Interactive CardioVascular and Thoracic Surgery 18 (2014) 360–370
doi:10.1093/icvts/ivt491 Advance Access publication 21 November 2013

Desmopressin for reducing postoperative blood loss and transfusion requirements following cardiac surgery in adults

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Received 19 June 2013; received in revised form 16 September 2013; accepted 14 October 2013

Abstract

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was, in adult patients undergoing cardiac surgery requiring extracorporeal cardiopulmonary bypass (CPB), does administration of desmopressin acetate (DDAVP) reduce postoperative blood loss and transfusion requirements? Altogether 38 papers were found using the reported search, of which 19 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Perioperative administration of DDAVP in adult patients undergoing cardiac surgery requiring CPB may result in a small but significant reduction in postoperative blood loss. However, this does not translate into a reproducible, clinically significant reduction in exposure to transfusion in unselected patients exposed to CPB. Several sub-groups of patients have been identified in whom DDAVP reduces postoperative blood loss and transfusion requirements. These sub-groups include patients who have received preoperative aspirin within 7 days of surgery, patients with CPB times in excess of 140 min and patients with demonstrable pre- or perioperative platelet dysfunction as determined by TEG analysis or platelet function assays. Platelet dysfunction at the time of surgery may be secondary to preoperative administration of antiplatelet medications, the result of pathological processes such as von Willebrands disease, uraemia or aortic stenosis with its associated sheer stress, as well as operative variables such as prolonged exposure to CPB. The evidence does not support the routine use of DDAVP in all cardiac surgery; indeed, it is clear that there is no significant reduction in postoperative blood loss or transfusion requirements with the administration of DDAVP in patients undergoing isolated coronary artery bypass grafting (CABG) in the absence of the features noted above. Given the absence of a clinically significant reduction in exposure to blood transfusion in unselected patients, we cannot recommend the routine use of DDAVP in patients exposed to CPB. However, DDAVP may reduce postoperative bleeding in patients who have received preoperative aspirin within 7 days of surgery, patients with CPB times in excess of 140 min and patients with demonstrable platelet dysfunction and should be used selectively in these subgroups.

Keywords: Review • Desmopressin acetate • Cardiothoracic • Surgery • Haemorrhage • Transfusion

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In adult patients undergoing cardiac surgery with CPB, does administration of DDAVP reduce postoperative blood loss and transfusion requirements?

CLINICAL SCENARIO

You have weaned the patient from CPB following a complicated and subsequently prolonged elective aortic valve replacement for severe aortic stenosis. The patient had been taking aspirin in the week prior to the operation. Despite appropriate reversal of heparin, the patient continues to have extensive coagulopathic bleeding. The anaesthetist suggests that DDAVP may be of benefit in terms of reducing blood loss and transfusion requirements postoperatively. You resolve to review the literature.

SEARCH STRATEGY

Medline 1950 to May 2013 using the OVID interface [DDAVP OR Desmopressin] AND [Cardiac surgery OR Cardiothoracic surgery] AND [Haemorrhage OR Blood loss OR Transfusion].

SEARCH OUTCOMES

Thirty-eight papers were found using the reported search. From these, 19 papers were identified that provided the best evidence to answer the question. These are presented in Table 1.

Table 1: Best evidence papers

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
Cattaneo *et al*. (1995), Thromb Haemost, Sweden [2] Meta-analysis (level 1)	Meta-analysis of 17 double-blinded, placebo-controlled, randomized trials involving 1171 patients assessing the effect of desmopressin on reducing blood loss and transfusion requirements following cardiac surgery in adults	Postoperative blood loss	Ratio of blood loss from patients receiving DDAVP to blood loss from patients receiving placebo was 0.91 (95% CI: 0.87–0.97) Ratio of blood loss from patients receiving DDAVP to blood loss from patients receiving placebo in trials with average placebo blood loss >1100 ml was 0.66 (95% CI: 0.56–0.77)	Significant 9% reduction in blood loss following cardiac operations in patients receiving DDAVP vs placebo Significant 35% reduction in blood loss following cardiac surgery in patients receiving DDAVP vs placebo in trials with high placebo group blood loss, No difference in trials with mean placebo group blood loss of < 1100 ml
		Postoperative transfusion requirements	Ratio of transfusion requirements for patients receiving DDAVP to transfusion requirements for patients receiving placebo was 1.0 (95% CI: 0.9–1.1)	No difference in transfusion requirements in patients undergoing cardiac operations between patients receiving DDAVP or placebo 14 of the 17 RCTs included in this meta-analysis had a case mix with a predominance of elective CABG operations—of the 1171 patients in the meta-analysis, 797 (68%) had isolated CABG operations
Levi *et al*. (1999), Lancet, Netherlands [3] Meta-analysis (level 1)	Meta-analysis of 16 double-blinded, placebo-controlled, randomized trials involving 1215 patients assessing the effect of desmopressin on reducing blood loss, transfusion requirements and complications such as a need for surgical re-exploration and perioperative thrombotic events following cardiac surgery in adults	Postoperative blood loss	Blood loss in patients receiving DDAVP was decreased when compared with placebo by 114 ml (95% CI: 84.2–144)	Significant but small decrease in blood loss following cardiac operations in patients receiving DDAVP vs placebo
		Postoperative transfusion requirements	Transfusion requirements in patients receiving DDAVP was reduced when compared with placebo by 0.12 U (95% CI: −0.04 to 0.28)/NS	No difference in transfusion requirements in patients undergoing cardiac operations between patients receiving DDAVP or placebo
		Postoperative complications	Re-exploration for bleeding in patients receiving DDAVP vs placebo had an odds ratio of 0.67 (95% CI: 0.33–1.37)/NS Perioperative myocardial infarction in patients receiving DDAVP vs placebo had an odds ratio of 2.39 (95% CI: 1.02–5.6) Mortality in patients receiving DDAVP vs placebo had an odds ratio of 1.02 (95% CI: 0.29–3.56)/NS	No difference in need for re-exploration for bleeding, although odds ratio is favourable for patients receiving DDAVP it did not reach significance (data from eight trials including 694 patients) Significant increased odds of perioperative MI following cardiac operations in patients receiving DDAVP vs placebo (data from seven trials) No difference in mortality for patients receiving DDAVP vs placebo (data from eight trials including 702 patients) 13 of the 16 RCTs included in this meta-analysis had a case mix with a predominance of elective CABG operations—of the 1167 patients (for whom there are data on operation type) in the meta-analysis, 764 (65%) had isolated CABG operations

