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REVIEW

# Blood loss after cardiopulmonary bypass, standard *vs* titrated protamine: A meta-analysis

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## ABSTRACT

Background: The aim of this meta-analysis was to determine whether standard or titrated dosing of protamine is more effective in facilitating haemostasis after cardiac surgery with cardiopulmonary bypass (CPB).
Methods: We searched MEDLINE, and Biomedical Central using the terms "cardiopulmonary bypass and heparin and protamine". Studies were included in the meta-analysis if they were randomised controlled trials (RCTs), controlled clinical studies, or cohort studies with designs comparing the postoperative volume of bleeding between the study group (titrated dose) and the control group (standard dose) for protamine reversal of surgical anticoagulation in CPB procedures. The primary outcome of interest was postoperative blood loss.
Results: There were 219 studies identified in the initial search; four of these were included in the meta-analysis. All studies were RCTs, involving a total of 507 patients. Postoperative blood loss was lower in the study group (range: 625-839 ml) compared with the control group (range: 765-995 ml) in all four studies. Transfusion of packed red blood cells was also lower in the study group compared with the control group in all four studies. There was no evidence of significant heterogeneity in postoperative blood loss among the four studies ($Q=4.224$, $I^2=28.98\%$, $p=0.238$); hence, a fixed-effects model of analysis was used. The overall/combined standardised difference in means of postoperative blood loss volume significantly favoured study treatment over control treatment ($-0.562\pm0.322$, $p<0.001$).
Conclusion: These findings suggest that titrated protamine dosing is more effective than standard protamine dosing for reducing postoperative bleeding after CPB.

## KEYWORDS

Cardiopulmonary bypass, heparin, protamine, standard, titrated

## INTRODUCTION

Management of haemostasis is a key facet of any surgical procedure. To this end, balancing the risk of thromboembolism with that of excessive bleeding is paramount. A number of anticoagulants are commonly used to reduce the risk of thromboembolism. These include heparin, vitamin K antagonists, such as warfarin, and antiplatelets, such as aspirin.[1] After surgery, the risk of bleeding complications may outweigh that of thromboembolism; hence, reversal of haemostasis is often warranted in patients taking anticoagulants. For patients on vitamin K antagonists, vitamin K or vitamin K-dependent coagulation factors may be given to ameliorate the anticoagulant effect of the antagonist.[1] For patients on antiplatelet drugs, amelioration of the anticoagulant effects may be achieved by the administration of platelet concentrate or de-amino d-arginine vasopressin (a vasopressin analogue).[1] In contrast, protamine sulphate is often used to counteract the effect of heparin.

Heparin is routinely administered prior to and during cardiopulmonary bypass (CPB) surgery to reduce the risk of thromboembolism. After surgery, however, the anticoagulant activity of heparin requires neutralisation to promote haemostasis and reduce the risk of bleeding. To this end, protamine is typically used to reverse the anticoagulant activity of heparin after CPD. Protamine exerts this effect by binding heparin (1:1 ratio) to form an inactive complex.[2,3] Approximately 1 mg of protamine has the capacity to rapidly neutralise 100 units of heparin.[3]

Although protamine is a very effective and generally safe means of reversing the anticoagulant activity of heparin, associated adverse events are not uncommon, occurring in slightly over 2% of patients after CPB.[4,5] These adverse events include various haemodynamic changes, pulmonary oedema, and anaphylactic reactions.[4-6] An increased risk of in-hospital mortality has also been reported in patients who received protamine after CPB.[6,7] Optimising the dose

of protamine is thought to be crucial for minimising the occurrence of adverse events.[2] Clearly, a balance must be struck between underdosing of protamine, which can result in inadequate haemostasis after CPB, and overdosing, which can lead to the aforementioned adverse events.

