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Health & Medicine, Body

Thesis Proposal: 1st Draft

How Temperature Effects Platelet Function During Hypothermic and Normothermic Cardiopulmonary Bypass

ABSTRACT

Background

During the process of Cardiopulmonary Bypass (CPB), the physiology of platelet functions subjected to different temperature conditions largely determines whether a patient will experience increased or reduced postoperative bleeding. This research paper showed that platelets levels in normothermic patients are preserved better than in the hypothermic patients.

Methods

Meta-analysis test was applied in numerous peer-reviewed journals. Among the articles I reviewed, one hundred patients were randomized into the normothermic perfusion (35 to 37Cº, N= 50) and the mild hypothermic CPB group (27-32Cº, N= 50). They compared temperature to the relative blood loss, platelet level in the primary coronary artery bypass grafting and also compared it with the transfusion requirements and then the platelet counts were measured before the operation started, 4hours after surgery and 6 days afterwards.

Results

There were no differences in the preoperative characteristics such as number of occluded vessels, age, sex and weight. In both the normothermic

cardiopulmonary bypass and hypothermia CPB bleeding was observed. However, the impaired platelet functionality increases postoperative blood loss. The normothermic patients appeared to bleed less at 24 hours. The platelet levels were preserved better in the normothermic patients than in the hypothermic patients.

Conclusion

The data from this research suggests that normothermic perfusions reduced postoperative blood loss and was able to preserve the platelets.

INTRODUCTION

- Purpose of the study

In this study, I will examine the effects temperature on platelets in the cardiopulmonary bypass and its ultimate effect on both the normothermic and hypothermic CPB. In order to produce better and more reliable results, there should be no difference in the preoperative characteristics of the patients such as age, sex, weight, number of occluded vessels and the platelet levels.

- Statement of Research Problem

Platelet deficiencies can lead to excessive hemorrhage whereas high platelet counts can lead to thrombosis causing strokes, myocardial infractions and pulmonary emboli. Platelets are often administered during and immediately after cardiopulmonary bypass in order to prevent such negative effects on the body. Plateletes need to be administered at room temperture and deviation of this protocol will negatively effect both platelet function and survivability of administrered plateletes within the body . This study will seek

to review different medical journals that will further explain and confrim why CPB should be carried out at room temperature or in normothermic conditions.

- Literature Review

Platelets are the smallest of all the blood cells and are well-known to be activated during cardiopulmonary bypass. Platelets play a major role in many associated complications in the cardiopulmonary bypass. Many complications have been demonstrated in this process as both qualitative and quantitative defects, resulting in micro vascular thromboembolism and hemorrhage. Since their interaction with endothelium is usually unraveled, the vital contribution that they make towards the systemic inflammatory responses to the operation in the cardiopulmonary bypass is progressively more evident (Murphy, Gardner, 1969).

The physiology of the of platelet function subjected to deep hypothermic conditions can be used to explain the reason why most patients ends up bleeding more if the Cardiopulmonary bypass is carried out in temperatures below the room temperature. The cooling effect results into a decreased platelet aggregation during the CPB. However, this effect is reversible after re-warming to temperatures around 37 °C (normothermic conditions). Compared to hypothermic patients, the normothermic patients tend to bleed less in 24 hour in the post-cardiopulmonary bypass. This is because the platelets levels in normothermic patients are preserved better than in the hypothermic patients. In respect to blood loss, Carrying out Cardiopulmonary bypass at room temperatures would therefore lead to reduced postoperative blood loss and preserved platelets.

Normally, platelets are 1. 5 to 3. 5nm in diameter anucleated circulating cells that are derived from precursor megakaryocytes. Per every liter of blood, a normal adult human being has between 150 to 400 X 109 and at any one time, the majority of the bloods platelets are sequestrated in the spleen (Ellison, and David 1988). In addition, the average survival period of the human platelet is between 5 to 9 days. The cardiopulmonary bypass (CPB) activates the platelets with the resulting structural and biochemical changes. The whole process causes alterations in the clot formation, platelet count, and in the manner at which platelets interact with other blood cells. Platelet deficiencies can lead to excessive hemorrhage whereas high platelet counts can lead to thrombosis causing strokes, myocardial infractions and pulmonary emboli. Platelets are often administered during and immediately after cardiopulmonary bypass in order to prevent such negative effects on the body. Plateletes need to be administered at room temperture and deviation of this protocol will negatively effect both platelet function and survivability of administrered plateletes within the body (Ellison, and David 1988). This is particularly important during cardiopulmonary bypass when there can be large levels of platelet consumption and significant variations in patient temperature when cooling and rewarming the patient.

