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The Authors' Reply

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Thank you very much for your comment on our manuscript "Results of the TOP Study: Prospectively Randomized Multicenter Trial of an Ex Vivo Tacrolimus Rinse Before Transplantation in EDC Livers."[1] We would like to take the opportunity to respond to the valuable comments of Kobayashi.[2]

In the tacrolimus organ perfusion (TOP) study marginal liver grafts exhibiting ≥ 2 extended donor criteria (EDC) were randomly flushed ex situ with Tacrolimus (20 ng/mL) dissolved in histidine tryptophane ketoglutarate (HTK) solution or with HTK only (control) to reduce ischemia reperfusion injury. Kobayashi suspects a potential warming of the grafts and harmful effects through this procedure. Facing this criticism, the authors state that the temperature of the rinse solution was 4°C at the beginning of the treatment (though it was not measured at the end of the perfusion as suggested by Kobayashi) and the procedure took on an average of 18 minutes only. Although the plastic bags containing the rinse solution were not cooled during the procedure (analogously with the systemic perfusion at organ harvesting), grafts undergoing the study treatment were continuously stored on ice until the beginning of implantation. Therefore, the authors assume a warming of the graft and a subsequent initiation of the hepatic metabolism to be extremely unlikely. Moreover, Kobayashi questions the anastomosis time and assumes that warm ischemia could counteract the protective effects of a rinse treatment. In this respect, he suggests a new in situ technique of organ perfusion. The authors would like to state that changes in the surgical procedure were beyond the scope of the TOP Study. Moreover, the rinse treatment itself was not the point of interest in our study, but to investigate the effects of Tacrolimus in a rinse of 1000 ml HTK compared to 1000 ml HTK only. Cava sparing transplantation including anastomoses was performed after the rinse treatment according to center specific standards in both groups. Therefore, the study treatment did not affect the time for vascular reconstruction. To the authors' best knowledge, a simple study treatment in combination with routine surgery is required to generate valid data in a multicentric trial in liver transplantation.

Kobayashi presents an interesting concept of an in-situ perfusion. The authors greatly appreciate any attempts (ie, organ preperfusion) to improve the utilization of EDC grafts. In this respect, an additional in situ flush of the graft may have protective effects. Nonetheless, this procedure does not represent an established procedure and would need to be evaluated in a prospective trial. Since the TOP study failed to show protective effects of Tacrolimus compared with control, this concept must be reevaluated and the authors suggest further analyses of this substance due to its proven anti-inflammatory effects. Therefore, an adjunct of Tacrolimus to an in-situ perfusion as described by Kobayashi or to machine perfusion could be an option to reduce ischemia reperfusion injury especially in EDC grafts thereby increasing the limited donor pool, which represents the most pressing problem in today's transplantation medicine.

REFERENCES

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