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Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
Carless *et al*. (2004), Cochrane Database Syst Rev, UK [4] Meta-analysis (level 1)	13 of the 16 RCTs included in this meta-analysis had a case mix with a predominance of elective CABG operations—of the 1167 patients (for whom there are data on operation type) in the meta-analysis, 764 (65%) had isolated CABG operations	Postoperative blood loss	Blood loss in patients receiving DDAVP was decreased when compared with placebo by 96.58 ml (95% CI: 30.12–163.04)	Significant but small decrease in postoperative blood loss following cardiac operations in patients receiving DDAVP vs placebo (data from 16 trials including 1107 patients)
		Postoperative blood loss in patients who received aspirin within 7 days of their cardiac operation	Blood loss in patients receiving DDAVP was decreased when compared with placebo by 109.57 ml (95% CI: 19.03–200.11)	Significant but small decrease in blood loss following cardiac operations in patients who took aspirin within 7 days of their cardiac operation receiving DDAVP vs placebo (data from 10 trials including 633 patients)
		Postoperative blood loss in patients with CPB times >140 min	Blood loss in patients receiving DDAVP was decreased when compared with placebo by 344.74 ml (95% CI: 210.97–478.5)	Significant decrease in blood loss following cardiac operations in patients with CPB times >140 min receiving DDAVP vs placebo (data from two trials including 171 patients)
		Combined intraoperative and postoperative blood loss	Blood loss in patients receiving DDAVP was decreased when compared with placebo by 237.92 ml (95% CI: 62.4–413.43)	Significant but small decrease in combined intra and postoperative blood loss following cardiac operations in patients receiving DDAVP vs placebo (data from seven trials including 496 patients)
		Postoperative transfusion exposure	Transfusion exposure in patients receiving DDAVP vs placebo had a relative risk of 0.95 (95% CI: 0.84–1.07)/NS	No difference in exposure to transfusion in patients receiving DDAVP vs placebo (data from 15 trials including 1196 patients)
		Postoperative transfusion requirements	Transfusion requirements in patients receiving DDAVP was reduced when compared with placebo by 0.39 U (95% CI: 0.01–0.77)	Significant but small decrease in transfusion requirements following cardiac surgery in patients receiving DDAVP vs placebo (data from 10 trials including 621 patients)
		Postoperative complications	Perioperative myocardial infarction in patients receiving DDAVP vs placebo had a relative risk of 1.38 (95% CI: 0.77–2.5)/NS	No difference in perioperative myocardial infarction in patients receiving DDAVP vs placebo (data from 12 trials (10 cardiac surgery trials) including 876 patients)
			Mortality in patients receiving DDAVP vs placebo had a relative risk of 1.72 (95% CI: 0.68–4.33)/NS	No difference in mortality for patients receiving DDAVP vs placebo (data from 12 trials (11 cardiac surgery trials) including 1061 patients)
Gratz *et al*. (1992), J Thorac Cardiovasc Surg, USA [5] Double-blind, placebo-controlled, prospective, RCT (level 2)	59 patients undergoing elective CABG requiring CPB Patients included only if they had aspirin within 7 days of operation DDAVP group, Placebo group	Postoperative blood loss (24 h)	Blood loss in DDAVP group 833 ± 311 ml vs placebo group 1176 ± 674 ml; $P = 0.016$	Significant ∼400 ml reduction in blood loss in patients undergoing elective CABG who have received aspirin within 7 days of operation in patients receiving DDAVP vs placebo
		Combined intraoperative and postoperative blood loss (24 h)	Blood loss in DDAVP group 1215 ± 381 ml vs placebo group 1637 ± 761 ml; $P = 0.0097$	

