LETTER TO THE EDITORS

Ex situ normothermic machine perfusion of donor livers using a haemoglobin-based oxygen carrier: a viable alternative to red blood cells

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Dear Editors,

With interest, we have read the systematic review by Eshmuminov *et al.* regarding porcine and human liver normothermic machine perfusion (NMP) [1]. The authors focused on studies using red blood cells (RBC) as oxygen carrier in the perfusion fluid and excluded studies using perfusion solutions based on artificial oxygen carriers. In their review, the authors state '*We excluded studies using artificial oxygen carriers. Results of studies with synthetic haemoglobin-based oxygen carriers (HBOC) were disappointing, even with stopping of the ongoing clinical trials by FDA due to safety reasons*'. We found this paragraph misleading as it suggests that studies on liver NMP using an HBOC have provided disappointing results. This, however, is not true. The German review article quoted by Eshmuminov *et al.* to support their statement does not mention the use of HBOC for *ex situ* NMP [2]. Potential side effects, such as described after *in vivo* clinical transfusion, are less likely to occur when an HBOC-based perfusion solution is used for *ex situ* NMP of donor livers, because the donor liver is extensively flushed prior to implantation. Moreover, although HBOC may not be as effective as RBC in treating severe anaemia in clinical trials, postmarketing experience in South Africa has recently resulted in FDA-approved clinical application for life-threatening anaemia in patients unable or unwilling to undergo RBC transfusion [3,4].

Several groups have reported experience with an HBOC-201 (HbO_2 therapeutics)-based perfusion fluid for *ex situ* liver machine perfusion, all of which showed favourable results [5–7]. Fontes *et al.* were the first to report on the use of an HBOC-based perfusion fluid in machine perfusion [5]. Subnormothermic machine perfusion was compared with static cold storage in a porcine liver transplantation model [5]. The machine perfusion group had a higher survival rate, better graft function and decreased reactive oxygen species (ROS) formation after reperfusion. Both Laing *et al.* from Birmingham and our group have reported a preclinical study on the efficacy of NMP with an HBOC-based perfusion solution using discarded human livers [6,7]. Laing *et al.* described improved vascular flow and decreased ROS formation after NMP with HBOC, compared to NMP with RBC [6]. We reported improved vascular flow, increased hepatic ATP concentration and increased bile production during NMP using an HBOC-based perfusion fluid, compared to NMP with RBC [7].

Based on the aforementioned studies and some unique properties of HBOC, such as the availability and the ability to be used at low temperatures, a clinical trial has been initiated in our centre to investigate the viability of high-risk donor livers using *ex situ* machine perfusion (www.trialregister.nl; NTR5972). Thus far, six extended criteria donor livers that were initially declined for transplantation nationwide were successfully transplanted after dual hypothermic machine perfusion, followed by controlled oxygenated rewarming and subsequent NMP, each phase using the same HBOC-201-based perfusion solution. All recipients are alive and clinically well, with 100% graft survival. Altogether, we strongly believe that HBOC-based perfusion solutions are a viable alternative to RBC for *ex situ* machine perfusion of the liver.

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Conflict of interest

The authors have nothing to disclose.

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