Journal of Kerman University of Medical Sciences
2021; 28(6): 568-574

10.22062/JKMU.2021.91828

Original Article

http://jkmu.kmu.ac.ir/

The Use of Albumin Add-on Therapy to Loop Diuretic for the Management of Pleural Effusion in Mechanically Ventilated Ill Children

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ABSTRACT

Background: Pleural effusion (PE) is common in children with acute illness that are admitted to the intensive care unit (ICU). The present study aimed to investigate the efficacy of albumin add-on therapy to furosemide in contrast to furosemide treatment only for treating transudative PE.

Methods: The present randomized clinical trial was conducted on fifty 1-12-year-old children (under mechanical ventilation admitted at ICU randomly allocated to treatment with daily furosemide only (2 mg/kg) or albumin (1 gr/kg) add-on therapy to furosemide (2 mg/kg) for three days. The vital signs, venous blood gas, the pleural effusion volume, serum potassium level, potassium, and dopamine requirement were measured daily and compared between the groups.

Results: Comparison of the two groups showed a significant decrease in the pleural fluid volume (P<0.001), base excess (P<0.001), diastolic blood pressure (P=0.004), heart rate (P=0.009), and potassium (P=0.005) in the intervention group than the control group. The mean of dopamine and potassium doses requirement were 2.25±0.95 and 2.60±0.89 for the intervention group, and 1.00±0.00 and 2.00±1.41 for the control group, respectively. The comparison of the two groups showed an insignificant difference between them (P=0.26 for the dopamine injection and P=0.57 for the potassium prescription).

Conclusion: As the first study worldwide, considerable benefits were observed in the use of albumin and furosemide combination among PICU-admitted children under mechanical ventilation who required negative fluid balance. In addition, no hemodynamic instability or death was reported. During this short-term follow-up period, a satisfactory percentage of children were separated from the ventilator and transferred to the ward.

Keywords: Loop diuretics, Albumin infusion, Mechanical ventilation, Intensive care

Citation: Habibzadeh MR, Shafa A, Zamani H. The use of albumin add-on therapy to loop diuretic for the management of pleural effusion in mechanically ventilated ill children. Journal of Kerman University of Medical Sciences 2021; 28(6): 568-574. doi: 10.22062/JKMU.2021.91828

Received: 20.05. 2021
Accepted: 28.07. 2021
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Published by Kerman University of Medical Sciences

Introduction

Pleural effusion is common in critically ill patients admitted to the intensive care unit (ICU). Due to the modalities used for the detection of pleural effusion, the determination of its prevalence in the ICU is challenging (1). A variety of factors, including pneumonia, volume overload, heart failure, hypoalbuminemia, and mechanical ventilation, are responsible for the incidence of pleural effusion among patients admitted to ICU (2). Although the causal relationship of pleural effusion with mechanical ventilation is unclear, the presence of pleural effusion is associated with elongated ICU stay and mechanical ventilation requirements. However, the association of pleural effusion with the clinical outcomes of patients under mechanical ventilation is not well-established (3).

The incidence of pleural effusion among mechanically ventilated patients differs from 8% to over 60% achieved from the pure physical examination assessments to the ultrasonographic study of the patients. Even computed tomographic study of the patients resenting from acute respiratory distress syndrome has revealed 83% of pleural effusion (4-6).

It has been demonstrated that pleural effusion interrupts the respiratory system coordination, reduces the respiratory system compliance, and poses intrapulmonary shunt; the conditions that all together lead to hypoxia. Although massive effusion drainage causes minor improvements in oxygenation, it leads to a significant dyspnea relief (7, 8).

To determine the treatment approach, pleural fluid analysis is required, in which the fluid is divided into two subgroups of exudates and transudates. The prevalence of each type varies from a study to another one, while it is estimated that up to one-third of the fluids is transudate (9). Transudative effusions occur due to serum ultrafiltration across pleural surfaces because of decreased oncotic pressure or increased hydrostatic pressure or both simultaneously (10,11).

Among the cases with transudative pleural effusion, diuretics such as furosemide can be used as a part of conservative fluid management posing diuresis, improved oxygenation and, pulmonary capillaries vasodilation; all together improve ventilation-perfusion matching (12). The combination of furosemide with albumin for the treatment of critically ill adults under mechanical ventilation has been demonstrated to be associated with transient improvement of PaO_2/FiO_2 (13), while pediatric data in this regard are limited. The present study was conducted to assess the feasibility and efficacy of furosemide in combination with albumin for the treatment of transudative pleural effusion in critically ill children admitted at the pediatrics ICU (PICU).

