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KLİNİK ARAŞTIRMA

Risk factors for pleural effusion after extracardiac Fontan procedure assessment of the commonest Fontan complication

Ekstrakardiyak Fontan ameliyatı sonrası plevral efüzyon oluşumunu etkileyen risk faktörleri

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SUMMARY

Aim: Fontan procedure is one of the most performed procedures for single ventricle physiology. After the procedure, patients are at risk for prolonged pleural effusion and other complications. We aimed to investigate the prolonged pleural effusion after Fontan procedure in terms of pulmonary arterial pressure, fenestration, diameter of the extracardiac graft, and thromboprophylaxis regimen.

Material and Methods: Hospital database was searched for the patients who underwent a Fontan operation. A logistic regression analysis model was constructed for pleural effusion.

Results: A total of 67 patients were enrolled in the study. Median age was 63 months, median weight was 18 kg. Pleural effusion occurred in 34 (51%) patients. In terms of thromboprophylaxis regimens, 28 (42%) patients were on warfarin, of those 19 (68%) had pleural effusion. Of 39 (58%) patients who were in aspirin group, 15 had (38%) pleural effusion (p=0.018). Pleural effusion was more frequent in the non-fenestration group (26 of 43, 60% vs. 8 of 24, 33%), significantly (p=0.03). Logistic regression analyses revealed that fenestrated group was less likely to (OR, 0.3; 95% CI, 0.1-0.96; p=0.04) and warfarin group was prone to (OR, 3.4; 95% CI, 1.1-9.8; p=0.02) have pleural effusion. In individuals who had a pulmonary artery pressure higher than 13 mmHg postoperatively, pleural effusion was more frequent (p=0.002).

Conclusion: Pleural effusion occurrence increased with higher postoperative pulmonary artery pressure, warfarin use, and absence of fenestration. Patients with relatively higher graft size index had a lower pulmonary artery pressure, although this is not reflected in pleural effusion occurrence.

Keywords: Extracardiac graft, fenestration, fontan, pleural effusion, warfarin

ÖZET

Giriş: Fontan ameliyatı tek ventrikül fizyolojisi için en sık yapılan ameliyatlardan biridir. Ameliyat sonrasında hastalar, uzamış plevral efüzyon ve başka komplikasyonlar açısından risk altındadır. Bu çalışmada; pulmoner arter basıncının, fenestrasyon yapılıp yapılmamasının, kullanılan ekstra kardiyak greftin çapının ve tromboproflaksi rejimlerinin Fontan ameliyatı sonrası uzamış plevral efüzyon gelişimine olan etkilerini araştırmayı amaçladık.
Materyal ve Metotlar: Hastane veri tabanında Fontan ameliyatı yapılan hastalar araştırıldı. Plevral efüzyon oluşumuna etki edebilecek potansiyel faktörler için lojistik regresyon modeli oluşturuldu.

Bulgular: Toplam 67 hasta çalışmaya dahil edildi. Hastaların ortalama yaşı 63 ay, ortalama kilosu 18 kg'dı. Plevral efüzyon 34 (%51) hastada gelişti. Tromboprofilaksi rejimi açısından değerlendirildiğinde warfarin kullanan 28 (%42) hastanın 19'unda (%68), aspirin kullanan 39 (%58) hastanın ise 15'inde (%38) plevral efüzyon görüldü. Fenestrasyon yapılmayan grupta (43 hastanın 26'sı %60) yapılanlara göre (24 hastanın 8'i %33) plevral efüzyon sıklığı anlamlı olarak daha yüksekti (p=0,03). Lojistik regresyon analizinde, fenestrasyon yapılanlarda daha az (OR, 0,3; 95% CI, 0,1-0,96; p=0,04), buna karşın warfarin kullananlarda ise daha sık (OR, 3,4; 95% CI, 1,1-9,8; p=0,02) plevral efüzyon riski olduğu görüldü. Ameliyat sonrası pulmoner arter basıncı 13 mmHg'ın üzerinde olanlarda plevral efüzyon sıklığı anlamlı olarak daha fazlaydı (p=0,002).

