Title: Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomised controlled trials

Short title: Desmopressin for platelet dysfunction

Authors

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Abstract

Background

Platelet dysfunction, including that caused by antiplatelet agents, increases the risk of peri-operative bleeding. The optimal management of patients with platelet dysfunction undergoing surgery is unclear.

Objectives

To assess whether desmopressin reduces peri-operative allogeneic red cell transfusion and bleeding for patients with platelet dysfunction.

Patients/Methods

We searched for randomised controlled trials in The Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, Embase, the Transfusion Evidence Library and ISI Web of Science to 7th July 2016. Data were pooled using mean difference (MD), relative risks or Peto odds ratios (pOR) using a random-effects model.

Results

Ten trials with 596 participants were identified, all in the setting of cardiac surgery. Platelet dysfunction was due to antiplatelet agents in six trials and cardiopulmonary bypass in four trials. Patients treated with desmopressin were transfused with fewer red cells (MD -0.65 units, 95% CI -1.16 to -0.13); lost less blood (MD -253.93 ml, 95% CI -408.01 to -99.85 ml); and had a lower risk of re-operation due to bleeding (pOR 0.39, 95% CI 0.18 to 0.84). Similar results were found for the subgroups with platelet dysfunction due to antiplatelet agents or other causes, with little evidence of statistical heterogeneity between subgroups. The GRADE quality of evidence was very low to moderate suggesting considerable uncertainty over the results

Conclusions

Desmopressin may be a useful agent to reduce bleeding and transfusion requirements for people with platelet dysfunction or with a history of recent anti-platelet drug administration undergoing surgery.

Introduction

Antiplatelet agent use is common in the developed world with approximately 6 to 8% people in the United Kingdom taking an antiplatelet agent [1]. Alongside the benefit of these drugs in patients with cardiovascular risk factors, is the need for protocols to manage unexpected or severe bleeding, and how to manage patients at the time of surgery. The degree of platelet dysfunction is correlated with bleeding risk [2] but stopping these agents may result in (rebound) cardiovascular morbidity [3]. Deficits of platelet function are also seen in other settings, notably cardiopulmonary bypass (CPB) where platelet dysfunction has been associated with a greater risk of post-operative bleeding [4]. Platelet dysfunction in CPB is likely to be due to reduced availability of platelet agonists rather than intrinsic platelet defects [5]; and CPB has been found to increase platelet activation markers such as thromboglobulin, platelet factor 4 and P-selectin [6].

When rapid reversal of antiplatelet therapy is necessary, many guidelines have recommended transfusion of 2 to 3 adult doses of platelets [7-9] but acknowledge the lack of evidence to support the strength of this recommendation [10, 11]. In addition, the optimal use of platelet transfusions has become less clear following the publication of the PATCH trial. This randomised trial of platelet transfusion versus standard care in intracranial haemorrhage [12] reported that platelet transfusion was of no benefit in reducing bleeding and led to a poorer outcome with increased mortality and poorer function. While the results of this trial may not be applicable in all settings where there is platelet dysfunction, they pose important questions about the risk to benefit ratio of platelet transfusions.

Desmopressin (also known as DDAVP or 1-deamino-8-D-arginine vasopressin) has been used for the treatment of congenital bleeding disorders for almost four decades. It acts by increasing plasma von Willebrand factor, factor VIII, intracellular platelet calcium/sodium ion concentrations, and by increasing formation of procoagulant platelets and platelet adhesion to collagen under flow, and [13-15]. Desmopressin is also recommended in a number of guidelines for

treatment of bleeding in patients with platelet dysfunction or on antiplatelet agents [9, 16-19], but there is has been no formal/systematic review of the size of benefit and the risks for desmopressin in the context of anti-platelet therapy. Desmopressin use is associated with side effects including hypotension, hyponatraemia, facial flushing and a theoretical risk of thrombotic events.

The aim of this review was to examine the evidence for peri-operative administration of desmopressin to reduce bleeding risk and transfusion requirements for people with platelet dysfunction due to anti-platelet drug therapy or CPB.

