Post-operative protamine infusion does not lead to reduced bleeding or transfusion following coronary artery bypass grafting

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Abstract

Aim: Post-operative bleeding remains a significant risk after cardiac surgery. Despite adequate protamine reversal of heparin intraoperatively, protein-bound heparin causes anticoagulant effect, leading to bleeding in the post-operative period. The aim of this study is to whether the use of a four-hour, low dose protamine infusion in intensive care would reduce post-operative bleeding and hence, blood transfusion requirements. **Methods:** A retrospective cohort study of seven hundred and two patients, who underwent elective or urgent coronary artery bypass grafting from April 2014 and January 2017, were divided into two groups based on who received post-operative protamine infusion (Group A, 472 patients) versus those who did not (Group B, 230 patients). They were assessed for amount of post-operative mediastinal and pleural drainage for the first 24 hours, use of post-operative transfusion of blood products, postoperative hospital stay, and re-exploration. **Results:** We found no significant difference between the rate of bleeding in either of the groups. No significant difference was observed in blood product requirements as well. In the sub-group consisting of patients with high BMI (BMI [?]30), who received protamine infusion, post-operative platelets transfusion was found to be significantly less. **Conclusions:** Our results suggest that a low dose protamine infusion given in the immediate postoperative period does not lead to any significant clinical benefits. Both patients receiving and not receiving the infusion had similar postoperative drainage, transfusion requirements, haemorrhagic morbidity, mortality and length of hospital stay.

TITLE PAGE

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VISUAL ABSTRACT

Key Question:

Does post-operative protamine infusion lead to reduced mediastinal drainage and decrease blood requirements in patients who have undergone cardiac surgery on cardiopulmonary bypass?

Key Findings:

Protamine infusion in the post-operative period is not found to decrease bleeding in comparison to patients who did not receive protamine.

Take-home message

Protamine infusion is not beneficial to prevent postoperative bleeding, even in patients with high BMI. Generic protamine infusion in post-cardiac surgery patients may even result in paradoxical bleeding and potential pulmonary hypertension, and further contradicts its use.

ABSTRACT

Aim: Post-operative bleeding remains a significant risk after cardiac surgery. Despite adequate protamine reversal of heparin intraoperatively, protein-bound heparin causes anticoagulant effect, leading to bleeding in the post-operative period. The aim of this study is to whether the use of a four-hour, low dose protamine infusion in intensive care would reduce post-operative bleeding and hence, blood transfusion requirements.

Methods: A retrospective cohort study of seven hundred and two patients, who underwent elective or urgent coronary artery bypass grafting from April 2014 and January 2017, were divided into two groups based on who received post-operative protamine infusion (Group A, 472 patients) versus those who did not (Group B, 230 patients). They were assessed for amount of post-operative mediastinal and pleural drainage for the first 24 hours, use of post-operative transfusion of blood products, postoperative hospital stay, and re-exploration.

Results: We found no significant difference between the rate of bleeding in either of the groups. No significant difference was observed in blood product requirements as well. In the sub-group consisting of patients with high BMI (BMI [?]30), who received protamine infusion, post-operative platelets transfusion was found to be significantly less.

Conclusions: Our results suggest that a low dose protamine infusion given in the immediate postoperative period does not lead to any significant clinical benefits. Both patients receiving and not receiving the infusion had similar postoperative drainage, transfusion requirements, haemorrhagic morbidity, mortality and length of hospital stay.

Key words: Protamine infusion, bleeding, heparin rebound, transfusion

Introduction:

Cardiopulmonary bypass is an integral component used in the majority of cardiac surgeries. The instigation and maintenance of cardiopulmonary bypass requires the administration of an anticoagulant, and this is routinely in the form of heparin due to its predictable and favourable pharmacology. One of the important aspects of heparin's pharmacology is the presence of a known and relatively safe reversal agent in the form of protamine. Protamine is routinely used after weaning patients from cardiopulmonary bypass, to reverse heparin's anticoagulant effect and therefore reduce the risk of post-operative bleeding.

