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Comparison of the Coagulation Effect Achieved by OctaplasLG Versus Fresh Frozen Plasma in Pediatric Cardiac Surgical Patients

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Abstract

OctaplasLG is indicated for use in patients undergoing cardiac surgery who require replacement of multiple clotting factors. The use of OctaplasLG over single-donor fresh frozen plasma (FFP) may have beneficial effects when considering the transmission of enveloped viruses. Additionally, it has the potential for fewer adverse reactions, reduced disease transmission, and a more homogenous coagulation factor composition. However, its efficacy and safety have not yet been evaluated in the pediatric population. Pediatric patients aged less than 2 years old and less than 10 kg, who underwent complete tetralogy of Fallot repair and received either OctaplasLG or FFP intraoperatively were identified over a 10-year period for this retrospective analysis. A review of case notes, intra-operative, and laboratory data were used to assess intraoperative blood product usage, blood loss, and postoperative coagulopathy. Data were analyzed to assess the efficacy of OctaplasLG in achieving hemostasis when compared to FFP. Results showed clinically better hemostasis postoperatively in OctaplasLG group compared with FFP group and better coagulation results. OctaplasLG was as effective as FFP when used in pediatric patients undergoing cardiac surgery.

Keywords

blood coagulation factors, hemostasis, pediatric thrombosis

Introduction

Fresh frozen plasma (FFP) is commonly used during pediatric cardiac surgery. The prion disease, variant Creutzfeldt-Jakob disease, was first identified in the United Kingdom in 1996. It is caused by the same strain as bovine spongiform encephalopathy. There have been concerns regarding secondary transmission of this disease from plasma. In 2002, in an effort to reduce the risks of secondary disease transmission from plasma administration, National Health Service (NHS) blood and transplant (NHSBT) produced methylene blue (MB)-treated UK plasma for all children born after 1996. However, techniques to improve safety by reducing the viral burden, such as MB treatment, can impair the therapeutic efficacy of the plasma.[1]

Methylene blue treatment involves the addition of 85 µg of MB in a closed gravity system aiming for a final concentration <0.3 µmol/L. The product is then exposed to white light for 30 minutes, which allows for the formation of free radicals. Treatment with MB reduces the risks of viral transmission by causing a reduction in viral replication but results in a marked decrease in functional fibrinogen.[2] Atance et al also noted an increased need for greater plasma volumes and addition of cryoprecipitate following introduction of MB-treated plasma.[3]

An alternative to MB-FFP is OctaplasLG. It is a commercially produced solvent-detergent blood group specific plasma. The solvent-detergent treatment aims to reduce the risk of enveloped viral transmission. OctaplasLG is prepared from 630 to 1520 single-donor units of the same blood group which reduces the variability in coagulation and inhibiting factors that is typically seen in single-donor FFP units. The pooled plasma is passed through a 1 µm filter to exclude cells and cell fragments. A combination of solvent and detergent is then used to

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inactivate enveloped viruses, which are later removed by oil and solid phase extraction, respectively, prior to filtration and storage in sterile bags. The solvent detergent process aims to inactivate lipid-encapsulated viruses, such as human immunodeficiency virus and hepatitis B and C. Although the solvent-detergent treatment process does not specifically aim to reduce the transmission of bacteria, prions, and nonencapsulated viruses, it may cause a reduction in bacterial and prion transmission.

The plasma pooling of up to 1520 donor units results in significant dilution and neutralization of antigranulocyte and antihuman lymphocyte antigen antibodies, thereby potentially causing a dramatic reduction in noninfectious, allergic complications such as transfusion-associated lung injury.[2,4] When compared to single-donor FFP, solvent-detergent treated plasma has been shown to have a 10% to 15% reduction in clotting factors and up to 40% to 70% lower protein S and plasmin inhibitor levels, but each unit has a more standardized plasma protein content.[4,7-9] Commercially produced OctaplasLG has reduced variability in the amount of clotting factors in each 200 mL unit. OctaplasLG contains concentrations of clotting factors V, VIII, and XI between 0.76 and 0.88 IU/mL. In a comparison of solvent-detergent treated plasma and FFP, Thesenger et al noted a significantly higher variability of individual coagulation factors among different FFP units.[9] This more consistent and narrower range of coagulation factor concentrations may make commercially produced plasma products more desirable when replacing coagulation factors. Despite these differences, no major clinical effects have thus far been identified.[2]