Continued

Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
		Postoperative red-cell transfusion (24 h)	Red-cell transfusion in the first 24 h in DDAVP and placebo groups was 2.38 ± 1.26 vs 2.9 ± 2.1 U, respectively; $P = 0.27$	No difference in red-cell transfusion requirements between groups
		Postoperative platelet transfusion (24 h)	Platelet transfusion in the first 24 h in DDAVP and placebo groups was 0.21 ± 1.11 vs 1.8 ± 4.21 U, respectively; $P = 0.053$	Decreased platelet transfusion requirements in patients receiving DDAVP vs placebo approaches significance
		Coagulation/platelet Function blood tests	Factor VIII: C (% activity) 90 min post DDAVP or placebo, 246 ± 91 vs 181 ± 85, respectively; $P = 0.007$	Significant increase in factor VIII: C 90 min after infusion of DDAVP, no difference in placebo group
			Ristocetin cofactor, von Willebrand factor (vWF), platelet count and bleeding time postinfusion of DDAVP or placebo—no significant differences between groups	No difference in other biochemical markers of platelet function between groups
Sheridan *et al*. (1994), Can J Surg, Canada [6] Double-blind, placebo-controlled, prospective RCT (level 2)	44 patients undergoing elective CABG requiring CPB Patients included only if they had aspirin within 7 days of operation DDAVP group, Placebo group	Combined intraoperative and postoperative blood loss	Blood loss in the DDAVP group 1543 ml (95% CI: 1269–1817) vs placebo group 2376 ml (95% CI: 1859–2893); $P < 0.01$	Significant ∼800 ml decrease in combined intraoperative and postoperative blood loss in patients undergoing elective CABG who have received aspirin within 7 day of operation receiving DDAVP vs placebo
		Postoperative transfusion requirements	Transfusion postoperatively in DDAVP and placebo groups was administered in 45% of patients vs 80% of patients, respectively; $P < 0.02$	Significant decrease in exposure to transfusion in patients undergoing elective CABG who have received aspirin within 7 day of operation receiving DDAVP vs placebo
		Postoperative red-cell transfusion	Red-cell transfusion in DDAVP and placebo groups was 0.72 ± 0.62 vs 1.27 ± 1.11 U, respectively; $P > 0.05$/NS	
		Postoperative fresh frozen plasma transfusion	FFP transfusion in DDAVP and placebo groups was 0.84 ± 0.68 vs 1.88 ± 0.96 U, respectively; $P = 0.001$	
		Coagulation/platelet function blood tests	Platelet aggregation time in response to ADP 2 h postoperatively in DDAVP and placebo groups was 188.96 ± 44.25 vs 286.16 ± 137.9 s, respectively; $P = 0.0131$	
Dilthey *et al*. (1993), J Cardiothorac Vasc Anesth, Germany [7] Double-blind, placebo-controlled, prospective, RCT (level 2)	39 patients undergoing elective CABG requiring CPB Patients included only if they had aspirin within 5 days of operation DDAVP group, Placebo group	Postoperative blood loss (24 h)	Blood loss in DDAVP group 1000 ml (range: 600–1800 ml) vs placebo group 1075 ml (range: 400–1740 ml); $P > 0.05$/NS	No difference in postoperative blood loss in patients undergoing elective CABG, who received aspirin within 5 days of the operation
		Postoperative transfusion requirements	Transfusion postoperatively in DDAVP and placebo groups was 2 U (range: 0–5 U) vs 3.5 U (range: 0–8 U), respectively; $P < 0.05$	Significant decrease in postoperative transfusion requirements in patients undergoing elective CABG, who received aspirin within 5 days of the operation