Methods

This systematic review followed the methods in the prospectively registered update of a Cochrane review [20]. Methodology was consistent with the definitions from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [21].

Eligibility criteria

We only included randomized controlled trials (RCTs) of participants undergoing any type of elective or emergency surgery. Participants were taking antiplatelet agents (cyclo-oxygenase-1 inhibitors, phosphodiesterase inhibitors or $P2Y_{12}$ inhibitors) or had established platelet dysfunction as measured by recognized tests including platelet function analyzer (PFA). Trials were included if at least 80% participants had evidence of platelet dysfunction, or were taking anti-platelet agents, or if it was possible to extract data on a subgroup of participants with platelet dysfunction. Trials were eligible for inclusion if their intervention was intravenous or subcutaneous desmopressin. Comparators were placebo or standard care.

Primary outcome:

Total volume of allogeneic red cells transfused

Secondary outcomes:

1. Risk of receiving an allogeneic red cell transfusion
2. Total blood loss
3. Re-operation due to bleeding
4. All-cause mortality
5. Thrombotic events: composite of myocardial infarction, stroke, venous thromboembolism
6. Clinically significant hypotension: hypotension requiring intravenous fluid administration or commencement (or an increase) of inotropes

Search strategy

We searched for RCTs in the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2016, Issue 6), MEDLINE (OvidSP, from 1946), PubMed (for epublications ahead of print), Embase (OvidSP, from 1974), the Transfusion Evidence Library (from 1950) and ISI Web of Science: Conference Proceedings Citation Index - Science (from 1990) on 07 July 2016. The search strategies are detailed in appendix 1. There were no search restrictions on date, language or publication status.

Data extraction

Trial selection

Two independent review authors initially used an online systematic review management tool (DistillerSR; https://v2.systematic-review.ca) to screen all electronically-derived citations and abstracts of papers identified by the review search strategy for relevance. Studies clearly irrelevant were excluded at this stage.

The full texts of all potentially relevant trials were then formally assessed for eligibility by two independent review authors against the criteria outlined above. All disagreements were resolved by discussion with the other authors. Further information was sought from study authors when an article contained insufficient data to make a decision about eligibility. A study eligibility form was

designed using an online systematic review management tool (Covidence; https://www.covidence.org/) for trials of desmopressin to help in the assessment of relevance. The reasons why potentially relevant studies failed to meet the eligibility criteria were recorded.

Risk of bias assessment and grading the quality of evidence

We assessed the risk of bias using the methods outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions [22]. Risk of bias was assessed as high, low or unclear for each of: selection bias; performance bias; detection bias; attrition bias, reporting bias; and other sources of bias. We did not assess publication bias, as identified fewer than ten trials contributing data towards the primary outcome.

We assessed the quality of evidence for each outcome according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. GRADE quality was classified as very low, low, moderate, or high [23].

Data synthesis and analysis

All statistical analyses were performed using Review Manager 5.3 (http://tech.cochrane.org/revman) and presented as forest plots. When meta-analysis was feasible, we used the random-effect model and the Mantel-Haenszel method for pooling the data. Meta-analysis was undertaken where data were sufficient. We reported risk ratios (RR) for dichotomous outcomes, with 95% confidence intervals (CI). Peto odds ratio (OR) was used for outcomes with low event rates. Mean differences (MD), with 95% CIs were calculated for continuous outcomes. Where appropriate we calculated number needed to treat, or number needed to harm.

Assessment of heterogeneity

Statistical heterogeneity of treatment effects between trials was assessed using a Chi^2 test with a significance level at $P < 0.1$. The I^2 statistic was used to quantify the percentage of variability that was due to heterogeneity (we defined heterogeneity of between 50% and 80% as moderate and >80% as substantial).

Sensitivity and subgroup analysis

Sensitivity analyses were performed by assessing results using only trials considered to be at low risk of bias from blinding of study outcome assessors. Trials where platelet dysfunction was due to antiplatelet agents or other causes were included in separate subgroups. We planned to examine different types of surgery in separate subgroups but all trials identified in this review were in the same setting (cardiac surgery). We examined statistical heterogeneity between subgroups using the I^2 statistic.