Materials and Methods

Study population

The present study is a double-blind randomized clinical trial. The study population included all children with pleural effusion that were admitted to the intensive care units (ICUs) of Imam Hossein Hospital during 2018-2019. The sample size was considered to be 25 patients in each group considering the confidence interval of 95%, test power of 80%, and the results of previous studies reporting the standard deviation of pleural fluid was equal to 1 in both groups and the error level obtained from the means of the two groups was equal to 0.8.

The inclusion criteria were as follows: ICU-admitted under mechanical ventilation children with the diagnosis of pleural effusion, the age range of 1-12 years, the systolic blood pressure above 100 mmHg, and the serum albumin levels less than 2.5 mg/dl.

Trauma to the chest and requirement for chest tube embedding were considered as unmet criteria.

Exclusion criteria consisted of hemodynamic instability (systolic blood pressure less than 70 mmHg unresponsive to dopamine therapy), refractory hypokalemia under 3 mg/dl unresponsive to potassium therapy, any indication for chest tube embedding, the diagnosis of the exudative type of pleural effusion, and death.

After obtaining the ethical code from the Ethics Committee of Isfahan University of Medical Sciences (Ethical code: IR.MUI.MED.REC.1398.512) and the code of clinical trial (IRCT20180520039739N4), the protocol was explained to the patients' legal guardians and the written consent was obtained. Then, the participants were selected using convenience sampling until achieving the desired population.

The patient with pleural effusion were randomly divided into two groups of treatment with albumin plus furosemide (intervention group) or furosemide only treatment in the ICU (control group) using Random Allocation software. Therefore, each of the patients was provided with a number, allocated her/him to one of the study groups.

Study protocol

The patients' age and gender were recorded in the study checklist, and all underwent Focused Assessment with Sonography for Trauma (FAST) to estimate the volume of effusion in pleural space.

The intervention group was treated with daily regimen of 1 gr/kg albumin 20% (5 ml/kg; Alborz Darou, Iran) plus furosemide (2 mg/kg; Aburaihan Company, Iran) for three days, and the control group underwent the treatment with furosemide (2 mg/kg; Aburaihan Company; Iran) plus 5 ml/kg of saline 0.9% as placebo.

In order to observe the blindness condition, two drugs of albumin plus furosemide and furosemide plus normal saline were already prepared by the ICU nurse, specified in ready-made syringes, labeled A and B, and provided to the researcher daily. Therefore, the researcher was not aware of the type of the prescription drugs. In addition, the patient and the data analyst were not informed of the type of intervention.

In cases where systolic blood pressure (SBP) decreased below 90 mmHg, dopamine administration was started at the dose of 3 mcg/kg/min (Caspiantamin Company, Iran), and if necessary, the dopamine dose was increased according to the intensivist prescription. Besides, the daily potassium level was measured for the patients and in the case of potassium decrease to 3 mEq/l, 1 mEq/kg was prescribed for the patients.

Primary outcomes

The measurements included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), venous blood gas, and the pleural effusion volume that were measured daily until four days following the interventions.

Statistical analysis

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) version 23 and analyzed. The descriptive data were presented in mean, standard deviation, percentages, and absolute numbers. For analytics, Chi-square, Mann-Whitney, and GEE tests were used. Statistical significant level was considered at $P<0.05$.

Results

In this study, 50 under mechanical ventilation children with the diagnosis of pleural effusion were randomly allocated to the intervention group treated with albumin plus furosemide (n=25) or control group treated with furosemide only (n=25).

Twenty-five patients (50%) were male, and 25 patients (50%) were female. The mean age of the study population was 3.69 ± 2.62 years. The two groups were not statistically different in terms of age and gender distribution ($P>0.05$), which are presented in Table 1.

