

Beggars Can't Be Choosers: Deceased Donor Liver Transplantation Donor Pool Expansion – Our Experience

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Abstract: *Introduction:* Liver transplantation is today the most sought after treatment for patients suffering from end stage liver disease. Unfortunately, organ donation has not kept pace with this rising demand, and a greater number of patients are dying each year while awaiting deceased donors. We are one of the leading centres in the country who are doing deceased donor liver transplantation (DDLT) regularly since 2007 and have changed our donor selection criteria to keep pace with this increasing demand. *Aims and Objectives:* To review the changing pattern of donor demographic profile from Mar 2007 till Jul 2014 and see the outcome of deceased donor liver transplantation using marginal grafts. *Materials and Methods:* It is a retrospective study. Donor and recipient data for liver transplantation at our centre from Mar 2007 till Jul 2014 were analysed. Donors were labeled as marginal donors based on presence of certain adverse parameters. Incidence of early graft dysfunction and primary non function of graft were primary endpoints while major post operative complications were the secondary endpoints of the study. *Results:* A total of 52 retrievals were divided into 2 groups based on the presence of the adverse factors: consisting of 38 marginal grafts and 14 ideal grafts for liver transplantation. While comparing the primary endpoints of the study it was noted that except early graft dysfunction (EGD), other parameters like incidence of primary non functioning graft (PNF) and mortality were comparable in both the groups. However, the incidence of (EGD) was more in the group which received marginal grafts. The secondary endpoints of the study like incidence of major postoperative complications, hepatic artery thrombosis (HAT), portal vein thrombosis (PVT), hepatic venous outflow tract obstruction (HVOTO) and biliary strictures were similar in both the groups. There were a total of six deaths within 1 year of transplant, 3 in each group. The causes of mortality within 30 days post transplant were PNF, excessive bleeding and HAT. While sepsis was responsible for deaths after 30 days. *Conclusion:* Marginal grafts do provide an immediate and significant expansion of the existing donor pool. Although beggars can't be choosers but by using any type of marginal donors we cannot compromise on the outcome of DDLT. So there is need for a prospective, multi centre data to define risk and delineate guidelines for ideal and marginal donors. The numbers in this study are small but it clearly indicates that marginal donors can be safely used in judiciously selected recipients for an acceptable outcome.

Keywords: deceased donor liver transplant, marginal donor, extended criteria donor

1. Introduction

Liver transplantation is today the most sought after treatment for patients suffering from end stage liver disease. In response to the increasing demand for liver transplantation, both number of transplant centres and number of patients on waiting lists have grown rapidly [1]. Unfortunately, organ donation has not kept pace with this rising demand, and a greater number of patients are dying each year while awaiting deceased donors [2]. The situation is even worse in our country. Brain stem deaths are infrequent, so more and more centres in our country have resorted to living donor liver transplantation (LDLT) to cope up with the increasing demand [3]. We are one of the leading centres in the country who are doing deceased donor liver transplantation (DDLT) regularly since 2007 and have changed our donor selection criteria to keep pace with this increasing demand.

2. Aims and Objectives

To review the changing pattern of donor demographic profile from Mar 2007 till Jul 2014 and see the outcome of deceased donor liver transplantation using marginal grafts.

3. Materials and Methods

It is a retrospective study. Donor and recipient data for liver transplantation at our centre from Mar 2007 till Jul 2014 were analysed. Donors were labeled as marginal donors based on presence of > 2 of the following factors: (1) age > 60 years; (2) macrovesicular steatosis > 30%; (3) prolonged

intensive care unit (ICU) stay (> 4 days); (4) hemodynamic risk factors (any two of the following): prolonged hypotension (systolic blood pressure < 60 mm Hg for more than 2 hours), use of dopamine > 10 mcg/kg/minute for more than 6 hours to sustain blood pressure, and need for 2 inotropic drugs to sustain donor blood pressure for more than 6 hours; (5) Deranged liver function test (any two of the following): Serum bilirubin > 2mg/dl, AST > 170 IU/L, ALT > 140 IU/L; (6) Increased Total Leucocytes Count (TLC) > 12000/cumm; (7) cold ischemic time > 12 hours; and (8) hypernatremia (Na peak > 155 mEq/L) before aortic cross clamp.