Unpublished data

We had access to individual patient data from one trial [24] and data on the subgroup of patients who were taking antiplatelet agents was extracted for incorporation into meta-analysis.

Results

Search results

The search strategy identified 3474 references which were reduced to 2322 after exclusion of duplicates (Figure 1). 2208 references were excluded as clearly not relevant to the review and the full texts of the remaining 114 references were analyzed in full. 104 references were excluded for the following reasons: 5 review articles; 14 not randomised controlled trials; 61 wrong participant group; 5 incorrect intervention; and 19 secondary citations of excluded trials. Ten trials (596 participants) were included in the qualitative synthesis and 9 trials were included in the quantitative synthesis.

Trial characteristics

Although all surgical procedures regardless of specialty were potentially eligible, all ten relevant trials were in the setting of cardiac surgery. Six trials included participants undergoing coronary artery bypass grafting (CABG) [25-30], one trial included aortic valve replacements [31] and three trials included a combination of CABG and valve replacements [24, 32, 33]. Nine trials included only elective surgery [24-26, 28-33] and one trial included only emergency cases [27]. Platelet dysfunction was due to antiplatelet agents in six trials: single agent

aspirin in four trials [25, 26, 29, 30]; dual antiplatelet therapy in one trial [27]; and a combination of single agent aspirin and dual antiplatelet therapy in one trial [24]. Platelet dysfunction was due to CPB in four trials [28, 31-33]. One trial was published in abstract form only [27].

Desmopressin was administered as a single intravenous dose of 0.3μg/kg in eight trials [24-29, 31, 32], 0.4μg/kg in one trial [33] and 10μg/m^2 body surface area in one trial [30]. One trial was a four arm trial comparing desmopressin 0.3μg/kg, standard care, combination of desmopressin 0.3μg/kg with tranexamic acid, and tranexamic acid as a single agent [27]. Desmopressin was given pre-operatively in one trial [31]; intra-operatively but after CPB in five trials [25, 26, 28-30]; post-operatively in three trials [27, 32, 33]; and either intra-operatively or post-operatively in one trial [24]. In nine trials desmopressin was administered prophylactically to prevent bleeding [25-33] and in one trial it was administered to treat bleeding [24]. Nine trials compared desmopressin to a matching 0.9% saline placebo [24-26, 28-33] and one trial was an open label trial comparing desmopressin to standard care or tranexamic acid [27]. Trials were published between 1992 and 2016. Characteristics of included studies are reported in Table 1.

Effects on outcomes

Total volume of allogeneic red cells transfused

This outcome was reported in seven trials [24-26, 28, 31-33]. One trial reported this in a way that could not be included in meta-analysis and is reported separately in Table 2 [28]. Overall, participants treated with desmopressin required fewer units of red cells than those treated with placebo (MD -0.65 units, 95% CI -1.16 to -0.13, I^2 = 36%, 388 participants, 6 trials, Figure 2a) [24-26, 31-33]. The sensitivity analyses supported the results of the main analysis: (MD -0.82 units, 95% CI -1.29 to -0.34, I^2 = 14%, 296 participants, 4 trials) [24, 26, 31, 33]. The GRADE quality of evidence was judged to be low (Table 3).

The effect was similar for the subgroup of participants with platelet dysfunction due to antiplatelet agents (MD -0.90 units, 95% CI -1.62 to -0.18, I^2 = 36%, 152

participants, 3 trials) [24-26] and with platelet dysfunction due to CPB (MD -0.43 units, 95% CI -1.22 to 0.37, I^2 = 56%, 236 participants, 3 trials) [31-33]. There was no evidence of heterogeneity between the subgroups: I^2 = 0%.

