

Effects of desmopressin on blood loss in hip arthroplasty

Controlled study in 50 patients

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50 patients undergoing elective total hip replacement under epidural anesthesia and dextran infusion were given two doses of the vasopressin analogue desmopressin 0.3 µg/kg BW or placebo in a double-blinded randomized prospective study.

Intraoperative blood loss and drainage loss did not differ significantly between groups, but desmopressin reduced the mean total blood loss (calculated from hemoglobin decrease and blood transfusions) by 310 mL ($P < 0.05$).

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Blood loss is a greater problem in total hip replacement (Flordal and Neander 1991) than in any other common surgical procedure. We investigated whether desmopressin could reduce blood loss in total hip replacement.

Patients and methods

50 patients scheduled for total hip replacement were studied (Table 1). Patients above the age of 80 or with

severe vascular, hepatic or renal disease were not included. All patients were medically and surgically assessed in hospital two weeks preoperatively, which ensured that no prostaglandin synthesis inhibitors were in use.

Stratification was used in the randomization for primary/revision arthroplasties and for cemented/cementless procedures. However, in 4 cases the choice of type of prosthesis was changed during surgery (Table 1).

On the afternoon before surgery, venous samples were anticoagulated with EDTA for determination of

Table 1. Descriptive data on included patients, n 25 in each group. Number or mean *SD*

	Control		Desmopressin	
Men	12		12	
Women	13		13	
Age	68	9	64	9
Body weight, kg	71	15	75	12
Body height, cm	171	11	172	9
Body mass index, kg/m ²	24	3	25	3
Primary arthrosis	21		23	
Secondary arthrosis	2		0	
Revision arthroplasty	2		2	
Cemented prosthesis	17		21	
Uncemented prosthesis	8		4	
Operation time, min	104	20	106	23
Preoperative				
Hb, g/L	134	12	135	11
platelet count, 10 ⁹ /L	258	53	257	50
prothrombin complex, percent of pop. mean	97	17	103	19
Ivy bleeding time, min	3.7	1.3	3.7	1.1

No significant differences between groups

Table 2. Infusions, injections, blood pressures and urine flow during the perioperative 24-hour period, n 25 in each group. Mean SD

	Control		Desmopressin		Difference
Ephedrine, mg	22	22	35	27	n.s.
Dextran, mL, 60 mg/mL	760	255	760	255	n.s.
Cristalloids, mL	3640	940	3820	620	n.s.
Mean systolic blood pressure, mmHg					
before anesthesia	146	16	148	22	n.s.
during surgery	117	13	111	14	n.s.
postoperatively	113	12	114	16	n.s.
Urine flow, mL	2040	600	2070	590	n.s.
Furosemide	8	9	12	19	$P < 0.05$

hemoglobin concentration (Hb, methemoglobin method), platelet count (Celldyne 2000 cell counter) and with citrate for prothrombin complex assay (Stago) and activated partial thromboplastin time (APTT, Cephotest®, Nycomed, Sweden) determinations. The bleeding time (modified after Ivy) was measured using the Surgicut device (Ortho Diagnostic Systems, U.S.A.) and 40 mmHg stasis. Hb and platelet count were again determined on the third postoperative day.

Ringer acetate 500 mL was infused before induction of spinal anesthesia with plain bupivacaine 0.5 percent (Marcain®, Astra, Sweden). All but 7 patients also had an epidural catheter for postoperative pain relief with bupivacaine infusion. Ephedrine was administered pre- or intraoperatively to treat hypotension. The operation was performed with the patients in the lateral position. During surgery, all patients received an i.v. infusion of 6 percent dextran 70 (Macrodex®, Pharmacia, Sweden) 500-1000 mL for thromboprophylaxis and plasma expansion, the volume infused depending on blood loss. In addition, a balanced isotonic crystalloid solution was infused at the rate of 2 mL/kg per hour intra- and postoperatively for the first 24 hours. A further 500 mL dextran was infused on the first postoperative day. Seven patients received 100-600 mL 20 percent albumin, without any significant difference between groups. Urine production was measured hourly and furosemide was administered intravenously to keep it at about 1 mL/kg per hour. The mean furosemide dose was 8 mg in the control group and 12 mg in the desmopressin group ($P < 0.05$). Other amounts injected and infused did not differ between groups (Table 2).

In a double-blind fashion each patient received an infusion of placebo or desmopressin (Minirin®, Ferring, Sweden) 0.3 µg/kg body weight diluted in 50 mL saline at the start of surgery. The same infusion

was repeated six hours later, on both occasions at an infusion rate of 20-30 minutes.

All swabs used during surgery were weighed on a ±0.1 g scale immediately after removal from the wound. At the end of surgery the contents of the suction bottle were also weighed, and a reduction was made for irrigation fluid used. Paper drappings were used, absorbing negligible amounts of fluid, and any fluid accumulated in folds was collected in the suction bottle. The compilation of these data defined intraoperative blood loss. A drain was placed in the wound before closure, connected to a vacuum drainage device. The blood loss in the drainage bag until the morning of the first postoperative day was measured.

