Inflammatory marker levels after hybrid treatment of selected congenital heart disease in children

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Abstract

Background: Hybrid treatment of congenital heart disease is indicated in a selected group of borderline patients who do not have clear indications for either surgery or interventional treatment. Hybrid procedures take the best from cardiac surgery and interventional cardiology to reduce patient risk and trauma. Hybrid closure of ventricular septal defect (VSD) and atrial septal defect (ASD) without the use of extracorporeal circulation (ECC) might be less traumatic for patient.

Aim: To compare levels of inflammatory markers and clinical symptoms of systemic inflammatory response syndrome during early postoperative care after conventional cardiac surgery and hybrid treatment.

Methods: Our study group of 36 paediatric cardiac surgical patients in Gdansk included 22 children with perimembranous VSD and/or ASD who underwent cardiac surgery using with ECC and 12 children with muscular VSD and 2 children with ASD who underwent hybrid treatment. We retrospectively evaluated inflammatory markers including C-reactive protein (CRP) level, white blood cell (WBC) count and mean platelet volume (MPV), and clinical variables including total duration of stay in the ward, blood transfusions, prolonged respiratory support, fever, arrhythmias, catecholamine support and wound infections. The Mann-Whitney U test was used to compare CRP levels, WBC count and MPV between the study groups.

Results: Surgical outcomes were good in all children, with no residual leakage. A similar, predictable increase in inflammatory markers (CRP, WBS, MPV) was found in all groups: conventional cardiac surgery with ECC, hybrid treatment without ECC, and hybrid treatment with ECC. Comparison of these groups showed no statistically significant differences between levels of inflammatory markers as well as other clinical variables.

Conclusions: Hybrid septal defect closure induces systemic inflammatory response syndrome activation as measured by CRP level, WBC count, and MPV, which is similar to that observed after cardiac surgery using ECC. Elevations of CRP level, WBC count, and MPV were similar after hybrid treatment with or without ECC. No significant differences were noted between trends of postoperative changes in the levels of inflammatory markers after treatment.

Key words: congenital heart diseases, paediatric cardiac surgery, hybrid procedures, systemic inflammatory response syndrome (SIRS)

INTRODUCTION

Hybrid treatment of congenital heart disease is indicated in a selected group of borderline patients who do not have clear indications for either surgery or interventional treatment. Hybrid procedures combine cardiac surgical and interventional cardiology techniques to develop a strategy to reduce procedural risk and trauma for the benefit of patients [1].
A special group of patients referred for hybrid procedures are small children with muscular ventricular septal defects (mVSD), suboptimal for conventional surgical closure, and patient with atrial septal defects (ASD) with other concomitant chest and great vessel anomalies. The strategy of hybrid closure of septal defects by right ventriculor or right atrial puncture, respectively, usually without the use of extracorporeal circulation (ECC), seems potentially less traumatic for the patient [2], and thus less severe manifestations of the systemic inflammatory response syndrome (SIRS) developing in response to a hybrid procedure may be expected [3].

Based on our experience with hybrid and conventional cardiac surgical closure of septal defects (mVSD and ASD), we attempted to compare selected laboratory and clinical variables used to assess the severity of SIRS in response to procedural trauma depending on the treatment strategy [4]. It seemed particularly interesting to evaluate a subset of children initially referred for a hybrid treatment in whom an unplanned conversion to ECC was necessary during the procedure [5].

The aim of the study was to compare levels of selected inflammatory markers and clinical symptoms of SIRS during early postoperative care after conventional cardiac surgery and hybrid treatment of intracardiac septal defects.

METHODS

Study group

Our study group consisted of 36 consecutive patients treated due to intracardiac septal defects in the Department of Pediatric Cardiac Surgery at the Mikolaj Kopernik Hospital in Gdansk, Poland, including 22 children with perimembraneous VSD and/or ostium secundum ASD (ASD II) who underwent cardiac surgery using with ECC and 12 children with mVSD and 2 children with ASD II who underwent hybrid treatment involving transcervical or transatrial implantation of an occluder from January 01, 2008 to December 31, 2013. Due to incomplete documentation, 4 patients with mVSD were excluded before the analysis. The clinical characteristics of the study group are shown in Table 1.

