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Our Experience in Anesthesia Management in Operations for Congenital Pediatric Cardiac Diseases

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Abstract

Objectives: Surgical treatment of congenital heart diseases (CHDs) is performed in many centers today. We aimed to review the pediatric cardiac surgery cases performed in our center and contribute to the literature with our data.

Materials and Methods: In this study, 92 patients who underwent palliative and complete correction for CHDs between March 2016 and March 2019 were evaluated retrospectively.

Results: A total of 92 patients, 37 (40.2%) females and 55 (59.8%) males, were retrospectively examined for this study. The number of patients under and over 1 year of age were 74 (80.44%) and 18 (19.56%), respectively. The most common congenital cardiac anomaly was ventricular septal defect (28.26%). All surgical procedures were classified according to complexity based on the Aristotle Basic Scoring system to find that 45 patients underwent Level 2, 23 patients underwent Level 4, 13 patients underwent Level

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Abstract

1 and 11 patients underwent Level 3 surgeries. Among our patients, 78.2% and 21.8% were operated with and without cardiopulmonary bypass (CPB), respectively. There were no significant differences between patient age groups in terms of operation time, CPB time and cross-clamp time, but the difference between the same parameters according to complexity level was statistically significant ($p<0.05$). As the complexity level increased, the durations were prolonged. Postoperative complications were found to be increased under 1 year of age and at high complexity levels (Levels 3 and 4). Similarly, it was found that mortality significantly increased under 1 year of age and with high complexity levels ($p<0.05$).

Conclusion: In surgical procedures for CHDs, complexity levels according to Aristotle Basic Scoring System and the patient's age are effective factors on outcome. We believe that it is necessary to share the experiences of the centers working in this field and to conduct randomized studies with larger sample sizes.

Keywords: Congenital heart disease, anesthesia management, pediatric cardiac surgery

Introduction

In the historical process, the heart has been the last organ to be surgical. In 1896, Ludwig Rehn was the first person to save a patient's life with a surgical procedure performed on the myocardium in heart injury(1). The successful treatment of patent ductus arteriosus by Robert Gross in 1938 is considered the beginning of both congenital and modern cardiac surgery. Aortic coarctation (AC) repair performed by Crawhord and systemic pulmonary shunt operation performed by Alfred Blalock to a patient with Tetralogy of Fallot are important milestones in congenital heart surgery. Successful results of atrial septal defect (ASD) repair performed in 1952 under hypothermic conditions and pulmonary valve resection in 1953 also contributed to the development of this field. In 1953, the use of a heart-lung pump revolutionized adult and congenital cardiac surgery(2).

Pediatric cardiac surgeries for congenital diseases are currently being performed in an increasing number of centers and significant improvements have been achieved. Important factors in this development include advances in pediatric cardiopulmonary bypass (CPB) technology and imaging systems, as well as increased knowledge and experience in surgical techniques, anesthesia and intensive care.

We aimed to contribute to the literature by retrospectively investigating the pediatric cardiac surgery cases performed in our center and sharing our results.

Materials and Methods

This study was conducted retrospectively in pediatric patients who underwent palliative and full corrective surgery for Congenital heart diseases (CHDs) in our hospital between March 2016 and March 2019. Approval of the local ethics committee was obtained in accordance with the Helsinki Declaration (Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University Ethical Committee of Clinical Research 2011-KAEK-25 2019/06-14). Data of the patients were obtained from patient files, anesthesia follow-up slips, and hospital registry. Demographic data, diagnosis, surgery, intraoperative and postoperative data, morbidity, and mortality factors were evaluated and recorded. Patients who were operated for CHD at the age of 18 years and under were included in the study, while patients over 18 years of age and those whose data were not available were excluded.

Preoperative Routine Procedure

After the diagnosis of a CHD, patients who were decided to undergo cardiac operation were evaluated in a pre-anesthesia examination. Physical examinations were performed after taking history and laboratory tests were examined. After informing the relatives of the patient, informed consent forms were obtained. Immediately prior to surgery, 5-10 mg/kg ketamine (KetalarR PhizerPharmaceuticals Ltd., Turkey) and 0.02 mg/kg atropine (Atropine Sulfate, Galen Pharmaceuticals, Turkey) were administered intramuscularly to patients who had no intravenous cannulas. 0.5-1 mg/kg ketamine was administered intravenously in patients with intravenous vascular access. After premedication, patients were immediately taken to the operation room for close follow-up.

