Terlipressin infusion during Whipple procedure: effect on blood loss and transfusion needs – a randomized clinical trial

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Context
Multivisceral resections including Whipple procedure are among the foremost common oncologic procedures during which massive bleeding and transfusion might happen intraoperatively or postoperatively. Terlipressin is a synthetic vasopressin analog with relative specificity for the splanchnic circulation where it causes vasoconstriction, with a hypothetical reduction in blood loss during abdominal surgeries.

Aims
We aim to assess the effect of terlipressin infusion on blood loss and blood transfusion requirements during Whipple procedure.

Settings and design
The current study was a prospective single center randomized placebo-controlled trial. The study was carried out in Al Rajhy Liver Hospital, Assiut University, Egypt between May 2016 and July 2017.

Patients and methods
In this trial 40 patients scheduled for Whipple procedure were randomly assigned either to receive terlipressin at the beginning of surgery as an initial bolus dose of (1 mg over 30 min) followed by a continuous infusion of 2 μg/kg/h throughout the procedure and gradually weaned over the first 4 h postoperatively (terlipressin group) or to receive the same volume and rate of 0.9% saline for the same duration (control group).The primary outcome was the amount of intraoperative blood loss.

Statistical analysis used
Statistical analysis was established using SPSS, version 16.0.

Results
The amount of intraoperative blood loss was significantly lower in the terlipressin group (690.00 ± 449.44) in comparison with the control group (1020.00 ± 284.88). Five (25%) patients received blood transfusion in the terlipressin group compared with 13 (65%) patients in the control group ($P = 0.011$). Significantly greater number of packed red blood cells units were transfused to the control group ($P = 0.013$).

Conclusion
Terlipressin infusion during Whipple procedure was associated with less bleeding and lower rates of blood transfusion requirements compared with placebo.

Keywords:
blood loss, terlipressin, transfusion needs, Whipple procedure

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Introduction

A pancreaticoduodenectomy or Whipple procedure is one of the most complicated general surgical operations. It is most often performed for tumors of the head of the pancreas. The procedure involves resection of the head of the pancreas, the duodenum, the proximal jejunum, the distal third of the stomach, and the lower half of the common bile duct followed by biliary, pancreatic, and gastric anastomoses to the jejunum [1].

Patients experiencing major oncological surgery are in danger for serious bleeding and massive blood transfusion because of tumor characteristics, preoperative chemoradiation, anatomic features of the surgical area (vascular closeness), intricacy of resection, duration of surgery, perioperative hypothermia, metabolic derangements, and intraoperative dilutional coagulopathy (blood transfusions and fluid administration). It is in this way significant for the anesthesia team to have an unmistakable comprehension of every one of those elements and to work intimately with a productive, and experienced careful group to limit perioperative blood loss [2].

It has been suggested that patients with cancer are more likely to be transfused with blood products than noncancer patients [3]. In addition, an unknown percentage of these patients are in danger for massive blood transfusion [4]. Massive blood transfusions during oncological surgery can be foreseen or unexpected.

In the former situation, since anesthesiologists, surgeons, and the blood bank services are aware of the likelihood of massive blood transfusion, precautionary measures are assumed to limit blood loss and maximize efficiency of blood product accessibility and administration. Unexpected cases of massive blood loss require quick control of surgical bleeding and measures to expeditiously assess the hemostatic defect [2].

Multivisceral resections are among the foremost common oncologic procedures during which massive bleeding and transfusion might happen intraoperatively or postoperatively [2]. The blood loss in these procedures ranges from 300 to 5000 ml [5]. In contrast to liver resection, most blood transfusions in multivisceral procedures are usually administered intraoperatively, and of course, extensive procedures involving additional organs/structures are associated with the biggest number of transfusions (0–44 U) compared with palliative procedures (0–15 U) or standard resections (0–35 U) [6,7].