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Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
		Coagulation/platelet function blood tests	vWF level (% activity) 4 h postoperatively in DDAVP and placebo groups was 147 ± 29 vs 104 ± 52, respectively; $P < 0.05$	Significant increase in vWF 4 h postinfusion of DDAVP, no difference in the placebo group
		Postoperative red-cell transfusion	Red-cell transfusion in DDAVP and placebo groups was 26 U in 11 patients vs 27 U in 9 patients, respectively; $P > 0.05$/NS	
		Postoperative transfusion (all products) requirements	Transfusion (all products) in DDAVP and placebo groups was 26 U in 13 patients vs 38 U in 14 patients, respectively; $P > 0.05$/NS	
		Coagulation/platelet function blood tests	Platelet count and APTT postoperatively in DDAVP and placebo groups—no significant difference	
Mongan *et al*. (1992), Anesthesiology, USA [8] Double-blind, placebo-controlled, prospective, RCT (level 2)	115 patients undergoing elective CABG requiring CPB with post-CPB platelet function assessment using TEG:MA MA >50 normal, <50 abnormal, Normal post-CPB platelet function DDAVP and placebo: Group 1 Abnormal post-CPB platelet function DDAVP and placebo: Group 2	Postoperative blood loss (24 h)	Blood loss in Group 1 DDAVP patients 769.6 ± 251.5 ml vs placebo patients 865.3 ± 384.4 ml; $P > 0.05$/NS Blood loss in Group 2 DDAVP patients 881.2 ± 594.6 ml vs placebo patients 1352.6 ± 773.1 ml; $P < 0.05$ Blood loss in Group 1 placebo patients 865.3 ± 384.4 ml vs Group 2 placebo patients 1352.6 ± 773.1; $P < 0.005$	No difference in postoperative blood loss in patients undergoing elective CABG with normal post-CPB platelet function Significant decrease in postoperative blood loss in patients undergoing elective CABG with abnormal post-CPB platelet function receiving DDAVP vs placebo Maximal amplitude on TEG is able to identify a subgroup of patients at risk of increased postoperative blood loss following elective CABG
		Postoperative red-cell transfusion (24 h)	Red-cell transfusion in the first 24 h in Group 1 DDAVP and placebo patients was 38 U in 36% of patients vs 75 U in 60% of patients, respectively; $P < 0.05$	Significant decrease in postoperative red-cell transfusion requirements in patients undergoing elective CABG with normal post-CPB platelet function receiving DDAVP vs placebo
Hackmann *et al*. (1989), N Engl J Med, Canada [9] Double-blind, placebo-controlled, prospective, RCT (level 2)	150 patients undergoing elective cardiac operations including elective CABG, valve and combined CABG + valve, requiring CPB DDAVP group, Placebo group	Combined intraoperative and postoperative blood loss (24 h)	Blood loss in DDAVP group 1138 ml (95% CI: 398–3238) vs placebo 1010 ml (95% CI: 473–3258); $P = 0.43$/NS	No difference in intraoperative, postoperative or overall blood loss between groups undergoing elective cardiac procedures, note 108 of 150 cases were elective CABG
		Postoperative red-cell transfusion (24 h)	Red-cell transfusion in the first 24 h in DDAVP and placebo groups was 600 ml (95% CI: 300–1830) vs 600 ml (95% CI: 300–2100), respectively; $P = 0.53$/NS	No difference in red-cell transfusion requirements between groups undergoing elective cardiac procedures
		Postoperative transfusion (all products) requirements (24 h)	Transfusion in the first 24 h in DDAVP and placebo groups was 1025 ml (95% CI: 300–4140) vs 860 ml (95% CI: 247–5346), respectively; $P = 0.23$/NS	No difference in transfusion (all products) requirements between groups undergoing elective cardiac procedures

Continued

Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
		Coagulation/platelet function blood tests	Ristocetin cofactor assay and vWF multimers postinfusion of DDAVP or placebo—no significant differences between groups	No differences in assays of platelet function between groups undergoing elective cardiac procedures
Horrow *et al*. (1991), Circulation, USA [10] Double-blind, placebo-controlled, prospective, RCT (level 2)	82 patients undergoing elective cardiac operations including elective CABG, valve, combined CABG + valve, ASD repair and redo operations, requiring CPB All operations performed by a single surgeon DDAVP group, Placebo group, Tranexamic acid group, Tranexamic acid + DDAVP group	Postoperative blood loss (12 h)	Blood loss in DDAVP group 443 ml (95% CI: 392–500) vs placebo group 462 ml (95% CI: 404–529); $P = 0.46$	No difference in postoperative blood loss or exposure to red-cell transfusion between groups undergoing elective cardiac procedures, note 68 of 82 cases were elective CABG
		Postoperative red-cell transfusion (12 h)	Red-cell transfusion in the first 12 h in DDAVP and placebo groups was required in 24 vs 18% of patients, respectively; $P > 0.05$/NS	
		Postoperative red-cell transfusion (120 h)	Red-cell transfusion in the first 120 h in DDAVP and placebo groups was required in 47% vs 36% of patients, respectively; $P > 0.05$/NS	
		Coagulation/platelet function blood tests	Factor VIII: C (% activity) 2 h post DDAVP or placebo, 108 ± 52 vs 105 ± 47, respectively; $P > 0.05$/NS	
			Platelet count 2 h post DDAVP or placebo, 249 ± 178 vs 232 ± 105, respectively; $P > 0.05$/NS	
Reich *et al*. (1991), J Cardiothorac Vasc Anesth, USA [11] Double-blind, placebo-controlled, prospective, RCT (level 2)	27 patients undergoing elective cardiac operations including elective CABG and single-valve replacement, requiring CPB DDAVP group, Placebo group	Combined intraoperative and postoperative blood loss (24 h)	Blood loss in DDAVP group 624 ± 351 ml vs placebo group 729 ± 200 ml; $P > 0.05$/NS	No difference in intraoperative, postoperative or overall blood loss between groups undergoing elective CABG or single-valve procedure, note 17 of 27 cases were elective CABG
		Haemodynamic variables postinfusion	Systemic vascular resistance (dyne/s/cm^5) 10 min after infusion of DDAVP or placebo, 1105 ± 363 vs 1500 ± 366, respectively; $P < 0.01$	Decreased SVR after infusion of DDAVP, no difference in placebo group (no difference in SVR prior to infusion)
de Prost *et al*. (1992), Thromb Haemost, France [12] Double-blind, placebo-controlled, prospective, RCT (level 2)	92 patients undergoing elective cardiac operations including elective CABG, valve, combined CABG + valve, aortic root and redo operations, requiring cardiopulmonary bypass Patients included only if they had overt bleeding (>75 ml/m^2/h) and an elevated BT (>10 min) at any time in the first 6 h postoperatively DDAVP group, Placebo group	Postoperative blood loss (24 h)	Blood loss per square metre of TBSA in DDAVP group 582 ± 410 ml vs placebo group 465 ± 303 ml; $P = 0.15$	No difference in postoperative blood loss or transfusion requirements in patients undergoing elective cardiac procedures who have early postoperative overt bleeding and elevated bleeding times Surgical source of blood loss identified in all but 1 patient in the placebo group No difference in biochemical markers of platelet function between groups
		Postoperative red-cell transfusion (24 h)	Red-cell transfusion in the first 24 h in DDAVP and placebo groups was 3.4 ± 2.6 vs 3.2 ± 2.4 U, respectively; $P = 0.71$	
		Postoperative transfusion (all products) requirements (24 h)	Transfusion of FFP and platelets in the first 24 h in DDAVP and Placebo—no significant difference between groups	
		Reoperation for haemorrhage	Reoperation for haemorrhage in DDAVP and placebo groups was 3 patients (6.4%) vs 8 patients (17.8%); respectively; $P = 0.12$	