Generally, there are two options for dosing of protamine after CPB: standard or titrated. Standard dosing typically comprises giving a fixed dose of protamine per unit of heparin given, whereas titrated dosing involves assessing plasma heparin concentrations and giving an appropriately titrated dose of protamine to neutralise the measured heparin concentration.[2] In theory, titrated dosing should be optimal in terms of facilitating haemostasis and minimising the risk of adverse events; however, this has not been a consistent finding in the studies conducted to date.[8-14] In the absence of any large-scale, double-blind, randomised controlled trials examining whether standard *vs* titrated protamine dosing is more effective in facilitating haemostasis after CPB, we felt compelled to perform a meta-analysis of the available literature to seek a more definitive answer. Here we present the findings from our analysis.

## MATERIALS AND METHODS

### Literature Search Strategy

MEDLINE and Biomedical Central databases were searched. The search involved use of the following terms: ("cardiopulmonary bypass"[MeSH Terms] OR ("cardiopulmonary"[All Fields] AND "bypass"[All Fields]) OR "cardiopulmonary bypass"[All Fields]) AND ("heparin"[MeSH Terms] OR "heparin"[All Fields]) AND ("protamine"[MeSH Terms] OR "protamine"[All Fields] OR "protamine"[All Fields]). The following search limits were applied where possible: [Clinical Trial], [Randomized Controlled Trial], and [English]. All searches included literature published / available online from inception to November 2012.

Reference lists of pertinent articles were hand-searched to indentify further potentially relevant studies.

### Selection criteria

Studies were eligible for inclusion in the meta-analysis if they were randomised controlled trials, controlled clinical studies, or cohort studies with designs comparing postoperative bleeding volume between the study group (titrated dose) and the control group (standard dose) for protamine reversal of surgical anticoagulation in CPB procedures in adult patients.

### Data extraction and quality assessment

Two independent reviewers extracted the data from eligible studies. A third reviewer resolved any disagreements. The following information / data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, type of study, number of participants in each treatment group, participants' age and gender, name(s) of the drug(s) given, name(s) of comparator drug(s), and blood loss.

The primary outcome of interest was postoperative blood loss.

### Data analysis

Means with standard deviations were calculated for blood loss, and were compared between participants who were treated with standard or fixed-dose protamine (control treatment) versus titrated-dose protamine (study treatment). A $\chi^2$-based test of homogeneity was performed using Cochran's Q statistic, and the inconsistency index ($I^2$) statistic was determined. An $I^2$ >50% indicated the existence of heterogeneity between studies and a random-effects model was used. Otherwise, fixed-effects models were used. Combined summary statistics of the standardised difference in the mean for each individual study are shown. A two-sided p value <0.05 was considered to indicate statistical significance. A funnel plot and the fail-safe N (which indicates whether the observed significance is spurious or not) were used to assess possible publication bias. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

## RESULTS

### Literature search

A total of 219 studies were identified by searching the specified databases (*figure 1*). Of these, four[8-11] met the eligibility criteria and were included in the meta-analysis.

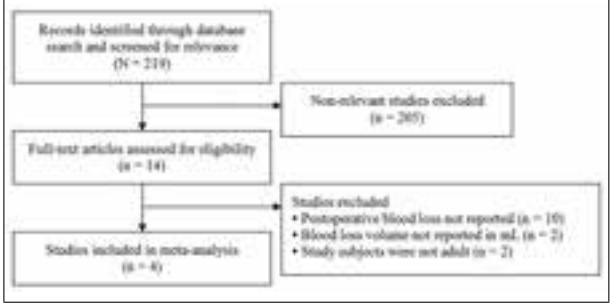
### Study characteristics

The characteristics of the four studies are summarised in *table 1*.

All were randomised controlled trials, involving a total of 507 patients, ranging from 20 to 247. Patients were generally similar in mean age between studies, and within studies between treatment groups (study *vs* control). The proportion of male participants varied considerably between studies, ranging from 54[11] to 90%.[8] The proportion of males was generally similar between treatment groups within each individual study.