The use of OctaplasLG over single-donor FFP may have beneficial effects when considering the more homogenous coagulation factor profile of each OctaplasLG unit over MB-FFP and in the transmission of enveloped viruses.[5] However, its efficacy and safety has not yet been evaluated in the pediatric population.[6]

At University hospital Southampton, from July 1, 2007, OctaplasLG replaced MB-treated FFP for perioperative coagulation factor replacement in pediatric patients undergoing cardiac surgery. This retrospective analysis compares the coagulation effect and safety profile achieved with OctaplasLG versus MB-FFP when replacing coagulation factors in the perioperative period for pediatric patients undergoing cardiac surgery.

We hypothesized that the outcomes in terms of coagulation effect achieved and safety profile would be identical for FFP and OctaplasLG in pediatric cardiac surgical patients.

Methods

Full NHS research ethics committee approval was obtained for this retrospective analysis.

This retrospective analysis sought to test the hypothesis that the outcomes after pediatric cardiac surgery would be identical for FFP and OctaplasLG. A patient population with one relatively homogenous congenital condition undergoing a complete repair as their primary procedure was identified, and data for a 10-year period consisting of 5 years of FFP use and 5 years of OctaplasLG use were analyzed.

An initial database review of cardiac surgical patients over a 10-year period was conducted (5 years of FFP use and 5 years of OctaplasLG use), which identified 2552 cardiac patients. Further analysis revealed that 135 possible patients would meet the following inclusion criteria.

1. Surgical procedure date: January 07, 2002 to January 07, 2012
2. Primary procedure: tetralogy of Fallot (TOF) repair
3. Age: less than 2 years old
4. Weight: less than 10 kg
5. Intraoperative coagulation product use: MB-treated FFP or OctaplasLG.

The notes and intraoperative records for these 135 patients were obtained for review. Only 105 of the reviewed patients met the inclusion criteria. Thirty patients were excluded following notes review due to the following reasons:

1. Did not receive FFP or OctaplasLG
2. Over 2 years of age
3. Over 10 kg

Demographic data collected included patient age and weight on date of surgical procedure, the surgical procedure performed, and the congenital cardiac diagnosis.

Intraoperative data consisted of preoperative medications affecting coagulation and platelet function. The times for anesthetic induction, cardiopulmonary bypass (CPB), aortic cross-clamp, and total intraoperative time were collected for all patients. Pre CPB data included pre- and postheparin activated clotting times (ACT), the heparin dose, use of aprotinin and tranexamic acid. Cardiopulmonary bypass data analyzed the type of CPB circuits used, CPB prime and constituents, CPB flow rates, use of aprotinin, tranexamic acid, use of blood products, heparin doses on CPB, and ACT values. In the operating room post CPB, the use and volumes of blood products, additional calcium gluconate, and intraoperative coagulation results were reviewed.

On admission to the pediatric intensive care unit (PICU), data for the additional use of blood products in the first 12 hours (type and volume) were collected, admission coagulation results included activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen and platelet counts. Chest drain output data were also collected for the first 12 hours.

Data for time to extubation, time to discharge from intensive care unit (ICU) and hospital, and survival to discharge were reviewed. Charts were then analyzed for any documented evidence of adverse transfusion reactions, postoperative wound infections, and other adverse reactions throughout the hospital stay for this procedure.

