Original Research Article

Comparison of 4% Succinylated Gelatin with 6% Hydroxyethyl Starch 130/0.4 for Preloading Prior to Cardiopulmonary Bypass in Coronary Artery Bypass Grafting Patients

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Abstract

Aims and Objective: The present study was carried out with an objective to compare 4% succinylated gelatin with 6% hydroxyethyl starch 130/0.4 for preloading prior to cardiopulmonary bypass in coronary artery bypass grafting patients with respect to haemodynamics status, blood loss, transfusion requirement, ICU stay and complication.

Methods: The study enrolling 60 patients of either sex, aged between 30-70 years undergoing elective coronary artery bypass grafting. These patients were randomly divided into two groups of 30 each. Group 1 received 500 ml 6% hydroxyethyl starch (HES) and group 2 received 500 ml 4% succinylated gelatins, on pump over a period of 25 minutes. Data were monitored included haemodynamic changes, postoperative blood loss, transfusion of PRBC and blood products, ICU stay and complications related to colloid usage.

Results: We found statistically significant difference in pulse rate 5 minutes after starting colloid. Also found statistically significant difference in mean arterial pressure immediately after shifting patient to ICU but no significant difference found subsequently. There was gradual increase in CVP in both the groups but majority of patients in group 2 showed higher CVP values as compared to group 1 patients. Measured chest tube drain and output higher in starch group as compared to gelatin group, there was no need of reexploration or greater need for blood and blood products in starch group. There was no significant difference in postoperative renal parameter between two groups.

Conclusions: Results of our study revealed that both the colloids i.e. 4% succinylated gelatin and 6% hydroxyethyl starch were comparable with respect to haemodynamics parameters, blood loss, transfusion requirement and complication.

Keywords: Succinylated gelatin, Hydroxyethyl starch, Cardiopulmonary bypass, Coronary artery bypass, PRBC, CVP.

1. Introduction

Controversy regarding the most suitable colloid for use as a plasma volume expander in cardiac surgery is unresolved, despite many ongoing studies. Although there have been improvement in technology, cardiopulmonary bypass is still associated with adverse effect on coagulation and multiple organ dysfunction [1]. Colloid chosen for preloading and priming the cardiopulmonary bypass circuit and volume replacement hence must not interfere with the coagulation system or any other body system and incur minimal risk of adverse reaction.

Gelatins are polydispersed polypeptides, produced by degradation of bovine collagen. Gelatin based colloids have been used as they are free of adverse effects on hemostasis, cross matching and renal function and there is no limit to their use [2]. Hydroxyethyl starch is a derivative of amylopectin, the highly branched polysaccharide component

of waxy maize, which closely resembles glycogen. With large volume of hydroxyethyl starch infused perioperatively, inhibitory effects on hemostasis most notably on Von Willebrand factor have been reported. These effects are most pronounced with large and highly substituted hydroxyethyl starch molecules such as hetastarch which has an average molecular weight of 450,000 daltons and degree of substitution of 0.7 (HES 450/0.7), however a new HES specification HES 130/0.4 offers a better pharmacokinetic and pharmacodynamic profile and can be safely used up to 50 ml/kg/day [3-5]. Also starch has more volume expansion capacity and has less allergic reaction incidence as compared to gelatins. It has been suggested that correction of hypovolemia with HES is associated with increased risk of acute renal failure and interest has recently focused on the influence of HES solution on renal function [6].

The aim of this study was to compare gelatin with HES for preloading prior to cardiopulmonary bypass in coronary artery bypass grafting patient and priming the cardiopulmonary bypass circuit and volume replacement and its effect on postoperative bleeding, blood transfusion requirement, renal function and outcome of coronary artery bypass surgery.

2. Materials and Methods

The designed was a open labeled, randomized, prospective comparative cohort study involving 60 patients of either sex, aged between 30-70 years undergoing elective coronary artery bypass grafting. Patients having left ventricular ejection fraction (LVEF) more than 35% were included in the study. After obtaining approval from institutional ethics committee, written informed consent was obtained from all patients. Patients with known renal dysfunction, hepatic dysfunction, congestive heart failure, recent antiplatelet therapy (<7 days), coagulopathy and patients with known allergic reaction to any of the colloid were excluded from the study.

