Journal of Anesthesia & Clinical Research - Open Access

Research Article
OPEN ACCESS Freely available online
doi:10.4172/2155-6148.1000104

Effects of Vasoactive Agents on Blood Loss and Transfusion Requirements During Pre-Reperfusion Stages of the Orthotopic Liver Transplantation

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Abstract

Objective: To evaluate the effects of vasoactive drugs, specifically low-dose vasopressin and phenylephrine infusions, on blood loss / transfusion requirements during dissection and anhepatic (pre-reperfusion) stages of orthotopic liver transplantations.

Methods: A retrospective analysis of 110 orthotopic liver transplantation (OLT) cases was performed. The variables studied were: blood loss before and after reperfusion of the liver graft; blood volumes returned by cell-saver and amounts of transfused blood products; amounts of infused colloids and crystalloids; hemodynamic parameters such as MABP, MPAP, CO/CI, SVR; dosage of vasoactive drugs. Short – and long-term outcome measures included length-of stay (LOS), ICU LOS, 48 –hours return to the OR rate, incidence of the primary non-function of the liver graft, amounts of fresh frozen plasma (FFP) and cryoprecipitate, administered in the ICU, and 1-year mortality. The study subjects were allocated in two groups. Study group consisted of 15 patients that received a low-dose (0.04U/min) vasopressin infusion alongside with other vasoactive agents, such as phenylephrine and epinephrine, during the dissection and anhepatic stages of the procedure. Control group consisted of 95 patients, that received the same vasoactive agents except a low-dose vasopressin infusion. Anesthetic and transfusion management in both groups were otherwise identical.

Results: The estimated blood loss before reperfusion of the liver graft was in 50.2% lower (p=0.0094) and total blood loss was in 38.8% lower (p=0.0548) in the vasopressin group in comparison with control group of subjects of the same age, sex and with the same MELD score. No statistically significant differences neither in hemodynamic parameters between the two groups, nor in transfusion requirements and volumes of crystalloid and colloids infused, were detected. No differences were found also in long-term outcome parameters.

Conclusions: The decrease in blood loss in the vasopressin group may be attributed to the use of a vasopressin infusion. A low-dose (0.04U/min) vasopressin infusion may be an effective technique for blood loss reduction during the pre-reperfusion stages in orthotopic liver transplantation.

Keywords: Vaso active agents; Vasopressin; Pre-reperfusion stage in orthotopic liver transplantations; Blood loss; Cell-Saver; Transfusion requirements

Introduction

Massive blood loss and associated blood transfusion remains one of the most important factors of perioperative morbidity and mortality in orthotopic liver transplantations [1-3]. A significant part of the overall blood loss occurs during the dissection phase of the recipient's native liver (pre-anhepatic phase). Portal hypertension with excessive collateral circulation, extensive adhesion development as a result of inflammatory processes in the course of chronic hepatitis, and pre-existing coagulation deficits appear to be the most important contributing factors. During the anhepatic phase, when the native liver is isolated from the blood circulation, production of coagulation factors is no longer possible, which worsens the ongoing hemorrage. Massive transfusions of blood and coagulation factors is therefore often required during this stage to compensate for rapidly developing acute anemia and consumption deficit.

Many different ways have been explored to limit the overall blood loss during orthotopic liver transplantations. Among those, different vasoactive agents, specifically dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressine have been used with various degrees of success. This retrospective study will evaluate the effects of vasoactive agents on blood loss, transfusion requirements and hemodynamics during the dissection and anhepatic phases of orthotopic liver transplantations.

Materials and Methods

The Transplant anesthesia division of the University of Washington Medical Center analyzes its database regularly. An analysis of the database revealed apparent differences in intra-operative blood loss in orthotopic liver transplant recipients with and without vasopressin infusions. Warranting further evaluation of the data, institutional review board approval for a retrospective study was sought and obtained. After obtaining institutional review board approval, a retrospective cohort study was conducted, collecting data

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Received August 30, 2010; **Accepted** September 26, 2010; **Published** September 28, 2010

Citation: Vitin AA, Martay K, Vater Y, Dembo G, Maziarz M (2010) Effects of Vasoactive Agents on Blood Loss and Transfusion Requirements During Pre-Reperfusion Stages of the Orthotopic Liver Transplantation. J Anesthe Clinic Res 1:104 doi:10.4172/2155-6148.1000104

from anesthesia, surgical and medical records. One hundred and ten patients of both genders, ASA III - IV, aged 18-65, diagnosed with End-Stage Liver Disease of various etiology (Hepatitis B or C, NASH, ETOH, primary hepatocellular carcinoma), MELD score range 14-35, that underwent their first orthotopic liver transplantation between January 2008 and June 2009, were studied. A period of 18 months was deemed short enough to minimize possible influences of changes in anesthetic and surgical practice. All orthotopic liver transplants were performed at the University of Washington Medical Center. Surgical techniques included "piggy-back" venous anastomosis with IVC preservation or total bi-caval variant. Veno-venous bypass was not routinely used in this procedure. Patients were included in this study regardless of the particular surgical technique applied. All organs were obtained from cadaver donors and no patient selection has been employed in respect to ischemia times.