Sonuç: Plevral efüzyon oluşumunun, ameliyat sonrasında pulmoner arter basıncının yüksek olması, warfarin kullanılması ve fenestrasyon yapılmaması ile arttığı görüldü. Greft size indeksi göreceli olarak büyük olanlarda pulmoner arter basıncı daha düşüktü; ancak bu durum plevral efüzyon oluşumuna etki etmedi.

Anahtar kelimeler: Ekstrakardiyak greft, fenestrasyon, fontan, plevral efüzyon, warfarin

INTRODUCTION

Before Francis Fontan first introduced that pulmonary circulation could be maintained without the right ventricle in the early 1970s, complex cardiac anomalies were palliated with pulmonary shunts from systemic arteries or veins in patients who were not candidates for total correction (1). Since that time, with some modifications, Fontan procedure was carried out increasingly and became the most frequently performed operation for single ventricle physiology (2). The rationale behind the procedure is rerouting the systemic venous return to the pulmonary circulation without a pumping ventricle and making the functional single ventricle work as systemic ventricle (3). Thus, intracardiac mixing reduces as a result of separation of the systemic venous return and the pulmonary venous return, in addition arterial oxygen saturation and workload of the systemic ventricle become nearly normal (4). Although good hemodynamic results are achieved and survival is improved after Fontan procedure, the patients are at risk for some complications such as prolonged pleural effusion, arrhythmias, stroke, thrombosis, failure of the systemic ventricle, and protein losing enteropathy (5,6,7). These complications may result in prolonged hospital stay, failure of the Fontan circulation, and mortality (8,9). In this retrospective study, we aimed to investigate the prolonged pleural effusion after extracardiac Fontan procedure regarding postoperative pulmonary arterial pressure, fenestration, duration of cardiopulmonary bypass as well as diameter of the extracardiac graft and thromboprophylaxis regimen.

MATERIAL AND METHODS

Hospital database was retrospectively searched between January 2004 and April 2014 for the patients who underwent Fontan operation. Of the 77 patients revealed, nine were excluded due to use of the lateral tunnel technique and one was excluded due to lack of follow-up data. 67 patients, operated on using extracardiac graft technique, were enrolled in the study.

The collected data comprised history, previous surgeries, echocardiographic findings including diagnosis, atrioventricular valve function, morphology and function of the systemic ventricle, as well as perioperative variables including duration of cardiopulmonary bypass, extubation time, volume and duration of chest tube drainage, length of intensive care unit and hospital stay, occurrence of pleural effusion, arrhythmias and other complications. Variables affecting postoperative pulmonary artery pressure including preoperative arterial oxygen saturation, McGoon index and presence of antegrade pulmonary blood flow were also collected.

All patients were operated on by the same surgical team, through a median sternotomy on beating heart under cardiopulmonary bypass. Tubular vascular polytetrafluoroethylene (PTFE) grafts (W. L. Gore & Associates, Inc, Flagstaff, AZ, USA) were used as extracardiac grafts. The diameter of the graft was used in the analyses by replacing with the graft size index. Graft size index was calculated as the ratio of the graft diameter in millimeters to the body surface area in square meter. Body surface area for each patient was obtained by using the Mosteller formula. We did not use fenestration routinely. The criterion for fenestration was a pulmonary artery pressure higher than or equal to 18 mmHg after establishing the Fontan circulation. Total duration of the pleural effusion included duration of the second chest tube in patients who had a second chest tube insertion after first chest tube removal. Early mortality was defined as mortalities in the first postoperative month.

In the postoperative period, either aspirin or warfarin was used for thromboprophylaxis randomly. In warfarin regimen, unfractionated heparin was added to treatment until achieving an International Normalized Ratio (INR) of 2.0. Loading dose of warfarin was 0.1 mg/kg/day and the dose was titrated to maintain an International Normalized Ratio (INR) between 2.0 and 3.0. Aspirin was administered 5 mg/kg/day.