If there have been no blood transfusions, the total blood loss (L), including hematomas, intravascular thrombus formation and hemolysis, may be calculated from pre- (Hb_{pre}) and postoperative (Hb_{post}) hemoglobin concentrations (Bourke and Smith 1974) from the formula $L = BV \times \log(Hb_{pre} / Hb_{post})$. The blood volume (BV) may be estimated by Nadler et al.'s method (1962). If blood has been transfused, Hb_{post} must be reduced by the amount derived from transfused erythrocytes. Of the hemoglobin transfused some is lost with the blood loss that is concomitant with blood transfusions. If Hb_{transf} is transfused while the blood loss is L, then $Hb_{transf} \times (1 - e^{-L/BV}) / L$ remains. Therefore,

$$L = BV \times \log\left(\frac{Hb_{pre}}{Hb_{post} - Hb_{transf} \times \frac{1 - e^{-L/BV}}{L}}\right)$$

Since L occurs on both sides, this non-linear equation is solved by simple iteration.

In order to empirically verify the formula, it was applied to the data of 114 patients who had previously undergone the same procedure. The correlation between calculated total blood loss and intraoperative

Table 3. Blood loss and transfusion requirements, n 25 in each group. Mean SD

	Control		Desmopressin		Difference
	Mean	SD	Mean	SD	
Intraoperative blood loss, mL	900	300	880	430	n.s.
Drainage loss, mL	730	340	640	300	n.s.
Total blood loss (calculated), mL	1860	710	1550	900	$P < 0.05$
Blood transfusions, units	1.5	1.2	1.2	1.0	n.s.
Hb decrease, g/L	27	14	22	15	n.s.
Platelet count decrease, $10^9/L$	56	34	26	45	$P < 0.01$

blood loss plus postoperative drainage loss was $r = 0.78$ ($P < 0.0001$) and the mean (SD) of the difference was 610 (600) mL. In these patients intraoperative blood loss was assessed in a simpler way, which was found in the present study to underestimate the mean intraoperative blood loss by 230 mL. Thus, according to the formula there was about 380 mL (610 minus 230 mL) postoperative blood loss that had not been drained.

Blood transfusions were given as microaggregate-poor erythrocyte concentrate, in units made from 450 mL donor blood, suspended in SAGM solution (Högman et al. 1983) to 300 mL, with a mean Hb of 200 g/L. The units had been stored at +4 °C for a mean of two weeks. According to the regular quality control of the blood bank 90-95 percent of such erythrocytes are alive 24 hours after transfusion.

The patients also underwent postoperative phlebography, as reported separately (Flordal et al. 1992).

The study was approved by the ethics committee at Karolinska Hospital. All patients gave their consent after receiving oral and written information.

Differences between groups were tested using the Mann-Whitney U-test (Siegel and Castellan 1989) and two-way repeated measures analysis of variance on logarithmically transformed blood loss data (Winer 1971, Brain Power 1986). Correlations were computed and tested by Spearman's method (Siegel and Castellan 1989). A P -value of less than 0.05 was considered to denote statistical significance.

Results

The mean total blood loss was 310 mL less in the desmopressin-treated patients than in the control patients ($P < 0.05$, Table 3). The differences in mean intraoperative blood loss, drainage loss and transfusion requirements were not statistically significant, but evaluation of all blood loss data in one single statistical test showed that the effect of desmopressin on

blood loss was statistically significant ($P < 0.05$).

The total blood loss was greater in patients who had uncemented prostheses (mean 2350 mL vs. cemented 1500 mL, $P < 0.001$). There were 8 uncemented procedures in the control group (mean blood loss 2180 mL) and 4 in the desmopressin group (2700 mL, n.s.). If these were excluded from analysis, desmopressin was seen to reduce mean total blood loss by 380 mL ($P < 0.05$).

Blood loss and transfusion requirements were not significantly correlated to preoperative prothrombin complex, APTT, platelet count or bleeding time.

Intraoperative blood loss correlated positively with the dose of ephedrine used ($r_s +0.35$, $P < 0.05$). This correlation was found in both the desmopressin and placebo groups. Postoperative blood loss had no relation to the ephedrine dose. There was no correlation between ephedrine dose and mean systolic blood pressure before, during or after surgery. Intraoperative blood loss was related to intraoperative blood pressure ($r_s +0.38$, $P < 0.01$). There was no such relation between postoperative blood loss and blood pressure and no significant difference between mean ephedrine doses administered to the placebo (22 mg) and desmopressin (35 mg) groups.

The platelet count decrease was smaller in the desmopressin group (Table 3).

