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ORIGINAL ARTICLE

Effectiveness of terlipressin for prevention of complications after major liver resection – A randomized placebo-controlled trial

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Abstract

Background: Elevated portal pressure in response to major liver resection is associated with impaired liver regeneration and increased postoperative complications. Terlipressin, a splanchnic vasoconstrictor used for treatment of hepatorenal syndrome, was tested for reduction of complications and renal protection after liver resection.

Methods: A randomized double-blinded placebo-controlled trial including patients undergoing elective major liver resection was performed. Terlipressin was administered to patients in the intervention group for five days. The primary outcome parameter was the incidence of a clinical composite endpoint of following liver specific complications 6 weeks after surgery: liver failure, ascites, bile leakage, intra-abdominal abscess and operative mortality. Postoperative kidney function was assessed as a secondary endpoint.

Results: 150 patients (mean age 63.4 years, 73.3% male) were included. No difference was found in the composite endpoint between the placebo and intervention group (32.8% versus 30.8%, relative risk 1.066, 95%CI 0.643 to 1.769, p = 0.85). Patients receiving terlipressin showed a significant lower decrease in postoperative estimated glomerular filtration rate compared to placebo (two way ANOVA, p = 0.005).

Conclusion: Perioperative administration of terlipressin during major liver surgery did not affect a composite endpoint of liver specific complications, but significantly protected from postoperative deterioration of kidney function compared to placebo.

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Introduction

The prerequisite for successful and safe liver surgery is optimal regeneration of the remaining hepatic tissue in order to fulfill the metabolic demands of the patient.[1] Elevation of portal pressure is a physiologic consequence of major liver resection, associated with portal venous hyper-perfusion of the remnant liver tissue.[2] This process is damaging to the residual liver and thereby impairs liver regeneration.[2–4]

In patients with an expected small-for-size liver remnant, only interventional or surgical methods have been shown to protect from liver dysfunction. These include two stage hepatectomies, with or without preoperative portal vein ligation or embolization, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) as well as intraoperative rescue measures such as splenic artery ligation or creation of a porto-caval shunt.[3–5] However, there is currently no known effective pharmacological treatment to improve liver regeneration. Pharmacological modulation of portal flow and pressure would be highly relevant as its effect can be permanently adjusted according to the

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clinical situation, it does not prolong surgery and it can be stopped once its effect is no longer needed.

The splanchnic vasoconstrictor terlipressin is an effective treatment for patients with liver cirrhosis and hepatorenal syndrome.[6–9] Its vasoconstrictive effect in the mesenteric arteries reduces blood flow to the liver, thereby decreasing the pooling of blood in the splanchnic venous system while improving kidney perfusion.[10] Recent clinical data and experiments in mice with non-cirrhotic livers have demonstrated a positive effect of terlipressin on portal hemodynamics and also on regeneration after living donor liver transplantation and extended liver resection.[11–13] Thereby we hypothesized that terlipressin could be used as an adjuvant treatment in liver surgery to reduce postoperative complications that were used as the primary end point.

A secondary endpoint was acute kidney injury, which is a common and severe complication after major liver resection with a reported incidence of 13% and which is associated with substantial mortality and chronic kidney disease.[14,15] Given that acute kidney injury after liver surgery is related to intraoperative fluid loss and renal hypoperfusion, terlipressin could potentially improve kidney perfusion and preserve renal function similar to patients with hepatorenal syndrome.

Thus, a randomized placebo-controlled trial was designed and performed to evaluate the impact of prophylactic terlipressin administration on severe postoperative complications in patients undergoing major liver resection.

Methods

Trial design

A randomized placebo-controlled double-blinded trial was performed at the Department of Visceral Surgery and Medicine at the University Hospital of Bern. The study was approved by the ethical committee of the canton of Bern (KEK 190/11) and registered at clinicaltrials.gov (NCT01921985).

