Immunopathologia Persa
http www.immunopathol.com
DOI:10.34172/ipp.2022.06

Evaluation of changes in plasma vitamin C levels in brain-dead organ donors

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Received 6 Apr. 2021
Accepted 10 July 2021
Published online 3 Aug. 2021

Keywords: Brain death, Transplantation, Ascorbic acid, Reactive oxygen species, Antioxidant

Abstract

Introduction: Inflammatory events after brain death (BD) generally influence the quality of donated organs and adversely affect the outcome of transplant surgeries. Vitamin C is a natural organic compound with potent antioxidant properties. Changes in serum levels of vitamin C (ascorbic acid) following BD are still unknown.
Objectives: This study aimed to assess the changes in serum vitamin C levels in brain dead donors in the time elapsed between BD diagnosis and at once before procurement procedure of donated organs.
Patients and Methods: In this experimental study, serum vitamin C levels were measured in 37 brain-dead donors (BDDs) at two time points, primarily on admission (R1) and just before organ procurement (R2). The difference between mean values of R1-R2 was analyzed according to the parameters of brain dead donor's, which consisted of gender, cause of BD, and type of blood group.
Results: A total of 37 BDDs (62.2% male) with a mean age of 26.48±18.1 years were included. Time interval between the two samplings was 40.09±12.10 hours. Overall, there was a statistically significant difference between serum ascorbic acid (AA) levels at admission (R1) and immediately before organ procurement (R2) ($P=0.016$). However, in terms of the cause of BD and blood type, no significant difference in serum AA at the two-time points was detected ($P=0.85$ and $P=0.79$ respectively).
Conclusion: Significant differences were observed between serum vitamin C levels in the duration between BD diagnosis and immediately before procurement surgery. Therefore, determining the most effective dose of vitamin C supplementation and the best time to administer it to the patients is highly recommended for future studies.

Citation: Milani S, Dalili A, Sadeghi M. Evaluation of changes in plasma vitamin C levels in brain-dead organ donors. Immunopathol Persa. 2022;8(1):e06. DOI:10.34172/ipp.2022.06.

Introduction

Organs transplantation from deceased donors has become the definitive treatment for many patients with organ failure (1). Brain death (BD) is associated with physiological changes that may affect all organs acceptable for transplantation. BD may also cause systemic inflammation. BD-induced "Catecholamine storm" is a severe inflammatory reaction characterized by increased plasma levels of cytokines (2). In the last decade, significant progress has been made in identifying the pathophysiology of traumatic brain injury (TBI) which is the most common cause of BD. At present, TBI classifications consist of initial (primary) and delayed (secondary) brain injury (3). The main consequences of secondary brain injury are inflammation and increased reactive oxygen species (ROS), leading to apoptosis.

ROS were recognized as part of the most important components of the inflammatory reaction; they act as by-products, participate in the reaction and create a vicious cycle. Moderate to low levels of ROS are produced as a part of normal cellular metabolism and defense systems. In fact, there is a balance between ROS and the antioxidant system under physiological conditions. Therefore, ROS are regulated and kept low by the antioxidant system. However, during pathological conditions such as intracerebral hemorrhage, additional sources of ROS are formed. High concentrations of ROS can disturbance the dynamic balance, causing adverse changes to cellular components,

Key point

Inflammatory events associated with brain death adversely affect donated organs and the outcome of transplant surgery. As a result, significant efforts have been conducted to protect the organs against inflammation. Ascorbic acid (AA) is of particular importance because of its antioxidant properties, which reduce oxidative damage in biological systems.

lipids, proteins, and DNA (4). Therefore, increased free radicals and ROS production lead to oxidative stress (5). The human antioxidant defense system contains endogenous antioxidants such as glutathione (GSH). This can eliminate excess ROS and reduce oxidative stress. However, this defense system might be incomplete without the supplement of exogenous antioxidants, such as ascorbic acid (AA) (6).

AA is especially significant in restricting oxidative harm in biological systems. It may protect from the dysregulation of the immune and inflammatory response by its antioxidant properties (7). AA acts not only as an antioxidant but also as a pro-oxidant. The influence of exogenous antioxidants (such as AA) on oxidative metabolism and inflammatory processes may depend on their concentration (6). Therefore, for maintaining or re-establish the balance between oxidation and antioxidants (redox homeostasis, an essential function of biological systems), physiological doses of exogenous antioxidants are needed (8).

