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Research Article

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

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KEYWORDS
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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-

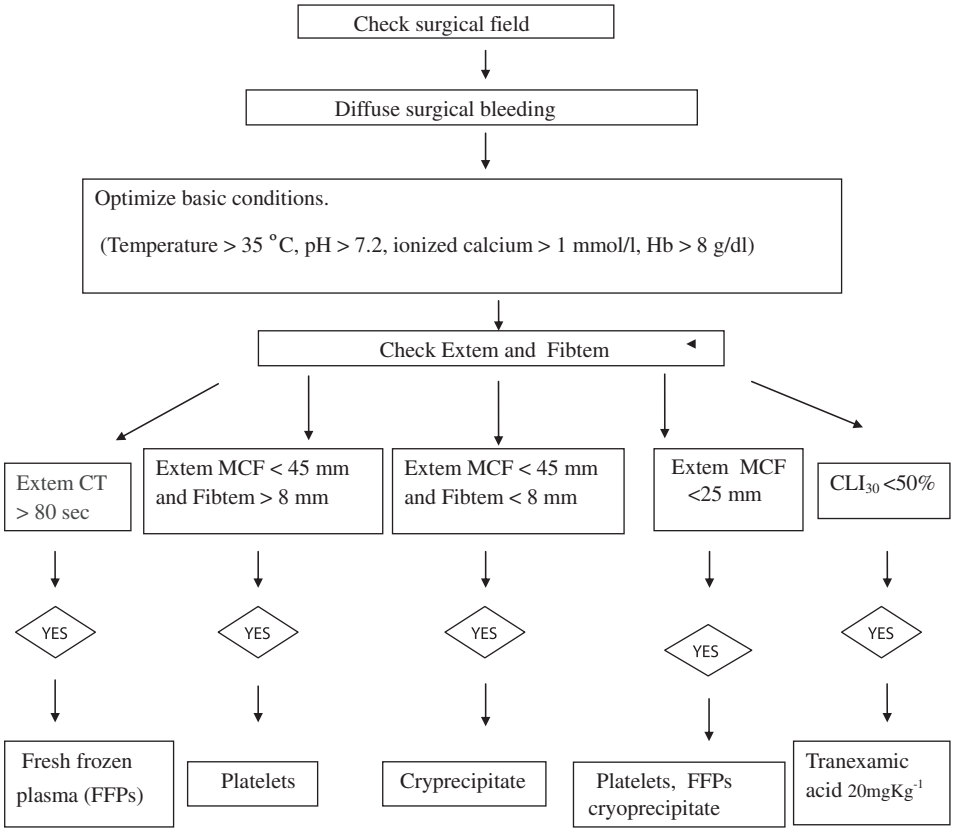

Figure 1 ROTEM guided hemostatic protocol. Extem; extrinsically activated thromboelastometry tests. FIBTEM; measures the fibrinogen activity. CT; clotting time, MCF; maximum clot formation. ML (the maximum lysis); represents the maximum fibrinolysis detected during the analysis, defined as the ratio of the lowest amplitude after reaching of the MCF and the MCF.

amic acid was given if there is evidence of hyperfibrinolysis as indicated by ROTEM in a dose of 20 mg kg^{-1}.

Intraoperative blood loss: (BL) was calculated from a modification of the Gross formula [22], in addition to the quantity of transfused red blood cells transfused to keep HCT 25%.

Same surgical techniques were used for all cases using the piggyback technique. The position of the venous clamp was adjusted to achieve an adequate cardiac preload with a stable arterial pressure. Neither venovenous bypass nor temporary portocaval shunting was used. After the completion of the portal vein anastomosis, the liver graft was reperfused via the consecutive release of the clamps over the hepatic and portal veins. The end-to-end anastomosis of the hepatic artery and the duct-to-duct anastomosis of the bile duct were performed sequentially. All patients were transported to the ICU at the end of the operation where they were extubated.