More significantly, blood loss and transfusion of blood considerably have an effect on postoperative morbidity and mortality [2]. Several authors have investigated the utilization of controlled hypotension, preoperative tumor embolization, temporary aortic occlusion, and the administration of antifibrinolytic therapy to decrease blood loss and future blood transfusions [3,8–11].

Terlipressin is a synthetic vasopressin analog with relative specificity for the splanchnic circulation where it causes vasoconstriction, with a hypothetical reduction in blood loss during abdominal surgeries [12].

In spite of the fact that there are generally few researches of plasma concentrations after bolus injection, it has been reported that bolus injection might cause sustained global or regional vasoconstriction [13]. On the opposite hand, continuous infusion of terlipressin in a low dose has been reported to be powerful in attenuating sepsis-induced arterial hypotension once given as a first-line vasoconstrictive agent [14].

Up to our data, no previous studies were done on the impact of terlipressin during Whipple procedures. Therefore, the present study aims to look at the effect of terlipressin infusion on blood loss and blood transfusion needs during Whipple procedure.

Patients and methods

Patients and design

The current study was a prospective single center randomized double-blind placebo-controlled trial registered at *http://www.clinicaltrials.gov* (NCT03572088). The study was carried out in Al Rajhy Liver Hospital, Assiut University, Egypt between May 2016 and July 2017. The study protocol was approved by Assiut Medical School Ethical Review Board. All participants signed informed consent before to inclusion within the study.

All patients older than 18 years of age, American Society of Anaesthesiology classification class I and II and assigned for Whipple procedure were included in this study. Exclusion criteria were patients with preoperative renal failure, severe liver dysfunction (Child–Turcotte–Pugh grade C), hyponatremia (Na^+ <132 mmol/l), severe valvular heart disease, heart failure, symptomatic coronary heart disease, bradycardic arrhythmia [heart rate (HR) <60/min], peripheral artery occlusive disease (clinical stadium II–IV), uncontrolled arterial hypertension (blood pressure >160/100 mmHg despite intensive treatment), and pregnancy.

Blinding and randomization

Patients' randomization was done just before the beginning of surgery by a computer randomization system to ensure adequate allocation concealment and assigned to receive either terlipressin (T; n = 20) or normal saline (C; n = 20) and given random numbers by a study coordinator, who also encodes the drugs with matching random numbers. Neither the researcher monitoring the outcomes (the attending anesthetist) nor the surgeon knew which patient is receiving which treatment until the study is over and the random code is revealed. All cases recruited to the study were done by one of two surgeons.

Interventions

Anesthesia was induced in all patients with propofol (2 mg/kg) and fentanyl (1 μg/kg). Muscle relaxation for intubation was achieved by rocuronium (0.6–0.8 mg/kg) in both groups. Anesthesia was maintained with sevoflurane 1 MAC in medical air oxygen mixture (fraction of inspired oxygen 0.5), fentanyl infusion (1 μg/kg/h), and rocuronium infusion (0.01–0.012 mg/kg/min). Mechanical ventilation was controlled through a tidal volume of

6–8 ml/kg, and the ventilator rate (8–12/min) was adjusted to maintain an end-tidal CO_2 of 35–40 mmHg. Intraoperative normothermia was achieved by the means of warm intravenous fluids, warm blanket, and humidifier. A 3-lumen central venous catheter was placed through the right internal jugular vein, and central venous pressure (CVP) was monitored. A 22-G angiocatheter was inserted into the radial artery (after performing modified Allen's test) and connected to the FloTrac/Vigileo monitor (software version 1.14; Edwards Life sciences, Irvine, California, USA) for monitoring of cardiac output (CO), cardiac index (CI), stroke volume variation (SVV), and systemic vascular resistance (SVR). All intravascular pressure measurements were referenced to the mid-axillary line level.

