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Open cardiac surgery in the first hours of life using autologous umbilical cord blood☆

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Abstract

Objective: This article describes the first clinical experience of complete repair of complex critical congenital heart diseases (CHDs) in the first hours of life using autologous umbilical cord blood (UCB). Prenatal diagnosis and harvesting of autologous UCB allow to modify perioperative management and to perform corrective surgery in the first hours of a patient's life. This approach can afford avoiding homologous blood transfusion and preventing development of hypoxemia and heart failure due to hemodynamic changes of complex critical CHD. **Methods:** The study group included 14 consecutive prenatally diagnosed patients with critical complex CHD during the period from September 2009 to August 2010. Autologous UCB was harvested in accordance to NetCord-FACT International Standards for Cord Blood Collection and was used during the surgery with cardiopulmonary bypass (CPB). In all cases, complete repair was performed during the first hours of life: arterial switch operation ($n = 9$); arterial switch operation with total anomalous pulmonary venous communication repair ($n = 1$); arterial switch operation with interruption of the aortic arch repair ($n = 1$); Ebstein's repair ($n = 2$); and aortopulmonary window repair with interruption of the aortic arch repair ($n = 1$). All procedures were performed using moderate hypothermia with cold-crystalloid cardioplegia, except one case that required deep hypothermic circulatory arrest. **Results:** A mean of 92 ± 16 ml of UCB was harvested. Autologous UCB was used during the surgery in all 14 cases. Mean age of newborns at operation was 4.7 ± 2 h (3—8). No patients required intensive care unit (ICU) admission, interventional procedures, mechanical ventilation, or medications before surgery. Twelve patients underwent bloodless open heart surgery; eight of them completely avoided homologous blood transfusion during the perioperative period. There was one postoperative death in our study (Ebstein's anomaly). **Conclusions:** The use of autologous umbilical cord blood is feasible in neonatal open heart surgery. Complete surgical repair of complex critical CHD can be applied successfully to neonates within the first hours of life.

Keywords: Neonates; Open heart surgery; Autologous umbilical cord blood

1. Introduction

Neonatal open heart surgery frequently requires homologous blood transfusion. The risks of homologous transfusion, especially in neonates, are well known [1,2]. Bloodless cardiopulmonary bypass (CPB) strategies in infants are proposed but they have limited application because of hemodilution, particularly in neonates with weight less than 4 kg [3]. Possibility and effectiveness of autologous umbilical cord blood transfusion in neonates were proved [4—7]. However, the use of umbilical cord blood (UCB) in neonatal open cardiac surgery has not been studied. Progressive improvement in prenatal diagnostics of congenital heart disease (CHD) allows to plan corrective surgery before delivery and to harvest autologous UCB for transfusion during the operation. Also, it was demonstrated [8] that the preoperative condition of neonates with critical CHD is better in those with a prenatal diagnosis. We assume that surgical repair of critical CHD immediately after birth avoids further development of hypoxemia and heart failure due to hemodynamic changes of complex critical CHD.

Therefore, we undertook a prospective clinical study of open cardiac surgery in the first hours of life using autologous UCB in neonates with prenatally diagnosed complex critical CHD to assess possibility and safety of this method and its impact on postoperative outcomes. This report describes the first clinical experience.

2. Materials and methods

The Institutional Review Board of the Ukrainian Children Cardiac Clinic (UCCC) approved this work and written

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consent was obtained from the parents of the patients. From September 2009 to August 2010, a total of 73 neonates with critical CHD underwent corrective open heart surgery at UCCC. The study group included 14 of them who were prenatally diagnosed and underwent corrective surgery in the first hours of life using autologous UCB.

Prenatal diagnoses of complex critical CHD were made at 22–28th week of gestation by echocardiography. At 36th week of gestation, reexamination was performed to confirm the diagnosis. Pregnant women were checked for blood infection and referred to maternity hospital. The nearest specialized maternity hospital was selected as a study partner to decrease period between delivery and heart surgery. After obstetric examination, the date of delivery was planned to prepare for cardiac operation. To ensure operation during working hours, all labors were planned for early morning of working days.