Measurements: hemodynamics; MAP, HR, TED parameters including (FTc, SVR, COP) are measured just predrug administration, just before reperfusion, just after reperfusion and 5 min after reperfusion and at the end of surgery. The incidence of PRS, need for rescue vasoconstrictor for hemodynamic instability at time of reperfusion, need for postreperfusion vasoconstrictor infusions, postreperfusion fibrinolysis indicated by fibrinogen level and maximum lysis parameter of ROTEM, AST, ALT, serum bilirubin and lactate, and postoperative duration of mechanical ventilation and ICU stay were compared between both groups.

3. Statistical analysis

Prospective power analysis showed that a sample size of 50 patients per study group would have 80% power at the 5% significance level to detect a difference of 26% in the incidence of hypotension in the study group compared with control, assuming a baseline incidence of 46% (median of published incidences ranging from 12% to 81%), as reported in a published study of a similar patient group [9–12].

Data were analyzed on a personal computer using IBM SPSS, version 20 (SPSS, Chicago, IL). Normality of quantitative data distribution was tested using the 1-sample Kolmogorov–Smirnov goodness-of-fit test. Normally distributed quantitative data were presented as mean (SD), and between-group differences were compared parametrically using the independent-samples Student's t test. Non-normally distributed numerical data were presented as median (range), and intergroup differences were compared non-parametrically using the Wilcoxon rank sum test. Qualitative data were presented as ratio, and differences between the 2 groups were compared using the personal χ^2 test with application of Fisher exact test, when appropriate. All reported P values are 2 tailed. $P < 0.05$ is considered statistically significant.

4. Results

One hundred and ten recipients were considered for the study; 3 cases were excluded preoperatively due to beta blocker

