Heart and Vessels (2020) 35:46–51
https://doi.org/10.1007/s00380-019-01466-2

ORIGINAL ARTICLE

C1 esterase inhibitor in pediatric cardiac surgery with cardiopulmonary bypass plays a vital role in activation of the complement system

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Received: 5 March 2019 / Accepted: 28 June 2019 / Published online: 5 July 2019

Abstract

Our prospective study was therefore designed to determine which part of the systemic inflammatory response after cardiac operations resulted from Cardiopulmonary bypass (CPB) in neonates and infants. After approval by the human ethical committee of the Gunma Children's Medical Center (GCMC) and informed consent of the parents, 40 consecutive term congenital heart disease patients aged until 1 year who underwent long CPB time (> 3 h) at surgery were included in the prospective study between January 2012 and December 2014. C1 esterase inhibitor (C1-inh) drug (@Berinert) was generously provided by CSL Behring (King of Prussia, PA). The C1-inh (20 IU/kg) was given intravenously 60 min after CPB. Blood samples for complement factors were obtained before and 48 h after administration of C1-inh. Six patients did not survive and their data were not included. Of 34 patients included, median age was 6.5 months, median body weight was 6050 g, and 16 (47%) were female. According to the Mann–Whitney *U* test, there were no differences between the two groups concerning demographic and intraoperative data, postoperative chemical data. C1q concentration was only significant lower in patients with C1-inh non-treated group than in patients with C1-inh treated group. But, the consumption of C1q, C3, C4, CH_{50}, and C1-inh in patients with C1-inhibitor non-treated group was observed early postoperatively. There is a significant difference in the values before and after C1-inh treatment between the two groups. The lower value in the C1-inh-treated group is explained by the activation of the classical pathway through the replenishment of complements by C1-inh treatment. This study proposes the administration of C1-inh is an effective therapy to reduce the activation and improve the clinical capillary leak syndrome.

Keywords C1 esterase inhibitor · Complements · Pediatric cardiac surgery

Abbreviations

ACC	Aortic cross clamp
AS	Aortic stenosis
ASO	Arterial switch operation
BDG	Bidirectional Glenn
BT	Body temperature
BTs	Blalock–Taussig shunt
BW	Body weight
CAVVR	Common atrioventricular valve regurgitation
cAVSD	Complete atrioventricular septal defect
CLS	Capillary leak syndrome
CoA	Coarctation of the aorta
CPB	Cardiopulmonary bypass
C1-inh	C1 esterase inhibitor
DKS	Damus–Kaye–Stanse procedure
DORV	Double outlet right ventricle
GCMC	Gunma Children's Medical Center
HAE	Hereditary angioedema
HLHS	Hypoplastic left heart syndrome
IAA	Interruption of the aorta
LVOTO	Left ventricular outlet tract obstruction
MAC	Membrane attack complex
PA	Pulmonary artery
PTFE	Polytetrafluoroethylene
SA	Single atrium
SV	Single ventricle
TAPVC	Total anomalous pulmonary vein connection

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TAPS	Total cavo-pulmonary shunt (Kawashima procedure)
TGA	Transposition of the aorta
ToF	Tetralogy of Fallot
VSD	Ventricular septal defect

Introduction

The use of cardiopulmonary bypass (CPB) is necessary for the correction of many complex cardiac defects in neonates and infants. Surgical results for most defects have improved over the last several years, but there persists significant morbidity related to the inflammatory insult of CPB. CPB in combination with anaesthesia, medication, vascular injury and surgical stress affects the extent of inflammatory response. Complement system protein may be activated through the classical, alternative and lectin pathways, leading to generation of biologically active products, such as C5a and the terminal membrane attack complex (MAC), and ultimately contributes to endothelial cell disruption during CPB. Significant differences in the complement factor levels indicate a higher grade of complement activation and simultaneous contact activation in patients during and after CPB. Thus, the main cause of systemic inflammatory reaction after CPB is the contact of the blood to non-biologic surfaces of the CPB circuit and not surgical procedures or anesthesia. To lessen the activation of the complement and contact systems during CPB, it is necessary to use inert materials in the CPB circuit. Because inhibiting drugs may lessen complement and contact system activation, they represent a further possibility for minimizing the damaging effects of CPB [1].