Objectives

This study aimed to evaluate the changes in serum AA levels in deceased solid organ donors between declaring BD and organ procurement.

Patients and Methods

Study design

This clinical research was performed between June 2014 and January 2015; plasma samples were obtained from 37 deceased organ donors in our procurement area. The standard management was based on the United Network for Organ Sharing (UNOS) recommendation for all BDDs. Methylprednisolone was given to all deceased donors. Blood samples were obtained from BDDs once in the intensive care unit (ICU) when they were accepted as organ donors and again in the operating room immediately before the organ procurement process. All specimens were obtained according to the standard procedure and stored at -20°C until the time of analysis.

AA was measured using a Human Vitamin C (VC) ELISA Kit (Cat No: E1538Hu), manufactured by the Bioassay Technology laboratory [China (Mainland)]. The practical technology of the ELISA kit is based on the double-antibody sandwich technology to detect human vitamin C. The assay range was 1-300 ng/mL with a sensitivity of 0.52 ng/mL.

Donor information regarding gender, hemoglobin level, and cause of death were recorded for all cases.

Statistical analysis

Data were analyzed with IBM SPSS Statistics software version 20 (IBM Corp, Armonk, NY). To assess the normal distribution of variables, the Kolmogorov-Smirnov test was used. Data were described as frequency (percent) or mean ± standard deviation. Wilcoxon signed-rank test was used to compare values of serum vitamin C (ng/mL) at admission (R1) and immediately before organ procurement (R2). Accordingly, $P<0.05$ was defined as statistically significant.

Results

In the present study blood samples were obtained from 37 BD donors; 23 men and 14 women with a mean age of 26.48 ± 18.1 years. TBI was the most common cause of BD (40.5 %) among the studied cases. The mean hemoglobin level was 11.95 ± 3.21 g/dL and the mean time between samplings was 40.09 ± 12.10 hours. The most common blood group type among donors was B positive. Table 1 shows summary of demographic data of the deceased donors.

Differences between the mean R1-R2 values were analyzed according to the parameters of brain-dead donors (BDDs), which included gender, cause of BD, and blood group type.

In total, the mean (standard deviation) of serum AA level at admission (R1) and immediately before organ procurement (R2) was 40.0 (82.0) and 39.5 (80.9), respectively. There was a statistically significant difference between serum AA level on admission (R1) and immediately before organ procurement (R2) ($P=0.016$). Table 2 shows plasma levels of AA in the deceased donors at admission (R1) and immediately before organ procurement (R2). Therefore, serum vitamin C levels were significantly reduced following BD.

Discussion

This study showed that the level of serum AA was significantly affected by the BD process during BD diagnosis and just before the procurement of donated organs (a median period range of 14-98 hours). TBI was the main cause of BD (40.5%) among the studied cases. It has been demonstrated that a significant reduction in plasma AA levels in brain-injured patients in comparison to healthy control subjects occurs on the first day. Interestingly, the plasma AA levels did not significantly change afterward (9). Nevertheless, our study showed that significant depletion of serum vitamin C occurs due to BD.

There are several mechanisms by which BDDs affect the graft function. These include significant changes in hemodynamics, hormonal changes, and systemic inflammation. Inflammatory responses in transplant surgery have been reported to be the main disorder caused by BD (10). Several clinical studies have shown that the anti-inflammatory plan of action for BDDs improves post-transplanted function. The impact of AA administration in BDDs has also been investigated; a beneficial effect for AA on the inflammatory response besides improvement of the primary allograft function has been reported in this regard (11,12). It is not clear whether anti-inflammatory strategies based on the combination of various antioxidants including vitamins C and E might be more efficient.