Normal distribution of continuous data was checked using Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation, whereas median (range) was used to express non-normal distribution. Continuous data between groups were analyzed by Student t test, or by nonparametric tests for small subgroups. Mann-Whitney U test was used for evaluation of differences in non-normally distributed data. Differences in categorical outcomes were analyzed with chi-square test. Logistic regression analysis model was constructed for pleural effusion. Out of the parameters, which would affect occurrence of pleural effusion, correlation of categorical data was assessed with non-parametric Spearman correlation analysis and correlation of continuous data was assessed with Pearson correlation test. Analyses were performed with the SPSS (ver. 17.0, SPSS Inc, Chicago, Illionis) and Wizard (ver:1.4.12 by Evan Miller) statistical software package. A p value <0.05 was considered statistically significant. Haydarpasa Numune Hospital Ethical Committee approved the study.

RESULTS

Median age of patients, enrolled in the study was 63 (53 - 85) months, median weight was 18 (15 – 21.5) kg, and median BSA was 0.75 (0.66 - 0.86) m2. 35 of them were male (52 %). Diagnoses of patients are shown in Table 1.

Table 1. Diagnoses of the patients

Diagnosis	n (%)
Single ventricle	19 (29)
Right ventricle morphology	4 (6)
Left ventricle morphology	13 (20)
Undetermined ventricle	2 (3)
Tricuspid atresia	16 (25)
CAVSD	8 (12)
IVS - PA	7 (10)
DORV	7 (10)
TGA	4 (6)
DILV	3 (4)
cc-TGA	3 (4)
Total	67 (100)

CAVSD: Complete atrioventricular septal defect; IVS - PA: Intact ventricular septum - Pulmonary atresia; DORV: Double outlet right ventricle; TGA: Transposition of great arteries; DILV: Double inlet left ventricle; cc-TGA: Congenitally corrected transposition of great arteries

Single ventricle and tricuspid atresia constituted the majority of the diagnoses. Systemic ventricle had left ventricular morphology in 55 patients (83%) and right ventricular morphology in 10 patients (14%). Ventricular morphology was undetermined in two patients.

Preoperative cardiac catheterization was performed in all patients. Table 2 shows the catheterization findings. Length of stay in intensive care unit was longer in patients who had an arterial oxygen saturation lower than 85% compared to those higher than 85%, significantly (p=0.02). None of the catheterization parameters affected pleural effusion occurrence.

Table 2. Preoperative cardiac catheterization records

Parameter	Value	p values		
		Pleural effusion	Length of ICU stay	Length of hospital stay
Systolic PAP (mmHg) (median)	15 (14 - 19)	0,92	0,67	0,92
Diastolic PAP (mmHg) (median)	7 (5 - 9)	0,83	0,99	0,88
Mean PAP (mmHg) (median)	12 (10 - 13)	0,44	0,67	0,96
Systolic aortic pressure (mmHg)	102,31 ± 12,91	0,40	0,54	0,06
Diastolic aortic pressure (mmHg)	61,94 ± 9,79	0,86	0,05	0,17
McGoon index (median)	2 (2 - 2,1)	0,26	0,34	0,85
Arterial oxygen saturation (%)	84,56 ± 4,23	0,26	0,02	0,41

PAP: Pulmonary artery pressure; ICU: Intensive care unit

A total of 41 patients (61%) had competent atrioventricular valves and the others had only mild atrioventricular valve regurgitation so we did not perform any intervention to the regurgitant atrioventricular valves. Postoperative pulmonary artery pressure (p=0.56) and pleural effusion (p=0.32) did not change significantly between regurgitant and non-regurgitant groups.

Pleural effusion occurred in 34 (51%) patients. Of those, four of them were detected after discharge from hospital in the first month. Tab. 3 demonstrates the comparative analysis of groups with and without pleural effusion. In terms of thromboprophylaxis regimens, 28 (42%) patients were on warfarin, of those 19 (68%) had pleural effusion. Of 39 (58%) patients who were in aspirin group, 15 had (38%) pleural effusion. The difference was statistically significant (p=0.018) (Table 3).