In group T, terlipressin was started at the beginning of surgery as an initial bolus dose of 1 mg over 30 min followed by a continuous infusion of 2 μg/kg/h throughout the procedure and gradually weaned over the first 4 h postoperatively. In the group C, patients received the same volume of normal saline. Intraoperative basal fluid replacement was attained in both groups through infusion of crystalloids (6–8 ml/kg/h), additional boluses of colloid solution in a dose of 3 ml/kg (Voluven 130/0.4 6%; Fresenius Kabi AG, Bad Homburg, Germany, Tetraspan 130/0.4 6%; B.Braun Melsungen Ag, Melsungen, Germany) were given when SVV raised above 12% (a sustained rise during the previous 5 min). Transfusion of packed red blood cells was allowed if the hemoglobin level has diminished below 7 g/dl, or reaching the maximum allowable blood loss. All patients were transferred postoperatively to the postanesthesia care unit.

Intraoperative data collection was done at 15 min after anesthesia induction, then every 30 min till the end of operation included HR, mean arterial blood pressure (MAP), CVP, CO, CI, SVV, SVR, and urine output (UOP). Fluid input (crystalloids, colloids, packed red blood cells, fresh–frozen plasma), and output (UOP, blood loss) were recorded. The mean postoperative hemodynamic data (HR, MAP, and UOP) were recorded from the averaged 24 h measurements of the first day after surgery. Hemoglobin and serum creatinine levels were also reported preoperative as a baseline and daily for the first three postoperative days.

Study outcomes

The primary outcome was the amount of intraoperative blood loss, that was recorded at the end of the operation by taking under consideration surgical sponges, suction canisters, and the cell salvage device (if used). Secondary outcomes included the number of patients needing blood transfusion, the number of red blood cell units transfused, hospital stay, and ICU stay.

Sample size

Sample size was calculated based on the primary outcome (the amount of intraoperative blood loss). Based on the results of previous study[15] and assuming that terlipressin infusion is effective in reducing blood loss by 25%, 20 participants in each group will have 80% power at 5% significance to detect such a difference, (Epi-info: Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Statistical analysis

Data were presented as a mean ± SD for parametric data, median for nonparametric data, ratios, and percentages as appropriate. Continuous data with normal distribution were compared by paired or unpaired *t* tests, non-normally distributed data were assessed using Mann–Whitney *U* test and Wilcoxon rank-sum test for unpaired and paired results, respectively. χ^2 test measured the association between qualitative variables. Statistical analysis was established using SPSS, version 16.0 (SPSS Inc., Chicago, Illinois, USA) for Windows. A *P* value of less than 0.05 was considered to be statistically significant.

Results

A total of 40 patients were enrolled in this study and randomly allocated to the two groups as shown in the CONSORT flow-chart (Fig. 1). There were no significant differences between both groups with regard to demographic data, clinical, and perioperative characteristics, comorbid risk factors, nor the duration of surgery (Table 1).

Hemodynamic changes are shown in Table 2. There were significant increases of intraoperative MAP and SVR as compared with their baseline values in the terlipressin group only, and there were a significantly higher intraoperative MAP and SVR in terlipressin group in comparison with the control group. Two patients in control group versus no patients in the terlipressin treated group required norepinephrine as a vasopressor but this was statistically insignificant (Table 2).

No significant difference was observed between both groups concerning HR, CVP, and SVV. There were significant reductions of CO and CI when compared with their baseline values in group T only, and there were a significantly lower intraoperative CO and CI in terlipressin group in comparison with the control group (Table 2).

Table 1 Demographic, clinical, and surgical variables

Parameters	T group (*n*=20)	C group (*n*=20)	*P*
Age (years)	54.35±2.99	53.25±9.16	0.613
Sex (male/female)	12/8	11/9	0.749
Weight (kg)	65.80±13.77	66.25±7.88	0.900
Height (cm)	160.15±8.93	163.50±3.26	0.124
BMI (kg/m^2)	25.50±3.88	24.82±3.28	0.557
ASA			
ASA I	3 (15)	7 (35)	0.144
ASA II	17 (85)	13 (65)	
Duration of surgery (h)	6.00 (5-8)	6.00 (4-9)	0.910

Data are presented as mean±SD, median (26) or *n* (%). ASA, American Society of Anesthesiologists. *P*<0.05 was considered statistically significant.