Intraoperative Period Routine Procedure

The patient was taken to the operating table in the previously heated room, and electrocardiographic and oxygen saturation probes were placed for monitorization. Invasive arterial monitorization was performed via the radial or femoral arteries, as needed. Medications administered before oral endotracheal intubation included 0.1 mg/kg midazolam (Zolamid, Vem Pharmaceuticals, Turkey), 1 mg/kg rocuronium (Myokron, Vem Pharmaceuticals, Turkey), and 5 mcg/kg fentanyl (Vem Pharmaceuticals, Turkey). Anesthesia was maintained with 0.1-0.3 mg/kg rocuronium, 0.02 mg/kg midazolam and 0.05-2 mcg/kg fentanyl. Sevoflurane (Sevorane, Abbott, USA), an inhalation anesthetic agent, was also administered with a minimum alveolar concentration of 0.5 to 2 according to the patient's hemodynamics. After intubation, ventilation was provided with a tidal volume of 8-10 mL/kg, and respiratory rate was adjusted to keep $PaCO_2$ value between 30 and 35 mmHg. Following the induction of anesthesia, central vein catheterization was performed with a double-lumen catheter, preferably from the right internal jugular vein. A heat probe and urine catheter were placed. Central venous pressure (CVP) and urine output were monitored from the central vein and the foley catheter, respectively. Intraoperative hemodynamic findings and drugs were recorded in the anesthesia follow-up charts and additionally on the perfusionist follow-up slips during the CPB period. Before the cannulation of patients performed with the standard method, 3 mg/kg heparin (Koparin vial, Koçak Pharmaceuticals, Turkey) was administered intravenously. Anticoagulation was assessed by activated coagulation time (ACT) prior to cannulation and extracorporeal circulation. The ACT value was expected to increase above 450 seconds for extracorporeal circulation. 1 mg/kg additional heparin was administered in case of low ACT values. Arterial blood gas monitoring was performed simultaneously with ACT monitoring and additionally when needed.

After the cannulation was completed, CPB was started. Mechanical ventilation was terminated before cross-clamping. Cardiac arrest was achieved with Del-Nido cardioplegia solution. Hypothermia was maintained during CPB. Upon the completion of the cardiac surgical procedure, intracardiac air and the cross-clamp were removed. The patient was started on ventilation. In patients with ventricular fibrillation, defibrillation was performed to start the heart. After achieving normothermia and normal filling pressures, CPB was terminated. Patients who were hemodynamically unstable due to ventricular dysfunction were supported with inotropic agents and ventricular support equipment. Following venous decannulation, 3-3.5 mg/kg protamine sulfate (Promin, Vem Pharmaceuticals, Turkey) was administered to neutralize the effects of heparin. Target ACT values following decannulation were between 90 and 140 seconds. Blood and blood products were transfused to keep the hematocrit level close to 30%.

Surgical intervention was performed by sternotomy, and right or left thoracotomy in patients who would be operated without CPB. After the completion of the surgical procedure, hemostasis was achieved in both groups. Patients were closed anatomically in accordance with sternotomy or thoracotomy procedures, not extubated and transported to the intensive care unit with a transport ventilator while being monitored.

Postoperative Routine Procedure

Electrocardiography, oxygen saturation, invasive artery, and CVP were monitored. Alert, conscious patients with spontaneous respiration and adequate muscle strength and airway reflexes were extubated during follow-up.

Before extubation, patients were made sure to be hemodynamically stable and to have blood gas values within normal limits.

Statistical Analysis

SPSS 24.0 (Statistical Inc. version Chicago, IL, USA) was used for statistical analysis of the data. Demographic data and findings related to congenital anomalies were presented separately for patients over and under 1 year of age. Complexity levels were compared by the chi-square test according to patient age groups. The Mann-Whitney U and Kruskal-Wallis tests were utilized to compare the continuous variables among intraoperative and postoperative data with respect to age groups and complexity levels, and the chi-square test was used for the comparison of categoric variables. Descriptive statistics were presented as mean ± standard deviation for continuous data and number of patients (%) for categoric data. Results were considered statistically significant when p was <0.05 within a 95% confidence interval.