According to the standardized institutional guidelines for anesthesia for orthotopic liver transplantations, general anesthesia was induced with Fentanyl (1-2 mcg/kg), etomidate (0.3 mg/kg) or propofol (2mg/kg) and Succinylcholine (1mg/kg), and was maintained with Isoflurane and continuous infusions of Fentanyl (3-5 mcg/kg/h) and Cisatracurium (1 mcg/kg/min). In addition to standard non-invasive monitoring (ECG, BP, SaO_2), invasive monitoring included arterial lines, continuous SvO_2 pulmonary artery catheter and in selected cases, transesophageal echocardiography. Arterial blood gases and lactate concentrations were continuously monitored in all patients, and the coagulation status was checked by thromboelastograms (TEGs). Cell-saver was used routinely in all procedures to maintain, together with red blood cell (RBC) transfusions, a hematocrit (Hct) of about 30% (Hb ~100g/dl). Fresh frozen plasma (FFP), cryoprecipitate and platelets were transfused to keep INR of about 2.0 and a fibrinogen concentration ≥ 90–100 mg/dl. Clinically significant "oozing" and lack of good quality clots in the surgical field were considered indicators for platelet transfusions, rather than platelets count; however, the lowest tolerable platelets level was considered to be 25,000–30,000/ml.

During the whole of the surgery, a dopamine (3mcg/kg/min) infusion run constantly, while infusions of phenylephrine (0.1–1.5 mcg/kg/min), epinephrine (0.01–0.1 mcg/kg/min), vasopressin (0.04–0.4U/min), and nitroglycerine (0.1-3mcg/kg/min) were used when required. The goal was to maintain a mean arterial blood pressure (MABP) of ± 80% of the baseline MABP (ideally 70-90 mmHg), and a central venous pressure (CVP) not greater than 10-15 mmHg.

In this retrospective study, effects of a low-dose vasopressin infusion on blood loss and transfusion requirements during the dissection and anhepatic stages of OLTs, were investigated. Of all 110 patients undergoing OLT, 15 patients received a continuous vasopressin infusion during the dissection and anhepatic stages of the surgery. No selection of the patients, receiving either vasopressin or other vasoactive drugs, or any of their combinations, had been employed in respect to either particular clinical situation (portal hypertension, history of variceal bleeding, ascitis, etc.) or laboratory values (baseline coagulation defect, specifically low platelet count, etc.). The choice of particular vasoactive drug or their combination was entirely of the anesthesia care provider. The vasopressin infusion rate used was 0.04U/min, and phenylephrine and epinephrine infusions were additionally administered as needed. These 15 patients comprised the vasopressin-treated study group. The other 95 patients received an identical vasopressor regime except vasopressin, and became the control group for the study. Continuous dopamine and phenylephrine infusion was used in all patients, and epinephrine infusions were used only rarely. For this reason, effects of epinephrine were not evaluated. This study is focused on the comparison between the effects of phenylephrine and low-dose vasopressin infusions on blood loss and transfusion requirements in OLTs.

For the study, the following pre-operative data and intraoperative variables were analyzed:

1. Demographic data: age, gender, height, weight, Body Mass Index (BMI), MELD score (Table 1)
2. Initial anemia and coagulation profile: PT, INR, fibrinogen, platelet count, HCT (Table 2)
3. Hemodynamic parameters: MAP, mean pulmonary artery blood pressure (MPAP), cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR).
4. Lactate concentration
5. Cell-Saver (ml) return, RBCs (ml), FFP (ml), cryoprecipitate (ml), platelets (ml), Colloids (ml), Crystalloids (ml) infused during dissection stage, anhepatic stage, and during the whole of OLT
6. Blood loss estimation, calculated using the following formula: EBL = Volume of Cell-Saver blood return x 3.5
7. Phenylephrine infusion rates (mcg/kg/min).

Hemodynamic parameters, and rates of vasoactive drugs and lactate concentrations in arterial blood samples were recorded at the following points during OLTs: 30 minutes after surgery start, 15 min before anhepatic phase start, 15 min after anhepatic phase start, 15 min before graft reperfusion, 15 min after graft reperfusion, 60 min after graft reperfusion, at the end of surgery. Cell-Saver blood volume returned (and estimated blood loss calculated), volumes of transfused blood products, colloids and crystalloids have been recorded at the end of dissection and anhepatic stages (just before venous graft reperfusion) and at the end of the surgery.

All statistical calculations were performed using R 2.10.0 program (www.r-project.org). To compare the baseline characteristics of the study sample between treatment and control, the proportions for binary variables and means and standard deviations for continuous

Demographic parameters	Vasopressin group Mean (St.dev)	Control group Mean (st.dev)	P-value
Gender	Male 67%	Male 78%	
Age, *years*	58.00 (3.16)	53.36(2.98)	0.0680
Height, *cm*	173.07(10.21)	174.67(9.89)	0.4861
Weight, *kg*	88.35(22.28)	87.03(15.63)	0.6776
BMI	28.82(4.96)	28.19(3.93)	0.7929
MELD	22.40(6.34)	22.97(6.71)	0.8978

Table 1: Demographic data.