Table 3. Comparative analysis of groups with and without pleural effusion

Parameter	Pleural effusion (+) (n=34, % 51)	Pleural effusion (-) (n=33, %49)	p value
Systemic ventricle had LV morphology (%)	27 (84)	28 (85)	0,96
McGoon index	2 (2 - 2,1)	2 (2 - 2,1)	0,49
Antegrade pulmonary blood flow* (n (%))	23 (68)	20 (61)	0,55
Systolic PAP* (mmHg) (median)	15 (14 - 18)	15 (14 - 20)	0,66
Mean PAP* (mmHg) (median)	12 (10 - 13)	12 (10 - 14)	0,78
Arterial oxygen saturation* (%)	83,74 ± 4,66	83,54 ± 3,49	0,11
Fenestrated patients (n (%))	8 (24)	16 (48)	0,033
Mild AV valve regurgitation (n (%))	12 (35)	9 (27)	0,32
Duration of CPB (min) (median)	75 (56 - 110)	80 (73 - 113)	0,54
Graft size / BSA ratio (mm/m^2)	24,3 (22,2 - 29)	26 (23,3 - 29)	0,21
Postoperative PAP (mmHg)	14,2 ± 0,8	12,1 ± 1,0	0,002
Warfarin use (n (%))	19 (56)	9 (27)	0,018
Length of ICU stay (day) (median)	2 (1 - 3)	3 (2 - 4)	0,88
Length of hospital stay (day) (median)	15 (12 - 23)	9 (7 - 12)	<0,001

*LV: Left ventricle; PAP: Pulmonary artery pressure; BSA: Body surface area; AV: Atrioventricular; CPB: Cardiopulmonary bypass; *: Preoperative*

We used a fenestration between the extracardiac conduit and the right atrium in 24 (36%) patients. Table 4 demonstrates the parameters comparing fenestration and non-fenestration groups. Pleural effusion was more frequent in the non-fenestration group (26 of 43, 60% vs. 8 of 24, 33%), significantly (p=0.03). Arterial oxygen saturation of fenestrated group at discharge from hospital was lower than that of non-fenestrated group, significantly (p<0.001). Although the arterial oxygen saturation on postoperative day 1 (p=0.46) and length of hospital stay (p=0.58) of fenestrated group was lower, the difference was not statistically significant.

Table 4. Observed parameters in fenestration and non-fenestration groups

Parameter	Fenestration (+) (n=24, %36)	Fenestration (-) (n=43, %64)	p value
Pleural effusion (n (%))	8 (33)	26 (60)	0,03
Postoperative PAP (mmHg) (median)	13 (12 - 15)	14 (11 - 16)	0,11
Arterial oxygen saturation on postoperative day 1 (%)	92 (90 - 98)	95 (94 - 97)	0,46
Duration of CPB (min) (median)	98 (73 - 121)	75 (53 - 110)	0,28
Duration of extubation (h) (median)	5 (2,5 - 10)	5 (3 - 10)	0,93
Arterial oxygen saturation at discharge from hospital (%)	90 (86 - 92)	96 (94 - 97)	<0,001
Length of ICU stay (day) (median)	3 (1 - 5)	2 (1 - 3)	0,41
Length of hospital stay (day) (median)	11 (9 - 16)	13 (8 - 17)	0,58

PAP: Pulmonary artery pressure; CPB: Cardiopulmonary bypass

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Multivariate analysis by logistic regression with adjustment for fenestration and warfarin use revealed that fenestrated group was less likely to (odds ratio [OR], 0.3; 95% confidence interval [CI] 0.1-0.96; p=0.04) and warfarin group was prone to (OR, 3.4; 95% CI, 1.1-9.8; p=0.02) have pleural effusion. Length of hospital stay was longer in whom pleural effusion occurred (p<0.001). Mean pulmonary artery pressure of patients was 13.2 ± 2.8 mmHg postoperatively. In individuals who had a pulmonary artery pressure higher than 13 mmHg postoperatively, pleural effusion was encountered more frequently, compared to individuals who had a pulmonary artery pressure lower than 13 mmHg, significantly (p=0.002). Length of hospital stay of higher pulmonary artery pressure group was longer than that of lower pulmonary artery pressure group, but the difference was not statistically significant (p=0.06). Table 5 shows parameters of higher and lower pulmonary artery pressure groups.