Prematurity was defined as gestational age at birth < 36 weeks, and intrauterine growth restriction was defined as birth weight < 2.5 kg. Perinatal infection was defined as the diagnosis made in the respective neonatologic unit and leading to antibiotic therapy. Respiratory distress and cyanosis was determined on admission, taking into account acid-base balance findings in the peripheral blood. Low body weight (below the 3rd percentile) was determined based on the current anthropometric measures (body mass and length) at the time of evaluation for cardiac surgery, and in infants below 9 months of age also based on the birth weight. Clinical evidence of a complex genetic syndrome were present in 1 child (no genetic testing), and trisomy 21 was found in 4 patients. DiGeorge syndrome was suspected based on the intraoperative finding of a small thymus combined with calcium abnormalities and susceptibility to respiratory tract infections in 4 patients (subsequently confirmed by genetic testing — a 22q11.2 deletion).

Inclusion and exclusion criteria

To our retrospective case-control study, we included patients with cardiac septal defects who underwent conventional cardiac surgery or hybrid treatment from January 01, 2008 to December 31, 2013 and survived the procedure and the early postoperative period. We aimed to include consecutive patients following cardiac surgery or hybrid treatment who were operated in the same period. Symptoms of a genetic syndrome, despite potential associated additional burden, were not an exclusion criterion. We excluded patients with a microbiologically confirmed infection, treated with antibiotics during 2 weeks before the procedure, and patients with additional extracardiac problems (abdominal anomalies, treatment for systemic disease). We did not include patients with complex cardiac anomalies that required staged treatment.

Study design

The study group of 32 patients was analysed retrospectively. Based on the treatment approach, patients were divided into two major groups: group A included patients with perimembraneous VSD who underwent conventional cardiac surgery using ECC, and group B included patients with mVSD and ASD II who underwent hybrid treatment. Our technique of hybrid treatment of selected cardiac septal defects (mVSD), including patient selection criteria, details of anaesthesia, and early postoperative care in children, were discussed previously [6].

To separate patients treated with or without ECC, the group of children treated electively using ECC also included those in whom hybrid mVSD closure was combined with cardiac surgical repair of a perimembraneous VSD using ECC (group A: 22 patients). Among the 10 children selected for hybrid treatment, we chose those in whom transcervical or transatrial septal defect closure was an isolated primary procedure, intended to be performed without ECC (7 children). An additional group consisted of patients in whom ECC was

Table 1. Clinical characteristics of the study group (n = 32)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* [months]</td>
<td>19.73 (2.7–107.5)</td>
</tr>
<tr>
<td>Body mass* [kg]</td>
<td>6.77 (4.5–23.3)</td>
</tr>
<tr>
<td>Boys/girls</td>
<td>14/18</td>
</tr>
<tr>
<td>Prematurity</td>
<td>6</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>10</td>
</tr>
<tr>
<td>Perinatal infection</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory failure before the procedure</td>
<td>7</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>19</td>
</tr>
<tr>
<td>Low body mass</td>
<td>17</td>
</tr>
<tr>
<td>Genetic syndrome</td>
<td>9</td>
</tr>
</tbody>
</table>

*Mean (range)
initiated during the hybrid procedure, either electively or due to haemodynamic instability (3 children). For this reason, group B (children undergoing hybrid treatment) was additionally divided into two subgroups: B1 — patients who underwent hybrid treatment without ECC, and B2 — patient who required the use of ECC or conversion to ECC during a hybrid procedure.

