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FOCUS ON: TRANSPLANTATION

Non heartbeating donation – The heart of the matter

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S U M M A R Y

Organ shortage is one of the most pressing issues concerning the field of transplantation. Non Heart Beating Donation (NHBD) has long been recognized as a potential tool to increase the size of the donor pool. In this study we have discussed the common issues, controversies and current trends relating to NHBD and possible solutions to establish a successful programme.

1. Introduction

Organ transplantation is now considered as a gold standard treatment for many end stage organ diseases and also for some life limiting conditions. Over the last few decades the field of transplantation has evolved immensely owing to its exceptional success in improving quality of lives and long term patient survival. The demand for human organs has now superseded the supply all around the world. Infact the demand in the UK is so overwhelming now that there is a considerable discrepancy in between the number of organ donors and number of patients on the waiting lists.[1] Therefore organ shortage is now one of the most important current challenges for the transplant fraternity pressing for urgent collaborative efforts to be made to increase the donor pool worldwide.

In the current scenario, organs from Heart Beating Donors (HBD)/Donation after Brain Death (DBD) are most commonly used all over the world and constitute the bulk of the donor pool globally. However the margins of the donor pools have started to vary considerably amongst different nations, with more and more attention being given to explore alternative organ sources such as living donation and Non Heart Beating Donation (NHBD)/Donation after Cardiac Death (DCD).[1,2] Living donation of kidneys is already very popular and is being widely practiced all over the world. Living lobar transplants for lung and liver disease are generating interest, although the practice is limited. Non Heart Beating Donation (NHBD) is also gaining recognition and is proving to be another such important alternative. Overwhelming evidence is available now to support for its effectiveness in expanding the donor pool.[3] In centers with well established programmes, NHBD has been reported to constitute almost 1/3rd of the donor pool.[3,4] Despite this, there seems to be some unwillingness amongst many nations to adopt the programme. In Europe, countries such as Germany, Hungary, Poland and Croatia, still do not legally allow NHBD (except for Maastricht Category IV). In Italy and Portugal, NHBD has not been practiced so far and France just has a pilot programme, despite not having any legal restrictions within these countries.[5] In this study, we aim to discuss the issues and controversies surrounding NHBD and highlight its potential as a major source for human organs in the 21st century.

2. History and current trends in NHBD

In 1950–60's – the early era of human organ transplantation, the initial transplants in humans were carried out using organs from Non heart beating donors.[6] The success rate at that time was very poor in comparison to modern standards. This is not surprising given the fact that little was known at that time about things such as the impact of ischaemic times in terms of graft survivals, techniques of organ preservation, organ preservation fluids, immunosuppressive agents and recipient care, etc. And therefore soon after the introduction of the concept of brain death in 1968,[7] when death could be confirmed in the absence of a cardiac standstill and thus organs could be retrieved with minimal warm ischaemic damage; heart beating donation (HBD) started gaining universal preference. HBD was then presumed to provide superior organ preservation

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quality and thus better long term graft survivals. It was only by early 1980's, that the notion of NHBD was re-explored in the wake of increasing organ demand and in a time when the knowledge in the field of transplantation and immunology had vastly improved from before. Pioneered by the Maastricht group in the Netherlands, they introduced a classification system of NHB donors which is now universally accepted. The donors are classified using four definitions; Category I (Found dead), Category II (Failed cardio-respiratory resuscitation), Category III (Non brain dead, withdrawal of support) and Category IV (Brain dead, cardio-respiratory arrest).[8] Category I and II are also called as uncontrolled donors as the death occurs outside the hospital or within the emergency room and resuscitation is continuing and unpredictable. Conversely Category III and IV are called as controlled donors as the death occurs within an intensive care unit/hospital setting and withdrawal of treatment is planned by the patient's medical team.[9] NHBD organs essentially have to suffer a period of primary warm ischaemia; the time period between sub-optimal perfusion/complete circulatory standstill in the donor, and commencement of cold perfusion.[9] This warm ischaemic period is shorter in the controlled donors and more pronounced in the uncontrolled. Although the warm ischaemia in itself does not preclude successful transplantation, it is the combination with cold ischaemia that is particularly damaging, which further is amplified at reperfusion with the generation of free radicles, leading to severe reperfusion insult.[10] This ischaemic/reperfusion injury cascade is primarily responsible for causing significant tissue dysfunction and ultimately organ failure.[9]

Most centers with an established NHBD programme therefore prefer using category III and IV donors (controlled donors) which effectively suffer minimal primary warm ischaemic insult. However, the time period of sub-optimal perfusion in such donors can be quite variable and essentially dictates the type and quality of organs used. Generally, most abdominal organs are considered best to be retrieved if the death occurs only within first hour after the withdrawal of treatment. Kidneys nevertheless can survive for longer durations, suffering nearly for as long as 4–5 h of sub-optimal perfusion. And if the patient does not die within this time gap, the donation process is then cancelled.

