Split liver transplantation

Moorlock, Greg; Neuberger, James; Draper, Heather

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INTRODUCTION

This paper will explore the ethical issues raised by the use of split liver transplantation to meet the shortfall of donated livers, and particularly the shortfall of grafts suitable for children. It will be argued that adults carry a significant adverse consequence from the burden of paediatric liver transplantation, particularly via split liver transplantation, and that this makes adults worse off. Although split liver transplantation is an effective method of increasing the number of children receiving transplants it masks the more fundamental problem of low paediatric donation rates and may provide a disincentive to addressing this underlying issue.

Liver transplantation has the capability to significantly extend and improve the lives of those who receive transplants. There is, however, a chronic shortage of livers available for transplantation.[1] Many patients endure long periods of ill-health before receiving a transplant, and up to 20% die or become too ill to receive a transplant before a graft becomes available. In the UK, 1186 patients were added to the National Transplant Waiting List during 2013/14 in the UK and adult patients wait on average 145 days for a liver transplant.[2](NHSBT Liver Activity) Between April 2013 and March 2014, 81 liver patients died while on the waiting list, and 134 patients were removed from it.[2] Experiences are similar in other countries.[3] Demand exceeding supply has been a consistent feature of liver transplantation, and this seems set to continue, particularly as improvements in transplantation means that it becomes the indicated treatment for more medical conditions. The shortage of livers poses a significant problem for the paediatric population because liver size is an important factor when selecting a recipient. A whole liver from an adult donor is normally too large for a child[4] which reduces the pool of potential suitable donors to other children or small adults. The situation is exacerbated because paediatric organ donation is itself rare.[2] The impact of the organ shortage on affected children is difficult to gauge as figures vary from country to country. Some have reported paediatric waiting list mortality of nearly 40%,[4] whereas others claim around 20%[5] prior to efforts to resolve the situation. Given the discrepancy between supply and demand for paediatric livers and its associated impact on the affected population, measures needed

to be taken to address the short-fall in potential grafts. Mortality rates improved significantly as a result, and paediatric waiting list mortality in the UK is now generally under 5%.[6]

REDUCED SIZE GRAFTS AND SPLITTING LIVERS

An early approach to resolving children's low access to livers was to divert adult livers to children[7] by 'cutting-down' adult-sized livers from deceased donors. This resulted in a smaller graft suitable for a paediatric recipient. Each additional liver transplant this provided for a child meant one fewer liver transplant available for adults. The technical and practical aspects of this approach (subjecting the donated liver to dissection and additional time outside the body) increased the risks associated with these livers compared with the equivalent whole liver. The increased risk of post-transplant morbidity and mortality therefore had to be balanced against an increased equality of access for children and avoidance of mortality on the waiting list.[8] Advances in transplantation technology and expertise have since enabled some donated livers to be split into two *useable* parts, with the left lobe going to a child or small adult, and the right lobe going to an adult.[4] This, in principle, increases the number of liver transplants for children, without decreasing the number of transplants for adults, and has therefore rendered the earlier form of cutting down livers obsolete.[7]

THE IMPACT OF SPLITTING LIVERS

Although split liver transplantation offers a better solution to the paediatric organ shortage than reduced-size transplantation, it does not create two excellent livers from one excellent liver. Instead it creates a reasonably low risk graft for a child, and a higher-risk (compared to the same liver whole) graft for an adult.[9] Although more people receive transplants as a result of splitting livers, the risks associated with the transplants are increased for adult recipients.[10] Data from the European Liver Transplant Registry suggest that the rate of 3-month mortality post-transplant is nearly twice as high for a split liver as for a whole liver donated after brainstem death (DBD),[11] for example, which is believed to be as a result of increased biliary complications with split livers.[12] To mitigate the increased risks, it is important

that livers that are split are of good quality, and various factors such as the way in which the donor died, the donor's age and the donor's lifestyle can affect the 'quality' of the liver. Some caution must be taken in interpretation of these data as there was no adjustment for case mix.

In the UK, allocation policy is proposed by the Liver Advisory Group (LAG) of NHS Blood and Transplant; the current policy specifies that livers from donors whose death has been diagnosed using brain-stem criteria, who are less than 40 years of age, who weigh more than 50kg and whose stay in ITU was less than 5 days must be offered for splitting.[13] Because these criteria are narrow, only a relatively small proportion of donated livers are considered for splitting. The potential adverse consequences for adult recipients of split lives may explain why there are compulsory criteria for consideration of liver splitting in the UK: an adult liver transplant centre might otherwise be reluctant to see the best livers split to benefit patients outside their centre given that one of their own patients could benefit more from a whole liver than from a split one.