Continued

Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
		Coagulation/platelet function blood tests	Factor VIII: C, vWF, platelet count and bleeding time 90 min postinfusion of DDAVP or placebo—no significant difference between groups	
Rocha *et al*. (1994), Circulation, Spain [13] Single-blind, prospective, RCT (level 2)	81 patients undergoing elective cardiac operations including CABG, valve, CABG + valve and redo operations requiring CPB DDAVP group: 2 doses, DDAVP group: 1 dose, Control group: no treatment	Postoperative blood loss (12 h)	Blood loss per square metre of TBSA in DDAVP (2 doses) group 208.8 ± 111.7 ml vs DDAVP (1 dose) group 278.7 ± 164.1 ml vs control group 214.5 ± 120.8 ml; $P > 0.05$/NS	No difference in postoperative blood loss or transfusion requirements in patients undergoing elective cardiac operations receiving DDAVP vs control (no treatment)
		Postoperative blood loss (72 h)	Blood loss per square metre of TBSA in DDAVP (2 doses) group 498.5 ± 235.6 ml vs DDAVP (1 dose) group 551.8 ± 324.1 ml vs control group 438.7 ± 228.1 ml; $P > 0.05$/NS	
		Postoperative transfusion requirements	Transfusion (all products) per square metre of TBSA in DDAVP (2 doses), DDAVP (1 dose) and control groups was 662.8 ± 380.7 vs 740.4 ± 416.4 vs 678.1 ± 462.2 ml, respectively; $P > 0.05$/NS	
Depotis *et al*. (1999), Lancet, USA [14] Double-blind, placebo-controlled, prospective, RCT (level 2)	173 patients undergoing elective cardiac operations including CABG, valve, valve + CABG and redo operations, requiring CPB with abnormal hemoSTATUS clotting ratio results (<60% of maximum in channel 5) after discontinuation of CPB DDAVP group (patients with abnormal clot ratio results after discontinuation of CPB) Placebo group (patients with abnormal clot ratio results after discontinuation of CPB) Untreated control group (patients with normal clot ratio results after discontinuation of CPB)	Postoperative blood loss (24 h)	Blood loss in DDAVP group 624 ± 209 ml vs placebo group 1028 ± 682 ml; $P < 0.01$	Significant ∼400 ml reduction in blood loss in patients undergoing cardiac operations with abnormal clot ratios post CPB receiving DDAVP vs placebo, no difference between DDAVP and untreated control group with normal clot ratios Significant decrease in postoperative red-cell, platelet and FFP transfusion and exposure to transfusion in DDAVP group vs placebo, no difference between DDAVP and untreated control group Significant increase in clot ratio postoperatively in DDAVP group vs placebo, no difference between DDAVP and untreated control group despite significantly lower platelet count in DDAVP group
		Postoperative red-cell transfusion	Red-cell transfusion in DDAVP and placebo groups was 1.1 ± 1.5 vs 2.1 ± 2.3 U, respectively; $P < 0.01$	
		Postoperative platelet transfusion	Platelet transfusion in DDAVP and placebo groups was 0.1 ± 0.3 vs 1.9 ± 3.2 U, respectively; $P < 0.01$	
		Postoperative fresh frozen plasma transfusion	FFP transfusion in DDAVP and placebo groups was 0.1 ± 0.5 vs 0.8 ± 1.5 U, respectively; $P < 0.01$	
		Postoperative transfusion (all products) requirements	Transfusion postoperatively in DDAVP and placebo groups was 1.6 ± 2.2 vs 5.2 ± 5.7 U, respectively; $P < 0.01$	
		Coagulation/platelet function blood tests	Clot ratio (% of maximum) postoperatively in DDAVP and placebo groups was 70 ± 20 vs 62 ± 15, respectively; $P < 0.05$	
Casas *et al*. (1995), J Thorac Cardiovasc Surg, Spain [15] Double-blind, placebo-controlled, prospective, RCT (level 2)	101 patients undergoing elective cardiac operations including CABG, valve, CABG + valve, ASD repair and redo operations, requiring CPB DDAVP group, Placebo group, Aprotinin group	Postoperative blood loss (24 h)	Blood loss in DDAVP group 1214 ± 78 ml vs placebo group 1386 ± 116 ml; $P > 0.05$/NS	No difference in postoperative blood loss in patients undergoing cardiac procedures requiring CPB No difference in postoperative blood loss with increase in CPB time in patients undergoing cardiac
		Postoperative blood loss (24 h) by CPB time	Blood loss in DDAVP group with CPB time <60 min 1242 ± 121 ml vs CPB time >90 min 1306 ± 140 ml; $P > 0.05$/NS	

