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The Effect of Terlipressin On Posthepatectomy Recovery Among Patients with Different Stages of Fibrosis: A Retrospective Study

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Abstract

Aim: Terlipressin, a kind of vasopressin analogue, has been used for reducing portal tension and increasing the kidney perfusion. This study aimed to find out how terlipressin could affect posthepatectomy recovery among patients with different stages of fibrosis.

Methods: A total of 106 patients were included retrospectively, with 54 patients in terlipressin group and others in control group. Terlipressin was administered after in terlipressin group postoperatively. Comprehensive comparisons, including clinical outcomes, laboratory tests and adverse drug effects, were conducted not only between two groups, but also between patients with different stages of fibrosis. The pharmacological efficacy on patients with high and low stages of fibrosis was also investigated.

Results: Patients with terlipressin from all stages of fibrosis had a significantly less median abdominal drainage volume on the first, second, third postoperative day and all three days ($p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$), more urine output on the third, fourth, fifth day and first five days overall ($p=0.018$, $p<0.001$, $p<0.001$, $p<0.001$) and shorter duration of abdominal drainage retainment ($p<0.001$), while lower creatine level was only observed on the fourth and fifth day ($p=0.044$, $p=0.047$) within the high stage fibrosis subgroup analysis. However, no significant difference was found in the pharmacological efficacy between distinct severities of fibrosis.

Conclusion: The use of terlipressin was associated with better recovery of patients with all stages of fibrosis by reducing abdominal drainage, increasing urine output and accelerating abdominal drainage removal, and offered a better protection of renal function in patients with severer fibrosis.

Keywords: posthepatectomy recovery, terlipressin, liver fibrosis, pharmacological efficacy

1. Introduction

Liver tumors, including benign and malignant ones, are still under a relatively high incidence rate.[1,2] Surgical resection is so far the only curative and also the first-line treatment towards them.[3] While with the tremendous progress obtained in the area of preoperative, intraoperative and postoperative care, the hepatectomy has already became considerably safe, with the mortality rate kept below 5 per cent.[4]

However, even with a great improvement on safety, those patients who underwent liver resection still have to face a considerably high risk of complications after surgery.[5] Posthepatectomy liver failure (PHLF), for example, it represents the most critical ones, always consuming enormous medical resources but turning out limited efficacy.[6] Ascites, one of the most common complications of hepatectomy, might attribute to electrolytes imbalance, hypoproteinemia, infections, liver dysfunction and so forth.[7] Those complications greatly affect the posthepatectomy recovery, however current strategies are still by large stalled in the passive symptomatic and supportive

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treatments.[5-7]

When we look back on where those complications derive, one of the main causes come to the surface that is the increased portal vein pressure.[6,8] It may ensue from hepatectomy and be regarded as an independent predictive biomarker of PHLF after major hepatectomy.[9] As for solution, surgical therapies like the shunt surgery, seem to be the most acceptable approach.[10] However, the drawback of that is also apparent. First of all, it is a permanent process, which means the side effects it brings cannot be repealed. And it may increase the risk during the operation and expand the trauma, which are unnecessary if we can manage it though out pharmacological method.

Terlipressin, a kind of long acting vasopressin analogue,[11] has brought benefits to various fields since the early 1990s, from esophageal varices[12] to hepatorenal syndrome,[13,14] septic shock[15] and so on. The physiological mechanisms of terlipressin are based on V1 vascular receptors and V2 renal receptors, while previous study has shown that terlipressin is more specific for V1 receptors as compared to V2 receptors,[16] Consequently, terlipressin can contribute to contracting the splanchnic artery to reduce portal tension and increasing the kidney perfusion at the same time,[17] which have already been validated by animal models[18] and patients with portal hypertensive.[19] We consider that terlipressin may be a potential effective drug creating a positive impact on posthepatectomy recovery according to its mechanism, which was seldom reported up to now.

