Desmopressin does not decrease blood loss and transfusion requirements in patients undergoing hepatectomy

[La desmopressine ne réduit pas les pertes sanguines et les besoins de transfusion pendant l'hépatectomie]

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Purpose: To determine the effects of desmopressin on coagulation and blood loss in patients undergoing elective partial hepatectomy.

Methods: A randomized, controlled and double-blind study on 59 patients who received either 0.3 $\mu g \cdot kg^{-1}$ of desmopressin or an equal volume of normal saline (control) infused intravenously over 20 min after induction of general anesthesia.

Results: There was an increase in plasma levels of factors VIII and von Willebrand after the infusion of study drug in both groups ($P < 0.001$). The activated partial thromboplastin time was shortened in Group D whereas prothrombin time was prolonged in Group C; ($P = 0.02$). A large range of intraoperative blood loss (400–7128 mL) was observed, with no significant differences between groups. There were no changes in plasma electrolyte levels or osmolality. Transfusion requirements were similar in both groups.

Conclusion: Desmopressin did not reduce intraoperative blood loss or transfusion requirements during hepatectomy despite raising clotting factor levels and improving tests of hemostasis.

Objectif : *Déterminer les effets de la desmopressine sur la coagulation et les pertes sanguines pendant une hépatectomie partielle réglée.*

Méthode : *Il s'agit d'une étude randomisée, contrôlée et à double insu auprès de 59 patients qui ont reçu, soit 0,3 $\mu g \cdot kg^{-1}$ de desmopressine ou un volume égale de soluté normal (témoin) administré par voie intraveineuse 20 min au moins après l'induction de l'anesthésie générale.*

Résultats : *On a noté une augmentation des niveaux plasmatiques des facteurs VIII et von Willebrand à la suite de la perfusion du médicament expérimenté chez les patients des deux groupes ($P < 0,001$). Le temps de céphaline activé a été plus court dans le groupe D tandis que le temps de prothrombine a été plus long dans le groupe T ; ($P = 0,02$). D'importants écarts ont été observés pour les pertes sanguines peropératoires (400–7128 mL), mais sans différence significative intergroupe. Aucune modification des niveaux plasmatiques d'électrolyte ou d'osmolalité n'a été notée. Les besoins de transfusion ont été comparables dans les deux groupes.*

Conclusion : *La desmopressine ne réduit pas les pertes sanguines ou les besoins de transfusion peropératoires pendant l'hépatectomie, malgré l'élévation des niveaux de facteurs de coagulation et l'amélioration de l'hémostase.*

DESMOPRESSIN (1-deamino-8-D-arginine vasopressin; DDAVP), a synthetic analogue of vasopressin has been employed as a non-transfusional treatment for mild to moderate hemophilia and von Willebrand's disease. It has also been shown to reduce the prolonged bleeding time that often accompanies uremia, hepatic cirrhosis, and other causes of platelet dysfunction. Hemostatic effects of desmopressin include: 1) an increase in plasma factors through

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endogenous release of coagulation factor VIII, von Willebrand factor and tissue plasminogen activator; 2) an increase in platelet adhesiveness; and 3) a reduction in bleeding time.[1] However, clinical research on the efficacy of desmopressin on reducing blood loss during surgery has produced conflicting results. Randomized, double-blind studies have been performed on patients undergoing various types of surgical procedures. In scoliosis,[2,3] joint arthroplasty[4] and aortic surgery[5] there was no reduction in intraoperative blood loss with desmopressin. On the other hand, a study in patients undergoing orthognathic surgery showed a significant reduction in intraoperative blood loss[6] and a study in patients undergoing lumbar fusion concluded that desmopressin was effective in reducing intraoperative blood loss when the anticipated bleeding exceeded 1 L.[7] The purpose of reducing intraoperative blood loss is to lessen the requirement for blood transfusion. A recent Cochrane review on desmopressin indicated a lack of evidence for its use to minimize perioperative allogeneic blood transfusion.[8]