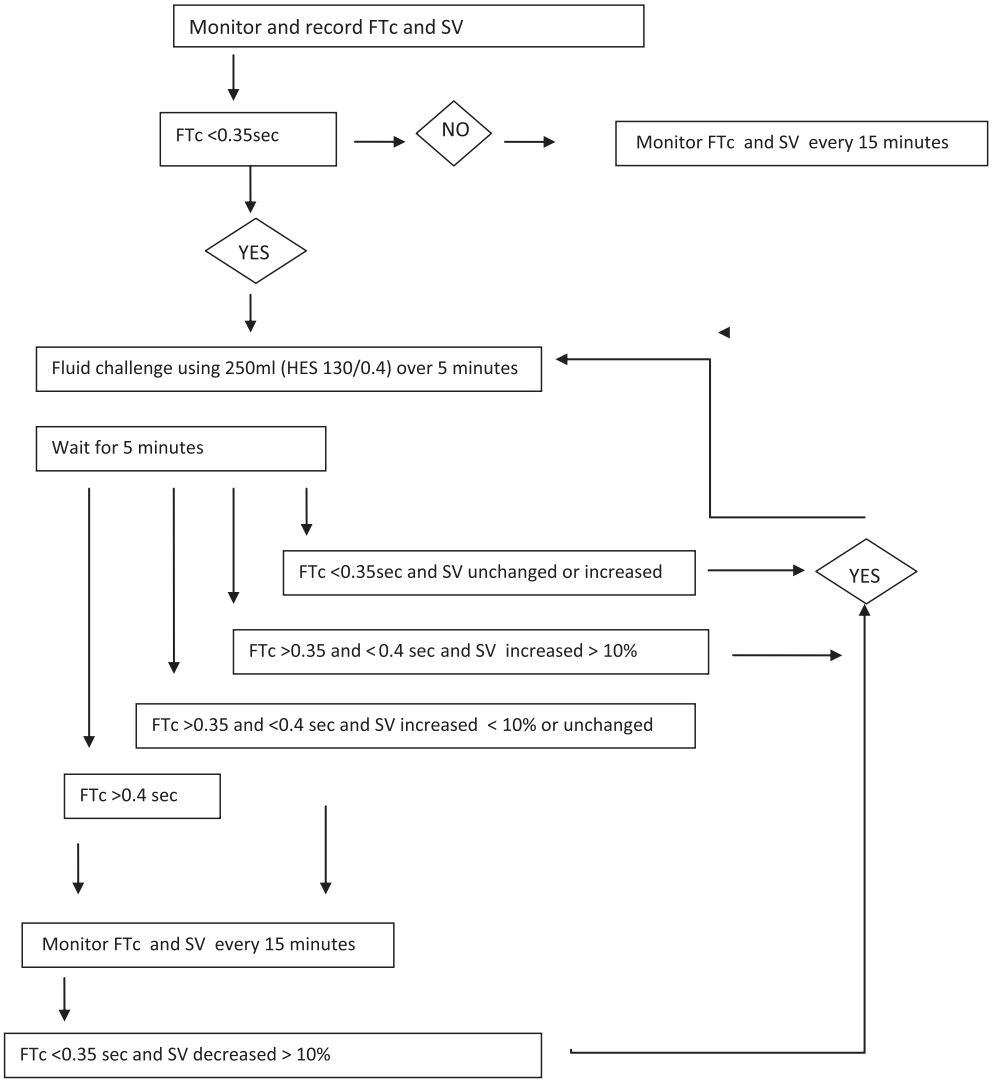

Figure 2 ODM guided fluid management, FTc; corrected flow time, SV; stroke volume.

admission, one case had cardiac problem, and 6 cases required intraoperative vasoactive drug infusion. The remaining 100 patients completed the study. Preoperative patients' characteristics are shown in Table 1. There was no statistically significant difference regarding MELD score, GBWR, cold ischemia time, duration of anhepatic phase, and total duration of surgery. The donors were all living, with steatosis $< 10\%$, of age (28.5 ± 4.8) and (26.9 ± 5.1) in both groups C and E respectively. Three patients in each group received tranexamic acid according to ROTEM readings. The mean dose of ephedrine required to achieve the target level of blood pressure was (12.5 ± 7.5 mg) with minimum 5 mg and maximum 25 mg. There was no statistically significant difference regarding blood loss and transfusion requirements of both fluids and blood products between the 2 groups. Table 2 shows the hemodynamic changes as presented by MAP, HR and TED parameters where group E had statistically significant increase in MAP, SVR, and COP Just before reperfusion, just after reperfusion and 5 min after reperfusion. While there were no statistical significant differences between the 2 groups at the end of surgery, the changes in FTc were inversely related to the SVR. 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 need for mechanical ventilation decreased significantly in group E, while there were no statistical significant differences regarding the laboratory results as shown in Table 3. Five cases in group C and 1 case in group E developed arrhythmia at reperfusion which was managed uneventfully and no reported cases of cardiac arrest.

5. Discussion

Prevention and treatment for PRS are important targets during liver transplantation. Protocols that aim to prevent hypotension may result in better outcomes than those designed to treat hypotension. Pharmacological interventions have been tried by many investigators. In this study, preemptive ephedrine could decrease the incidence of PRS by 40% (60% in group C vs. 20% in group E). Also ephedrine attenuated the hypotensive response to reperfusion (36% drop in blood pressure in group C vs. 26% drop in MAP in group E when

Table 1 preoperative patients' characteristics and clinical data.

Variables	Group C (n = 50)	Group E (n = 50)
Age	44.95 ± 8.7	41.5 ± 10.7
Sex	42/8	44/6
Etiology; HCV/HCV + HCC	38/12	35/15
MELD	16.1 ± 3.1	17.7 ± 3.6
GBWR	1 ± 0.16	1.03 ± 0.18
Cold ischemia time (Min)	34 ± 3.6	35 ± 3.1
Warm ischemia time (Min)	45.75 ± 6.8	46.55 ± 5.9
Duration of surgery (H)	12.55 ± 1.5	12.25 ± 1.61
Duration of anhepatic phase (Min)	114.5 ± 31	117.1 ± 29
Blood loss (ML)	2198.5 ± 719	2219.5 ± 779
Ringer acetate (L)	5.13 ± 0.86	4.92 + 0.69
Albumin (L)	1.2 ± 0.25	1.1 + 0.30
Voluven 130/0.4 (L)	2.05 ± 0.49	1.93 + 0.44
Packed red blood cells (units)	4.12 ± 2.4	3.9 ± 2.8
Fresh frozen plasma (units)	4.62 ± 3.1	4.8 ± 2.9
Cryoprecipitate (units)	3.2 ± 1.8	2.9 ± 1.9
Platelets (units)	1.8 ± 1.1	1.6 ± 1.2