Participants

All patients seen at the visceral surgical outpatient department and scheduled for liver resection between November 2013 and December 2017 were assessed for eligibility. Inclusion criteria were: expected resection of at least three liver segments, age above 18 years and written informed consent. Exclusion criteria were: preoperative severe renal failure (estimated glomerular filtration rate (eGFR) < 30 ml/min), severe liver dysfunction (Child-Turcotte-Pugh grade C), hyponatremia (<132 mmol/l), severe aortic or mitral regurgitation, symptomatic coronary heart disease, bradycardic arrhythmia, peripheral arterial occlusive disease (≥Fontaine stage II), dilatative arteriopathy, history of subarachnoidal bleeding, decompensated hypertension, mesenteric ischemia, septic shock and pregnancy.

Intervention

Patients in the intervention group received infusions of 1 mg of terlipressin (trade name: Haemopressin, PROREO Pharma Innovation AG, Liestal, Switzerland) in 100 ml of normal saline, administered over 2 h. The first dose was administered intraoperatively just prior to mobilization of the liver, and was followed by a dose every six hours for five days, resulting in a total of 20 doses.

In the placebo group infusions of 100 ml of normal saline were administered according to the same scheme. The dosage was adopted from regimens used for the treatment of patients suffering from hepatorenal syndrome or esophageal variceal bleeding.[16]

Outcomes

The primary outcome of the study was the incidence of a validated, repeatedly used clinical composite endpoint (CEP) that consists of frequent complications after hepatic resection as published before.[17–19] The CEP includes following complications: Liver failure (bilirubin above 50 µmol/l AND international normalized ratio greater than 1.5 or hepatic encephalopathy grade 3 or 4 on or after postoperative day 3), ascites (loss of >500 ml per day of intra-abdominal clear fluid via drain or wound), bile leakage (via abdominal wound or drains), intra-abdominal abscess (purulent fluid in the abdominal drain or presence of a walled-off collection in the abdominal cavity on radiological examination) and mortality. The CEP was met if one or more of the aforementioned complications occurred within 6 weeks after surgery.

Secondary outcomes were: Postoperative kidney function (eGFR, calculated according to the CKD EPI equation[20]), acute kidney injury (according to the Acute Kidney Injury Network definition[21]), occurrence of post-operative complications other than those in the CEP (pleural effusion, pneumonia, sepsis, intra-abdominal hematoma and surgical site infections defined according to the CDC definition[22]). The assessment of severity of the complications was done using the Clavien-Dindo classification.[23]

Adverse drug reactions to terlipressin, such as acute hypertension, arrhythmias and hyponatremia were registered.

The follow-up consisted of a consultation in our outpatient clinic six weeks postoperatively, where a physical examination was performed and the outcome assessed via questionnaire.

Sample size

Initial sample size calculation was performed based on data from our department showing an incidence of the CEP of 44% prior to initiation of the trial. The study was powered to detect a relative risk reduction of 33% in the intervention group, as this was judged a clinically relevant difference. Randomization was 1:1, in a superiority design. Calculating with a power of 80% and a level of significance of 5% a total of 348 patients needed to be included in the study.

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According to the study protocol, an interim analysis was performed after inclusion of 150 patients. This analysis showed a lower than expected incidence of the CEP in both groups and no trend towards either a clinically or statistically significant difference between the groups as to the primary endpoint (see results section). A conditional power calculation was performed according to Proschan *et al.*[24] This analysis revealed an estimate for a statistically significant result of 2.19% in case of continuation of the study, assuming trend continuation.[25] Based on the very low chance of finding a significant effect of terlipressin, the recruitment of patients was stopped after 150 patients.

Randomization

Randomization was performed in permuted blocks of 20 patients, using the online-tool "Randomization.com" by an external study nurse and documented in consecutively numbered and sealed envelopes.

