Effect of Regular Medication Using Super High Dose Diuretics for Pleural Effusions at Early Stage After the Fontan Procedure

TOMOYUKI FUJITA*, SHIJI KAWASAKI*, SATOSHI MATSUSHITA*, HIROTAKA INABA*, TERUMASA MORITA*, KENJI KUWAKI*, TAIRO YAMAMOTO*, KEICHI TAMBARA*, KAN KAJIMOTO*, ATSUSHI AMANO*

*Department of Cardiovascular Surgery, Juntendo University Faculty of Medicine, Tokyo, Japan

Pleural effusions after the Fontan procedure contribute to morbidity, prolonged hospital stay, increased risk of infection, and may necessitate a pleurodesis procedure. Although the exact pathophysiological pathways are not fully understood, diuretics are generally used for the treatment of pleural effusions. On the other hand, postoperative elevation in antidiuretic hormone and decrease in atrial natriuretic peptide have been proven, indicating an effect of resistance to diuretic therapy. This paper reports on the efficacy of a high-dose diuretics regimen to prevent pleural effusions in the early postoperative period after the Fontan procedure.

From June 1997 to November 2012, 36 cases underwent the Fontan procedure. From August 2008, a new regimen using high-dose diuretics has been adopted and applied to 15 patients. Four out of 15 patients were excluded from this study due to early death or serious complications, so 11 patients were defined as the high-dose group. Before August 2008, 3 out of 21 patients were excluded for a similar reason, with 18 patients being defined as the control group. The high-dose group received a high-dose diuretic regimen that consisted of 20 mg of furosemide and 20 mg of spironolactone, three times a day after every meal. Perioperative data and postoperative course were compared between the two groups retrospectively.

Patient characteristics were not significantly different between the two groups. However, preoperative body weight was lower in the high-dose group (10.3 ± 1.12 vs. 11.8 ± 2.34 kg, p < 0.05). The average amount of urine from postoperative day 1 to day 3 was significantly higher in the high-dose group (49.2 ± 10.7 vs. 40.0 ± 14.6 ml/kg/day, p < 0.05). The amount of chest drainage was significantly lower in the high-dose group (486 ± 182 vs. 870 ± 635 ml, p < 0.05). No patients received drip infusions of albumin preparation in the high-dose group, while 6 out of 18 patients received it in the control group. Further pleural drainage after the removal of chest tubes was performed on eight patients in the control group, but it was performed only twice on one patient in the high-dose group (p < 0.05). No patient showed serious complications, such as renal failure, thrombus formation, arrhythmias, reintubation, the need for increasing inotropic support, or the need for pleural sclerosis.

The high-dose diuretics regimen using furosemide and spironolactone after the Fontan procedure increased urine in the early postoperative period, reduced overall pleural effusions, and minimized the need for additional treatment.

Key words: univentricular heart, Fontan procedure, pleural effusions, diuretics, postoperative management

Introduction

The Fontan procedure redirecting systemic venous blood into the pulmonary arteries via lateral tunnel or an extra cardiac conduit is correction of congenital heart defects unsuitable for biventricular repair. The Glenn procedure, bidirectional cavopulmonary shunt, is a staging operation for the Fontan procedure. The Fontan procedure has undergone several modifications in the recent past. Although recent survival rates have been excellent, postoperative morbidity remains a problem. Pleural effusions after the Fontan procedure contribute to postoperative morbidity and prolonged hospital
stay, increase in infection, and may necessitate a pleurodesis procedure. The exact pathophysiological pathways of pleural effusions after the Fontan procedure are yet to be unraveled and effective treatment is not yet available. Postoperative medical management after the Fontan procedure varies among institutions and physicians. Although diuretics play an important role in reducing pleural effusions, a standard regimen does not exist. The usual management in our institution consists of regular oral diuretics, using furosemide and spironolactone, 20 to 30 mg each every day, as well as additional diuretics which are administered either as intravenous injection or oral medicine based on patient’s body weight, amount of chest drainage, and chest X-ray findings. The problems with this method are that it is physician dependent and that it requires a large amount of additional diuretics as a result. Extensive additional treatment including intravenous injection is very invasive for pediatric patients and makes the postoperative management complex. Meanwhile, elevation in antidiuretic hormone and decrease in atrial natriuretic peptide have been shown in the early postoperative period after the Fontan procedure. This suggests that the patient needs a large amount of diuretics after the Fontan procedure to prevent fluid retention and pleural effusions. We hypothesized that the regular high dose diuretics at early postoperative period instead of sporadic use would reduce the amount of postoperative pleural effusions. A strategy to administer high dose oral diuretics, furosemide and spironolactone 60 mg each every day was tested, and the efficiency of this newly designed postoperative management regimen for the Fontan procedure was reported.

