

Negative Effects Of Protamine On Myocardium In Paediatrics Patients Undergoing Cardiac Surgery Using A Cardiopulmonary Bypass Machine

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Keywords

Negative Effects, Protamine, Myocardium, Paediatrics Patients, Cardiac Surgery, Cardiopulmonary Bypass Machine.

ABSTRACT

The administration of protamine, a heparin reversal agent, is an integral part of cardiovascular bypass protocols, particularly in the post-bypass phase. In paediatric cases, protamine is administered in a titration dose. The use of protamine is associated with various adverse events, including myocardial impairment. Proper dosage adjustment is crucial during protamine administration, as excessive doses may result in the depression of myocardial function. Experimental studies examining protamine usage have revealed myocyte impairments, such as reduced myocyte contractility, dysfunction in signaling pathways, and alterations in cardiac receptors. Despite these findings, research on the impact of pediatric protamine on the myocardium remains limited and necessitates further investigation.

INTRODUCTION

Cardiac surgery in paediatric patients often involves the use of a cardiopulmonary bypass machine to facilitate procedures such as open-heart surgery. In these cases, the anticoagulant heparin is routinely administered to prevent blood clotting during the bypass (Binka et al., 2023; Tadphale et al., 2021). To reverse the anticoagulant effects of heparin post-surgery, protamine, a positively charged protein derived from salmon sperm, is commonly employed.

While protamine is essential for neutralizing heparin, its usage is associated with potential negative effects on the myocardium, particularly in the vulnerable paediatric population. The myocardium, the heart's muscle tissue, plays a crucial role in maintaining cardiac function. Therefore, understanding and mitigating any adverse impacts of protamine on the myocardium are paramount to ensuring the overall success and safety of cardiac surgeries in paediatric patients (Hu et al., 2022; Kravec et al., 2023; Singab et al., 2021).

Research in this area is crucial due to the unique physiological characteristics of paediatric patients, such as their smaller size, immature cardiovascular systems, and the presence of congenital heart diseases (Elhaddad et al., 2022; Nasr et al., 2021). Unlike in adults, where adverse reactions to protamine are more extensively studied, the paediatric population may exhibit different responses and susceptibility to the negative effects of protamine.

Moreover, the dosage and administration of protamine in paediatric cardiac surgeries are not precisely regulated by specific guidelines. This lack of standardized protocols underscores the need for

comprehensive research to investigate the dosage-related impact of protamine on the myocardium in paediatric patients undergoing cardiac surgery with a cardiopulmonary bypass machine (Scherrer et al., 2022; Spraidner et al., 2023).

The negative effects of protamine may include immunological reactions, inflammatory changes, and potential cardiovascular complications such as pulmonary vasoconstriction, bradycardia, and altered inotropic response (El Gameel et al., 2023). Understanding these potential complications is essential for refining protocols, adjusting dosages, and implementing preventive measures to enhance the safety and efficacy of cardiac surgeries in paediatric patients.

This research is motivated by the use of protamine as a heparin neutralizer in patients undergoing open-heart surgery, particularly in the pediatric population. Protamine is a positively charged protein derived from salmon sperm. Generally, heparin is used as an anticoagulant during cardiopulmonary bypass procedures in heart surgery (Shiferaw et al., 2022). Protamine is administered to counteract the anticoagulant effects of heparin post-surgery. However, the use of protamine is not without risks of side effects, such as immunologic reactions, inflammatory changes, anaphylaxis with hypotension, pulmonary vasoconstriction, bradycardia, and allergies. In children with congenital heart disease, there is an additional risk associated with coagulation disorders or the use of medications affecting the coagulation process (Hamed Al-Farsi et al., 2022; Joshi et al., 2023).

In this literature, the research focus is on the negative impact of protamine on the myocardium in the pediatric population. Currently, protamine dosage is not specifically regulated by particular guidelines, but generally, the dosage ranges from 1.0 to 1.3 mg per 100 units of total heparin used during the bypass procedure. The use of protamine in children, especially infants, may require dosage adjustments based on the protamine-to-heparin ratio. The use of Automated Whole Blood-Activated Clotting Time (ACT) is currently recommended in the protamine regimen for children (Poltak et al., 2022).

Although the prevalence of adverse events related to protamine in children is not well-established, studies indicate that adverse reactions to protamine in patients under 16 years old are lower compared to adults. Risk factors such as high protamine dosage and low heparin dosage are found to contribute to protamine side effects in females (Zhao et al., 2023).

