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REVIEW

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Prevalence of infection in kidney transplantation from living versus deceased donor: systematic review and meta-analysis

Prevalência de infecção em transplante renal de doador vivo *versus* falecido: revisão sistemática e metanálise

Prevalencia de infección en trasplante renal de donante vivo *versus* fallecido: revisión sistemática y metanálisis

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ABSTRACT

Objective: To verify if the type of donor is a risk factor for infection in kidney transplant recipients. **Methods**: Systematic Review of Literature with Meta-analysis with searches conducted in the databases MEDLINE, LILACS, Embase, Cochrane, Web of Science, SciELO and CINAHL. **Results:** We selected 198 studies and included four observational studies describing infections among patients distinguishing the type of donor. Through meta-analysis, it was shown that in patients undergoing deceased donor transplant, the outcome infection was 2.65 higher, than those who received an organ from a living donor. **Conclusion**: The study showed that deceased kidney donor recipients are at an increased risk for developing infections and so the need for establishing and enforcing protocols from proper management of ischemic time to the prevention and control of infection in this population emerges.

DESCRIPTORS

Kidney Transplantation; Tissue Donors; Living Donors; Infection; Review.

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INTRODUCTION

Kidney transplantation was introduced as large scale replacement therapy in the 1960s, achieving significant growth in the 1980s[1].

The introduction of new immunosuppressive agents provided significant reduction in the incidence of acute rejection (AR)[1].

As criteria for kidney transplantation, we considered: medical, surgical and psychosocial assessment of the patient. Exams and assessment of compatibility with the potential donor (HLA-Human Leukocyte Antigens)[1-3].

Absolute and relative contraindications for patient transplantation are: active infection, low survival prognosis, severe psychiatric problems, uncontrolled psychosis, addiction, heart disease, active hepatitis and possible non-adherence to treatment. It is not included among the contraindications: advanced age, and previous transplants[1-2].

In the year 2014, according to the Brazilian Society of Nephrology, the number of people with kidney disease, in Brazil, was on the order of 54.000, it was estimated that 48,198 required hemodialysis and only 6.2% of patients with chronic renal failure were submitted to kidney transplantation.

In 2010, in the period from January to June 1,486 kidney transplants were carried out, a 21% increase over the same period from the previous year. In 2013 5,433 kidney transplants were performed in Brazil. This increase can be explained by a possible increase in collection of organs due to a greater awareness of Brazilian society and the growth of access to treatment in the period[3].

The huge challenge in kidney transplantation is the management of infectious complications which significantly increase morbidity and mortality in this population[4]. Several risk factors related to infectious complications are present after kidney transplantation, highlighting the need for ongoing use of immunosuppression, socioeconomic conditions, HLA compatibility and donor type[5-6]. The incidence of post-renal transplant infections complications found in the literature ranges from 49% to 80%[7-10].

Motivated by the problem of infections in kidney transplant patients and the significant increase in transplants, especially kidney recipients of deceased donors, we performed a Systematic Review of Literature with Meta-analysis in order to determine whether the type of donor is a risk factor associated with developing infections.

METHOD

Ethical aspects**:** The study was approved by the Research Ethics Committee of the *Universidade Federal de Sao Paulo*, Unifesp, protocol 56526.

Study protocol

This Systematic Review with Meta-analysis followed the methodology proposed by the Cochrane Collaboration[11]. The search for studies was carried out regardless of the language or form of publication and with the following research designs: randomized controlled trials, quasi-experimental studies, prospective and retrospective observational cohort studies and cross-sectional studies.

*Inclusion criteria***:** We included studies that evaluated the outcome presence of infection with the comparison type of donor.

Search strategy for identification of studies

Studies were identified through electronic search in PubMed (January1966 to January 2014), LILACS (January 1982 to January 2014), Embase January 1985 to January 2014), SciELO (June 1998 to January 2014), The Cochrane Library (including the Cochrane Controlled Trials Register, contained in the Cochrane Library 2014), Web of Science (1945 to January 2014) and CINAHL (January 1981 to January 2014). We also searched the database www.controledtrials.com and conference abstracts, references of review articles and systematic review, published and references of randomized clinical trials identified until January 2014.

The search strategy was developed in MEDLINE, through PubMed, as shown in Figure 1, adapted to all other databases mentioned.

