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ORIGINAL ARTICLE

The use of intraoperative mannitol during the laparoscopic nephrectomy in living kidney donor and the prevention of delayed graft function

Uso de manitol intraoperatorio durante la nefrectomía por laparoscopia en donante vivo de riñón y la prevención de función retardada del injerto

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Abstract

Background and objectives: *The administration of mannitol during laparoscopic hand-assisted nephrectomy in the living donor has been controversial with various recommendations about it. This study aims to evaluate the effect of the intraoperative mannitol in the living kidney donor and the incidence of delayed graft function (DGF).* **Methods:** *This study was a retrospective observational study with living kidney transplant recipients and donors who underwent laparoscopic hand-assisted nephrectomy at Colombiana de Trasplantes from January 2015 to September 2019. We assessed the impact of mannitol administration in living donors on the main transplant outcomes such as DGF, urinary volume, acute rejection, and mortality at 3 months of follow-up. We performed a descriptive analysis of demographics and clinical variables in our cohort.* **Results:** *A total of 367 recipients were evaluated. The incidence of DGF was 5.9% without mannitol versus 6.2% with mannitol (p = 0.99). The acute rejection episodes (12.2% without mannitol versus 4.7% with mannitol) had a trend difference between the comparative groups, but it was still not significant in the bivariate analysis (p = 0.06). The mortality rate in the recipient was not significant (p = 0.69). The mean serum creatinine did not have significant differences at 1 and 3 months of follow-up comparing both groups.* **Conclusion:** *The use of mannitol in living donors does not have a significant impact on the incidence of DGF in kidney recipients. A trend of association between mannitol administration and reduced acute rejection episodes was observed, though it was not statistically significant.*

Keywords: *Kidney transplant. Mannitol. Living donor transplantation. Laparoscopic hand-assisted nephrectomy. Delayed graft function. Tubular necrosis.*

Resumen

Antecedentes y objetivo: *La administración de manitol durante la nefrectomía laparoscópica en el donante vivo ha sido discutida con diversas recomendaciones. El objetivo es evaluar la administración de manitol intraoperatorio en el donante vivo de riñón y la incidencia de función retardada del injerto en el receptor.* **Métodos:** *Estudio observacional retrospectivo con receptores de riñón y donantes vivos que tuvieron nefrectomía laparoscópica en Colombiana de Trasplantes entre enero de 2015 a septiembre de 2019. Evaluamos el impacto de administrar manitol en los principales desenlaces del trasplante: función retardada del injerto, volumen urinario, rechazo agudo y mortalidad del receptor a los 3 meses post-trasplante. Se realizó un análisis descriptivo de las características demográficas y clínicas.* **Resultados:** *Se evaluaron 367 receptores con una incidencia de función retardada del injerto de 5.9% sin manitol versus 6.2% con manitol (p = 0,99), el rechazo agudo (12,2% sin manitol versus 4,7% con manitol) tuvo una tendencia de diferencia entre ambos grupos no significativa (p = 0,06) y la mortalidad del receptor tampoco mostró diferencias significativas (p = 0,69). La media de creatinina sérica al mes y*

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Date of reception: 07-02-2023
Date of acceptance: 09-08-2023
DOI: 10.24875/RUC.23000029

Available online: 26-09-2023
Urol. Colomb. 2023;32(3):86-92
www.urologiacolombiana.com

3 meses no tuvo diferencias significativas en los grupos. **Conclusión:** *El uso de manitol en los donantes vivos de riñón no impactó significativamente la incidencia de función retardada del injerto en los receptores de trasplante. Se encontró una tendencia de asociación en la administración de manitol intraoperatorio y la reducción de los episodios de rechazo agudo al tercer mes post-trasplante en los receptores. No obstante, esta tendencia no tuvo la suficiente relevancia estadística.*

Palabras clave: *Trasplante riñón. Manitol. Trasplante de donante vivo. Nefrectomía laparoscopia mano-asistida. Retardo en la función del injerto. Necrosis tubular.*

Introduction

Chronic kidney disease (CKD) is a pathology that affects 10% of the global population with high impact and mortality[1]. Living kidney transplant is the best therapeutic option for patients with CKD due to higher graft survival, lower cold ischemia time, and decreased risk of delayed graft function (DGF). The incidence of DGF in recipients with a cadaveric donor is 21.8% versus 3.5% in recipients with living donors[2].

