

Single Dose Corticosteroid Therapy After Surgical Repair of Fallot's Tetralogy; A Randomized Controlled Clinical Trial

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Background: Inflammatory reaction can produce several complications after cardiac surgery. Many attempts have been made to reduce these complications; perioperative corticosteroid therapy is one of the simplest methods.

Objectives: We conducted a randomized study to evaluate the efficacy of single dose methylprednisolone, prescribed after surgery, for reducing the complications. Repair of Tetralogy of Fallot was chosen as a homogenous large group for the study.

Patients and Methods: One hundred children who underwent total repair of Tetralogy of Fallot were enrolled in this study. After the surgery, all patients were transferred to pediatric ICU and were randomized (in a double-blind fashion) in 2 groups (A and B); a single dose of methylprednisolone (30 mg/kg of body weight) was injected to participants of group "A" just at the time of ICU entrance. Group "B" received no drug. Then, clinical outcomes and laboratory data were compared between the two groups.

Results: The only significant differences were lower incidence of bacteremia and higher incidence of hyperglycemia in the group who were used methylprednisolone.

Conclusions: Using a single postsurgical dose of methylprednisolone does not significantly alter the clinical outcome after repairing Tetralogy of Fallot.

Keywords: Heart Disease; Congenital; Tetralogy of Fallot; Corticosteroid; Cardiac Surgery

1. Background

Systemic inflammation is a natural response to cardiopulmonary bypass (CPB)(1-3). Inflammatory mediators can cause severe complications such as low cardiac output syndrome (LCOS) and profound vasodilatory hypotension (4). Minor complications like postpericardiotomy syndrome are also known as inflammatory reactions(5). Inflammatory response to CPB is more severe in younger patients. Several attempts have been made to regulate this inflammatory response. Using modified ultrafiltration (MUF) and administration of perioperative corticosteroids are the commonly accepted methods (6). Inflammatory process continues after the surgery and it lasts as tracheal tube left in place as well as the tubes for thoracic and mediastinal drainage.

2. Objectives

Based on the existing literature, we attempted to evaluate the benefit of an additional single dose of corticosteroid at the entrance to Intensive Care Unit (ICU) for children underwent cardiac surgery for repairing Tetralogy of Fallot (TOF). TOF was chosen as a relatively common congenital heart disease. Therefore, a large sample of a

homogenous entity with similar surgical method could facilitate the evaluation for the drug efficacy.

3. Patients and Methods

3.1. Participants

One hundred children (aged 0-15 years) who underwent total repair of Fallot's tetralogy in Rajaie Cardiovascular Medical and Research Center (The main tertiary center of pediatric cardiology and cardiac surgery) were enrolled. The study was approved by the Ethics Committee of the center. A consent form was taken from the parents. In all cases, the general anesthesia was induced with fentanyl (10-15 mg/kg), sodium thiopental (3-5 mg/kg) and pancuroniumbromide (0.15 mg/kg). The anesthesia was continued with sevoflurane inhalation and bullous doses of fentanyl. A single dose of methylprednisolone (30 mg/kg) had been used before cardiopulmonary bypass (CPB). After the surgery, all patients were transferred to pediatric ICU.

3.2. Intervention

After ICU entrance, the patients were randomized into 2 groups (A and B); a single dose of methylprednisolone

(30 mg/kg of body weight) was injected for group “A” just at the time of ICU entrance. Group “B” received no drug. For all patients, dobutamine (0.01 mg/kg/min) plus milrinone (0.1 mg/kg/min) was started just after the surgery. All patients received cefazolin (100 mg/kg/day) in 3 divided doses for 3 days. Inotropes and antibiotics were adjusted based on the individual needs of the patients.

3.3. Outcome

All patients were monitored in the same ICU and managed by one pediatric cardiologist. For all participants, heart rate, arterial pressure, and blood oxygen saturation were continuously monitored. Complete blood count (CBC), including red blood cell (RBC), white blood cell (WBC) and platelet (PLT) count, erythrocyte sedimentation rate, C reactive protein, blood glucose, sodium, potassium, calcium, magnesium, prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) were checked for all participant at the onset of ICU admission and then daily until discharge. A blood sample was also sent for bacteriology and culture at the onset of ICU admission and the day after. All patients received mechanical ventilation support with synchronized intermittent mandatory ventilation. Then, any abnormal laboratory data were compared between the two groups.

3.4. Randomization

We used balance block randomization. The Random Allocation Software version 1.0 (Isfahan University of Medical Sciences, Isfahan, Iran) was used for randomization.

3.5. Concealment

Because of the special milky appearance of methylprednisolone, a placebo could not be prepared. Three nurses were in charge of the drug prescription, they recorded their data in confidential forms marked by the patients’ codes. Medical management was done by a pediatric cardiologist who was blind to the study results. All laboratory data were reported by a web-based computerized system and the laboratory personnel did not know about the study.