Total number of participants receiving an allogeneic red cell transfusion

This outcome was reported in six trials [24-26, 28-30]. One trial was not included in the analysis because every participant in both arms was transfused [26]. No difference was found in the risk of allogeneic red cell transfusion for participants treated with desmopressin compared to placebo (RR 0.83, 95% CI 0.66 to 1.04, I^2 = 14%, 258 participants, 5 trials, Figure 2b) [24, 25, 28-30]. The sensitivity analyses supported the results of the main analysis: (RR 0.91, 95% CI 0.62 to 1.32, I^2 = 43%, 185 participants, 3 trials) [24, 28, 30]. The GRADE quality of evidence was judged to be low (Table 3).

The effect was similar for the subgroup of participants with platelet dysfunction due to antiplatelet agents (RR 0.82, 95% CI 0.61 to 1.10, I^2 = 32%, 229 participants, 4 trials) [24, 25, 29, 30], but was smaller for those with platelet dysfunction due to CPB (RR 0.92, 95% CI 0.58 to 1.46, 29 participants, 1 trial) [28]. There was no evidence of heterogeneity between the subgroups: I^2 = 0%.

Total volume of blood loss

This outcome was reported in all trials. Three trials reported this in a way that could not be included in meta-analysis and are reported separately in Table 2 [25, 27, 32]. Overall, participants treated with desmopressin lost less blood than those treated with placebo (MD -253.93 ml, 95% CI -408.01 to -99.85 ml, I^2 = 75%, 422 participants, 7 trials, Figure 3a) [24, 26, 28-31, 33]. The sensitivity analyses supported the results of the main analysis: (MD -370.00 ml, 95% CI -556.65 to -183.35, I^2 = 63%, 276 participants, 5 trials) [26, 28, 30, 31, 33]. The GRADE quality of evidence was judged to be low (Table 3).

The effect was similar for the subgroup of participants with platelet dysfunction due to antiplatelet agents (MD -249.90 ml, 95% CI -535.26 to 35.46 ml, I^2 = 78%, 249 participants, 4 trials) [24, 26, 29, 30] and with platelet dysfunction due to

CPB (MD -295.73 ml, 95% CI -484.20 to -107.26 ml, I^2 = 61%, 173 participants, 3 trials) [28, 31, 33]. There was no evidence of heterogeneity between the subgroups: I^2 = 0%.

Re-operation due to bleeding

This outcome was reported in six trials [24, 28, 29, 31-33]. The risk of re-operation due to bleeding was lower for participants treated with desmopressin compared to placebo (pOR 0.39, 95% CI 0.18 to 0.84, I^2 = 0%, 413 participants, 6 trials, Figure 3b) [24, 26, 28-31, 33]. The number needed to treat to prevent one patient requiring re-operation due to bleeding was 17. The sensitivity analyses supported the results of the main analysis: (pOR 0.48, 95% CI 0.17 to 1.34, I^2 = 37%, 292 participants, 4 trials) [24, 28, 31, 33]. The GRADE quality of evidence was judged to be moderate (Table 3).

There was moderate evidence of heterogeneity between the subgroups: I^2 = 52.5%. The effect was smaller for the subgroup of participants with platelet dysfunction due to antiplatelet agents (pOR 0.77, 95% CI 0.23 to 2.54, 148 participants, 2 trials) [24, 29] than those with platelet dysfunction due to CPB (pOR 0.24, 95% CI 0.09 to 0.66, I^2 = 0%, 265 participants, 4 trials) [28, 31-33].

Adverse events

All-cause mortality

This outcome was reported in seven trials [24, 26, 28-31, 33]. Four trials reported no deaths in either arm [28-31]. No difference was found in the risk of all-cause mortality for participants treated with desmopressin compared to placebo (pOR 0.72, 95% CI 0.12 to 4.22, I^2 = 24%, 422 participants, 7 trials) [24, 26, 28-31, 33]. The baseline risk of mortality was less than 1%, limiting interpretation of these results due to imprecision. The GRADE quality of evidence was judged to be very low (Table 3).