Results

A total of 92 patients, 37 (40.2%) females and 55 (59.8%) males, were examined in this study. Seventy-four patients (80.44%) were under and 18 patients (19.565) were over 1 year of age. Among all, 46.7% of patients were newborns. The lowest-weighing patient was 1240 grams. The demographic data of the patients are summarized in Table 1.

The examination of congenital cardiac anomalies of the patients revealed that anomalies were either isolated or coexisted with multiple anomalies. The most common anomaly was ventricular septal defect (VSD) with a rate of 28.26% in all patients. Other most common anomalies were ASD (16.3%), AC (11.96%), hypoplastic left heart (11.96%) and transposition of great arteries (10.87%). Pulmonary artery atresia (four cases) and ASD (three cases) were the most common anomalies concomitant with VSD. The most common anomalies among patients younger and older than 1 year of age were VSD with a rate of 32.43% and ASD with a rate of 50%, respectively (Table 2).

The surgical procedures were classified according to complexity based on the Aristotle Basic Scoring system to find that 45 patients underwent Level 2, 23 patients underwent Level 4, 13 patients underwent Level 1 and 11 patients underwent Level 3 surgeries. Complexity levels of 1 and 3 were significantly more frequent in patients older than 1 year, and all patients who underwent level 4 surgical procedures were under 1 year of age (Table 3).

The ratio of patients operated with and without CPB were 78.2% and 21.8%, respectively. There were no significant differences between patient age groups in terms of operation, CPB and cross-clamp times (p=0.953, 0.360, and 0.936 respectively) (Table 4). Although the frequency of hemofiltration use was higher in the under-1-year-old group, this difference was not statistically significant (0.062) (Table 4). All patients who received Extracorporeal Membrane Oxygenation (ECMO) support were under 1 year of age (Table 4). Bleeding and infection were the most common complications

Table 1. Demographic data

Groups	Gender (F/M)		Age (day/years)	Weight (kg)
	n	%	Mean ± SD	Mean ± SD
Patients under 1 year of age	29/45	39.2/60.8	67.55±84.84 days	3.58±1.33
Patients over 1 year of age	8/10	44.4/55.6	4.75±3.05 years	15.94±7.56
Total	37/55	40.2/59.8	-	6.00±6.03

n: Number of patients, SD: Standard deviation, kg: Kilograms, F: Female, M: Male in all patients. Neurological complications occurred because of cerebral hemorrhage due to coagulopathy after ECMO and sepsis in all patients. All patients with renal insufficiency were under 1 year of age (Table 4). Mortality was observed in the first 10 days in 20.03% of the patients under 1 year of age, and 5.6% of the patients over 1 year of age (Table 4).

Analysis of intraoperative and postoperative data showed that operation time, CPB time, and cross-clamp time were found to differ significantly according to complexity levels.

According to the paired comparison results, it was found that the duration of operation and CPB were longer in Level 3 and 4 surgeries than those of Levels 1 and 2. A significant relationship was found between the use of hemofiltration, ECMO support, bleeding, infection, renal failure, and mortality in the first 10 days and complexity levels (Table 5).

Mortality rate in the first 10 days was 17.39% among all our patients. Ventricular insufficiency (50%), renal insufficiency (25%), hemorrhage (12.5%) and sepsis (12.5%) were the most common causes of mortality.

Table 2. Distribution of congenital cardiac anomalies

	Patients under 1 year of age		Patients over 1 year of age		Total	
	n	%	n	%	n	%
VSD	24	32.43	2	11.11	26	28.26
ASD	6	8.11	9	50	15	16.3
Aortic coarctation	12	16.22	-	-	12	13.04
Hypoplastic left heart	11	14.86	-	-	11	11.96
Transposition of great arteries	10	13.51	-	-	10	10.87
AV channel defects	6	8.11	2	11.11	8	8.7
PDA	8	10.81	-	-	8	8.7
Tetralogy of fallout	3	4.05	4	22.22	7	7.61
Pulmonary artery atresia	6	8.11	-	-	6	6.52
Tricuspid atresia	3	4.05	2	11.11	5	5.43
Double outlet right ventricle	4	5.41	-	-		4.35
Hypoplasia of the right ventricle	3	4.05	2	11.11	5	5.43
Pulmonary stenosis	2	2.7	4	22.22	6	6.52
TAPVR	2	2.7	-	-	2	2.17
Truncus arteriosus	1	1.35	-	-	1	1.09
Dextrocardia	1	1.35	-	-	1	1.09

n: Number of patients, VSD: Ventricular septal defect, ASD: Atrial septal defect, AV: Atrioventricular, PDA: Patent ductus arteriosus, TAPVR: Total anomalous pulmonary venous return