3.6. Statistical Analysis

Data were reported as mean \pm standard deviation (SD) for interval and count (%) for categorical variables. We

used the chi-square test for categorical variables and Student t test for numerical variables and Mann-Whitney U test for Analysis of 2-Between-Group Data with a Quantitative Response Variables. Multivariate logistic regression models were used to investigate adjusted associations between variables. P value $<$ 0.05 is considered as statistically significant result. SPSS 15 for Windows (SPSS Inc. Chicago, Illinois) was used for statistical analysis.

4. Results

One hundred patients (46 girls) with mean age of 39 ± 22.3 months were enrolled in the study. Number of the patients, gender distribution, age range and the body weights of the two groups were not significantly different (Table 1). The number of patients who had undergone palliative procedure, namely modified Blalock-Taussig shunt was also not significantly different between the two groups. Seventy patients experienced at least one clinical or paraclinical unwanted situation. The total number of these adverse events was not statistically different between the two groups (Table 2). When the adverse events were compared one by one, bacteremia was significantly more common in drug users and hyperglycemia was significantly more common in the control group. All 6 cases of bacteremia were seen in corticosteroid non-user group. In 4 cases the bacterium was *Staphylococcus aureus* and in 2 *Pseudomonas aeruginosa*. Some other differences were seen, but they were not statistically significant. Low cardiac output syndrome was mostly seen in corticosteroid non-users. Low cardiac output syndrome was defined when decrease in cardiac output manifested with hypotension, respiratory insufficiency, oliguria, enteral feeding intolerance and increased serum lactate. Tachyarrhythmias were slightly more frequent in corticosteroid non-user group. The most frequent arrhythmia was junctional ectopic tachycardia, which was observed in 14 cases. Frequent ventricular ectopies and ventricular tachycardia were seen in two patients; in one of them junctional ectopic tachycardia was also seen. One case experienced atrial tachycardia. All arrhythmias were medically controlled. Outcomes of the two groups are compared in Figure 1. Multivariate analysis with adjusted confounders showed no significant differences in adverse outcomes between the patients received corticosteroid and the control group (Table 3).

Table 1. Comparison of Demographics Between Corticosteroid Users and the Control Group ^a

Demographics	Group A, Corticosteroid Users	Group B, Corticosteroid Non-Users	P Value
Gender			1.000
Female	23	23	
Male	27	27	
Age, mon	39.8 \pm 24.7	38.2 \pm 19.8	0.917
Body weight, Kg	12.9 \pm 4.3	12.7 \pm 3.7	0.992
Previous shunt operation	16 (32)	17 (34)	0.832
Modified Ultra-Filtration	10 (20)	9 (18)	0.799
PUMP time for surgery	106.2 \pm 27.8	111.12 \pm 31.8	0.505

^a Data were described as Mean \pm SD or No. (%).

Table 2. Comparison of Outcome Between Corticosteroid Users and the Control Group ^a

	Group A, Corticosteroid Users	Group B, Corticosteroid Non-Users	P Value
Clinical situations			
Fever, rectal temperature > 37.6 for infants and > 38 for children	9 (18)	15 (30)	0.160
Abnormal bleeding, >10 mL/kg	13 (26)	19 (38)	0.198
Oliguria, < 0.5 mL/kg/h	3 (6)	1 (2)	0.307
Renal failure, creatinine clearance <10 mL/min	2 (4)	0	0.153
Sepsis, systemic inflammatory response resulting from a suspected or proven infection	2 (4)	4 (8)	0.400
Duration of mechanical ventilation, h	18.2 ± 11.04	25.5 ± 31.3	0.688
Low cardiac output syndrome	1 (2)	3 (6)	0.307
ICU stay, d	3.02 ± 1.9	3.22 ± 2.1	0.565
Arrhythmia			
Tachyarrhythmia	6 (12)	10 (20)	0.275
Complete heart block	1 (2)	1 (2)	1.000
Abnormal Hematology			
Anemia, hemoglobin level of less than the 5th percentile for age	1 (2)	0	0.315
Thrombocytopenia, PLT count <150000/mm ³	3 (6)	1 (2)	0.307
Coagulopathy, (PT > 12 s, INR > 1, or PTT > 35 s)	8 (16)	6 (12)	0.564
Leukocytosis, WBC count > 2 SD for age			
Polynucleosis, Neutrophil count > 50% of total WBC count	0	1 (2)	0.315
Bacteremia, positive blood culture for a specific microorganism	0	6 (12)	0.012
Electrolyte imbalances			
Hyperglycemia, serum Glucose > 150 mg/dL	31 (62)	21 (42)	0.045
Hypocalcaemia, total serum calcium < 8.5 mg/dL	6 (12)	4 (8)	0.505
Hypokalemia, serum potassium < 3.5 meq/L	1 (2)	3 (6)	0.366
Hypomagnesaemia, serum Magnesium < 1.5 mg/dL	0	1 (2)	0.315
Adverse outcome ^b			
	37 (74)	33 (66)	0.383

^a Data were described as Mean ± SD or No. (%).