In operation theatre, multipara monitors-pulse oxymeter, non-invasive BP and cardioscope were applied to the patient and baseline parameters were recorded. While securing central venous line and arterial line an infusion of ringer lactate started through peripheral line at 5 ml/kg/hr rate. Sixty patients were randomly divided using computer generated randomization in to two groups of 30 each. Patients of group 1 received 500 ml 6% HES 130/0.4 and patients of group 2 received 500 ml 4% succinylated gelatin. Over a period of 25 minutes for preloading prior to cardiopulmonary bypass guided by CVP which was used to maintain below 6-8 mm of Hg. Bypass circuit was also primed with same colloid. Anaesthesia was induced with fentanyl 8-10 μg/kg, midazolam 2 mg and vecuronium 0.1 mg/kg and maintained with sevoflurane to achieve minimal anaesthetic concentration of one intravenous tranexemic acid 10 mg/kg was given after induction. Before establishing CPB, intravenous heparin 300 u/kg was given to achieve an activated clotting time >480 second. Depending on the group, perfusionist primed CPB circuit with either gelatin or hydroxyethyl starch. Packed red blood cells were given if the hematocrit fell below 25%. Blood cardioplegia was used in all cases. On termination of CPB, coagulation was reversed to baseline value with protamine sulphate.

Postoperatively patients were transferred to cardiac intensive care unit and mechanically ventilated chest tube drainage was recorded hourly up to 24 hours and bleeding needing re-exploration was defined as chest tube drainage >200 ml/hr for 2 consecutive hours along with deterioting condition of patient and not responding to conservative management. PRBC as transfused when Hb level < 9 gm/dl. Fresh frozen plasma, platelet concentrates and cryoprecipitate were transfused when there was bleeding perioperatively in

the presence of abnormal coagulation values (INR > 1.5 activated PT > 60 sec, platelet count < 100×10^9/L) or suspected platelet dysfunction or clotting factor deficiency. Primary outcome variable included postoperative blood loss (measured hourly for first 4 hours and at 24 hour in ICU), transfusion of PRBC, blood products and total volume of colloids infused per treatment group intraoperatively and in first 24 hour postoperatively in ICU. Other data monitored included duration of mechanical ventilation, complication related to colloid usage, amount of loading intravenous fluid, ICU stay and renal function based on estimated glomerular filtration rate using the modification of diet in renal disease formula - $186 \times (\text{Sr. creatinine} + 88.4)^{-1\,154} \times (\text{age})^{0\,203} \times (0.742 \text{ if female})$
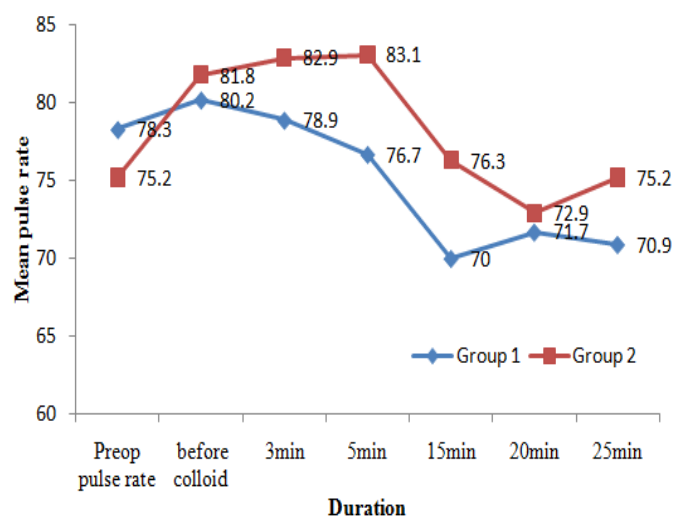
3. Observations and Results

The two groups were comparable in respect to age, weight, sex and height and difference was not statistically significant (p>0.05), (Table 1).

Table 1: Comparison of Demographic Data of the Patients between Two Groups

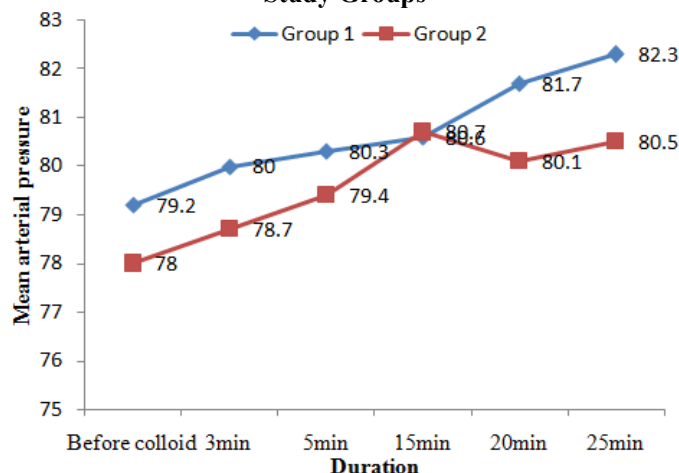| Variable	Group 1	Group 2	P Value
Age (years)	60.5±7.89	58.5±7.15	0.292
Weight (kgs.)	61.1±9.11	58.9±9.25	0.358
Height (cm)	165.9±11.58	163.6±8.17	0.371
Sex (Male/Female)	19/11	21/9	0.300