All patient data were link anonymized and held in accordance with trust data protection policies. IBM SPSS was used to analyze the data. Data were looked at for normal or abnormal distributions. Appropriate statistical tests were used to produce descriptive data comparing both groups depending on the

Table 1. Showing Demographics for Both Groups.[a]

	OctaplasLG (N = 65)	FFP (N = 40)	*P* value[b]
Age, days	151.6 (106.6)	179.0 (67.06)	.0023
Gender			.4670
Female	34 (52.3%)	18 (45.0%)	
Male	31 (47.7%)	22 (55.0%)	
Weight, kg	5.6 (1.33)	6.1 (1.63)	.0361

Abbreviations: FFP, fresh frozen plasma, SD, standard deviation.
[a]Mean (SD) values.
[b]*P* values: Age, weight = Wilcoxon rank-sum; gender = Pearson χ^2.

distribution of data. *P* values were obtained by Wilcoxon rank-sum for age and weight, and Pearson χ^2 was used for gender analysis. Fisher's exact test was used to obtain *P* values for the 2×2 contingency tables, and *t* test (Satterthwaite and pooled) was used when comparing the equality of means for the volumes of coagulation and blood products transfused.

Results

From 2002 to 2012, 105 children younger than 2 years underwent complete TOF repairs and were included in the study for analysis. Of these, 104 children survived to hospital discharge. The results below are descriptive, and all data presented are mean (standard deviation) values.

Table 1 shows the age and weights of the children. In the OctaplasLG group, children were younger and smaller than those in the FFP group (5.6 kg vs 6.1 kg, respectively, *P* value = .0361). The mean age in the OctaplasLG group was 151.6 days compared to 179 days in the FFP group, *P* value = .0023. An equal gender distribution was observed between both groups.

Before CPB, the children in the OctaplasLG group had statistically significant lower baseline ACT results (OctaplasLG 114.64 vs FFP 136.49 seconds, *P* value < .0001), they received less heparin (OctaplasLG 1787.5 vs FFP 2120 units, *P* value = .0064), and had lower post heparin ACT results than the FFP group (OctaplasLG 481.54 vs FFP 833.69 seconds). Aprotinin was used in 27 patients, all of whom belonged to the FFP group, its use was discontinued prior to the introduction of OctaplasLG (Table 2).

Table 3 shows the volume and constituents of the CPB circuit. All patients had their CPB circuit primed with packed red blood cells. A standardized prime protocol dependent on the circuit type and patient weight was used for the CPB circuits. Prime included packed red blood cell (PRBC), sodium bicarbonate, albumin, calcium, and mannitol. The mean bypass and cross-clamp time were similar between the 2 groups, 110.94 and 74.723 minutes (*P* value = .76) for OctaplasLG versus 108.73 and 76.025 (*P* value = .83) minutes for FFP, respectively.

Most children (OctaplasLG 93.8%, FFP 85%) received a transfusion of plasma after CPB in the operating room before the chest closure. Children in the OctaplasLG group who were smaller received a greater volume of plasma after CPB than those in the FFP group. Mean values were 10.44 mL/kg versus 9.43 mL/kg (Table 4).

Table 5 show the other intraoperative blood and blood product transfusion. There was no statistical difference in the

Table 2. Showing Initial Heparin Dose and ACTs.[a]

	OctaplasLG (N = 65)	FFP(N = 40)	*P* value[b]
ACT baseline, seconds	114.64 (11.363)	136.49 (16.546)	<.0001
ACT postheparin prebypass, units	481.54 (89.301)	833.69 (330.51)	<.0001
Pre bypass heparin dose, units	1787.5 (455.74)	2120 (652.49)	.0064

Abbreviations: ACT, activated clotting times; FFP, fresh frozen plasma; SD, standard deviation.
[a]Mean (SD) values.
[b]*P* value: 2×2 yes/no contingency table = Not Applicable (N/A); equality of means = *t* test (Satterthwaite).

Table 3. Showing Cardiopulmonary Bypass and XC Times (Min, Mean and [SD] value) and Prime Volumes and Constituents.