The clinical effect of desmopressin on patients undergoing hepatectomy remains unclear. Hepatectomy may result in significant blood loss and patients requiring hepatectomy may have chronic liver disease e.g., cirrhosis or chronic hepatitis. Hepatocellular carcinoma (HCC) is the commonest indication for hepatectomy in Hong Kong. Minimizing blood loss and, hence, transfusion requirements should decrease the associated risks as there is accumulating evidence that perioperative blood transfusion during resection of cancer may have a deleterious effect on prognosis.[9]

Desmopressin, which has been shown to improve the hemostatic system in patients with liver cirrhosis,[10,11] may also have a beneficial effect on coagulation and, therefore, on blood losses in hepatectomy patients who may have pre- or intraoperative hepatic derangement. The aim of this study was to determine the effect of administration of desmopressin on coagulation and intraoperative blood loss in patients undergoing hepatectomy.

Methods

Approval for this prospective, double-blind, randomized study was obtained from the local University Research Ethics Committee. Sixty adult patients scheduled for hepatectomy in Queen Mary Hospital, Hong Kong were assigned to one of two groups - Group D (desmopressin) and Group C (control). Patients with coronary artery disease, congenital or acquired coagulation disorders other than liver cirrhosis, blood sodium level < 130 $mmol \cdot L^{-1}$, non-steroidal anti-inflammatory drug or aspirin ingestion within seven days of scheduled surgery and history of thrombovascular disorders or pulmonary thromboembolism were excluded. Informed consent was obtained from all patients. All hepatectomies were performed by the same team of surgeons, all with extensive experience of this operation. Advanced electro surgical technology, argon arc (plasma scalpel) and cutting ultrasound apparatus, were used in all cases.

Patient randomization was by drawing a sealed envelope specifying a prescription for either desmopressin or placebo, which was then prepared by an independent investigator and blinded to the patient, attending anesthesiologist and surgeon. The attending anesthesiologist recorded all the necessary data. General anesthesia was induced with fentanyl 2 $\mu g \cdot kg^{-1}$ and thiopentone 4 $mg \cdot kg^{-1}$, and was maintained with a mixture of nitrous oxide 65% and oxygen 35% with isoflurane titrated to clinical requirement. Atracurium 0.5 $mg \cdot kg^{-1}$ was given to facilitate endotracheal intubation which was followed by intermittent positive pressure ventilation to a normal end-tidal carbon dioxide partial pressure. Shortly after induction, patients in Group D received 0.3 $\mu g \cdot kg^{-1}$ of desmopressin in 50 mL of normal saline and those in Group C received 50 mL of normal saline given intravenously over 20 min. Intravenous morphine was administered for analgesia. Fluid management consisted of warmed crystalloids, colloids and blood to maintain a normal pulse and blood pressure, a hematocrit greater than 30%, and a urine output greater than 0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$. When urine output was below 0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$, furosemide in 5 mg increments every 15 min was administered until the urine output reached the target level of greater than 0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$. Intraoperative monitoring included invasive arterial blood pressure, nasopharyngeal temperature, capnography, isoflurane concentrations, pulse oximetry, central venous pressure (CVP), urine output, and peripheral nerve stimulation. Forced air warming was used to maintain normothermia.

The following data were collected before desmopressin or placebo infusion and repeated one hour after infusion: baseline hemoglobin, platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT), factor VIII, von Willebrand factor (vWF), plasma sodium and potassium levels and osmolality. Blood loss was calculated by weighing swabs and measuring losses in suction bottles, then subtracting irrigation fluid volumes. It was assessed in three phases: pre, during, and post-transection of the liver. Duration of surgery, the presence of liver cirrhosis and the application of a portal clamp (Pringle's maneuver) during liver resection were also recorded.