In this study, we intended to find out whether terlipressin is associated with better recovery of patients after hepatectomy. Furthermore, increasing number of patients in the face of hepatectomy are also suffering from parenchymal dysfunction,[1,6] especially fibrosis, which may cause portal hypertension and influence postoperative rehabilitation.[10,20,21] In view of this, we also took a further step to explore the effects that terlipressin exerts on the patients with different stages of fibrosis.

2. Methods

2.1 Patients

A total number of 106 patients were enrolled in this study from September 2018 to December 2019 retrospectively. Among them, 97 patients were diagnosed as hepatocellular carcinoma (HCC), 4 Intrahepatic cholangiocarcinoma (ICC), 2 focal nodular hyperplasia (FNH), 2 combined hepatocellular carcinoma and cholangiocarcinoma(cHCC-CC) and 2 hepatic hemangioma. All of them were evaluated and met the criterion of surgical intervention.

Inclusion criteria was regarded as: (1) age between 18 and 75; (2) liver resection was performed and was for the first time. Exclusion criteria was as follows: (1) preoperative liver function of Child-Pugh Class C; (2) renal dysfunction; (3) preoperative severe electrolytes imbalance; (4) severe cardiac, cerebral, pulmonary and other important organ diseases; (5) any other contraindications for terlipressin.This study was approved by Hospital Research Ethics Committee (IRB[S]NO:202005056) and informed consent was written by all patients.

2.2 Study design

As shown in Figure 1, firstly, we divided all patients into terlipressin group (T group) and control group (C group). Then, subgroup sets were created base on different stages of fibrosis. In other word, T group and C group were furthermore divided into high fibrosis stage subgroups (Th and Ch subgroup) and low fibrosis stage subgroups (Tl and Cl subgroup). Moreover, different fibrosis stages would be considered in its entirety respectively when we compare the efficacy of terlipressin between them.

In conclusion, comparison was implemented in three steps (Fig.1). In the first step, differences between terlipressin group and control group were initially investigated (T vs C group) in order to find its effect on overall population. Those effects proved functional by the first step were analyzed in the second step, to identify whether terlipressin is effective in different stages of fibrosis, in which comparison was made between two subgroups with same severity of fibrosis (Th vs Ch subgroup and Tl vs Cl subgroup). Moreover, if indicators were found different in both stage of fibrosis, then the third step was taken, so as to find out whether the efficacy on those indicators were distinct, by comparing patients with high stage fibrosis to those with low stage fibrosis using factorial design method.

2.3 Histological fibrosis classification and subgroup sets

Pathological section of non-lesion liver tissue was collected from each patient and was classified by two experienced pathologists in accordance with the Laennec staging system.[22] Low stage of fibrosis in this study is defined as stage 0,1,2 and 3 fibrosis; high stage otherwise be defined as stage 4, which is also regarded as cirrhosis according to the Laennec standard. All pathological sections were processed

with the hematoxylin-eosin (HE) staining method and examined by an Olympus BX53 microscopy.

Sample histological photomicrographs of different stages of fibrosis were shown in Figure 2 respectively.