The differences between the normothermic (> 35°C) and hypothermic (27° to 28°C) systemic perfusion in the cardiopulmonary bypass has been largely documented. The platelet aggregation was shown to be substantially decreased by the hypothermic as compared to the normothermic effect. By the first postpoperative, the platelet aggregation had already reverted to normal in the normothermic but in the hypothermic group it had not yet

reverted fully. A study by Thomas J refers to the influence of normothermic surgery as ’warm heart surgery’ and involves a continuous warm blood normothermic and cardiophelagia systemic perfusions. Their study showed that there was a reduction in bleeding in all the normothermic patients that had been involved in their study versus the moderately hypothermic patients. This was explained through a statistical difference after 6 and 12 hours but not later than 24 hours.

Homeostasis is a very complex which involves many factors that interact simultaneously such as the fibrinolytic system, clotting proteins and the complement. Most of these systems are purely temperature dependant. In particular, the complement activation formed part of the larger humoral response to cardiopulmonary bypass. There was platelet division that led to P-selection expression occurring in response to the complex C5b-9. Additionaly, changes in platelet during CPB for instance (Gravlee, Glenn, 2008) thrombocytopenia and a situation of decreased platelet force generation may ultimately lead to hermorrhage micro vascular by compromising the role of platelets in the role of homeostasis process. This is because the commencement of CPB usually causes a decrease in the platelet count due to the dilution of blood in the circuit used by the CPB.

Despite aprotinin being a vital protease inhibitor which works to activate the platelet in the Cardiopulmonary bypass, some research journals such as the Platelet function and hypothermic cardiopulmonary bypass by Dr. Boldt shows that the use of aprotinin failed to prevent bleeding in normothermic patients. He reported that, although aprotinin is useful in patients who are undergoing a cardiac operation in moderate hypothermia, when it was not

administered, both the hypothermic and normothermic patients bled less than the moderate hypothermic patients.

HYPOTHESIS

Normothermic CPB is superior over hypothermic CPB in sustaining platelet function and low postoperative bleeding.

NULL HYPOTHESIS (Ho)

Differences in temperature during CPB (Normothermic and hypothermic) shows no significant variation in the platelet function and postoperative bleeding.

MATERIALS AND METHODS

- Data Sources

I used fifteen peer-reviewed medical journals showing studies that compared normothermic CPB to hypothermic CPB from different medical search engines such as: Chest, PubMed, N Engl JMed and the British Journal of Anaesthesia medicine.

- Research Protocal

I will derive my research methods based on the information derived from the clinical trials and other numerous studies from various medical journals that I will review. It will encompass a number of prospective clinical and non clinical trails as well as meta analysis journals that will be analyzed to determine the optimal temperature for platelet administration during cardiopulomonary bypass (Gravlee, Glenn, 2008). Several factors that are being considered are; core body temperature of the patient pre and post operation; volume of slavaged red cells and the amount of transfusin of

blood bank products that are reinfused intraoperatively; time-depenedent up-regulation of platelet surface markers such as von Willibrand Factor, P-selection, thromboxane (TX)A2 and phosphatidylserine that are activated during bypass; any other hemostatic defects, such as a reduction in platelet number, size and mass; and inadequate heparin reversal or excessive protamine (FRCPS, Pierre Pagé, 2005).

- Research Methogdology

I will put more emphasis on the clinical trials that were carried out by Dr. Despotis, and Dr. Goodnough. In their test, they used one hundred patients who were randomized into the normothermic perfusion (35 to 37Cº, N= 50) and the mild hypothermic CPB group (27-32Cº, N= 50). In this research method, they compared temperature to the relative blood loss, platelet level in the primary coronary artery bypass grafting and also compared it with the transfusion requirements. The leucocytes and platelet counts were measured before the operation started, 4hours after surgery and 6 days afterwards. In this research, the patient must be rewarmed since mostly the moderate hypothermia of between 25-30ºC may have been used to slow down myocardial rewarming and reduce central nervous system complications after the cold cardiplegia. During this time, the temperature measurement of the heater must be set right and include the arterial and nervous blood, and in doing so, one has to remember that it is customary to keep the arteriovenous gradient to less than 10ºC. Normally, the criteria for rewarming depends on the institution but usually requires a nasopharynx (the uppermost part of the phyarnx that extends from the skull to the soft palate) temperature of 37 ºC, while the rectal and bladder temperature is set

at 35 ºC. In order to avoid a situation whereby the patient’s brain is being overheated, the heater temperature during rewarming is supposed to be set at temperatures of around 40-42 Cº, this is particularly important because it makes it achievable to maintain both the nasopharynx, rectal and bladder temperature while at the same time ensuring a conducive brain temperature. This temperature comparison between the heater/cooler and other vital parts of the body creates an optimal temperature for platelet function

According to a research carried out by Anita S, Shukri and Robert Velarie in their medical journal the platelet function defect of cardiopulmonary bypass, they used meta analysis test approach to analyze a 10 time points, before, during and after the Cardiopulmonary bypass. Using a whole blood flow cytometric assay to carefully study platelet surface and glycoproteins. The peripheral blood, activated in vitro by either the thromboxane (TX) A2, phorbal myristate acetate, or a combination of adenosine diphosphate and epinephrine. In addition, they used blood obtained from a bleeding time wound (shed blood). In this study, the GBIb levels were shown to be decreased by the CPB. They showed that the minimum levels of expression were usually at around 120 minutes after the start of the cardiopulmonary bypass. The expressions afterward were seen to gradually increase taking more than three hours for them to return to the prebypass levels.