Postoperative bleeding remains a significant risk after cardiac surgery with a national prevalence of 2.6% (1). Blood transfusion is therefore often required in the postoperative period. There are a number of studies showing that red blood cell transfusion has a significant detrimental impact on both short- and long-term outcomes (2, 3), therefore reducing the transfusion requirements for patients is paramount.

Bleeding after coronary artery bypass grafting (CABG) is often multifactorial, and risk factors include patient demographics and comorbidities, perioperative pharmacology and technical factors (4). One factor which has been theorised to contribute to postoperative bleeding is that of heparin rebound, with a prevalence of up to 52% (5). In heparin rebound, previously bound or incompletely neutralised heparin leads to anticoagulation in the early postoperative period despite seemingly adequate neutralisation initially with protamine intraoperatively. It is theorised that there are a number of different factors which combine leading to heparin rebound, these include the release of extra-circulatory deposits of heparin postoperatively (6) and the binding of heparin to intravascular proteins leading to incomplete neutralisation by the initial dose of protamine (7). Due to increased knowledge of the heparin rebound phenomenon many centres now routinely use thromboelastography with pre- and post-heparinase levels, in those patients bleeding excessively postoperatively, to identify the patients who may require further protamine in intensive care (8).

Administration of protamine however does not come without risk. One side effect of overzealous protamine administration is its anticoagulant effect at high doses, an effect which has shown in randomised controlled data post-cardiac surgery (9). In addition, protamine has been shown to cause significant and sometimes profound vasoplegia with a reduction in systemic blood pressure, along with pulmonary hypertension with an increase in pressures of up to 9.9 mmHg (10).

In our centre a number of cardiac surgeons utilise postoperative low dose protamine infusions with the aim of reducing heparin rebound and the potential postoperative bleeding along with the morbidity and mortality associated with this. Other surgeons in our centre do not use the infusion due to current poor-quality evidence for its use and potential side-effects of protamine over administration.

Our aim was to study whether the use of a four-hour, low dose protamine infusion in intensive care would reduce post-operative bleeding and transfusion requirements. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Anonymised data were obtained from the institutional database normally utilised for patient care and therefore the need for informed consent was waived by the institutional Medical Ethical Committee. Baseline, and outcome data were prospectively collected, validated and entered into the database, which was analysed retrospectively.

Many studies focused in calculating heparin dose according to ideal body weight (not actual body weight) especially for those with high body mass index. (11, 12, 13), in which heparin dose was sufficient when adjusted to ideal or lean body weight. Moreover, Mya S. Baker et al concluded that some overweight and obese patients presenting for cardiac surgery may require as much as 25% less heparin and subsequently protamine than previously thought (12). So, we also studied the effect of protamine infusion in patients with high BMI as we thought that heparin might be is overdosed in those patients. In this study we also tried to study if we could achieve better outcome in obese patients with protamine infusion as many authors believed that the heparin dose calculated for these patients based on actual body weight was likely to be more and thereby increasing chances of Heparin rebound and bleeding(11-13)

Method:

A retrospective cohort study was conducted including seven hundred and two patients who underwent elective

or urgent CABG in our unit between April 2014 and January 2017. Those who underwent emergent CABG were excluded from the study due to their intricate higher bleeding risk from other factors.

All patients included within the study were managed using our unit's standard operating protocols. Preoperatively aspirin was held 5 days pre-operatively except in those with high-risk coronary anatomy (significant left main-stem (LMS) disease or LMS equivalent). Clopidogrel was held for 5 days and ticagrelor for 3. With regards to other anticoagulants warfarin was held for 5 days with a preoperative INR check performed 1 day prior to surgery. Direct oral anticoagulants were held for 3 days and low molecular weight heparin was held the night before surgery. For those patients requiring a preoperative heparin infusion this was held a minimum of 6 hours pre-operatively.

Intraoperatively a baseline activated clotting time (ACT) was taken prior to heparin administration. 300 mg/kg (measured body weight) of heparin was administered in all patients. Cardiopulmonary bypass was established with a minimum ACT of 480 seconds, between aortic and dual-stage right atrial cannula used for commencing cardiopulmonary bypass. After weaning from cardiopulmonary bypass protamine was administered via a standardised protocol based on the previous ACT measurement with a final ACT taken after administration to ensure return to baseline.