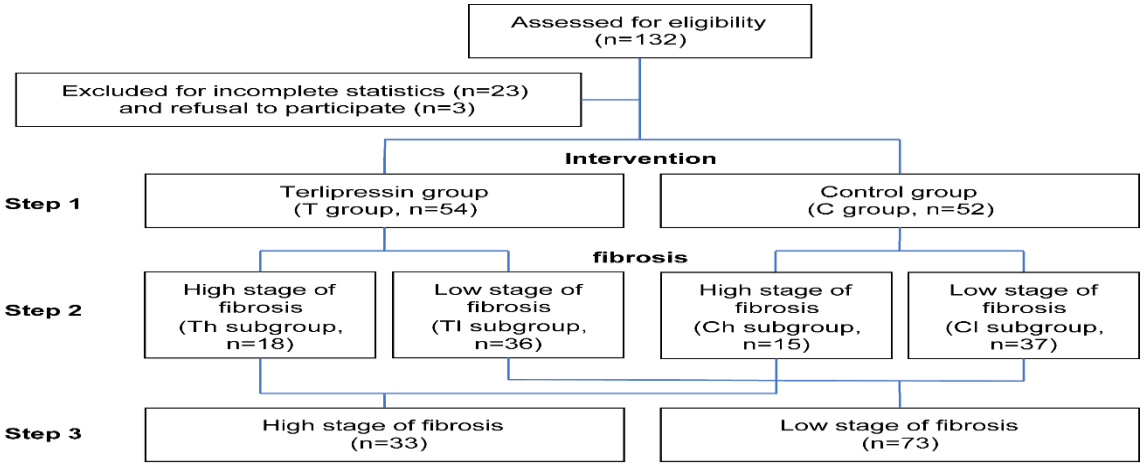

Figure 1. Flow chart of grouping methods and study design.

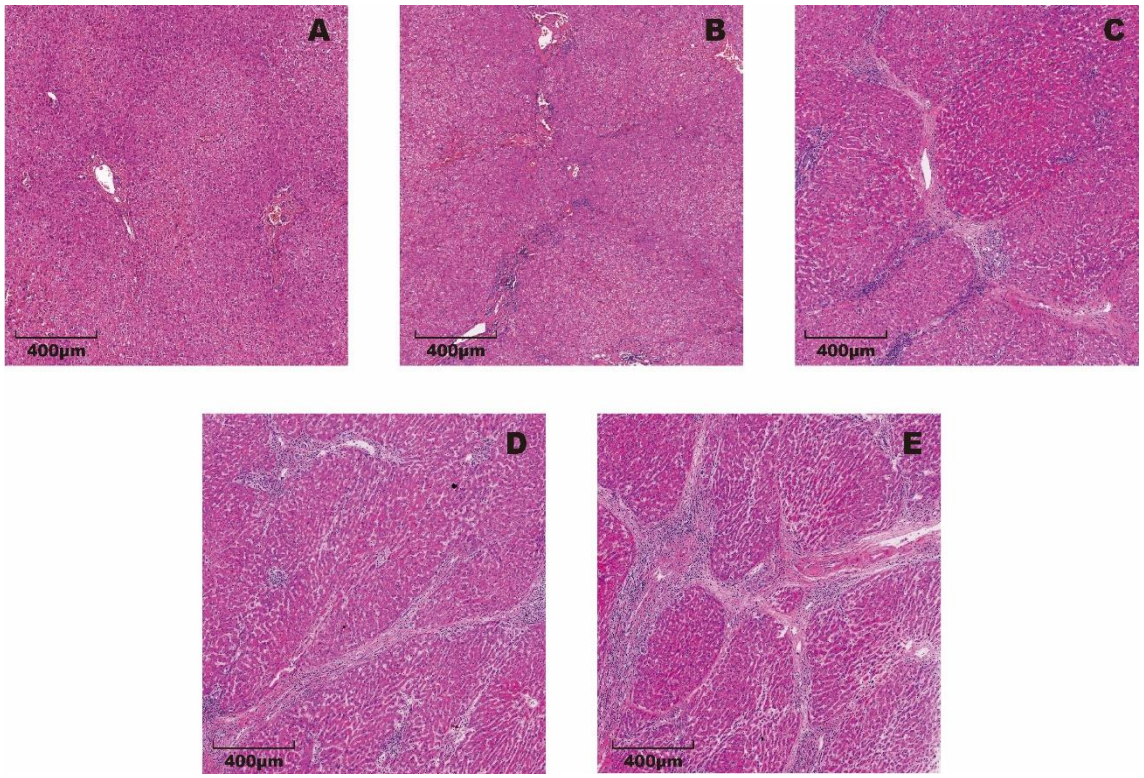

Figure 2. **Photomicrographs of different stages of fibrosis. Sample photomicrographs of different stages of fibrosis, which were shown as stage 0 (A), 1 (B), 2 (C), 3 (D) and 4 (E) respectively, based on the Laennec staging system.**

2.4 Pharmacological and surgical interventions

Conventional treatments were given in both T group and C group, comprising antibiotics and other symptomatic and supportive treatments. Certain amount of human serum albumin (HSA) was administrated in all patients to maintain the serum albumin concentrations above 35 g/L.