("kidney"[MeSH Terms] OR "kidney"[All Fields]) AND ("tissue donors"[MeSH Terms] OR ("tissue"[All Fields] AND "donors"[All Fields]) OR "tissue donors"[All Fields] OR "donor"[All Fields]) AND ("infection"[MeSH Terms] OR "infection"[All Fields] OR "communicable diseases"[MeSH Terms] OR ("communicable"[All Fields] AND "diseases"[All Fields]) OR "communicable diseases"[All Fields]) AND type[All Fields] AND ("tissue donors"[MeSH Terms] OR ("tissue"[All Fields] AND "donors"[All Fields]) OR "tissue donors"[All Fields] OR "donor"[All Fields])

Figure 1 – Specific terms used for the search in electronic databases.

Methods of review

Complete copies of all relevant studies were read in order to establish whether the studies met the inclusion criteria, assessment of methodological quality by two independent reviewers, A and B. In case of doubt or disagreement, another reviewer, C, was requested to settle.

Assessment of methodological quality and statistical analysis

The assessment of methodological quality, defined as the confidence that the design and the study report are free of bias[11], we conducted it using the recommendations of Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE)[12]. Based on these recommendations the assessment of studies was divided into three categories: A - in the case of studies fulfil a value equal to or greater than 80% of the established criteria; B - reaching 80% and 50% of criteria; and C - reaching less than 50% of the established criteria.

The software Review Manager 5.1, available from The Cochrane Collaboration was used in the statistical analysis[13-14].

For dichotomous variables, we used odds ratio (OR) with 95% confidence interval, calculated by the random and fixed effect models. We also calculate the square I- (I^2) of Mantael-Haenzel[14] to search for heterogeneity. I^2 values greater than or equal to 50% are considered heterogeneous. The heterogeneity test is only calculated when the meta-analysis contains two or more studies.

RESULTS

According to the descriptors shown in Figure 1, 198 studies were found in the databases PubMed, LILACS, Embase, SciELO, The Cochrane Library, Web of Science and CINAHL.

The screening of titles and abstracts of studies followed the Cochrane methodology available in the Handbook[11].

A total of 14 studies, all available in English were included. Of these, five studies were included for full-text reading. After contacting an author, one study was excluded and only four studies met the inclusion criteria and presented the outcome infection among kidney transplants from living versus deceased donors.

The studies included in this review are observational, being two retrospective cohort and two prospective.

Chart 1 shows the description of the studies and the methodological quality.

The Chart 1 presents a description of the included studies. It was observed that most donors were deceased, reflecting the national and international policies for organ donation stimulus. The Brazilian study which included the largest number of participants, as Brazil is the 2nd country in transplant numbers and this study was conducted at the national reference center for Kidney Transplantation.

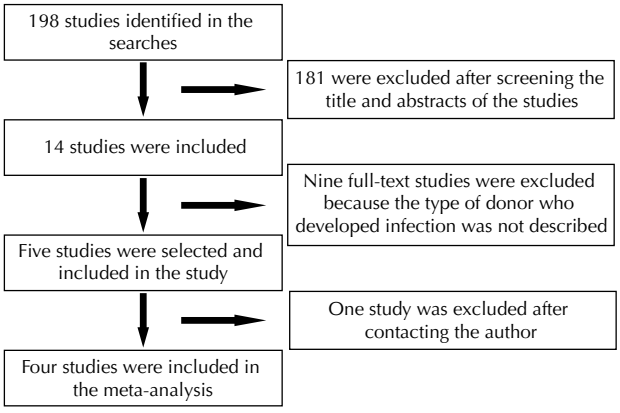


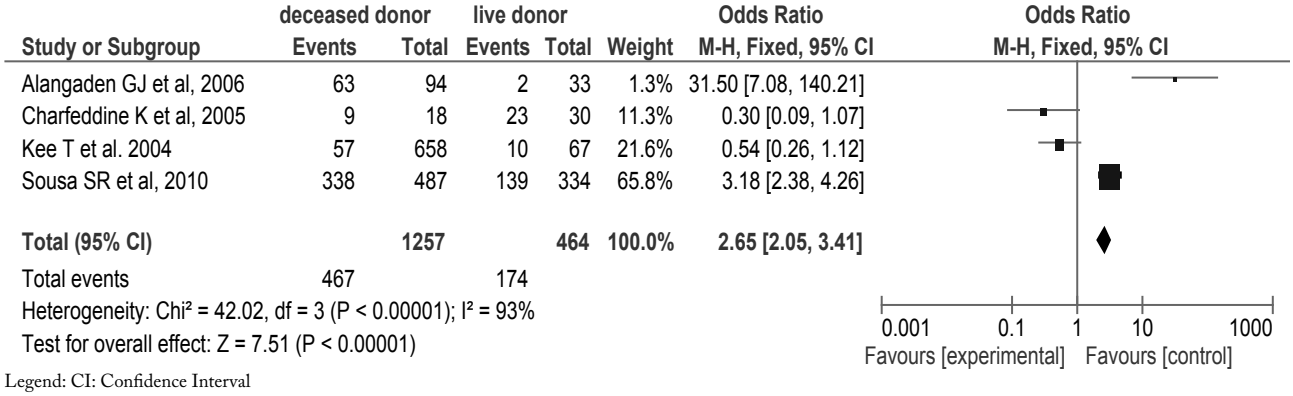
Figure 2 – Flowchart for the identification and selection of studies.