Coagulation parameters	Vasopressin group Mean (St.dev)	Control group Mean (St.dev)	P-value
PT, *sec*	20.93(4.51)	21.75(9.12)	0.6349
INR	1.92(0.62)	1.99(1.22)	0.6873
Fibrinogen, mg/dl	131.142(27.76)	129.765(30.08)	0.9046
PLT, ml^{-1}	87510.66(2350.56)	91304.79(1989.92)	0.7888
HCT, %	28.85(2.81)	29.14(2.11)	0.7575

PT- Protrombin time, *sec.*; INR – International Normalized Ratio; PLT - Platelets count,, ml^{-1}; HCT - hematocrit,%;

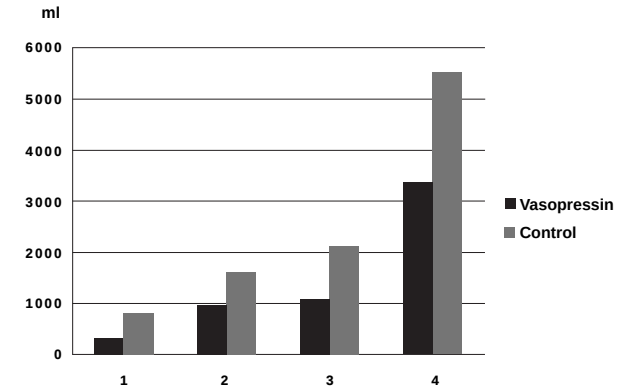
Table 2: Coagulation status and HCT at baseline.

variables (MABP, MPAP, CI, CO, SVR and rates (dosages) of phenylephrine infusion) have been summarized and compared using the Fisher's exact test (proportions) and t-tests (means). Measures for which information was available at the time periods , mentioned above, were averaged and reported as mean ± standard deviation. The potential associations between baseline patient characteristics and outcome measures were investigated using scatterplots using only the control sample. Any baseline characteristics that appeared to be strongly associated with the outcome were considered to be potential confounders or precision variables.

The following intraoperative outcome measures were considered:

- Blood loss before reperfusion
- Blood loss total (before and after)
- Cell-saver before reperfusion
- Cell-saver total (before and after)
- Red packed cells transfused amount
- Fresh frozen plasma (ml) transfused amount
- Cryoprecipitate (ml) transfused amount
- Albumin 5% (ml) (colloid) amount infused
- Crystalloids (ml) amount infused

In primary analysis our null hypothesis was that the "administration of vasopressin has no effect on the blood loss during dissection and anhepatic stages of liver transplantation surgery". Blood loss before reperfusion and total blood loss were the primary outcomes and treatment with vasopressin was the primary predictor. Adjustments were made for the following covariates: age, gender (demographic covariates) and MELD score.Since MELD, INR and PT were found to be associated with the outcomes and highly correlated with one another, we chose to only adjust for MELD. In addition, MELD was not associated with the treatment in this dataset, so MELD played a role of a precision variable in the analysis. We considered, whether the normality assumption for the outcome measures would be appropriate by plotting the untransformed and transformed histograms of the outcome data. Since several of the outcome measures were highly skewed to the right, the log transformed outcome measures were used. For each of the outcome measures two models were built: a linear model with treatment as the main predictor with no adjustment for any covariates, effectively performing a simple t-test; in the second model the treatment was again the main predictor, but now adjusted for age, gender and the MELD score. Corresponding analysis was done with log transformed blood loss total as the outcome, as well as for (log transformed) measures of albumin, phenylephrine, red packed cells transfused amount, fresh frozen plasma, cryoprecipitate transfused amount and crytalloids amount infused as outcomes.



1. Cell-saver return before reperfusion (during dissection and anhepatic stages)
2. Cell-saver total returned volume (during all procedure)
3. EBL before reperfusion
4. EBL total

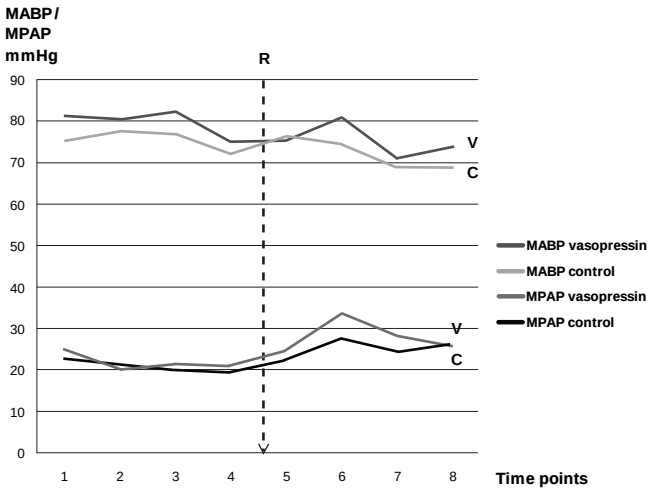
Figure 1: Cell-Saver return volumes and estimated blood loss (EBL).