Table 3. Distribution of surgical procedure complexity

	Cases under 1 year of age		Cases over 1 year of age		p
	n	%	n	%	
Complexity Level 1	7	9.46	6	33.33	<0.001
Complexity Level 2	38	51.35	7	38.88	0.206
Complexity Level 3	6	8.11	5	27.77	<0.001
Complexity Level 4	23	31.08	-	-	-

n: Number of patients, p<0,05: Significant

Discussion

CHD is a congenital structural and functional disorder of the cardiovascular system with an incidence of 0.6-1% in all live births[2,3]. The progressive development of surgical techniques and intensive care facilities in these patients has led to more successful results. The number of pediatric patients undergoing cardiac surgery is increasing day by day, which exposes more anesthesiologists to such cases. In pediatric cardiac surgical anesthesia, physiopathology, diagnosis and treatment of congenital heart malformations and principles of pediatric and cardiac anesthesia should be known. Although adult and pediatric cardiovascular anesthesia have similar aspects, there are some crucial differences, which include the maturation process of newborn and infant organs, physiopathology in CHDs, variations in surgical repair and CPB management[4].

Table 4. Comparison of intraoperative and postoperative data with respect to age groups

	Cases under 1 years of age		Cases over 1 years of age		p
	Mean ± SD		Mean ± SD		
Operation duration (min)	250.81±111.35		247.33±89.42		0.953
CPB Duration (min)	148.78±61.51		132.24±80.87		0.360
CC Duration (min)	86.78±50.67		88.00±58.63		0.936
	n	%	n	%	
Hemofiltration	37	50	6	33.33	0.062
ECMO Support	10	13.51	-	-	-
Bleeding	12	16.2	1	5.6	0.016
Infection	11	14.9	2	11.1	0.433
Neurological Complications	3	4.1	-	-	-
Renal Failure	9	12.2	-	-	-
Mortality (In the first 10 days)	15	20.3	1	5.6	0.006

n: Number of patients, p<0.05: Significant, SD: Standard deviation, min: Minutes, CPB: Cardiopulmonary bypass, CC: Cross clamp, ECMO: Extra corporeal membrane oxygenation

Table 5. Comparison of intraoperative and postoperative data according to complexity levels

	Complexity level 1		Complexity level 2		Complexity level 3		Complexity level 4		p
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		
Operation Duration (min)	150.31±56.08		215.13±91.48		295.82±71.40		353.17±77.58		<0.001
CPB Duration (min)	66.38±31.64		119.16±51.95		171.30±65.56		195.35±47.91		<0.001
CC Duration (min)	39.63±18.56		75.63±36.71		98.00±66.34		113.74± 56.62		**0.005**
	n	%	n	%	n	%	n	%	
Hemofiltration	-	-	14	31.11	7	63.64	22	95.65	0.020
ECMO Support	-	-	2	4.4	1	9.1	7	30.43	<0.001
Bleeding	-	-	2	4.4	2	18.2	9	39.1	<0.001
Infection	-	-	2	4.4	2	18.2	9	39.1	<0.001
Neurological Complications	-	-	-	-	1	9.1	2	8.7	0.759
Renal Failure	-	-	1	2.2	1	9.1	7	30.4	<0.001
Mortality (In the first 10 days)	-	-	4	8.9	3	27.3	9	39.1	<0.001

n: Number of patients, p<0.05: Significant, SD: Standard deviation, min: Minutes, CPB: Cardiopulmonary bypass, CC: Cross clamp, ECMO: Extra corporeal membrane oxygenation

Intra and extra cardiac shunts due to underlying pathology, more frequent use of total circulatory arrest, application of routine hypothermia, less circulating blood volume, higher oxygen consumption and immature thermoregulation complicate the management strategy[5].