Patients in T group were additionally infused with 1 mg of terlipressin (FERRING GmbH, Germany) in 50 ml of normal saline, administered over 2 hours. The first dose was given until the patients' hemodynamics stayed steady after surgery and was followed by a dose every 12 hours for four days. The regimen used for hepatorenal

syndrome, which is in a relatively low level, was taken for our dosage above.[13]

Indocyanine green retention rate at 15 minutes (ICG15) and relative residual liver volume (RLV%) in addition to preoperative blood tests were used to evaluate the risk of hepatectomy. ICG15 was measured according to Au *et al*.[23] And we evaluated the RLV% by XP-Liver (Myrian, Version 1.14.1) following the methods provided by Schindl *et al*.[24] The extent of resection, the amount of intraoperative blood loss and blood transfusion, and the duration of Pringle maneuver were recorded. If 3 or more liver segments were removed, we defined it as a major resection. Relatively, minor resection means removal less than 3 segments.[25]

2.5 Clinical outcomes

The amount of abdominal drainage and urine were recorded every day for the first 3 days and 5 days respectively. The abdominal drainage was removed once no ascitic fluid was retained in abdomen via ultrasound detection and bile leakage was excluded[26]. Liver, renal and coagulation function in addition to serum electrolytes were accessed in the first five postoperative days through the daily routine blood tests.

Other definitions are explained below. Postoperative complications are graded by Clavien-Dindo classification,[27] comprising PHLF, ascites and bile leakage. As for PHLF, it is defined as an increased INR and hyperbilirubinemia on or after postoperative day 5.[28] Ascites is characterized by draining more than 500 ml clear fluid per day from abdomen. Bile leakage means bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after postoperative day 3 or need radiologic or operative intervention.[29] Moreover, the adverse drug effects of terlipressin were recorded as acute hypertension, electrolytes disorder and abdominal pain.

2.6 Statistical methods

Continuous variables are reported as mean (standard deviation[SD]) or median (interquartile range [IQR]), categorical variables are reported as numbers and percentages. The t-test and ANOVA are used to compare continuous variables; Chi-square test for categorical variables. SPSS (IBM, Version 26.0) was used for all calculations. A P value less than 0.05 indicates statistical significance.

3. Results

3.1 Baseline characteristics

Statistics of 106 patients were collected from September 2018 to December 2019, with 54 and 52 patients in terlipressin group and control group respectively. 97 of them are male (91.5%); Nine females (8.5%), with an average age of 53 years old. The population in low and high stages of fibrosis comes to 73 (68.9%) and 33 (31.1%) respectively. Major resection was done among 27 patients (25.5%) and other 79 (74.5%) patients were performed with a minor resection. The average amount of intraoperative blood loss and transfusion was 367ml and 42.4ml respectively, with the average 11.4 minutes of Pringle maneuver. All baseline statistics were compared between T and C group. No significant difference was found as shown in Table 1.

3.2 Abdominal drainage and urine

Substantial differences were noticed in the volume of both abdominal drainage and urine after hepatectomy. Patients intervened with terlipressin generated much less abdominal drainage than those who do not on the first day (250 vs 355 ml; p<0.001), second day (200 vs 300 ml; p<0.001), third day (30 vs 120 ml; p=0.001) and in all first three days after surgery (175 vs 280 ml; p<0.001). A reversed situation was shown on the amount of urine that the T group overwhelmed C group on the third day (2700 vs 2425 ml; p=0.018), fourth day (3250 vs 1925 ml; p<0.001), fifth day (3740 vs 2250 ml; p<0.001) and all first five days (2500 vs 1900 ml; p<0.001) (Fig. 3).

A similar trend was found in step 2 when we divided those patients into high and low levels of fibrosis subgroups. The medium overall volume of abdominal drainage and urine was found significant difference when Th vs Ch subgroup (abdominal drainage: 200 vs 350 ml; p<0.001, urine: 2490 vs 1995 ml; p=0.001) and Tl vs Cl subgroup (abdominal drainage: 150 vs 300 ml; p<0.001, urine: 2560 vs 1870 ml; p<0.001) (Fig. 3C and D).