Some of the general medical aspects of laparoscopic living donor nephrectomy (LDN) have been evaluated in different publications[3-5]. For example, the use of mannitol during the living donor laparoscopic nephrectomy is associated with increasing the renal blood flow, decreasing endothelial swelling, and mitigation of free oxygen radicals[3,6].

Mannitol ($C_6H_8(OH)_6$) is an alcohol that releases prostaglandins leading to renal vasodilatation and increased diuresis. The literature reported that these effects contribute to the protection of renal injury and the preservation of kidney function[7]. In kidney transplantation, the living donor kidney is susceptible to ischemic reperfusion insult while clamping the donor's renal artery and flushing it with a cooled preservation solution. The intraoperative mannitol in LDN results in the mitigation of this ischemic injury and the reduction of tubular cell swelling to prevent acute tubular necrosis (ATN) and DGF in kidney transplant recipients[6]. However, some studies assessing mannitol have contradictory findings[4,8].

DGF is determined as an indication for dialysis in the 1st week after kidney transplantation and is associated with post-transplant oliguria, a higher risk of acute rejection, and lower graft survival[9]. The DFG increases the risk of acute rejection by 20-40%[10]. Some studies published that the administration of mannitol declined the incidence of acute rejection[11].

In Latin America, there are no studies with evidence that allow extrapolating data about the administration of mannitol during LDN and its benefits in kidney transplant. This research aimed to evaluate the administration of mannitol during the hand-assisted LDN (HALDN) and the incidence of DGF. Furthermore, this study aimed to achieve two specific objectives. First, the clinical and sociodemographic characteristics of donors and transplant recipients will be described within the timeframe of January 2015 to December 2019. Second, we will conduct a comparative analysis of post-operative outcomes, focusing on different follow-up times, specifically between recipients who received mannitol and those who did not receive mannitol. Our hypothesis was to examine the differences following the administration of mannitol since according to multiple scientific studies, the administration of mannitol has been demonstrated to reduce the occurrence of acute rejection. In addition, we are interested in determining whether these differences are statistically significant.

Methodology

Study design

A retrospective cohort observational study was performed including living kidney donors (LKD) and their recipients during the period from January 2015 to September 2019 at Colombiana de Trasplantes. A non-probabilistic convenience sampling method was employed for the non-random allocation of the intervention. We obtained through Stata 14 a sample size of 124 (62 per group). Our transplant center performs 44% of the total living donor kidney transplant activity in Colombia[12]. During the study period, 367 patient recipients and their donors were assessed. Electronic clinical records were reviewed for all study populations. Demographic data and clinical outcomes were collected from institutional medical records for our database.

Donor evaluation

All LKDs are evaluated by a multidisciplinary team and the Ethics Committee. Laboratory studies were performed to determine the suitability of the LKD. The LKD glomerular filtration rate is measured by 24-h urinary creatinine clearance. Computed tomography angiography was performed to identify the renal vascular

anatomy. Our inclusion criteria for the donor were individuals aged over 18 years, approved by the Medical Board and Ethics Committee, and with donation dates falling between January 2015 and December 2019. As for the recipient, we included individuals aged over 18 years who received a kidney transplant from a living donor within the specified time frame. However, we excluded recipients who underwent auto-transplantation.

Recipient selection

The evaluation of kidney transplant candidates was performed by mental health, transplant nephrology, and transplant surgery. It is imperative that the kidney transplant benefits the recipient over the risks, the candidate tolerates the surgery, and the immunosuppression would not deteriorate or does not cause exacerbation of comorbidities.

Hand-assisted laparoscopic living donor nephrectomy

The HALDN was the technique of choice in our transplant group. Donors were positioned in a "flank-up" position. The HALDN requires a hand port, two trocars (5 and 12 mm), and a 30° video endoscope. The pneumoperitoneum had a flow rate of 400 cm/min and 15 mmHg of intra-abdominal pressure. The ultracision (HARMONIC® HD ultracision johnson 1000i) mobilized the colonic splenic flexure, and renal artery vessels and ureters were identified and dissected. Renal vessels were clamped using two large-size non-absorbable polymer ligating clips (Weck® Hem-o-lok®). The use of a 60 mm endovascular cutting stapler obtains a reasonable vessel length to mobilize and remove the left kidney. The kidney is immediately removed to minimize the warm ischemia time. The kidney was delivered through the hand port. A laparoscopic inspection was done to check for hemostasis and closure of the abdominal cavity.

