ANESTHESIOLOGY

Fresh Frozen Plasma *versus* Crystalloid Priming of Cardiopulmonary Bypass Circuit in Pediatric Surgery

A Randomized Clinical Trial

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ABSTRACT

Background: In congenital cardiac surgery, priming cardiopulmonary bypass (CPB) with fresh frozen plasma (FFP) is performed to prevent coagulation abnormalities. The hypothesis was that CPB priming with crystalloids would be different compared with FFP in terms of bleeding and/or need for blood product transfusion.

Methods: In this parallel-arm double-blinded study, patients weighing between 7 and 15 kg were randomly assigned to a CPB priming with 15 ml · kg^{-1} PlasmaLyte or 15 ml · kg^{-1} FFP in addition to a predefined amount of packed red blood cells used in all patients. The decision to transfuse was clinical and guided by point-of-care tests. The primary endpoints included postoperative bleeding tracked by chest tubes, number of patients transfused with any additional blood products, and the total number of additional blood products administered intra- and postoperatively. The postoperative period included the first 6 h after intensive care unit arrival.

Results: Respectively, 30 and 29 patients in the FFP and in the crystalloid group were analyzed in an intention-to-treat basis. Median postoperative blood loss was 7.1 ml · kg^{-1} (5.1, 9.4) in the FFP group and 5.7 ml · kg^{-1} (3.8, 8.5) in the crystalloid group ($P = 0.219$); difference (95% CI): 1.2 (–0.7 to 3.2). The proportion of patients additionally transfused was 26.7% (8 of 30) and 37.9% (11 of 29) in the FFP and the crystalloid groups, respectively ($P = 0.355$; odds ratio [95% CI], 1.7 [0.6 to 5.1]). The median number of any blood products transfused in addition to priming was 0 (0, 1) and 0 (0, 2) in the FFP and crystalloid groups, respectively ($P = 0.254$; difference [95% CI], 0 [0 to 0]). There were no study-related adverse events.

Conclusions: The results demonstrate that in infants and children, priming CPB with crystalloids does not result in a different risk of postoperative bleeding and need for transfusion of allogeneic blood products.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Fresh frozen plasma is often used to prime the cardiopulmonary bypass circuit for pediatric cardiac surgical patients to help offset dilutional coagulopathy that might result in increased perioperative bleeding and allogeneic blood transfusion
- Prior randomized trials of crystalloid *versus* fresh frozen plasma prime have reported conflicting results, but the vast majority of these studies were not blinded

What This Article Tells Us That Is New

- In this double-blind randomized controlled trial of patients undergoing pediatric cardiac surgery with cardiopulomonary bypass, postoperative bleeding and the need for allogeneic blood products does not differ significantly between patients for whom the cardiopulmonary bypass circuit was primed with crystalloid *versus* fresh frozen plasma

Despite modern surgical and cardiopulmonary bypass (CPB) techniques, infants and children undergoing cardiac surgery with CPB often need transfusion of allogeneic blood products. Excessive hemodilution due to a priming volume exceeding the infant's calculated blood volume results in a significant drop in platelet count and coagulation factors.[1] This is even more pronounced in neonates.[2] Therefore, fresh frozen plasma (FFP) is often used to prime the CPB circuit. However, the prophylactic priming of CPB with FFP has been questioned in several prospective randomized studies.[3–8] However, in all those trials except one,[3] the responsible physicians in charge of the patients were not blinded to the allocation group. Moreover, the results of these studies are conflicting with those showing no benefit of a FFP priming strategy,[4–7] compared with others that are rather in favor of its use.[3,8]

We therefore sought to conduct a double-blind trial. We hypothesized that CPB priming with crystalloids would be different compared to FFP in terms of postoperative

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bleeding and/or need for transfusion of allogeneic blood products in infants and small children weighing between 7 and 15 kg and undergoing congenital cardiac surgery.

Materials and Methods

This study was approved by Comité d'Ethique Hospitalo-Facultaire Saint-Luc Université Catholique de Louvain on September 7, 2015 (2015/20AOU/449). The study was registered before patient enrollment by the principal investigator (M.M.) at ClinicalTrials.gov (NCT02567786) on September 29, 2015. Parental written informed consent was obtained for all children.

Inclusion Criteria and Randomization

In this parallel-arm double-blind single-site study, all infants and children weighing between 7 and 15 kg were randomized 1:1 to either a CPB priming with 15 ml · kg^{-1} PlasmaLyte (Baxter, S.A., Belgium) or 15 ml · kg^{-1} FFP in addition to a predefined amount of packed erythrocytes. This weight range has been chosen for different reasons. First, the volume of CPB prime and the type of oxygenator will be the same for all included patients. If we had included infants weighing less than 7 kg, the type of oxygenator and consequently the volume of CPB would have been different compared with that required for children weighing more than 7 kg. This means that the amount of FFP and packed erythrocytes to prime the CPB machine would have been different compared with a higher weight range group. This would have obviously biased the results. Therefore, we have not included smaller patients. In our institution, 1 unit of FFP corresponds approximately to a volume of 240 ml; the total administered FFP for a child weighing 15 kg (the maximum weight) is 225 ml. This means that for those patients belonging to the FFP group, a maximum of 1 unit of FFP will be used. If children with higher weights had been included, the risk of using a second unit of FFP would have been high, resulting in an increased number of donor exposures, which might have influenced the primary endpoint. Second, to avoid excessive hemodilution at the start of the CPB and to keep the study solution blinded to the physicians in charge of the patients, packed erythrocytes had to be used for all children at the time of priming. Because we do not routinely prime with packed erythrocytes in children weighing more than 15 kg, children weighing more than 15 kg were not included.

The exclusion criteria were patients with preoperative coagulation abnormalities, parental refusal, patients with preoperative chronic kidney disease (glomerular filtration rate of less than 60 ml · min^{-1} per 1.73 m^2 for greater than 3 months) or hepatic dysfunction (liver enzyme tests twice the normal values together with low albumin levels) and emergency surgery. Trained study staff evaluated eligibility and proposed the trial. After obtaining parental written consent, a study nurse used a computerized randomization technique to randomize the patients in blocks of five. The allocation was concealed with sequentially numbered sealed envelopes. On the day of surgery, the perfusionist handling the CPB opened the envelope and primed the CPB circuit in a separate room with restricted access. The perfusionist was thus not blinded to the study group allocation. Nevertheless, intraoperative transfusion of any allogeneic blood products is solely the responsibility of the handling anesthesiologist. The perfusionist in charge of the CPB was not involved in any intraoperative transfusion decision-making. To ensure full blinding of the study solution, the blood bank of the hospital held the information regarding the administered FFP for priming in the transfusion file of the patient, which is only accessible to the blood bank department. This information was not made visible in the medical file, as is usually the routine procedure in our institution. The trial was conducted in accordance with the original protocol.