Autologous UCB was collected in accordance with NetCord-FACT International Standards for Cord Blood Collection [9]. Collections were performed *in utero* (while placenta is still in uterus by puncture of the umbilical vein) into blood bag system with citrate–phosphate–dextrose–adenine anticoagulant (CPDA-1) solution. The collection bag contained 39 ml of CDPA-1. We adjusted the volume of CDPA-1 solution as 20 ml per 100 ml of UCB using 20-ml plastic syringe just before harvesting. UCB was harvested after umbilical vein was clamped and cut. The umbilical cord was cleaned using povidone–iodine and wiped with 70% alcoholic solution before collection. After collection, blood bags with UCB were stored at 4 °C in the portable refrigerator. At the beginning of the study, we separated red blood cells (RBCs) and plasma from UCB with a cell separator, but, for the four last cases, we used whole UCB for autologous transfusion. Each sample of UCB was tested for sterility – aerobic and anaerobic bacterial culturing. Additionally, all samples of UCB were tested with CITO TEST HIV1/2 (Farmasco™) before surgery. All blood bags were registered as 'autologous umbilical cord blood', labeled with HIV1/2 test result, group type, surname of donor, volume of blood product and sent to the hospital blood transfusion service.

After delivery, patients were transported to UCCC by ambulance. There was no necessity for mechanical ventilation, medications, or infusions during transfer. Neonates were admitted to the hospital at an average age of 1 h after birth. Before surgery, they were examined by echocardiography and computer tomography for specification of the CHD anatomy.

Anesthesia was induced with intravenous fentanyl (10 mcg kg^{-1}), vecuronium (0.1 mg kg^{-1}), and was maintained with sevoflurane (or isoflurane) 1.5–2 vol.%. Infusion of morphine sulfate (40 mcg kg^{-1} h^{-1}) and additional doses of fentanyl during the operation were administered as needed. Fentanyl was also used during CPB. Central venous and arterial catheters were placed after induction of anesthesia.

In all cases, median sternotomy was employed and a standard technique of neonatal CPB was used. Miniaturized bypass circuit includes 3/16-in. inner diameter tubes for arterial line and 1/4 in. for venous and pump lines and connected to the Baby RX oxygenator (Terumo Cardiovascular Systems, Ann Arbor, MI, USA) without arterial filter. Primary volume of CPB was decreased up to 130 ml and did not contain

Table 1. Perioperative characteristics.

Diagnose	Patients (*n*)	Collected UCB (ml)	Birth weight (kg)	Age at operation (h)	Procedure	CPB time (min)	Ao CCT (min)	Preop Hct (%)	Hct at 5th min of CPB (%)	Hct in 1 day (%)	Preop Lac (mmol/l)	Lac at the end of CPB (mmol/l)	Lac in 1 day (mmol/l)	Ventilation (h)	ICU stay (days)
TGA, IVS[a]	8	87 ± 32	3.45 ± 0.5	3–6	ASO	180 ± 44.1	74.4 ± 11.9	44 ± 8.4	24 ± 5.4	35.4 ± 6.1	3.9 ± 1.8	6.4 ± 2.9	4.3 ± 1.9	70.1 ± 41.4	8 ± 3.63
TGA, VSD	1	100	3.6	8	ASO, VSD repair	196	82	39	24	29	2	4.2	2.9	45	8
TGA, TAPVC	1	80	2.5	5	ASO, TAPVC repair	240	118	39	19	37	3	6.9	4.2	1056	107
Taussig-Bing anomaly, IAA	1	70	2.95	5	ASO, VSD repair, aortic arch repair	234	112	37	20	26.7	6.3	12	4.4	116	16
Ebstein's anomaly	1	75	3.06	7	Ebstein's repair	73	31	47	25	36	3.1	6.3	5.8	377	16
Ebstein's anomaly, PA	1	86	3.29	5	Ebstein's repair; valvuloplasty, pulmonic	271	46	45.1	28	39	1.1	5.3	3.3	162	12
APW, IAA	1	67	2.2	8	APW repair, aortic arch repair	145	65	57	24	38	1.6	8.6	7.2	2880	120

TGA: transposition of the great arteries; IVS: intact ventricular septum; VSD: ventricular septal defect; TAPVC: total anomalous pulmonary venous communication; IAA: interruption of the aortic arch; PA: pulmonary atresia; APW: aortopulmonary window; ASO: arterial switch operation; UCB: umbilical cord blood; CPB: cardiopulmonary bypass; Ao CCT: aortic cross clamp time; Htc: hematocrit level; Lac: serum lactate level.

