Renal transplant collection from donors following fatal methanol or carbon monoxide intoxication

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KEY WORDS

kidney ◗ methanol intoxication ◗ cadaveric donor ◗ kidney transplantation

ABSTRACT

The aim of the study. The aim of this work is preliminary evaluation whether it is possible to collect kidneys following methanol or carbon monoxide poisoning.
Material and methods. Between 2006 and 2008 the Regional Transplantation Team received reports on 5 potential organ donors who died as a result of methanol or carbon monoxide poisoning. 10 kidneys were eligible for transplantation. Nine of them were transplanted to adult recipients at the Department of Urology and Kidney Transplantation at M. Pirogow Hospital; one was transferred to the Child Health Centre in Warsaw for a recipient below 16 years of age.
Results. The observation period was from 0 to 24 months following KTx. In the group of 10 recipients two died, including one with an active transplant. After 6 months from transplantation in 4 out of 7 adult recipients renal function was very good (creatinine levels ≤2 mg%). None of the patients experienced symptoms which may have suggested the influence of toxic substances on the functions of the transplanted kidney.
Conclusions. Preliminary results indicate that the kidneys collected from donors following methanol and/or carbon monoxide intoxication are full quality organs complying with the criteria of safe transplantation.

INTRODUCTION

Acute and chronic methanol intoxication is a significant problem in Poland. Cases of such intoxication are both accidental and intentional [1]. Methanol is absorbed from the gastrointestinal tract, skin and respiratory tract. Its metabolites are toxic: formic aldehyde is responsible for the degeneration of the retina and optic nerve, liver, heart and kidney cells, whereas formic acid is a source of metabolic acidosis which is life-threatening [2]. The final effect of intoxication is the production of reactive oxygen forms, namely free radicals and the activation of proteases which directly affect cell structures or react with other ions which are important to cell transformations [3].

The fatal dose of methanol is 4 g/kg cc. The time to the manifestation of toxic symptoms differs and it is sometimes difficult to estimate. The first phase of poisoning is similar to ethanol intoxication and includes nausea, vomiting, vertigo. During the second phase metabolic acidosis develops and its symptoms include: severe stomachache, flushed face, conjunctiva reddening, vomiting, decreased blood pressure. The phase of CNS damage manifests with vision disturbances, distraction of motoric functions, then the elation phase follows, then coma and respiratory collapse with ceasing of all physiological reflexes [2].

Treating methanol intoxication, depending on its phase, involves inducing vomiting in conscious patients and oral administration of 40% ethyl alcohol to slow down methanol metabolism and to induce its elimination from metabolic pathways. In all cases specialist help is necessary, including the elimination of metabolic acidosis, haemodialysis, proper hydration and intravenous administration of ethyl alcohol as well as maintaining vital functions (pressor amines, artificial ventilation). This poisoning is associated with high mortality due to its specific features and latency.

Carbon monoxide (CO) is the third reason for intoxication in Poland with respect to frequency. Annually about 1400 people become poisoned and a large number of these cases are suicidal attempts [4]. Carbon monoxide, a product of incomplete carbon combustion (coal-fired, gas-fired furnaces, combustion gases), is colourless, odourless, tasteless, lighter than the air and difficult to identify, it exerts its toxic effects by binding reversibly, although potently, with haemoglobin. The resulting carboxyhaemoglobin not only does not transport oxygen but it inhibits its dissociation from oxyhaemoglobin. Deep tissue hypoxia damages the central and peripheral nervous systems and circulation system in the first place. The extent of intoxication depends on the exposure time, minute ventilation and carbon monoxide levels in the inhaled air. The level of 0.15% in the inhaled air causes death in a short time. The carboxyhaemoglobin blood levels rarely correlate with the extent of intoxication (e.g. in smokers); however, the level of 70% indicates fatal intoxication in most cases [2, 5]. Similarly as for methanol, non-characteristic symptoms of intoxication include headache, tinnitus, nausea, dyspnoea. The next phase of intoxication is associated with convulsions, confusion, decreased blood pressure, tachycardia, pulmonary oedema and respiration disturbances including apnoea. At high levels of carboxyhaemoglobin pink and grey skin tone is frequent. Treatment includes 100% oxygen or hyperbaric oxygen therapy, blood transfusion, treating CNS oedema, severe metabolic acidosis and maintaining vital functions.

