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Original Research

The Impact of Heparin Therapy in Deceased Donors on Early Graft Survival for Kidney and Liver Recipients: A Clinical Trial Study

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Abstract

Background: Significant hemodynamic, hormonal, and metabolic impairment of a brain-dead organ donor is often associated with the deterioration of graft viability. This study aimed to compare the effect of heparin therapy as a therapeutic dose after brain death confirmation on early graft survival in kidney and liver recipients. **Method and Materials**: The deceased donors were sorted into two groups based on their D-dimer level. After confirming brain death, one group was given a heparin injection (case group), while the other group did not receive any heparin (control group). A total of 71 brain death donors and matched kidney and liver transplants were included in the case group. A total of 43 brain death donors and matched kidney and liver transplants were included in the control group. A total of 5000 units of heparin were administered every 6 hours to the deceased donor case group. **Results**: The mean age of the case and control groups were 36.27 $\pm$ 16.13 and 36.15 $\pm$ 18.45, respectively. An independent *t* test showed that there were no differences between the number of procured organs in both groups ($p = 0.29$). There was no significant difference between the graft survival rate and the doses of heparin injection to the liver recipients ($p = 0.06$). However, a significant difference was revealed between the graft survival rate and the dose of heparin injection ($p = 0.004$) in kidney recipients. **Conclusions**: The data suggest that administering low therapeutic doses of heparin to donors before organ donation may potentially prevent thrombosis and provide a protective benefit. We showed that heparin therapy had no significant effect on the number of donated organs and graft survival.

Keywords: brain death; heparin; transplantation; kidney; liver

1. Introduction

Brain death is characterized by the irreversible loss of brain function, including the brain stem and cortex function [1,2]. Biomarkers and neurological tests can help medical staff avoid futile care by predicting poor outcomes early after ICU admission [3].

Medical staff play an important role in the management of brain death cases by identifying potential donors, declaring brain death, and providing appropriate medical care [4,5].

Improving organ quality after brain death and prior to transplantation could help optimize the process [6]. Based on the precise standards for donor evaluations prior to any donation, the transplant team may be required to follow protocols in order to conduct a comprehensive donor screening [7].

Based on studies, the existence of a massive storm called a "catecholamine storm" affects the brainstem and leads to a severe hypertensive crisis. Widespread peripheral vasoconstriction leads to organ ischemia, by changing the metabolism from aerobic to anaerobic. Subsequent vasodilatation, hypovolemia, and cardiac dysfunction often impair hemodynamics, pressure, and blood flow to organs [8].

"Cytokine storm" refers to a dysregulation of the immune system, with a significant release of proinflammatory cytokines, which leads to severe tissue damage [9].

According to previous studies, the upregulation of cytokines, adhesion molecules, and endothelial antigens and the increased infiltration of leukocytes, in all organs suitable for transplantation, were associated with compromised organ function after transplantation [10–12].

Thus, grafts derived from brain-dead donors lead to the stimulation of an accelerated inflammatory response with rapid infiltration of mononuclear cells and an increased rate of acute rejection [13].

Different management protocols have been proposed for the treatment of potential donors, and drug interactions can be a concern in their treatment. In addition, another important concern when evaluating potential donor treatment is the risk of transplant rejection in recipients [14]. Signif-

icant hemodynamic, hormonal, and metabolic impairment of the brain-dead organ donor is often associated with a deterioration in graft viability, leading to organ exclusion or acceptance with a high risk for poor initial graft function [15]. The use of hormone therapy for donors and recipients has been studied by previous researchers [16–18]. Administering hormone therapy to donors increases the number of organs available for transplantation, including hearts, lungs, kidneys, and pancreas [19,20].

The experience of medical staff to care for brain death with new methods, as well as management of brain death can have a huge impact on the organ donation rate [21].

D-dimers are produced as a result of the degradation of cross-linked fibrin, which is mediated by plasmin. The presence of D-dimers in the blood indicates the production and degradation of cross-linked fibrin, reflecting the coagulation and fibrinolysis processes occurring concomitantly [22]. Production and breakdown of fibrin cause an increase in D-dimer levels. D-dimer levels increase in patients with disorders such as pulmonary emboli (PE), deep vein thrombosis (DVT), solid tumors, leukemia, severe infections, trauma or a postoperative state, disseminated intravascular coagulation (DIC), pregnancy, acute stroke, sickle-cell anemia, congestive heart failure, and chronic kidney failure [23]. Heparin, one of the oldest medicines still in widespread clinical use, is a naturally occurring glycosaminoglycan that functions mainly by inhibiting the coagulation of blood [24]. The administration of heparin to potential cadaveric donors is primarily intended to prevent the formation of blood clots in the kidneys and liver. Blood clot formation in an organ reduces the chance of successful or even possible transplantation [25].

This study aimed to compare the effect of heparin therapy as a therapeutic dose after brain death confirmation on early graft survival for kidney and liver recipients.

2. Material and Methods

Data from the 304 brain death cases enrolled in the Sina organ procurement unit at the Tehran University of Medical Sciences in 2020–2022, as well as data of the recipients, were retrospectively analyzed.