Complement factor C1 esterase inhibitor (C1-inh) levels decrease with CPB in infants. Stiller and colleagues [2] examined C1-inh levels in such patients. They found that after CPB, generalized edema, pulmonary edema, and weight gain were greater in infants with lower C1-inh levels. At 30 min post-CPB, the infants demonstrating these effects had C1-inh activity levels that were 51% of controls compared with 80% of controls in those who did not demonstrate capillary leak syndrome (CLS). This decrease was greater in infants who suffered post-CPB CLS. CLS show evidence of complement activation, decreased complement levels. We thus consecutively investigated several complement compounds before and after pediatric cardiac surgery with CPB. Based on this hypothesis, we tested whether C1-inh supplementation after CPB would ameliorate C1-inh decrease in pulmonary and cardiac dysfunction after CPB. Our prospective study was therefore designed to determine which part of the systemic inflammatory response after cardiac operations resulted from CPB in neonates and infants.

Patients and methods

After approval by the human ethical committee of the Gunma Children's Medical Center (GCMC) and informed consent of the parents, 40 consecutive term congenital heat disease patients aged until 1 year who underwent long CPB time (> 3 h) at surgery were included in the prospective study between January 2012 and December 2014. Though there was no evidence, it was thought that congenital heart disease patients who underwent short CPB time did not present pulmonary edema and capillary leak syndrome. Conventional general anesthesia was conducted with diazepam, fentanyl sulfate, and vecuronium. After induction of anesthesia, nasotracheal intubation was performed in the patients not receiving ventilatory support, and central venous catheters and peripheral arterial catheter were inserted. Perioperative antibiotic prophylaxis consisted of ampicillin. The CPB circuit included a roller pump, a disposable membrane oxygenator, and an arterial filter. Cooling and rewarming were carried out with a heat exchanger. The priming solution consisted of a crystalloid solution, mannitol (3 ml/kg), and leukocyte-depleted packed red blood cells to obtain a hematocrit value of the circulating volume of about 25%. For vasodilatation in the cooling and rewarming periods, all neonates received a continuous infusion of sodium nitroprusside 2 μg/kg/min and chlorpromazine 1 mg/kg. CPB was instituted with a perfusion index of 2.7 L/(min m^2), which was maintained throughout the cooling phase. The pump was primed with 80–100 ml of packed cells and 50 ml of lactated Ringer's solution, 1000 IU of heparin, 2.0 ml/kg of sodium bicarbonate 4.2%, and 3 ml/kg of mannitol 20% were added. CPB was instituted at a flow rate of 2.7 L/min/m^2 after systemic anticoagulation, and administration of dexamethasone, 1 mg/kg. During CPB the pH–stat method was used, with correction of PaO_2 to the patients' hypothermic temperature to maintain a pH value of 7.40. After deep hypothermia was reached (minimal nasopharyngeal temperature averaging 25 °C), aortic cross-clamping was done and cardioplegia was induced with a single intra-aortic injection of a 4 °C cold St. Thomas solution (30 mL/kg), and cardiac arrest was instituted for a target period of not longer than 60 min. The surgical procedure was continued under high-flow perfusion (50% of the calculated initial perfusion rate). Rewarming was achieved under full-flow conditions. The lungs of the neonates were reventilated when core temperature reached 30 °C. Neutralization of heparin was achieved with protamine sulfate in a 1:1.5 ratio. Epinephrine, dopamine, olprinone and nitroglycerin were systematically administered for weaning the patients from CPB. After coronary reperfusion and at the end of the operation, the cardiac surgeon, as explained, assessed

intraoperative myocardial function here. In cases of hemodynamic instability or myocardial dysfunction at the end of the operation, sternal closure was delayed until stabilization, and sternal wounds were closed with a polytetrafluoroethylene (PTFE) membrane.