We retrospectively analysed selected inflammatory markers, evaluated routinely during 24 h before the procedure and at 1, 2, and 3 days after the procedure, including C-reactive protein (CRP) level, white blood cell (WBC) count and mean platelet volume (MPV). In addition, we evaluated the total duration of stay in the ward after the procedure, and the rates of additional events such as the need for packed red blood cell transfusion, prolonged respiratory support, body temperature increases above 37.5°C within 3 days after the procedure, early postoperative arrhythmias (within 3 days after the procedure), catecholamine support past 48 h after the procedure (within 3 days after the procedure), and impaired postoperative wound healing (within 10 days after the procedure). We also analysed the total duration of follow-up after the procedure and total survival time.

In 30 patients treated for VSD and ASD, the same surgical approach of median sternotomy was used. Patients with perimembraneous VSD were operated using the conventional MAQUET ECC system (Maquet, EU) with direct cannulation of both venae cave with metal Pacifico-DLP Medtronic® cannulae (Medtronic, EU) under therapeutic hypothermia. In 2 children selected for hybrid transatrial ASD II closure, a minimally invasive approach by anterolateral parasternal minithoracotomy was used. Perimembraneous septal defects were closed with Dacron-Savage® or Gore-Tex® patches sewn using the same technique of monofilament continuous suture. For cardiac arrest and protection, intracoronary cold cardioplegic solution (PLEGISOL®, Hospira, USA) was administered.

In children undergoing hybrid treatment, we used Amplatzer VSD occluders in 6 patients, Amplatzer Duct Occluder II® in 5 patients, and Amplatzer Septal Occluder in 2 patients (AGA Med. Corp, Minneapolis, USA).

Among patients undergoing hybrid treatment, ECC was used for hybrid closure of mVSD in 2 patients and ASD II in 1 patient after conversion became necessary due to unexpected haemodynamic deterioration (3 patients — group B2). In 7 children, a typical hybrid closure procedure was performed without ECC and additional complications. This group was analysed as uncomplicated hybrid treatment according to the planned strategy (group B2).

Baseline anthropometric measures and clinical characteristics of the study groups are shown in Table 2 (group A — elective treatment using ECC, group B1 — hybrid treatment without ECC, group B2 — hybrid treatment with ECC or conversion).

### Table 2. Baseline anthropometric parameters and clinical characteristics of patients in the study subgroups

<table>
<thead>
<tr>
<th></th>
<th>Surgical repair using ECC (group A, n = 22)</th>
<th>Hybrid procedures without ECC (group B1, n = 7)</th>
<th>Hybrid procedures with ECC and conversion (group B2, n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* [months]</td>
<td>7.4 (3.2–31.9)</td>
<td>12.7 (5.8–36.6)</td>
<td>39.1 (2.7–107.5)</td>
</tr>
<tr>
<td>Body mass [kg]</td>
<td>6.1 (3.5–20)</td>
<td>7.2 (5.8–10)</td>
<td>10.9 (4.5–23.3)</td>
</tr>
<tr>
<td>Boys</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Perinatal infection</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory failure before the procedure</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>14</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low body mass</td>
<td>12</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Genetic syndrome</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Mean (range); ECC — extracorporeal circulation

### Statistical analysis

During the first step of statistical analysis using the Mann-Whitney U test, we confirmed homogeneity of the overall study group of 32 patients, with additional analysis of baseline variables in the study subgroups. CRP level, WBC count, and MPV in subsequent days after the procedure were analysed using the Mann-Whitney U test for small samples. Statistical analyses were performed using the STATISTICA 10 (StatSoft) software.

### RESULTS

All patients in the study group survived the procedure and the early postoperative period (survival rate 100%), and the mean duration of follow-up after the procedure was 18.86 (range 3.9–51.33) months. In all children, a good final treatment effect was obtained, with tight closure of the septal defect confirmed by follow-up echocardiography within 1 month after the surgery. During the evaluated medium-term follow-up
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period, all patients remained alive and were periodically followed up on an outpatient basis. During the follow-up, none of the patients required reoperation or cardiac intervention. Pre- and postoperative variables were collected and then subjected to statistical analysis using our original, archived medical records and documented therapeutic procedures.