Mannitol administration

The decision to administer mannitol was made based on the surgeon's clinical judgment and expertise, taking into consideration the existing scientific literature and evidence supporting its potential benefits in reducing the incidence of acute rejection. During HALDN, before renal artery clamping, a 30-min infusion of 20% mannitol was administered to all exposed patients, following the clinical practice guidelines.

Variables and measurements

The study included the following variables: age, sex, creatinine, DGF, urinary volume in 24 h, acute rejection at 3 months, and mortality at 3 months. In terms of the outcomes, DGF was defined as the requirement for dialysis within the first 10 days following transplantation. Acute rejection was identified based on biopsy findings using the BANFF criteria. Mortality was documented through clinical records. We employed standardized protocols for data collection, utilized reliable data sources, and conducted assessments at consistent time points

Statistical analysis

Descriptive analyses reported the population demographics, and clinical data according to the nature of the variable and distribution. The data were displayed as frequencies and percentages to describe categorical variables. Central tendency and dispersion measures were used to describe quantitative variables. The study population was divided into two groups (with or without mannitol administration) comparing the main clinical outcomes. Bivariate analysis was performed to compare the main clinical outcomes (DGF, urinary volume in 24 h post-transplantation, acute rejection, and mortality after 3 months of kidney transplant) between the mannitol group and without mannitol group. $p < 0.05$ was accepted as statistically significant.

Analysis was performed using Software R version 4.0.3.

Ethics considerations

This study is approved by the Ethics Committee according to the national and international legislation whether it be the Declaration of Helsinki[13], and the Declaration of Istanbul[14].

Results

Demographics and baseline characteristics

A total of 367 recipients and their donors were evaluated during the study period. Among those, 129 (35%) had the administration of mannitol. The mean age of donors was 37.9 ± 11.1 years. Approximately half of donors were female (50.1%). The recipients had a mean age of 36.6 ± 14.1 years old, and most of the patients were male compared to the gender proportion (58% versus 42%). There were no significant differences in the bivariate analysis corresponding to age or gender

Table 1. Demographics and baseline characteristics in LKD and recipients using or without mannitol

Variables	Without mannitol (n = 238)	Mannitol (n = 129)	Total (n = 367)	p value
Donor age, years, mean (SD)	37.7 (11.4)	38.3 (10.7)	37.9 (11.1)	0.898
Donor sex, n (%)				0.997
Female	119 (50.0%)	65 (50.4%)	184 (50.1%)	
Male	119 (50.0%)	64 (49.6%)	183 (49.9%)	
Recipient age, years, mean (SD)	36.1 (13.8)	37.5 (14.7)	36.6 (14.1)	0.673
Recipient sex, n (%)				
Female	95 (39.9%)	59 (45.7%)	154 (42.0%)	0.559
Male	143 (60.1%)	70 (54.3%)	213 (58.0%)	
Pulse rate, mean (SD)				
Before intervention	83.8 (15.3)	83.9 (14.8)	83.8 (15.1)	0.516
After intervention	87.5 (14.6)	89.0 (13.3)	88.1 (14.1)	0.824
Systolic blood pressure, mean (SD)				
Before intervention	130.3 (17.1)	128.7 (19.9)	129.7 (18.2)	0.227
After intervention	126.2 (16.8)	127.0 (16.8)	126.6 (16.8)	0.662
Diastolic blood pressure, mean (SD)				
Before intervention	80.9 (12.4)	80.1 (12.6)	80.6 (12.5)	0.272
After intervention	75.7 (12.8)	75.5 (12.0)	75.6 (12.5)	0.441

SD: standard deviation; LKD: living kidney donors.

either in LKD or recipients with or without administration of mannitol. Table 1 depicted demographics and baseline characteristics of LKD and recipients with or without mannitol use.

