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Research Article

Goal directed preemptive ephedrine attenuates the reperfusion syndrome during adult living donor liver transplantation

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Abstract *Background:* End-stage liver disease is associated with marked hemodynamic disturbances that are further deteriorated during liver transplantation and is aggressively represented in the form of postreperfusion syndrome (PRS).
Aim: The aim was to test the hypothesis that preemptive ephedrine administration pre-reperfusion targeting a rational level of mean arterial blood pressure (MAP) of 85–100 mmHg, may reduce the incidence of PRS.
Patient and methods: One hundred recipients for adult living donor liver transplantation (ALDLT) were prospectively randomized into 2 groups; group C, control group and group E, who received ephedrine 2.5–5 mg/min starting 5 min before reperfusion till mean arterial blood pressure (MAP) reached 85–100 mmHg. Hemodynamic parameters including MAP, heart rate (HR), Transesophageal Doppler (TED) parameters including corrected flow time (FTc), systemic vascular resistance (SVR), and cardiac output (COP) were measured; just predrug administration, just before reperfusion, just after reperfusion, 5 min after reperfusion and at the end of surgery. Cold and warm ischemia times (C/WIT), duration of anhepatic phase and total duration of surgery were recorded. The incidence of PRS, the need of rescue vasoconstrictor for hemodynamic instability at time of reperfusion, need for postreperfusion vasoconstrictor infusions, over shooting of hemodynamics, postreperfusion fibrinolysis indicated by fibrinogen level and maximum lysis parameter of rotational thromboelastometry (ROTEM) were compared between both groups.
Results: The mean dose of ephedrine required was (12.5 ± 7.5 mg). Group E had statistically significant increase in MAP, SVR, and COP; just before reperfusion, just after reperfusion and

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5 min after reperfusion readings. There were no statistical significant differences between the 2 groups at the end of surgery. The incidence of PRS and the need of rescue adrenaline at the time of reperfusion, and the postreperfusion need for vasoconstrictor infusion decreased significantly in group E when compared to group C. Also postoperative mechanical ventilation decreased significantly in group E.

Conclusion: The preemptive goal directed titration of ephedrine against a target MAP pre-reperfusion could decrease the incidence of PRS by 40%, attenuated the hypotensive response to reperfusion and decreased the need for postreperfusion vasoconstrictor support without over shooting of any of the monitored hemodynamic indices.

1. Introduction

End-stage liver disease is characterized by hyperdynamic, hyporeactive circulation with reduced effective circulating volume, presented with increased COP, low SVR, and low arterial blood pressure [1]. Liver transplantation surgery adds further hemodynamic burden with significant instability which is aggressively presented in the form of PRS [2]. PRS occurs at graft reperfusion namely after unclamping of the portal vein and characterized by a marked decrease in systemic blood pressure, SVR, and a moderate increase in pulmonary arterial pressure [3]. The underlying mechanisms of these severe hemodynamic changes are complex. The immediate severe hemodynamic effects of PRS may be the result of the heart and vasculature being transfused from the new graft with a large bolus of acidotic, hyperkalemic, cold fluid containing other vasoactive agents that have an immediate deleterious effect on cardiac function and vascular tone [4].

Proinflammatory cytokines such as interleukin 6 or tumor necrosis factor alpha are produced during ischemia and are also possibly involved in the production of hypotension at that time [5,6]. Moreover, ischemia/reperfusion syndrome, occurring in every liver transplant procedure, could be correlated with the hemodynamic changes. PRS was considered when the mean arterial blood pressure was 30% lower than the previous value immediately at the end of the anhepatic stage and lasted for at least 1 min within the 5 min after unclamping [3,5,7], development of asystole, significant arrhythmias, or significant fibrinolysis requiring pharmacological intervention [8]. The reported incidence of PRS varies greatly (12–81%) with the study design [9–12].

PRS is important in that it is associated with increase in blood transfusion, a higher incidence of postoperative allograft loss, higher recipient mortality and worse outcomes [8,13,14].

Many trials have been attempted to attenuate the effect of RPS through either targeting the implicated mediators [9,15,16] or preventing the hypotensive response to the reperfusion event using vasoconstrictors [17–19].

This study tested the hypothesis that preemptive ephedrine administration pre-reperfusion targeting a rational level of MAP (85–100 mmHg) can reduce the incidence of PRS without over shooting of hemodynamics.

2. Patients and methods

After approval of the local ethical committee and written informed consent, recipients of ALDLT, in the period between May 2010 and January 2013 were prospectively considered for the study. Patients with cardiac dysfunction, including dysrhythmia, pulmonary hypertension, coronary artery disease, and valvular heart disease, patients on preoperative beta blockers, intraoperative hemodynamically unstable patients required additional intravascular volume and vasoactive drug infusion or had uncorrectable electrolytes and an acid–base imbalance for at least 10 min before reperfusion were excluded. Patients were randomly allocated via a computer-generated random number table to control group (group C) and ephedrine (group E) who received ephedrine 2.5–5 mg every minute (according to the response) starting 5 min before reperfusion till MAP reaches 85–100 mmHg. The volume of the injectate was adjusted to 10 mL containing 25 mg ephedrine and given 1–2 ml/min. via the external jugular line. An event marker was added to the anesthesia monitoring system, and the timer was started at reperfusion. The onset of hypotension was noted when MAP fell more than 30% within 5 min after reperfusion vs. the baseline level at the time of reperfusion and continued therefore more than 1 min. If the patients developed PRS, rescue incremental boluses of epinephrine (10 μg) each were given to restore hemodynamic stability. Patients who developed PRS received noradrenalin infusion when MAP continued to be < 60 mmHg after reperfusion despite adequate volume resuscitation.

Anesthetic management was the same in both groups. An intermittent rescue intravenous ephedrine 2.5 mg every minute was given for intraoperative hypotension (defined as a 20% decrease from baseline mean arterial pressure). An arterial pH less than 7.2 that was accompanied by a base deficit greater than 10 mmol/L was treated with sodium bicarbonate. An ionized calcium level less than 1.0 mmol/L was treated with calcium chloride, and hyperkalemia (> 6 mmol/L) after acidosis correction was treated with glucose/insulin infusion. TED probe (cardio QTM; Deltex Medical, Chichester, UK) was inserted orally and then the probe was rotated on its axis to achieve an optimal signal for hemodynamic monitoring and fluid optimization. All patients received Ringer's acetate: 6 mL kg^{-1} h^{-1} as a continuous infusion. TED protocol adopted by Ivan and colleagues [20] Fig. 1 was followed to correct hypovolemia using HES130/0.4. Albumin 5% was given for more colloid requirements and to compensate for half the volume of ascites if present.

Blood product transfusion was managed according to ROTEM based protocol [21] Fig. 2. FFPs were given in a dose of 10 ml kg^{-1}, cryoprecipitate in a dose of 1 unit 10 kg^{-1}, and platelets in a dose of 6–12 units to be repeated when indicated. HCT was kept always above 25% by giving PRBCs. Tranex-