Table 2 Hemodynamic variables

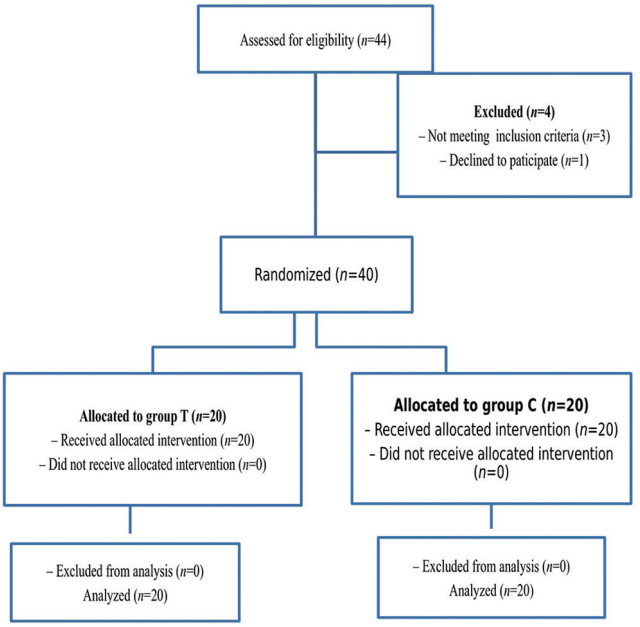
Parameters	T group (*n*=25)	C group (*n*=25)	*P*
Crystalloids (ml)	3000 (2000-4000)	3500 (2000-6500)	0.146
Colloids (ml)	0.00 (0-500)	0.00 (0-500)	0.382
RBCs (U)	0.00 (0-1)	0.00 (0-2)	0.013#
FFP (U)	0.00 (0-2)	0.00 (0-2)	0.253
Blood loss (ml)	690.00±449.44	1020.00±284.88	0.009#
ICU stay (days)	1.00 (1-3)	2.00 (1-3)	0.379
Hospital stay (days)	5.00 (4-10)	8.00 (2-20)	0.108
Complications			
AKI (number of patients)	1 (4)	2 (8)	0.50
Hematoma (number of patients)	0 (0)	1 (4)	0.50

Data are presented as mean±SD or median (26) or *n* (%). RBC, red blood cell. *P*<0.05 was considered statistically significant.
#Significant difference between the two groups.

The amount of intraoperative blood loss was significantly lower in the terlipressin group (690.00 ± 449.44) in comparison with the control group (1020.00 ± 284.88) (Fig. 2, Table 3). Five (25%) patients received blood transfusion in the terlipressin group compared with 13 (65%) patients in the placebo group (P = 0.011). Significantly greater number of packed red blood cells units were transfused to the placebo group (P = 0.013). But there were no significant differences between the two groups regarding the number of transfused fresh–frozen plasma units, fluid requirements (crystalloids and colloids), the total number of patients who developed postoperative hematoma (Table 3), or hemoglobin level (Table 4).

UOP was significantly higher in the T group than C group during the intraoperative period and during the first postoperative day (Table 2), and this was reflected on serum creatinine level that was significantly lower in the T group than C group during the first postoperative day (Table 4). But there was no significant difference in the total number of patients who developed renal complications [acute kidney injury (AKI)] (Table 3). Moreover, there were no statistically significant differences in the duration of ICU stay or hospital stay between the two groups (Table 3).

Figure 1



Consort flow diagram.

Discussion

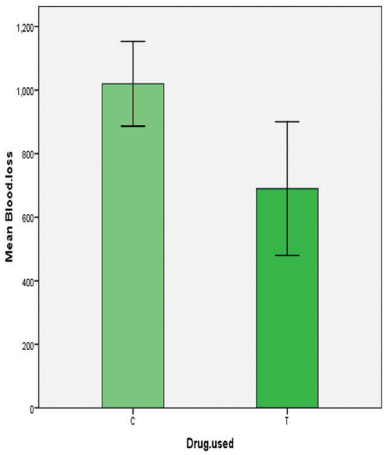
The current study demonstrated that terlipressin infusion during the Whipple procedure diminished blood loss and blood transfusion needs. There is increasing interest in medications, for example, vasopressin that can be used during surgery to selectively limit blood flow to the gut to reduce surgical bleeding [16].

