INVITED ARTICLE

Brain dead donor kidneys are immunologically active: is intervention justified?

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Abstract

The improvement in the field of kidney transplantation, during the last decades, has brought kindey transplantation to the top of patient preference as the best kidney replacement therapy[1]. The use of marginal kidney grafts, which are highly immunogenic has become common practice because of lack of kidney donors.

Inflammatory activity in the kidneys after brain death is an ongoing phenomenon. The inappropriate treatment of brain dead donor may result to primary non function (PNF) of the graft, delayed graft function (DGF) or to long term graft dysfunction and shortened graft survival. Therefore correct handling of the brain dead donor is of paramount importance. The impact of various pharmacologic agents (catecholamines, glucocorticoids, carbamylated recombinant human erythropoietin, recombinant soluble P-selectin glycoprotein ligant, heme oxygenase-1, carbon monoxide, and mycophenolate mofetil) on the immunogemicity of brain dead donor kidneys is discussed.

Key words: brain death, kidney donor, kidney transplantation, immunosuppression, immunointervention, cortico steroids, mycophenolate mofetil, cyclosporine A

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Significant electrocardiographic, hemodynamic and hormonal disturbances, the sum of which has been characterised as "storm of autonomic nervous system" occur during the induction of brain death[2-4]. The result is initially an increase of systemic vascular resistance followed by loss of vascular tone, hypotension, endocrine organ failure and cellular metabolism derangement.

Brain death induces an inflammatory activation ending to vascular endothelial injury. Blood-brain barrier dysfunction results in peripheral circulation of cytokines produced in the damaged brain (complement activation, S100A9, S100β, IL-6, coagulation disorders). IL-6, IL-8, IL-10 and monocyte chemoatractant protein (MCP-1) are increased in the serum after brain death. These cytokines activate NF-κB, selectins adhesion molecules causing production of chemokines leading to cellular influx in the kidneys. P- and E- selectins attract leukocytes in the kidneys and generate direct alloimmune responses that later may mediate allograft rejection[5]. Mitogen activated protein kinases (MAP-kinases) mediate inflammatory responses and seem to play important role in the inflammatory reactions in the kidney[6]. Brain death is associated with significant increase in blood neutrophil integrins CD11b and CD18[7].

At the same time there is increased expression of HLA class I and II antigens, B7 co-stimulatory molecule, cytokine desregulation and adhesion molecule upregulation in the kideys[7-14]. Self antigens seem to play a role in alloimmunity[15-19] of the brain dead patient because hypoxia of kidneys happening in this setting can significantly alter the nature of self peptides and break down immune tolerance mechanisms. Immune reaction against self antigens in these kidneys can develop through both allorecognition pathways. Donor passenger antigen presenting cells (APC) may have the potential to induce an immune response against self-proteins in these kidneys through the direct pathway[20,21].

Endothelial cells express also significant pro-coagulant activity that may have a significant negative impact on graft behaviour (Aα/Bβ fibrinogen mRNA from the first 30 min after brain deafh, fibrinogen localization on the peritubular capillaries and significant increase of plasma von Willebrand factor). The new markers of tubular damage heart-fatty acid- binding protein and N-acetyl-glucosaminidase are maximally increased at four hours after brain death[22].

The above mentioned mechanisms, during brain death, result in dense infiltration of the kidneys by leukocytes, macrophages and dendritic cells before kidney harvesting[9,12,13,23]. These non specific inflammatory events cause vacuolization, atrophy and necrosis of renal tubules, glomerulitis and interstitial inflammation in the kidneys of the brain dead donor[24] and may amplify native and recipient alloresponsiveness and influence early and late allograft function irrelevant of the presence of donor systemic normotension[5,25].

Infammatory activity after brain death is an ongoing phenomenon and kidney procurement should be done as soon as possible after death declaration[13]. This inflammatory activity might justify pharmacological immune intervention on brain dead donor before renal transplantation[25-27].