These patients may be asymptomatic in the preoperative period or they may be critical patients in need of hemodynamic and respiratory support. Therefore, preparation of the patient and family is an important aspect of preoperative evaluation in CHDs. In our clinic, the relatives of the patients are informed and prepared by the operator, pediatrician, and anesthesiologist prior to cardiac surgery.

Although technological advances have increased the success rate of pediatric cardiac surgery cases, they remain complex. In particular, the fact that the patients are young and low-weight create difficulties in surgical and anesthetic management[6,7].

In our study, we grouped our cases as under and over 1 year of age by referring to the studies of Yüzkat et al.[6] and Ceyhan and Baş[7], which were conducted in patients undergoing pediatric heart surgery. In our study, most of our cases were young and low weight. The rate of cases under 1 year of age was 80.43%. 46.7% of all patients were in the newborns (Table 1). The lowest weight belonged to a patient of 1240 grams.

The most common pathology among CHDs is VSD[7,8]. VSD may be isolated or accompanied by additional cardiac anomalies. In our patients, the most common cardiac pathology was VSD (Table 2), and the most common concomitant anomalies were pulmonary artery atresia and ASD.

The agents to be used in the induction of anesthesia are determined according to whether early extubation is planned, and the degree of cardiac dysfunction in the patient[7]. Studies in the literature report that induction with inhaler-neuromuscular blockade agents is well tolerated in pediatric patients with good cardiac reserve, and opioid-muscle relaxant combination provides better results in patients undergoing cardiac surgery[9]. In our clinic, we mostly use the combination of opioid-neuromuscular agents during the induction stage.

In their study, Yüzkat et al.[6] have shared their experience in pediatric congenital heart surgery anesthesia and emphasized the importance of experienced anesthesia technicians, perfusionists, equipment and technical infrastructure. They have also stated that the first cases should be chosen among those which CPB will not be performed. In our entire case series, the rates of patients with and without CBP were 78.2% and 21.8%, respectively. Cardiac arrest was achieved with del-Nido cardioplegia solution in all patients who underwent CPB. No problems were encountered at this stage.

It is important to determine the risk factors for mortality and morbidity in patients undergoing cardiac surgery. This is even more important in exceptional cases, such as pediatric cardiac surgery. Today, problems such as the increasing demand for health services, the inadequacy of health centers to meet this demand, and an insufficient number of available intensive care beds render it especially important to predict hospitalization time along with mortality and possible complications when lining up patients for surgery. Although scoring systems have been used regularly in adult patients, they do not fully meet the need in congenital heart surgery. One of the most important reasons for this is the numerous and different diagnostic and surgical procedures in CHDs[10].

In 1999, surgeons of the European Association of Cardiothoracic Surgeons, European Congenital Heart Surgery Association, Society of Thoracic Surgeons, and Congenital Heart Surgeons Society began working to develop a new risk assessment method for congenital heart surgery. In this study, approximately 200 anatomical diagnoses and 150 surgical procedures were evaluated. This comprehensive scoring system was called Aristotle Basic Scoring. Starting this project in 1999, surgeons faced two difficulties: Firstly, corporate hospital registry systems were new and not very dependable. Secondly, many high-mortality centers were reluctant to share their data due to lack of a risk classification method[11].

The Aristotle Basic Scoring system is based on surgical procedures and drawbacks, and as the difficulty level increases, so does the scores, from 1.5 to 15. These scores correspond to four complexity levels: 1,5-5,9=Level 1, 6-7,9=Level 2, 8-9.9=Level 3, 10-15=Level 4. Complexity level distributions of our patients were presented in Table 3. The maximum number of cases was found at the level of complexity 2.

Studies state that the duration of surgery, pump and aortic cross clamp time affect the postoperative period due to long intensive care stay[12,13]. Prolonged CPB times elicit a systemic inflammatory response: Blood components on artificial surfaces in the extracorporeal circuit are activated, and endotoxin translocation and ischemia-reperfusion injury occur. Surgical trauma, blood and blood product transfusion and hypothermia contribute to this systemic inflammatory response[14]. Inflammation is reported to cause oxidative stress associated with CPB[15]. Oxidative stress normally maintains balance in the body, but in cases with CHDs, the biological needs of tissues cannot be met, and the body is exposed to oxygen radicals. This negatively affects the treatment process[15,16].

In their large-scale study conducted on patients undergoing coronary bypass surgery, Wesselink et al.[17] also reported that prolonged CPB times was a crucial factor on adverse events in the postoperative period.