Kidney transplantation from NHBD's (both controlled and uncontrolled) is already well established[3,8,11–13] and the use of other solid organs (usually from controlled NHBD) such as liver, lungs and pancreas is also gaining considerable interest. For controlled donor livers, the results have been encouraging so far in terms of reasonable graft survivals[10,14–16] but in terms of long term complications, some centers have reported a word of caution of an increased incidence of ischaemic cholangiopathy in post transplant patients.[14,15,17] Early results of NHBD Lung transplants using controlled donor organs have also been very promising in centers around the world. The incidence of primary graft dysfunction in such lungs is almost nil in comparison to 10–20% in HBD lungs.[18] The inherent ability of the inflated lungs to withstand long warm ischaemic times[19] and the absence of damaging inflammatory sequelae of brain-stem death are believed to be the possible reasons for this success.[18] Infact the general consensus amongst the lung transplant surgeons now favours NHBD lungs in comparison to lungs from HBD.[18] Similar success stories have also been reported after pancreas transplants from controlled NHBD. Their long term outcomes have been reported to be comparable to HBD's[20,21] and the current evidence now even favours for such pancreas to be used for islet cell transplants.[22,23]

However, in contrast to the controlled donors organs from uncontrolled donors (category I and II donors) are not used by many. Their usage is restricted due to increased risk of organ damage caused by extended warm ischaemic times and thus increased risk of primary non function. Currently organ procurement from such donors is primarily limited to the kidneys, partly owing to their ability to endure relatively longer warm ischaemic times, and partly due to the availability of renal replacement therapy in cases of delayed graft function/primary non function. In the UK, our center in Newcastle is the only unit in the country successfully using Maastricht category II kidneys, in addition to the controlled donor organs.[12,24] The Madrid group also have reported impressive results after using uncontrolled donor organs including even category I donor kidneys.[3] However, in their study, Category I donors although dead on arrival, had a witnessed arrest, so the agonal time period was known in those patients, which usually is unknown in patients who arrest outside a hospital setting. Nonetheless, in addition to this impressive success with the kidneys, various other Spanish groups have also successfully transplanted other solid organs from uncontrolled donors such as livers from category II donors[16] and lungs from category I donors.[25] Their experience with the Livers is encouraging given that the 2 year graft survival is 83% using cardiopulmonary support as a preservation technique,[16] with the main drawback being on increased incidence of biliary complications in the recipients.[17] Their lung experience is so far limited to only 2 patients, both recovering well and satisfactorily discharged.[25]

3. Donation rates

The overall donation rates generally vary quite considerably all around the world. Even all across the UK, the donation rates have been found to vary from region to region. Average organ donation in the UK for the year 2008 was 13.4 per million population (pmp). These donation rates were recorded highest in Wales at 15.2 per million population (pmp) for the year 2007–08, followed by 13.6 pmp in England, 12.8 pmp in Northern Ireland and 10.6 pmp in Scotland.[1] As in most parts of the world, bulk of the organ donations in the UK is from HBD's. Currently there are 20 renal transplant centers/alliances in the UK and 17 are running a NHBD programme[1] with only Newcastle running an established programme using even Maastricht category II donors. NHBD in the UK has seen a steady growth over the last decade. In the year 1998–99, NHBD contributed by only 3% (30 donors) to the total donor pool. The contribution continued to rise slowly to reach 12% (200 donors) in 2007–08.[1] Of those generous 200 donors 98% (195) were able to gift a kidney, 44% (87) donated a liver, 26.5% (53) gave a pancreas whereas, thoracic donation was made possible in 6% (12). As a result, 341 additional kidneys, 68 more livers and 36 more pancreas were transplanted last year due to the generosity of non heart beating donors.[1] This overall growth in the organ donation rates although indicates a steady progress but still is far from its maximum potential.

4. Problems with non heart beating donation

4.1. Logistics

Running a successful and an efficient NHBD programme essentially requires a mix of highly skilled teams working closely with each other such as transplant coordinators, Intensive care and Accident and emergency staff, organ retrieving/transplanting team and teams providing tissue cross-match results, etc. Once a potential donor is identified and referred, a multitude of tasks need to be performed by the transplant coordinators; all within a very restricted time frame. It involves from the very difficult task of discussing and obtaining a full and informed consent from the distraught family and friends of the donor, informing all the members of the retrieval teams, liaising with the operating theatre staff to arrange for a suitable theatre space and personnel and