Anesthesia

Anesthesiologists (A.M., M.M.) with experience in congenital heart disease were in charge of the patients and were involved in intraoperative transfusion decision-making. All children received anesthesia based on the institution's standard of care. Intraoperative regional cerebral oxygen saturation was monitored with near-infrared spectroscopy (Somanetics Invos Oximeter, USA). Tranexamic acid was administered at a total intraoperative dose of 30 mg · kg^{-1} (15 mg · kg^{-1} at the induction of anesthesia and 15 mg · kg^{-1} in the pump prime). Cefazoline was administered at a dose of 30 mg · kg^{-1}.

Routine hematologic and coagulation tests were performed the day before surgery. The point-of-care tests ROTEM (TEM International, Germany) and Multiplate (Dynabyte, Germany) were performed *via* an indwelling arterial catheter at different time points: (1) after the induction of anesthesia but before surgical incision, (2) upon CPB separation, and (3) upon arrival at the pediatric intensive care unit. For ROTEM, the EXTEM and FIBTEM activated tests were used. The ROTEM parameters measured included the clotting time, clot formation time, maximum clot firmness and maximum of lysis for the EXTEM test, and maximum clot firmness for the FIBTEM test. The normal values for infants and children were used as a reference range.[9] For the Multiplate test, the following agonists were used: the adenosine diphosphate test, the arachidonic acid test, and the thrombin receptor–activating peptide test. At the moment of weaning from CPB in addition to ROTEM and Multiplate tests, a platelet count was performed. The latter and the point-of-care tests are the only blood analyses that were performed for the purposes of the study. All the other biologic tests were the standard of care in our institution and therefore performed on a routine basis. The results of the point-of-care tests were available to the anesthesiologists and the intensive care unit physicians in care of the patients. The use of point-of-care tests is the standard of care in our institution for both adults and children.

The decision to transfuse the patient was a clinical decision and guided by the point-of-care tests. An internal algorithm

based on the point-of-care tests was used in transfusion decision-making of hemostatic factors and is illustrated in figure 1. If there were signs of clinical bleeding in the operating room or there was postoperative bleeding of more than 5 ml · kg^{-1} · h^{-1} and the point-of-care tests showed abnormalities, the patient was transfused. Whenever the point-of-care tests showed abnormalities but there was no clinical bleeding, the patient was not transfused. In cases of severe clinical bleeding in which the point-of-care tests were within normal range, surgical revision was considered. Packed erythrocytes or autologous blood from cell salvage was transfused to achieve a hematocrit of 33 to 35% in patients with cyanotic heart disease and 27 to 30% in children with noncyanotic heart disease. Because of cost issues, the administration of human fibrinogen in our institution is only allowed if the FIBTEM maximum clot firmness test is less than 6 mm. The given dose ranges between 50 and 120 mg · kg^{-1} in function of the severity of bleeding and FIBTEM maximum clot firmness test results. Note that cryoprecipitate is not available in our institution.

Cardiopulmonary Bypass

Nonpulsatile normothermic (core temperature, 36°C) CPB was conducted at a cardiac index of 3 l · min^{-1} · m^2 by using a roller pump (Stockert S.V., Germany). Moderate hypothermia (core temperature, 32°C) was performed in few cases and at surgical request. All cases were performed by the same surgeons (J.R., A.P.). The CPB circuit included the same oxygenator (Sorin KIDS D101 physio, LivaNova, Italy) for all the patients. The priming was realized either with 15 ml · kg^{-1} PlasmaLyte and packed erythrocytes (crystalloid group) or with 15 ml · kg^{-1} FFP and packed erythrocytes (FFP group). The minimum desired hematocrit during CPB was 30% in patients with cyanotic heart disease and 25% for those with noncyanotic heart disease. The amount of packed erythrocytes required in the prime was calculated using the following equation and based on the estimated blood volume:

$$\text{Packed erythrocytes needed for priming (ml)} = [(\text{estimated blood volume} + \text{circuit volume}) \times (\text{desired hematocrit on CPB})] - (\text{estimated blood volume} \times \text{hematocrit}) \,/\, \text{hematocrit of packed erythrocytes estimated at 65\%}$$

A maximum of one unit of packed erythrocytes was used for priming the CPB circuit. The priming also included 600 units of unfractioned heparin per 100 ml of priming, 15% mannitol with a maximum dose of 500 mg · kg^{-1}, 2 to 3 mEq of sodium bicarbonate, 15 mg · kg^{-1} tranexamic acid, and 15 mg · kg^{-1} cefazoline. Before initiating the CPB, 400 units · kg^{-1} of unfractioned heparin was administered to reach an activated clotting time of more than 450 s. During the CPB, the administration of additional amounts of crystalloids or packed erythrocytes was allowed based on the target hematocrit. Modified ultrafiltration was not performed in any patient. Conventional ultrafiltration was allowed. No corticosteroids were administered. The residual blood in the CPB circuit was treated at the end of the procedure. This cell salvage blood could be administered when necessary.

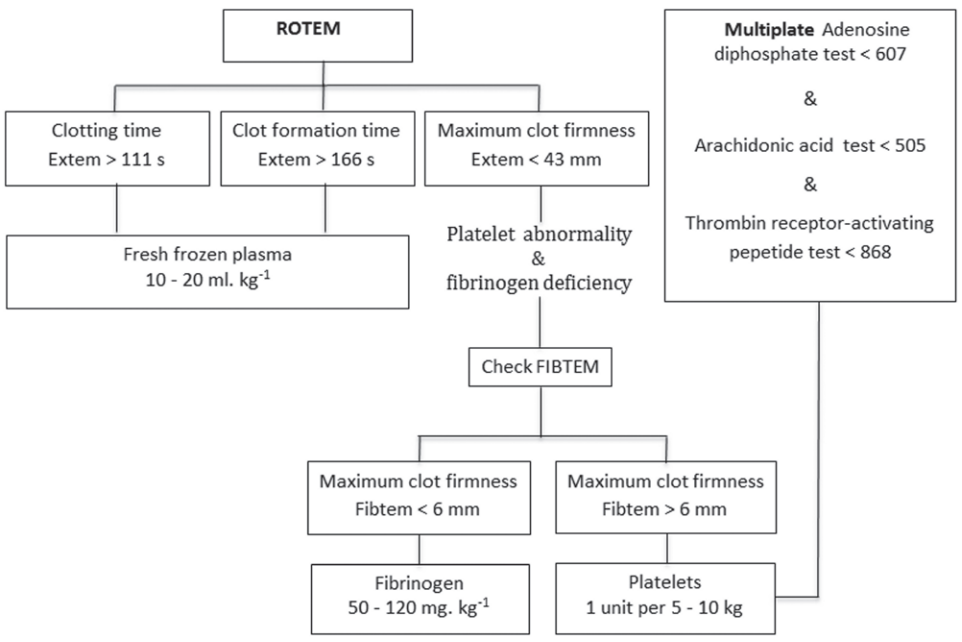

Fig. 1. Point-of-care test guided algorithm for transfusion of hemostatic factors in case of clinical bleeding.