Thrombotic events

This outcome was reported in seven trials [24, 26, 28-31, 33]. No difference was found in the risk of a thrombotic events for participants treated with

desmopressin compared to placebo (pOR 1.58, 95% CI 0.60 to 4.17, I^2 = 0%, 422 participants, 7 trials) [24, 26, 28-31, 33]. The event rate was low for individual causes of thrombotic events with no overall difference in the incidence in any type of thrombotic event: myocardial infarction (pOR 2.72, 95% CI 0.60 to 12.37, I^2 = 0%, 277 participants, 5 trials) [24, 26, 28, 29, 31]; ischemic stroke (pOR 1.21, 95% CI 0.07 to 20.17, I^2 = 0%, 157 participants, 3 trials) [24, 26, 30]; or venous thromboembolism (pOR 0.56, 95% CI 0.06 to 5.50, 248 participants, 4 trials) [24, 26, 29, 31]. The GRADE quality of evidence was judged to be low (Table 3).

Clinically significant hypotension

This outcome was reported in five trials [24, 25, 28, 29, 33]. No events occurred in either arm of two trials [28, 33]. There was an increase in the risk of clinically significant hypotension for participants treated with desmopressin compared to placebo (pOR 9.78, 95% CI 2.48 to 38.58, I^2 = 0%, 315 participants, 5 trials) [24, 25, 28, 29, 33]. The number needed to treat for one episode of clinically significant hypotension was 17. The GRADE quality of evidence was judged to be low (Table 3).

Other adverse events

Other adverse events were not reported in the included trials. In particular, no trial reported incidence of hyponatraemia, seizures, chest tightness, hypertension, abdominal pain, headache, nausea or allergic reactions.

Risk of bias

Key potential sources of bias for these trials were blinding of outcome assessors and incomplete outcome data. In six trials we considered blinding of outcome assessors to be at low risk of bias because the person preparing the desmopressin or matching placebo was not otherwise involved in the trial [24-26, 29, 31, 33]. One trial was open label and was considered to be at high risk of bias [27]. Insufficient details were reported in the manuscripts of the remaining trials for an assessment of bias to be made [28, 30, 32].

A key problem for several trials was whether to include individuals with exsanguinating or large volume haemorrhages after randomisation. We considered five trials to be at low risk of bias because all participants were included in the final analysis [24, 26, 28, 30, 33]. Three trials were considered to be at high risk of bias because at least one individual with a large volume haemorrhage was excluded from the final results [25, 29, 32]. With such small trials, such an individual could significantly alter the results for the continuous outcomes: volume of allogeneic red cells transfused and total blood loss. The remaining trials did not report sufficient information for an assessment of bias to be made [27, 31].

GRADE quality of the evidence

Overall the GRADE quality of evidence was very low to moderate suggesting considerable uncertainty over the results and that further clinical trial information may significantly alter the results (Table 3). The quality assessment of all outcomes was downgraded one point for risk of bias. Volume of red cells transfused, risk of red cell transfusion and blood loss were downgraded one point due for inconsistency, as there were significant variations in baseline blood loss and transfusion requirements between studies. All-cause mortality was downgraded two points for imprecision, as the event rate was very low and consequently the confidence interval included both significant benefit and significant harm. Risk of a thrombotic event and clinically significant hypotension were downgraded one point for imprecision.

Discussion

Antiplatelet agent use is rising in many countries and yet the treatment options to manage major bleeding or cover for urgent surgery are limited. This is particularly problematic following the recent publication of the PATCH trial [12]. Platelet dysfunction is also expected as a consequence of CPB, when again there uncertainty about the role of platelet transfusions. This meta-analysis identified ten randomised trials with 596 participants where the effects of desmopressin were assessed. All trials were in the setting of cardiac surgery; platelet dysfunction was caused by antiplatelet agents in 6 trials and CPB in 4 trials.

Desmopressin may be an attractive agent for use in this patient population, given its ease of administration, mechanism of action and low cost.