C1-inhibitor drug (@Berinert) dosing and postoperative care

C1-inh drug (@Berinert) was generously provided by CSL Behring (King of Prussia, PA). The C1-inh (20 IU/kg) was given intravenously after CPB. If necessary, fentanyl and midazolam were administered for analgesia and sedation. All patients were weaned from the ventilator as soon as possible. Dopamine and epinephrine were infused continuously as necessary to optimize mean arterial pressure, central venous pressure, pulse amplitude, capillary refill time, and diuresis. Furosemide, ethacrynic acid, and spironolactone were administered to promote diuresis.

Collection of samples

Blood samples for complement factors were obtained before and 48 h after administration of C1-inh. Arterial blood gas analysis was performed, and hemodynamic parameters were evaluated at the second day points.

Statistical analysis

Differences in the measured parameters in the two groups were assessed by the Mann–Whitney *U* test. We investigated the influence of age, weight, and sex on the determined concentrations and activities in a multiple regression analysis. Statistical significance was assumed when the *p* value was less than 0.05.

Results

Six patients (two that received Berinert and four that non-received Berinert) did not survive and their data were not included. These patients need the extracorporeal membrane oxygenation until 48 h after an open-heart operation in operating room and in the intensive care unit. Accordingly, obtaining the blood samples of complement factors until 48 h after administration of C1-inh was not possible. Of 34 patients included, median age was 6.5 months, median body weight was 6050 g, and 16 (47%) were female. Table 1 shows the mean age, body weight, diagnosis, duration of operation, duration of anesthesia, duration of CPB time, duration of aortic cross-cramp time, and nadir body temperature with C1-inhibitor non-treated group (non-INH, 26 cases) and Table 2 with C1-inhibitor treated group (INH, 8 cases). According to the Mann–Whitney *U* test, there were no differences between the two groups concerning demographic and intraoperative data. There were no differences between the two groups concerning demographic and intraoperative data (Tables 1, 2). Postoperative chemical data and 48 h after CPB, AST, ALT, lactate, CK-MB, WBC, CRP, duration of inotropic support, duration of mechanical ventilation and duration of ICU stay did not differ between the two groups (Table 3). The results of the pre and postoperatively activated complement and contact system are summarized in Table 4. Preoperatively, there were no differences in complement between two groups. Postoperatively, C1q concentration was only significant lower in patients with C1-inhibitor non-treated group than in patients with C1-inhibitor treated group. But, the consumption of C1q, C3, C4, CH_{50} and C1-inh in patients with C1-inhibitor non-treated group was observed early postoperatively. C1-inhibitor activity differed in the two groups.

Discussions

There are three kinds of course inclusive of classical pathway, alternative pathway and lection pathway, which activated by many factor that much protein in a complement system in sequence. To the best of our knowledge, cardiopulmonary bypass can result in a post-CPB syndrome that is characterized by increased vascular permeability, generalized edema, pulmonary dysfunction, and cardiac dysfunction [3–5]. This syndrome seems to be more intense in neonates and can result in prolonged ventilation, coagulopathy, postcardiotomy cardiac failure, and increased mortality. This is a systemic inflammatory response that appears to be fueled by activation of the complement, contact, coagulation, and fibrinolytic pathways [6]. More recently, Tassani et al. have shown that prophylactic administration of C1INH before CPB is an effective therapeutic approach to reduce the inflammatory response and improve clinical parameters after cardiac surgery requiring CPB in neonates [7].

Thus, although the complement system is originally a defense system for protection against foreign microorganisms, its strong activation induces excessive complement consumption and persistent inflammatory reactions. After surgery, it impairs vascular endothelial cells in the lungs and kidneys, causes swelling of parenchymal cells, and triggers an organ failure. Therefore, multiple defense systems are established by several proteins, called complement regulators, to prevent excessive and persistent complement activation and invasion of autologous cells [8, 9]. C1-inhibitor, called C1 inactivator, covalently binds to and inhibits the active sites (serine) of activated C1r and C1s in the C1 step of the classical pathway to suppress

Table 1 Clinical data and duration of cardiac operation with C1-inhibitor non-treated group