Outcomes

The primary endpoint consisted of the following three outcomes: (1) postoperative bleeding per kg weight tracked by the chest tubes, (2) number of patients transfused with any allogeneic blood products intra- and postoperatively in addition to the packed erythrocytes and the FFP used in the CPB prime, and (3) the total number of allogeneic blood products administered per child in the intra- and postoperative period in addition to the blood products used to prime the CPB machine. The second and the third primary outcomes evaluated the risk of donor exposure.

The secondary endpoint was the total volume of transfused allogeneic blood products per kg weight of the child intra- and postoperatively in addition to the packed erythrocytes and the FFP used in the CPB prime. The postoperative period was considered as the first 6 h after admission in the pediatric intensive care unit.

Statistical Analysis

This is a superiority study with an alternative hypothesis being that priming with FFP or crystalloids would result in a different risk of bleeding and transfusion of allogeneic blood products. The sample size was calculated based on the primary endpoint. Internal analysis of the postoperative data of children in this weight range who had received FFP in the pump prime revealed an amount of bleeding of 6.3 ± 3.3 (mean ± SD) ml · kg^{-1} in the first 6 h postoperatively. We estimated that a 40% increase of this amount in the crystalloid group is clinically significant. A minimum of 28 patients was required in each group for a two-tailed $\alpha = 0.05$ and a power of 80%. On the other hand, the actual proportion of children who require any allogeneic blood products with a CPB prime based on FFP is 30%. We estimated that an increase of 40% in the crystalloid group (70%) is clinically significant. For this analysis, a minimum of 21 patients were required in each arm for a two-tailed $\alpha = 0.05$ and a power of 80%. Finally, the number of allogeneic blood products administered per child is 3 ± 2 (mean ± SD). We estimated that an increase of this number to a mean number of 5 in the crystalloid group would be significant. For this analysis, a minimum of 16 patients was required in each arm for a two-tailed $\alpha = 0.05$ and a power of 80%. We therefore decided to include 30 patients in each arm to answer the primary endpoint taking into account any eventual dropouts.

The primary analysis was conducted on an intention-to-treat basis and included all patients except those that withdrew consent before the start of anesthesia. We also carried out a per-protocol analysis for the primary and secondary endpoints. Patients with an open chest and those who needed a surgical revision were excluded for a per-protocol basis, because the volume of postoperative blood loss, being one of the primary outcomes, would have been affected.

An interim analysis was planned at 30 patients. If all the patients in the crystalloid group had needed transfusion of blood products and if the postoperative bleeding was 80% higher than in the FFP group, the study would have been stopped. The results of the interim analysis were reported to the data safety monitoring board of the local ethical committee. No adjustments were made for the interim analysis, and the study was completed as originally planned.

The Kolgomorov–Smirnov test was used to check the normality of the data. The categorical data are presented as numbers and percentages. Continuous variables are presented as means ± SD or medians (25th percentile, 75th percentile), depending on whether they were normally distributed or not. Comparison of continuous variables between the two study arms was performed with an independent *t* test or Mann–Whitney U test, depending on the normality assumption. A Pearson chi-square test or Fisher's exact test was used to compare categorical variables between the two groups. The primary outcome was evaluated using a Mann–Whitney U test and a Pearson chi-square test for continuous and categorical variables, respectively, and the secondary outcome was evaluated using a Mann–Whitney U test. A two-tailed *P* value of less than 0.05 was considered significant. A Bonferroni method was used to address multiplicity issues as three primary outcomes were evaluated separately. For the primary endpoint, the difference between the two groups was significant at level 0.05 for each of the three endpoints for which the endpoint's *P* value was less than 0.017. CI values for median differences were calculated using Hodges–Lehmann estimates. The statistical analyses were performed using IBM SPSS Statistics version 25 and SAS version 9.4.

Results

Figure 2 shows the flowchart of the study. In total, 30 patients in the FFP arm and 29 patients in the crystalloid group were analyzed on an intention-to-treat basis. As illustrated in table 1, the baseline characteristics of both study arms and their perioperative data were very similar. There were 14 (46.7%) patients with cyanotic heart disease in the FFP group and 13 (44.8%) in the crystalloid group ($P = 0.887$). The proportion of patients undergoing a redo surgery was statistically lower in the crystalloid group (20.7% *vs.* 46.7%; $P = 0.035$).

There were no study protocol violations. No data were missing or lost. All physicians in care of the patients adhered to the transfusion algorithm. Table 2 illustrates the results regarding the primary and secondary outcomes. There was no statistically significant difference regarding the total amount of allogeneic blood products transfused between the two groups when the CPB prime was not taken into account (FFP, 0 [0, 1] *vs.* crystalloid, 0 [0, 2]; $P = 0.254$; difference [95% CI], 0 [0 to 0]). When the CPB prime was instead taken into account, this number was significantly higher in the FFP group as illustrated in table 3 (FFP, 2 [2, 3] *vs.* crystalloid, 1 [1, 3]; $P = 0.003$). Eight patients (26.7%) in the FFP arm and 11 (37.9%) in the crystalloid group were transfused with additional allogeneic blood products ($P = 0.355$; odds ratio [95% CI], 1.7 [0.6 to