In line with our results, Fayed and colleagues evaluated the impact of intraoperative and postoperative terlipressin infusion on systemic, hepatic, and renal hemodynamics during adult living donor liver transplantation. Their results demonstrated that intraoperative blood loss was significantly lower in the terlipressin group than in the control group [2212.5 (679) vs. 2787.5 (812) ml, respectively; P<0.05) [17].

Johnson and Murphy explored the impact of desmopressin on intraoperative blood loss during lumbar fusions in 42 patients (52 operations) and compared with a control group of 55 patients (63 operations). They found that mean hemoglobin and hematocrit levels on admission and discharge were indistinguishable for both groups. They likewise detailed that patients treated with desmopressin required less than one-half the number of autologous transfusions than the control group. In addition, desmopressin was successful in diminishing blood loss in operations in which intraoperative bleeding was more noteworthy than 1000 ml [18].

Rather than our results, Mukhtar and colleagues evaluated the effect of terlipressin infusion on systemic

Figure 2



Intraoperative blood loss.

and splanchnic hemodynamics and renal function during living donor liver transplantation. Their results showed that the amount of intraoperative blood loss was comparable among both groups (2350 ± 895 and 2800 ± 1000 ml in terlipressin and control groups, respectively) [13].

Albeit no information on the impact of vasopressin/terlipressin on intraoperative bleeding in Whipple procedure are available, terlipressin has been appeared to diminish blood loss in liver transplantation in patients with portal hypertension [17]. This has been ascribed to the fall in portal venous pressure seen with vasopressin due to precapillary mesenteric vasoconstriction (mediated by terlipressin action through V1 receptors in the vascular smooth muscle in the splanchnic blood vessels) and a pressure drop along the intestinal vascular bed with a consequent fall in portal venous pressure.

Raedler *et al.*[19] showed that vasopressin diminished bleeding and improved outcome after blunt liver trauma and uncontrolled hemorrhagic shock in a pig model. Recently, short-term vasopressin injection was effectively utilized during liver transplantation with a significant decrease in portal venous pressure with no evidence of splanchnic hypoperfusion [20].

We found that terlipressin increased the intraoperative MAP and SVR with a significant reduction in CO and CI (but remained within the accepted clinical ranges). The results of the present study support the findings of Narahara *et al.* [21], who also reported the effect of terlipressin injections on systemic hemodynamics in patients with cirrhosis. However, Wagener *et al.* [20], as well as Mukhtar *et al.*[13] in their studies did not observe any decrease in CO during the infusion of terlipressin.

Traditionally, terlipressin has been administered by intermittent intravenous bolus injection rather than by continuous infusion. Late studies have proposed that terlipressin may likewise be administered as a low-dose continuous infusion (1.3–2.6 μg/kg/h) in the early course of distributive shock. This approach

Table 3 Differences in fluid requirements, transfusions, blood loss, complications, ICU stay, and hospital stay between terlipressin group (T) and control group (C)