As a result of effects of these two substances the above mentioned patients frequently die due to irreversible damage to cerebral functions. Constant toxicological and neurological monitoring and evaluation of functions of other organs and systems make it possible to identify potential donors in the group of patients with severe CNS damage. Within many years of history of transplantology the donor acceptance criteria have evolved significantly, mainly due to a growing body of evidence and amazing progress in the field of basic sciences related to organ transplantation. Collecting organs from donors following cardiac arrest, "domino" transplantations involving an exchange of organs between two recipients: heart and heart-lung transplant recipient, transplantation of organ fragments or multi-organ transplantations as well as transplanting organs from donors following intoxication, all of these have become acceptable, and the results of such procedures are not poor to the ones

for organs collected from donors who died as a result of vasogenic CNS damage [6]. In Poland, as in other countries, poisoned donors constitute a small, 1%, percentage of referred patients [7].

MATERIAL AND METHODS

As a result of cooperation with the Clinic of Acute Poisoning of the Prof. J. Nofer Memorial Institute of Occupational Medicine in Łódź in 2005 the Regional Transplantation Team reached an agreement regarding the identification of potential organ donors in the group of intoxicated patients. Since 2006 there have been reports on patients with fatal carbon monoxide or methanol poisoning in whom the presence of toxic substances in their blood was not observed in a follow-up toxicological examination as a result of treatment and whose parameters of the acid-base balance, carbohydrate and ion metabolism were stabilised and circulation was controlled. In such cases when a neurological examination had been performed in order to assess the CNS damage and the toxicological treatment had been completed the coordinator of the Regional Transplantation Team was notified about a possibility of further diagnostics for a patient with suspected brain death.

Having been transported in an ambulance and admitted at the Intensive Care Unit of M. Pirogow Hospital, the potential donor was subject to standard examinations in order to assess the extent of irreversible CNS damage using clinical and radiological tests and to assess the efficiency of other organs and systems. The examinations included: CT of head, chest and abdomen, possible abdominal ultrasound, assessing blood type and Rh factor, CBC, ionogram, liver and pancreatic enzymes, evaluation of the acid-base balance, clotting parameters, general urinanalysis. Usually these tests were repeated every 4 hours during donor hospitalisation. The standard tests aimed at avoiding the transmission of infectious and neoplastic diseases included urine culture and bronchial secretion culture, HIV markers, hepatitis B and C markers, EBV markers, CMV markers, toxoplasmosis and syphilis markers as well as cancer markers: CEA, AFP, β HCG, CA 19-9, CA 125. The following parameters were evaluated constantly: heart rate, blood pressure, liquid balance with daily urine collection, blood saturation, the parameters of artificial ventilation and administration of pressor amines.

At the same time pursuant to the Directive of Health Ministry regarding the criteria to determine permanent and irreversible discontinuation of brain stem functions and to the Announcement of Health Ministry of 17 July 2007 regarding the criteria and methods to determine permanent and irreversible discontinuation of brain functions the Committee to Pronounce Death was being called according to the method and time presented in the stipulations of the documents mentioned above. When death was pronounced and confirmed by the protocol signed by the Committee members, the Transplantation Organization Centre POLTRANSPLANT, District Prosecutor's Office were communicated and the family of the deceased was informed about a possibility of organ procurement (retrieval) organization of further stages of medical proceedings was undertaken. In all cases the family of the deceased had no reservations regarding organ collection.

When biological material (donor lymph nodes) was collected, it was transferred to the Laboratory of Tissue Compatibility of the Transplantology Institute in Warsaw and the Laboratory of Transplantation Immunology of the Kopernik Hospital to select renal transplant recipients listed in the National and Regional List of Recipients. The organs were collected by the members of the Regional Transplantation Team. When the kidneys were prepared and secured the recipients were expected to come to M. Pirogow Regional Specialist Hospital.

Renal transplant procedures were performed by doctors from the transplantation team immediately after the recipients had come and had been qualified as eligible for general anaesthesia. All transplant procedures were carried out according to the centre standard procedure. Following hospitalisation at the Department of Urology and Renal Transplantation recipients were referred to the Department of Nephrology of the Kopernik Hospital.