No	Sex	Age (m)	BW (g)	Diagnosis	Procedure	Duration of operation	Duration of CPB time	Duration of ACC time	Nadir BT during CPB
1	F	0.2	3500	TGA	ASO	613	219	112	30.1
2	M	0.33	2937	TGA	ASO	331	210	119	27.8
3	M	0.4	2800	TGA	ASO	377	245	118	29.2
4	F	0.47	2670	TGA	ASO	440	278	141	27.8
5	F	2	3390	AS, IAA, VSD	Norwood	619	461	98	29.6
6	M	3	3500	CoA, VSD	CoA repair VSD closure	410	212	96	28.8
7	M	3	4324	AS, CoA DORV	Norwood	445	282	102	25.4
8	F	3	3170	TAPVC (II) SA, VSD	TAPVC repair VSD closure	445	273	136	28.8
9	M	4	4500	AS, IAA VSD	Norwood	457	287	87	25.8
10	M	4	6000	SV, CoA	Arch repair, BDG	560	365	123	31.2
11	M	4	4054	SV. CAVVR	cAVV repair, BDG	439	304	77	28
12	F	4	4900	AS, IAA VSD	Norwood	569	376	107	29.7
13	F	4	5000	DORV, LVOTO	ASO	451	308	184	29.1
14	F	5	6100	cAVSD	cAVSD repair	390	237	75	32.9
15	F	7	4760	CoA, SV, s/pBTS	CoA repair, BDG	426	257	42	28.1
16	M	7	7300	TOF	ToF repair	381	255	134	34.4
17	M	8	8400	SV	DKS, BDG	381	216	105	30.3
18	F	8	7200	DORV, PA	Rastelli ope	401	234	128	31.2
19	F	8	6800	TOF, PA	Rastelli ope	451	284	141	31.9
20	M	9	7700	SV	DKS, TCPS	375	218	53	32.1
21	M	9	4500	VSD,s/p CoA repair	VSD closure PA plasty	355	190	88	34
22	F	10	7600	TOF	ToF repair	332	228	124	34.3
23	M	11	8400	DORV	DORV repair	434	267	143	34
24	M	11	8900	cAVSD	cAVSD repair	564	401	230	29.7
25	M	11	7400	VSD	VSD closure	484	289	162	33.7
26	M	11	6500	cAVSD	cAVSD repair	347	188	114	34.4
Median		4.5	4950			436.5	262	116	29.9

Table 2 Clinical data and duration of cardiac operation with C1-inhibitor treated group

No	Sex	Age (m)	BW (g)	Diagnosis	Procedure	Duration of operation	Duration of CPB time	Duration of ACC time	Nadir BT during CPB
1	M	0.07	3240	TAPVC, CoA	TAPVC repair Arch repair	539	236	83	25.9
2	M	6	3446	HLHS	Norwood	900	397	57	25.1
3	F	6	6200	cAVSD	cAVSD repair	572	202	127	32.9
4	F	8	6600	TOF, PA	Rastelli	490	260	114	31.9
5	F	11	6700	VSD, PS	VSD closure PA plasty	410	185	108	34.8
6	M	11	7290	IAA, VSD s/p Norwood	Rastelli	625	255	143	33.7
7	F	11	8700	cAVSD	cAVSD repair	515	260	185	29.1
8	F	11	6600	cAVSD	cAVSD repair	578	265	197	32.1
Median		9.5	6600			417	258	121	32.0

Table 3 Post-operative clinical outcome data

	C1-inhibitor non-treated group ($n=26$)	C1-inhibitor treated group ($n=8$)	*P* value
AST (< 30 IL/l)			
Post 0 h	157.9 ± 74.2	195.3 ± 87.9	0.51
Post 48 h	52.4 ± 26.3	67.9 ± 27.7	0.43
ALT (< 30 IL/l)			
Post 0 h	18.9 ± 13.7	25.4 ± 9.5	0.15
Post 48 h	20.4 ± 12.4	26.8 ± 15.0	0.28
Lactate (0.5–1.6 mmol/l)			
Post 0 h	1.7 ± 1.8	1.8 ± 1.6	0.63
Post 48 h	1.0 ± 0.4	1.1 ± 0.5	0.39
CK-MB (< 20 U/l)			
Post 0 h	130.9 ± 63.5	155.6 ± 87.1	0.69
Post 48 h	44.0 ± 65.8	22.3 ± 9.9	0.55
WBC (< 9000/μL)			
Post 0 h	10,796 ± 3173	12,512 ± 2740	0.13
Post 48 h	10,939 ± 2996	12,112 ± 2580	0.16
CRP (< 0.3 mg/dl)			
Post 0 h	0.3 ± 0.3	0.1 ± 0.2	0.30
Post 48 h	8.3 ± 5.5	8.6 ± 5.8	0.66
Duration of inotropic support (h)	204.9 ± 101.8	180.8 ± 109.3	0.57
Duration of mechanical ventilation (h)	179.3 ± 121.8	164.4 ± 115.0	0.78
Duration of ICU stay (days)	12.8 ± 6.0	12.8 ± 9.1	0.85