Blinding

Physicians and patients were blinded to the investigational medicinal product (IMP) terlipressin or placebo. An independent non-blinded study nurse prepared a plastic box for each patient according to randomization. The box contained 20 infusion

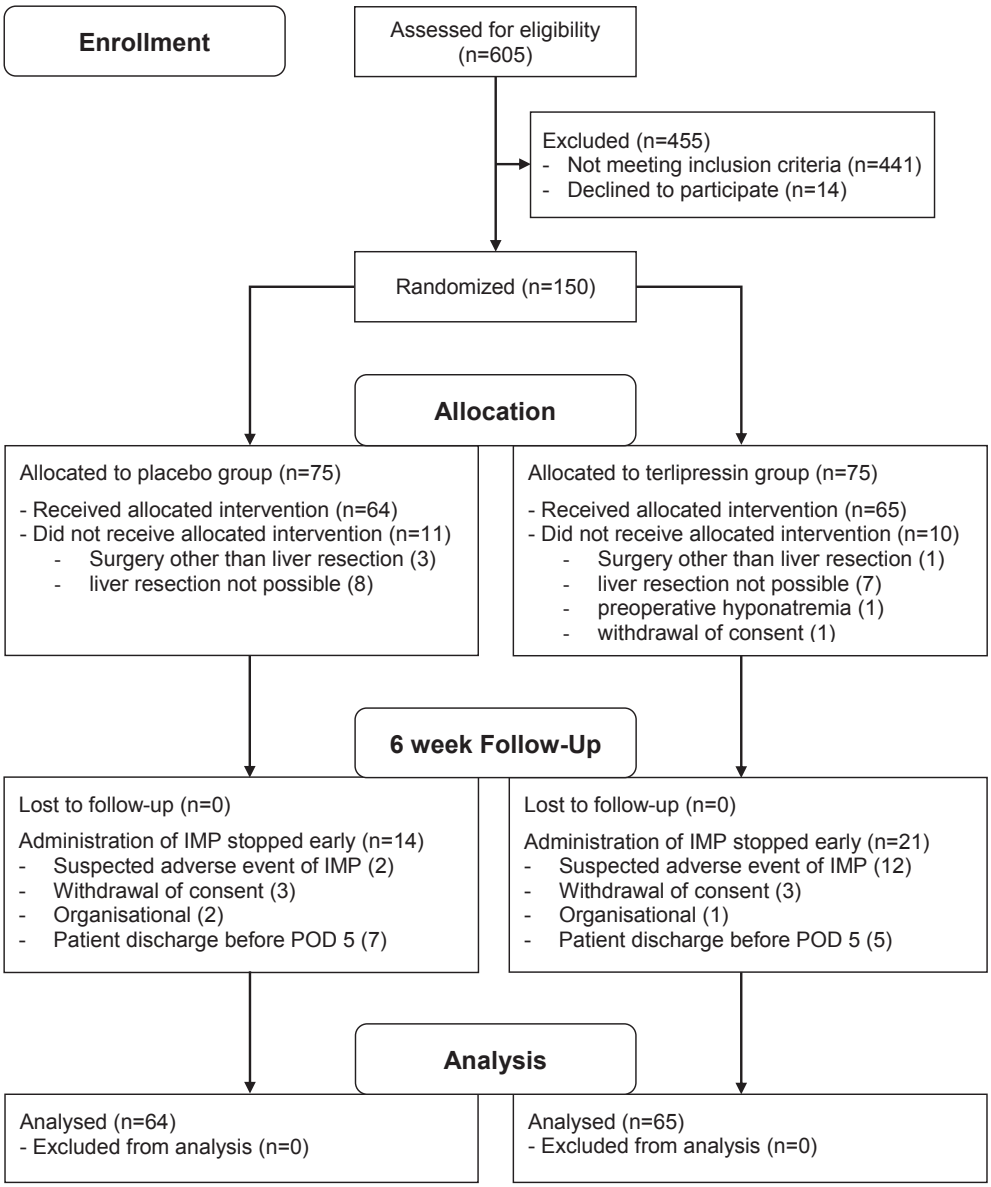

Figure 1 CONSORT diagram. CONSORT flow diagram showing enrollment, allocation and follow-up process with the respective patient numbers and reasons for exclusion