3.3 Abdominal drainage retainment, anal exsufflation time, hospital stay and laboratorial outcomes

T group retained the abdominal drainage system for a shorter time than C group (3.9 vs 5.1 days, p<0.001) (Table 2) and the difference also existed in the second step analyze, with 4 vs 5.7 days (p=0.017) in high stage fibrosis cohort and 3.9 vs 4.9 days (p=0.007) in low stage fibrosis cohort (Table 3). Anal exsufflation time and length of stay for hospital were basically identical in two groups. No mortality happened in hospital during the whole period.

Table 1. **Baseline characteristics of patients from terlipressin group (T group) and control group (C group).**

	T group (n=54)	C group (n=52)	P value
Age, y	52.46 (10.44)	53.62 (13.69)	0.626
Gender			0.772
Male	49 (90.7%)	48 (92.3%)	
Female	5 (9.3%)	4 (7.7%)	
WBC, $\times10^9$/L	4.87 (1.88)	5.27 (1.4)	0.223
PLT, $\times10^9$/L	142.57 (85.3)	155.00 (75.46)	0.429
ALB, g/L	40.62 (4.26)	41.02 (3.82)	0.611
TB, μmol/L	14.21 (5.84)	12.78 (6.05)	0.220
Cr, μmol/L	81.05 (14.93)	84.23 (20.66)	0.365
PT, s	14.05 (1.42)	13.71 (1.77)	0.278
RLV, % (IQR)	76.9 (58.0-88.3)	81.3 (67.5-88.0)	0.576
ICG15, %	7.80 (5.60)	7.02 (4.42)	0.428
Intraoperative bleeding, mL	362.04 (271.95)	372.31 (350.48)	0.866
Pringle maneuver, min	8.83 (13.13)	7.77 (11.07)	0.653
Tumor size, cm	6.26 (4.46)	5.57 (3.95)	0.399
Tumor number			0.930
1	45 (83.3%)	43 (82.7%)	
>1	9 (16.7%)	9 (17.3%)	
Child-Pugh score			0.777
5	43 (79.6%)	44 (84.6%)	
6	10 (18.5%)	7 (13.5%)	
7	1 (1.9%)	1 (1.9%)	
Operation extent			0.913
Major	14 (25.9%)	13 (25.0%)	
Minor	40 (74.1%)	39 (75.0%)	
Laennec stage			0.975
0	3 (5.6%)	4 (7.7%)	
1	9 (16.7%)	8 (15.4%)	
2	13 (24.1%)	13 (25.0%)	
3	11 (20.4%)	12 (23.1%)	
4	18 (33.3%)	15 (28.8%)	
Indication for Surgery			0.683
HCC	50 (92.6%)	47 (90.4%)	
Others	4 (7.4%)	5 (9.6%)	