Clinical outcomes in recipients

The incidence of DGF was 5.9% in the group without mannitol compared to 6.2% with mannitol (p = 0.99). The urinary volume (diuresis) in the first 24 h after the kidney transplant was de 9740 ± 4720 ml without mannitol versus 9860 ± 5490 ml with mannitol. No significant differences were found in diuresis and mortality between both groups (p = 0.97 and p = 0.69, respectively). The incidence of acute rejection had a trend in the difference between the groups (without mannitol 12.2% versus mannitol 4.7%) but was still not significant in the bivariate analysis (p= 0.06) (Table 2).

Serum creatinine after kidney transplant

The serum creatinine mean was 1.59 ± 1.28 mg/dl without mannitol versus 1.54 ± 0.925 mg/dl with mannitol (p = 0.92) 1 month after kidney transplantation. At 3 months of follow-up, serum creatinine mean was 1.58 ± 1.61 mg/dl without mannitol compared to 1.35 ± 0.6 mg/dl with mannitol (p = 0.34) (Fig. 1).

Discussion

This is the first study in Colombia that sheds light on the role of mannitol administration, considering clinical and sociodemographic variables, as well as post-operative outcomes in our population. Mannitol is one of the main osmotic and diuretic medications used in kidney transplant[15]. The intraoperative administration of mannitol during the HALDN is associated with the prevention of DGF[6] and acute kidney injury[8] in LKD recipients. To the best of our knowledge, there are no publications about the assessment of the effect of mannitol in HALDN or kidney transplantation in Latin America. This study described the impact of intraoperative use of mannitol during HALDN in LKD and the incidence of DGF in kidney transplantation.

In our study, the demographic characteristics showed a gender distribution in LKD and recipients akin to the previous publications[16].

At first glance, the main clinical outcomes analyzed for the recipients in this study without or with the use of mannitol were as follows: kidney function, the incidence of DGF, urinary volume after 24 h of a kidney transplant, the incidence of acute rejection, and mortality at 3 months of follow-up.

In the literature, the DGF is correlated with a higher risk of multiple post-transplant complications and less graft survival in kidney transplant recipients[9,17].

Table 2. Clinical outcomes in the recipients without or with mannitol

Clinical outcomes	Without mannitol (n = 238)	Mannitol (n = 129)	Total (n = 367)	p value
Creatinine 1-month post-transplant, mean (SD)	1.59 (1.27)	1.54 (0.92)	1.58 (1.16)	0.345
Creatinine 3 months post-transplant, mean (SD)	1.58 (1.61)	1.35 (0.59)	1.50 (1.36)	0.072
DGF, n (%)	14 (5.9)	8 (6.2)	22 (6.0)	0.992
Urinary volume in 24 h, ml, mean (SD)	9740 (4720)	9860 (5490)	9780 (5000)	0.979
Acute rejection at 3 months, n (%)	29 (12.2)	6 (4.7)	35 (9.5)	0.0638
Mortality at 3 months, n (%)	10 (4.2)	8 (6.2)	18 (4.9)	0.699

DGF: delayed graft function; ml: mililiters; SD: standard deviation.