[a] Data are presented as mean ± SD.

any homologous blood components. Prime solution for CPB circuit contains mannitol 15% – 1 g kg^{-1}, albumin 20% – 10 ml kg^{-1}, sodium bicarbonate 4% – 3 ml kg^{-1}, NaCl 0.9% – if required. Autologous RBC (or whole UCB) was used for priming the circuit when estimated hematocrit level at the onset of bypass was lower than 20–25%. High-flow CPB (150–200 ml kg^{-1} min^{-1}) was used. All procedures were performed using moderate hypothermia (t = 28–30 °C) except one case of aortopulmonary window with interrupted aortic arch when deep hypothermic circulatory arrest (18 °C) was used. The myocardium was protected with a cold-crystalloid cardioplegia.

Whole autologous UCB or derived components (RBC, plasma) were used in all cases for transfusion after weaning from CPB to compensate for hemodilution and surgical bleeding. The blood remaining in the circuit after termination of CPB was centrifuged and transfused back into the patient intra-operatively or in intensive care unit (ICU) to achieve an appropriate hematocrit.

Blood parameters, including hematocrit level (%) and serum lactate (mmol l^{-1}), were analyzed at the following times: before incision, at the 5th min of CPB, at the end of CPB, and at the 1st postoperative day. Clinical outcomes, including time (hours) to extubation and discharge from the intensive care unit (days), were recorded in all patients (see Table 1).

3. Results

Elective cesarean section was performed due to obstetric indications in five women, other nine labors were induced. All newborns were mature and three of them weighed less than 3 kg. Harvesting of autologous UCB was feasible in all patients enrolled in the study. The average volume of harvested UCB was 92.8 ± 15.9 ml. Calculated volume of UCB and derived products per body weight are presented in Table 2. Aerobic and anaerobic bacteriological cultures of the collected UCB were obtained on the 7th day after delivery and were negative in all cases.

The mean time of patient transportation by ambulance was 10–15 min. The mean age at operation was 4.7 ± 2 h. All neonates had no preoperative morbidity. They did not require ICU admission, interventional procedures, mechanical ventilation, or medications before surgery. All patients underwent primary complete repair. Operations were performed during working hours as 'elective' and were planned a few days before patient's delivery. Arterial switch operation was performed in 11 patients with transposition of the great arteries (d-TGA). Two of them had associated complex defects that were corrected simultaneously: (1) d-TGA with infracardiac total anomalous pulmonary venous communication (TAPVC), diminutive pulmonary veins and intramural coronary arteries, (2) Taussig–Bing anomaly with interruption of the aortic arch type A. Hetzer valvuloplasty of tricuspid valve was performed in two patients with Ebstein's anomaly, type C. Also, pulmonary valvuloplasty was done in case of Ebstein's anomaly with pulmonary atresia type I. Patient with aortopulmonary window, interrupted aortic arch type B and associated genetic pathology (CHARGE syndrome) required 21 min of total circulatory arrest with deep hypothermia (18 °C) during the operation.

Table 2. UCB products.

	Mean	Range
Whole UCB (ml/kg[a])	28	22–30
RBC (ml/kg)	11	8–12
Plasma (ml/kg)	16	12–17

UCB: umbilical cord blood; RBC: red blood cells.
[a] kg of body weight.

In all cases, the autologous UCB was used during the operation. The mean time of blood usage was 7 h (4–9) after collection. Twelve patients from our study group avoided homologous blood transfusion intra-operatively. Total bloodless series included eight patients who underwent the arterial switch operation and their hematocrit level was not lower than 35% before discharge. Homologous blood was transfused in six cases: patient with complex Ebstein's anomaly, pulmonary atresia required prolonged CPB with use of homologous RBC because of hemodynamic instability; surgical bleeding led to reset of CPB and homologous blood transfusion during the arterial switch operation in one case; four patients were transfused with homologous blood products postoperatively at the ICU to maintain hematocrit level above 30%.