^b The number of patients who experienced at least one of the abnormal clinical or paraclinical findings.

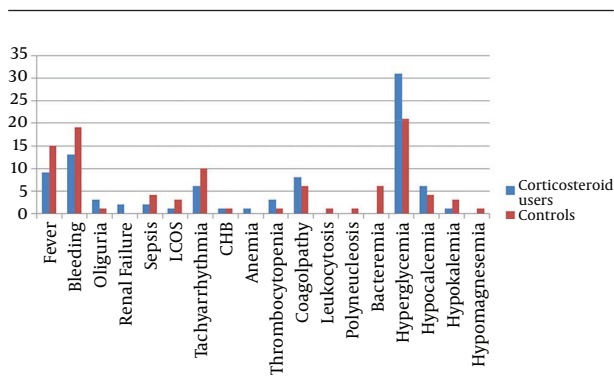


Figure 1. Comparison of the Unwanted Findings Between the Corticosteroid Users and the Control Group

Table 3. Multivariate Analysis for Adjusting Confounders and Assessment of the Corticosteroid Effect on Adverse Outcomes

Variable	Coefficient	P Value	Odds Ratio	C.I. 95.0% for Odds Ratio	
Group	0.384	0.402	1.468	0.590	3.601
Age	0.044	0.134	1.045	0.987	1.107
Gender	0.311	0.511	1.365	0.539	3.457
Body weight	-0.147	0.305	0.864	0.653	1.143
PUMP time	-0.004	0.652	0.996	0.981	1.012
Modified Ultra-Filtration	0.322	0.600	1.379	0.414	4.597
Previous shunt operation	0.738	0.214	2.092	0.654	6.694

5. Discussion

Although corticosteroids are widely used in perioperative period for children undergoing cardiac surgeries (7), there was serious controversies about their clinical benefit. However, effectiveness of corticosteroids has been shown in inotrope refractory neonates with low cardiac output syndrome after cardiac surgery (8). Clarizia et al. reported that intraoperative steroid administration can improve postoperative outcome in children undergoing high risk cardiac surgeries (9). Crow et al. evaluated dexamethasone levels in infants who had received the drug before cardiopulmonary bypass (10). Methylprednisolone significantly lowers the plasma concentrations of interleukins 6 and 8 and increases the level of interleukin 10, all in favor of decreasing inflammatory response. However, a significant clinical benefit was not observed by many authors (11). While intraoperative corticosteroid is used in many centers for pediatric cardiac surgeries, Graham et al. showed that an additional preoperative dose does not enhance the clinical outcome and even may exacerbate perioperative renal dysfunction (4). In a large multicenter study, Pasquali et al. could not find a significant benefit for perioperative corticosteroid in pediatric congenital heart surgeries (12). Mastropietro et al. reported that greater cumulative doses of corticosteroid in the perioperative period were associated with higher rate of postoperative infections (13). Verweij et al. and Green et al. showed that the effect of hydrocortisone in post-op low cardiac output does not directly depend on the adrenal sufficiency and the plasma cortisol levels (14, 15).

Our study focused on the clinical outcome. We also evaluated the common paraclinical disturbances that can potentially alter the patient's condition. We found few benefits for using the additional corticosteroid dose at ICU entrance. One of the significant different outcomes between two groups was hyperglycemia. It was more common in patients who received additional dose of the corticosteroid. Our multivariate analysis showed no significant difference in outcome between hyperglycemic and non-hyperglycemic patients. However, Alaei et al. found higher mortality and morbidity in children with severe hyperglycemia after cardiac surgery (16). Bacteremia without clinical findings of sepsis syndrome was less common in our patients who received additional doses of the corticosteroid. The multivariate analysis again showed no significant difference in clinical outcome; however, it is likely for a child with bacteremia to exhibit aseptic complications, especially in immunocompromised conditions. It was shown that different anesthetic regimens may affect the outcome in TOF operation (17), although the regimen was similar in our cases. It is not guaranteed that study with other kinds of anesthetic drugs would yield the similar results.

One serious limitation for our study was the small number of patients who were used modified ultrafiltration; a

method that can seriously affect the outcome. The other limitation was the lack of long-term follow-up. In pediatric patients undergoing surgical repair for Fallot's tetralogy, a postoperative additional dose of methylprednisolone does not significantly improve the clinical outcome.

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Authors' Contributions

Mohammad Dalili developed study concept and design and drafted the manuscript. Ahmad Vesal contributed to the data acquisition. Avisa Tabib supervised the study and did critical revision of the manuscript for important intellectual content. Leila Khani-Tafti contributed to data analysis and interpretation. Shirin Hosseini contributed to statistical analysis. Ziae Totonchi had critical revision of the manuscript for important intellectual content.

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