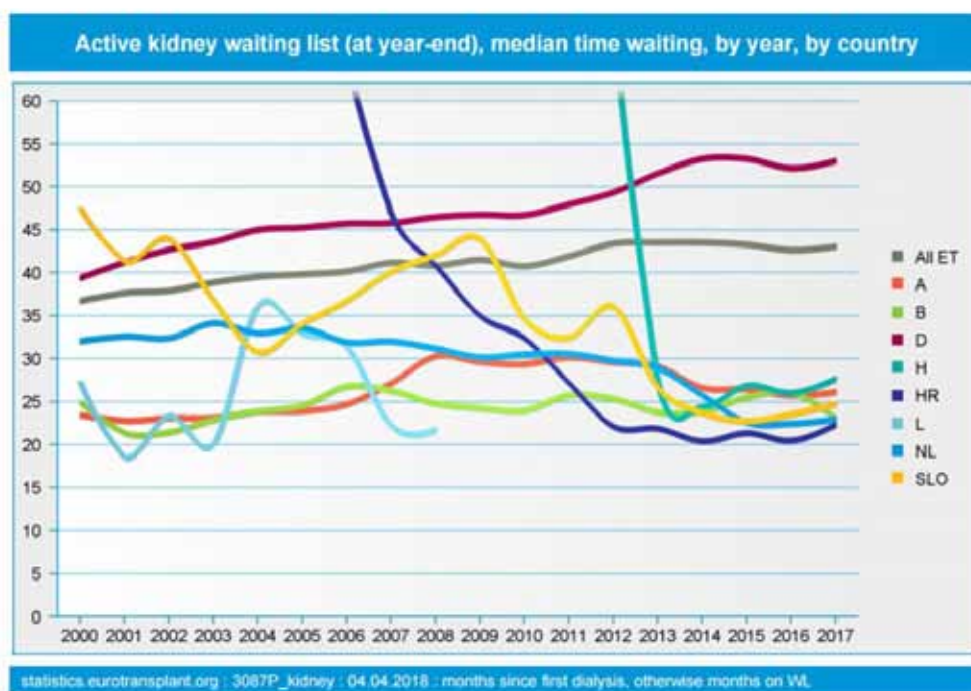


Figure 3. Eurotransplant. Active kidney waiting list, median time, by year, by country.

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