Methods

1. Patients
From June 1997 to November 2012, the Fontan procedure was performed on 36 patients at Juntendo University Hospital. Seven patients were excluded from the study due to early deaths or serious complications. The remaining patients were divided into two groups. The high dose group included eleven patients who underwent the procedure from August 2008 to November 2012 and were placed on a regular high dose diuretics regimen. The remaining patients were included in the control group.

The following patients characteristics were compared between the two groups: age, gender, preoperative body weight, preoperative oxygen saturation, preoperative hematocrit, atrioventricular valve regurgitation, pulmonary artery pressure, pulmonary artery index, time of extracorporeal circulation, graft size, postoperative central venous pressure, time of mechanical ventilation, duration of chest drainage, amount of chest drainage, amount of drip infusion of albumin preparation, postoperative hospital stay, amount of urine, additional use of diuretics and complications. The number of additional diuretics administration and re-chest drainage were counted in points and presented as ‘treatment score’.

2. Operation
All patients underwent total cavopulmonary connection using expanded polytetrafluoroethylene graft as extracardiac conduit via median sternotomy under cardiopulmonary bypass. Myocardial protection was achieved using cold crystalloid cardioplegic solution with topical cooling, when cardiac arrest was necessary. All procedures were carried out by the same surgeon. Patients were extubated either in the operating room or the intensive care unit. Inotropic support was quickly weaned after surgery. Warfarin was used as postoperative anticoagulation therapy to target the international normalized ratio of 1.5 to 2.0.

3. The control group
Intravenous furosemide of 20 mg was administered immediately after operation and 12 hours later. On postoperative day 1 enteral feeding as well as oral furosemide and spironolactone 10 or 15 mg twice a day was initiated. Additional intravenous or oral diuretics were given according to the patient’s body weight, amount of chest drainage and chest X-ray findings. The dose of each additional diuretic was determined as 10 or 20 mg of intravenous furosemide, or of oral furosemide and spironolactone once or twice a day, based on the patient’s condition.

4. The high dose group
Diuretics were used in the same way as the control group on post operative day 0. On postop-
operative day 1, enteral feeding as well as oral diuretics, 20 mg of furosemide and 20 mg of spironolactone 3 times a day with each meal, was initiated. When the patient body weight was decreased to that of preoperation, the dose of diuretics was reduced to 20 mg each morning and evening. Additional diuretics were used as in the control group.

5. Chest drainage
Chest drainage tubes were positioned into bilateral thoracic cavity at operation. The amount of chest drainage was measured every day. Chest drainage tubes were taken out when drainage decreased to <10 ml/kg/day. Some patients received re-drainage in cases of pleural effusions which were uncontrollable by diuretics.

6. Others
Fluid and diet intake was limited to 600 g/day until patients weighed less than their preoperative body weights. None of the patients were on a low-fat diet. Postoperative body weight was measured every day until discharge. In the control group, the electrolytes were analyzed at sporadically considering patients' condition. In the high dose group, the electrolyte exam was done on postoperative day 1, 3, and 5.

7. Statistical analysis
The statistical analysis was performed using StatMate III (Atomusu Ltd.). Continuous variables were presented as the mean ± standard deviation. Categorical variables were presented as case numbers, and were analyzed with the Mann–Whitney test. Statistical significance was identified as a p value of less than 0.05.