Data on how the relative gains and losses of splitting livers compare are mixed, and outcomes vary from centre to centre: Collett *et al*, in the UK, found that the gains to children were less than the losses to adults.[14] Malik *et al* have compared outcomes of split livers and livers donated after circulatory determination of death (DCD) at a single UK transplant centre, and found that adults' outcomes with split livers were less favourable than with livers from DCD donors,[12] although this has been contested and conflicts with findings by other transplant centres.[15,16] Some of the discrepancy may be attributed to variations in the pattern of splitting and centre experience but recent UK data have shown that a comparison of unadjusted transplant survival (either death of patient, or graft failure) outcomes between split liver and whole liver adult recipients done between 1st April 2009 and 30th September 2012 shows no difference.[17] When transplants from 1st April 2006 and 30th September 2012 are considered, transplant survival outcomes for adult recipients of split livers are slightly worse than for whole livers. [17] Although a risk-adjusted analysis is required for more valid comparison, the data may

suggest that split liver outcomes are improving. Other recent research from the US has suggested that outcomes (in terms of patient/graft survival) for both paediatric and adult split liver recipients are equivalent to outcomes for whole liver transplants.[18,19,20] There has been a suggestion in the literature that since the splitting of livers is a complex procedure, there has been a distinct learning curve.[19] Improvements in surgical techniques and expertise, along with lessons learned in donor selection and recipient matching may be responsible for the improved survival outcomes.

While graft/patient survival outcomes appear to have improved, many studies report increased complications with split livers.[21] A study conducted in the US found that adults have a reduced life expectancy with a functioning graft with split liver transplantation compared to receiving a whole liver, and suggested that receiving a split liver may therefore be an unattractive option to adult patients.[22] Although there is variance in outcomes from centre to centre, the relatively widespread use of split liver transplantation appears to suggest that split livers are considered to offer *acceptable* outcomes to adult patients. Splitting a liver does, however, as far as adult recipients are concerned, effectively convert an excellent relatively low-risk liver into a higher-risk marginal liver.[23] Using marginal or extended-criteria livers has become relatively uncontroversial, as in many cases having a transplant with a marginal liver is preferable to not having a transplant at all,[24] but it is perhaps more controversial to start with an excellent liver and make it marginal before transplanting it.[23]

ADULTS ARE WORSE OFF, BUT ARE THEY HARMED?

Splitting livers has raised some concerns in the transplantation community, and some people perceive that adults are suffering as a result of it. Collett *et al*, for instance, have suggested that "adults are being harmed while children are benefiting from a split liver programme".[14] This is a strong claim, and one which we think, upon further reflection, may not accurately capture the current situation.

First, one needs to be precise about the subject of the harm: in the case of splitting livers, although it may be possible to consider the harms on individual levels, this rapidly becomes complex. The uncertainties and risks inherent to transplantation mean that individuals can sometimes have their lives shortened or worsened, so all transplantation has the capacity to make some unfortunate individual patients worse off. To say that splitting livers harms individuals is therefore true in some cases, but not true in others, and at the time of transplant this is uncertain. To keep discussion manageable we will henceforth assume that the claim at hand is that the current policy of splitting livers results in adult patients being systematically harmed when considered as a group. All other things being equal, a group of people is worse off in situation B if they have lower *expected* utility than in situation A. Adult liver transplant patients as a group can therefore be considered worse off as a result of liver splitting because they are exposed to greater risks than if the same livers were kept whole.

Adults may be worse off, but whether they are harmed is another matter. If one considers a simplistic account of harm[25] (e.g. S is harmed if an event makes things worse for S, on the whole, than if the event had not happened), then splitting livers may appear to harms adults. If no splitting occurred, adults would have access to the best quality whole livers and would therefore be better off. Conversely, however, if it is possible to split livers and a decision is made to not do so, then potential paediatric recipients would be harmed. Under this account of harm, in times of shortage, practically *any* allocation decision is going to harm those who could receive benefit but do not. To say that a certain allocation decision or policy harms people, then, is trivially true in times of scarcity. In addition, although adults are worse off than if livers were kept whole, they still receive some benefit, as split livers still provide good outcomes in most cases. This account of harm does not accurately capture the nature of adults being made worse off in this situation: adults are still benefitting from liver transplants, but not as much as they could do.

Klocksiem makes helpful distinctions between harm and sub-optimal benefit, and suggests that the latter ordinarily falls short of constituting harm. According to Klocksiem, "S is sub-optimally benefited if S is benefited and there is another close counterfactual trajectory that involves greater welfare than the actual situation."[26] When considering the splitting of livers, a close possible alternative trajectory would be that of transplantation using only whole livers, which would likely result in better welfare for adults. Adult patients receive benefit from split liver transplantation, but less than the possible alternative of keeping the best livers whole. Of course, there are a range of close possible trajectories, and receiving a split liver is unlikely to be the worst. Split liver transplantation *does* seem preferable, for instance, to the other close possible trajectory, namely the previous practice of cutting down adult livers for use in paediatric transplantation (where adults would receive no benefit), so it is not the worst option for adults. Equally, receiving a split liver from a younger DBD donors may be better than receiving whole livers from elderly DCD donors that have their own increased risks.[27] The fact remains, however, that by splitting livers, adults as a group receive less benefit that if they had received the same livers whole. It therefore seems correct to say that adults are *not* harmed by split liver transplantation but are instead sub-optimally benefitted.