Some previous studies also highlight the effects of protamine on the cardiovascular system, including a decrease in myocardial contractile function and peripheral vasodilation. Some studies note that protamine can cause depression in the myocardial system and reduce inotropic response. Protamine is also involved in changes to cardiovascular receptors, including cardiac glycoside receptors and β -adrenergic receptors.

This research will also consider the influence of protamine on neurogenic reflex mechanisms, although some studies do not support the involvement of parasympathetic reflex mechanisms. Cardiovascular effects of protamine, such as increased pulmonary artery pressure, myocardial oxygen consumption, heart rate, systemic vascular resistance, and cardiac output, are linked to nitrite oxide production, antibody formation, histamine release, thromboxane activation, and complement activation. Protamine side effects are known to increase in patients with myocardial dysfunction.

The research methodology may include retrospective analysis of cohort data in the pediatric population receiving protamine during open-heart surgery. The research focus may involve monitoring protamine side effects, especially hypotension-related or isolated to right-sided heart failure. Protamine dosage data, inotropic response, and other cardiovascular parameters can also be collected and analyzed to better understand the impact of protamine use on the myocardium in children.

METHODS

This literature review's methodology involves identifying literature sources using scientific databases and specific keywords. Inclusion and exclusion criteria are applied to select literature relevant to using protamine in children during open-heart surgery. Literature analysis identifies key findings, classifies results, and constructs a conceptual framework. The literature review report is organized with a critical analysis of research methodologies, providing conclusions, and suggesting directions for further research or clinical implications. The report is reviewed and corrected to ensure accuracy, and a bibliography is included. The goal is to provide a comprehensive overview of the impact of protamine use on the myocardium in children during open-heart surgery.

RESULTS

Protamine is a positively charged protein that originated from salmon sperm. Protamine is mostly known as a heparin neutralizer by binding to anionic heparin (Boer et al., 2018). The anticoagulation effect of heparin is reversed by protamine. During open heart surgery, heparin is used for cardiopulmonary bypass (Hendry et al., 1987). In the post-operative phase, a measure to hinder the heparin effect is administering protamine. The administration of protamine is linked with side effects such as immunological and inflammatory alteration, instigating anaphylactic reactions with hypotension, pulmonary vasoconstriction, bradycardia, and allergy (Boer et al., 2018). Protamine is also associated with coagulation abnormalities in patients who undergo cardiac surgery. In paediatrics, infants that have congenital heart disease already have coagulation defects or using drugs that alter the coagulation process. This literature will highlight the negative effect of protamine on the paediatric myocardium.

Protamine administrations in the post-bypass phase are related to heparin usage. Although no specific guidelines regulate protamine dose, it is known that the dosage of protamine is 1.0 to 1.3 mg per 100 units of total heparin usage in the bypass procedure. However, protamine administration shouldn't affect the treatment of coagulopathies associated with bypass in infants. Protamine is usually given intravenously over 10 to 15 minutes to suppress the side effects (Chaney, Devin Roberts, et al., 2016). It is postulated that titration dose can be given as a guide to paediatrics. Younger age-like infants may require dose modification with protamine to heparin ratio (Anderson et al., 2013). The current protamine regimen in children uses automated whole blood-activated clotting time (ACT) (Gruenwald et al., 2010).

The protamine adverse events prevalence in children is not yet established. Meanwhile, adult patients have varying percentages of significant adverse reactions, which is 0.1% to 24%. However, a study showed that protamine adverse reactions in patients under 16 years old are lower than in adults with 1.76% to 2.88% percentage. In females, a higher protamine dose and a little heparin dose are the risk factors for adverse effects (Anderson et al., 2013).

Hendry et al. implied the toxic effect of high protamine concentration on myocytes in humans. Protamine has the effect of causing depression in the myocardial system. However, the toxicity is reduced in the heparin-protamine complex. The protamine administrations played an important role, and it's suggested that slow protamine administration under 500 mg/20 min, though limitation in operative time might force all protamine to be delivered simultaneously, around 450 mg/10 min (Hendry et al., 1987).

Several studies reported the protamine effect on cardiovascular. Protamine has an impact on the myocardium and peripheral vascularization. After protamine injection, Fadali et al. found a significant decrease in dogs' myocyte contractile function. Protamine also showed significant hypotension of femoral arteries after administration into arterial and extracorporeal circulation. It is recommended to use inotropic agents while administering protamine, such as calcium gluconate, calcium chlorate, epinephrine, or

isoproterenol, except for patients with arrhythmias. The vasodilatation effect can be compensated with fluid administered and reversed using norepinephrine (Fadali et al., 1976).