- Why Use Meta-Analysis?

Meta-analysis is the most preferred test in this study since it uses a more statistical approach that combines multiple results form an array of studies. Some of its advantages over other medical research tests such as the

student t-test, chi square or the analysis of variance is that the results can be generalized easily to a larger population. In addition, the accuracy and precision of the estimates can be developed further as more data is being used. This therefore makes it a preferred test in most of the clinical trials during medical research. Other tests such as the Chi square have limitations that make them unfavorable in the study of the effect of temperature during cardiopulmonary bypass. For instance, comparing only two categories e. g. Normothermic and hypothermic CPB using the Chi square should strictly not be used due to differences in the Yates correlation.

RESULTS

In regard to homeostasis, both the cardiopulmonary bypass and hypothermia contribute to bleeding (Despotis and Goodnough, 2000) The CPB activates the platelets in the blood leading to platelet degranulation, depletion and deposition. The impaired platelet functionality increases postoperative blood loss. The platelets formed during the cardiopulmonary bypass form conjugates both between the red blood cells, themselves and the white blood cells. In the many journals that I reviewed, the Vitro studies have shown that the platelet-monocyte and platelet neutrophil binding is mediated through the p-selection which is usually expressed on the activated platelets.

In our quest to improve on how Temperature effects platelet function during hypothermic and normothermic cardiopulmonary bypass, a retrospective review of the systemic perfusion on the CPB blood loss rate is required. To evaluate further the effect of the normothermic systemic perfusion on the

postoperative blood loss, a review of bleeding in patients should be carried out in a randomized clinical trial that compares the normothermic and hypothermic techniques in carrying out of heart surgery

The cooling effect during hypothermia has a great impact in the perfusion during the cardiopulmonary bypass. For instance, the reduction of temperatures will lead to a more pronounced alteration of platelet aggregation and all the endothelial-related coagulation, on the other hand the reduction in temperature will cause the plasma levels of soluble thrombomodulin to increase. This can be attributed to the numerous postoperative extensive endothelial damage or its activation due to the hypothermic conditions during CPB. Hypothermia thereafter leads to a dysfunction in the membrane through inducing a reversal platelet formation. It activates the fibrinolytic cascades and eventually activated the clotting factors (Gravlee, Glenn, 2008).

UTILITY

It is therefore evident that normothermic CPB is the most favorable method during a cardiac surgery. Most journals showed that normothermic systemic perfusion was largely associated with reduced postoperative blood loss (Forestier, Coiffic, Ekouevi and Chene, 2002). Consequently, normothermic perfusions are vital since they can end up reducing cost, improves on the management of the whole cardiac surgery unit and also it has proven to be a more comfortable method for patients.

DISCUSSIONS

There has been a lot of concern regarding transfusion–related morbidity and death; this has led to most cardiac surgeons initiating blood conservation programs. In the journal Management approaches to platelet-related microvascular bleeding in cardiothoracic surgery, Dr. Despotis, and Dr. Goodnough randomly assigned patients who were undergoing a coronary bypass grafting in their clinical trial both warm and cold perfusions surgical groups. After the whole process, the patients in the warm group were observed to be having reduced postoperative blood loss by 40% after 6hours, 35% after 12hour and 30% after 24hours and was compared to the by the other patients who were perfused hypothetically (Despotis and Goodnough, 2000).

In their discussion, Dr. Despotis, and Dr. Goodnough explained why systemic perfusions at 35 to 37Cº rather than the 27 to 32ºC largely reduced blood loss at 6, 12 and 24hours after the operation. They explained that, the warm perfusions had a lower frequency of red blood cells transfusions and therefore received reduced ended up receiving a lower number of units of RBC per patient (Despotis and Goodnough, 2000). For that reason, the warm perfusion is effective in the reduction of blood loss and transfusions requirement.

CONCLUSIONS

Based on numerous medical journal reviews and studies, it is evident that during cardiopulmonary bypass, the process of platelet administration should occur at room temperature so as to maximize the efficacy of platelet

administration (Ellison, and David 1988. In addition, the homeostasis factor plays a major role in the cardiopulmonary bypass as temperature variation of platelet administration will negatively affect both platelet function and survivability of the administered platelets within the body.

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