Table 1. Demographic data of the deceased donors

Variable	Gender		Total
	Male	Female	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)
Age (y)	29.3±16.9	21.6±19.6	26.48 ± 18.1
Time[a] (h)	51.4±71.5	45.6±10.5	40.09 ± 12.10
Hemoglobin (g/dL)	12.0±3.3	11.9±3.2	11.95 ±3.21
Cause			
Head trauma	13 (56.5)	2 (14.3)	15 (40.5)
Cerebrovascular accident	4 (17.4)	5(35.7)	9(24.3)
Anoxia	3 (13.0)	4 (28.6)	7 (18.9)
Poisoning	2 (8.7)	0 (0.0)	2 (5.4)
Others	1 (4.3)	3 (21.4)	4 (10.8)
Blood group			
A+	4 (17.4)	6 (42.9)	10 (27.0)
B+	6 (26.1)	5 (35.7)	11 (29.2)
B-	1 (4.3)	0 (0.0)	1 (2.7)
O+	9 (39.1)	1 (7.1)	10 (27.0)
O-	1 (4.3)	0 (0.0)	1 (2.7)
AB+	2 (8.7)	2 (14.3)	4 (10.8)
Total	23 (62.2%)	14 (37.8%)	37

[a] Time; the time interval between samplings (h).

Table 2. Plasma levels of ascorbic acid in the deceased donors at admission (R1) and immediately before organ procurement (R2)

	R_1*	R_2*	R1 -R2*[a]	*P* value **
Gender				
Male	19.5 (22.8)	38.0 (75.5)	-18.4 (71.0)	0.213
Female	73.6 (125.6)	42.0 (92.0)	31.6 (88.9)	0.778
Total	40.0 (82.0)	39.5 (80.9)	0.5 (80.9)	0.016
Cause				0.85
Head trauma	13.4 (9.25)	13 (17.5)	0.5 (10)	
Cerebrovascular accident	13.5 (6.2)	14.5 (89)	2.5 (40.45)	
Anoxia	16.5 (6.9)	15.5 (84)	-1 (26.25)	
Poisoning	14 (7)	10.5 (8)	-3.5 (17.25)	
Blood group				0.79
A	21.25 (10.3)	15.25 (12.50)	-3.75 (21)	
B	13.4 (6.75)	10.5 (6.75)	0 (4.75)	
O	13.75 (11.38)	13.75 (48.22)	-0.25 (26.48)	
AB	13 (8.5)	10 (5.12)	-0.25 (7.87)	

[a] R1 -R2 shows the difference between values of serum vitamin C levels (ng/mL) at admission (R1) and immediately before organ procurement (R2).
* Mean (SD) , ** Wilcoxon rank sign test.

The present study showed a significant change in the serial measurement of serum vitamin C levels in brain-dead patients. This finding suggests that a standard dose of vitamin C should be considered in the management guidelines of BD cases.

Conclusion

Solid-organ transplantation is the best choice of treatment in many patients with end-stage organ failures. Obtaining organs from deceased donors is the only option for many of the patients. However, BD is a process that can trigger pathophysiological events and cause significant dysfunction in the donated organ. Thus, significant efforts have been made to ameliorate the function of donated organs by protecting them from the events. Vitamin C is an important nutrient that is especially significant in restricting oxidative harm in biological systems. It can protect against impaired immune and inflammatory responses. In our study, significant decreases in serum vitamin C levels were observed in BDDs, in addition to previous reports of early depletion of such levels in brain-injured patients. Therefore, determining the most effective

dose of vitamin C supplementation and the best time to administer it to the patients is highly recommended for future studies.

Limitations of the study

The small sample size was the main limitation. Moreover, the exact relationship between plasma and brain levels of vitamin C in brain-death patients has not yet been considered.

Acknowledgments

We would like to thank M. Mirzadeh at the Organ Transplant Center of Mashhad University of Medical Sciences for her assistance in data collection.

Authors' contribution

Conception and design: SM and MS. Literature search and data acquisition: NN. Drafting the manuscript: SM. Analysis and interpretation of data: MS and SM. Critical revision of the manuscript for important intellectual content: AD. All authors read and approved the final paper.

Conflicts of interest

Authors declare no sources of funding and potential conflicting interest.

Ethical issues

The research followed the Declaration of Helsinki principles. The Ethics Committee of Mashhad University of Medical Sciences approved this study (Ref: 1400/176358). The donors (or their closest relatives) consented to donate blood/tissue for medical research. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

The authors have no sources of funding for this study.

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