FORUM

Graft implantation in liver transplantation - The clock is ticking

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This Forum discusses the paper by Al Kurdi et al: Short recipient warm ischemia time improves outcomes in deceased donor liver transplantation. Transpl Int. 2021:8;1422.

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In this issue of *Transplantation International*, Al Kurdi et al. report that both early liver graft function and long-term survival are affected by recipient warm ischaemic time (rWIT) [1]. The effect temperature has on cellular metabolism is well known, and the period in which the surgeon completes the implantation represents a time in which the graft temperature (and adenosine triphosphate consumption) is rising [2,3]. The rise in temperature of the liver graft during implantation has been previously assessed with needle probes [3,4] and ranges from 8.7° at 20 minutes and 17.2°C after 45 minutes of implantation [3] to 12.5°C after only 15 minutes [4], depending on the depth of measurements. According to the linear mode of temperature rise demonstrated by Hertl et al, the temperature a surgeon can expect the graft to be after rWIT of 30 minutes is 12.5-15.0°C. The nature of the graft insult during implantation is similar to that sustained during the donor warm ischaemic time (dWIT) in donation following circulatory death (DCD) and the retrieval hepatectomy [5,6]. Evidence that a prolonged rWIT has a negative effect on liver transplantation has been reported by other authors [6–9]. Al Kurdi et al. report the novel finding that attainment of rWIT below a certain time threshold, ideally ≤30 minutes, improves short- and long-term patient survival.

Al Kurdi et al (2021) performed a single-centre retrospective cohort study utilizing DBD liver grafts only with the aim to investigate the positive prognostic effect of a short rWIT (<30 minutes) on 1- and 5-year survival. Secondary outcomes were early allograft dysfunction (EAD) and intraoperative blood product transfusion requirement, the latter being used as a surrogate for intraoperative bleeding. Time-to-event analysis was stratified via rWIT (≤30, 31-40, 41-50 and ≥50 minutes), with a secondary analysis that also further separated based on CIT (≤6 and >6 hours). The risk of graft loss after 1 and 5 year was significantly lower in rWIT ≤30 minutes in comparison with all other groups. After dividing the cohort based on CIT, the prognostic benefit of rWIT <30 minutes became even more apparent for those receiving a graft with more than 6 hours of CIT. This indicates a potential interaction between longer CIT and rWIT, suggesting rWIT potentiates an established graft injury. The EAD rate was significantly lower in the rWIT ≤30-minute group (18%) in comparison with the 41-50 (30%) and ≥50-minute group (50%). The increase in EAD risk appeared to increase with each group in a nonlinear pattern.

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Despite solid methodology of the reported study, there remain some unanswered questions. Firstly, separation of rWIT >30 minutes into subsequent intervals of 10 minutes is clinically applicable but it may obscure the identification of either a linear or a nonlinear relationship with graft damage over time. Although rWIT was not included as a continuous variable in the present study, the relation appears to be nonlinear with an increasing effect size as rWIT lengthens. This is in contrast with a previous report, where the incidence of EAD increased in a linear manner by 15% for every 10 minutes rWIT [6]. Secondly, stipulating a reference standard of rWIT $\leq$ 30 minutes does not allow insight into whether outcomes can be further improved by keeping rWIT ultrashort (e.g. 15-20 minutes).

Variation in implantation time or rWIT may reflect both the complexity of the individual procedure as well as the technical skill and knowledge of the surgeon. A fine balance between the implant time, accuracy of surgical technique and perfectionism is required. Technical complications, such as venous outflow obstruction, portal vein stenosis or thrombosis, and bleeding, leading to graft loss, may occur if the implant is done in 'haste'. Authors do not provide the data on technical complications leading to graft loss and whether a quick implantation time comes at this expense. In addition to implantation time, the complexity of the recipient hepatectomy, vascular and biliary reconstructions may impact patient recovery and graft survival. These factors may be associated with a prolonged rWIT, but rWIT is not necessarily included in the corresponding causal pathway. The authors attempted to correct for potential confounding through a mediation analysis using total blood loss as an intermediate factor between rWIT and subsequent graft loss or EAD. This allows, to some extent, assessment of the 'direct' effect rWIT has on graft loss and EAD. Although the isolated effect of rWIT appears to be attenuated in the mediation analysis, the overall trends remained consistent. Although many donor and recipient characteristics were included in the risk adjustment, graft steatosis was not included in this study. Steatotic grafts are known to be more susceptible to necrosis during periods of ischaemia and subsequent reperfusion injury [10,11]. A prolonged period of warm ischaemia during implantation would therefore be expected to be more detrimental for steatotic grafts. Buccholz et al. demonstrated graft steatosis was in itself associated with a longer rWIT [7]. Graft steatosis and rWIT may therefore synergistically impact on outcomes.

Accumulated experience with different graft/recipient combinations may provide insight into the subtle aspects of each case that will make it more or less challenging. The choice of caval anastomosis technique, surgical efficiency, preparation of the operative field and awareness of the implications of rWIT all undoubtedly impact the implant time [12]. Although the graft selection is done with the best intent of ideal matching, it is not unusual to encounter grafts that are larger than expected, or a hypertrophied right lobe, which makes the caval anastomosis challenging. These cases require certain strategies to minimize implantation times. The impact of implantation time should be emphasized to surgical trainees, as they learn the key steps of caval and portal vein anastomosis, and should be considered by the lead surgeon when selecting the best individual for the task. Whilst the data in the present and previous studies are convincing for the benefits of keeping rWIT short, the question of how much shorter it should be remains unanswered. The balance between shorter implant times, complications and subsequent outcomes should be monitored in a robust manner. The advantage of the data presented in this manuscript is that it supports the findings of previous authors that outcomes get much worse when rWIT extends beyond 30 minutes; therefore, this could be viewed as an acceptable standard. Given the importance of rWIT on outcomes, we would suggest that it is reported more commonly in liver transplant clinical research.

Conflicts of interests

The authors have no conflicts of interest to declare.

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