Group C, control group; group E; ephedrine group; HCV; hepatitis C virus, HCC; hepatocellular carcinoma, MELD; model of end-stage liver disease, GBWR; graft body weight ratio. No statistically significant differences between both groups regarding the listed parameters.

comparing the pre-reperfusion readings with the just after reperfusion readings) and decreased the need for postreperfusion vasoconstrictor support without over shooting of any of the monitored hemodynamic indices. The postoperative course was comparable when comparing both groups apart from the duration of postoperative need for mechanical ventilation support which was significantly lower in group E.

In this study, a mean dose of (12.5 ± 7.5 mg) ephedrine was given, and Iqbal et al. [23] found that a dose of 15 mg of prophylactic intravenous ephedrine can effectively prevent spinal induced maternal hypotension during cesarean section without adverse effects like reactive hypertension.

Pharmacological block of the postreperfusion hemodynamic changes including bradycardia and hypotension has been previously tried. Acosta et al's. study was conducted with atropine which abolished bradycardia even when PRS occurred but failed to block the decrease in MAP [18].

In a recent study, Ryu et al. [19] have demonstrated that commonly used vasopressors such as epinephrine and phenylephrine are helpful in preventing PRS as phenylephrine is effective in treating acute hypotension caused by systemic vasodilatation, which is the most suspected cause of hypotension in liver transplant recipients, especially during the reperfusion period. In addition, frequent bradycardia during reperfusion of the liver graft makes epinephrine an appropriate rescue drug of choice.

A major concern after preempetive vasopressor administration was hemodynamic indices overshooting. As not all recipients will develop PRS, a preemptive management could result in unintended hemodynamic overshooting in some patients at reperfusion. This what Ryu et al. [19] tried to avoid in their study by adjusting doses on the basis of the literature [17] and their clinical experience with PRS but they had still recorded some cases of hemodynamic overshooting. To solve this problem the current study used ephedrine, which is many times less potent than epinephrine. The protocol of titrating the dose of ephedrine against target level of blood pressure has effectively prevented hemodynamic overshooting, as we did not report any case of hemodynamic overshooting, as well as it decreased the incidence of PRS compared to that reported by Ryu et al. [19] using epinephrine and phenylephrine (the decreased incidence in the current study was 40% compared to the study of Ryu who reported 38% decrease with epinephrine and 29% with phenylephrine). The incidence of PRS in control patients of Ryu et al's. [19] study was 77% vs. 60% in the current study. This may be explained by only including living donors in our study while Ryu et al. included living and deceased donors with possible higher CIT which could affect the incidence of PRS.

Ephedrine may be a good choice in preventing PRS during liver transplantation for 2 reasons; 1st, ephedrine causes higher blood pressure, and less increase in hart rate when used in treatment of hypotension when compared to phenylephrine as reported by Simin et al. [24] and this appeared more appropriate for the hyperdynamic state of cirrhotic patients; 2nd, the effects of ephedrine last 7–10 times longer than epinephrine which could help maintaining an acceptable level of blood pressure after reperfusion and so has a sparing effect on other vasoconstrictors requirement .

The factors that could affect the incidence of PRS were comparable in both groups. Of these factors; CIT, It has been found that the duration of cold ischemia is a risk factor for PRS [25,26]. Also, the duration of anhepatic phase and total duration of surgery were comparable in both groups. Ijtsma et al. [27] showed that an anhepatic phase over 100 min is an independent factor for predicting graft dysfunction as the prolonged duration of an anhepatic phase can aggravate acidosis of the gut, which may subsequently influence the hemodynamics after reperfusion.