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Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
			Blood loss in the placebo group with CPB time <60 min 1152 ± 126 ml vs CPB time >90 min 1623 ± 231 ml; *P* < 0.05	procedures receiving DDAVP Significant increase in postoperative blood loss with increased CPB time in patients undergoing cardiac procedures receiving placebo
		Postoperative transfusion requirements	Transfusion (all products) postoperatively in DDAVP and placebo groups—no significant difference	
		Coagulation/platelet function blood tests	PTT postoperatively in DDAVP and placebo groups was 54.3 ± 3.5 vs 71.1 ± 5.5 s, respectively; *P* < 0.05	Significant decrease in postoperative PTT in patients receiving DDAVP
Temeck *et al*. (1994), South Med J, USA [16] Double-blind, placebo-controlled, Prospective, RCT (level 2)	83 patients undergoing elective cardiac operations requiring CPB DAVP group, Placebo group	Postoperative blood loss (24 h)	Blood loss in DDAVP group 1214 ± 78 ml vs placebo group 1386 ± 116 ml; *P* > 0.05/NS	No difference in postoperative blood loss in patients undergoing cardiac procedures requiring CPB
		Postoperative blood loss (24 h) by CPB time	Blood loss in DDAVP group with CPB time <60 min 1242 ± 121 ml vs CPB time > 90 min 1306 ± 140 ml; *P* > 0.05/NS	No difference in postoperative blood loss with increase in CPB time in patients undergoing cardiac procedures receiving DDAVP
			Blood loss in the placebo group with CPB time <60 min 1152 ± 126 ml vs CPB time >90 min 1623 ± 231 ml; *P* < 0.05	Significant increase in postoperative blood loss with increased CPB time in patients undergoing cardiac procedures receiving placebo
		Postoperative transfusion requirements	Transfusion (all products) postoperatively in DDAVP and placebo groups—no significant difference	
		Coagulation/platelet function blood tests	PTT postoperatively in DDAVP and placebo groups was 54.3 ± 3.5 vs 71.1 ± 5.5 s, respectively; *P* < 0.05	
Salzman *et al*. (1986), N Engl J Med, USA [17] Double-blind, placebo-controlled, prospective, RCT (level 2)	70 patients undergoing elective cardiac operations including valve, valve + CABG and redo operations, requiring CPB No isolated CABG procedures DDAVP Group, Placebo group	Combined intraoperative and postoperative blood loss (72 h)	Blood loss in DDAVP group 1317 ± 486 ml vs placebo group 2210 ± 1415 ml; *P* = 0.001	Significant ∼900 ml reduction in blood loss in patients receiving DDAVP vs placebo
		Postoperative red-cell transfusion (72 h)	Red-cell transfusion in the first 72 h (Units) in DDAVP and placebo groups was 2.6 ± 2.1 vs 3.7 ± 3.3, respectively; *P* = 0.079	Trend toward reduced red-cell transfusions in the first 3 days postoperatively in the DDAVP group
		Coagulation/platelet function blood tests	Platelet count post DDAVP or placebo, 116 630 ± 43 600 vs 95 760 ± 35 920, respectively; *P* = 0.04	No difference in platelet count or Factor VIII: vWF between groups prior to administration of DDAVP
			Factor VIII: vWF (U/ml) post DDAVP or placebo, 1.80 ± 0.53 vs 1.46 ± 0.55, respectively; *P* = 0.02	Improvement in blood tests used to assess platelet function in the DDAVP group
			Patients with low preoperative Factor VIII: vWF tended to have greater blood loss in the placebo group; this was not found to occur in the DDAVP group	