	OctaplasLG (N = 65)	FFP (N = 40)	*P* value[a]
CPB time min (SD)	110.94 (24.89)	108.73 (41.55)	.76
XC time min (SD)	74.72 (17.95)	76.02 (34.77)	.83
Prime volumes mean and constituents (total vol)			
PRBC prime volume, mL (SD)	213.8 (56.29)	250.65 (19.45)	<.0001
Albumin prime volume, mL (SD)	248.54 (62.30)	249.13 (42.93)	.9546
Sodium bicarbonate 8.4%, mL (SD)	10.17 (3.63)	13 (3.61)	.0015
Mannitol 10%, mL (SD)	24.33 (7.98)	33.87 (10.34)	.0002
Calcium gluconate, mL (SD)	4.83 (4.53)	5 (0)	.9551

Abbreviations: CPB, cardiopulmonary bypass, FFP, fresh frozen plasma; SD, standard deviation; XC, cross-clamp. PRBC, packed red blood cell
[a]*P* value: 2×2 yes/no contingency table = N/A; equality of means = *t* test (Satterthwaite).

Table 4. Intraoperative Plasma Volume FFP or OctaplasLG Transfused.[a]

	OctaplasLG (N = 65)	FFP (N = 40)	*P* value[b]
Any intraoperative plasma volume transfused?			.17
No	6.2%	15.0%	
Yes	93.8%	85.0%	
Plasma volume transfused, mL/kg (SD)	10.44 (7.578)	9.43 (15.193)	

Abbreviations: FFP, fresh frozen plasma; SD, standard deviation.
[a]Mean (SD).
[b]*P* value: 2×2 yes/no contingency table = Fisher exact test; equality of means = *t* test (Satterthwaite).

Table 5. Showing Intraoperative PRBC Volume Transfused.[a]

	OctaplasLG (N = 65)	FFP (N = 40)	P value[b]
Intraoperative PRBC transfusion?			.68
No	64.6%	60.0%	
Yes	35.4%	40.0%	
Intraoperative PRBC volume transfused, mL/kg (SD)	9.36 (5.5168)	17.74 (37.06)	.2900

Abbreviations: PRBC, packed red blood cell; FFP, fresh frozen plasma; SD, standard deviation.
[a]mL/kg, number, mean (SD).
[b]*P* value: 2 × 2 yes/no contingency table = Fisher exact test; equality of means = *t* test (Satterthwaite).

Table 6. INR and APTT on PICU.[a]

	OctaplasLG (N = 65)	FFP (N = 40)	*P* value[b]
INR and APTT on PICU			1.0000
No	1.5%		
Yes	98.5%	100.0%	
INR (SD)	1.26 (0.14)	1.46 (0.25)	<.0001
APTT (SD)	1.36 (0.32)	1.63 (0.73)	.035

Abbreviations: APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio; PICU, pediatric intensive care unit; SD, standard deviation.
[a]Mean (SD).
[b]*P* value: 2 × 2 yes/no contingency table = Fisher exact test; equality of means = *t* test (Satterthwaite).

amounts of intraoperative PRBC, platelet, or cryoprecipitate used between the 2 groups. The OctaplasLG group received less PRBC intraoperatively than the FFP group 9.36 mL/kg vs 17.74 mL/kg, respectively ($P = .29$); 40% of patients in the OctaplasLG group received an intraoperative platelet transfusion compared to 45% in the FFP group. The FFP group received greater volumes of platelets compared to the OctaplasLG group (11.87 mL/kg [FFP] vs 6.41 mL/kg [OctaplasLG], $P = .202$). Of note, PICU admission platelet counts were similar for both groups (149.31 vs 151.05, $P = .89$ for OctaplasLG and FFP, respectively). Cryoprecipitate was only used intraoperatively on 4 patients, all of whom received OctaplasLG with an average transfusion volume of 63 mL, with a range of 10 to 30 mL/kg.

The immediate postoperative coagulation results, which were drawn on admission to the PICU, are shown in Table 6. These results indicate that the INR and APTT were significantly lower for the OctaplasLG group versus FFP (INR 1.26 vs 1.46, $P < .0001$); APTT 1.36 vs 1.63, $P = .0353$). The fibrinogen was higher in the OctaplasLG group. The clinical effectiveness of the coagulation product replacement was measured by looking at the postoperative chest drain output for both groups in the first 12 hours and the requirement for further blood product replacement during this time.