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bottles (100 ml of 0.9% saline) and 20 doses of terlipressin if the patient was in the intervention group or 20 infusion bottles alone if the patient was in the placebo group. Nursing staff was instructed to dissolve one dose of terlipressin in one bottle of saline directly prior to infusion if both were present in the box. All infusion bottles were labelled similarly.

Statistical methods

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bern. After export, analyses were performed using SPSS (IBM, Version 21) and Prism (Graph Pad, Version 6) software.

Continuous variables were described using mean and standard deviation. For categorical values, proportions were calculated. Differences between groups were compared using t-test and ANOVA for continuous variables and Chi-square test for categorical variables. Analysis was performed according to the intention to treat principle.

Results

Study population

From November 2013 through December 2017, 150 patients (mean [SD] age 63.4 [11.3] years; 110 [73.3%] male) were included in the study, of whom 75 were assigned to the placebo group and 75 to the terlipressin group. Because of an intraoperative change in treatment strategy, 11 patients in the placebo and 8 patients in the terlipressin group did not undergo liver resection after surgical exploration. One patient had withdrawn consent prior to surgery and one patient showed preoperative hyponatremia. The IMP was not administered to those 21 patients because they no longer met the inclusion/exclusion criteria

Table 1 Patient characteristics

		Placebo (N = 75)	Terlipressin (N = 75)
Baseline Characteristics			
Age, y, median (IQR)		61 (54–69)	66 (58–73)
Male gender		73.3% (55/75)	73.3% (55/75)
ASA classification			
1		10.7% (8/75)	6.7% (5/75)
2		25.3% (19/75)	26.7% (20/75)
3		60.0% (45/75)	62.7% (47/75)
4		4.0% (3/75)	4.0% (3/75)
Liver Disease			
Cirrhosis	Child-Pugh A	17.3% (13/75)	17.3% (13/75)
	Child Pugh B	1.3% (1/75)	2.7% (2/75)
Indication for Surgery			
Hepatocellular Carcinoma		28.0% (21/75)	24.0% (18/75)
Cholangiocellular Carcinoma		13.3% (10/75)	22.7% (17/75)
Colorectal Liver Metastasis		28.0% (21/75)	28.0% (21/75)
Other Metastasis		8.0% (6/75)	4.0% (3/75)
Neuroendocrine Tumor		6.7% (5/75)	5.3% (4/75)
Echinococcus		4.0% (3/75)	12.0% (9/75)
Other		12.0% (9/75)	4.0% (3/75)
Neoadjuvant Chemotherapy		18.7% (14/75)	12.0% (9/75)
Kidney Function			
Chronic kidney disease stage 2–3		49.33% (37/75)	57.33% (43/75)
eGFR 30–90 ml/min/1.73 m^2 (SEM)			
Chronic kidney disease stage 3		12% (9/75)	12% (9/75)
eGFR 30–60 ml/min/1.73 m^2 (SEM)			
Surgery			
Operating time, min		210 (96)	211 (68)
Blood loss; ml		916 (717)	1209 (1063)

Continuous Data displayed as mean (SD) if not otherwise specified, Nominal Data as % (n/N). IQR: interquartile range. ASA: American society of anaesthesiologists. No statistically significant differences were found between groups.

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and they were excluded from the study (Fig. 1). Baseline characteristics were similar between the groups (Table 1).

Primary outcome

The composite endpoint occurred in 32.8% (21/64) of patients in the placebo group and in 30.8% (20/65) of patients in the terlipressin group, corresponding to a relative risk of 1.066 (95% CI 0.643 to 1.769). The individual complications that are included in the composite endpoint were not significantly different between the groups (Table 2).