In this study some surgical maneuvers might also affect the incidence of PRS as piggyback technique which is used in all cases. This technique demonstrated better hemodynamic balance and less frequent PRS in comparison with total clamping of the inferior vena cava (IVC) and venovenous bypass [18].

Table 2 Hemodynamic changes in both groups throughout the study period.

Variables	Measuring point										
	Group	Pre drug	*P*	Just before reperfusion	*P*	Just after reperfusion	*P*	5 min after reperfusion	*P*	End surgery	*P*
MAP (Mm/Hg)	C	73.35 ± 5.6	0.2	67.95 ± 7.43	0.0002	43.45 ± 5.2	0.009	54.3 ± 5.5	0.02	62 ± 6.7	0.1
	E	74.1 ± 6.4		90.6 ± 5.4		69.1 ± 5.5		68.5 ± 7.5		69 ± 6.3	
HR (B/Min)	C	93.75 ± 9.18	0.35	100.25 ± 8.58	0.0006	119.35 ± 6.70	0.19	112.85 ± 6.47	0.30	109.85 ± 5.61	0.3
	E	94.05 ± 9.5		110.6 ± 8.9		115.25 ± 12.8		113.1 ± 7.07		103.6 ± 6.57	
FTc (ms)	C	330.4 ± 19.12	0.59	325.1 ± 7.04	0.0004	383.8 ± 17.3	0.01	371.3 ± 9.3	0.01	368.3 ± 14.5	0.53
	E	327.55 ± 14.31		316.6 ± 6.81		362.1 ± 11.01		365.7 ± 10.6		369.6 ± 12.7	
SVR (Dynes s/cm^5)	C	714 ± 109	0.8	674.5 ± 65.25	0.0001	579.5 ± 72.1	0.01	615.5 ± 76.05	0.04	625.5 ± 74.5	0.72
	E	719 ± 99. 6		788.65 ± 83.6		693.65 ± 94.40		678.65 ± 81.64		633.1 ± 62.3	
COP (L/M)	C	7.9 ± 0.8	0.52	8.39 ± 1.0	0.002	10.94 ± 1.0	0.001	10.2 ± 1.2	0.04	9.4 ± 1.2	0.05
	E	7.8 ± 0.7		9.485 ± 0.7		9.8 ± 0.83		9 ± 1.4		8.9 ± 1.13	
HCT (%)	C	31.6 ± 3.08	0.76	28 ± 1.97	0.76	25.75 ± 1.63	0.47	25.8 ± 1.4	0.3	27.15 ± 1.63	0.77
	E	31.9 ± 3.21		27.8 ± 2.16		26.4 ± 1.69		26.3 ± 1.5		27.4 ± .69	

Group C, control group ($n = 50$); group E; ephedrine group ($n = 50$); MAP; mean arterial blood pressure, HR; heart rate, FTc; corrected flow time, SVR; systemic vascular resistance, COP; cardiac output, HCT; hematocrit value. $P < 0.05$ indicates statistically significant difference.

Table 3 Patients clinical and laboratory outcome in both groups.

Variables	Measuring point	Group C (n = 50)	Group E (n = 50)
Incidence of PRS (%)		30/50 (60%)	10/50 (20%)*
Rescue adrenalin at reperfusion			
	% of patients required	80%	20%*
	Dose/ug median (range)	30 (5–50)	5 (0–20)*
Postreperfusion noradrenalin infusion		9/50	3/50*
Duration of postoperative MV (H)		8.23 ± 7.76	6.69 ± 8.679*
ICU stay/days		5.53 ± 2.51	5.77 ± 2.44
ML (%)	Preoperative	10.9 ± 05.6	11.1 ± 04.8
	½ h after reperfusion	12.8 ± 05.4	12.2 ± 04.9
Fibrinogen (mg/dl)	Pre-reperfusion	121 ± 17.8	126 ± 19.3
	End surgery	62.9 ± 8.9	65.1 ± 9.2
Bilirubin (mg/dl)	Preoperative	3.79 ± 1.62	3.66 ± 1.48
	POD2	6.23 ± 4.35	6 ± 4.75
Lactate	Preoperative	10.8 ± 4.1	11.6 ± 2.9
	POD2	17.07 ± 6.4	18.38 ± 7.7
AST (IU/L)	Preoperative	59.4 ± 29.7	55.24 ± 24.1
	POD2	282.5 ± 177	274 ± 185
ALT (IU/L)	Preoperative	47.60 ± 21.08	45.8 ± 22.8
	POD2	336.05 ± 215	323 ± 229