Intervention to suppress the non-specific inflammation in the kidney of the brain-dead donor

Catecholamines

Dopamine causes in vitro decreased production of a) chemokine (C-X-C motif) ligand 1 (CXCL-1), epithelial neutrophil activating peptide-78 (ENA78), and IL-8 in proximal tubular epithelial cells[28] b) CXCL-1 and ENA78 reduced production in endothelial cells and c) delayed expression of ICAM-1, and VICAM-1 after TNF-α stimulation in these cells. Dopamine, also, induces heme oxygenase-1 (HO-1), inhibits P-selectin expression, and decreases mononuclear infiltration in experimental brain dead models[29]. These immunological effects seen in experimental conditions might explain in part the improved renal transplantation outcome after catecholamine treatment of the brain dead donor.

In cadaveric kidney transplantation catecholamines stabilize hemodynamically the brain dead donor. This effect combined with their anti-inflammatory action renders catecholamines independent beneficial factors in early graft function and long term renal transplant outcome in the clinical setting[30-33] (Table 1).

Glucocorticosteroids

Experimentally, glucocorticosteroid treatment (10 mg/kg bw) of brain dead rats improved kidney graft survival after transplantation to a level comparable to living donor transplants. In this study, steroids suppressed cellular infiltration and expression of cytokines and the intensity of morphological changes were noticeably different in the recipients of untreated brain dead donor kidneys[34].

In this experimental model MHC class II antigens were already expressed before the organ removal in untreated animals[34]. This finding suggests that steroid pretreatment with pulses (one pulse at induction of brain death or at donation approval and another one hour before harvesting the kidneys) might be more efficacious[34].

Table 1: Suggested management of brain dead donor to suppress non-specific inflammation.

1. Dopamine infusion (< 5 μg/kg/min) or adrenaline (< 0.1 μg/kg/min).
   (Preferred MBP 80 mmHg and diurisis of 1 ml/kgBW/h).
3. Use of immunosuppressive agents (corticosteroids, MMF).
4. Use of monoclonal antibodies against cytokines (TNF-a, IFN-γ, IL-2, IL-6)??
   Inhibitors of chemokines (MCP-1, MIP-1a, MIP-1β)?
5. Use of Carbamylated recombinant human Erythropoietin (CRHE).
6. Use of Recombinant P-Selectin Glycoprotein Ligand-lg (rPSGL-lg).
7. HO-1 induction (Cobalt Protoporphyrin (CoPP)).
8. Carbon monoxide (CO).

High corticosteroid dose inhibits the expression of NF-κB-mediated IL-1, IL-2, TNF-α, IFN-γ synthesis in cultured cells and in mice[35].

In the only prospectively designed human study on liver transplantation it is reported that serum and tissue expression of pro-inflammatory cytokines were reduced after steroid therapy of the brain dead donor[36]. In kidney transplantion, the best time to give steroid pulses before harvesting and the best dose are not known[37]. Long-term results after kidney transplantation, and have not been reported yet.

Carbamylated recombinant human erythropoietin (CRHE)

CRHE is a derivative of erythropoietin without hematopoietic action, which can reduce the non-specific inflammation of the kidneys of the brain dead donor (attenuate the increase of E-selectin and P-selectin mRNA, reduce VCAM-1 expression in the kidney) and improve creatinine clearance in anesthetized rats[38,39].

Recombinant soluble P-selectin glycoprotein ligand (sPSGL)

P-selectin is translocated within minutes from intracellular stores to the surface of vascular endothelial cells and/or platelets in response to inflammatory stimuli in a brain death mice model and E-selectin is expressed on the endothelial surfaces after transcriptional induction of its mRNA. These adhesion molecules react with their ligands on circulating polymorphonuclear leukocytes (PMN) to promote transient sticking (tethering) and slowing (rolling) along vessel walls. With stronger attachment to endothelium and diapedesis into the tissues via the sequential activity of other adhesion molecules, PMN become activated by locally produced chemokines and cytokines and trigger a further cascade of inflammatory /immunologic events[40-42].

Treatment of the donor with the recombinant soluble P-selectin glycoprotein ligand, an inhibitor of P-, E- and L-selectin, has been shown advantageous in experimental models[9,42]. sPGL and the Cytotoxic T lymphocyte antigen 4 (CTLA4-Ig) treatments blocked expression of brain death – induced macrophage associated (IL-1, Il-6, IFNγ) and T-cell associated (IL-2, IL-2R, IL-4, IFNγ) factors[9] .