We have also investigated any potential effects of vasopressin infusion administered during pre-reperfusion stages of the surgery on some of the long-term outcome measures. These long-term outcome measures, analyzed in the study, included:

1. Length of stay (LOS)
2. ICU LOS
3. 48-hours return to the OR rate
4. Incidence of the primary non-functioning graft
5. Amounts of fresh frozen plasma and cryoprecipitate administered in the ICU
6. 1-year mortality

Results

Demographic data of the patients, baseline coagulation status, and hematocrit are summarized in Table 1 and Table 2, respectively. Patients in vasopressin-treated and control groups do not appear to be meaningfully (and statistically) different with respect to baseline characteristics.



R –venous graft reperfusion point
V, vasopressin group
C, Control group
Time points:
1. 30 minutes after surgery start
2. 15 min before anhepatic phase start (portal vein clamping)
3. Immediately before hepatic artery clamping
4. 15 min after anhepatic start (double clamping)
5. 15 min before venous graft reperfusion
6. 15 min after venous graft reperfusion
7. 60 min after dual graft reperfusion;
8. At the end of surgery

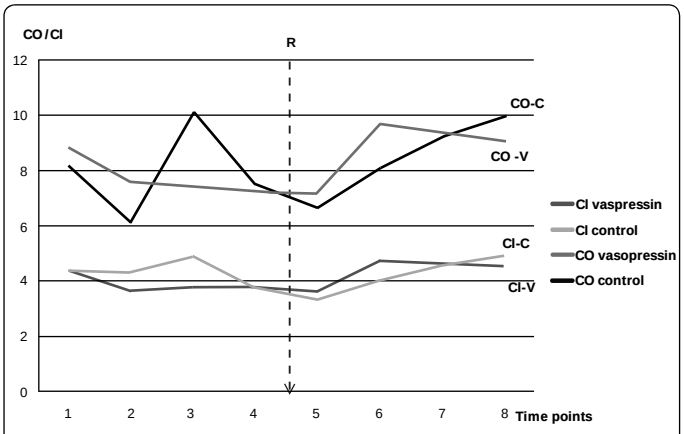
Figure 2: Mean arterial (MABP) and mean pulmonary artery (MPAP) pressures (mmHg) dynamics.

Outcome	Vasopressin group		Control group		Difference		P-value
	Mean (St. dev)	95%CI	Mean (St.dev)	95%CI	Mean (St.dev), %	95% CI	
Blood loss before reperfusion	1195.92 (1413.36)	327.64; 2336.36	2401.45 (2625.85)	1648.41;2555.16	1205.53 (940.3) (50.2%)	988.45; 1515.2	0.0094
Blood loss total	3474.04 (4945.35)	1032.03;6509.31	5676.53 (5612.74)	4132.94;6419.69	2202.49 (2109.45) (38.8%)	1776.98; 3445.88	0.0548

Table 3: Blood loss reduction.

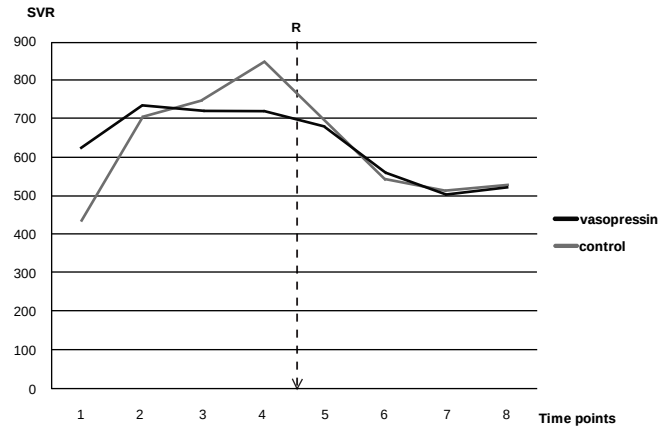
Blood products	Vasopressin group		Control group		Difference		P-value
	Mean (St. dev)	95% CI	Mean (St.dev)	95% CI	Mean (St.dev), %	95% CI	
Red packed cells	1120.00 (765.27)	696.21; 1543.79	1297.37 (1388.734)	1014.47; 1580.27	928.92 (657.77) (- 28.8%)	717.86; 1009.94	0.403
Fresh frozen plasma	1394.54 (1108.87)	1028.56; 2143.31	2012.33 (1722.38)	1058.51; 2966.16	617.79 (453.89) (- 30.7%)	422.35; 878.9	0.273
Cryoprecipitate	142.37 (110.73)	79.39; 257.41	151.77 (143.02)	122.63; 180.90	9.4 (4.16) (- 6.2%)	4.2;11.7	0.661
Albumin 5%	447.42 (294.86)	267.24; 809.60	1232.50 (394.88)	1013.32; 1450.68	785.1 (336.13) (- 63.7%)	641.75; 978.66	0.071
Crystalloids	5795.14 (2378.98)	4215.90; 7850.77	8173.68 (3277.72)	7505.98; 8841.39	2378.54 (998.81) (- 29.1%)	1888.87; 3004.12	0.266

Table 4: Blood products, colloids and crystalloids.