TABLE I Demographic and operative data

	Desmopressin n = 30	*Control n = 30*	*P value*
Age (yr)	47.4 (11.3)	54.9 (11.8)	0.015*
Weight (kg)	59.1 (12.7)	60.6 (128)	0.75
Sex (M/F)	20/10	17/13	0.43
Duration of surgery (min)	405 (210–800)	435 (180–780)	0.89
Liver resection area (cm^2)	45 (15–192)	46 (12–123)	0.77
Cirrhotic patients	13 (43%)	10 (33%)	0.43
Blood transfusion	3 (10%)	5 (17%)	0.45
Furosemide administered	9 (30%)	4 (13%)	0.12
Pringle's maneuver	17 (57%)	18 (60%)	0.79

Data expressed as mean (SD), median (range) or numbers where appropriate.* Indicates a statistically significant difference.

TABLE II Blood loss (mL) and weighted blood loss ($mL \cdot cm^{-2}$) between groups total, pre (1), during (2) and post (3) liver transection

	Desmopressin n = 30	*Control n = 29*	*P*
TBL	832.5 (350–2955)	800 (250–7128)	0.93
wTBL	22.25 (4.94–105.54)	19.23 (5.26–145.47)	0.78
BL1	110 (10–1200)	182 (20–1540)	0.26
wBL1	2.52 (0.18–42.86)	3.62 0.35–46.15)	0.18
BL2	405 (150–1700)	450 (76–4253)	0.88
wBL2	12.47 (1.82–53.75)	10.87 (1.53–86.8)	0.55
BL3	832.5 (350–2955)	800 250–7128)	0.93
wBL3	22.25 (4.94–105.54)	19.23 (5.26–145.47)	0.78

Data expressed as median (range). TBL = total blood loss; wTBL = weighted total blood loss.

We felt that a 20% reduction in blood loss would be clinically useful. In order to demonstrate this with a power of 80% at the 0.05 level of significance, we calculated that 30 patients would be required in each group. Results are expressed as mean, standard deviation, median and range. Parametric data were compared using Student's t test while non-parametric data were analyzed with Chi-square test and Mann-Whitney U test. All statistical calculations were performed with the SAS System Release 8.00 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered significant.

Results

Sixty Chinese patients were recruited for the study but one of these was excluded due to exceptionally heavy and precipitous bleeding (14 L) secondary to accidental damage to the inferior vena cava. Patient demographic data are shown in Table I. Forty-six patients (78%) were undergoing hepatectomy for HCC, seven (12%) for recurrent pyogenic cholangitis, four (6.8%) for secondary liver metastasis, one (1.7%) for Klaskin tumour and one for cystadenoma.

Three patients in Group D received a transfusion. The number of units of packed red cells transfused was 2, 1 and 4. Five patients in Group C received a transfusion and the number of units of packed red cells transfused was 2, 2, 10, 2 and 5. There was a wide range of blood loss (400–7128 mL). Blood losses were not distributed normally and are reported as median (range). Weighted total blood loss (wTBL) was derived from dividing TBL by the resection surface area of the liver and is displayed in Table II. There was no difference in mean blood loss between the two groups at any stage of

TABLE III Blood loss (mL) and weighted (mL·cm^{-2}) blood loss in cirrhotic patients

	Cirrhotic patients receiving desmopressin n = 10	*Cirrhotic patients receiving placebo n = 13*	*P*
TBL	900 (350–2955)	944 (250–2630)	0.87
wTBL	23.54 (8.75–105.54)	19.99 9.33–62.62)	0.47

Data expressed as median range. TBL = total blood loss; wTBL = weighted total blood loss.

TABLE IV Results of coagulation testing pre and one hour after administration of desmopressin or control

		Desmopressin		*Control*	
APTT	Pre	31.1 (5.95)		31.0 (5.51)	
(sec)			$P = 0.02$		$P = 0.56$
	Post	29.9 (5.26)		31.3 (5.30)	
PT	Pre	14.0 (1.59)		14.39 (1.08)	
(sec)		$P = 0.09$		$P = 0.01$	
	Post	14.3 (1.39)		14.61 (1.13)	
Factor VIII	Pre	1.95 (0.58)		2.16 (0.77)	
(IU·mL^{-1})			$P < 0.001$		$P < 0.001$
	Post	2.75 (0.67)		2.48 (0.76)	
VWF	Pre	1.63 (0.55)		1.86 (0.85)	
(IU·mL^{-1})			$P < 0.001$		$P < 0.001$
	Post	2.22 (0.64)		2.13 (0.83)	