Table 5. Parameters of higher and lower PAP groups

Parameter	PAP < 13 mmHg (n=24, %36)	PAP ≥ 13 mmHg (n=43, % 64)	p value
Pleural effusion (n (%))	6 (25)	28 (65)	0,002
Length of ICU stay (day) (median)	2 (1 - 4)	2 (1 - 4)	0,67
Length of hospital stay (day) (median)	11 (6 - 14)	14 (9 - 17)	0,06

PAP: Pulmonary artery pressure; ICU: Intensive care unit

Median extracardiac graft size index was 24.4 mm/m2 (23.0 – 28.6). In individuals with a graft size index higher than 25 mm/m2, postoperative pulmonary artery pressure was significantly lower than that of those with a graft size index lower than 25 mm/m2 (12.45 ± 1.1 mmHg vs. 13.89 ± 0.8 mmHg, p=0.032).Pleural effusion was less frequent (p=0.06) and length of intensive care unit stay was shorter (p=0.99) in patients who had a higher graft size index. However, the difference was not statistically significant. Length of hospital stay was significantly shorter in higher graft size index group (p=0.01). Table 6 demonstrates the parameters in higher and lower graft size index groups.

Table 6. Observed parameters in groups according to graft size index

Parameter	Graft size index < 25 (n=36, % 54)	Graft size index≥ 25 (n=31, % 46)	p value
Postoperative PAP (mmHg)	13,89 ± 0,8	12,45 ± 1,1	0,032
Pleural effusion (n(%))	22 (61)	12 (39)	0,06
Length of ICU stay (day) (median)	2 (1 - 5)	2 (1 - 4)	0,99
Length of hospital stay (day) (median)	14 (11 - 22)	10 (6 - 14)	0,01

PAP: Pulmonary artery pressure; ICU: Intensive care unit.

Median duration of cardiopulmonary bypass was 78 (57 – 111) minutes. Occurrence of pleural effusion was not associated with duration of cardiopulmonary bypass (p=0.18).

Overall, median length of intensive care stay was 2 (1- 4) days and median length of hospital stay was 12 (8 - 17) days. Of 5 patients who were readmitted to hospital, 4 had pleural effusion and 1 had elevated INR level. 5 (7%) patients died in first month postoperatively. Of those, 3 suffered elevated pulmonary artery pressure. Following Fontan take-down procedure, extracorporeal membranous oxygenation was employed due to severe low cardiac output state which resulted in loss of all patients after a prolonged intensive care unit stay. One patient with refractory pleural effusion was died of pulmonary emboli during the course of prolonged hospital stay. Another patient was died of severe pneumonia in early follow-up after discharge.

DISCUSSION

Pleural effusion after Fontan surgery is one of the most widely investigated complications in the literature. It is basically ascribed to inflammatory and hydrostatic processes, and hormonal factors (7). In this study, we sought the effects of some additional parameters on pleural effusion such as atrioventricular valve regurgitation, extracardiac graft size, and thromboprophylaxis regimen.

Elevated mean pulmonary artery pressure in preoperative and postoperative period was found to be a risk factor for prolonged pleural effusion (10). Fu and colleagues analyzed factors influencing pleural effusion after Fontan surgery in 95 patients and demonstrated the association of high preoperative pulmonary artery pressure with the volume of the pleural effusion and the failure of Fontan circulation (7). Haas and colleagues reviewed the early and midterm outcomes of 45 patients who underwent an extracardiac Fontan procedure and reported the preoperative and postoperative pulmonary artery pressure as a risk factor for prolonged intensive care unit stay (11). However, François and colleagues investigated the effects of lisinopril over pleural effusion occurrence after Fontan surgery in their prospective study of 21 patients and found no association of preoperative and postoperative pulmonary artery pressure with prolonged effusion (12). This result might be due to the small patient size of the study. In our study, pleural effusion occurred more frequently in patients with a postoperative pulmonary artery pressure higher than 13 mmHg, significantly. Length of hospital stay was longer in patients with higher pulmonary artery pressure, although the difference was not statistically significant. In conclusion, postoperative high pulmonary artery pressure may lead to pleural effusion as in our study, consistent with the bulk of the literature.