Table 1. Demographic information of intervention group versus control group

Variable	Intervention Group (n=25)	Control Group (n=25)	P-value
Age (year)	3.88±2.62	3.50±2.66	0.59
Gender, n (%)			
Female	13 (52%)	12 (48%)	0.77
Male	12 (48%)	13 (52%)	

Table 2 demonstrates detailed information on comparing the intervention group versus controls in terms of pleural effusion volume, oxygen saturation, VBG-related data, blood pressure, and heart rate. As shown in this table, none of the variables were significantly different between the two groups at baseline ($P>0.05$). At the end of the interventions, both of the groups revealed a remarkable decrease in the volume of pleural fluid and a significant increase in oxygen saturation, arterial oxygen pressure, bicarbonate, and diastolic blood pressure ($P<0.05$). Comparison of the two groups showed a more significant decrease in the pleural fluid volume ($P<0.001$), base excess (BE) ($P<0.001$), diastolic blood pressure (DBP) ($P=0.004$), heart rate ($P=0.009$), and potassium ($P=0.005$) in the intervention group than the control group.

Table 2. Comparison of the effects of interventions on pleural fluid volume, venous blood gas, blood pressure, heart rate, and serum potassium levels among intervention group versus control group

Variable	Group	First Day	Second Day	Third Day	Fourth Day	P-value (GEE) Between the Groups	P-value (GEE) Intergroup
Pleural fluid volume	Intervention group	9.28±2.52	4.32±2.89	1.68±1.60	1.08±0.48	<0.001	<0.001
	Control group	8.28±2.57	6.32±2.60	5.60±2.75	4.20±2.94		<0.001
P-value (Mann-Whitney)		0.16	0.006	<0.001	<0.001		
Oxygen saturation	Intervention group	93.24±4.56	95.64±2.17	96.88±1.98	97.48±2.14	0.43	<0.001
	Control group	93.32±5.61	95.96±1.96	96.24±1.39	96.40±1.89		0.001
P-value (Mann-Whitney)		0.62	0.57	0.091	0.036		
paO2	Intervention group	70.56±16.46	79.64±9.58	82.08±10.43	84.44±10.33	0.21	<0.001
	Control group	74.04±15.95	80.56±10.18	84.12±6.86	86±8.57		<0.001
P-value (Mann-Whitney)		0.45	0.68	0.79	0.51		
pH	Intervention group	7.24±0.59	7.40±0.10	7.38±0.02	7.39±0.03	0.24	0.17
	Control group	7.35±0.06	7.37±0.03	7.26±0.59	7.14±0.83		0.35
P-value (Mann-Whitney)		0.77	0.72	0.92	0.26		
BE	Intervention group	-2.88±3.72	-1.60±2.67	-1.20±2.38	-0.36±1.91	<0.001	0.01
	Control group	-4±2.61	-3.24±1.69	-2.92±1.44	-2.56±1.35		0.03
P-value (Mann-Whitney)		0.34	0.028	0.008	<0.001		
PCO_2	Intervention group	39.36±6.74	36.84±3.92	36±3.31	34.92±3.16	0.36	0.003
	Control group	39.12±7.13	37.56±4.32	36.64±3.41	36.16±3.60		0.13
P-value (Mann-Whitney)		0.86	0.63	0.44	0.25		
HCO_3	Intervention group	22.92±3.22	23.96±2.33	25.12±3.01	25.60±3.26	0.85	0.005
	Control group	23.48±3.44	24.28±2.13	24.80±1.87	25.32±1.65		0.037
P-value (Mann-Whitney)		0.53	0.55	0.98	0.35		
Systolic blood pressure	Intervention group	90.56±13.13	91.72±10.90	92±9.78	94.56±10.52	0.051	0.61
	Control group	91.52±12.26	94.56±10.75	96.68±9.78	97.9±9.85		0.14
P-value (Mann-Whitney)		0.76	0.32	0.12	0.15		
Diastolic blood pressure	Intervention group	47.60±6.95	48.12±6.31	48.80±6.56	49.24±6.21	0.004	0.80
	Control group	47.60±8.82	51.28±7	51.96±6.12	54±6.47		0.01
P-value (Mann-Whitney)		0.83	0.10	0.087	0.012		
Heart rate	Intervention group	144.84±25.59	138.16±23.31	136.60±22.55	132.24±24.14	0.009	0.29
	Control group	151.68±12.68	145.12±10.61	142.84±9.69	139.16±9.85		<0.001
P-value (Mann-Whitney)		0.43	0.35	0.54	0.33		
Potassium	Intervention group	4.01±0.26	3.90±0.25	3.93±0.21	3.86±0.15	0.005	0.10
	Control group	4.03±0.21	4±0.09	4.01±0.13	3.96±0.11		0.40
P-value (Mann-Whitney)		0.99	0.31	0.14	0.01		

The mean of dopamine and potassium doses requirement was 2.25±0.95 and 2.60±0.89 mEq/l for the intervention group, and 1.00±0.00 and 2.00±1.41 mEq/l for the control group, respectively. The comparison of the two groups showed an insignificant difference between them (P>0.05). Table 3 demonstrates the distribution of dopamine and potassium administration based on the day of the intervention.