Data expressed as mean (SD). Comparisons are made between within group pre and post values. APPT = activated partial thromboplastin time; PT = prothrombin time; VWF = von Willebrand factor.

surgery. Desmopressin did not decrease blood losses in cirrhotic patients (Table III). Actual and weighted total blood losses were not different between those who received desmopressin or placebo.

Coagulation test results are shown in Table IV. Clotting factors, factor VIII and vWF, were significantly raised in both groups. After infusion of study drug, APTT was shortened in Group D, whereas PT was prolonged in Group C. The potassium level rose post-infusion in both groups (D group $P = 0.053$; C group $P = 0.042$). The other hematological and biochemical laboratory tests performed were not different between groups or following infusion of desmopressin (Table V).

Other perioperative data (presence of cirrhosis, duration of operation, application of Pringle's maneuver, transection surface area and percentage of patients transfused) were equally distributed between groups (Table I). Twenty-three patients were found to be mildly cirrhotic at operation. To investigate whether cirrhosis had any effect on bleeding, blood losses at different stages were compared in cirrhotic and non-cirrhotic patients and within the treatment groups. There were no differences in blood losses at any stage.

Discussion

The risk of major hemorrhage is a prime concern during liver resection. A reduction in the intraoperative use

TABLE V Other laboratory test results

		Desmopressin		*Control*	
Hb	Pre	12.5		11.8	
($mg \cdot dL^{-1}$)		(1.42)	$P = 0.42$	(1.68)	$P = 0.94$
	Post	12.2		11.8	
		(1.47)		(1.62)	
Platelet count	Pre	193.6		192.8	
($\times 10^9 \cdot L^{-1}$)		(61.57)	$P = 0.88$	(87.03)	$P = 0.97$
	Post	191.2		193.7	
		(59.56)		(87.03)	
Osmolality	Pre	291.5		289.5	
($mmol \cdot L^{-1}$)		(6.71)	$P = 0.41$	(7.32)	$P = 0.42$
	Post	292.9		291.1	
		(6.56)		(7.60)	
Na	Pre	139.7		139.1	
($mmol \cdot L^{-1}$)		(3.45)	$P = 0.38$	(3.00)	$P = 0.43$
	Post	139.0		138.4	
		(2.68)		(3.24)	
K	Pre	3.38		3.42	
($mmol \cdot L^{-1}$)		(3.78)	$P = 0.053$	(0.30)	$P = 0.042$
	Post	3.58		3.59	
		(0.42)		(0.33)	

Data expressed as mean (SD). Within group comparisons are made between pre and post values.

of allogeneic blood is becoming increasingly important because of potential associated complications, immune hazards and risk of transmission of infection. Excessive bleeding and subsequent transfusions correlate with increased postoperative morbidity. Our results show that desmopressin did not reduce bleeding and transfusions associated with hepatectomy.

Desmopressin lacks vasoconstrictor activity and rapidly increases levels of factor VIII and vWF when administered intravenously. The proposed site of release of factor VIII is the sinusoid liver endothelial cells and vWF comes from vascular endothelial cells. Desmopressin also causes an increase in the platelet adhesiveness, the mechanism of which is not fully understood.[1] In both groups, there was a significant increase in factor VIII and vWF levels. The increase in the levels was much more striking in the patients receiving desmopressin. As in previous studies, APTT was significantly shortened by desmopressin, and in the C group, without desmopressin, PT was found to be prolonged.[10,11]

The main concern with the use of desmopressin is its potential antidiuretic effects. However, we found no significant difference in plasma osmolality, sodium or potassium levels between the pre- and post-infusion samples in the D group. Thirty percent of patients in group D were administered furosemide because of lower urine output but the difference between groups was not statistically significant.