Primary Endpoints

- Incidence of Early graft dysfunction (EGD) which is defined as presence of at least one of the following— serum bilirubin >10 mg/dL on postoperative day 7, INR ≥ 1.6 on postoperative day 7, and ALT or AST > 2,000 IU/mL within the first 7 days.
- Incidence of primary non function of graft (PNF), defined as non life-sustaining function of the liver requiring retransplantation or leading to death within 7 days after liver transplantation.
- Mortality on day 7, 30, 6 months and at 1 year.

Secondary Endpoints

- Incidence of major post operative complications graded as Clavien Dindo grade 3 or above.
- Incidence of portal vein thrombosis (PVT), hepatic artery thrombosis (HAT), bile duct strictures and hepatic venous outflow obstruction (HVOTO).
- Length of ICU stay and length of hospital stay.

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4. Results

A total of 120 brain stem deaths were counselled at our Institute. Out of which 34 successful multi organ retrieval were done (conversion rate - 30%). We have performed retrievals from other hospitals in our state (Delhi/NCR) and few from other states (14 from hospitals of Delhi/NCR and 4 were interstate transfers). The causes of death in donors are as shown in Fig 1. More than half of the donors had intra cerebral bleeds as the cause of death. The causes of rejection of a deceased donor was analysed and compared between two periods during the study (2007-2008 and 2009 till Jul 2014) and shown in Table 1. It is seen that donors with TLC >12000/cumm, steatosis >30%, raised liver enzymes twice the normal value, serum sodium >155meq/L and hemodynamic instability which were factors for rejection during the former period did not influence the acceptance criteria in the later period.

A total of 52 retrievals were divided into 2 groups based on the presence of the adverse factors: consisting of 38 marginal grafts and 14 ideal grafts for liver transplantation. The clinical and biochemical parameters were comparable in both the groups and highlighted in Table 2.

During the study period a total of 53 DDLT (including one split liver transplant) were performed. The recipients being transplanted with grafts from both the groups were comparable with respect to pre and per operative parameters (Table 3).

While comparing the primary endpoints of the study it was noted that except EGD, other parameters like incidence of PNF and mortality were comparable in both the groups. However, the incidence of EGD was more in the group which received marginal grafts. The secondary endpoints of the study like incidence of major postoperative complications, HAT, PVT, HVOTO and biliary strictures were similar in both the groups (Table 4).

There was a total of six deaths within 1 year of transplant, 3 in each group (Table 5). The causes of mortality within 30 days post transplant were PNF, excessive bleeding and HAT. While sepsis was responsible for deaths after 30 days.

5. Discussion

The increasing shortage of deceased donors has in a way compelled transplant centres over the world to use marginal donors. The initial dogma of poorer outcome using marginal grafts is now gradually fading away and more and more centres are using grafts with increasing adverse factors [4-7]. The situation is even worse in our country where the incidence of declaration of brain stem deaths is not a common practice [8, 9]. So a large number of these potential donors get unnoticed. As an alternative measure more and more centres in our country are doing LDLT routinely for end stage liver disease [10]. We are one of the centres in the country who are performing DDLT regularly since 2007 [11].

The initial step in the acceptance of marginal donors is to identify those that will result in poor survival as a result of

sub optimal function, or disease transmission to the recipient. The differentiation of a donor as standard versus marginal should be based upon evidence based literature that reflects the present state of the art in liver transplantation. However, the liver transplant literature is filled with contrasting guidelines differentiating standard donors from marginal donors [12, 13]. Much of the rules for utilisation of deceased liver were written in the late 1980s and early 1990s at a time when most liver transplant programs were within the learning curve for operative procedures and outcomes were yet to be known [14, 15]. During the initial years of transplantation our criteria for donor selection were very stringent but however, with growing experience and encouraging results from the western world we started expanding our donor selection criteria. Thus the use of a specific organ depends on protocol set by the transplant centre, judgment of the transplant surgeon, and needs of the recipient. A large number of single centre studies have identified predictors of potentially poor graft function, and with the increasing scarcity, utilisation of marginal organs with satisfactory outcome has become quite common. However, the outcome which is of concern is "Graft malfunction," which has multifactorial etiology. It is of varying severity; the severest form is the irreversible state of primary non function, with less severe forms exhibiting reversible graft dysfunction termed as early graft dysfunction. PNF is the most severe end result of initial allograft malfunction and may occur in 1.4 % to 8.5 % of cases following orthotopic liver transplantation and requires urgent retransplantation to avoid mortality [14, 16-18].

