TRANSPLANT TRIAL WATCH

Edited by Liset Pengel

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Randomized controlled trial 1

Double-blind placebo-controlled randomized trial of N-acetylcysteine infusion following live donor liver transplantation. Thirunavayakalathil MA, et al. *Hepatology International Hepatology International 2020*; *14(6)*: *1075–1082*.

Summary

Aims

This study aimed to examine the effect of N-acetylcysteine (NAC) infusion after live donor liver transplantation.

Interventions

Participants were randomized to either the NAC group or the placebo group.

Participants

150 live donor liver transplant recipients.

Outcomes

The primary outcome was the incidence of acute kidney injury (AKI) and early allograft dysfunction (EAD). The secondary outcomes were primary graft nonfunction, international normalized ratio, post-transplant hospital stay, intraoperative bleeding, mortality (in-hospital), levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine.

Follow-up

Immediate post-transplant period.

Jadad score

4.

Data analysis

Per-protocol analysis.

Allocation concealment

Yes.

Trial registration

CTRI/2015/12/09/006401.

Funding source

Not reported.

Extended commentary

Commentary on: Double-blind placebo-controlled randomized trial of N-acetylcysteine infusion following live donor liver transplantation. Thirunavayakalathil MA, Varghese CT, Bharathan VK, Chandran B, Nair K, Mallick S, Mathew JS, Amma BS, Menon, RN, Gopalakrishnan U, et al. *Hepatology International 2020*; *14(6)*: *1075–1082*.

N-Acetylcysteine (NAC) increases hepatic glutathione levels, giving it antioxidant properties that have been reported to reduce hepatic injury and confer renoprotection against acute kidney injury (AKI). This has led to interest in the use of NAC in the prevention of ischaemia reperfusion injury following transplantation. Previous studies have investigated the use of NAC in deceased organ donors, suggesting an improvement in liver graft survival, especially for suboptimal grafts [1]. However, a previous randomized controlled trial in deceased donor liver recipients

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demonstrated no clinical benefit to postoperative NAC infusion in liver recipients, albeit at relatively low doses [2].

In a study recently published in Hepatology International, Thirunavayakalathil and colleagues randomized 150 living donor liver recipients to receive NAC infusion or placebo (saline) for 91 h post-transplant [3]. Primary endpoint was a slightly odd composite of early allograft dysfunction and AKI, presumably as an overall measure of reperfusion injury. The study was well designed, and outcomes were well defined. The authors reported no difference in the primary composite outcome, or the constituents, although there were reductions in peak transaminase levels in the NAC group. There were no adverse events related to infusion.

The reduction in peak transaminase levels does suggest that NAC may play a role in reducing ischaemia reperfusion injury (IRI), although this does not seem to confer any short-term clinical benefit in terms of reduction in AKI, hospital stay, complication rates or graft survival (accepting that there is insufficient power for many of these outcomes). The failure of the trial to meet its primary endpoint is most likely due to an overoptimistic sample size calculation, based upon a proposed reduction in the incidence of the composite endpoint from 20% to 5%, whereas the real effect is likely much smaller.

Ultimately, the authors have recruited a population with a relatively low risk of the outcome of interest. It is likely that the benefits of NAC, if proven, are likely to be seen in those recipients receiving livers with a higher risk of IRI, such as steatotic livers or those from more marginal deceased donors. Further studies are needed to define those populations in which benefit may be greatest. NAC appears to be safe in this setting, and as a readily available, relatively cheap drug may have some promise.

REFERENCES

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2. Hilmi IA, Peng Z, Planinsic RM, *et al.* N-acetylcysteine does not prevent hepatorenal ischaemia-reperfusion injury in patients undergoing orthotopic liver transplantation. *Nephrol Dial Transplant* 2010; **25**: 2328.
3. Thirunavayakalathil MA, Varghese CT, Bharathan VK, *et al.* Double-blind placebo-controlled randomized trial of N-acetylcysteine infusion following live donor liver transplantation. *Hepatol Int* 2020; **14**: 1075.

Randomized controlled trial 2

Steering transplant immunosuppression by measuring virus-specific T cell levels: the randomized, controlled IVIST trial. Ahlenstiel-Grunow, T., et al. *Journal of the American Society of Nephrology 2020; 32(2) 502–516*. https://jasn.asnjournals.org/content/32/2/502.long

Aims

The aim of this study was to determine whether additional steering of immunosuppressive therapy by evaluating virus-specific T-cell (Tvis) levels optimizes dosing of immunosuppressants.

Interventions

Participants were randomized to either the intervention or control group, both of which received trough-level monitoring of immunosuppressive therapy. The intervention group received additional steering of immunosuppressive therapy by Tvis levels.

Participants

64 paediatric renal transplant recipients.

Outcomes

The primary outcome was estimated glomerular filtration rate (eGFR). The secondary outcomes were the incidence and number of acute rejections, viral infections, development of donor-specific antibodies, adverse events, serious adverse events, and doses and trough levels of immunosuppressants.

Follow-up

2 years.

CET Conclusion

This interesting multicentre study investigates the use of virus-specific T-cell activity for monitoring of immunosuppression (in addition to trough levels) in a paediatric kidney transplant population. The authors conclude that the monitoring strategy is safe and allows a reduction in immunosuppression exposure without compromising clinical outcomes. The primary endpoint of an improvement in eGFR at 24 months was not met. The study suffers from being underpowered – the original sample size calculation only allowed for a power of 50% to detect a 7.5 ml/min difference in GFR. It would be interesting to see larger studies with more conventional immunosuppression, and also in adult populations, to fully evaluate this monitoring strategy.

Jadad score

2.

Data analysis

Strict intention-to-treat analysis.

Allocation concealment

Yes.

Trial registration

ISRCTN89806912.

Funding source

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