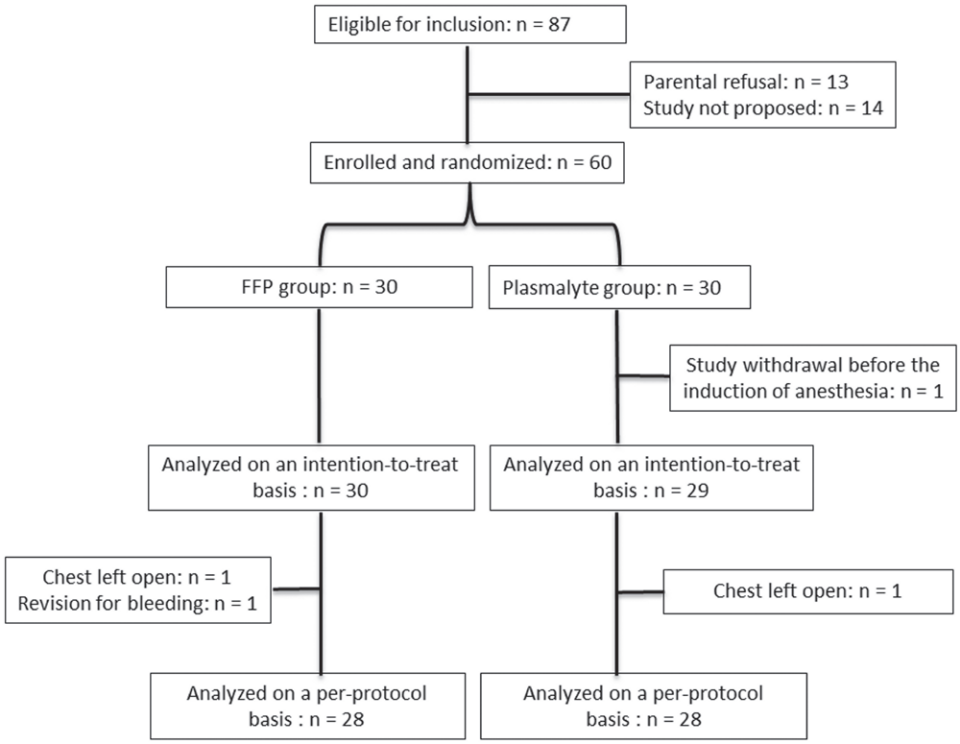

Fig. 2. Flowchart of the study. FFP, fresh frozen plasma.

5.1]) in addition to CPB prime (table 2). There was no statistically significant difference in the amount of postoperative blood loss per kg weight between the groups (FFP, 7.1 [5.1, 9.4] *vs.* crystalloid, 5.7 [3.8, 8.5]; $P = 0.219$; difference [95% CI], 1.2 [−0.7 to 3.2]) as shown in table 2. When excluding the CPB prime, the total volume of allogeneic blood products transfused per kg of weight in the intra- and postoperative period was not statistically different between the two study arms as presented in table 2. However, as shown in table 3, when the total volume of FFP was analyzed considering the fixed amount (15 ml · kg^{-1}) added to prime CPB circuit, patients in the FFP group had significantly received a higher amount of FFP per kg of weight (ml · kg^{-1}; FFP, 15.0 [15.0, 15.0] *vs.* crystalloid, 0 [0, 6.3]; $P < 0.001$).

Table 3 provides complete information regarding any transfusion performed in the intra- and postoperative period. Two patients in the crystalloid group received fibrinogen concentrate. In one patient (6 months old, 9 kg, aortic valve repair), the fibrinogen concentrate was administered immediately after CPB separation. The ROTEM test and specifically the maximum clot firmness of FIBTEM in this patient showed significant abnormalities. These abnormalities were accompanied with a significant decrease in the Multiplate test as well as the platelet count and with concomitant clinical bleeding. The anesthesiologist in charge of the patient decided to administer fibrinogen concentrate, which resulted in immediate stopping of the clinical bleeding and no need for further transfusion of any allogeneic blood products. In another patient in the crystalloid group (17 months old, 10.9 kg, double switch operation), the fibrinogen concentrate was administered together with FFP and platelet concentrate because of important clinical bleeding and abnormal point-of-care tests. In both children, moderate hypothermia had been applied. The median time between the end of the CPB and the closure of the chest was 52 min (45, 72) in the FFP group and 47 min (37, 64) in the crystalloid group ($P = 0.093$). No colloids were used in the intra- and postoperative period. Ultrafiltration was performed in one patient in the crystalloid group and in none of the patients in the FFP group.

Table 4 shows the results of the biologic parameters and point-of-care tests during the study period. The maximum clot firmness and the clot formation time of the EXTEM test and the maximum clot firmness of the FIBTEM test were significantly lower in the crystalloid group upon weaning from CPB. Upon arrival at the pediatric intensive care unit, there was no significant difference any more in any of the ROTEM tests between the two study arms. The area under the curve of the adenosine diphosphate test and the thrombin receptor–activating peptide test of Multiplate were significantly lower in the crystalloid group at the moment of CPB separation. However, this was not associated with a statistically significant difference in the platelet count at the end of CPB as demonstrated in table 4.

Table 1. Characteristics of the Patients

Variables	FFP (N = 30)	Crystalloid (N = 29)	*P* Value
Age, months	20 (11, 39)	18 (12, 32)	0.585
Minimum to maximum	5–63	6–54	
Weight, kg	9.8 (8.0, 13.4)	9.9 (8.2, 11.8)	0.611
Minimum to maximum	7.0–15.0	7.1–15.0	
Male/female, no. (%)	16 (53.3)/14 (46.7)	19 (65.5)/10 (34.4)	0.341
Cyanotic heart disease, no. (%)	14 (46.7)	13 (44.8)	0.887
Redo surgery, no. (%)	14 (46.7)	6 (20.7)	0.035
Risk adjustment for congenital heart surgery: categories, no. (%)			
1	2 (6.7)	1 (3.4)	0.574
2	14 (46.7)	16 (55.2)	0.514
3	13 (43.3)	10 (34.5)	0.486
4	1 (3.3)	1 (3.4)	0.981
5	0	0	> 0.999
6	0	1 (3.4)	0.492
Type of surgery			
Ventricular septal defect repair	2 (6.7)	2 (6.9)	
Atrial septal defect repair	2 (6.7)	1 (3.4)	
Ventricular septal defect + aortic valve repair	1 (3.3)	1 (3.4)	
Atrial septal defect repair + other	1 (3.3)	2 (6.9)	
Ventricular septal defect + atrial septal defect repair	1 (3.3)	0	
Atrioventricular septal defect repair	2 (6.7)	4 (13.8)	
Bidirectional cavopulmonary anastomosis	2 (6.7)	2 (6.9)	
Fontan procedure	6 (20.0)	2 (6.9)	
Subaortic membrane resection	2 (6.7)	1 (3.4)	
Tetralogy of Fallot repair	3 (10.0)	6 (20.7)	
Pulmonary homograft + other	3 (10.0)	0	
Pulmonary venous stenosis repair	1 (3.3)	0	
Mitral valve repair	1 (3.3)	0	
Aortic valve repair	1 (3.3)	2 (6.9)	
Pulmonary atresia repair	0	1 (3.4)	
Damus–Kaye–Stansel procedure	0	1 (3.4)	
Double switch procedure	0	1 (3.4)	
Kawashima procedure	1 (3.3)	0	
"Réparation à l'étage ventriculaire" procedure	1 (3.3)	0	
Tetralogy of Fallot + total anomalous pulmonary venous return	0	1 (3.4)	
Cor triatrial repair	0	1 (3.4)	
Aortic valve repair + aortoplasty	0	1 (3.4)	
Cardiopulmonary bypass time, min	136 ± 59	145 ± 79	0.632
Aortic cross-clamp time, min	53 ± 44	72 ± 52	0.127
Hypothermic cardiopulmonary bypass, no. (%)	2 (6.7)	6 (20.7)	0.145