It is important to note that it is not only the adverse donor factors but also recipient factors along with operative factors which influence the outcome of DDLT [19]. However, the present study focusses on the influence of marginal donors on outcome. Although both the ideal and marginal groups were well matched, whether other recipient and operative factors were also responsible for the outcome were not within the purview of this study, which is a major drawback of this study.

In this study, 73% of the grafts used were marginal grafts. The incidence of use of marginal donors has been higher than in most other centres that have reviewed the subject. This may be because of differences in graft grading score systems being used and local deficiencies in donor maintenance [20]. There is no consensus regarding a universally accepted grading system for assessing liver graft quality. Therefore these grading systems vary from centre to centre and so it is reasonable to assume that grafts were classified in different categories depending on the system adopted. Regarding local deficiencies in donor maintenance, it is difficult to compare organ procurement in our country with centres from other developed countries. In India, there is no accepted donor maintenance protocol and vary from centre to centre. These deficiencies in India may influence graft quality, thereby causing a higher incidence of marginal liver use.

The overall rates of EGD and PNF in the present study were 21.2 % and 1.9 %, respectively. This is similar to most reported studies [21-25]. Ploeg et al. reported that the rate of EGD was 22 %, and that of PNF was 6 % [17]. However, when we compared the incidence of postoperative complica-

tions in the recipients of ideal and marginal group, it was seen that except the rate of EGD all other complications were comparable in both the groups. The 1- and 6-month survival rate were similar in both the groups and comparable to those of Bachella et al. [26]. In this study, we observed that the first month following transplantation was decisive for defining the overall marginal graft outcome. Some authors have used all marginal grafts and managed any EGD by means of aggressive retransplantation [27]. However, this wouldn't be an ethical practice in our country where DDLT isn't so common and there is no concept of super urgent status for organ allocation.

Identification of marginal donors that provide graft and patient survival equivalent to ideal donors will be important to minimise wastage of useable livers. In our study we have used livers from donors of elderly age group, raised liver enzymes, presence of hypernatremia, raised total leucocyte count and with significant steatosis without significantly compromising the outcome of the recipients. Although all these factors have been identified as risk factors for EGD and PNF in various studies [14, 28-31]. Although not within the purview of this study however, it is important to identify recipient who would perform poorly with marginal grafts. Poor risk recipients should not receive marginal grafts. Thus judicious use of marginal grafts in selected regoup of recipients will definitely have good and comparable outcomes. Moreover, there are certain factors which can modify the outcome by minimising the stress on the already physiologically compromised liver grafts. They are : 1) reducing the cold ischemic time, 2) use of strict donor maintenance protocol at the intensive care unit and 3) use of piggyback technique in caval reconstruction to decrease the warm ischemic time [32-33].

6. Conclusion

To summarise marginal grafts do provide an immediate and significant expansion of the existing donor pool. However, due to organ scarcity more and more centres are using marginal donors. Although beggars are not choosers but by using any marginal donors we cannot compromise on the outcome of DDLT. So there is need for a prospective, multi centre data to define risk and delineate guidelines for ideal and marginal donors. Such data would likely expand the existing deceased donor pool by encouraging the utilisation of donors that are currently deemed unsuitable for transplantation. The numbers in this study are small but it clearly indicates that marginal donors can be safely used in judiciously selected recipients for an acceptable outcome.

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Table 1: Changing Pattern in Rejection Criteria of Donors Since 2007

VARIABLES	2007-08	2009 – JUL 2014
TLC	< 12,000/cumm	No signs of gross sepsis/ bowel ischemia
Steatosis (on visual inspection)	< 30 %	30-50% (normal liver enzymes)
Liver enzymes	< 2 times the normal values	< 1000 IU/L
Serum Sodium	< 155 mEq/L	No definite upper limit
Hemodynamic instability	Rejected	Accepted

Table 2: Demographic, Clinical and Biochemical Parameters of the Donors

Variables	Marginal (38)	Ideal (14)
Age (mean ± SD)	56.36 ± 16.94	34.76 ± 26.21
Gender M/F	21/17	7/6
ICU stay (mean ± SD)	4.1 ± 1.33	2.73 ± 0.65
Dopamine > 10 mcg/Kg/min	11(29%)	1(8%)
Use of > 2 vassopressors	28 (74%)	3 (23%)
AST (IU/L), mean ± SD	234.4 ± 78.53	98.56 ± 22.21
ALT (IU/L), mean ± SD	178.7 ± 49.06	86.45 ± 18.45
Total Bilirubin (mg/dL), mean ± SD	1.46 ± 0.56	1.21 ± 0.48
Serum Sodium (mEq/L), mean ± SD	154.34 ± 9.92	138.3 ± 6.34
CIT (hrs), mean ± SD	4.5 ± 1.5	4.3 ± 0.97
Hepatic Steatosis >30 %	12 (32%)	1 (8%)