Use of a fenestration in Fontan patients is still under debate since it was first introduced in the late 1980s. In single ventricle circulation, fenestration of Fontan pathway to the pulmonary venous atrium results in improved cardiac output at the expense of a right to left shunt (7,13-15). Volume overloaded functional single ventricle in parallel circulation exhibits diastolic dysfunction after conversion to the Fontan circulation because the ventricle commences to work unloaded and mass-volume ratio of the ventricle increases acutely (16). Considering the preload dependence of the functional single ventricle for maintaining the adequate cardiac output in Fontan circulation, use of a fenestration may overcome the diastolic dysfunction by increasing the preload despite the acceptable desaturation effect. Therefore, some authors advocate routine fenestration in order to smooth the adaptation to the single ventricle physiology (9,14-17). Several studies reported decreased volume and duration of pleural effusion as well as shorter length of hospital stay in patients with fenestration (6,7,13,18-20). However, in some of these studies, fenestration is recommended in high risk patients who have a Fontan pressure ≥18 mmHg, transpulmonary gradient > 10 mmHg, lower McGoon index, pulmonary artery distortion, and atrioventricular valve regurgitation (4,7,19). Some other reports advocate fenestrated Fontan procedure in high-risk patients due to comorbid diseases (7,14,15,20). Bradley assessed the effects of the fenestration over the single ventricle physiology and concluded that it was impossible to guess in which patient pleural effusion would occur after Fontan surgery (13). Thus, these studies are debatable in terms of the effects of the fenestration per se on mortality and morbidity. Lemler and colleagues investigated the effects of fenestration in a prospective randomized trial (13). They randomized their patients to have fenestration or no fenestration irrespective of preoperative risk, pulmonary artery pressure and other parameters. In follow-up, they demonstrated that pleural effusion occurred more frequently in non-fenestration group and fenestration was associated with improved results even in low-risk patients (13). In other reports, outcomes of high-risk patients with fenestration were found to be similar to that of low-risk patients and the authors advocated use of fenestration (10). Atz and colleagues showed that length of hospital stay in patients with fenestration was shorter compared to that in non-fenestration group, in their study of 536 patients (15). In our study, we used fenestration in whom pulmonary artery pressure remained 18 mmHg or higher after Fontan circulation was established and fenestration reduced pleural effusion consistent with the literature. Length of hospital stay was shorter in our fenestration group although the difference was not statistically significant. Based on the short-term results of our study, use of a fenestration may be considered in high-risk patients and randomized controlled trials including large patient groups are needed to elucidate the routine use of fenestrated Fontan procedure.

The main drawback of the extracardiac Fontan procedure is the lack of the growth potential of the conduit (19,21). Diameter of the extracardiac graft is crucial considering the studies encouraging the extracardiac Fontan surgery in younger ages. Giannico and colleagues presented early and midterm outcomes of 193 extracardiac Fontan patients in their study and found no association of the diameter of the extracardiac graft with the obstructions of the cavopulmonary pathway (4). However, Fu and colleagues analyzed factors influencing pleural effusion after Fontan surgery in 95 patients and showed that pleural effusion occurred more frequently in patients with smaller extracardiac grafts (7). Iyengar and colleagues investigated Australian - New Zealand database, which included 1071 Fontan patients, retrospectively in their multicenter study and concluded that larger grafts in smaller patients caused a deficiency in respiratory pump dynamics which is essential for inspiratory augmentation of the pulmonary flow (22). They speculated that larger grafts could promote stagnation of cavopulmonary flow and thrombosis formation. Ikai and colleagues grouped 72 patients retrospectively according as their weight was under 10 kgs or not in their study and showed no gradient between inferior vena cava and extracardiac graft (19). In our study, use of a larger graft was not found to be associated with thrombosis. However, postoperative pulmonary artery pressure was significantly lower and length of hospital stay was significantly shorter in patients with larger grafts. Pleural effusion occurrence was less frequent in patients with larger grafts, although the difference was not statistically significant. In the light of these results, using a larger graft, which is more suitable to vascular anatomy, may be reasonable. Grafts, which range from 16 mm to 20 mm in diameter, are generally used according to the literature (19). However, to the best of our knowledge, there is not any guideline or measurement for selecting the appropriate graft size. Graft size index may be a promising parameter for selecting the graft size for patients undergoing an extracardiac Fontan procedure. Randomized controlled studies are necessary in order to determine the cut-off value for the graft size index.