Secondary outcomes

Postoperative kidney function improved in the terlipressin compared to the placebo group (Fig. 2 and Table 3). Glomerular

Table 2 Postoperative complications

		Placebo	Terlipressin	Relative risk (95% CI)	P Value
Composite endpoint (primary endpoint)					
Liver Failure		6.3% (4/64)	6.2% (4/65)		1.00[a]
Ascites		15.6% (10/64)	10.8% (7/65)		0.45[a]
Bile Leakage		10.9% (7/64)	18.5% (12/65)		0.32[a]
Intraabdominal abscess		14.1% (9/64)	9.2% (6/65)		0.42[a]
Mortality		3.1% (2/64)	1.5% (1/65)		0.62[a]
Composite endpoint reached		*32.8% (21/64)*	*30.8% (20/65)*	*0.94 (0.57–1.56)*	*0.85*[a]
Other complications					
Pleural effusion		20.3% (13/64)	13.8% (9/65)	0.68 (0.31–1.42)	0.36[a]
Pneumonia		6.3% (4/64)	4.6% (3/65)	0.74 (0.17–3.17)	0.72[a]
Sepsis		14.1% (9/64)	9.2% (6/65)	0.66 (0.25–1.74)	0.42[a]
Intraabdominal hematoma		3.1% (2/64)	3.1% (2/65)	0.98 (0.14–6.78)	1.00[a]
Surgical Site Infection	superficial	7.8% (5/64)	4.6% (3/65)	0.59 (0.15–2.37)	0.49[a]
	deep	0% (0/64)	0% (0/65)		
	Organ/Space	21.9% (14/64)	12.3% (8/65)	0.56 (0.25–1.25)	0.17[a]
Subgroup analysis (eGFR<90, composite endpoint of complications associated with fluid redistribution)					
Ascites		16.1% (5/31)	13.1% (5/38)		0.74[a]
Pleural effusion		25.8% (8/31)	16.1% (5/31)		0.53[a]
Acute kidney injury		22.6% (7/31)	6.5% (2/31)		0.15[a]
Mortality		3.2% (1/31)	0% (0/31)		1.00[a]
Composite endpoint reached		45.2% (14/31)	21.1% (8/38)	0.47 (0.23–0.97)	0.04[a]
Classification of complications					
Total patients with complications		35	33		
Clavien-Dindo classification:					
I		31.4% (11/35)	24.2% (8/33)		
II		17.2% (6/35)	27.3% (9/33)		
III		37.1% (13/35)	39.4% (13/33)		
IV		8.6% (3/35)	6.1% (2/33)		
V		5.7% (2/35)	3.0% (1/33)		0.82[b]
Suspected Adverse Drug Reaction					
Hypertensive Crisis		4.7% (3/64)	15.4% (10/65)		0.08[a]
Bradycardia/New Arrhythmia		3.1% (2/64)	6.2% (4/65)		0.68[a]
Myocardial Ischemia		0% (0/64)	1.5% (1/65)		–
Mesenteric Ischemia		0% (0/64)	0% (0/65)		–
Stroke		0% (0/64)	0% (0/65)		–
Peripheral vasoconstriction		1.6% (1/64)	0% (0/65)		–

Data is displayed as % (n/N).
[a] Fisher Exact test.
[b] Chi-square test.