Continuous variables are expressed as medians (25th percentile, 75th percentile) or means ± SD.

Table 5 shows the postoperative data of the patients. There was no significant difference between the postoperative characteristics of both groups. The median intubation time was 5 h (4, 13) in the FFP group and 5 h (3, 19) in the crystalloid group ($P = 0.704$). The proportion of patients with thromboembolic events was 3.3% in the FFP group *versus* 6.9% in the crystalloid group ($P = 0.612$). There was no in-hospital mortality.

The preplanned subgroup analysis on children with cyanotic heart disease (N = 27) did not reveal any significant differences with regard to the primary and the secondary endpoints. The number of patients transfused with any allogeneic blood product was 4 (4 of 14 = 28.6%) in the FFP group and 6 (6 of 13 = 46.2%) in the crystalloid group ($P = 0.440$). There was no statistically significant difference with regard to the total number of allogeneic blood products transfused in addition to the CPB prime (FFP, 0 [0, 1]; crystalloid, 0 [0, 2]; $P = 0.583$) and in the amount of postoperative blood loss per kg of weight (ml · kg^{-1}; FFP, 7.7 [5.6, 10.0]; crystalloid, 8.2 [5.7, 8.8]; $P = 0.793$).

There were 28 patients in each study arm in the per-protocol analysis. When the analysis was carried out on a per-protocol basis, no significant difference could be found between the two study arms with respect to the primary and the secondary endpoints (table 6).

Discussion

The results of this study show that in infants and small children, priming CPB circuit with crystalloids is not different

Table 2. Primary and Secondary Outcome Data

	FFP (N = 30)	Crystalloid (N = 29)	*P* Value	Difference (95% CI)
N total allogeneic blood products (erythrocytes, FFP, platelets; priming not included)*	0 (0, 1)	0 (0, 2)	0.254	0 (0–0)
Minimum to maximum	0–4	0–9		
Patients transfused with any product (priming not included), no. (%)*	8 (26.7)	11 (37.9)	0.355	1.7‡ (0.6–5.1)
Chest drain blood loss 6 h postop, ml · kg^{-1}*	7.1 (5.1, 9.4)	5.7 (3.8, 8.5)	0.219	1.2 (–0.7 to 3.2)
Total volume erythrocytes transfused (priming not included), ml · kg $^{-1}$†	9.3 (0, 20.8)	12.1 (0, 20.8)	0.601	0 (–7.7 to 3.7)
Minimum to maximum	0–61.0	0–95.8		
Total volume FFP transfused, ml · kg^{-1} (priming not included)†	0 (0, 0)	0 (0, 6.3)	0.196	0 (0 to 0)
Minimum to maximum	0–43.2	0–62.4		
Total volume Platelets transfused ml · kg^{-1}†	0 (0, 0)	0 (0, 0)	0.240	0
Minimum to maximum	0–16.3	0–76.1		(0 to 0)

All continuous variables are expressed as medians (25th percentile, 75th percentile).
*Primary endpoint. †Secondary endpoint. ‡Odds ratio.
FFP, fresh frozen plasma.

compared with priming based on FFP in terms of postoperative blood loss and transfusion of allogeneic blood products. Indeed, the proportion of patients transfused with any allogeneic blood products in addition to what was used in the CPB prime and the total amount of additional transfused allogeneic blood products in the intraoperative period and in the first 6 h postoperatively was not different between the two study arms. Moreover, postoperative blood loss was not significantly different between the two groups. These results were consistent when the data were analyzed on an intention-to-treat basis as well as on a per-protocol basis.

Although several randomized studies have previously questioned the usefulness of a priming strategy based on FFP, our study distinguishes itself from other trials.[3–8] This study is the first to compare priming based on FFP with priming based on crystalloids alone. Indeed, in the previous trials, FFP was compared with either albumin[4,7,8] or gelatins.[5,6] In the study conducted by McCall *et al.*,[3] PlasmaLyte was compared with FFP. However, albumin was added to the CPB prime in all patients to maintain plasma oncotic pressure. It has been suggested that adding albumin to the CPB prime improves platelet function by coating the oxygenator with a protein layer, resulting in a delay in the adsorption of circulating fibrinogen and reduced surface activation of platelets during CPB.[10,11] However, the clinical implication of this theory is controversial.[12,13] In our study, platelet dysfunction was somehow more obvious in the crystalloid group when compared with the FFP group. However, there was no statistically significant difference in the platelet count after CPB separation between the two groups. Moreover, the platelet dysfunction in the crystalloid group did not result in an increased need for transfusion of platelet concentrates.