Desmopressin administration resulted in transfusion of fewer units of red cells (equivalent to a 25% reduction compared to control), less blood loss (equivalent to a 23% reduction compared to control) and a lower risk of requiring a re-operation due to bleeding. No difference was found in the risk of receiving an allogeneic red cell transfusion. Similar results were found for the subgroups with platelet dysfunction due to antiplatelet agents and due to CPB, with little evidence of statistical heterogeneity between subgroups. One exception to this was risk of re-operation due to bleeding where the risk of returning to theatre with bleeding was lower in the subgroup with platelet dysfunction due to CPB than those taking antiplatelet agents.

Event rates were low for adverse events with no difference found in the risk of all-cause mortality or thrombotic events (myocardial infarction, stroke and venous thromboembolism). There were too few participants in the published trials to be certain whether there is an increased risk of thrombotic events with administration of desmopressin, but the low number of thrombotic events in this high risk group of patients offers some reassurance that if there is an increased risk, it is likely to be small. Patients treated with desmopressin had an increased risk of clinically significant hypotension, which is consistent with the results of other reviews [20, 34]. This adverse event is more common when desmopressin is administered rapidly [35], and it is unclear whether transient hypotension has more severe outcomes, although no other imbalances of risks were documented across all trials. Other adverse events such as facial flushing, hyponatraemia and seizures were not reported.

To our knowledge, this is the first meta-analysis investigating the role of desmopressin for reversal of antiplatelet agents or other causes of platelet dysfunction. Overall the results suggested that desmopressin may have some effect in reducing blood loss and red cell transfusion requirements for patients with platelet dysfunction who undergo cardiac surgery. The efficacy of

desmopressin for the treatment of patients taking antiplatelet agents appears to be greater than for treatment of unselected patients, across a range of participant settings and indications [20, 34].

Our results may support a wider role for desmopressin in patients on antiplatelet agents who require an agent to reverse their action in order to prevent bleeding. The results of this review are consistent with the recommendations in some guidelines to consider desmopressin in the setting of platelet dysfunction [9, 16-19].

Limitations of this review

However, the limitations of the included studies, the heterogeneity in the nature and timing of desmopressin administration in the trial protocol and the low quality GRADE levels of evidence indicate the need for further research to clarify the safety and size of effect. All trials were small and 5 of the 10 trials were undertaken more than 20 years ago when different standards of practice in cardiac surgery existed. Many trials were considered to be at risk of bias due to insufficient information on blinding of study outcome assessors and incomplete outcome data. All of the trials were in the setting of cardiac surgery. Patients undergoing emergency surgery were included in only 1/10 trials and desmopressin was used for treatment (rather than prophylaxis) of bleeding in 1/10 trials. The majority of patients taking antiplatelet agents were taking single agent aspirin, with relatively few patients taking dual antiplatelet therapy or other antiplatelet agents. Caution should be exercised before applying these findings to other clinical settings. It is unclear if tranexamic acid, or other anti-fibrinolytic agents may be superior to desmopressin, or if the two agents could be used in combination in this setting.

Meta-analysis of total volume of allogeneic red cells transfused and total blood loss were limited due to inconsistency in baseline levels of red cell transfusion and blood loss. The findings of our review were also limited by data published in a format that could not be incorporated into meta-analysis which showed inconsistent results. There were few numbers of events for all-cause mortality,

thrombotic events and clinically significant hypotension which limited interpretation of the results due to imprecision.

Conclusion

Overall this review provides some evidence for the use of desmopressin to reduce bleeding and transfusion requirements for people taking antiplatelet agents undergoing surgery. However, there remains uncertainty in the size of benefit and the risks in cardiac surgery, including thrombotic events. Significant gaps also include the use of desmopressin outside cardiac surgery (including in acute blood loss), use for treating antiplatelet agents other than aspirin, and the role of desmopressin in conjunction with an anti-fibrinolytic agent. To a degree, these findings reproduce the programme of clinical research for use of tranexamic acid, which is still on-going. The biological rationale and findings of this review support a priority for further research into the use of desmopressin the setting of platelet dysfunction and management of bleeding or peri-operative protocols in patients taking anti-platelet agents.