Three days after transplantation, untreated brain dead donor kidneys showed severe tubular necrosis and mononuclear infiltration, whereas recipients of whom the donor was treated with recombinant soluble P-selectin glycoprotein ligand showed similar serum creatinine levels to living donor iso- and allograft recipients. Pre-treatment with recombinant soluble P-selectin glycoprotein ligand affects chronic transplant function in animals transplanted with brain dead donor kidneys and reduces long-term graft injury to a level seen in the living donor situation[42].

Heme oxygenase-1 (HO-1)

Heme oxygenase is the rate limiting step in heme degradation and the oxidation of the α-*meso* carbon of the protoporphyrin ring leads to the formation of free iron, biliverdin and carbon monoxide. The inducible isoform of HO, HO-1, is a heat shock protein (HSP32) induced by diverse stress related conditions[43]. The HO and HO-1 system provides generalized endogenous anti-inflammatory protection against oxidative stress. The mechanism is not clear[44,45].

HO-1 is a cytoprotective and anti-oxidant substance. The immunomodulating effects of upregulated HO-1 could be of use in the improvement of deceased donor transplantation. Selective up-regulation of HO-1 has been proven to be beneficial in different models of stress or damage, including ischemia/ reperfusion[46] and experimental renal transplantation[47]. Because of its antioxidative, antiapoptotic, and immune regulatory effects, HO-1 has been used in experimental transplantation after upregulation by cobalt protoporphyrin (CoPP) treatment (a selective HO-1 inducer) in the brain dead donor[48]. The CoPP treated animals showed a reduction in the infiltration of $ED1^+$ monocytes/macrophages, $CD4^+$ T cells and $CD8^+$ T cells which was combined with improved renal allograft survival[48]. Therefore, the application of HO-1 induction in the setting of kidney brain dead donor can be regarded a possible option to improve renal transplant outcome.

Carbon monoxide

It has been shown in transplant induced ischemia/reperfusion injury experimental models that the exposure to 20-250 parts per million of CO has cytoprotective effect. At these concentrations CO acts as a signal molecule and presents anti-inflammatory, anti-apoptotic and vasodilating properties[49,50].

Low-dose inhalation of carbon monoxide in a rodent experimental transplant model has shown protection of kidneys from the development of chronic allograft nephropathy[51]. The application of low-dose CO as anti-fibroinflammatory agent in the setting of brain dead donor should be possibly beneficial in the long-term after kidney transplantation.

Immnosuppressive agents

Effects of MMF in vitro

MMF seems to reduce significantly the release of soluble E-selectin expressed by Human Ubilical Vein Endothelial Cells (HUVECs) after stimulation with TNF-α[52] and monocyte binding to HUVEC and inhibits the upregulation of ICAM-1 and MHC-II expression on monocytes after stimulation. Experimentally, donor treatment with MMF demonstrated less primary non-function and less ischemia/ reperfusion injury[53]. According to Glomsda et al MMF could be used as anti-adhesive treatment to prevent inflammatory cell infiltration[54]. In lymphocytes and monocytes MMF decreases the synthesis of mannose and fucose of membrane glycoproteins which are ligands of the selectin adhesion molecules on the vascular endothelium[55]. MMF down-regulates the co-stimulatory and adhesion molecules CD40, CD54, CD80, CD86 and the cytokines IL-8, TNF-α, IL-10, IL-12 of MDDC (monocyte derived dendritic cells)[56]. Allison et al first published data demonstrating that MMF altered cell adhesion in activated human peripheral blood lymphocytes[57]. Mycophenolic Acid (MPA) reduces attachment of human monocytes to endothelial cells[58]. At a therapeutic dose monocytes treated with MPA were less adherent to living HUVECs by approximately 30%. If the endothelial cells were stimulated with IL-1β then the effect was more pronounced at 50% reduced adherence. Under phase contrast microscopy MMF reduced peripheral blood lymphocyte (PBL) adhesion to HUVEC cultured monolayers by up to 70-80%[59,60]. MMF blocks both T lymphocytes and WiDr colon adenocarcinoma cells binding to HUVEC by 80%. Surface expression of the endothelial cell T cell receptors was reduced by MMF in a dose dependent manner. MMF specifically suppressed T cell attachment to ICAM-1, VCAM-1 and P-selectin[61]. It has been proven that MMF inhibits cytokine-induced NO synthesis in vitro[62]. Blaheta et al[59] have shown strong inhibition of CD4+ and CD8+ adhesion to and penetration through endothelial cells by MMF. The main mechanism of action proved to be reduced binding capacity of VLA-4, LFA-1 and PSGL to VCAM-1, ICAM-1 and P-selectin respectively. The expression of cell adhesion molecules requires > 12 hours pretreatment and is half-maximal at 1μM MPA. Pre-treatment of EC do not reduce the expression of ICAM-1 induced by TNF-α. There is 2-3 fold increase of VCAM-1 and E-selectin[63].