Postoperatively all patients were transferred to our intensive care unit. Colloid and packed red cells were infused as per protocol with a transfusion threshold of haemoglobin under 80 grams/litre used. Mediastinal and pleural drainage were monitored hourly and any deviation from standard prompted the running of thromboelastogram (TEG) testing and targeted fresh-frozen plasma, platelet and cryoprecipitate transfusion. In those not receiving a protamine infusion an extra bolus of protamine (25-50mg) was given in those with significant pre- and post-heparinase values.

Mixed practice exists between surgeons within our unit with some preferring the routine use of a postoperative protamine infusion in intensive care and some not. Our postoperative protamine infusion has been standardised for those who did receive it, consisting of 100mg protamine mixed in 100ml 0.9% saline given over 4 hours intravenously. This was started on arrival in the intensive care unit.

Demographics along with outcome data were collected from our CVIS database. Outcome measures assessed were; post-operative mediastinal and pleural drainage for the first 24 hours (this was indexed against body weight), post-operative transfusion of blood products including packed red blood cells, fresh frozen plasma and platelets, postoperative hospital stay, and re-exploration for bleeding, tamponade or other cardiac complication rate. Patients with high body mass index (BMI) defined as BMI [?] 30 kg/m^2 are subdivided into two groups depending of having post-operative Protamine. Blood loss and blood products transfusion were analysed to study the effect of Protamine infusion in this group of patients.

Results were statistically analysed using the chi-squared test for categorical data and the 2-sample t-test for continuous data. $P<0.05$ was considered statistically significant.

RESULTS

Patient demographics

Patients were divided into 2 groups. Those who received a postoperative protamine infusion (group A, 472 patients), and those who did not receive the infusion (group B, 230 patients). Table 1

There were no significant differences found between the baseline demographics of the 2 groups. Group A had a mean age of 67.6 +/- 9.8 years with 382 patients being male and a mean BMI of 29.8 +/- 5.8. Group B had a mean age of 67.4 +/- 9.2 years with 191 patients being male and a mean BMI of 28.4 +/- 4.9.

Post-operative bleeding

Post-operative drainage from both mediastinal and pleural drains were measured with a mean total over the first 24 hours of 418.9 +/- 262.4ml for group A and 413.1 +/- 239.1ml for group B. There was no significant difference found between the groups (p 0.781).

Post-operative transfusion

With regards to transfusion group A received a mean of 0.87 units of packed red cells, 0.44 units of FFP and 0.16 pools of platelets per patient, whereas group B received 0.67 units of packed red cells, 0.69 units of FFP and 0.23 pools of platelets per patient. There was no significant difference between packed red cell and platelet transfusion between the 2 groups (p 0.178, and 0.097 respectively), however group B had a significantly lower number of units of FFP transfused (p 0.015).

Clinical outcomes

The average postoperative stay for group A was 8.58 +/*11.5 days and for group B was 7.31 +/- 7.5 days with no significant difference between groups (p 0.13). With regards to mortality and major haemorrhagic morbidity there was no significant differences between groups. There were 2 deaths in each group and in group A, seven patients required re-operation for bleeding, tamponade (1.5%) , whereas in group B this figure was 3 (1.3%).

Patients with a high BMI

It is proven that the dose of heparin calculated with actual body weight (in our case) as compared to the ideal body weight would lead to overdose of heparin thereby increasing the risk of heparin rebound and bleeding (1/7). We hypothesized that protamine infusion might have better outcomes in this group.

Our study included 278 patients with high BMI (defined as BMI [?]30), 203 of them received protamine infusion. We could not demonstrate statistically significant difference in total drainage, blood transfusion, FFP, or indexed blood loss in the two groups. Platelets transfusion was significantly less in patients who received protamine (0.11 unit / patient vs 0.27) P value was 0.023. (Table 2)

Adverse outcomes:

We did not encounter any significant adverse outcome like immediate post-operative MI, GIT bleeding, vascular complications or strokes in either group, confirming safety and not increasing cardiovascular risk with protamine infusion.