CI, cardiac index , L / min / m^2;
CO, cardiac output, L/min
R, venous graft reperfusion point
CO-V, Cardiac output – vasopressin group
CO-C, Cardiac output – control group
CI-V, Cardiac index – vasopressin group
CI-C, Cardiac index – control group
Time points:
1. 30 minutes after surgery start
2. 15 min before anhepatic phase start (portal vein clamping);
3. Immediately before hepatic artery clamping
4. 15 min after anhepatic start (double clamping)
5. 15 min before venous graft reperfusion
6. 15 min after venous graft reperfusion
7. 60 min after dual graft reperfusion
8. At the end of surgery

Figure 3: CI / CO dynamics.



SVR, systemic vascular resistance, dynes / sec / cm^5
R, venous graft reperfusion point
Time points:
1. 30 minutes after surgery start
2. 15 min before anhepatic phase start (portal vein clamping)
3. Immediately before hepatic artery clamping
4. 15 min after anhepatic start (double clamping)
5. 15 min before venous graft reperfusion
6. 15 min after venous graft reperfusion
7. 60 min after dual graft reperfusion
8. At the end of surgery

Figure 4: Systemic vascular resistance dynamics.

Estimated blood loss before reperfusion in vasopressin-treated group was in 50.2% lower (p=0.0094) in comparison with that in the control group in subjects of the same age, sex and same MELD score. Estimated total blood loss was estimated to be in 38.8% lower p = 0.0548) in the vasopressin-treated group compared to that in the control subjects, and this difference was not statistically significant. A similar trend was observed, when comparing the Cell-Saver returned volumes between the two groups. (Figure 1, Table 3). The likely reason for the lack of the significant difference is that the substantial, potentially bigger part of blood loss occurs during post-reperfusion stages of the surgery, than during pre-reperfusion stages.

Amounts of blood products, received by the patients in the vasopressin group, were lower than those in the control group. Amounts of transfused red packed cells in the vasopressin group was in 28.8% lower than in the control group, and amounts of the fresh frozen plasma was in 30.7%. The most substantial differences was observed with amounts of 5% albumin, were vasopressin group patients received less in 63.7% , and also amounts of crystalloids infused (Table 4) . These differences, however, were not statistically significant.

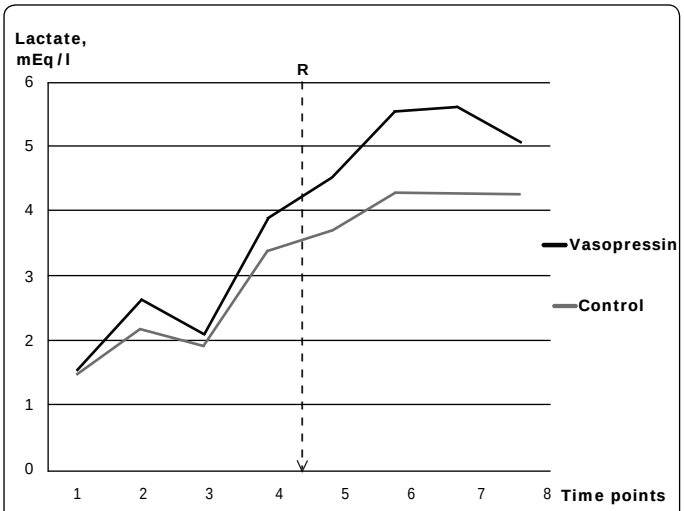
Hemodynamic data analysis in the vasopressin–treated group and in the control group reveals no statistically significant differences during the procedure. MABP and MPAP (Figure 2), as well as CO and CI (Figure 3), SVR (Figure 4) appear to have remained nearly identical almost at every time point in both groups.

Outcome measures	Vasopressin group		Control group		Difference (%)	P-value
	Mean (St. dev)	CI (95%)	Mean (St.dev)	CI (95%)		
LOS, days	13.9 (4.33)	7.22; 19.65	14.2 (5.69)	7.37; 20.42	+0.3 (2.1%)	0.867
ICU LOS, days	2.7(1.4)	1.25;4.54	2.8 (1.9)	1.61;5.02	+0.1(3.6%)	0.774

Table 5: Length of stay (LOS) and ICU LOS.

Blood products	Vasopressin group		Control group		Difference, ml (%)	p-value
	Mean(St.dev)	CI(95%)	Mean(St.dev)	CI (95%)		
FFP, ml	1475.56 (1224.33)	988.77; 1785.61	1635.27 (1333.39)	1199.03; 1805.49	159.71 (-9.7%)	0.675
Cryoprecipitate, ml	168.02 (111.53)	122.68; 226.65	186.91 (132.08)	117.69; 298.77	18.89 (-10.1%)	0.457

Table 6: Blood products, administered in the ICU during 48 hours postoperatively.