Group C, control group; group E; ephedrine group; MV, mechanical ventilation; POD, postoperative day.
* Denotes statistically significant difference ($P < 0.05$).

Immediate and homogeneous reperfusion of the liver graft rather than preflushing with lactated Ringer's solution was followed in all cases and this might partially contribute to cardiovascular instability [28], as preflushing of the graft is known to provide hemodynamic stability in comparison with IVC venting without flushing [29,30]. Another potential contributor to the high incidence of PRS was the use of a histidine tryptophan ketoglutarate solution for organ preservation [31].

In this study, systemic vascular resistance (SVR) was significantly higher in group E than in group C just before reperfusion, just after reperfusion, and 5 min after reperfusion. It has been reported that, after ephedrine administration, there was a sequence of a transient increase in after load, followed by a transient decrease (possibly b2-mediated) and then a sustained increase in SVR (probably mediated by noradrenalin release) [32]. Also cardiac output was significantly higher in group E compared to group C just before reperfusion. Ephedrine has a predominant ß-effect that causes increase in arterial blood pressure by increasing cardiac output [33]. After reperfusion, COP was significantly higher in group C compared to group E which may be due to extra use of epinephrine in the control group represented by a higher number of patients received epinephrine (80% in group C vs. 20% in group E) and higher dose required in group C compared to group E (30 μg vs. 5 μg respectively).

The FTc readings were comparable at the predrug measurement and were at the lower normal range (330–360 ms) this could be due to the use of the piggy back technique at time of revascularization with partial IVC clamping and it was significantly lower in group E when compared to that in the group C just before reperfusion and this was inversely related to the changes in SVR induced by ephedrine. The 5 min after reperfusion results also showed that FTc was still significantly lower in group E compared to group C this might be explained by the more decrease in SVR in group C as a response to reperfusion compared to group E in which preempetive ephedrine prevented this excessive drop. As it is known, FTc is inversely correlated with the SVR and a longer FTc may be associated with a low SVR, a condition that is typically occur at the time of reperfusion of the newly implanted graft.

At the end of surgery there was no statistical significant difference between the hemodynamic changes in both groups. This could be achieved in control group by an extra use of postreperfusion vasoconstrictor infusion to help maintain acceptable hemodynamic parameters (9 patients out of 50 in group C vs. 3 out of 50 in group E required postreperfusion vasoconstrictor infusion).

Despite a trend toward better postoperative laboratory results in the group E there were no significant differences between the 2 groups and this may be due to the multi factors affecting these results beside reperfusion.

Some investigators [8,34] considered excessive fibrinolysis as a part of PRS. The current study did not reveal any statistically significant difference when comparing parameters reflecting fibrinolysis including maximum lysis (ML) and serum fibrinogen level also the number of patients required anti fibrinolytic drug was comparable in the 2 groups.

In this study, the duration of postoperative mechanical ventilation was significantly shorter in group E compared to group C while there was no statistically significant difference regarding the duration of ICU stay. Hilmi et al. [8] found that the ICU length of stay and days on a ventilator are greater in patients with PRS. The limitations of this study are that, the study was not blind as the protocol of titration of the drug against MAP did not allow this. Also, the study did not follow up the patients' long term outcome including complications and survival rate. In conclusion, the goal directed titration of ephedrine against a target MAP pre-reperfusion, could de-

crease the incidence of PRS by 40%, attenuated the hypotensive response to reperfusion and decreased the need for postreperfusion vasoconstrictor support without overshooting of any of the monitored hemodynamic indices.

Conflict of interest

None.

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