Results
All patients in this study had extra cardiac conduit Fontan procedure. Table-1 lists the patient characteristics of the control group. In this group, 17 cases were staged operation, and patients had also undergone palliative procedures as follows: pulmonary artery banding, modified Blalock-Taussig shunting or bidirectional superior vena cava to pulmonary artery anastomosis. Aortic cross clamping was used in 8 cases. There was no difference in the degree of common atrioventricular valve regurgitation between the two groups. Pulmonary artery pressure (PAP) and pulmonary artery index (PA index) were not assessed in some of the patients.

Additional patient information is listed in Table-3, and postoperative courses are shown in Table-4. Preoperative body weight was lower in the high dose group compared to the control group (10.3 ± 1.12 vs. 11.8 ± 2.34 kg, p < 0.05). There were no significant differences between the high dose group and the control group in age (29.2 ± 5.84 vs. 28.6 ± 12.5 months, NS), preoperative oxygen saturation (84.0 ± 4.80 vs. 84.7 ± 9.57%, NS), preoperative hematocrit (46.2 ± 2.76 vs. 48.0 ± 5.73%, NS), cardiopulmonary bypass time (104 ± 46.4 vs. 124 ± 40.7 min, NS), extra cardiac conduit size (16.0 ± 0.00 vs. 16.4 ± 1.29 mm, NS), postoperative central venous pressure (12.4 ± 4.61 vs. 12.6 ± 3.63 mmHg, NS), mechanical ventilation time (173 ± 166 vs. 256 ± 399 min, NS), number of days until chest drainage tube was removed (3.91 ± 1.22 vs. 3.67 ± 2.47 days, NS), or hospital stay (14.1 ± 5.56 vs. 14.4 ± 5.80 days, NS).

In the high dose group, no patients received additional intravenous furosemide, and 2 patients received additional oral furosemide and spironolactone. One patient received further pleural drainage twice after removing chest drainage tubes. No patients received drip infusions of albumin preparation. In the control group, medical management varied greatly among patients. Additional intravenous furosemide use was sporadic, with 6 out of 18 patients receiving this therapy. Additional oral diuretics were used in 15 patients. A significantly high number of further pleural drainages, a total of 12 times in 8 patients, were performed after removing chest drainage tubes (p < 0.001). The amount of drip infusions of albumin preparation was 152 ± 338 ml in the control group. Drip infusions of albumin preparation was used in 6 out of 18 patients and was significantly frequent (p < 0.001).
The average amount of urine from postoperative day 1 to day 3 was significantly higher in the high dose group (49.2 ± 10.7 vs. 40.0 ± 14.6 ml/kg/day, p < 0.05). The number of additional intravenous and oral diuretics administration was 4.94±3.95 in the control group. This was significantly reduced in the high dose group to 0.45±1.21 (p < 0.001). Figure-1 shows the total number of treatment for pleural effusions in ‘treatment scores’, which were 5.61±4.69 point in the control group and 0.64±1.80 point in the high dose group (p<0.001). The amount of chest drainage during hospitalization was significantly lower in the high dose group compared with the control group (486
The number of days it took for the body weight to decrease to the preoperative level was significantly less in the high dose group (2.91 ± 1.45 vs. 6.40 ± 4.10 days, p < 0.01).

Table 5 shows the analysis of potassium, blood urea nitrogen and creatinine in the high dose group. Potassium supplementation was required in 1 patient with hypokalemia from postoperative day 1 to day 3. No other electrolyte abnormalities or dehydration were indicated.

No serious complications, such as renal failure, thrombus formation, or arrhythmias occurred, and none of the patients required reintubation, increased inotropic support, or pleural sclerosis.

Comparison of postoperative stay could not be show exact clinical course comparison because 3 patients in the high dose group were transferred to the pediatric department for antihypertensive medication.

Table 5  Electrolyte exam of the high dose group

<table>
<thead>
<tr>
<th>Postoperative day</th>
<th>Postoperative day</th>
<th>Postoperative day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Potassium, mEq/l</td>
<td>3.88 ± 0.70</td>
<td>3.72 ± 0.59</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>18.0 ± 3.95</td>
<td>23.6 ± 10.3</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.48 ± 0.23</td>
<td>0.36 ± 0.13</td>
</tr>
</tbody>
</table>

Figure 1  Treatment for pleural effusions

5.61 ± 4.69 point in the control group and 0.64 ± 1.80 point in the high dose group (p < 0.001).