No abnormal postoperative wound healing or other local effects were noted in any of the subgroups. Our analysis of empirical antibiotic therapy, arrhythmias and the mean duration of catecholamine support in the study subgroups is summarised in Table 3.

The mean values of selected inflammation markers before the procedure and at 1, 2 and 3 days after the procedure in the overall study group and subgroups are shown in Table 4. Based on the analysis of CRP level, WBC count, and MPV changes in subsequent postoperative days, trends of these parameters are shown graphically in Figures 1, 2 and 3; CRP — C-reactive protein level; ECC — extracorporeal circulation; MPV — mean platelet volume; WBC — white blood cell count.

Similar postoperative increases in the evaluated inflammatory markers (CRP level, WBC count, MPV) were noted in all subgroups, with the most evident rising trend seen for CRP level. No significant differences were seen in regard to the total duration of stay in the ward after the procedure, and the rates of additional events including packed red blood cell transfusion, prolonged respiratory support, increased body temperature, arrhythmias, prolonged catecholamine support, and postoperative wound healing. The total duration of follow-up and total survival time did not differ significantly between groups A, B1, and B2.

We found no significant differences in the evaluated SIRS parameters between children undergoing hybrid treatment without ECC and those undergoing conventional surgical treatment, including those who required conversion.

Differences in inflammation markers between children undergoing hybrid treatment with ECC or requiring conversion to ECC during the hybrid procedure and those undergoing conventional surgical treatment were not significant.

A limitation of our analysis is the small number of patients in the study subgroups, with additional selection of a subset of patients undergoing hybrid treatment with conversion to ECC.

**DISCUSSION**

Every cardiac surgical procedure, particularly if requiring the use of ECC, induces specific SIRS activation seen in the early post-
indicators of a developing infectious process [5]. Based on our own observations, we can confirm that laboratory indicators of SIRS in subsequent postoperative days in children after cardiac surgery show typical, predictable trends.

Hybrid closure of mVSD and ASD is a relatively new technique that has been introduced also in our centre. It may be used as an alternative to conventional cardiac surgery, particularly with an unfavourable location of a defect and in patients with extracardiac comorbidities [9]. Often, hybrid treatment is the only possible surgical option in patients that were previously considered candidates for palliative treatment only. Hybrid procedures combine cardiac surgical and interventional cardiology techniques which may lead to cumulative beneficial effects but may also result in new, atypical complications and adverse reactions [10].

Due to the need for comprehensive clinical evaluation of the hybrid approach, analysis should include not only the final treatment outcomes but also systemic inflammatory response to the treatment strategy, surgical access route, and the foreign material implanted by direct puncture of the cardiac wall. The available literature includes papers that document the development and increasing popularity of hybrid techniques, but no studies on hybrid treatment of cardiac septal defects in children have been published. The aim of our study was to evaluate selected inflammatory markers in the early postoperative period in patients undergoing hybrid treatment which were compared with the same parameters in children after a classic, most frequently performed surgical closure of the most common defect in this population, i.e. perimembranous VSD. We retrospectively evaluated routine laboratory and clinical variables which are a part of everyday clinical practice in our centre.

Figure 1. Changes in C-reactive protein level in subsequent postoperative days (mean; standard deviation) in the study subgroups; Group A — surgical repair using extracorporeal circulation (ECC); group B1 — hybrid procedures without ECC; group B2 — hybrid procedures with ECC and conversion; G — Group

Figure 2. Changes in white blood cell count in subsequent postoperative days (mean; standard deviation) in the study subgroups; Group A — surgical repair using extracorporeal circulation (ECC); group B1 — hybrid procedures without ECC; group B2 — hybrid procedures with ECC and conversion; G — Group