To eliminate confounding factors, only recipients who received an organ procured at Sina organ procurement unit (OPU) were included in the study.

All brain death cases were screened before organ procurement for a hypercoagulable state by measuring the prothrombin time, partial thromboplastin time, platelet count, protein S, protein C, antiphospholipid antibody, anticardiolipin antibody, and kaolin clotting time [26].

The deceased donors were sorted into two groups based on their D-dimer level. After confirming brain death, one group was given a heparin injection (case group), while the other group did not receive any heparin (control group).

Those with a normal coagulation panel received 5000 units of heparin every 6 hours. In the case of a brain death donor, the administration of heparin occurred after the declaration of death. Conversely, the control group (66) did not take heparin before organ procurement.

In the 137 cases, there were 71 brain death donors, 117 matched kidneys, and 65 matched liver recipients included in the case group, while 43 brain death donors, 48 matched kidneys, and 22 matched liver recipients were included in the control group, with 23 brain death cases extracted due to failing the exclusion criteria.

This study was conducted according to the declaration of Helsinki as a statement of ethical principles for medical research. Written informed consent was obtained for the publication of information from donors' families before the heparin was injected.

2.1 Data Collection

Short-term outcomes of the patients were followed up at our institution through 30 September 2022. Clinical, demographic, laboratory, treatment, and outcome data were extracted from hospital records using a standardized data collection form. In addition to basic descriptive parameters, data on comorbidities and infection detection and selected laboratory parameters in kidney and liver recipient groups were analyzed (postoperative serum creatinine level parameters were measured at 7 days for kidney recipients; postoperative alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALK-P) parameters were measured at 7 days for liver recipients).

Finally, the number of kidney and liver recipients with thrombosis was collected one week after transplantation; the graft survival rate of recipients was evaluated 6 months after transplantation.

2.2 Statistical Analysis

Numerical variables are expressed as the mean, standard deviation, and interquartile range (lower and upper quartiles). Categorical variables are presented in percentages as absolute frequencies and relative frequencies.

The defined groups were compared using one-way ANOVA and Chi squared tests. Independent sample Student t tests were used with $p < 0.05$ considered as significant. Data were analyzed in SPSS (Version 18, IBM Corp., Chicago, IL, USA).

3. Results

Detailed descriptive donor data are presented in Table 1. The most common blood group in all donors was A (36.6%), and the least common was AB (8.5%).

According to Table 1, there are no differences between age ($p = 0.31$), BMI ($p = 0.3$), gender ($p = 0.5$), cause of brain death ($p = 0.5$), blood group ($p = 0.14$), number of the procured organ ($p = 0.29$), creatinine (Cr) level ($p = 0.4$), and platelet (PLT) ($p = 0.46$) in the case and control groups.

Based on Table 2, the most common gender in the kidney recipients was male in both the case and control groups.

Table 1. Demographic characteristics of the participants.

Variable		Case group		Control Group		*p*-value
Age		36.27 ± 16.13		36.15 ± 18.45		0.31
Body mass index		25.22 ± 3.74		24.94 ± 4.11		0.30
Cr (Creatinine) (Time of procurement)		1.4 ± 1.2		1.3 ± 0.94		0.4
PLT (platelet count) (Time of procurement)		153.74 ± 12.93		150.65 ± 16.27		0.046
Variable		*F*	*%*	*F*	*%*	*p*-value
Gender	Female	21	29.6	20	46.5	0.5
	Male	50	70.4	23	53.5	
Cause of brain death	Vascular	35	50.7	22	51.2	0.5
	Non-Vascular	36	49.3	21	48.8	
Blood Group	O	24	33.8	24	55.8	0.14
	A	26	36.6	8	18.6	
	B	15	21.1	10	23.3	
	AB	6	8.5	1	2.3	
Number of procured organs	1	9	12.7	3	7	0.29
	2	6	8.5	3	7	
	3	38	53.5	24	55.8	
	4	16	22.5	13	30.2	
	5	2	2.8	-	-	
Number of injected Doses	1	63	88.7	Not applicable for control group		
	2	2	2.8			
	3	3	4.2			
	4	1	1.4			
	5	1	1.4			

Characteristics for the kidney and liver recipients are shown in Table 2.

The independent *t* test showed that there were no differences in the number of procured organs between both groups ($p = 0.29$, $F = 0.64$).

No recipient in either group developed an allograft arterial or venous thrombosis. According to the Chi square test, there was no significant difference between the graft survival rate and the doses of heparin injection in the liver recipients ($p = 0.06$). However, it also revealed a significant difference between the graft survival rate and the dose of heparin injection ($p = 0.004$) in kidney recipients.

The one-way ANOVA test showed that there is a significant difference between the doses of heparin injection and the level of AST on the 7th day post-transplantation ($p = 0.013$) in the liver recipients, although it also revealed that there was no significant difference between the doses of heparin injection and the level of ALK-P in the liver recipients on the 7th day.