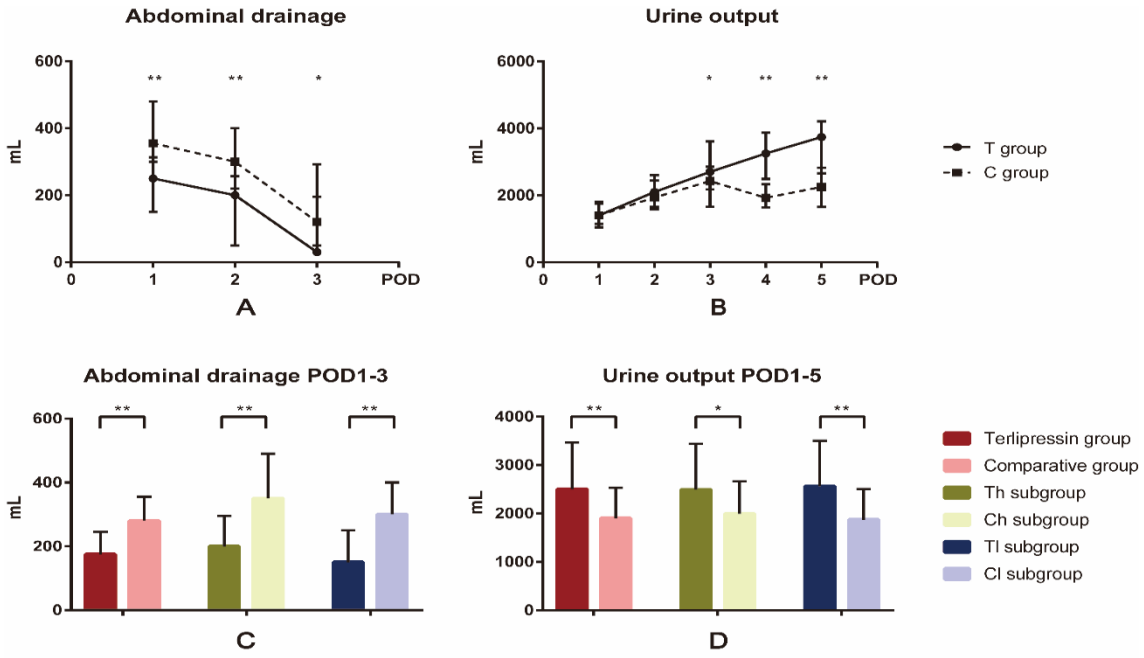

Figure 3. **The amount of abdominal drainage and urine output.**

Patients in terlipressin group had less abdominal drainage volume (A) on the first, second and third day (p<0.001, p<0.001, p=0.001), more urine output (B) on the third, fourth, fifth day (p=0.018, p<0.001, p<0.001). Similar results were found in the overall amount of abdominal drainage (C) and urine output (D), within Terlipressin vs Control group (abdominal drainage: p<0.001, urine: p<0.001), Th vs Ch subgroup (abdominal drainage: p<0.001, urine: p=0.001) and Tl vs Cl subgroup (abdominal drainage: p<0.001, urine: p<0.001). POD, postoperative day. *p < 0.05; **p < 0.001

Table 2. **Comparison of clinical outcomes, laboratory tests and adverse drug effects between terlipressin group (T group) and control group (C group).**

	T group (n=54)	C group (n=52)	P value
Cr, μmol/L			
POD1	85.4 (16.9)	89.1 (15.9)	0.246
POD2	85.7 (23.9)	87.5 (21.8)	0.686
POD3	76.0 (19.4)	83.2 (20.2)	0.063
POD4	70.9 (18.4)	78.4 (15.6)	0.025
POD5	69.8 (19.3)	76.6 (13.8)	0.040
TB, μmol/L			
POD1	23.6 (8.9)	25.2 (9.9)	0.398
POD2	28.6 (12.7)	25.4 (11.1)	0.167
POD3	21.4 (9.7)	21.6 (7.9)	0.915
POD4	25.6 (21.5)	20.9 (8.7)	0.149
POD5	24.0 (21.6)	19.7 (9.2)	0.188
ALB, g/L			
POD1	34.1 (4.6)	34.9 (5.0)	0.430
POD2	36.5 (3.3)	37.1 (4.3)	0.481
POD3	34.5 (3.1)	35.0 (2.8)	0.376
POD4	34.7 (2.7)	34.7 (2.7)	0.973
POD5	34.7 (2.4)	34.0 (2.8)	0.199
HSA supplement, g	73.5 (34.8)	62.5 (34.4)	0.104
PT, s			
POD1	16.1 (1.8)	16.0 (1.7)	0.912
POD2	16.7 (2.3)	16.7 (1.8)	0.884
POD3	16.4 (2.1)	16.5 (1.9)	0.792
POD4	15.5 (1.7)	15.1 (2.0)	0.215
POD5	15.3 (2.1)	15.2 (2.6)	0.799
Hospital stay, d	7.7 (2.9)	7.7 (3.1)	0.957
Abdominal drainage retainment, d	3.9 (1.4)	5.1 (1.9)	0.000
Anal exsufflation time, d	3.1 (0.5)	3.1 (0.4)	0.975
Adverse drug effects			
Total patients with adverse effects	28 (51.9%)	17 (32.7%)	0.046
Abdominal pain	5 (9.3%)	2 (3.8%)	0.262
Acute hypertension	3 (5.6%)	2 (3.8%)	0.678
Hypokalemia	10 (18.5%)	12 (23.1%)	0.563
Hyponatremia	17 (31.5%)	3 (5.8%)	0.001
Postoperative complications			
Total patients with complications	12 (22.2%)	17 (32.7%)	0.227
Bile leakage	2 (3.7%)	3 (5.8%)	0.616
Ascites	6 (11.1%)	13 (25.0%)	0.062
PHLF	2 (3.7%)	3 (5.8%)	0.616
Clavien-Dindo classification			0.765
I	11 (91.7%)	15 (88.2%)	
II	1 (8.3%)	2 (11.8%)	