Table 7. First 12 Hours Postoperative PRBC's and Plasma Volume Transfused (FFP or OctaplasLG).

	OctaplasLG (N = 65)	FFP (N = 40)	*P* value[a]
Any PRBC within 12 hours postoperative?			
No	70.8%	47.5%	.0229
Yes	18.5%	52.5%	
PRBC volume transfused within 12 hours postoperative, mL/kg (SD)	8.63 (4.097)	11.534 (8.63)	.1893
Any plasma volume transfused within 12 hours postoperative?			
No	81.5%	50.0%	.0010
Yes	18.5%	50.0%	
Plasma volume transfused within 12 hours postoperative, mL/kg			
Mean	9.109 (7.76)	11.609 (7.344)	

Abbreviations: FFP, fresh frozen plasma; PRBC, packed red blood cell; SD, standard deviation.
[a]*P* value: 2 × 2 yes/no contingency table = Fisher exact test; equality of means = *t* test (pooled).

In the first 12 hours, the chest drain output on PICU was higher but not statistically significant for the OctaplasLG group than for the FFP group (14.48 mL/kg vs 11.68 mL/kg, $P = .109$). Also noted was the higher rate of PRBC replacement in the FFP group; 52.5% of the FFP group required PRBC transfusion on PICU compared to 29.2% of the OctaplasLG group, which was statistically significant ($P = .0229$). The mean volumes for the first 12 hours PRBC transfusion on PICU for the OctaplasLG group was lower than the FFP group (8.63 mL/kg vs 11.53 mL/kg, $P = .1893$; Table 7).

The results indicate that significantly more patients in the FFP group received further plasma transfusion on PICU in the first 12 hours versus the OctaplasLG group; 50% of the FFP group received further FFP transfusion on PICU compared to 18.5% of the OctaplasLG group who required more OctaplasLG ($P = .001$). The volume of MB-treated FFP transfused was higher than that of OctaplasLG in the PICU (11.61 mL/kg [FFP] vs 9.11 mL/kg [OctaplasLG]); 10.8% (OctaplasLG 7/65 patients) versus 7.5% (FFP 3/40 patients) received postoperative platelet transfusions, with mean volumes of 11.89 mL/kg (OctaplasLG) and 12.19 mL/kg (FFP). Only 5 of these patients had platelet counts below 100 associated with high postoperative drain output. Cryoprecipitate was used on PICU on 5 patients (4 OctaplasLG patients and 1 FFP patient).

No adverse transfusion reactions were identified in the intraoperative and postoperative period in either group.

There was a higher rate of postoperative infections in the FFP group (30%) than in the OctaplasLG group (10.8%), $P = .0185$. Of these, 6 respiratory tract infections and 6 wound infections were observed in the FFP group, whereas 2 respiratory tract infections and 5 wound infections were reported in

Table 8. Wound Infections.

	OctaplasLG (N = 65)	FFP (N = 40)	*P* value[a]
Any significant postoperative infections requiring antibiotics?			.0185
No	89.2%	70.0%	
Yes	10.8%	30.0%	
Length of stay in PICU (days)	3.67 (2.23)	4.3 (6.43)	.557

Abbreviations: FFP, fresh frozen plasma; PICU, pediatric intensive care unit.
[a]*P* value: 2 × 2 yes/no contingency table = Fisher exact test; equality of means = *t* test (Satterthwaite).

the OctaplasLG group. Although not statistically significant, the mean length of stay on the PICU was less (3.68 days) for the OctaplasLG patients versus a mean length of stay of 4.3 days for the FFP group (P value = .56; Table 8).

Discussion

In Southampton, OctaplasLG has been used in place of single-donor MB-treated FFP since July 2007. OctaplasLG has several theoretical advantages over FFP, such as reduced viral transmission, fewer immune-mediated reactions, and more consistency in the levels of coagulation and inhibiting factors.[1,4,7-9] However, its efficacy in the pediatric cardiac surgical population has not been assessed. With this retrospective analysis, the coagulation effect and safety achieved by OctaplasLG and FFP in pediatric cardiac surgical patients undergoing similar procedures was compared over a 10-year period.