DISCUSSION

Our results suggest that a low dose protamine infusion given in the immediate postoperative period does not lead to any significant clinical benefits. Both patients receiving and not receiving the infusion had similar postoperative drainage, transfusion requirements, hemorrhagic morbidity, mortality and length of hospital stay. Patients who received Protamine infusion needed less FFP (.044 vs 0.69 unit/patient), P value 0.015 (Table 1)

Even in patients with high BMI who received protamine, there was no significant difference in total and indexed blood loss.

There is limited evidence for the use of additional postoperative protamine administration to combat heparin rebound in the intensive care setting. A single randomised controlled trial has been performed showing a significant biochemical improvement in heparin rebound with a modest reduction of postoperative bleeding with the use of a 6-hour protamine infusion in intensive care. Similar to our study however the clinical benefit of this was unclear with no significant transfusion benefit found. A similar complication profile was noted with no significant difference found between the groups with regards to morbidity and mortality (11)

Whilst little doubt remains regarding the phenomenon of heparin rebound after cardiopulmonary bypass there is little evidence to show a significant number of patients suffer clinical consequences. In addition, our study along with previous evidence fails to show any significant clinical benefit in providing additional protamine in the postoperative phase.

Haemorrhage and the transfusion requirements associated with this continue to have significant morbidity and mortality consequences for our patients post cardiac surgery. This bleeding is multifactorial in aetiology

and it appears whilst heparin rebound may have a role in this its clinical significance is limited and the reversal of the effect with protamine infusion lead to little if any significant benefits for our patients. When compared, the two groups did not show any difference in terms of the total postoperative stay.

LIMITATIONS

This is a single centre study which has inherent limitations. Furthermore, the patients were not randomised but rather divided based on the operating surgeon which may introduce a bias. The patients of all surgeons are managed according to a unit policy; however, this is an important limitation.

CONCLUSION

Given the rare but serious side effects of protamine administration including paradoxical bleeding and pulmonary hypertension it is suggested the routine use of postoperative protamine infusions is not conducted unless further contradictory evidence becomes available.

In our study, protamine infusion doesn't look to be beneficial, even in patients with high BMI in which heparin rebound is meant to be more obvious.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

Table 1: Patients' characteristics

			G
Number	Number		47
Age in years	Age in years	Mean (SD)	67
		Median [IQR]	68
Sex = M (%)	Sex = M (%)	Mean (SD)	38
Height	Height	Mean (SD)	1.
		Median [IQR]	1.
Weight	Weight	Mean (SD)	86
		Median [IQR]	85
BMI	BMI	Mean (SD)	29
		Median [IQR]	29
Total Drainage (ml)	Total Drainage (ml)	Mean (SD)	41
		Median [IQR]	37
Transfusion	Blood (Units)	Mean (SD)	0.
	FFP (Units)	Mean (SD)	0.
	Platelets (Units)	Mean (SD)	0.
Indexed blood Loss	Indexed blood Loss	Mean (SD)	14
		Median [IQR]	13
Re-operation for bleeding or tamponade N (%)	Re-operation for bleeding or tamponade N (%)		7
ITU stay in hours (mean (sd))	ITU stay in hours (mean (sd))	Mean (SD)	67
		Median [IQR]	35
Postoperative hospital stay (in days) (mean (SD))	Postoperative hospital stay (in days) (mean (SD))	Mean (SD	8.
		Median [IQR]	6.
Died in cardiac unit	Died in cardiac unit		2

Table 2: Patients' characteristics in sub-group with high BMI:

	Protamine	No Protamine	P- value
Number	203	75	

	Protamine	No Protamine	P- value
Total Drainage (mean (SD)	392.26 (277.50)	403.51 (209.49)	0.75
Blood transfusion in units (mean (SD)	0.65 (1.83)	0.48 (0.86)	0.439
FFP transfusion (mean (SD)	0.39 (1.21)	0.61 (1.36)	0.197
Platelets (mean (SD)	0.11 (0.42)	0.27 (0.70)	0.023
Indexed blood loss (mean (SD)	11.54 (8.50)	12.27 (6.76)	0.507

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