Thromboembolic events can complicate Fontan circulation in any stage. Haas and colleagues presented outcomes of extracardiac Fontan procedure in 45 patients and advocated that prosthetic materials in humans were not endothelialized beyond the first 5- 10 mm, thus even if the lateral tunnel baffle might be endothelialized completely or partially, extracardiac graft would likely never become completely endothelialized (11). Thrombosis within the extracardiac graft can lead to pulmonary embolism and -in the presence of a fenestration- systemic embolism. Monagle and colleagues compared the efficacy of aspirin and heparin/warfarin on preventing thromboembolic events in their multi-center randomized study of 111 Fontan patients and reported the incidence of thromboembolic events as 19% in two-year follow-up (3). There was no significant difference between aspirin

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and heparin/warfarin regimens in terms of preventing thromboembolic events. The authors advocated that the INR should be above 2.0 so that the heparin/warfarin regimen would be effective because they encountered more thromboembolic events when the INR is lower than 2 with this regimen. Two regimens were similar with respect to major bleeding; however, minor bleeding was more frequent in heparin/warfarin group. Therefore, according to the study, heparin/warfarin regimen is not superior to aspirin regimen on preventing thromboembolic events and has more limiting effects on the quality of the life due to need of INR control (3). Patients should be on life-long thromboprophylaxis irrespective of the chosen regimen because the risk of the thromboembolism persists (3). Outcomes of the regimens of the thromboprophylaxis are not available in our study due to the lack of the data about mid-term and long-term follow-up of the patients. More frequent occurrence of the pleural effusion in warfarin group as in our study is not widely accepted in the literature. Warfarin might cause an increase in the transudation of fluids from the operative field by preventing coagulation, therefore the volume and the duration of the pleural effusion might increase. However, more studies are needed to reveal the mechanisms by which warfarin increases the pleural effusion. Effective thromboprophylaxis regimen is indispensable because thromboembolic events can collapse Fontan circulation. Studies including long-term follow-up in larger patient groups are needed to determine the risk factors and establishing the appropriate prophylaxis regimen for each individual.

Gersony and colleagues reported that severe atrioventricular valve regurgitation was poorly tolerated in Fontan patients (6). They recommended repair or replacement of the regurgitant valve and advocated the atrioventricular valve regurgitation as a risk factor for protein losing enteropathy (6). Earing and colleagues suggested atrioventricular valve regurgitation as a risk factor for late supraventricular arrhythmias in their series of 225 patients with double inlet left ventricle (23). However, Stephenson and colleagues did not find any association of severity of atrioventricular valve regurgitation with arrhythmias in their multicenter, cross-sectional study of 520 patients (24). Haas and colleagues presented impaired early and midterm results due to atrioventricular valve regurgitation in their series of 45 extracardiac Fontan patients (11). The degree of atrioventricular valve regurgitation was mild in our study and we did not find any association of mild atrioventricular valve regurgitation with mortality and morbidity as well as occurrence of pleural effusion or arrhythmias consistent with the literature. Mild atrioventricular valve regurgitation might be treated conservatively in these patients.