Authorship details

M. J. R. Desborough made the initial draft of this manuscript. C, Doree devised the search strategy. M. Crivellari performed individual patient data analysis on one of the trials. M. J. R Desborough and K. A. Oakland extracted the data. M. J. R. Desborough performed the analysis. L. J. Estcourt and S. J. Stanworth provided clinical and methodological expertise and oversaw the writing of the manuscript and the analyses. All authors critically revised the manuscript.

K. A. Oakland and C. Doree have no conflicts of interest to declare. M. J. Desborough, L. J. Estcourt and S. J. Stanworth are investigators for a trial using desmopressin. M. Crivellari was an original investigator of one of the studies included in this review. There was no specific funding for this meta-analysis.

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Figure legends

Figure 1. Study flow diagram.

Figure 2. Forest plots of: **2a.** Volume of red cells transfused. **2b.** Risk of allogeneic red cell transfusion. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals. Risk of bias categories were: (A) Sequence generation, (B) Allocation concealment, (C) Blinding of participants and personnel, (D) Blinding of outcome assessors, (E) Incomplete outcome data, (F) Selective outcome reporting, and (G) Other sources of bias. High risk of bias for a category is indicated by −, unclear risk of bias by ? and low risk of bias by +.

Figure 3. Forest plots of: **3a.** Total volume of blood loss. **3b.** Re-operation due to bleeding. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals. Risk of bias categories were: (A) Sequence generation, (B) Allocation concealment, (C) Blinding of participants and personnel, (D) Blinding of outcome assessors, (E) Incomplete outcome data, (F) Selective outcome reporting, and (G) Other sources of bias. High risk of bias for a category is indicated by −, unclear risk of bias by ? and low risk of bias by +.

Tables

Trial [Country]	Arm	Timing	n	Male/ female	Age (years)	Surgery	Platelet dysfunction	Blinding bias risk
Antiplatelet agents								
Bignami 2016 [24] [Italy]	Desmopressin	After heparin reversal or post-op	25	22/3	67 ± 13	Elective CABG or valve replacement	Aspirin continued throughout (other anti-platelets stopped 5 days before surgery)	Low
	Placebo		29	22/7	66 ± 13			
Dilthey 1993 [25] [Germany]	Desmopressin	After heparin reversal	19	19/0	56 ± 9	Elective CABG	Aspirin within 5 days of surgery	Low
	Placebo		20	20/0	58 ± 8			
Gratz 1992 [26] [USA]	Desmopressin	After heparin reversal	29	19/10	62 ± 10	Elective CABG	Aspirin within 7 days of surgery	Low
	Placebo		30	23/7	63 ± 12			
Hemşinli* 2012 [27] [Turkey]	Desmopressin	Post-op	10	-	-	Emergency CABG	Dual antiplatelet therapy	High
	Standard care		10	-	-			
	Desmopressin & TXA		16	-	-			
	TXA		18	-	-			
Pleym 2004 [29] [Norway]	Desmopressin	After heparin reversal	46	40/6	63 ± 9	Elective CABG	Aspirin within 1 day of surgery	Low
	Placebo		46	36/10	64 ± 8			
Sheridan 1994 [30] [Canada]	Desmopressin †	After heparin reversal	20	20/0	57 (53-60)	Elective CABG	Aspirin within 7 days of surgery	Unclear
	Placebo		24	24/0	62 (59-65)			
Platelet dysfunction due to cardiopulmonary bypass								
De Prost 1992 [32] [France]	Desmopressin	Up to six hours post-op	47	37/10	60 ± 13	Elective CABG or valve replacement	Prolonged bleeding time	Unclear
	Placebo		45	32/13	55 ± 16			
Despotis 1999 [33] [USA]	Desmopressin‡	Post-op	50	30/20	64 ± 10	Elective CABG or valve replacement	HemoSTATUS <60% in channel 5	Low
	Placebo		51	34/17	66 ± 10			
Mongan 1992 [28] [USA]	Desmopressin	After heparin reversal	13	9/4	59 ± 11	Elective CABG	TEG MA 50mm or less	Unclear
	Placebo		16	11/5	66 ± 10			
Steinlechner 2011 [31] [Austria]	Desmopressin	After induction of anaesthesia	20	8/12	72 ± 10	Elective aortic valve replacement	Prolonged closure time on PFA-100	Low
	Placebo		23	7/16	73 ± 8			