± 182 vs. 870 ± 635 ml, p < 0.05). The number of days it took for the body weight to decrease to the preoperative level was significantly less in the high dose group (2.91 ± 1.45 vs. 6.40 ± 4.10 days, p < 0.01).

Table 5 shows the analysis of potassium, blood urea nitrogen and creatinine in the high dose group. Potassium supplementation was required in 1 patient with hypokalemia from postoperative day 1 to day 3. No other electrolyte abnormalities or dehydration were indicated.

No serious complications, such as renal failure, thrombus formation, or arrhythmias occurred, and none of the patients required reintubation, increased inotropic support, or pleural sclerosis.

Comparison of postoperative stay could not be show exact clinical course comparison because 3 patients in the high dose group were transferred to the pediatric department for antihypertensive medication.
Discussion

The Fontan procedure has been used successfully to palliate a univentricular heart. Mortality and morbidity after this procedure is low in the recent years due to the advance in surgical technique and postoperative management. However, persistent pleural effusions continue to be a significant source of morbidity in the postoperative period. Previous reports show that pleural effusions after this procedure prolong hospital stay, increase the risk of infection, and may necessitate a pleurodesis procedure. There are many reports on the risk factors of persistent pleural effusions after the Fontan procedure, but reports and literatures about improvement in management of pleural effusions are rare. Although the exact pathophysiological pathways of pleural effusions after the Fontan procedure are not fully understood, three mechanisms are considered to be involved. First, the inflammatory response results from the exposure to cardiopulmonary bypass, causing increased capillary leakage. Second, the hormonal mechanisms including the activation of the renin-angiotensin system are involved. Third, increased hydrostatic pressure in the Fontan circulation causes an increase in central venous pressure. The cause of pleural effusions after the Fontan procedure is unclear and multifactorial, thus effective therapy is not available at present.

Patients after the Fontan procedure need volume load to stabilize the new circulation at an early stage, but also it results in the elevation of central venous pressure at the same time. High central venous pressure causes pleural effusions, which leads to the decrease in circulating volume and plasma osmolality as a result. Since the inflammatory response and high central venous pressure cause vascular water volume to leak into the third space, excessive volume is necessary to compensate. We hypothesized that the effective use of diuretics to control the central venous pressure to the lowest level without interfering with the Fontan circulation would reduce pleural effusions.

Diuretics have been used conventionally for reducing pleural effusions. Joseph R. et al reported that administration of diuretics at fixed intervals was effective in reducing pleural effusions after the Fontan procedure. The diuretics used in their regimen were hydrochlorothiazide and spironolactone, 2 mg/kg/day each. Although the dose of diuretics in our usual management is also 2 mg/kg/day, there is no standard guideline for the appropriate dosing in pediatric patients with Fontan circulation. In fact, extra diuretics are frequently used in addition to regular oral diuretics during our usual management and total amount of diuretics exceed the initially planned dose. Richard et al hypothesized the hormonal response play an important role in the development of fluid retention and pleural effusions after Fontan or Glenn procedure. They reported the levels of antidiuretic hormone, cortisol, aldosterone, renin, and angiotensin II were all elevated 1 hour after operation and the elevation in these hormones persisted 3 to 4 postoperative days. Further, decrease in atrial natriuretic peptide after the Fontan procedure was reported by M Burch et al. Atrial natriuretic peptide is the only hormone that had a positive correlation with urinary output. We hypothesized that the dose of furosemide and spironolactone, 2 mg/kg/day of each, is not enough for postoperative management and made a new regimen of 6 mg/kg/day of each drugs. Traditionally, heart failure due to congenital heart disease has been treated using two drugs, which are spironolactone and one of the following: thiazide, furosemide, or ethacrynic acid. Our regimen was established and drugs were selected in accordance with this concept. We supposed from past experiences that regular high dose of diuretics was necessary to reduce pleural effusions, and oral administration was an easier method for pediatric patients.