Shikata and colleagues compared two groups according as cardiopulmonary bypass was used or not and reported that prolonged cardiopulmonary bypass was associated with an increase in the volume of pleural effusion but did not change the duration of the effusion, in their study of 74 patients (25). Fu and colleagues proposed that prolonged cardiopulmonary bypass increased the volume of the chest tube drainage, in their study of 95 patients (7). Ikai and colleagues grouped 72 patients retrospectively according as their weight was under 10 kgs or not in their study and advocated that effusions might be reduced by minimizing the use of cardiopulmonary bypass, thereby the secretion of inflammatory cytokines (19). Bokesch and colleagues reported elevated concentrations of inflammatory mediators in the peritoneal fluid. They suggested that peritoneal fluid might act as a depot for inflammatory mediators after cardiopulmonary bypass, and withdrawal of the peritoneal fluid could lower serum concentrations of the harmful mediators (26). François and colleagues found a positive correlation between prolonged cardiopulmonary bypass and duration of the pleural effusion, in their randomized prospective study of 21 patients (12). Bartz and colleagues investigated outcomes of 142 patients with heterotaxy syndrome after Fontan surgery, and reported that prolonged cardiopulmonary bypass was associated with early mortality and duration of cardiopulmonary bypass longer than 2 hours was associated with late mortality (27). Mascio reviewed 4 studies concerning pleural effusion occurrence after Fontan surgery and revealed that amount of pleural drainage and time to extubation decreased significantly in patients who underwent an off-pump surgery (10). Tireli and colleagues concluded that time to extubation and length of intensive care and hospital stay were shorter, use of blood products were less in patients who underwent an off-pump surgery in their series of 10 patients (28). Inflammatory response stimulated by cardiopulmonary bypass deteriorates the Fontan physiology evidently. Duration of cardiopulmonary bypass was not found to be associated with occurrence of plural effusion in our study. However, prolonged cardiopulmonary bypass increased the length of stay in intensive care unit and in hospital significantly. Based on our results and recent literature, we suggest that cardiopulmonary bypass time should be as short as possible and off-pump surgery is reasonable in selected patients with appropriate anatomy.

François and colleagues investigated the effects of lisinopril over pleural effusion occurrence after Fontan surgery in their prospective randomized study of 21 patients and pleural effusion occurrence was similar in lisinopril group and control group (12). However, serum level of aldosterone, renin, and antidiuretic hormone was higher in patients with prolonged pleural drainage, significantly. The authors speculated administration of spironolactone, which is an aldosterone antagonist, as a substitute for angiotensin converting enzyme inhibitors in order to decrease the pleural effusion occurrence (12). Randomized controlled studies of larger patient groups are needed to demonstrate the effect of spironolactone on pleural effusion after Fontan surgery. Tansel and colleagues

reported a single case in which prolonged pleural effusion after Fontan surgery was treated successfully by administering bleomycin which is usually used for pleural effusion arising from malignancies (29). In our patient group, we used fluid and salt limitation and diuretics to decrease the pleural drainage as widely accepted in the literature. Results for this treatment strategy are not reported due to the absence of the control group. Considering that length of hospital stay is shorter in patients in whom pleural effusion did not occur, significantly, prevention of pleural effusion after Fontan surgery may lead to a decrease in infections, thromboembolic events and health-care costs. Ohuchi and colleagues demonstrated association of atrioventricular valve regurgitation with impaired exercise performance (30). Prolonged hospital stay was reported to be an independent risk factor for lower psychomotor development index in a study which investigated the effects of cardiac surgery carried out in infant period on neurological development at one year of age (13). Respiratory infections can jeopardize Fontan circulation and one patient died due to severe pneumonia in our study.

In conclusion, pleural effusion occurrence increased with higher postoperative pulmonary artery pressure, warfarin use, and absence of fenestration. Patients with relatively higher graft size index had a lower pulmonary artery pressure, although this is not reflected in pleural effusion occurrence maybe due to the small patient group. Pleural effusion prolonged the hospital stay consistent with the literature.

There are some limitations of this study. First, the patient group is small. Some result might be statistically significant in a larger patient group. Second, midterm and long-term results of the patients are not available. Third, this is a retrospective study. Effects of some parameters such as graft size index and warfarin use should be investigated in prospective randomized trials in order to achieve certain results.

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