R, venous graft reperfusion point
Time points:
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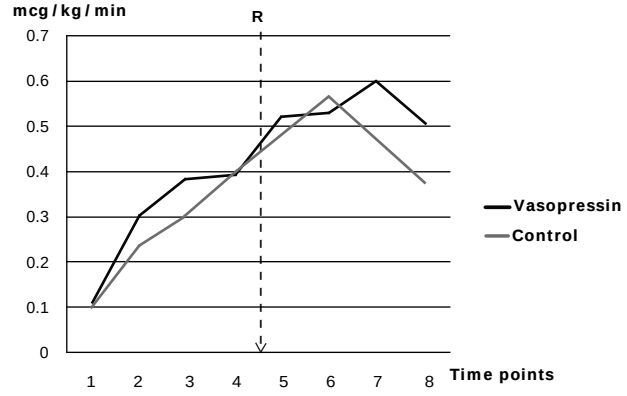
3. Immediately before hepatic artery clamping
4. 15 min after anhepatic start (double clamping)
5. 15 min before venous graft reperfusion
6. 15 min after venous graft reperfusion
7. 60 min after dual graft reperfusion
8. At the end of surgery

Figure 5: Lactate concentration dynamics.



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5. 15 min before venous graft reperfusion
6. 15 min after venous graft reperfusion
7. 60 min after dual graft reperfusion
8. At the end of surgery

Figure 6: Phenylephrine infusion rates.

Lactate concentrations, while remained approximately equal during pre-reperfusion stages, reveal substantial (higher approximately in 40% in the vasopressin group), however short-lived differences during post-reperfusion period (Figure 5). The general pattern of exponential concentration raise after reperfusion was identical in both groups.

Phenylephrine infusion rates in both the vasopressin-treated and the control group revealed generally the same pattern of almost linear increase during almost entire procedure with subsequent decrease toward end of the surgery (Figure 6).

Length of stay (LOS) and ICU LOS were analyzed, using unpaired *t*-test. The results analysis (Table 5) revealed no statistically significant differences.

Return to the operating room for explorative re-laparotomy within 48 hours after OLT occurred in 1 case (6.7%) in the vasopressin group and in 6 cases (6.3%) in the control group. The main indication was postoperative bleeding. However, no obvious bleeding source has been identified in almost all cases; it was mostly diffuse bleeding due to coagulation deficit.

Primary non-function of the liver allograft occurred only in 1 case (1.05%), in the control group.

During first 48 hours of the postoperative period, in most cases INR has returned to the value of 1.5 and lower. Amounts of FFP and cryoprecipitate, administered in the ICU, were less in 9.7 % and 10.1%, respectively, in the vasopressin group. However, these differences were not statistically significant (Table 6).

1-year mortality rate overall was 5.4%, with 1 case in the vasopressin group (6.7%) and 5 in the control group (5.3%).

Discussion

Blood loss and associated massive blood transfusion remains one of the central issues in OLTs despite progress made during the last decade [1,2]. Blood loss itself, despite extreme rarity of death due to massive intraoperative hemorrhage, remains a major cause of morbidity and mortality [3,4]. With introduction of improved surgical techniques, pharmacological treatments and refined infusion/transfusion guidelines, current trends clearly display considerable decrease in transfusion requirements, with amounts of RBCs decreased from average of 20 units in the 1980s to 2 unit [3], and even to 0 units in some centers [4], with median current RBC consumption less than 5 units [2].

Several studies have looked into the factors, determining survival rates after liver transplantation, graft survival, and major complications. It has been found, that intraoperative massive blood transfusion significantly decreased one-year survival in 62.5% in cases with more than 4 units RBCs transfused [5], and had a negative impact on the 1 and 5 year patient and graft survival rate in cases where more than 6 units of RBC [6] and platelets [7] have been transfused. In one study, it was found impossible to distinguish between negative effects of RBC and FFP, but obtained results demonstrated a decrease of the 3-year survival rate in 64% of patients, that received more than 20 units, in comparison with 88% of those, that received less than 20 units [8].

A number of studies during the last decade investigated the pre- and intraoperative predictors for massive blood transfusions. In some studies, a strong correlation was found between blood loss and transfusion requirements and factors such as MELD score and Child–Pugh score, age, gender, type and severity of liver disease, history of previous upper abdominal surgery, duration of surgery, cold ischemia time, preoperative levels of albumin, hemoglobin [9,10], creatinin, bilirubin, coagulation factors (INR, PT, platelet count, fibrinogen concentration) [12-14] , and also difficult-to-standardize parameters such as surgeon and anesthesiologists' experience and even attitude [2,12,15] Other studies reported no such correlations, particularly in respect to MELD score [16] and INR [14,17]. To date, blood loss and associated massive blood transfusion during OLTs remains difficult to predict [10,14]. Another factor of major impact is a substantial variability in institutional transfusion practices, specifically transfusion thresholds, that may cause significant variation in the volumes of RBCs and other blood products transfused in cases with similar blood loss [2,18,19].

Many different strategies have been explored to minimize blood loss during liver transplant surgery [20]. Over the years, surgical techniques were modified to achieve this goal. Several studies have demonstrated the advantages of piggyback hepatectomy, that allows to avoid veno-venous bypass and complete IVC clamping [21,22] and thus decreases blood loss, vasoactive drug requirements, and fluid amounts required for volume resucitation. Other strategies, proposed to reduce blood loss and thus transfusion requirements, included acute intraoperative isovolemic hemodilution, preoperative erythropoietin administration and blood donation, intraoperative blood salvage with use of Cell-Saver, maintenance of low central venous pressure, and maintenance of normotermia to prevent hypothermia-induced coagulopathy [23]. In our practice, we routinely use Cell-Saver and adhere to normothermia maintenance.