Earlier studies have suggested that adding albumin to CPB prime results in a net negative fluid balance and decreased weight gain.[13–15] We did not measure the postoperative weight gain. However, the duration of postoperative intubation was not statistically different between the two groups, indicating that any eventual weight gain did not significantly influence the postoperative outcome. We also decided not to use hydroxyethyl starch for priming the CPB circuit due to the lack of evidence and absence of high-quality randomized controlled trials showing the safety and efficacy of hydroxyethyl starch use in children.[16] In addition, an *in vitro* study showed a pronounced inhibitory effect on coagulation parameters detected by the ROTEM test when colloids were compared with crystalloids.[17]

Second, in our study all the caregivers (except the perfusionist) were blinded to the study solution, which is an important aspect when it comes to deciding to transfuse. McCall *et al.*[3] also conducted a double-blind trial. However, only 20 patients were included in their study. Third, we based our transfusion algorithm on the point-of-care test results obtained at the moment of separation from CPB and in the pediatric intensive care unit. Although point-of-care tests have been used in several studies evaluating the priming strategy,[5–8] the decision to transfuse allogeneic blood products based on point-of-care tests in the operating room as well as in the intensive care unit was only performed in two studies.[5,8] This is an important point to consider because the use of intraoperative thromboelastometry has been associated with reduced transfusion prevalence in pediatric cardiac surgery.[18,19]

Last, we used a fixed amount of FFP (15 ml · kg^{-1}), resulting in the use of a maximum of 1 unit of FFP in the CPB prime. In other studies, this amount of FFP was variable, which obviously may have influenced the obtained results.[3–7]

Based on the difference between the two groups in the intraoperative volume of FFP (ml · kg^{-1}) administered, which was 0 (0, 0) in the FFP group and 0 (0, 6.3) in the crystalloid group ($P = 0.084$), one could speculate that the groups did not differ in the outcome because in the FFP group patients received FFP during CPB, whereas in the crystalloid group patients received FFP post-CPB. However, the total amount of transfused FFP taking into account the fixed volume (15 ml · kg^{-1}) that was used in the CPB prime

Table 3. Transfusion Data Intraoperatively and up to 6 h Postoperatively

	FFP (N = 30)	Crystalloid (N = 29)	*P* Value
N total allogeneic blood products (erythrocytes, FFP, platelets; priming included)	2 (2, 3) 2–6	1 (1, 3) 1–10	0.003
Total volume FFP transfused (priming included), ml · kg^{-1}	15.0 (15.0, 15.0)	0 (0, 6.3)	< 0.001
N packed erythrocytes intraoperative (priming not included)	0 (0, 0) 0–1	0 (0, 1) 0–2	0.468
N FFP intraoperative(priming not included)	0 (0, 0) 0–1	0 (0, 0) 0–3	0.133
N platelet concentrates intraoperative	0 (0, 0) 0–1	0 (0, 0) 0–2	0.113
N packed erythrocytes postoperative	0 (0, 0) 0–1	0 (0, 0) 0–1	0.537
N FFP postoperative	0 (0, 0) 0–2	0 (0, 0) 0–0	0.326
N platelet concentrates postoperative	0 (0, 0) 0–1	0 (0, 0) 0–1	0.288
Total N packed erythrocytes (priming not included)	0 (0, 1) 0–1	0 (0, 1) 0–3	0.604
Total N FFP (priming not included)	0 (0, 0) 0–2	0 (0, 0) 0–3	0.283
Total N platelet concentrates	0 (0, 0) 0–1	0 (0, 0) 0–3	0.133
Volume erythrocytes transfused, intraoperative (priming not included), ml · kg^{-1}	8.8 (0, 13.5) 0–61.0	12.1 (0, 20.8) 0–72.8	0.432
Volume FFP transfused, intraoperative (priming not included), ml · kg^{-1}	0 (0, 0) 0–27.3	0 (0, 6.3) 0–62.4	0.084
Volume platelets transfused, intraoperative, ml · kg^{-1}	0 (0, 0) 0–16.3	0 (0, 0) 0–44.0	0.126
Volume erythrocytes transfused, postoperative, ml · kg^{-1}	0 (0, 0) 0–23.8	0 (0, 0) 0–22.9	0.564
Volume FFP transfused, postoperative, ml · kg^{-1}	0 (0, 0) 0–43.2	0 (0, 0) 0–8.4	0.999
Volume platelets transfused, postoperative, ml · kg^{-1}	0 (0, 0) 0–13.5	0 (0, 0) 0–32.1	0.281
Volume cell-saver transfused, ml · kg^{-1}			
Intraoperative	11.9 (7.1, 17.5) 0–28.3	12.8 (7.9, 17.6) 0–52.5	0.671
Postoperative	0 (0, 0) 0–14.0	0 (0, 0) 0–19.4	0.977
Patients receiving fibrinogen, no. (%)	0	2 (6.9)	0.237

All continuous variables are expressed as medians (25th percentile, 75th percentile) and minimum to maximum.
FFP, fresh frozen plasma.

was significantly higher in the FFP group ($P < 0.001$). This clearly illustrates that by avoiding routine CPB priming, the total amount of transfused FFP is significantly reduced without putting the patient at risk of postoperative bleeding. This consequently decreases the number of donor exposures, because the total number of allogeneic blood products—priming included—was lower in the crystalloid group.

Although we did not objectively measure the intraoperative blood loss, we chose as outcome the total number of intraoperative and postoperative transfused blood products. If the intraoperative blood loss had been significantly different between the two groups, this would have resulted in transfusion of higher amounts of blood products intraoperatively, which was not the case in our study.

A preplanned subgroup analysis was performed on patients with cyanotic heart disease. We did not observe any statistically significant difference in the primary and secondary endpoints when analyzing cyanotic patients, but the number of these children was rather small, and therefore no firm conclusions can be made with regard the cyanotic group. Cyanotic heart disease can impact the coagulation system.[20] Whether this will result in an increased need for transfusion of allogeneic blood products is not yet fully elucidated. In a retrospective study, Faraoni and Van der Linden[21] showed that postoperative blood loss was increased in cyanotic infants between 1 and 6 months of age when compared with a noncyanotic group, but this difference was no longer observed after the age of 6 months. Otherwise, in a prospective study in children with cyanotic heart disease, the use of FFP to prime the CPB circuit was not superior to priming with gelatin.[5] Future well powered trials need to evaluate the impact of CPB priming on the risk of bleeding in infants and children with cyanotic heart disease.

Avoiding transfusion of any allogeneic blood products is of utmost importance, but this is especially true for FFP, because transfusion of FFP during congenital cardiac surgery may have important implications. Indeed, studies have demonstrated an increased incidence of thromboembolic complications in children receiving FFP.[22,23] This may be specifically an issue in children with single ventricle physiology, who are reported to be at higher risk of thromboembolic complications.[24,25] We did not observe any statistical difference in the incidence of thromboembolic events between the two study groups. Nevertheless, this study was not powered to answer any safety issues.