This high dose diuretics regimen was beneficial, because it eliminated the necessity of albumin preparation. The drip infusions of albumin preparation make up the circulation volume loss, but the required amount is affected by the amount of pleural drainages. In fact, there is no standardized guideline for the use of albumin preparation at early postoperative period after the Fontan procedure. Therefore, drip infusions of albumin preparation are supportive care. We hypothesized that reducing pleural effusions leads to decreasing the use of albumin preparation. The amount of pleural effusions after the Fontan procedure was very small, and no patients needed drip infusions of albumin preparation in the high dose group. We believe that
the reduction of pleural effusions in the high dose group was achieved by the lower central venous pressure due to aggressive diuresis.

Another benefit of this medical regimen is that postoperative management became minimally invasive. Keeping an intravenous drip line in pediatric patients is troublesome. Further chest drainage makes the medical staff exhausted from anesthesia and the care of tubes. Decreasing additional treatment for pleural effusions such as intravenous injection, oral medicine, and further chest drainage, makes the management simple and non invasive. The patients receiving this medical regimen rarely needed additional treatment, and postoperative care was very simple. This result suggested the possibility of creating pathway for postoperative management of patients who underwent the Fontan procedure.

There are two points of notice with the medical regimen of high dose diuretics. First, dehydration may occur due to increased urine. Because of its unique physiology, appropriate volume load is necessary to maintain the Fontan circulation. We observed patient’s body weight as an indicator of circulation volume. To prevent dehydration, the dose of diuretics should be decreased when patient body weight is decreased to preoperative body weight. Patients after the Fontan procedure require careful management therefore the use of high dose diuretics has been avoided due to the risk of dehydration. The effect of using high dose diuretics after the Fontan procedure has not been thoroughly investigated, and to our knowledge, ours is the first study of a medical management using high dose diuretics. The dose of our regiment with 2 drugs, each 6 mg/kg/day is more than three times the normal dose used for heart failure. We defined our regimen as "super" high dose. Second, electrolytes disorder is a concern, sodium, chloride, especially potassium. In patients with a regimen of high dose diuretics, there were no significant hyperkalemia or hypokalemia. However, frequent clinical assessments and electrolyte monitoring should be done in patients with appropriate ingestion for prevention and early detection of complications.

This study suggests that postoperative medical management with regular high dose diuretics for patients undergoing the Fontan procedure plays an important role in reducing pleural effusions. We hypothesize that regular high dose diuretics reduced vascular water volume and successfully reduced pleural effusions. But the actual mechanism of water volume and pleural effusions in the Fontan circulation is still unknown. It is necessary to clarify this mechanism and consider the use of high dose diuretics regimen in high risk patients in the future. Further, this study showed only short postoperative course and the long term results of these patients with our new regimen are unknown. They should be followed up carefully about pleural effusions, hypovolemic status and other complications.

Some limitations of this study have to be considered. It is a retrospective, observational study and analyzing the results of only perioperative period. Long-term results of this regimen, impact on the Fontan circulation and other effects, are unknown. Further, in this study, multivariate analysis was not performed for a small number of subjects. It is desirable to increase the number of subjects and continue to long term follow up. Second, despite pleural effusions were decreased in the high dose group, there was no difference in the length of hospital stay after surgery between in the two groups. The reason may be that 3 patients of high dose group had continued hospital stay for adjustment of oral medicine for pulmonary hypertension. In some papers, pleural effusions after the Fontan procedure has been defined to be a factor prolonging hospital stay. In recent years, oral medicine for pulmonary hypertension that did not exist previously plays an important role in the postoperative management and takes time to adjust. Therefore comparison of the length of hospital stay after surgery would not be important.

Conclusions

The medical regimen using high doses of 2 diuretics, furosemide and spironolactone, after the Fontan procedure increased urine at early postoperative stage, reduced pleural effusions, and minimized the need for additional treatment. This study suggests that in addition to reducing invasive treatment, this regimen for patients after the Fontan procedure plays an important role in making postoperative management simple and safe.
Acknowledgement

We thank Ms. Yuko Kojima for correcting the English in this paper.

References