Effects of MMF on experimental models

Experimental studies in rats have shown that the use of mycophenolate mofetil, is beneficial when given to the donor before harvesting of the kidneys. MMF was associated with the least proteinuria at twelve weeks after transplantation compared to steroids, FK-506 and CsA. Best time interval before harvesting and drug dose and combination are not known[64]. In heart grafts, donor treatment with MMF protects against primary non-function[53]. MMF can reduce the generation of reactive oxygen species reducing in this way cytokine production and apoptosis[65]. MMF treatment of 5/6 nephrectomized rats prevents or slows down the increment of serum creatinine and proteinuria[65]. The final result is inhibition of lymphocyte and monocyte infiltration in the damaged or ischemic tissue area[58,66,67]. MMF suppresses the lymphocyte and macrophage cytokine production[68] and abrogates the talk between macrophages and renal cells inhibiting cell proliferation and matrix expansion and finally glomerulosclerosis and interstitial fibrosis[69-72]. Insufficient IL-12 and CD80 expression by antigen presenting cells has been incriminated for anergy and tolerance and T cell func-

tional unresponsiveness[73]. Oral MMF administration to rats exerts its maximal inhibitor action on T cell proliferation and surface antigen expression (LFA-1 and ICAM-1 included) 6 hours after dosing which is dose related[74]. When kidneys were transplanted into Lewis rats treated with or without MMF, infiltration of neutrophils and macrophages was considerably lower in the MMF-treated animals[75]. It has been proven that MMF inhibits NO generation in a rat renal model of ischemia reperfusion injury (IRI)[76]. MMF prevents macrophage infiltration of the kidney in a model of anti-GBM nephritis in the rat when applied in the early stages of GN[77]. VCAM-1 expression in kidney cortex biopsies of patients with SLE was significantly decreased after treatment with MMF[78].

Effects of MMF on clinical grounds

MMF suppresses the lymphocyte and macrophage cytokine production preventing chronic scarring[79], is not associated with renal toxicity[80] and inhibits up-regulation of CD18+ in lymphocytes[66]. MMF can reduce the generation of reactive oxygen species reducing in this way cytokine production and apoptosis[81].

Effects of Cyclosporin A

It is well known that the CsA use is associated with significant renal toxicity[82]. Interstitial fibrosis is produced by activated fibroblasts and their origin is central to understanding the pathogenesis of progressive renal transplant damage. Epithelial to mesenchymal transition (EMT) is a highly regulated process whereby epithelial cells go through a series of programmed phenotypic changes, characterised by a loss of epithelial markers and function, migration into the extracellular space and metamorphosis into myofibroplast phenotype expressing α-smooth muscle actin (α-SMA).

A substantial proportion of infiltrating myofibroplasts within the neointima, adventitia and interstitium of graft biopsies are of donor origin[83]. It is known that CsA up-regulates TGF-β1. It has been claimed that CsA is factor responsible at least partly for this myofibroplast transformation[84,85]. Ischemia/reperfusion injury may be the cause of the early interstitial fibrosis and missed EMT-induced interstitial fibrosis at later time points. In this setting the use of CsA in the brain dead donor is not indicated.

In conclusion inhibition of the immunologic activation due to brain death is one of the strategies to improve transplant outcome in experimental models and should be in human transplantation. Many challenging options exist to counteract the deleterious effects of brain death on the donor kidney. The i.v. infusion of corticosteroids in combination with MMF possibly could be the first option since they are easy to use, there is great experience, they are cheap and the most significant they lack deleterious effects on the other organs in man.

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