The major indication for hepatic resection in our population is HCC (78% of the recruited patients). This is often secondary to chronic hepatitis B and, therefore, cirrhosis is a common co-morbidity (39% of the patients). In this study, the cirrhosis was mild and there were no signs or symptoms of impaired hepatic function preoperatively. Desmopressin has been shown to improve *in vitro* tests of hemostatic function in patients with chronic moderate and severe liver cirrhosis[10,11] but the clinical relevance of this finding remains unclear. We evaluated the clinical impact of coagulation changes induced by desmopressin by comparing intraoperative blood losses. Despite the improvement in laboratory hemostasis, there was no significant reduction in intraoperative blood loss in patients receiving desmopressin. Cirrhosis was not associated with a greater blood loss either between or within groups. This may be due to the mild grade of cirrhosis in our patients. We noted, however, a very wide range of total blood losses (400–7128 mL), occurring mostly during the transection phase of surgery. The large sample variance resulted in a low power of the test (27.4%) in our study. We calculated that a sample size of 251 patients in each group would be needed to increase the power to 80%. Narrower ranges of blood losses were noted in group D (Table II). This may reflect an ability of desmopressin to limit the extent of blood loss. A similar finding occurred in

another study on desmopressin, from which the authors concluded that desmopressin was effective in reducing intraoperative blood loss when anticipated bleeding exceeded 1 L.[7]

In patients receiving a blood transfusion, the number of units of packed red cells administered ranged from 1–5. Blood transfusion was prescribed individually according to each patient's clinical condition, considering hemoglobin value and cardiovascular function. Factors contributing to transfusion requirement were analyzed. These were: low preoperative hemoglobin concentration, high actual and wTBL and female sex. The increased transfusion requirement in the female patients, however, is probably due to lower initial hemoglobin concentrations compared to male patients. The patients who received desmopressin were slightly younger than those in the C group (Table I). However the average age difference is less than eight years and this is unlikely to be a confounding factor in relation to transfusion.

In a recent Cochrane review on desmopressin,[8] the authors concluded there was insufficient evidence that desmopressin reduced perioperative allogeneic red cell transfusion in patients who did not have congenital bleeding disorders. Out of 17 studies in the meta-analysis, 14 were conducted on cardiac surgeries. The other surgeries were vascular (abdominal aortic aneurysm or aorto femoral bypass), bimaxillary osteotomy and total hip replacement. Hepatectomy was not studied. In a review on systemic hemostatic medications for reducing surgical blood loss by Erstad,[12] randomized studies involving conjugated estrogens, epsilon-aminocaproic acid, tranexamic acid, desmopressin, and aprotinin for systemic hemostasis were analyzed. The author concluded that there was substantial evidence from a number of randomized trials documenting desmopressin's lack of efficacy, and although certain subsets of patients (e.g., those with prolonged bleeding times preoperatively) warranted additional investigation, the routine use of desmopressin as a hemostatic agent should be discouraged.

Aprotinin works on the other arm of the coagulation system as an antifibrinolytic agent. Lentschener *et al.*[13] investigated the effect of aprotinin on reducing blood loss during hepatectomy. They obtained a similar range of blood loss in their placebo group (215–6300). Yet, they were able to show a significant blood loss reduction in the aprotinin group (P = 0.048). Intraoperatively, there was a significantly lower increase in fibrinolysis in the aprotinin group. However, no definitive conclusion was drawn on the mechanism by which aprotinin inhibited intraoperative fibrinolysis.

Recent advances in liver surgery have allowed many patients to undergo liver resection without the need for blood transfusion. However, the risk of intraoperative bleeding remains high and is particularly likely in circumstances such as extended resection, co-existent liver cirrhosis, repeat surgery and when the portal vein is thrombosed. Although there is evidence that desmopressin may be useful in patients with a bleeding tendency,[14] our study did not show any clinical benefit on blood loss reduction in hepatectomy surgery even in patients with liver cirrhosis.

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