In our study, the durations of operation, CPB and cross-clamp were similar between the age groups (Table 4), but significantly differed with respect to complexity levels (Table 5). They were found to increase with increasing complexity, which is due to the escalated difficulty of surgical procedures.

Journois et al.[18] found that hemofiltration decreased interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor and complement 3a levels in patients undergoing CHD surgery and concluded that hemofiltration removed cytokine-containing substances. The removal of cytokines leads to decreased inflammatory response and oxidative damage.

In a different study conducted on pediatric congenital heart surgery, it is stated that ultrafiltration reduces tissue edema, volume burden, blood loss and the need for transfusion, while improving left ventricular functions during surgery procedure[19].

In our case series, hemofiltration was used insignificantly more frequently in the under-1-year-old group (50%) compared to the group older than 1 year (33.3%) (Table 4). On the other hand, the increased level of complexity in our patients significantly increased the rate of hemofiltration (p=0.020) (Table 5).

Literature states that it is possible to switch to ECMO when there is difficulty in separating from CPB during the postoperative period, inotropic drug support is at a level that disrupts peripheral perfusion, and low cardiac output syndrome develops after separation[20,21].

Bleeding is one of the most common complications during ECMO use[22], cerebral hemorrhage can also be seen as another complication[23]. Possible bleeding due to coagulopathy requires good management of the anticoagulation regimen.

In our study, we found that all patients receiving ECMO support were under 1 year of age (Table 4) and that the rate of ECMO use increased significantly with the complexity level of the surgical procedure (Table 5).

Low cardiac output is encountered in the early postoperative period and results in hypotension and decreased urine output due to insufficient pumping function of the heart[24].

Low cardiac output, intravascular catheterization, ECMO cannula directly associated with the mediastinum, bleeding-induced revisions, and prolonged intubation are factors that increase the tendency to infection in these patients. Infection is also associated with increased mortality and morbidity factors after cardiac surgery[25-27].

Bleeding and infection were the most common complications in our study. The rate of bleeding significantly differed with respect to age groups and complexity levels, and was higher in patients under 1 year of age and those who underwent surgeries at the complexity level of four. Infection was higher in patients younger than 1 year of age, which was not statistically significant (Table 4). Comparison with respect to the complexity level yielded similar results to those of bleeding (Table 5). Renal insufficiency and cerebral hemorrhage were among the possible complications in our series, in accordance with the literature.

Mortality factors in pediatric cardiac surgery can be related to the patient, surgery and intensive care unit conditions[28]. Ceyhan and Baş[7] reportedly encountered mortality in 11 patients (13.10%) in the first 10 days postoperatively among 84 patients who underwent pediatric heart surgery. The most common cause was ventricular failure.

In our series of 92 cases, mortality rate was 17.39% (n=16) within the first 10 days. Ventricular failure was the most common cause of mortality in accordance with the study of Ceyhan and Baş[7]. We found that the rate of mortality in our patients was significantly higher in the group under 1 year of age and cases with complexity levels 3 and 4. Based on these results, we believe that both age and the level of complexity of the surgical procedure are important in influencing mortality.

Study Limitations

The limitations of our study are its retrospective design and the small number of patients.

Conclusion

The results in CHD surgery procedures are affected by the patient's age, weight, and complexity levels based on the Aristotle Basic Scoring system. The surgical procedures for CHD are challenging for both the anesthesiologist and the surgeon in terms of application and management. We believe that this is the case for all centers working in this field, and any positive or negative experience in the field of congenital heart surgery should be shared in the literature for amelioration. In our opinion, further randomized trials are needed with larger series in this subject.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., F.A., M.D., K.A., M.K., Y.A., Ü.K., S.S., C.E., Yu.A., Concept: B.Ö., M.G., N.K., Design: B.Ö., M.G., Data Collection or Processing: B.Ö., F.A., M.D., K.A., M.K., Y.A., Ü.K., Analysis or Interpretation: B.Ö., M.G., Ü.K., Yu.A., N.K., G.E., A.E., Literature Search: B.Ö., F.A., M.D., K.A., M.K., Y.A., M.G., Ü.K., Yu.A., N.K., G.E., A.E., Writing: B.Ö., G.E., A.E.

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