The most common reason for surgery was coronary artery bypass grafting.[8,10,11] The reason for CPB was not specified in the study reported by Despotis *et al.*[9] The initial heparin dose was generally 300 U/kg; however, most studies required patients to attain a specified activated clotting time (>400[8] or >480 seconds).[9-11] Study group

**Figure 1.** *Flow diagram of study selection*




protamine dosing was determined using the Hepcon Heparin Management System (HMS) in three studies[9-11] and using the Hemochron system in the study reported by Keeler *et al*.[8] The means of determining protamine dosing in the control group were different between all studies, but was generally based on the heparin dose.

Postoperative blood loss was lower in the study group (range: 625-839 ml) compared with the control group (range: 765-995 ml) in all four studies (*table 1*). Transfusion of packed red blood cells (PRBCs) was also lower in the study group (range: 0.2-1.8 U; 558-659 ml) compared with the control group (range: 0.3-2.7 U; 633-1559 ml) in all four studies (*table 1*). Only two studies[9,11] reported on the transfusion of fresh frozen plasma (FFP) after surgery, with Despotis *et al*. reporting that patients in the study group received more units of FFP than patients in the control group (2.7 *vs* 1.4 U),[9] and Koster *et al*. reporting the opposite (0.2 *vs* 0.3 U) (*table 1*).[11]

Only two studies reported on complications after surgery. Ohata *et al*. reported that no patients experienced neurological accidents, myocardial infarction, or any other complications related to CPB.[10] However, in the control group one patient experienced transient pulmonary hypertension and one patient sudden systemic hypotension. There were no other complications in the study group. Koster *et al*. reported that three patients in both groups required re-exploration because of postoperative haemorrhage.[11]

**Postoperative blood loss and other outcomes**

Two[10,11] of the four studies included in the meta-analysis had standardised difference in means of postoperative blood loss volume that significantly favoured study treatment over control treatment (*figure 2*). There was no evidence of significant heterogeneity in postoperative blood loss among the four studies (Q=4.224, $I^2$=28.98%, p=0.238); hence, a fixed-effects model of analysis was used for meta-analysis and generated an overall / combined standardised difference in means of postoperative blood loss volume of -0.325 with a 95% confidence interval (CI)

**Table 1.** *Characteristics of studies included in the meta-analysis*

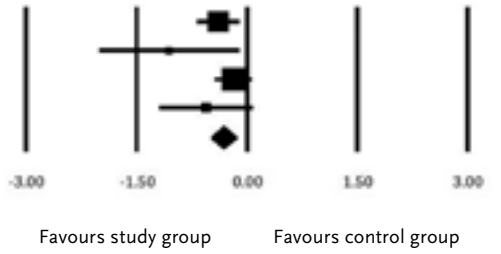
| Study | Participants (study vs control) | Age, years (study vs control) | % Males (study vs control) | Surgery type | Heparin dosing | Study group protamine dosing | Control group protamine dosing | Postoperative blood loss, ml (study vs control) | Transfusion required (study vs control) |
|---|---|---|---|---|---|---|---|---|---|
| Koster et al., 2002 | 100 vs 100 | 66±17 vs 64±13 | 54 vs 55 | CABG, valve replacement / recon-struction | 300 U/kg (+ additional to achieve ACT >480 sec) | Titration by Hepcon HMS | 1:1 according to initial heparin dose needed to achieve target ACT | 625±312 vs 765±397 | PRBCs 0.2±0.1 U vs 0.3±0.2 U FFP 0.2±0.1 U vs 0.3±0.1 U |
| Ohata et al., 1999 | 12 vs 8 | 59.3±2.7 vs 62.4±1.6 | NA | CABG | 300 U/kg (+ additional to achieve ACT >480 sec) | Titration by Hepcon HMS | 1.67 mg/mg total heparin | 821±131 vs 960±132 | PRBCs 659±224 mL vs 1559±323 mL |
| Despotis et al., 1995 | 124 vs 123 | 64±11 vs 65±11 | 69 vs 70 | NA | Control group: 250 U/kg (+ additional to achieve ACT >480 sec) Study group: dosing based dose-response assay | Titration by Hepcon HMS | 0.8 mg/mg total heparin | 839±377 vs 924±520 | PRBCs 1.8±1.9 U vs 2.7±4.7 U FFP 2.7±4.7 U vs 1.4±2.5 U |
| Keeler et al., 1991 | 20 vs 20 | 58.4±7.18 vs 54.0±8.14 | 75 vs 90 | CABG | 300 U/kg (+ additional to achieve ACT >400 sec) | Titration by Hemochron system | 6 mg/kg | 769±286 vs 995±492 | PRBCs 558±422 mL vs 633±477 mL |