One patient in the crystalloid group received fibrinogen as first-line therapy, which was immediately efficacious in stopping bleeding and avoided transfusion of allogeneic blood products. Studies in adult cardiac surgery[26,27] and noncardiac surgery in children[28] have shown the efficacy of fibrinogen as first-line therapy in decreasing the need for allogeneic blood product transfusion. However, in all these trials a much higher cutoff for maximum clot firmness of FIBTEM was chosen. The maximum clot firmness of FIBTEM in our patient who received fibrinogen as first-line therapy was 5 mm. The use of fibrinogen for acquired hypofibrinogenemia is off-label and

Table 4. Biologic Parameters and Point-of-Care Tests during the Study Period

Variable	FFP (N = 30)	Crystalloid (N = 29)	*P* Value
Hemoglobin, g · dl^{-1}			
Preoperative	13.7 ± 2.5	13.3 ± 2.4	0.610
End cardiopulmonary bypass	10.0 (9.1, 11.9)	10.3 (9.9, 11.1)	0.396
Upon pediatric intensive care unit arrival	13.8 ± 2.1	13.7 ± 1.6	0.992
Platelet count, cells × 100 µl^{-1}			
Preoperative	354 ± 121	323 ± 93	0.267
End cardiopulmonary bypass	165 (124, 200)	142 (94, 182)	0.105
Upon pediatric intensive care unit arrival	176 ± 68	182 ± 71	0.733
Preoperative fibrinogen, mg · dl^{-1}	330 ± 80	338 ± 75	0.753
Preoperative activated partial thromboplastin time, s	32.6 ± 5.5	31.4 ± 3.1	0.300
Preoperative prothrombin time, s	12.5 ± 0.8	12.3 ± 1.2	0.595
Preoperative international normalized ratio	1.10 ± 0.07	1.10 ± 0.10	0.595
EXTEM clotting time, s			
Postanesthesia induction	66 ± 8	69 ± 9	0.256
End cardiopulmonary bypass	80 (73, 91)	87 (82, 97)	0.088
Upon pediatric intensive care unit arrival	76 ± 9	74 ± 13	0.579
EXTEM maximum clot firmness, mm			
Postanesthesia induction	62 ± 6	61± 6	0.852
End cardiopulmonary bypass	52 ± 8	47± 8	0.027
Upon pediatric intensive care unit arrival	51 ± 7	51 ± 8	0.827
EXTEM clot formation time, s			
Postanesthesia induction	76 (64, 109)	89 (69, 100)	0.627
End cardiopulmonary bypass	149 ± 52	216 ± 98	0.002
Upon pediatric intensive care unit arrival	155 (119, 208)	154 (109, 206)	0.935
EXTEM maximum lysis, %			
Postanesthesia induction	11 ± 4	14 ± 7	0.427
End cardiopulmonary bypass	7 ± 5	6 ± 5	0.308
Upon pediatric intensive care unit arrival	4 (2, 11)	5 (2, 9)	0.645
FIBTEM maximum clot firmness, mm			
Postanesthesia induction	13 (10, 16)	13 (10, 17)	0.879
End cardiopulmonary bypass	9 (8, 13)	7 (6, 10)	0.049
Upon pediatric intensive care unit arrival	9 (7, 11)	8 (6, 12)	0.901
Multiplate AUC adenosine diphosphate test			
Postanesthesia induction	771 ± 222	734 ± 226	0.537
End cardiopulmonary bypass	399 ± 287	271 ± 191	0.049
Upon pediatric intensive care unit arrival	344 ± 183	403 ± 237	0.300
Multiplate AUC arachidonic acid test			
Postanesthesia induction	997 ± 239	1,005 ± 309	0.918
End cardiopulmonary bypass	941 ± 546	709 ± 541	0.106
Upon pediatric intensive care unit arrival	739 ± 389	776 ± 434	0.742
Multiplate AUC thrombin receptor-activating peptide test			
Postanesthesia induction	1,017 ± 229	1,075 ± 268	0.377
End cardiopulmonary bypass	1,036 ± 535	721 ± 465	0.019
Upon pediatric intensive care unit arrival	657 ± 297	687 ± 405	0.757

All data are expressed as medians (25th percentile, 75th percentile) or means ± SD.
AUC, area under the curve; FFP, fresh frozen plasma.

Table 5. Postoperative Data of the Patients

Variable	FFP (N = 30)	Crystalloid (N = 29)	*P* Value
Intubation time, h	5 (4, 13)	5 (3, 19)	0.704
Vasoactive–inotropic score day 1	4 (2, 8)	6 (0, 8)	0.794
Vasoactive–inotropic score day 2	2 (0, 4)	0 (0, 4)	0.629
Peak postoperative (24 h) lactic acidosis	2.1 (1.7, 2.8)	2.3 (1.9, 2.7)	0.611
No renal failure, no. (%)	24 (80.0)	23 (79.3)	0.948
RIFLE criteria, no. (%)			
R	6 (20.0)	5 (17.2)	0.786
I	0	0	
F	0	0	
L	0	1 (3.4)	0.492
E	0	0	
PICU stay, days	4 (2, 5)	3 (2, 5)	0.787
Hospital stay, days	12 (10, 15)	12 (10, 22)	0.715
Thromboembolic events, no. (%)	1 (3.3)	2 (6.9)	0.612
Revision for bleeding, no. (%)	1 (3.3)	1 (3.4)	> 0.999

Vasoactive–inotropic score = dopamine dose (µg · kg^{-1} · min^{-1}) + dobutamine dose (µg · kg^{-1} · min^{-1}) + 100 × epinephrine dose (µg · kg^{-1} · min^{-1}) + 10 × milrinone dose (µg · kg^{-1} · min^{-1}) + 10.000 × vasopressin dose (U · kg^{-1} · min^{-1}) + 100 × norepinephrine dose (µg · kg^{-1} · min^{-1}). Continuous variables are expressed as medians (25th percentile, 75th percentile).

PICU, pediatric intensive care unit; RIFLE, risk/injury/failure/loss/end-stage renal disease.

costly in many European countries. Future trials in congenital cardiac surgery need to analyze whether the administration of fibrinogen as first-line therapy is more efficacious in decreasing perioperative bleeding and transfusion of allogeneic blood products and whether this is also the case when using lower maximum clot firmness FIBTEM values as the cutoff for fibrinogen transfusion.[29,30]

This study has some limitations. Despite the routine use of normothermic CPB in our institution, moderate hypothermia was performed in some cases. Hypothermia can influence perioperative bleeding and coagulation parameters. However, there was no statistical difference between the two groups with regard to the proportion of patients having undergone hypothermic surgery. Second, the proportion of patients undergoing redo surgery was lower in the crystalloid group. Although redo surgery is generally considered to be a risk factor of postoperative bleeding, our surgeons use a protective synthetic membrane before each sternal closure. This reduces the risk of ventricular laceration and massive bleeding. Nevertheless, the higher proportion of redo surgeries in the FFP group may have influenced the lack of observed differences in the bleeding and the transfusion outcome. Based on the study design and the calculated power analysis, it can be speculated that this study was very likely to produce statistically nonsignificant findings. Indeed, there were three primary outcomes in this study, and each was interpreted at the 0.017 level of statistical significance. Further, the power calculation, which assumed only a 0.05 α level, called for a 40% difference between groups, which can be considered quite