Among the most common infections described in the studies were Urinary Tract Infections and the microorganism related was E. coli. Such data are in agreement with the literature.

Chart 1 – Description of included studies and assessment of methodological quality.

Publication and year	Country	Type of study	No transplant/ donor living versus deceased (prevalence)	Episodes of infection/ living versus deceased donors	Microorganisms	Site of infection	STROBE
Kee T et al., 2004[15]	Singapore	Prospective cohort 1982-2002	658/67 (9.8)	57/10	*E. coli; K. ssp and S. aureus*	UTI and BSI	B
Charfeddine K et al., 2005[16]	Tunisia	Propective cohort 1994-2003	18/30 (0.6)	9/23	Not described	Not described	B
Alangaden GJ et al., 2006[9]	EUA	Retrospective cohort 2001-2004	94/33 (2.8)	63/2	*S aureus, M. catarrhalis and E. agglomerans*	UTI, PNM BSI	C
Sousa SR et al., 2010[7]	Brazil	Retrospective cohort 2006-2010	487/334 (1.4)	338/139	*E. coli, E. sp, k. pneumoniae, P. aeruginosa*	UTI, SSI and BSI	C

*UTI: urinary tract infection, PNM: Pneumonia, BSI: Bloodstream infection, SI: Surgical Site Infection



Legend: CI: Confidence Interval

M-H: Mantel-Haenszel

Figure 3 – Infectious events: deceased donor versus living donor.

Figure 3 demonstrates a greater risk for the group of patients transplanted from deceased donors in relation to the group of living donors for the outcome infection with an odds ratio of 2.65 (95% confidence interval from 2.05 to 3.41 p <0.00001). The heterogeneity among the included studies was I^2=93%, p <0.00001, which can be explained by the low number of studies that met the inclusion criteria.

DISCUSSION

In order to conduct a systematic review is imperative to follow the appropriate methodology with all the necessary scientific rigor, avoiding biases and inaccuracies, which makes it different from narrative and traditional literature review[14-15].

The best way to control biases in a systematic review is to include randomized controlled trials as recommended by Cochrane Collaboration, which was not possible in this review, being composed of observational studies, which is appropriate design to analyze the expected outcomes. An alternative to minimize biases that the study is subject, was to use the STROBE instrument for assessing the methodological quality of observational studies. This instrument provides recommendations for critical and transparent analysis of the data of this type of study to assess what results can be included in a systematic review[12,17-18,20].

Through meta-analysis is possible to obtain a higher statistical power, because data from more than one study are combined, increase the sample size, and thus the statistical power, thus reducing the possibility of incorrect acceptance or rejection of the null hypothesis[19].

The number of transplants in Brazil increased from 920 in 1988 to 5,639 in 2014, highlighting Brazil as the second major kidney transplant center in the world[3]. The relationship between the number of transplants with living and deceased organ donors remains close to 50% between 1994 and 2007. The proportion of transplants with deceased organ donors has grown substantially, and in 2014, among the 5,639 kidneys transplanted around country, 4,251 were performed with organs from deceased donors[3].

The first objective of the study was to analyze if the type of donor is infection risk factor for the recipient, and was evidenced figure 3 that the deceased donor was a risk factor 2.65 for the outcome infection in kidney transplant patients with an odds ratio 2.65, 95% CI (2.05 to 3.41, p <0.00001).

Among the various conditions studied that show significant association with the risk of developing infectious episodes after kidney transplantation, we highlight those related to cold ischemia time on the graft and the immune factors[7,21].

A study conducted in a referral center for kidney transplantation in Brazil showed that the increase of 30 minutes in the cold ischemia time on the graft from deceased donor had a significant and independent association with the risk of developing infectious episodes (OR 3.29, 95% CI 2.37–4.58)[7].