Table 3: Recipient Characteristics in Both the Groups

Variables	Marginal (N=38)	Ideal (N=15)
Gender; M/F	29/9	11/3
Age; (mean ± SD)	39.56 ± 11.89	41.24 ± 13.4
MELD score; (mean ± SD)	17.45 ± 3.69	17.02 ± 4.81
CTP score; (mean ± SD)	9.69 ± 1.89	9.38 ± 1.31
WIT; min, (mean ± SD)	43.38 ± 10.09	44.23 ± 12.43
Serum Sodium; mEq/L, (mean ± SD)	126.3 ± 3.14	127.1 ± 2.04
Massive Transfusion (%)	36.4%	34.3%

Table 4: Postoperative Outcome In Both The Groups

Variables	Marginal; N=38 (%)	Non Marginal; N= 15 (%)
Primary Non function (PNF)	1 (2.6%)	0 (0)
Early graft dysfunction (EGD)	9 (23.6%)	2 (14.3%)
Hepatic artery thrombosis (HAT)	3 (7.9%)	1 (7.2%)
Portal Vein Thrombosis (PVT)	1 (2.6%)	0 (0)
Biliary Stricture	4 (10.5%)	2 (14.3%)
Other Complications; Clavien Dindo Grade (3 or above)	10 (26.3%)	3 (21.4%)
ICU stay; days, (mean ± SD)	9.6 ± 2.4	9.43 ± 1.9
Hospital stay; days, (mean ± SD)	35.2 ± 9.56	33.2 ± 10.67

Table 5: Causes of Mortality in Both the Groups

Causes of Death	Marginal (n=3)	Ideal (n=3)
PNF	1	0
HAT	1	1
Sepsis	1	0
Bleeding	0	2

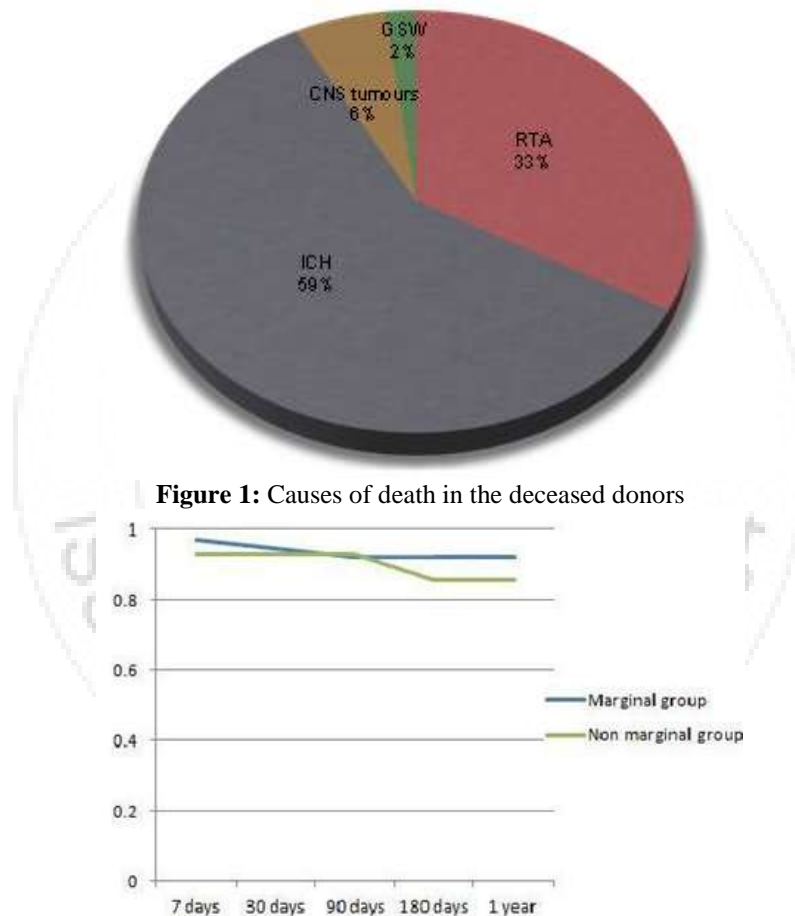


Figure 2: Survival analysis in both the group