Routine blood tests were implemented for the first five days after the operation in order to follow the variation towards the patients' liver, renal and coagulation function and serum electrolytes. We

found that creatine (Cr) level in T group was much lower than that in C group on the fourth day (71 vs 78 μmol/L; p=0.025) and the fifth day (70 vs 77 μmol/L; p=0.04) (Table 2), which was also found in the subgroups of high stage fibrosis on the fourth day (73 vs 84 μmol/L; p=0.044) and the fifth day (71 vs 82 μmol/L; p=0.047), but not in the low ones (Table 3). No significant difference was found among other indexes.

Table 3. **Comparison of Cr level and abdominal drainage retainment time within high stage (Th vs Ch subgroup) and low stage (Tl vs Cl subgroup) of fibrosis subgroups.**

	Th subgroup (n=18)	Ch subgroup (n=15)	P value†	Tl subgroup (n=36)	Cl subgroup (n=37)	P value‡
Cr, μmol/L						
POD1	96.9 (15.0)	87.4 (14.4)	0.074	86.0 (15.4)	84.4 (18.1)	0.691
POD2	97.4 (25.3)	86.2 (17.0)	0.138	83.5 (19.1)	85.5 (26.9)	0.717
POD3	90.2 (25.0)	78.8 (16.9)	0.131	80.3 (17.5)	74.5 (20.6)	0.198
POD4	72.7 (13.0)	83.8 (17.3)	0.044	70.0 (20.6)	76.2 (14.5)	0.138
POD5	71.1 (16.2)	82.0 (13.6)	0.047	69.1 (20.9)	74.4 (13.5)	0.201
Abdominal drainage retainment, d	4.0 (1.6)	5.7 (2.2)	0.017	3.9 (1.3)	4.9 (1.8)	0.007

Continuous Data displayed as mean (SD). Abbreviations: Cr, creatine; POD, postoperative day. †: Comparison between Th and Ch subgroup. ‡: Comparison between Tl and Cl subgroup.

3.4 Pharmacological efficacy between different fibrosis stages

Indicators including the volume of abdominal drainage, urine output and abdominal drainage removal time were found different in both stages of fibrosis in step 2. Then, the third step of comparison was implemented to investigate whether the efficacy of terlipressin on those indicators was distinct in different severity of fibrosis. Factorial design method was used for analyzing, whereas no difference was found as shown in Table 4.

Table 4. **Pharmacological efficacy between different fibrosis stages.**

	F	P value
Abdominal drainage		
POD1	0.134	0.715
POD2	3.483	0.065
POD3	0.035	0.853
POD1-3	0.786	0.376
Urine output		
POD1	1.048	0.308
POD2	0.755	0.387
POD3	0.185	0.668
POD4	0.131	0.718
POD5	0.215	0.644
POD1-5	0.080	0.778
Abdominal drainage retainment	0.800	0.373

Statistical comparison by factorial design method. Median value was used in abdominal drainage and urine output. Mean value was used in abdominal drainage retainment time. Abbreviations: POD, postoperative day

3.5 Adverse drug effects and complications

Adverse drug effects happened in 28 (51.9%) patients from T group and 17 (32.7%) patients from C group with significant difference (p=0.046). Specifically, the incidence of hyponatremia is much higher in T group than C group (31.5% vs 5.8%, p<0.001), while distinctions in other adverse effects of drug were found insignificant. A total number of 29 (27%) patients suffered from postoperative complications, with 26 in Clavien-Dindo grade one and 3 in grade two, no difference between two groups (p=0.765). Ascites tended to inflict patients in C group more than T group (13 vs 6, p=0.062), whereas no difference was found in addition to other complications (Table 2).