Table 6. Data of the Patients Analyzed on a Per-Protocol Basis

Variable	FFP (N = 28)	Crystalloid (N = 28)	*P* Value	Difference (95% CI)
N total allogeneic blood products (erythrocytes, FFP, platelets; priming not included)*	0 (0, 1)	0 (0, 2)	0.313	0 (0 to 0)
Patients transfused with any product (priming not included), no. (%)*	7 (25.0)	10 (35.7)	0.383	1.7‡ (0.5 to 5.3)
Chest drain blood loss 6 h postoperative, ml · kg^{-1}*	6.9 (5.1, 9.4)	5.7 (3.7, 8.4)	0.225	1.2 (−0.7 to 3.0)
Total volume erythrocytes transfused (ml · kg^{-1} (priming not included)†	8.8 (0, 17.2)	10.9 (0, 17.8)	0.641	0 (−6.8 to 4.4)
Total volume FFP transfused (ml · kg^{-1}) (priming not included)†	0 (0, 0)	0 (0, 3.2)	0.173	0 (0 to 0)
Total volume platelets transfused, ml · kg^{-1}†	0 (0, 0)	0 (0, 0)	0.231	0 (0 to 0)
N total allogeneic blood products including priming (erythrocytes, FFP, platelets)	2 (2, 2)	1 (1, 3)	0.001	
Total volume FFP transfused (priming included), ml · kg^{-1}	15.0 (15.0, 15.0)	0 (0, 3.2)	< 0.001	
Total N packed erythrocytes (priming not included)	0 (0, 1)	0 (0, 1)	0.709	
Total N FFP (priming not included)	0 (0, 0)	0 (0, 0)	0.263	
Total N platelet concentrates	0 (0, 0)	0 (0, 0)	0.124	
Patients receiving fibrinogen, no. (%)	0	1 (3.5)	0.999	

The continuous variables are expressed as medians (25th percentile, 75th percentile).
*Primary endpoint. †Secondary endpoint. ‡Odds ratio.
FFP, fresh frozen plasma.

large. Nevertheless, when considering the 95% CI width of the difference between groups, none of our results were in favor of a significant difference between the two groups.

Finally, some might advocate that based on the available evidence priming the CPB with FFP should no longer be performed and that the evidence for this is only unclear in children less than 6 months old, categorizing them to the gray zone.[31] This means that in our study, smaller infants should have been included. However, up to now, no double-blind, randomized, and well powered study has demonstrated this in older children. Our study is the first to add this evidence to the literature.

In summary, the results of this single-center, parallel-arm double-blinded study show that priming with FFP can be avoided in infants and children weighing between 7 and 15 kg. Future well designed trials need to evaluate whether this strategy can also be applied in newborns and very small infants undergoing complex cardiac surgery.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: mona.momeni@uclouvain.be. Raw data available at: mona.momeni@uclouvain.be.

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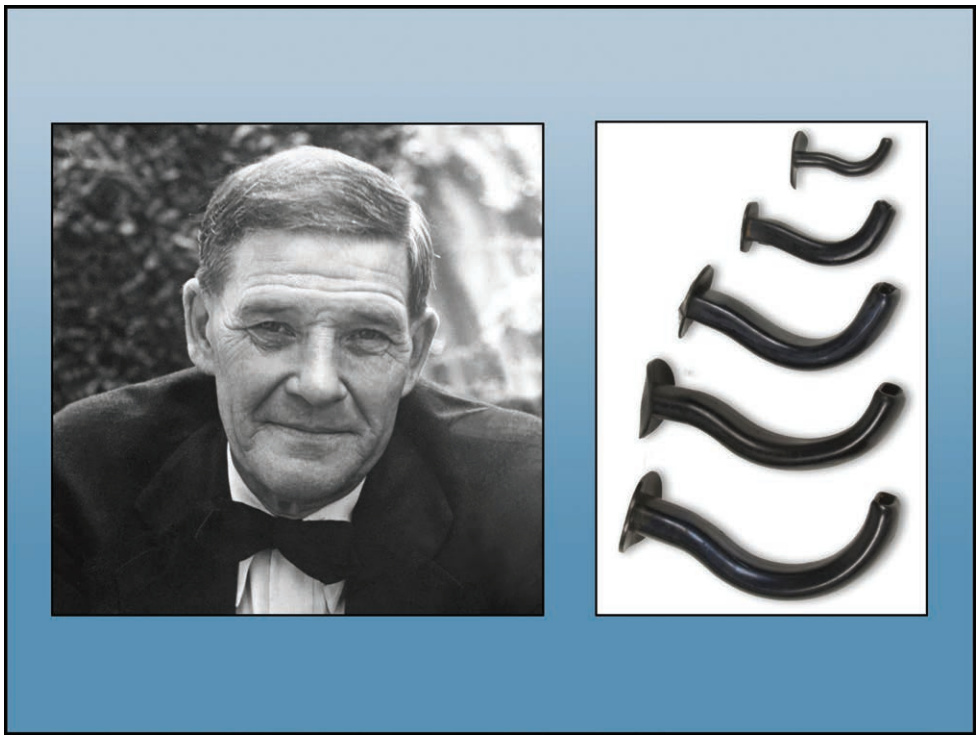
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

In True Beverly Hills Style, Both Form and Function: Arthur Guedel's 1933 "Nontraumatic Pharyngeal Airway"



In the early twentieth century, many physician-anesthetists packed example(s) of an oropharyngeal airway in their toolboxes. Although metal varieties invented by Connell or Waters were *status quo*, these forced physicians to tolerate a patent but potentially traumatized patient airway in the form of bruised lips and chipped teeth. Enter Arthur E. Guedel, M.D. (1883 to 1956, *left*), with his "nontraumatic pharyngeal airway," publicized in 1933 from his adopted hometown of Beverly Hills, California. Constructing his semicircular oropharyngeal airway of rubber that could flex to any individual's anatomy, Dr. Guedel included initially a short metal insert to prevent occlusion by the teeth. As materials improved, metal-free Guedel airways (*right*) were manufactured from more rigid rubbers and then plastics. Still used today, the Guedel airway has withstood the test of time. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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