JUSTIFYING MAKING ADULTS WORSE OFF: EQUITY OR UTILITY?

Although it is incorrect to say that adults are harmed by split liver transplantation, they *are* made worse off by it than they otherwise could be, and this requires some, albeit less, justification. Just as not all instances of harm are instances of wronging, the same seems true of making people worse off if there is a morally defensible justification for doing so. One potential justification is simply that splitting livers makes children better off, as they would otherwise be severely disadvantaged in terms of waiting times and waiting list mortality (one need only look at pre-splitting statistics to see this).[4] Allocation in the UK aims to provide equity of access to transplants,[28] which splitting livers helps to achieve by providing more transplants to children , and this provides an argument in favour of the practice. Equity has the

potential to compete with other factors in organ allocation, such as utility, and how these should be balanced is always open to debate. As part of this balancing of competing factors, it is reasonable to accept that some utility may be compromised in favour of increased equity. Although split liver transplantation appears to increase overall utility,[22] one presumes that increasing equity was the justification for the introduction of its precursor, reduced size liver transplantation, and could also provide a justification for split liver transplantation if outcomes were, as suggested by some data,[14] somewhat worse. Some people argue that children should be prioritised *because* they are children (and a recent qualitative study found that this view was shared by many transplant patients and staff alike[29]). The argument from equity here, however, does not require appeal to any special property or quality that children possess by virtue of being children.

Splitting livers has proven very effective at reducing paediatric waiting times, which are now around half that of adults in the UK.[2] It has been so effective that the original problem of high waiting times for children in comparison to adults has been reversed: it is now adults who wait longer than children for liver transplants, so the equity argument alone cannot justify splitting livers. Indeed, the equity argument is only sound up to the point that adults and children are similarly well off in terms of access to liver transplantation. A secondary justification is therefore required to justify splitting livers beyond this point. As experience has been gained, outcomes have improved, which allows for this second justification of liver splitting to be formulated on the grounds of the extra benefit gained by splitting livers. Splitting a liver allows two people to benefit and therefore increases the benefit generated by each donated liver (even if one or both of the recipients fare slightly worse than if they had received a whole liver).

The overall situation is therefore relatively complex: diverting livers from adults to children could originally be justified by improvements in equity, even if this made adults worse off. The introduction of split liver transplantation, even with its initially inferior results, could be justified on the same grounds.

As techniques have been developed further, and outcomes and children's waiting times have improved, the justification for splitting livers has changed: it is now the overall utility gains that justify the practice, which outweigh the cost to adults.

But what of the original equity concerns? If, in the late 1980s and early 1990s it was desirable to improve the situation for children (a group faring relatively badly within transplantation) even though doing so rendered adults worse off), it would be inconsistent for similar adjustments not be considered for adults now that they are worse off than children and having to wait longer for transplants.

POSSIBLE SOLUTIONS

There are several ways in which equity between adults and children could be promoted. One option is to split fewer livers, which would increase paediatric waiting times back into line with adult waiting times, and adults would have improved access to the best quality livers. This would, however, likely reduce overall utility, since fewer people would be benefitting from liver transplants. This is therefore not an appealing option, as it shares many features of 'levelling down'. Levelling down occurs when equity is promoted by bringing down the welfare of one group to pull it into line with another, and there is no corresponding gain in welfare for the other group (so overall utility is reduced).[30] Although in this case there could be some gain in welfare for adults (they would have access to the best quality livers, and rates of complications/re-transplants may be lower), this would be outweighed by the loss to paediatric patients. To be clear, to split fewer livers would be a waste of the additional potential benefit that splitting liver offers to patients, and wasting benefit in this way is undesirable in times of shortage.