Table 1. Study characteristics. Desmopressin dose 0.3ug/kg intravenously unless stated otherwise. Placebo 0.9% saline in all cases. *Published in abstract form only; †Desmopressin dose 10μg/m^2 body surface area; ‡Desmopressin dose 0.4ug/kg, CABG – coronary artery bypass graft, PFA-100 – platelet function analyser-100, TEG MA – thromboelastography maximum amplitude, and TXA – tranexamic acid. Age stated as mean ± standard deviation or median (range).

Trial	Reason not included in meta-analysis	Desmopressin	Placebo
Total volume of allogeneic red cells transfused			
Mongan 1992 [28]	Reported as mean (no SD)	2.4 units (n = 13)	2.2 units (n = 16)
Total blood loss			
De Prost 1992 [32]	Reported as ml/m^2 body surface area (mean ± SD)	582 ± 410 ml/m^2 (n = 44)	465 ± 303 ml/m^2 (n = 37)
Dilthey 1993 [25]	Reported as median (range)	1000 (600 to 1800) ml (n = 19)	1075 (400 to 1740) ml (n = 20)
Hemşinli 2012 [27] [Desmopressin vs standard care]	Reported as mean (no SD)	1430 ml (n = 10)	1767 ml (n = 10)
Hemşinli 2012 [27] [Desmopressin & TXA vs TXA]	Reported as mean (no SD)	574 ml (n = 16)	535 ml (n = 18)

Table 2. Summary of data excluded from meta-analysis due to reporting method in original publications. SD – standard deviation and TXA – tranexamic acid.

Number of participants			Effect		GRADE Quality Assessment
№ of RCTs	Desmopressin	Placebo	Relative (95% CI)	Absolute (95% CI)	
Total volume of allogeneic red cells transfused					
6	190	198	-	**MD 0.65 units less** (1.16 to 0.13 units less)	⊕⊕◯◯ LOW*†
Risk of red cell transfusion					
5	56/123 (45.5%)	73/135 (54.1%)	**RR 0.83** (0.66 to 1.04)	**9 fewer per 100** (from 2 more to 18 fewer)	⊕⊕◯◯ LOW*†
Total blood loss					
7	203	219	-	**MD 253.93 ml less** (408.01 to 99.85 ml less)	⊕⊕◯◯ LOW*†
Re-operation due to bleeding					
6	8/202 (4.0%)	21/211 (10.0%)	**pOR 0.39** (0.18 to 0.84)	**6 fewer per 100** (from 1 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE*
All-cause mortality					
7	2/203 (1.0%)	3/219 (1.4%)	**pOR 0.72** (0.12 to 4.22)	**0 fewer per 100** (from 1 fewer to 4 more)	⊕◯◯◯ VERY LOW*‡
Thrombotic events					
7	10/203 (4.9%)	7/219 (3.2%)	**pOR 1.58** (0.60 to 4.17)	**2 more per 100** (from 1 fewer to 9 more)	⊕⊕◯◯ LOW*§
Clinically significant hypotension					
5	9/153 (5.9%)	0/162 (0%)	**pOR 9.78** (2.48 to 38.58)	**Not calculable**	⊕⊕◯◯ LOW*§

Table 3. Assessment of the quality of the evidence using GRADE criteria. CI: Confidence interval; MD: Mean difference; pOR**:** Peto odds ratio; RCT: randomised controlled trial; RR: Risk ratio. *Downgraded one point due to risk of bias from blinding of outcome assessors and incomplete outcome data. †Downgraded one point for inconsistency due to variation in baseline level of transfusion and blood loss. ‡Downgraded two points for imprecision, as confidence intervals include clinically significant benefit and clinically significant harm with low background event rate. §Downgraded one point for imprecision.