Between January 2006 and February 2008 we received reports on 5 potential donors (4 men and one woman) aged 48 to 56 years (mean 50 years old) from Acute Poisoning. Patients were hospitalised at IMP for 2 to 9 days before referring to the transplantation coordinator. In four cases the cause of death was fatal methanol intoxication resulting in a massive cerebral oedema combined with a subarachnoid haemorrhage and in one case accidental carbon monoxide poisoning resulting in a sudden cardiac arrest complicated by cerebral oedema. In all cases patients were qualified as eligible for organ donation based on imaging tests and biochemistry of kidneys (renal morphology, circulation, creatinine levels, creatinine clearance). Liver and pancreas collection was cancelled due to an extensive loss of organ functions visible in the ultrasound and CT examinations (features of steatosis and/or ischaemia) and in the levels of biochemical markers (the levels of ASPAT, ALAT, GTP and lipase exceeded the norm at least three times.) Heart and lung collection was cancelled due to the age of donors and parameters indicating possible damage to the myocardium and limited pulmonary ventilation ability (RKZ and troponin).

Recipients included 5 women and 5 men aged from 13 do 67 (mean age 47). The reasons for renal insufficiency of their own kidneys were as follows: 4 cases of glomerulonephritis, 3 cases of diabetic nephropathy, one case of haemolytic-uraemic syndrome and in two recipients the reason for renal insufficiency had not been diagnosed. A period of dialysis therapy before

Table 1. Transplantation results for kidneys from donors with carbon monoxide and/or methanol intoxication.

Date	Donor	HLA score	CIT hour	Function	Creat 0	Creat 6	Creat 12	Creat 24	Death
2006	M 35	7	20	ATN	4,6	2,5	2,5	1,6	-
2006	K 57	12	22	-	3,2	2,2	1,9	1,9	-
2007	K 50	14	16	-	2,6	1,5	1,3	-	-
2007	M 39	16	21	-	3,1	0,9	1,1	-	-
2007	M 55	12	18	-	2,4	2,0	1,5	-	-
2007	M 56	14	23	-	2,3	-	-	-	Myocardial infraction
2008	K 67	16	23	Graft.	-	-	-	-	Pulmonary embolism
2008	M 63	14	18	-	2,3	2,4	-	-	-
2008	K 36	18 /II	22	-	4,3	2,0	-	-	-

transplantation was between 3 to 47 months (mean 20.3 months). In the case of 9 recipients it was the first transplantation. The process of selection was not associated with any specific criteria related to the donor's cause of death. The kidney for a recipient below 16 years of age was transferred to the Child Health Centre in Warsaw according to current procedures. The cold ischaemia time in our centre ranged from 16 to 23 hours (mean 20 hours). In all recipients the kidney was transplanted on the right side and connected with the external iliac vessels, the ureter was implanted into the bladder using the Lich-Gregoir technique and a duble J catheter was left. Patients received triple drug immunosuppression (8 patients tacrolimus; 1 patient cyclosporin A) and standard antithrombotic, antiviral, antibacterial agents, as well as proton pump inhibitors.

RESULTS

Among nine recipients who received a transplant in the Regional Transplantation Team 7 patients are still alive and their transplants are active. One recipient died with an active transplant after 6 days since transplantation due to acute coronary syndrome with pulmonary oedema. The death of the second recipient as a result of sudden cardiac arrest occurred within a day after graftectomy due to acute graft rejection in a recipient with advanced atherosclerosis and systemic lupus.

The female recipient who received transplant at the Child Health Centre in Warsaw is alive with an active transplant.

Table 1 presents preliminary results of observation.

The observation period was from 0 to 24 months. Very good renal functions (creatinine level ≤2 mg%) after 6 months since transplantation were observed in 4 out of 7 recipients. One recipient experienced delayed renal function in the course of acute tubular necrosis (ATN.) None of the recipients experienced symptoms which may have suggested the effects of a toxic substance on the functions of the transplanted kidney.