Postoperative morbidity was observed in four cases: (1) patient after arterial switch operation and TAPVC repair with diminutive pulmonary veins had severe pulmonary hypertension and acute right heart failure that required repeat sternotomy at the ICU on the day of surgery. Respiratory failure due to alveolar edema caused by diminutive pulmonary veins in this patient required prolonged mechanical ventilation using a high-frequency oscillatory ventilator. Delayed sternal closure was performed on the 14th day after primary correction. Hybrid balloon angioplasty of pulmonary veins stenosis was successfully performed on the 60th postoperative day that allowed the infant to be extubated. (2) Patient with aortopulmonary window and interrupted aortic arch type B was hemodynamically stable after surgery, but had severe respiratory failure due to associated CHARGE syndrome that required extended ventilation for 4 months after surgery. (3) Patient with Ebstein's anomaly and pulmonary atresia had a heart failure and left the operating room without sternal closure. Delayed sternal closure was performed on the third day. (4) Patient with d-TGA and ventricular septal defect had heart failure due to a massive intra-operative bleeding and required delayed sternal closure on the second day after arterial switch operation.

One patient died 16 days after surgery (Ebstein's anomaly). The cause of death was a massive postoperative intracranial hemorrhage into congenital brain cyst, which was not diagnosed previously.

4. Discussion

In infants and especially in neonates, anemia is one of the primary problems observed during and after heart surgery. Because of the small circulating volume of blood, the use of CPB induces hemodilution and homologous blood transfusion is required. However, a blood transfusion can potentially cause a variety of complications, such as an immunologic

reaction that causes organ dysfunction and transmissions of pathogens [1,2]. To eliminate these risks, numerous blood management strategies were proposed to avoid homologous blood transfusions in congenital cardiac surgery, including miniaturized bypass systems, modified ultrafiltration, retrograde autologous priming, cell salvage, and autologous blood donation [3,10—12]. Bloodless CPB strategies in infants are proposed but they have limited application, particularly in neonates with weight less than 4 kg [3]. One of the most potentially limiting factors to neonatal bloodless heart surgery is the low perioperative hematocrit level. Some investigators [11,12] reported that low-hematocrit bypass was effective in avoiding the need for homologous transfusion. Kurth et al. [13] also reported that the lowest safe hematocrit level was approximately 15%. However, the safety of such low hematocrit is still not determined [14].

At the same time, numerous studies in neonatology have proven the feasibility, effectiveness, and safety of autologous UCB transfusion in premature neonates and those requiring surgical intervention at or near the time of delivery [4—7]. UCB conserved by CDPA can be used for as long as 3 weeks after harvesting and even longer if separated into components. However, the use of autologous UCB in neonatal open heart surgery has not yet been studied or reported, although UCB probably can reduce hemodilution — a major limiting factor of homologous bloodless surgery. Progressive improvements in prenatal diagnosis of CHD allow us to work out an innovative approach to surgical treatment of neonates by harvesting of autologous UCB for transfusion during corrective heart surgery.

Prenatal diagnosis of critical complex CHD may offer some additional benefits. Bonnet et al. [8] suggested that the preoperative condition of neonates with critical CHD (including D-TGA) is better in those with a prenatal diagnosis. Also, it was demonstrated that delay in diagnosis and treatment can be associated with preoperative cerebral ischemia and injury [15] and prenatal diagnosis of critical CHD allows to reduce risks of profound hypoxemia [16]. No preoperative morbidity even in patients with complex critical CHD in our study confirms these statements. It is logical to assume that correcting the critical CHD immediately after birth influences the cardiovascular systems toward normal status and may be beneficial to nervous, pulmonary, and other organs systems. Reddy et al. [17] suggested that delayed intervention does not confer any benefit and may in fact increase morbidity and mortality. In their experience, delay in intervention was associated with increased complications, including ventilatory dependency, failure to thrive, sepsis, chronic pulmonary disease, necrotizing enterocolitis, and acute renal failure. Successful heart surgery on neonates within 24 h of life was demonstrated earlier [18]. We assume that complete surgical repair of critical CHD in the first hours of life in prenatally diagnosed neonates allows to avoid further development of hypoxic injury and heart failure due to hemodynamic changes of complex critical CHD.