Figure 3. Changes in mean platelet volume in subsequent postoperative days (mean; standard deviation) in the study subgroups; Group A — surgical repair using extracorporeal circulation (ECC); group B1 — hybrid procedures without ECC; group B2 — hybrid procedures with ECC and conversion; G — Group
Our analysis focused on the novel hybrid treatment strategy targeted at patients in whom the morphology of a cardiac defect was previously often considered not amenable to surgical repair. When evaluating inflammatory markers, however, one should also consider additional burdens in "suboptimal" patients which may affect SIRS activation in patients undergoing hybrid treatment [11, 12]. Also postoperative care after a hybrid procedure, as compared to that in children operated using ECC, requires some modifications to the treatment strategy, investigations, and drug therapy due to the need for prolonged administration of anticoagulant and antiplatelet drugs which potentially modify SIRS in children [13].

Based on the analysis of preoperative characteristics, major additional problems in our patients undergoing hybrid treatment included a muscular location of the VSD, structural chest defects, and mediastinal vessel anomalies. Regarding overall clinical status, the hybrid patients were characterised by similar comorbidities compared to patients undergoing conventional treatment (Table 1).

Levels of selected SIRS parameters in children undergoing hybrid or conventional treatment did not differ significantly which may indicate that hybrid treatment is only apparently less invasive for patients. We also did not find a significant increase in SIRS parameters in those patients who required conversion from a hybrid procedure to ECC. Similarly, the severity of selected laboratory and clinical SIRS parameters was similar in patients undergoing hybrid treatment without ECC or with conversion to ECC (Figs. 1–3).

**Limitations of the study**

Limitations of our study included the small number of patients undergoing hybrid treatment, reflecting the demographic characteristics of congenital heart disease and concomitant defects, and retrospective analysis of the data. In addition, to limit the confounding effect of additional factors, we included patients in whom all procedures were performed by the same team, during the same period and in the same paediatric cardiac surgical centre. We also did not randomise patients in our study group to various treatment approaches. Clearly, analyses of SIRS parameters should be continued with further development of hybrid treatment of cardiac defects in children.

**CONCLUSIONS**

Hybrid septal defect closure induces SIRS activation as measured by selected parameters (CRP level, WBC count, MPV) which is similar to that observed after cardiac surgery using ECC.

The use of ECC during hybrid procedures does not result in more severe SIRS activation as measured by selected parameters (CRP level, WBC count, MPV).

Trends of early postoperative changes in the levels of selected SIRS indicators did not differ between patients after hybrid procedures and conventional cardiac surgery.

**Conflict of interest:** none declared

**References**


Wykładniki odczynu zapalnego w hybrydowym leczeniu wybranych wrodzonych wad serca u dzieci

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Streszczenie

Wstęp: Terapia hybrydowa wrodzonych wad serca jest dedykowana wybranej grupie pacjentów (tzw. granicznych), którzy nie spełniają jednoznacznych kryteriów kwalifikacji do leczenia kardiochirurgicznego i interwencyjnego. Procedury hybrydowe są oparte na zasadzie wzajemnego wsparcia kardiochirurgii i kardiologii interwencyjnej, którego wspólnym celem jest wypracowanie strategii zapewniającej korzyść pacjentom, z ograniczeniem ryzyka i towarzyszącego urazu. Strategia hybrydowego zamykania ubytków przegród serca implantem z nakłucia odpowiednio prawej komory i prawego przedsionka, zazwyczaj bez zastosowania krążenia pozaustrojowego (ECC), wydaje się potencjalnie mniej urazowa dla chorego.

Cel: Celem pracy było porównanie wybranych wykładników laboratoryjnych i parametrów klinicznych zespołu systemowej odpowiedzi zapalnej u dzieci we wczesnym okresie po typowym kardiochirurgicznym i hybrydowym zamknięciu ubytków przegród serca.