DISCUSSION

Based on the data collected by the Department of Scientific Information of the Institute of Occupational Medicine in Łódź in the years 1970-2000 we know that the main reason for intoxication in Poland is accidental and intentional intoxication with hypnotics and psychotropic agents. A growing trend is visible in the group of intoxication with non-food alcohol substances (8% in 1980 – 30.8% in 2000). The third reason for poisoning is carbon monoxide (respectively 15.3-5.1%). [8, 9]. The analysis of data from 1993-1998 regarding methanol poisoning in the USA indicates a growing rate of intentional intoxications which are associated with high mortality. The problem of chronic methanol intoxication in children and diabetics should be noticed. Aspartame-sweetened products stored at high temperature and some powdered supplements and foodstuffs contain or release significant amounts on methanol during heat treatment [10]. Materials collected in the years 1993-1996 at the University in Leuven contain the analysis of 287 patients who intentionally had taken toxic substances. In the group of 10 deaths 3 were caused by medications and 2 by methanol [11]. On the other hand, data from the UK presented in 2002 indicated that carbon monoxide is the most frequent, isolated cause of fatal intoxication, and analgesics follow [12]. These data indicate that intoxications have a similar structure irrespective of social and economic conditions. In this group of patients the core problem with regard to transplantation is appropriate death pronouncement and the method to evaluate organ functions regarding specific toxic damage.

First reports on transplanting organs collected from donors with carbon monoxide or methanol intoxication are from the early 1990s [13]. These reports are not numerous; however, they contain information on collecting almost every organ, including transplantation of lungs collected from a methanol-intoxicated donor [14]. In Europe and the USA so far only 1% of organs for transplantation are from donors whose direct or indirect cause of death was poisoning [12]. According to Polish data published in 2008 patients who died as a result of intoxication are rarely eligible (approx. 1.05% in years 2004-2007), and more frequently they are disqualified as organ donors. They are multi-organ donors to a small extent (21% vs. 43% in general) although based on observation of 38 renal recipients it has not been confirmed that the obtained results suggest poorer functions of the collected organs [7].

Similar conclusions can be drawn from previously quoted British literature [12]. Reports from the University St-Luc in Belgium present analyses of data of 1174 patients with acute poisoning treated at the intensive care unit. In this group 12 subjects were qualified as organ donors with regard to organ specific criteria and toxic factor criteria. Apart from 22 kidneys which were collected, 5 hearts, 4 livers, 4 pancreas and/or pancreatic isles were collected. During the observation period three patients died as a result of cardiovascular complications and two in the course of chronic post-transplantation nephropathy and hepatopathy. None of the deaths correlated with a toxic factor from the donor [15]. Similar reports are presented by Duque et al. [16]. A relatively low toxicity of tricyclic antidepressants and serotonin antagonists towards organs of low tolerance to hypoxia has been confirmed in the reports on transplantation of heart and liver collected from donors following suicidal intoxications. [17, 18]. Reports on organ transplantation from donors with cyanide, pesticide and plant toxin (Conium maculatum) intoxications are extremely interesting [19, 20, 21]. The literature also contains reports on the role of carbon monoxide which in the future may be used to reduce the level of post-reperfusion injury to transplanted organs and to reduce their immunogenicity [22, 23]. It should be emphasised that irrespective of the possibility to collect vascularized organs from donors with carbon monoxide or methanol intoxication there is a possibility to qualify them for tissue collection, especially heart valves, bones or corneas [24].

Intoxications represent a small percentage of reasons for hospitalization in Intensive Care Units (ICU). The main one is medication (antidepressants), alcohol (ethanol, methanol) and carbon monoxide (CO) poisoning. Most often death is related to the consumption of ethylene glycol, methanol, ammanita phaloides and exposure to carbon monoxide. The influence of methanol and CO finally leads to heavy damage of the central nervous system (CNS) while other organs and tissues remain well-functional. Potential donors can be found in this group of patients. As a result of cooperation with the Regional Toxicological Center in Łódź – Nofer Institute of Occupational Medicine, we have prepared a programme for the identification and qualification of organ donors from fatally poisoned patients. In the years 2006-2008 we received applications from 5 potential donors from whom we collected 10 kidneys after clinical evaluation and considering the reason of death. Nine of these kidneys were transplanted in the Department of Urology and Kidney Transplantation in Łódź and one was transferred to the Child Health Center in Warsaw for a recipient below 16 years of age. The follow up period was from 0 to 24 months. In the group of ten recipients two died and one had a functioning graft. Preliminary results show that kidneys collected from donors after methanol and\or carbon monoxide poisoning are safe for transplanting.

CONCLUSIONS

In the era when donor acceptance criteria are being extended it seems sensible to pay attention to the possibility of collecting organs from patients

with irreversible CNS damage as a result of direct or indirect effects of toxic substances.

Extensive literature from this field confirms that functions of transplanted organs are appropriate and comparable to the ones in other groups of donors.

Cooperation between Transplantation Teams and Toxicology Centres in Poland may result in an increase in the number of identified donors.

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