The baseline values of haemodynamic parameters were not significantly different in the two groups. There was decrease in pulse rate after starting colloid in group 1 while increase in pulse rate in group 2 after starting colloid up to 5 minutes. We found statistically significant difference in pulse rate 5 minutes after starting colloid. However after 5 minutes pulse rate started falling in group 2 towards baseline and at 20 minutes after starting colloids, pulse rate were almost similar in both the group though there was no statistically significant change in pulse rate values amongst two groups (Figure 1).

Figure 1: Comparison of Pulse Rate among Study Group

We found increase in mean arterial pressure after starting colloid and difference was statistically insignificant. At 15 minutes after starting colloid MAP in both the group almost similar after which MAP continue to increase in group 1whereas it falls slightly in group 2. After 20 minutes of starting colloid MAP was continue to increase in both the group. There was statistically significant difference in mean arterial pressure immediately after shifting patient to ICU but no significant difference found subsequently, (Figure 2).

Figure 2: Comparison of Mean Arterial Pressure among Study Groups

There was gradual increase in CVP in both the group statistically not significant. But majority of patient in group 2 showed higher CVP values as compared to group 1 patients. When comparing change in hematocrit in both the group at before surgery, 20 hours and day 2 postoperatively, we found significant difference in hematocrit value in both the groups. We found no difference in number of patient of HES group requiring blood transfusion and fresh frozen plasma transfusion as compared to number of patient of gelatin group. Both the groups were comparable with respect to baseline activated clotting time (ACT) and which was statistically insignificant. Both group show similar trend of rise in ACT after giving heparin and returning to baseline after giving protamine (Table 2).

Table 2: Comparison of ACT and Bypass Time amongst Study Groups

ACT (Sec)	Group 1	Group 2	P Value
ACT before heparine	104.1±12.18	101.8±11.14	0.455
ACT after heparine	494.1±53.92	491.1±38.68	0.805
ACT after protamine	104.0±8.42	103.4±9.47	0.785
Bypass time (min)	80.4±32.82	71.8±22.28	0.238

In our study, no patient in any group gone in renal failure as well as both group show similar trend of rise in urine output postoperatively. None of the patients in this study required any form of renal replacement therapy during the postoperative period. There was statistically significant amount of drain immediately after surgery and in ICCU but no patients of either group show chest tube drainage >200 ml/hr for 2 consecutive hours. The mean duration of ICU stay

was similar in both groups. No patient required reexploration due to bleeding as well as no adverse effects related to use of colloids and no mortality.

4. Discussion

Since hemodilution was introduced into cardiac surgery in the early 1960s, there have been continuous effects in searching for the right priming solution for cardiopulmonary bypass [7]. During the early years, the complete extracorporeal circuit was primed with fresh heparinised homologous blood that is known to have many disadvantages, demanded a search for alternative priming solutions. Nowadays, after at least three decades of research and development on various types of crystalloids and colloids, there is still a lack of straight forward guidelines in choosing the right priming solution for adult cardiopulmonary bypass. Similarly, continuous controversies remain in choosing the ideal intravascular volume replacement regimens for other surgical patients and critically ill patients in the intensive care unit. Crystalloid solutions are easy to handle during priming and de-airing of the extracorporeal circuit. They are considerably cheaper than colloids and are free of anaphylactoid reactions. Improved postoperative pulmonary and renal function has been observed by using crystalloid priming alone. However, a major drawback of a crystalloid is its inability to maintain the colloid pressure. For this reason, many institutions choose to add albumin into the priming solution to compensate for this effect. Colloid solutions are inexpensive alternatives which have similar efficacy to albumin in maintaining the colloid pressure for cardiopulmonary bypass patients. However, adverse effects on blood coagulation and the occasional occurrence of allergic reactions have questions about the suitability of these synthetic colloids when used as priming fluids. Overall, the selection of priming fluids for cardiopulmonary bypass varies from institution to institution.