**ACT = activated clotting time; CABG = coronary artery bypass graft; FFP = fresh frozen plasma; HMS = Heparin Management System; NA = not available; PRBCs = packed red blood cells; U = units.**

**Figure 2.** *Forest plot showing the standardised difference in means (SD in means) of postoperative blood loss volume for the four studies included in the meta-analysis. Patients received a titrated (study group) or standard (control group) dose of protamine for the reversal of heparin after cardiopulmonary bypass. A fixed-effects model was used according to the heterogeneity test (Q=4.224, $I^2$=28.98%, p=0.238). The overall effect of an SD in means of -0.325 (95% confidence interval [CI]: -0.499, -0.150) indicates the results favoured the study group over the control group (p<0.001)*

| Study name | SD in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | P value |
|---|---|---|---|---|---|---|---|
| Koster et al, 2002 | -0.392 | 0.143 | 0.020 | -0.672 | -0.112 | -2.746 | 0.006 |
| Ohata et al, 1999 | -1.056 | 0.486 | 0.236 | -2.009 | -0.104 | -2.173 | 0.030 |
| Despotis et al, 1995 | -0.187 | 0.126 | 0.016 | -0.434 | 0.059 | -1.488 | 0.137 |
| Keeler et al, 1991 | -0.562 | 0.322 | 0.104 | -1.194 | 0.070 | -1.742 | 0.082 |
| Overall | -0.325 | 0.089 | 0.008 | -0.499 | -0.150 | -3.646 | 0.000 |

Heterogeneity: Q statistic=4.224, df=3 (P value=0.238) I2=28.975 %
Test for overall effect: Z statistic=-3.646 (P value<0.001)



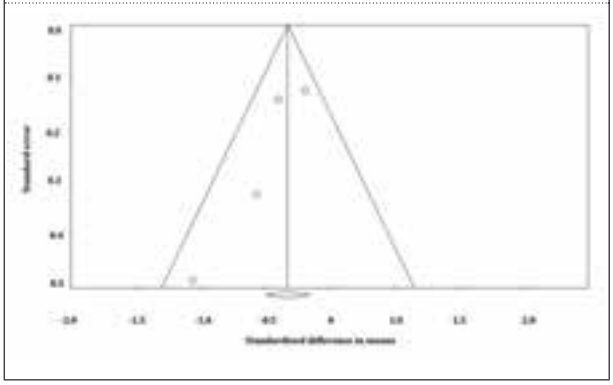

(-0.499, -0.150). The overall effect significantly favoured study treatment over control treatment (p<0.001).

Only two studies reported on postoperative complications / reoperation.[10,11] Koster *et al.* reported that three patients in the study group and five patients in the control group underwent reoperation because of postoperative haemorrhage. Ohata *et al.* reported that no patients experienced neurological accidents, myocardial infarction, or any other CPB-related complications;[10] however, two patients in the control group experienced postoperative systemic hypotension or transient pulmonary hypertension.