4. Discussion

The conception of posthepatectomy recovery is so broad that we can hardly define, as it is composed of various factors such as the variation of laboratorial indicators, amount of abdominal drainage and urine, length of hospital stays, time of abdominal drainage removal, complications and so on. What is more, it is playing an even more critical role in the whole process of liver tumor treatment since the safety of hepatectomy has been significantly heightened. Terlipressin, seems to provide us a new approach. In this study, we administered terlipressin in part of those patients with different stages of fibrosis, and we found it could accelerate posthepatectomy recovery in some aspects.

Firstly, our results indicated that terlipressin could decrease the amount of abdominal drainage, thus shorten the period of abdominal drainage retainment. This effect may account for the pharmacological effects of terlipressin which could reduce the pressure of portal vein[30] contributing to less amount of abdominal drainage.[31] Although previous studies has reported that the regeneration of liver after hepatectomy was improved in rat models,[32] no substantial improvement was found in liver function related indexes (TB, ALB, PT) in addition to the amount of total HSA supplement. The reason of that may, on the one hand, account for the difference between animal model and human, on the other hand be explained that the recovered liver volume is not in coordinate with functional improvement.[33] Anyhow abdominal drainage system can be removed earlier, which directly speed up the postoperative recovery. Terlipressin could also increase the urine output and lower the Cr level, which is identical with its pharmacological effects of increasing the kidney perfusion.[11] It was also reported by Kam *et al* that postoperative renal function was improved in the use of terlipressin after liver transplantation, which is consistent with our results.[34]

Subsequently, we found that the abdominal drainage volume, urine output and the duration of abdominal drainage retainment are all significantly different in both stages of fibrosis, which means terlipressin may be effectual for those indicators in all patients regardless of fibrosis status. What noticeable is that the decrease of Cr only observed in patients with high stage fibrosis, which suggests that the effect of terlipressin in improving renal function may be more significant for those with severer fibrosis instead of milder ones.

Whereas in the third step of our research, when we use factorial design method to analyze the efficacy between different fibrosis stages, we found that terlipressin was effective and had basically the same efficacy towards all patients with different severity of fibrosis, in terms of abdominal drainage volume, urine output and duration of abdominal drainage retainment.

The intervention of terlipressin did not seem to affect the incidence of postoperative complications, which is identified with previous study.[35] And the extent of complications based on Clavien-Dindo classification was found no significant difference either. However, adverse drug reactions specifically hyponatremia occurred more frequently in terlipressin group, even though those side effects were subtle under most circumstances and could be corrected easily with supplement of electrolytes. Similar report was noticed when terlipressin was utilized in variceal bleeding and it was believed that hyponatremia may be explained by the increased water reabsorption moving electrolyte-free water into the blood circulation through V2 receptors.[36] The equivalent anal exsufflation time between two groups may imply that terlipressin exerts a minimum influence on intestinal function recovery after hepatectomy.

As far as we know, this is by far the only novel study to explore the effect of terlipressin on posthepatectomy recovery based on different histology situations. We further elaborated that terlipressin may affect differently among patients with different stages of fibrosis.

There are also several limitations in this study. Firstly, the sample size is limited which may influence the credibility of our results to some extent. Secondly, as a retrospective study, we were not able to measure portal vein pressure. So, we could not validate whether the highlights we found was account for the decrease of portal vein pressure in this study. Hence, an RCT with a relatively large sample size is anticipated to make a further study.

In conclusion, we have learnt that terlipressin may have a positive effect on reducing abdominal drainage, increasing urine output, accelerating abdominal drainage removal in patients regardless of stages of fibrosis, and offer a better protection of renal function in patients with severer fibrosis.

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