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Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
Rocha *et al*. (1988), Circulation, Spain [18]	100 patients undergoing elective cardiac operations including valve and ASD repairs, requiring CPB	Intraoperative blood loss	Blood loss per square metre of TBSA in DDAVP group 131 ± 106 ml vs placebo group 193 ± 137 ml; $P < 0.02$	Significant but small reduction in intraoperative blood loss in the DDAVP group
Double-blind, placebo-controlled, prospective, RCT (level 2)	No isolated CABG procedures DDAVP group, Placebo group	Postoperative blood loss (72 h)	Blood loss per square metre of TBSA in DDAVP group 458 ± 206 ml vs placebo group 536 ± 304 ml; $P > 0.05$/NS	No difference in postoperative or overall blood loss per square metre of TBSA between groups
		Postoperative red-cell transfusion (72 h)	Red-cell transfusion in the first 72 h in DDAVP and placebo groups was 1642 ± 705 vs 1574 ± 645 ml, respectively; $P > 0.05$/NS	No difference in red-cell transfusion requirements between groups
		Coagulation/platelet function blood tests	Bleeding time 90 min post DDAVP or placebo, 5.9 ± 0.3 vs 13.8 ± 1.1 min, respectively; $P < 0.001$	Improvement in blood tests used to assess platelet function in the DDAVP group; however, this did not translate to reduced blood loss or transfusion requirements (no difference in preoperative or pretreatment Factor VIII: C between groups)
			Factor VIII: C (U/ml) 90 min post DDAVP or placebo, 1.62 ± 0.12 vs 0.96 ± 0.07, respectively; $P = 0.02$	
Ansell *et al*. (1992), J Thorac Cardiovasc Surg, USA [19]	83 patients undergoing elective cardiac operations including valve, combined CABG + valve and redo operations, requiring CPB	Postoperative blood loss (24 h)	Blood loss in the DDAVP group 1064.8 ± 647.1 ml vs placebo group 844.4 ± 507.6 ml; $P > 0.05$/NS	No difference in postoperative blood loss or transfusion requirements in patients undergoing elective cardiac procedures
Double-blind, placebo-controlled, prospective, RCT (level 2)	No isolated CABG procedures DDAVP group, Placebo group	Postoperative red-cell transfusion (24 h)	Red-cell transfusion in the first 24 h in DDAVP and placebo groups was 1.4 ± 1.62 vs 1.27 ± 1.58 U, respectively; $P = 0.50$	Significant increase in factor VIII: C 1 h after infusion of DDAVP, no difference in placebo group
		Postoperative transfusion (all products) requirements (24 h)	Transfusion in the first 24 h in DDAVP and placebo groups—no significant difference between groups	
		Coagulation/platelet function blood tests	Factor VIII: C (% activity) 1 h post DDAVP or placebo, 103 ± 49 vs 76 ± 33, respectively; $P = 0.01$	
			vWF and bleeding time after infusion of DDAVP or placebo—no significant difference between groups	
Steinlechner *et al*. (2011), Ann Thorac Surg, Austria [20]	43 patients undergoing elective isolated aortic valve replacement due to severe aortic stenosis with platelet dysfunction as measured by collagen adenosine diphosphate closure time (CADP-CT) >170 s	Postoperative blood loss	Blood loss in DDAVP group 250 ± 141 ml vs placebo group 434 ± 125 ml; $P < 0.001$	Significant decrease in postoperative blood loss in patients undergoing AVR for severe AS with impaired platelet function preoperatively according to PFA-100 assessment on CDP-CT
Double-blind, placebo-controlled, prospective, RCT (level 2)	No isolated CABG procedures DDAVP group, Placebo group	Postoperative red-cell transfusion	Red-cell transfusion in DDAVP and placebo groups was 436 ± 493 vs 496 ± 484 ml, respectively; $P = 0.6$/NS	
		Coagulation/platelet function blood tests	CADP-CT 1 h postinfusion of DDAVP was shortened by 48% vs placebo and baseline; $P < 0.001$	No difference in red-cell transfusion requirements between groups

Continued

Table 1: (*Continued*)

Author, date and country Study type, (level of evidence)	Patient group	Outcomes	Key results	Comments
			Factor VIII:C, vWF:Ag, vWF:Gp1b, vWF:RCo and vWF:CBA levels 1 h postinfusion of DDAVP were increased by 73, 65, 80, 90 and 75%, respectively, vs placebo; $P < 0.001$	Significant increase in platelet function assays 1 h postinfusion of DDAVP vs placebo (no difference in preoperative platelet function assays)

RESULTS

The papers included have been divided based on the types of procedures included in the studies: (i) 14 studies of isolated CABG; (ii) 8 studies of mixed cases with isolated CABG included; (iii) 3 studies of mixed cases with isolated CABG excluded and (iv) 1 study of isolated aortic valve replacement. Results from three meta-analyses are also presented.