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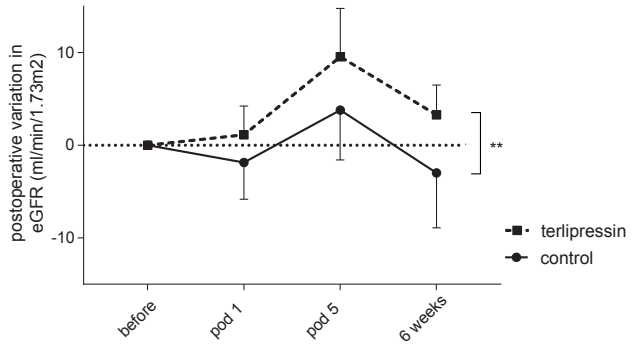

Figure 2 Postoperative kidney function. Representation of post-operative kidney function, showing variation in eGFR compared to preoperative eGFR. Glomerular filtration rate decreased significantly more in the control group, compared to the terlipressin group and was significantly different between day 1, day 5 and week 6 (two way ANOVA, p = 0.005 for treatment group; p = 0.003 for timepoint). No interaction was found between treatment group and time (p = 0.686 for interaction). **p = 0.005; pod: post-operative day

filtration rate decreased significantly more in the control group and was significantly different between day 1, day 5 and week 6 (two way ANOVA, p = 0.005 for treatment group; p = 0.003 for timepoint). No interaction was found between treatment group and time (p = 0.686 for interaction).

The incidence of complications other than those reported in the composite endpoint was not significantly different between the two groups. Graduation of complications according to the Clavien-Dindo classification did not show differences between the groups (Table 2).

A subgroup analysis revealed that patients with impaired renal function (eGFR<90 ml/min/1.73 m^2) in the terlipressin group showed less fluid redistribution related complications (composite endpoint of acute kidney injury, ascites, pleural effusion, mortality) compared to patients with impaired renal function in the placebo group (placebo 45.2% (14/31), terlipressin 21.1% (8/38), RR 0.47 (0.23–0.97), p = 0.041).

Adverse drug reactions were suspected in 7.8% (5/64) of patients in the placebo group and in 24.6% (16/65) of patients in

Table 3 Liver and kidney function parameters

Liver function		Placebo	Terlipressin	Effect size (SE)	P Value
Bilirubin, umol/l	baseline	17.4 (31.8)	16.8 (29.6)	0.6 (5.7)	0.92
	increase day 1	12.7 (43.5)	17.1 (29.2)	–4.5 (7.2)	0.53
	increase day 5	0.0 (39.5)	7.9 (35.9)	–7.9 (8.4)	0.35
	increase week 6	–7.2 (38.1)	–5.4 (32.8)	–1.8 (8.0)	0.83
INR	baseline	1.08 (0.24)	1.12 (0.40)	–0.04 (0.06)	0.52
	increase day 1	0.10 (0.21)	0.04 (0.42)	0.06 (0.07)	0.38
	increase day 5	–0.01 (0.20)	–0.10 (0.43)	0.09 (0.07)	0.23
	increase week 6	0.01 (0.32)	0.31 (1.61)	–0.30 (0.26)	0.26
AST, U/L	baseline	48 (31)	55 (57)	–7 (9)	0.41
	increase day 1	463 (671)	475 (568)	–12 (121)	0.92
	increase day 5	31 (75)	41 (98)	–10 (19)	0.61
	increase week 6	–16 (30)	0 (84)	–16 (14)	0.27
ALT, U/L	baseline	56 (50)	72 (119)	–15 (17)	0.37
	increase day 1	341 (392)	389 (411)	–48 (79)	0.55
	increase day 5	128 (202)	144 (196)	–16 (44)	0.72
	increase week 6	–33 (58)	–31 (143)	–3 (25)	0.91
Thrombocytes, G/L	baseline	244 (124)	222 (62)	22 (22)	0.33
	increase day 1	–47 (95)	–83 (54)	36 (21)	0.09
	increase day 5	–40 (142)	–39 (56)	–1 (31)	0.97
	increase week 6	8 (80)	–9 (72)	17 (27)	0.54
Kidney function		Placebo	Terlipressin	Effect size (95% Conf Int)	P Value
Delta eGFR, ml/min/1.73 m^2 (SEM)	day 1	–1.9 (1.98)	1.1 (1.56)	3.0 (–2.01–7.98)	0.24
	day 5	3.8 (2.64)	9.5 (2.58)	5.75 (–1.6–13.1)	0.12
	week 6	–3.0 (2.91)	3.3 (1.59)	6.28 (0.06–12.5)	0.048
Perioperative AKI	until day 1	9.4% (6/64)	6.2% (4/65)		
	until day 5	12.5% (8/64)	10.8% (7/65)		

Continuous Data displayed as mean (SD). Statistical comparison by two-sided students t-test. AKI: acute kidney injury.