Intraoperative blood salvage, with use of different Cell-Saver models during OLT and other surgical procedures, has been extensively studied and found to be efficient. The reported recovery efficiency for liver transplant procedure ranged from 35 to 65%, with an average autologous transfusion volume reduction of approximately 45-55%. However, hemodilution, irrigational fluids, used in the surgical field, and blood lost in drapes and sponges, substantially decrease blood salvage technique efficacy [24-31].

The blood loss estimation has always been difficult during OLT. With a variety of blood loss assessment methods, that have been proposed and validated for different kinds of surgical procedures (direct measurement, gravimetric, photometric, etc.,) [32], none proved to be reliable enough and practical for OLT. Intraoperative blood salvage technique only provides a way for blood loss estimation with considerable approximation. Correspondent guidelines, based on calculations of hematocrit during blood loss (25-30%) and that of returned red blood cells by Cell-Saver (approximately 55-65% depending on Cell-Saver model), have been developed. Authors calculated estimated blood loss by multiplying the total volume of Cell-Saver returned RBCs by factor 3,4–4.0 [31]. While being fully aware of this method's limitations and potential impreciseness, we have adopted this formula for estimated blood loss calculations in our practice and also used it in this study.

Despite the emerging trend in favor of low central venous pressure maintenance during OLT, the whole concept remains controversial. The advantages of low CVP maintenance, that included potential for blood loss decrease, therefore lowered transfusion requirements, resulting in substantial improvements in the 1-year survival rate, as well as oxygen delivery improvement to the liver graft by creating a greater MABP/CVP gradient, have been convincingly demonstrated in several studies [3,34,35]. To achieve and maintain a CVP around 5 cm H_2O, crystalloid, colloid and FFP volume restrictions, the use of diuretics, nitroglycerine infusions, and phlebotomy have been proposed [3,33,34]. To date, however, only a few prospective studies on liver transplant populations, exploring the effects of a low CVP on different aspects of outcome, have been performed. Using CVP monitoring for volume status assessment and right heart performance has been demonstrated to be of doubtful validity across a very variable liver transplant patient population and also provided little, if any, help in blood loss management [35,36]. In another retrospective study, increased rates of postoperative renal failure and 30-days mortality in the low-CVP group have been found, and authors concluded, that low CVP should be avoided in liver transplant patients [37]. It has also been demonstrated, that low CVP maintenance often requires increased dosage of vasopressors, thus aggravating peripheral vasoconstriction, promoting metabolic acidosis, and increasing risk of post-operative renal failure [38]. In this context, CVP appears to be a controversial parameter of questionable value as an end-point for hemodynamic management, and may not be unequivocally recommended to guide fluids and transfusion management in OLTs. In our practice, and also in the patients in this study, we did not pursue maintenance of CVP level lower than 10-15 cm H_2O in both study and control groups.

The common for end-stage liver disease hyperdynamic circulatory state with high CI and CO, and low SVR, bears a substantial resemblance to that in endotoxic or septic shock. Effects of vasoactive agents, specifically vasopressin and norepinephrine, used for hemodynamic stabilization in experimental septic [39-42] and hemorrhagic [42] shock, and in critically ill patients in vasoplegic endotoxic and septic shock, have been extensively studied and described [44-49].

Hemodynamic instability during OLT due to blood loss, graft reperfusion and post-reperfusion vascular tone adjustment, substantial fluid shift often necessitates the use of vasoactive agents. Different vasopressors have been used for hemodynamic optimization and end-organ perfusion improvement during OLTs for decades. These include dopamine, epinephrine, norepinephrine, phenylephrine, vasopressin, and, more recently, terlipressin and octreotide [50-53]. Norepinephrine and, lately, phenylephrine have been shown to have a substantial and universal vasoconstrictor effect due to their almost pure α-receptor stimulation, thus effectively increasing systemic vascular resistance, while decreasing cardiac index, pulmonary artery pressure, peripheral and portal blood flow [43,49,51]. However, norepinephrine in higher doses has been shown to cause severe peripheral vasospasm and promote metabolic (lactic) acidosis [41,49].

Vasopressin has been demonstrated to have a dose-dependent vasoconstrictor effect on the peripheral vasculature with substantial SVR increase, while having a little effect on heart rate, systemic arterial blood pressure, and CI in normotensive patients [51].

In this study hemodynamic parameters in both groups were mostly identical during the pre-reperfusion stage of the procedure. Interestingly, phenylephrine requirements became even higher in the vasopressin group toward the end of procedure, after the vasopressin infusion was already discontinued for long while. A low-dose vasopressin (0.04 u/min) infusion apparently exerted only a minimal effect on the general hemodynamic parameters of the patients.