Hydroxyethyl starch (HES) solution was frequently used plasma expanders that are indicated to restore and maintain intravascular volume, to stabilize hemodynamic conditions and to improve tissue perfusion. Niemi and colleagues [8] reported that the greatest impairment of coagulation was seen with HES. However, the newer starch formulation of 6% HES 130/0.4 has been shown to be safe and comparable to gelatin-based colloids in cardiac surgery [9,10]. In the present study we compare 4% succinylated gelatin with 6% hydroxyethyl starch 130/0.4 for preloading prior to cardiopulmonary bypass in coronary artery bypass grafting patients with respect to haemodynamics status, blood loss, transfusion requirement, ICU stay and complication.

When comparing baseline values of various haemodynamic parameters, we found no significant difference in the two groups. There was decrease in pulse rate after starting colloid in group 1 while increase in pulse rate in group 2 after starting colloid up to 5 minutes. There was

statistically significant difference in pulse rate 5 minutes after starting colloid. However after 5 minutes pulse rate started falling in group 2 towards baseline and at 20 minutes after starting colloids, pulse rate were almost similar in both the group though there was no statistically significant change in pulse rate values amongst two groups. The maximum decrease in the mean pulse rate was between 5 to 15 minutes after starting colloid in both the group through statistically not significant. There was statistically significant difference in mean arterial pressure (MAP) immediately after shifting patient to ICU but no significant difference found subsequently. Postoperatively we observed increase in pulse rate while shifting the patient from operation theatre to ICCU in both the groups, difference was not statistically significant. On subsequent monitoring after shifting patient to ICCU it was observed that again there was decrease in pulse rate towards baseline up to 12 hours. After 12 hours group 1 patient show slight increase in pulse rate while group 2 patients shows steady pulse rate around baseline. We observed increase in mean arterial pressure while shifting the patient from operation theatre to ICCU in both the groups but it was statistically more significant in group 2 as compared to group 1. After 4 hour and 12 hour there was fall in mean arterial pressure though statistically non significant. After 12 hours again increase in mean arterial pressure in both the groups, and difference was not statistically significant. Central venous pressure (CVP) was measured before giving colloid and at regular interval after that up to 20 hours postoperatively and found that there was gradual increase in CVP in both the group though statistically not significant. Majority of patient (93.3%) in group 1 and (83.3%) in group 2 has CVP on lower side, while few patient in both the group has higher CVP. After 3 minutes of starting colloid, patient in group 2 have higher CVP as compared to group 1.

Renal failure is one of the most serious complications after cardiac surgery and there was concern about the influence of HES on kidney function, whereas gelatin has no such adverse effects. Haisch *et al* [1] concluded that gelatin-based volume replacement strategy showed a greater inflammatory response with more endothelial injury and short-term impaired kidney integrity than 6% HES 130/0.4; however, there was no difference in renal function between the 2 groups 60 days after discharge from hospital. We calculated perioperative estimated glomerular filtration rate and found no significant difference in both groups on postoperative day 2. We excluded patients with preexisting renal dysfunction (based on elevated serum creatinine levels) as development of renal dysfunction is one of the major concerns with the use of HES. Urine output was measured up to 20 hours postoperatively. Both the group show similar trend of rise in urine output postoperatively. None of the patients in this study required any form of renal replacement therapy during the postoperative period.

There was continuous rise in amount of chest tube drain in both the group though amount was higher in group 1 as compared to group 2 continuously. There was statistically significant amount of drain immediately after surgery and in ICCU. But no patients of either group show chest tube drainage >200 ml/hr for 2 consecutive hours. Hence there was neither a single case of reexploration in either group. Although it initially increases postoperative blood loss, subsequent finding 4 hour and 20 hour after surgery suggested that it did not significantly increase postoperative blood loss or allogenic transfusion. Also there was no difference in number of patient of HES group requiring blood transfusion and fresh frozen plasma transfusion as compared to number of patient of gelatin group. Our results were consistent with different studies [1,11,12].

There were no adverse reactions in either group, but the sample size was too small to address this issue. Another limitation of this study is that we were unable to reliably blind the investigators to the use of the 2 colloids, due to technical reasons. Measurements of coagulation in these patients could have been performed more objectively, for example using thromboelastography. This study has shown that when 6% HES 130/0.4 was used as the priming solution for CPB as well as volume replacement for CABG, though there was greater rise in drain as compared to 4% gelatin group, there was no significant difference between the two colloids when used for CABG.

5. Conclusion

From the observations of the present study, it is safely concluded that both 4% succinylated gelatin and 6% hydroxyethyl starch are comparable with respect to various variables like haemodynamic parameters, blood loss, blood and blood product transfusion requirement, postoperative complication.

Acknowledgement

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