Fourteen studies of patients undergoing isolated coronary artery bypass grafting

Within the meta-analyses performed by Cattaneo *et al.* [2], Levi *et al.* [3] and Carless *et al.* [4], 14 RCTs investigated the administration of DDAVP in 818 patients undergoing isolated CABG. Ten of these trials found no significant difference in postoperative blood loss or transfusion requirements with DDAVP. Of the four remaining RCTs [5–8], three [5–7] were trials where administration of preoperative aspirin was an inclusion criterion. Gratz *et al.* [5] and Sheridan *et al.* [6] looked at patients who had received aspirin within 7 days of their elective CABG. Both found significant reductions in combined intra- and postoperative blood loss with DDAVP. Sheridan *et al.* [6] also found a significant reduction in postoperative exposure to transfusion with DDAVP. Dilthey *et al.* [7] looked at patients who had aspirin within 5 days of their elective CABG operation. Despite no significant reduction in postoperative blood loss, they did find a significant reduction in postoperative transfusion requirements with DDAVP. Mongan *et al.* [8] identified a subgroup of patients with platelet dysfunction on the basis of post-CPB maximal amplitude on TEG analysis, who had significantly reduced postoperative blood loss with DDAVP.

From these results, we can conclude that in the absence of either preoperative aspirin administration or demonstrable platelet dysfunction, there is no benefit from DDAVP in terms of postoperative blood loss or transfusion requirements in patients undergoing isolated CABG.

Eight studies of mixed cases with isolated coronary artery bypass grafting included

A further eight RCTs [9–16] investigated the use of DDAVP in 789 patients undergoing a variety of cardiac operations including isolated CABG. Seven of these trials [9–15] documented the numbers of each type of operation performed, of which six trials [9–14] had a predominance of isolated CABG. Of these six trials, five [9–13] found no significant difference in postoperative blood loss or transfusion requirements with DDAVP. Given the findings of the RCTs in patients undergoing isolated CABG, it is not surprising that the RCTs with mixed cases, and a predominance of CABG operations have similar results. Despite this, several subgroups within these 'mixed RCTs' have been shown to benefit from DDAVP.

Depotis *et al.* [14] identified a subgroup of patients with platelet dysfunction on the basis of post-CPB clot ratios using a point-of-care platelet function assay (hemoSTATUS), who had significantly reduced postoperative blood loss and transfusion requirements with DDAVP.

Casas *et al.* [15] identified a subgroup with prolonged CPB time >120 min who had significantly reduced postoperative blood loss with DDAVP. Temeck *et al.* [16] demonstrated a significant increase in postoperative blood loss in the placebo group with prolonged CPB >90 min compared with <60 min, while no such increase occurred in the DDAVP group. No subgroup analyses were performed with regard to transfusion requirements.

Three studies of mixed cases with isolated coronary artery bypass grafting excluded

Three RCTs [17–19] investigated the use of DDAVP in patients undergoing a variety of cardiac procedures excluding isolated CABG. Salzman *et al.* [17] showed a significant reduction in combined intra- and postoperative blood loss of ~900 ml with DDAVP, yet despite this no significant difference in transfusion requirements. Rocha *et al.* [18] and Ansell *et al.* [19] both found no significant difference in postoperative blood loss or transfusion requirements with DDAVP; however, they make no note of preoperative aspirin administration, subgroup analysis based on CPB time or platelet function analysis.

One study of isolated aortic valve replacement

Steinlechner *et al.* [20] limited their investigation to patients undergoing aortic valve replacement for severe aortic stenosis with platelet dysfunction on the basis of a platelet function analyser (PFA 100). They demonstrated a significant decrease in postoperative blood loss with DDAVP. However, this did not translate to a significant difference in postoperative transfusion requirements.

Three meta-analyses

Cattaneo *et al*. [2], Levi *et al*. [3] and Carless *et al*. [4] performed three meta-analyses with significant overlap in terms of the RCTs included. They reviewed 17, 16 and 22 RCTs, including 1171, 1215 and 1679 patients, with a 68, 65 and 71% predominance of isolated CABG, respectively. These meta-analyses all found a small but significant reduction in postoperative blood loss of 9%, 114 and 97 ml, respectively, with DDAVP. Only Carless *et al*. [4] found any difference in terms of postoperative transfusion requirements with a small but significant reduction of 0.39 units with DDAVP; despite this, there was no difference noted in exposure to blood transfusion. They also noted the decrease in blood loss was greater in patients with aspirin administration within 7 days of operation and those with CPB times >140 min. It is possible larger effects in the identified subgroups mentioned previously may have been diluted by the inclusion of a large proportion of patients undergoing isolated CABG in these meta-analyses.

CLINICAL BOTTOM LINE

Given the absence of a clinically significant reduction in exposure to blood transfusion in unselected patients, we cannot recommend the routine use of DDAVP in patients exposed to CPB. However, DDAVP may reduce postoperative bleeding in patients who have received preoperative aspirin within 7 days of surgery, patients with CPB times in excess of 140 min and patients with demonstrable platelet dysfunction, and should be used selectively in these subgroups.

Conflict of interest: none declared.

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