Increased lactate concentrations during pre-reperfusion stages of OLTs is thought to be secondary to increased lactate production in the gut and decreased lactate extraction by liver [52]. Phenylephrine, which was used in both groups, has been shown to have no effect on lactate production and hepatic lactate utilization [53], but has been associated with substantial decrease of blood lactate concentrations [54]. Degree of phenylephrine contribution to lactate dynamics in OLTs remain unclear and may warrant further investigations.

Vasopressin has been shown to have a stimulation effect on lactate production by liver cells and adipose tissue in the septic model [53,55,56]. In our study, the lactate concentrations in the vasopressin group were higher during the pre-reperfusion stage. This may be attributed to increased production of lactate by the gut and to impaired elimination of lactate by the native liver with additional vasopressin-related stimulation of lactate production. Difference in lactate concentrations between vasopressin and control groups substantially diminished toward the end of procedure, when vasopressin administration had been discontinued already some time ago and the liver graft may have already resumed lactate processing.

The ability of vasopressin to selectively constrict splanchnic vasculature, and thus decrease portal blood flow, is thought to constitute a physiological basis for variceal bleeding control by a higher vasopressin (0.4 U/min) dose [3,41,57]. The concept of blood loss reduction by specifically controlling the splanchnic blood flow during OLTs has been adopted by anesthesiologists from the hepathology field. Use of a low-dose vasopressin (0.04U/min) infusion in attempt to reduce blood loss, which had been proposed more than a decade ago [57] seems to be a promising and feasible technique.

Vasopressin decreases portal vein pressure and blood flow in the native liver [58], as do terlipressin and octreotide [59]. The theoretical possibility of liver graft hypoperfusion secondary to portal vein blood flow decrease may be considered. To date, however, no cases of liver graft damage, caused by a low-dose vasopressin infusion, have been documented. However, case, where a high-dose vasopressin (0.8U) bolus, followed by a vasopressin infusion (4U/h) to attenuate refractory hypotension secondary to graft reperfusion, were used without causing any identifiable liver graft damage, has been reported [60].

This retrospective study was designed to elucidate an association between vasopressin infusion and blood loss during the pre-reperfusion period of OLTs. The study found a substantial reduction in blood loss (by 50.2% before reperfusion ($p=0.009$), 38.8% total ($p=0.05$)) during dissection and anhepatic stages of OLT in patients receiving a low-dose vasopressin (0.04U/min) infusion. We believe, that lack of statistical significance of the total blood loss reduction in the study group may be attributed to the fact, that substantial part of the blood loss has occurred after graft reperfusion, thus minimizing the effects of blood loss decrease during pre-reperfusion stages. Also, decrease in volumes of transfused red pack cells, fresh frozen plasma, cryoprecipitate, colloids (albumin) and crystalloids were observed in the vasopressin-treated group of the patients, but found not statistically significant.

In this study, we investigated potential effects of low-dose vasopressin infusion on short – and long-term outcome measures. So far, low-dose vasopressin infusion has never been documented as independent risk factor for any of existing short- or long-term outcome measures.

Length of stay (LOS) is considered a reliable index for general assessment of liver transplant procedure outcome. In one multicenter study, factors such as donor age, weight, gender, MELD, INR, and cold ischemia time were found to be associated with LOS [61]. In our study, where demographic data and other mentioned factors were not different in both study and control groups, LOS was nearly identical in both groups, as well as ICU LOS. Several factors have been identified as negative outcome predictors and also were independently associated with prolonged ICU stay. Among these factors, amounts of fresh frozen plasma, administered in ICU, and graft complications, such as primary non-function, were found to have a greatest impact [62]. In our study, either FFP amounts, given in the ICU, nor those of cryoprecipitate, were different (a difference of -9.7%, p-value 0.675 and -10.1%, p-value 0.457, respectively) between groups. Primary graft dysfunction has occurred only once in all patients' population, included in the study.

Early (within 48 hours) return to the operation room for re-exploration has occurred almost invariably for postoperative diffuse bleeding, without any identifiable source found. The incidence was not different between two groups (6.7% in the study group, which consisted of just one case, versus 6.3% - 6 cases in the control group).

Several factors, independently associated with 1-year patient and graft survival (and mortality), such as donor age, primary diagnosis of Hepatitis C, in-hospital post-OLT infection and cardiac complications, have been identified in another study [63]. Any evidence of the effects of vasopressin, administered in the operation room or in the ICU, on 1, 3 or 5 years survival, could not be found. Our data reveals identical rates of 1-year mortality in the study and control groups, however low numbers of patients each group included for the meaningful analysis of this parameter.

Our analysis of short- and long-term outcome measures in both study and control groups of patients revealed no evidence of any effects of low-dose vasopressin infusion during pre-reperfusion stages of the OLT on outcome measures such as LOS, ICU LOS, 48-hours-return to the operating room, amounts of blood products, administered in the ICU, incidence of the graft complications and 1-year mortality.

In conclusion, low-dose vasopressin infusion appears to be helpful technique for blood loss reduction during pre-reperfusion stages of the liver transplant surgery. The results of this retrospective study appear to be encouraging enough to trigger further studies of the vasopressin effects on blood loss reduction during orthotopic liver transplantation.

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