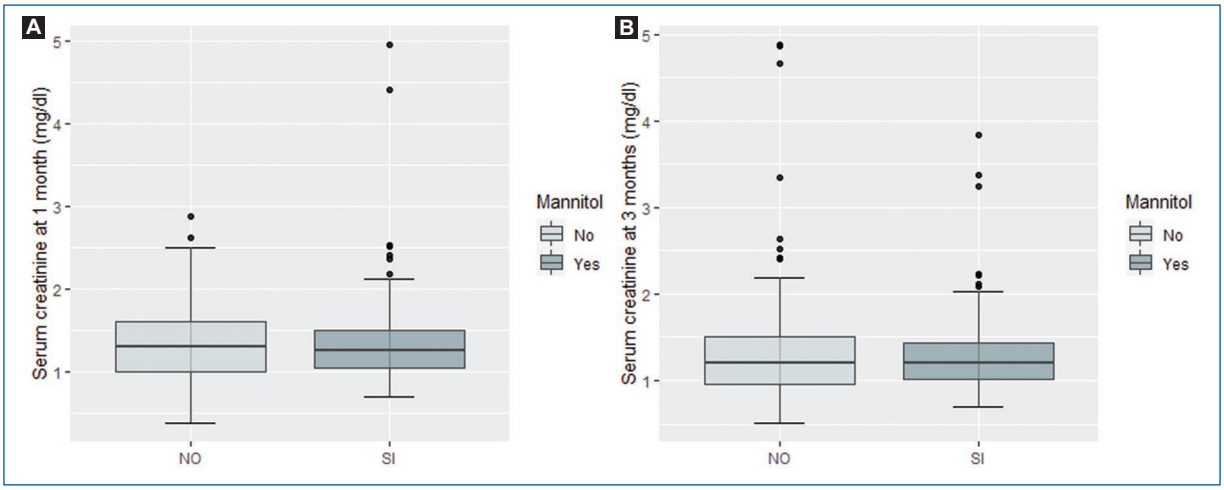

Figure 1. Follow-up of serum creatinine in living kidney donor recipients without or with mannitol. **A:** 1-month post-transplant. **B:** 3 months post-transplant.

In our findings, the incidence of DGF did not have a significant difference within the comparison groups similar to a study of 413 LKD with laparoscopic nephrectomy[18]. Andrews et al.[6] evaluated varying degrees of ATN by performing an optical coherence tomography in LKD comparing mannitol infusion for 15 min versus 30 min in the renal tubules. They found a higher incidence of ATN in the group with mannitol infusion for 30 min than with mannitol infusion for 15 min. In kidney transplantation, a meta-analysis that included two studies with 569 LKD recipients described that the use of intraoperative mannitol decreased the incidence of DGF from 30-55% to 14-21% in the mannitol groups (p = 0.02)[8].

Esfahani et al.[4] published a random clinical trial with 60 LKD with or without intraoperative mannitol evaluating the effect of mannitol on diuresis and serum creatinine concentration. The outcome did not show significant differences between mannitol and placebo in a way similar to our results. On the contrary, the meta-analysis mentioned above found in a study with kidney transplant patients that those who received mannitol had higher diuresis than the control group. In parallel, serum creatinine showed heterogeneous results in this meta-analysis[8].

On the other hand, the reduction in the incidence of acute rejection at 1 year of follow-up in the Williams et al.[18] results was not significant with the administration of mannitol in LKD equivalent to our findings. In addition, a total of 90 kidney recipients were evaluated to determine the incidence of acute rejection with or without mannitol in kidney transplantation. In this report, there was no significant association between a lower risk of acute rejection and the use of mannitol[8]. Finally, there were no publications that evaluated mortality and intraoperative mannitol use in LKD or kidney transplant recipients.

The study has several limitations that should be acknowledged. First, selection bias may exist due to the lack of standardized criteria for participant inclusion, potentially affecting the generalizability of the findings. Second, subgroup comparisons might be challenging due to the heterogeneity within the subgroups. Third, the use of retrospective measurement introduces the possibility of measurement bias and data quality issues. Inaccuracies or missing information may affect the reliability of the results. Finally, confounding bias could be present as unmeasured factors associated with both the exposure and outcome may influence the observed associations. Given that this study was conducted in a single healthcare center, the ability to extrapolate the findings is considered limited, and further studies are needed to gain a better understanding of the studied phenomenon. Consequently, the study exhibits low external validity and highlights the need for additional research.

The study has several strengths that enhance its value and credibility. First, despite its retrospective design, it provides valuable insights and allows for the examination of associations and trends over time. Second, the comprehensive data collection approach utilized in the study, including data retrieval from a reliable database, ensures a robust dataset for analysis. Third, the longitudinal analysis enables the assessment of outcomes and exposures over multiple time points, enhancing the understanding of temporal relationships. In addition, the inclusion of relevant variables, such as kidney function, provides valuable clinical information and allows for an in-depth analysis of relevant outcomes. Finally, the study's retrospective design reflects real-world clinical practices, offering the potential for real-world application and insights into the effectiveness of interventions in routine healthcare settings. These strengths collectively contribute to the study's overall significance and strengthen the validity and applicability of its findings.

Conclusion

The use of intraoperative mannitol in LKD during HALDN did not significantly impact the incidence of DGF in kidney transplant recipients. Lower episodes of acute rejection were documented in patients with mannitol administration but were not statistically significant.

Acknowledgements

The authors thank Colombiana de Trasplantes for their support.

Funding

This study was supported by Colombiana de Trasplantes.

Conflicts of interest

The author reports that there are no conflicts of interest in this research.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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