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the terlipressin group. Hypertensive crisis and cardiac arrhythmias were the most common adverse drug reactions (Table 2). No suspected unexpected severe adverse reactions (SUSAR) were observed. In 14 patients (2 in the placebo group and 12 in the intervention group) the IMP was stopped due to adverse events with possible relationship to terlipressin.

Discussion

In this randomized placebo-controlled trial, perioperative administration of terlipressin was not associated with a reduction of liver specific complications after major liver resection as assessed by the primary endpoint. However, terlipressin administration was associated with a superior preservation of kidney function compared to placebo controls.

Thus, the investigated perioperative modulation of splanchnic perfusion by terlipressin is not sufficient to decrease the incidence of clinically relevant endpoints such as liver failure, ascites, bile leakage, intra-abdominal abscess and mortality. Furthermore, potential surrogate parameters of liver function such as laboratory liver function tests and coagulation parameters were not significantly different between the two groups. This study allows to conclude that liver specific complications may occur independently from terlipressin induced hepatic hemodynamic alterations.

This study revealed a specific renal protective effect of terlipressin in patients undergoing major liver surgery. Presumably, renal function impairment after major liver surgery follows a similar mechanism to hepatorenal syndrome in the cirrhotic liver.[6,7,26] Potentially increased resistance to portal blood flow in the remnant liver leads to pooling of blood in the splanchnic vasculature, as seen in patients with liver cirrhosis and portal hypertension. Similar to patients with liver cirrhosis, terlipressin therefore reduces splanchnic blood pooling and consequently improves renal perfusion.[10] A peak in eGFR on postoperative day five was observed in both treatment groups (Fig. 2). Presumably, this is the consequence of intravenous fluid administration during the postoperative course. After discontinuation of intravenous hydration, the eGFR levels decreased at the 6-week follow-up measurement. Our measurement of elevated delta eGFR in patients in the terlipressin group compared to patients in the placebo group supports the hypothesis that fluid redistribution is clinically relevant. The ongoing protective effect six weeks postoperatively is in line with the literature showing that acute kidney affection has a negative effect on long-term kidney function.[27,28]

Suspected adverse drug reactions were observed in response to terlipressin (Table 2), many of them leading to discontinuation of terlipressin administration. Given the impact of this drug on the circulatory system, close monitoring of patients receiving terlipressin is mandatory in order to detect relevant cardiovascular reactions such as hypertensive crises or arrhythmias. In the context of the study terlipressin was administered as a bolus within 2 h according to current guidelines.[16] However, continuous infusion might both reduce side effects as well as increase efficacy.[29]

A limitation of the study is that not only extensive resections were explored. Potentially, terlipressin could have a beneficial effect only in extreme resections close to 70% of total liver mass where hemodynamic changes are more distinct than in this study cohort.

In conclusion, perioperative administration of terlipressin after major liver resection does not reduce liver specific complications. However, terlipressin protected kidney function after major liver resection. The use of terlipressin in patients with poor kidney function may be a promising approach to decrease their operative morbidity.

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Terlipressin is approved in most European countries and Australia for the treatment of bleeding from esophageal varices and in hepatorenal syndrome. The prophylactic use during liver surgery is investigational. There is no FDA approval for terlipressin so far.

Registered at ClinicalTrials.gov, Identifier NCT01921985.

Conflicts of interest

None declared.

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