In this retrospective observational study, improved hemostasis was seen clinically in the OctaplasLG group postoperatively, in that they not only had better coagulation results but these children required less PRBC and plasma transfusion.

Children in the OctaplasLG group were younger and smaller than those in the FFP group (5.6 kg vs 6.1 kg, respectively), this is due to changes in surgical practice over time to undertake complete repairs in TOF patients earlier in life. Advances and improvements in the manufacture of smaller cardiopulmonary bypass circuits allowed complete TOF repairs to be performed at a younger age as the primary procedure. Prior to this, some children may have needed a modified Blalock-Taussig shunt performed as the primary procedure, allowing the child to grow before undertaking a complete repair.

We have seen that the prebypass heparin doses were lower in the OctaplasLG group, and the heparin doses used in the bypass circuit were higher. Overall, the ACTs measured in the OctaplasLG group were lower. These observations are in part is due to changes in practice over time. More heparin was given to the FFP group because aprotinin was still being used in some of these patients. Secondly, the machines used to measure the ACT values were changed in 2007, which may explain the lower values observed in the OctaplasLG group.

The intraoperative plasma transfusion volumes for the OctaplasLG group was higher than that for the FFP group (56.9 vs 42.9.mL, $P = .0359$), which resulted in a significantly lower INR (1.26 vs 1.46, $P < .0001$) and APTT (1.36 vs 1.63, $P = .0353$) on the PICU admission blood results. This was coupled with a reduction in both further red blood cell transfusion and plasma replacement in the first 12 hours when compared to the FFP group. This analysis did not find any statistically significant differences in the volume of platelets transfused between the groups. Cryoprecipitate was used intraoperatively in 4 patients, all from the OctaplasLG group.

Some of the observations seen with this retrospective analysis can be explained by changes in practice over time. For example, more normal coagulation results postoperatively can be explained by the more aggressive intraoperative replacement of coagulation factors, indicated by the use of higher volumes of intraoperative plasma and the additional use of cryoprecipitate. Although cryoprecipitate was only used intraoperatively in 4 patients in the OctaplasLG group, its occurrence is most likely due to a greater importance associated with fibrinogen replacement in these patients. Better hemostasis was seen clinically in the OctaplasLG group postoperatively, in that they not only had better coagulation results, but these patients required less red blood cell transfusion and plasma replacement postoperatively.

Our study has several weakness and limitations. Firstly, as a retrospective study we were unable to control for any confounding variables. It is impossible to be certain that any benefits of OcatplasLG that we have seen are true. This is because not only have many changes in practice occurred over the time course of this study but improvements in surgical techniques may have also occurred in the same time frame. Lastly, thromboelastography has been utilized intraoperatively at the University Hospital Southampton in pediatric cardiac surgery since 1997. However, the older charts (FFP group) lacked some data that would have proven beneficial, such as intraoperative coagulation/thromoelastography results, which were present in many of the OctaplasLG charts.

Interestingly, there were significantly fewer postoperative infections noted in the OctaplasLG group (10.8% vs 30%, $P < .018$), this is an association and not a causal relationship given the retrospective nature of the data. It should be further investigated given the pathogen reduction caused by the solvent-detergent treatment process. No transfusion-related adverse events were seen in either group.

Our hypothesis was proven. This study shows that OctaplasLG is as effective as MB-treated FFP when used in children undergoing cardiac surgery. It is a safe and a cheaper alternative to MB-treated FFP. At the University Hospital Southampton, OctaplasLG is available cheaper than MB-treated FFP with approximate savings of £100 for each adult-sized unit. Given the retrospective nature of this observational study and changes in surgical and hemostatic management of children undergoing heart surgery that have occurred in the last 15 years, we would urge caution when interpreting the possible benefits of OctaplasLG, such as improved hemostasis and reduced infection rates. Given the considerable cost savings of OctaplasLG in this patient group, further investigation is merited.

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Declaration of Conflicting Interests

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