It is known that prolonged tissue ischemia facilitates and amplifies the exposure classes of MHC class I and II antigens of the transplanted organ to the immune system of the recipient, favoring immune recognition and raising the chances of triggering the rejection process[20]. Another important variable for graft patient survival is delayed graft function (DGF), which is directly related to negative outcomes of transplantation, including graft loss and risk of infection[21].

Although the incidence of infectious episodes are highly variable among the different studies, usually the incidence of infection is higher in the first month follow-up after transplantation and directly related to the dose of immunosuppression used. In the first months after kidney transplantation predominant nosocomial infections, especially those located in the urinary tract and surgical wound [7,9-10].

The microbiology of infections in post-kidney transplantation tends to follow patterns directly related to the type and intensity of immunosuppression therapy and prophylaxis of these components has been significantly effective in reducing the incidence of opportunistic early infections[9].

In kidney transplantation patients, infection is one of the main causes of hospital admissions and represents 51% of readmissions that occur within six months after transplantation, preceded only by surgical complications[22].

A study conducted with 280 transplant patients at the Universidade Federal de Sao Paulo showed that colonization by Vancomycin-resistant Enterococcus in this population was 14.5%[23]. And recently demonstrated by molecular typing of isolated bacteria from this population that cross-transmission of multi-resistant bacteria happens among these patients[24].

Added to this, the number of patients on the waiting list for a kidney transplant is large and annually presents an increasing trend, this is due to progressive improvement in the quality and life expectancy afforded by dialysis interventions[25-26]. Facing this scenario, there is a need for further studies aiming to establish protocols for the management of deceased donor transplant, aiming at the reduction of related infection.

CONCLUSION

This systematic review and meta-analysis has revealed that deceased kidney donor recipients have 20% higher risk for developing infections.

Implications for practice

This study points to the need for new studies that show ways to minimize the reduction in infection with deceased donor transplant patients. In short term, the implementation of protocols to reduce cold ischemia time on the organ and proper preservation would be possible; review of protocols and screening of deceased donors to detect serological conditions and body integrity; strict adherence with the existing protocols for prevention and control of multidrug-resistant bacteria in order to reduce morbidity and mortality related to infection in this patient population.

RESUMO

Objetivo: Verificar se o tipo de doador é fator de risco para infecção nos pacientes transplantados renais. **Método**: Revisão Sistemática da Literatura com Metanálise realizada nas bases de dados MEDLINE, LILACS, Embase, Cochrane, Web of Science, SciELO e CINAHL. **Resultados:** Foram selecionados 198 artigos e incluídos quatro estudos observacionais que descreveram as infecções apresentadas entre os pacientes distinguindo o tipo de doador. Através da metanálise, foi evidenciado que em pacientes submetidos a transplante de doador falecido, o desfecho infecção foi 2,65 maior, em relação aos que recebem o órgão de doador vivo. **Conclusão**: O estudo permitiu verificar que receptores de rim de doador falecido apresentam maior risco para o desenvolvimento de infecções e que emerge a necessidade de estabelecimento e cumprimento de protocolos desde o manejo adequado do tempo de isquemia à prevenção e controle de infecção nesta população.

DESCRITORES

Transplante de Rim; Doadores de Tecidos; Doadores Vivos; Infecção; Revisão.

RESUMEN

Objetivo: Verificar si el tipo de donante es factor de riesgo para infección en los pacientes trasplantados renales. **Método:** Revisión Sistemática de la Literatura con Metanálisis llevado a cabo en las bases de datos MEDLINE, LILACS, Embase, Cochrane, Web of Science, SciELO y CINAHL. **Resultados:** Se seleccionaron 198 artículos y se incluyeron cuatro estudios observacionales que describieron las infecciones presentadas entre los pacientes, distinguiéndose el tipo de donante. Mediante el metanálisis, se evidenció que en pacientes sometidos a trasplante de donante fallecido, el resultado infección fue 2,65 mayor, con relación a quienes reciben el órgano de donante vivo. **Conclusión:** El estudio permitió verificar que receptores de riñón de donante fallecido presentan mayor riesgo para el desarrollo de infecciones y que emerge la necesidad de establecimiento y cumplimiento de protocolos desde el manejo adecuado del tiempo de isquemia hasta la prevención y el control de infección en esa población.

DESCRIPTORES

Trasplante de Riñón; Donantes de Tejidos; Donadores Vivos; Infección; Revisión.

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