The first clinical experience of an innovative approach for corrective surgery of prenatally diagnosed critical complex CHD includes two modifications: the use of autologous UCB for perioperative transfusion and time of surgery at the first hours of the patient's life, which is encouraging and has shown feasibility and safety of the described method. Autologous UCB has the potential to be an alternative source for transfusion in newborns that require surgical intervention at or near the time of delivery and allows to completely avoid or substantially reduce homologous blood transfusion in cases of uncomplicated surgery of complex critical CHD. Also, corrective surgery immediately after birth may improve clinical outcome, decreasing interventional procedures and associated complications that are described [19—21]. Nonetheless, we identified a few limitations of our method such as a limited volume of autologous UCB and applicability of this approach only to neonates with prenatally diagnosed congenital malformations. Risk of bacterial contamination is described in the majority of the observational studies [4,7]. Some studies mentioned that the extensive training and experience could significantly lower the contamination rates [22,23]. As described above, there was no bacteriological contamination of UCB samples in our study due to the technique we used. There are concerns expressed toward the surgery in the early hours of life due to the high pulmonary vascular resistance; however, in our view, benefits of early operation exceed the potential drawbacks. In our opinion, associated severe noncardiac congenital lesions, such as some genetic syndromes and extracardiac malformations that do not appear just after delivery, could be the potential drawbacks of the neonatal open-heart surgery at the first few hours of life.

4.1. Study limitations

This is a feasibility study that included a small number of patients and as such no clear conclusion could be drawn from our work. However, promising initial experience led us to believe that further multicenter clinical trial, preferably randomized, with longer follow-up and well-selected endpoints will help us fully determine safety and effectiveness of the open heart surgery during the first hours of life using autologous UCB.

4.2. Conclusions

The use of autologous UCB is feasible in neonatal open heart surgery. Complete surgical repair of complex critical CHD can be applied successfully to neonates within the first hours of life.

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Appendix A. Conference discussion

Dr C. Schreiber (*Munich, Germany*): I have just two or three questions, and maybe you can answer them briefly. I would like to know what was really triggering your investigations and what was the background?

In addition, we elucidated brain function and brain monitoring during this year's Techno-College. How important is it in your mind, or is it maybe riskier to operate on someone within the first hours of life? As an example, for a patient with a TGA, should we not wait beyond four, five, or six days and then embark on an operation?

Dr Yemets: I think that using the umbilical cord blood, in combination with a minimized bypass circuit, allowed us to reduce homologous blood transfusion requirement and associated blood transfusion side effects.

And our second main objective was to perform surgery for critical congenital heart disease in the first hours of life without any medication and palliative interventions. All patients in our study group had absolutely stable conditions without any medication and did not require stabilization in intensive care before surgery. I think everybody who is doing cardiac surgery have had some cases where neonates with critical congenital heart defects died before operation because of delayed surgery.

Dr G. Sarris (*Athens, Greece*): Two questions, please. One is, in addition to the 70—100 ml blood collected, how much, on average, additional homologous blood did you use for the operation?

And the second question is whether you noticed, with this very early approach to performing these operations, any difference in problems such as the inflammatory response to bypass, tissue edema, and so forth, that are frequently associated with neonatal operations?

Dr Yemets: I think that we need a randomized study, to identify the advantages and disadvantages of autologous umbilical cord blood transfusion in neonatal cardiac surgery.

In answer to you first question, of course we had limitation with volume. It depends how big the fetus is, and approximately 30% of the blood there is in the placenta, in the cord.

In our series for 14 consecutive patients, we got 28 ± 2 ml/kg.

Dr Sarris: That was quite clear from your presentation. The question was how much additional blood, homologous blood, did you end up using? You used 70 to 100 ml on average.

Dr Yemets: From 14 consecutive patients in our study group, 8 patients did not get any additional homologous blood.

Dr Sarris: Any additional blood?

Dr Yemets: Only 6 patients out of 14 required transfusion of homologous blood because of intraoperative bleeding or some difficulties in the ICU postoperatively.

Dr C. Brizard (*Victoria, Australia*): A very nice idea. I understand your concept, and I understand why you may want to operate very early in life. The problem is the selection of the patient and why would you choose one patient rather than the other?

We work with cord blood stem cells. I wonder if you had thought of investigating what is the effect in your patient of the stem cells that have been injected during your recirculation with your priming, taking into account that this blood was circulating in the patient 3 hours or 4 hours before you were operating?

Dr Yemets: I believe that stem cells, hormones, growth factors and other bioactive peptides are very useful for patients undergoing cardiac surgery. And that is why we have just started with our group of researchers to investigate how we can use the blood. Maybe in the future, stem cells will be the best option for congenital malformations in tissue engineering in congenital heart surgery too.

Dr Brizard: But have you investigated or thought of trying to track these stem cells and find where they eventually lodge in your patients?

Dr Yemets: An umbilical cord blood stem cells investigation program has just started at our institution.