Table 4 Pre and postoperative complement data

	C1-inhibitor non-treated group ($n=26$)	C1-inhibitor treated group ($n=8$)	*P* value
C1q (8.8–15.3 mg/dl)			
Pre	6.14 ± 2.12	6.46 ± 1.22	0.508
Post	4.77 ± 0.92	5.86 ± 1.13	**0.045**
P value	**0.048**	0.564	
C1 inh (70–130%)			
Pre	93.2 ± 18.7	90.9 ± 22.2	0.964
Post	71.3 ± 13.7	80.4 ± 18.0	0.115
P value	**< 0.001**	0.3706	
C3 (86–160 mg/dl)			
Pre	80.0 ± 17.1	79.0 ± 24.9	0.873
Post	56.3 ± 11.5	61.8 ± 11.6	0.121
P value	**< 0.001**	0.124	
C4 (17–45 mg/dl)			
Pre	16.2 ± 6.6	15.8 ± 3.2	0.964
Post	10.9 ± 4.1	12.3 ± 3.0	0.628
P value	**0.002**	0.072	
CH_{50} (25–50/ml)			
Pre	43.0 ± 14.0	37.6 ± 21.8	0.873
Post	31.9 ± 13.3	31.3 ± 21.2	0.792
P value	**0.042**	0.482	

Bold values indicate worse results than another group

complement activity. In addition, it inhibits, the enzymatic activities of the coagulation, kallikrein, and plasmin systems, besides the complement system. In fact, in cases deficient in congenital complement control (e.g., Hereditary Angioedema; HAE), bradykinin, as well as C3a and C5a strongly induced by the classical pathway initiated by C1 activation, is deeply involved [10].

In the present study, after the prolonged use of CPB, complement components significantly reduced by about 20–40%, as reported by the authors. In the C1-INH-treated group, it reduced by about 15%, suggesting suppressed complement reduction. Of note, there is a significant difference in the values before and after C1-INH treatment between the two groups. The lower value in the C1-INH-treated group is explained by the activation of the classical pathway through the replenishment of complements by C1-INH treatment. In the future, bradykinin and cytokine levels will be examined.

In summary, C1 INH is an important regulator of plasma protein cascade systems such as the classical pathway of complement, the intrinsic pathway of coagulation and inflammatory reactions. Thus, severe diminished C1 INH in pediatric cardiac surgery with cardiopulmonary bypass plays a vital role in activation of these systems. This study proposes the administration of C1 INH is an effective therapy to reduce the activation and improve the clinical capillary leak syndrome.

Limitations

Despite the strengths of our methodology and the consistency of our findings, some limitations should be delineated. First, although powered to detect a difference in postoperative CLS between those who did and did not receive C1-inh, the dosage of C1-inh was relatively small and the incidence of CLS was lower in this study. It is therefore possible that the large dosage may observe the difference in those groups in large trials. Second, anesthetic management was left to the discretion of treating anesthesiologists. This may have affected the outcome given the potential differing effects of anesthetic medications on the development of postoperative CLS. Third, the limited sample size from a single center and restrictive inclusion may place some limitations on generalizability. As this was a single-center study, the results should be replicated in a large multi-center trial.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Informed consent Informed consent was obtained from the patient/participant (delete as appropriate) for publication of their individual details and accompanying images in this manuscript. The consent form is held by the authors' institution.

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