Discussion

Desmopressin reduced total blood loss in patients undergoing total hip replacement. This is compatible with the effects of desmopressin in identically treated patients, where it was found to normalize the otherwise prolonged bleeding time and increase the otherwise low factor VIII and von Willebrand factor values (Flordal et al. 1991).

Reduced transfusion requirements in desmopressin-treated patients have previously been shown in complicated thoracic surgery (Salzman et al. 1986, Czer et

al. 1987) and spinal fusion surgery (Kobrinisky et al. 1987), but not in uncomplicated coronary artery bypass surgery.

The patients in the control group had a mean Hb fall from 134 g/L preoperatively to 107 g/L on postoperative day 3, but the desmopressin-treated patients only from 135 g/L to 113 g/L. The difference corresponds to 0.4 transfusion units. If both groups had been allowed the same Hb drop, the difference in transfusion requirements would have been 0.7 instead of 0.3 units (Table 3) and possibly statistically significant.

The drainage loss as an estimate of postoperative blood loss may give falsely high or falsely low results. It does not include hematomas that are known to be potentially extensive in the thigh region. It also does not include thrombus formation or hemolysis, causing problems like those in other types of blood loss. Blood loss measurements may also give falsely high results, since the volumes or weights are of fluids that are not 100 percent blood. According to unpublished data from patients in a previous study (Flordal et al. 1991) the fluid lost from the wound during surgery is 84 percent blood and in the postoperative drain 82 percent blood, with large interindividual variations.

An even more serious objection to the use of drainage loss as the single estimate of postoperative blood loss in studies comparing the effects of hemostatically active drugs is that such drugs may influence the effectiveness of the drain, thereby introducing a systematic error. In the present study total blood loss was reduced by desmopressin, while intraoperative blood loss and drainage loss were not. This indicates a reduction mainly of postoperative hematoma formation. It is compatible with a better drainage function in desmopressin-treated patients, since desmopressin is a potent fibrinolysis activator (Mannucci et al. 1975).

Calculating total blood loss in the way we have done has the advantage that it takes into account all forms of blood loss which the patient is subjected to—including hematoma and thrombus formations and hemolysis. The formula has the limitation that a constant blood volume is assumed. From the data provided by Schött et al. (1985), who studied patients in similar circumstances, mean perioperative blood volume was calculated to be 98 percent of the preoperative value. Recalculations from our data assuming that the perioperative blood volumes were randomly 90–100 percent of estimated preoperative blood volumes did not disturb the statistical significance of the blood loss difference.

The formula for calculated blood loss includes contributions from hemolysis of the patient's own erythrocytes, but not of transfused erythrocytes. According to our quality control, such hemolysis is 5–10 percent after 24 hours and can then be expected to be about the

same on the third postoperative day (Mollison et al. 1987). The introduction of up to 20 percent hemolysis of transfused erythrocytes in the blood loss calculations did not disturb the significance of the difference between groups.

The platelet count decreased significantly less in the desmopressin group. A possible explanation is that the von Willebrand factor increase induced by desmopressin improved platelet function (Mannucci 1988), so that hemostasis was achieved with less platelet consumption.

A correlation between ephedrine dose and blood loss has not been previously shown. The relation was not explained by the effect of ephedrine on blood pressure, since the mean blood pressure did not correlate with the ephedrine dose. Thorburn (1985) did not find any difference in blood loss between two groups of total hip replacement patients receiving ephedrine or no treatment for hypotension. However, a correlation is in accordance with the finding that ephedrine prolongs the bleeding time in healthy volunteers and inhibits platelet aggregation in vitro (Flordal and Svensson 1991).

Unfortunately, since the hemostatic effects of ephedrine were not previously known, this study was not standardized to equalize ephedrine usage between groups. The mean dose was more than 50 percent greater in the desmopressin group, which is explained by the fact that ephedrine is used to treat hypotension and desmopressin may contribute to blood pressure reduction. The blood loss difference in favor of desmopressin might have been greater if ephedrine had been used in similar doses in both groups.

The present study confirms our previous finding (Flordal and Ljungström 1992) that despite the use of high doses of desmopressin, a potent antidiuretic drug, there was no water retention. The amounts of intravenous liquids infused and 24-hour urine production did not differ between groups and only 4 mg more furosemide was administered to the desmopressin group. A water retention still remaining in the desmopressin group on postoperative day 3 is implausible and moreover, if present, would only increase the calculated total blood loss difference between groups.

No adverse reactions referable to desmopressin treatment were noted. A proposed risk of arterial thrombosis was not confirmed in a review (Mannucci and Lusher 1989) and no suspected cases were noted in the elderly patients in the present study.

To conclude, desmopressin reduced blood loss. This effect may be more pronounced in procedures where more blood loss is to be expected (for instance, revision arthroplasties), or especially when anti-inflammatory drugs are not so ambitiously excluded as they were in this study.

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