**Publication bias**

The funnel plot for publication bias (standard error by standardised difference in means of postoperative blood loss volume) demonstrated moderate asymmetry (*figure 3*), indicating the existence of moderate publication bias. For postoperative blood loss volume, the combined effect size yielded a Z value of -4.075 with a corresponding p value <0.001. The significant results indicate the fail-safe N value were relevant.

**Figure 3.** *Funnel plot of the standard error by standardised difference in means of postoperative blood loss volume for the four studies included in the meta-analysis. Patients received a titrated (study group) or standard (control group) dose of protamine for the reversal of heparin after cardiopulmonary bypass. The combined effect size yielded a Z value of -4.075 with a P value 0.0001*



## DISCUSSION

We carried out a meta-analysis to determine whether standard or titrated dosing of protamine is more effective in facilitating haemostasis after CPB. Four RCTs met our eligibility criteria and were included in the meta-analysis. The findings from our meta-analaysis suggest that titrated protamine dosing is more effective than standard protamine dosing for reducing postoperative bleeding after CPB.

The major finding of our meta-analysis was that patients who had tirated protamine dosing experienced less postoperative blood loss after CPB than patients who had standard protamine dosing. Whether or not the decreased postoperative blood loss with titrated protamine dosing is of clinical significance remains to be determined. Indeed, there was little information on clinical outcomes in the four studies included in our meta-analysis. Although we did not perform any meta-analyses on other variables, all four studies included also reported that postoperative transfusion of PRBCs was lower with titrated *vs* standard protamine dosing. This is not surprising given the decreased blood loss. Three of the studies included in our meta-analysis

used the Hepcon HMS for titrating protamine doses,[9-11] while one study used the Hemochron system.[8] Other studies not eligible for inclusion in our meta-analyses also used the Hepcon HMS[15,16] and Hemochron system[17] for effectively titrating protamine doses. A number of studies, however, have questioned the effectiveness of protamine dose titration using these systems.[13,14] Specifically, Hardy *et al.* have suggested that the Hepcon HMS does not accurately assess heparin concentrations when compared with laboratory evaluation,[14] whereas Shore-Lesserson *et al.* found that protamine dose titration using the Hemochron system did not reduce postoperative blood loss compared with standard protamine dosing.[13] Hardy *et al.* however, did not examine clinical outcomes, specifically bleeding volume, which are clearly more important indicators of the system's utility than laboratory-equivalent accuracy in the evaluation of heparin concentrations. The disparate findings reported by Shore-Lesserson *et al.* are difficult to explain, but may reflect the somewhat small number of patients (n=28 in the protamine titration group) in the study and thus a possible lack of statistical power. We suggest that additional large-scale RCTs are needed to further explore the effectiveness of the Hemochron system for protamine dose titration.

Concerns have been raised about the safety of protamine for reversing the anticoagulant activity of heparin.[4-7] We did not focus on examining the safety of protamine dosing in this meta-analysis; hence, we cannot provide any definitive comments on this issue. However, neither of the two studies reporting complications after surgery presented evidence suggesting that safety was a significant concern.[10,12] Indeed, theoretically, one of the key advantages of protamine dose titration should be reducing the likelihood of overdosing and the associated adverse events / complications, which can occur with standard dosing.[18]

Our meta-analysis has a number of limitations. First, our analysis included only a small number of studies, and as a consequence, a relatively small number of patients for a meta-analysis. Further confirmatory, large-scale RCTs are needed. Secondly, there were some differences between studies that may have confounded the analyses, specifically differences in the type of surgery and the means of determining protamine dosing. This is reflected in our finding that there was evidence of moderate publication bias among the studies. Nevertheless, all of the studies included were RCTs (albeit non-double-blinded), and thus free of the inherent biases associated with non-randomised, retrospective, and observational studies.

In conclusion, the findings from this meta-analysis suggest that titrated protamine dosing is more effective than standard protamine dosing for alleviating postoperative bleeding after CPB. As such, titrated protamine dosing may help improve patient outcomes and reduce the need for supportive therapy due to postoperative bleeding.

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