Parameters	T group (*n*=25)	C group (*n*=25)	*P*
HR (beat/min)			
Baseline	78.25±3.72	77.85±8.33	0.846
Intraoperative	77.92±10.78	74.76±7.08	0.280
Postoperative	83.30±14.62	79.90±8.60	0.376
MAP (mmHg)			
Baseline	83.20±8.32	84.15±11.60	0.768
Intraoperative	91.78±6.81*	85.93±4.34	0.003#
Postoperative	84.60±11.18	84.45±6.57	0.959
CVP (mmHg)			
Baseline	13.65±1.92	13.15±2.73	0.508
Intraoperative	12.27±2.77	12.20±3.17	0.937
Postoperative	8.70±1.59*	7.85±1.49*	0.090
CO (l/min)			
Baseline	5.57±1.40	6.24±1.42	0.139
Intraoperative	5.31±0 0.95	6.28±1.28	0.010#
CI (l/min/m^2)			
Baseline	3.31±0 0.78	3.58±0 0.72	0.266
Intraoperative	3.09±0.21	3.55±0 0.56	0.001#
SVV (%)			
Baseline	5.85±3.29	6.95±2.23	0.224
Intraoperative	10.30±2.40*	10.08±1.33*	0.721
SVR (dyne.s/cm^5)			
Baseline	976.35±260.29	933.05±308.87	0.634
Intraoperative	1142.14±213.83*	949.47±213.54	0.007#
UOP (ml/kg/h)			
Intraoperative	2.81±2.27	0.909±0.465	0.001#
Postoperative day 1	2.31±1.91	0.88±0.25	0.002#
Number of patients needing inotropes	0 (0)	2 (10)	0.090
Inotropic score (points)	0.00 (0-2)	0.00 (0-4)	0.152

Data are presented as mean±SD or median (26) or *n* (%). CI, cardiac index; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial blood pressure; SVR, systemic vascular resistance; SVV, stroke volume variation; UOP, urine output. *P*<0.05 was considered statistically significant. *Significant difference in comparison to the baseline value within the same group. #Significant difference between the two groups.

Table 4 Perioperative laboratory values

Parameters	T group (*n*=25)	C group (*n*=25)	*P*
Hb (g/dl)			
Preoperative	11.70±1.05	12.10±21.71	0.385
Day 1	11.60±1.06	11.41±1.75	0.681
Day 2	10.51±1.24	10.65±1.32	0.741
Day 3	10.80±0.92	10.31±0.63	0.068
Creatinine (μmol/l)			
Preoperative	76.20±10.43	83.55±34.11	0.363
Day 1	56.20±16.76*	72.85±17.12*	0.004#
Day 2	69.05±27.01	84.40±42.50	0.181
Day 3	72.10±7.09	74.45±6.67	0.287

Data are presented as mean±SD or median (26). Hb, hemoglobin. *P*<0.05 was considered statistically significant. *Significant difference in comparison to the baseline value within the same group. #Significant difference between the two groups.

adequately increased SVR without undesirable side-effects, such as an exaggerated increase in peripheral resistance [22,23]. The doses used in our study were like the range of doses previously used for low-dose infusion.

Terlipressin administration can also improve renal functions through several mechanisms. First, decreasing plasma concentrations of rennin, aldosterone, and norepinephrine. This reduction in the vasoconstrictors leads to an increase in renal blood flow [21,24]. Second, improvement of MAP and SVR. Third, splanchnic vasoconstriction that reduces portal venous pressure, and shifts blood to systemic circulation maintaining systemic perfusion of the kidney, and thus offers some renal protection [25].

In our study, patients treated with terlipressin demonstrated a significant increase in UOP during the intraoperative period and during the first postoperative day with a significant reduction in serum creatinine during the first postoperative day compared with controls. Terlipressin increases UOP not only due to improvement in renal function but also by stimulating V1a receptors [25]. The incidence of postoperative complications including renal dysfunction in patients given intraoperative terlipressin infusion was not significantly different from the control.

Limitations

First, the relatively small number of patients. Second, we included patients with and without portal hypertension as portal pressure was not measured during the study. Finally, the study was not powered enough to assess the secondary outcomes as the occurrence of adverse events from terlipressin. Nevertheless, the present study is significant in that it demonstrates the beneficial effects of low-dose terlipressin infusion on reducing blood loss and blood transfusion needs during Whipple procedure.

Conclusion

Terlipressin infusion during Whipple procedure was associated with less bleeding and lower rates of blood transfusion requirement compared with placebo. Further trials should be done to confirm our results.

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Conflicts of interest

There are no conflicts of interest.

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