A study by Hird et al. showed that unbound protamine directly affects the myocyte contractile process and transduction system in the left ventricle (LV). After cardiopulmonary bypass, significant changes are happening in the LV and neurohormonal system. Protamine has the effect of decreasing the response of β -adrenergic and resting membrane potential of myocyte in porcine. The administration of 40 $\mu\text{g}/\text{mL}$ protamine lowers the myocardial contractility to the baseline value. A decrease of 35% in myocyte velocity and shortening percentage after administering 40 $\mu\text{g}/\text{mL}$ protamine. Meanwhile, myocyte contractile function is further declined in administering 80 $\mu\text{g}/\text{mL}$ protamine. It is found that protamine alters cardiac receptors such as cardiac glycoside receptors and β -adrenergic. The experiment with rabbit hearts showed that protamine is not only affecting the myocyte due to the molecule's positive charge, but it happened to cross myocardium vasculature and have direct contact with the myocyte. Aside from myocyte contractility, protamine also induces inotropic responsiveness. Meanwhile, the heparin-protamine complex didn't show the same findings (Hird et al., 1994).

The effect of protamine in the myocardium is also considered due to the neurogenic reflex mechanism. However, Fadali et al. study couldn't support the involvement of the parasympathetic reflex mechanism (Fadali et al., 1976). Protamine is known to cause several cardiovascular effects, such as pulmonary artery pressure increase, oxygen consumption of myocytes, heart rate, systemic vascular resistance, and cardiac output. These phenomena are due to nitrite oxide production, antibody formation, histamine release, thromboxane, and complement activation. Protamine adverse effects are exaggerated in patients with myocardial dysfunction (Moeinvaziri et al., 2009). An *in vitro* study by Pearson et al. also establishes the previous finding that protamine-inducing nitric oxide release from endothelial vasculature leads to vasodilatation (Pearson et al., 1992).

Protamine is commonly injected intravenously over a 10- to 15-minute period in the cardiac operating room; this gradual infusion is meant to reduce the possibility of adverse effects that may happen if infused too quickly. Many anesthesiologists may deliver a modest bolus of protamine in the cardiac operating room, known as a "test dose," to allow for the early diagnosis of side effects, including hemodynamic instability. Studies have indicated that protamine supplied through a central line can raise plasma histamine levels and decrease systemic vascular resistance. Hence protamine is frequently administered via a peripheral intravenous line instead of a central line.¹⁰ The remainder of the protamine dosage is injected if there are no negative side effects. correct dosage of heparin is reversed by protamine is debatable and differs throughout the medical literature.¹¹

Protamine is sold as an intravenous solution with a 10 milligram/milliliter concentration. For every 100 units of heparin, 1 to 1.5 mg of protamine is administered to neutralize it. One milligram of protamine is administered for every 100 units of the low molecular weight heparin given as the first step in treating dalteparin, tinzaparin, or enoxaparin overdose. If bleeding persists 4 hours later, more protamine dosages in the 0.5 mg per 100 unit range might be administered. The activated clotting time or a thromboelastogram test can be used to gauge how well protamine-reversing heparin works. In clinical studies, protamine infusion through the ascending aorta lowered hemodynamic alterations and arterial oxygenation changes compared to a central venous line, suggesting that this may be the preferred delivery route (Chaney, Roberts, et al., 2016).

A retrospective cohort study by Seifert et al. studied protamine usage in paediatrics. The study does not document the adverse event of protamine, which is hypotension that is associated or isolated with right-side cardiac failure (Seifert et al., 2003).

CONCLUSION

Protamine usage is associated with several adverse effects. The protamine usage in children has no specific guideline, although titration dose based on heparin usage is recommended. The high dose of protamine can lead to depression of myocardial function. Unbound protamine affects myocyte contractility, LV transduction activity and alters cardiac receptors. It is recommended to use inotropic agents while administering protamine, such as calcium gluconate, calcium chlorate, epinephrine, or isoproterenol, except for patients with arrhythmias. The vasodilatation effect can be compensated with fluid administered and reversed using norepinephrine. However, the study that explained the effects of protamine administration in children is still limited. Despite experimental studies that support the negative effect of protamine on myocytes, further study is needed. A cohort study that evaluates myocardium changes after protamine administration should be done, especially in children.

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