An alternative option is to sometimes change the way that livers are split, so that benefit is not lost but is instead distributed between two adults instead of an adult and a child. Some studies have shown that reasonable results can be obtained for adult recipients by performing full left/right splits on livers,[32,33] although risks of biliary complications are relatively high.[34] Because of the increased risks, this form of liver splitting is not widely used. If the technical obstacles associated with this form of splitting could be

overcome (and it is not currently clear that they can be), and satisfactory risk levels and outcomes achieved for two adults to benefit, then this could improve the situation for adults without reducing overall utility. Some livers that otherwise might have been split for an adult and child could instead be split for two adults, thus improving liver availability for adults. Paediatric patients may have to wait longer, but there would be a corresponding benefit to adults so it would not be levelling down. At present, the risks associated with this form of splitting suggest that it is perhaps best considered as a potential longer term solution. It is, however, important that boundaries are continually pushed. Performing transplants with increased risks may seem undesirable, but this must be balanced against the risks of patients staying on the waiting list. By performing only low-risk transplants, post-transplant mortality may be minimal, but waiting list mortality may be correspondingly high. Whilst there are people dying waiting for livers to become available, some level of post-transplant mortality is justifiable if it comes about as a result of trying to reduce waiting list mortality and provide more transplants. It is possible that, as with conventional splitting, techniques and expertise may improve over time and result in improved outcomes with full left/right splits, so the potential longer term benefits also need to be borne in mind.

A third option is to increase the number of living liver donations. Using techniques similar to deceased split liver transplantation, healthy adults are now able to donate part of their liver so that an adult or child can benefit. If this helped to meet demand for livers suitable for children, then fewer livers from deceased donors would need to be split, and adults would be better off as a result. The downside with this form of donation is the risk to perfectly healthy donors. The risks to the donor are generally considered acceptable, but are greater than kidney donation, for instance.[35] Living liver donation can provide excellent outcomes for recipients, but its capacity to cause harm to healthy living donors is undesirable. The risks associated with living liver donation have caused some controversy, which has been discussed elsewhere. [36,37] There is always going to be balancing of harms and benefits to carry out,

but it seems *prima facie* wrong to risk harming healthy individuals to benefit others if there are lower risk options available.

Arguments can be formulated in favour of each of these potential solutions, but none of them currently provides an ideal course of action. The first two options are simply adjusting the allocation of the existing supply of livers, promoting equity by making paediatric liver patients worse off than they currently are. The third option may increase the supply of donated livers, but since it is primarily adults who are living donors, it would again be adults carrying the burden of paediatric liver transplantation. There is a further option which, rather than papering over the cracks, directly tackles the underlying problem.

TACKLING THE UNDERLYING PROBLEM

We have argued that adults are primarily carrying the burden of paediatric transplantation and are worse off as a result. *Something* needed to be done to make up for the shortage of paediatric liver donors, and having access the supply of livers donated by adults has significantly improved the situation for children who need liver transplants. Our recent research[29] has shown that many adult patients are willing to carry this burden, but this does not mean that alternative solutions should not be explored.

Rather than adjusting allocation criteria to provide livers for children, or relying on adult living donors, increased efforts could be made to tackle the shortage of deceased paediatric donors. We must prefix this suggestion by acknowledging that there are many natural obstacles to paediatric organ donation, and some of these would require significant changes to overcome. For instance, many children who die will have received aggressive medical therapies, which may render organ donation problematic and some children suffer from diseases that make their organs unsuitable for transplantation. [38] Other barriers may pose reasonable restrictions. For instance, aspects of the donation process that could compromise the ordinary end-of-life care of children, as organ donation requires that the patient dies in hospital, but it is common for paediatric palliative care to aim to enable children to die with their family at home. Consent rates where organ donation *has* been considered for children are much higher for DBD

(72%) than DCD (37%),[39] which may suggest that some aspects of DCD are particularly off-putting to next-of-kin.

Efforts to identify and remove unnecessary barriers to organ donation for adults have resulted in many changes relating to how organ donation is presented to the next-of-kin, and in end-of-life care. [40] This has given many more adults the opportunity to become organ donors. Barriers to paediatric organ donation may be more difficult to overcome, but there have been recent calls for revision to policy to facilitate increased paediatric donation rates, [41] and the UK Donation Ethics Committee is about to publish a position paper on this issue.[42] It is certainly time to ask which barriers to paediatric donation can be robustly justified, and which barriers are acting as needless obstacles to ethical organ donation.

It is clear from existing data that the number of potential paediatric organ donors is relatively small,[41] so even maximising the rates of paediatric donation is unlikely to fully meet demand. This does not, however, provide a reason to not attempt to increase paediatric donation rates. As a result of the current low paediatric donation rates, successes in paediatric liver transplantation are largely a result of free-riding on the relative success of adult organ donation. Reconsidering or removing some of the barriers to paediatric donation, if this could be done in an ethical manner, would afford more children and their families the opportunity to contribute an important and life-saving resource. We accept that some barriers to paediatric donation are well-justified and it would be wrong to attempt to remove these. It seems dubious, however, for paediatric transplantation to continue dipping into the adult pool if it has not made strong efforts to improve its own pool. [43] Making these efforts and identifying and removing those barriers which can ethically be removed would benefit not just paediatric liver patients, but also the adult liver patients who currently silently shoulder the burden of the shortfall between supply and demand of livers for children.

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