Metody: Grupę badawczą stanowiło 36 kolejnych pacjentów leczonych na Oddziale Kardiochirurgii Dziecięcej Szpitala im. Mikołaja Kopernika w Gdańsku z powodu ubytków przegród serca: 22 pacjentów z okołobłoniastym ubytkiem międzkomorową (VSD) i/lub ubytkiem przegrody międzyprzedsionkowej typu secundum (ASD II) leczonych kardiochirurgicznie z zastosowaniem ECC, 12 pacjentów z mięśniowym VSD i 2 dzieci z ASD II leczonych techemiką hybrydową z przekomorową i przeprzedsionkową implantacją zestawu zamykającego. Retrospektywnej analizie poddano wybrane wykładniki odczynu zapalnego, oznaczane rutynowo w okresie do 24 h przed zabiegiem oraz w 1., 2. i 3. dobie pooperacyjnej: osoczowe stężenie białka C-reaktywnego (CRP), zawartość leukocytów (WBC) w morfologii krwi obwodowej i średnią objętość płytek krwi (MPV). Dodatkowo oceniano całkowity czas pobytu na oddziale po zabiegu oraz częstość zdarzeń dodatkowych, takich jak konieczność przetoczenia preparatów krwiochodnych (koncentrat krwinek czerwonych — KKCz), przedłużony czas mechanicznej wentylacji, wzrosty temperatury ciała powyżej 37,5°C występujące do 3. doby po zabiegu, obecność zaburzeń rytmu we wczesnym okresie pooperacyjnym (do 3. doby po zabiegu), leczenie aminami katecholowymi w okresie powyżej 48 h po zabiegu (do 3. doby po zabiegu) oraz miejscowe odczyny gojenia ran (do 10 dni po zabiegu). Analizę wartości CRP, WBC i MPV w kolejnych wybranych dobach po zabiegu wykonano z zastosowaniem testu U-Manna Whitneya dla małych grup.

Wyniki: U wszystkich dzieci uzyskano końcowy dobry efekt leczenia ze szczelnym zamknięciem ubytków przegród serca, potwierdzony w kontrolnych badaniach echokardiograficznych w okresie miesiąca od operacji. U wszystkich pacjentów zaobserwowano porównywalny wzrost analizowanych wykładników uogólnionej reakcji zapalnej po zabiegu (CRP, WBC, MPV), o najbardziej wyraźnym trendzie wzrostowym w przypadku CRP. Nie stwierdzono statystycznie znamiennej różnicy analizowanych wskaźników zespołu systemowej odpowiedzi zapalnej (SIRS) w grupie dzieci leczonych hybrydowo bez ECC i operowanych klasycznie, w tym także u pacjentów z konwersją. Różnica w poziomie wskaźników odpowiedzi zapalnej u osób leczonych hybrydowo z zastosowaniem ECC oraz u dzieci wymagających konwersji do ECC w trakcie procedury hybrydowej, w porównaniu z operowanymi klasycznym, jest nieistotna. Nie stwierdzono statystycznie znamiennych różnic w całkowitym czasie pobytu na oddziale po zabiegu oraz częstości zdarzeń dodatkowych — przetoczenia KKCz, przedłużony
czas mechanicznej wentylacji, podwyższone temperatura ciała, zaburzenia rytmu serca, przedłużony czas terapii aminami katecholowymi oraz miejscowe odczyny gojenia ran.

Wnioski: Procedura hybrydowego zamknięcia ubytków przegród serca powoduje aktywację SIRS ocenianej na podstawie wybranych parametrów (CRP, WBC, MPV) o nasileniu zbliżonym do obserwowanej u pacjentów leczonych kardiochirurgicznie z zastosowaniem ECC. Wykorzystanie ECC w trakcie procedury hybrydowej nie powoduje zwiększenia objawów ubocznych w postaci nasilenia SIRS ocenianej na podstawie wybranych parametrów (CRP, WBC, MPV). Trendy zmian wybranych wskaźników SIRS we wczesnym okresie pooperacyjnym u pacjentów po zabiegu hybrydowym i klasycznym kardiochirurgicznym nie różnią się.

Słowa kluczowe: wrodzone wady serca, kardiochirurgia dziecięca, leczenie hybrydowe, zespół systemowej odpowiedzi zapalnej (SIRS)

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