Finally, the ANOVA test showed that there was a difference between the doses of heparin injection and the ALT levels in the liver recipients on the 7th day post-transplantation ($p = 0.001$).

The one-way ANOVA test showed that there was no significant difference between the doses of heparin injection and the mean BUN levels and serum creatinine levels in the kidney recipients on the 7th day post-transplantation ($p = 0.65$ and $p = 0.71$, respectively).

4. Discussion

The outstanding progress in all types of solid organ transplantation during recent years has dramatically increased [27]. According to previous studies, kidney transplant recipients are known to be in a high-risk group for infections and viruses [18].

There were no significant differences between the doses of heparin injection and the BUN and serum creatinine levels in the kidney recipients. Nagra *et al.* [28] stated in 2004 that they did not find any differences in the initial thrombosis of kidney transplant patients with intraoperative heparin, and no difference was observed in the levels of BUN and serum creatinine in patients. The results of their study are consistent with this study.

There is a difference between the doses of heparin injection and the level of AST on the 7th day after transplantation in the liver recipients. There was no significant difference between the heparin injection and the ALk-P levels in the liver recipients on the 7th day.

There was a difference between the doses of heparin injection and the ALT levels on the 7th day of transplantation in the liver recipients.

There was a significant difference in the ALT and AST levels in the transplant patients, which is similar to the findings in the study by AJ Hessheimer *et al.* [29]. In sum-

Table 2. Characteristics of the kidney and liver recipients.

Variable		Kidney recipients	
		Case	Control
Age		39.87 ± 16.91	39.44 ± 16.15
BUN1		93.92 ± 35.79	77.98 ± 162.59
BUN2		77.51 ± 19.67	95.46 ± 46.69
Cr1		6.92 ± 2.46	6.21 ± 1.93
Cr2		2.34 ± 1.23	2.79 ± 1.61
Gender	Female	42 (35.9%)	14 (29.2%)
	Male	75 (64.1%)	34 (70.8%)
Variable		Liver recipients	
		Case	Control
Age		40.82 ± 15.38	38.94 ± 14.19
ALT1		151.51 ± 127.58	635.37 ± 998.086
ALT2		383.59 ± 480.81	198.73 ± 224.27
AST1		1325.01 ± 1771.72	1096.8 ± 167.13
AST2		74.77 ± 93.55	91.01 ± 111.94
ALK-P1		416.1 ± 236.63	382.24 ± 439.46
ALK-P2		40.82 ± 15.38	428.15 ± 259.43

BUN1, blood urea nitrogen in transplant time; BUN2, blood urea nitrogen in discharge time; Cr1, creatinine in transplant time; Cr2, creatinine in discharge time; ALT1, alanine aminotransferase in transplant time; ALT2, alanine aminotransferase in discharge time; AST1, aspartate aminotransferase in transplant time; AST2, aspartate aminotransferase in discharge time; ALK-P1, alkaline phosphatase in transplant time; ALK-P2, alkaline phosphatase in discharge time.

mary, their study showed that fibrinolytic treatment does not play a role in improving the quality of organ and liver transplants.

Consistent with a previous study undertaken by Irish *et al*. [30], there was a significant relationship between heparin injection and thrombosis after kidney transplantation.

Jenna *et al*. [31], studying the use of early postoperative low-dose heparin infusion and its effect on vascular thrombosis rates within 30 days post-transplant, found that low-dose heparin in the postoperative period may provide a protective benefit in the prevention of early organ loss resulting from thrombosis. In addition, Yoo *et al*. [32] demonstrated that during living donor hepatectomy, the low-dose heparin group did not have increased incidences of hepatic artery and portal vein thromboses.

5. Conclusions

The data suggest that administering low therapeutic doses of heparin to donors before organ donation may potentially prevent thrombosis and provide a protective benefit. We showed that heparin therapy had no significant effect on the number of donated organs and graft survival.

However, several limitations should be noted: a sample size of 71 in the case group meant that the study was underpowered in the detection of a difference between the two groups, which is reflected in the fact that clinically significant differences in outcome rates failed to reach statistical significance. Considering that it is not possible to refer to similar research data, there was another limitation in the present study, the most important of which is the lack of a similar study with which to generalize the results. Further prospective studies evaluating potential risk factors and intervention strategies are needed to determine whether routine clinical screening for thrombophilia risk factors is warranted.

Availability of Data and Materials

The data sets used during the current study are available from the corresponding author on reasonable request.

Author Contributions

Design of the work: EP, HR, SD. Acquisition: SD. Analysis: MK. Interpretation of data for the work, writing draft: ML, EP, MK. Drafting the work or reviewing it critically for important intellectual content: ML, HR. Final approval of the version to be published: All Authors. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted according to the declaration of Helsinki as a statement of ethical principles for medical research. Written informed consent was obtained for the publication of information from donors' families before the heparin was injected. The ethical committee for medical research of Tehran University of Medical Sciences was approved the protocol (Approval ID: IR.TUMS.SINAHOSPITAL.REC.1401.080).

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Conflict of Interest

The authors declare no conflict of interest.

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