Table 3. The distribution of dopamine and potassium use for the treatment of the study population based on the day of administration

	Intervention Group	Control Group
Dopamine use		
Day 1	1 (25%)	2 (100%)
Day 2	1 (25%)	0 (0%)
Day 3	2 (50%)	0 (0%)
Potassium use		
Day 1	0 (0%)	1 (50%)
Day 2	3 (60%)	0 (0%)
Day 3	1 (20%)	1 (50%)
Day 4	1 (20%)	0 (0%)

It should be mentioned that no hemodynamic instability or death was observed in the follow-up performed in this study. In addition, one patient (4%) of the control group and 4 patients (16%) of the intervention group were separated from the ventilator and transferred to the ward on the fourth day.

Discussion

To the best of our knowledge, the present study is the first study assessing the use of furosemide in combination with albumin for the treatment of transudative pleural effusion among mechanically ventilated children admitted at PICU. The findings of the present study revealed significant superiority of the albumin plus furosemide combination therapy to placebo for the treatment of fluid overload without remarkable life-threatening alterations in hemodynamic indices, arterial blood gas indices, dopamine requirement, and serum potassium levels.

It has been estimated that the use of albumin can lead to improved diuresis by furosemide. In other word, resistance to furosemide may be related to hypoalbuminemia. Inoue et al. (1987) were among the first groups of researchers who assessed the value of albumin add-on therapy to furosemide among hypoalbuminemic rats who represented significantly improved dieresis due to the furosemide bound to albumin treatment (14). Fliser et al. (1999) were the other group investigating the value of albumin therapy added to furosemide for the treatment of patients with nephrotic syndrome. In this small study that had involved only 9 patients, the outcomes showed only a slight improvement in the efficacy of furosemide dieresis (15). A review article published by Elwell et al. (2003) was the latter study assessing the use of this combination for the treatment of diuretic resistant edema among patients with nephritic syndrome. Although they declared that the data in this regard were insufficient, they presented outcomes in favor of albumin use in combination with furosemide for the treatment of target patients (16). Phillips et al. (2014) were the next groups who assessed the value of 25% albumin, adding to furosemide among patients with heart failure in a small number of patients. Although due to their sample size, their findings were not generalizable, they showed improved diuresis among their patients causing earlier ICU discharge (17). On the other hand, Doungngern et al. (2012) opposed the use of albumin added to intravenous furosemide used for the treatment of volume overload among cancerous patients. They administered continuous 6 hours of 25% albumin infusion among ICU-admitted cases under continuous intravenous furosemide treatment and represented an insignificant difference in net volume loss and urine output of the intervention group as compared to those under furosemide treatment only (18).

Despite the recent evidence regarding the use of furosemide in up to 80% of mechanically ventilated pediatrics admitted at PICU, the routine use of furosemide for mechanically ventilated pediatrics requiring negative balance is still a question. The study conducted by Reddy et al. (2014) on children with dengue fever requiring mechanical ventilation due to acute respiratory distress syndrome showed dramatic response to furosemide therapy (19), while the study by Kulkarni et al. (2019) on mechanically ventilated pediatrics due to bronchiolitis revealed insignificant oxygenation improvement following furosemide administration (13). However, the present study showed significant improvement of oxygenation due to the use of furosemide among mechanically ventilated pediatrics resenting from pleural effusion.

As demonstrated above, studies in the literature have been conducted on adults, and none of them have evaluated albumin add-on therapy to furosemide for the treatment of transudative pleural effusion in children.

The only study in this regard was performed by Reddy et al. (2018), who assessed this combination on 44 children with volume overload. Their study protocol was similar to ours, and they primarily assessed the efficacy of this compound on fluid balance that showed better outcomes for the intervention group compared to controls, but insignificantly. Besides, their secondary outcomes included 28-day all-cause mortality and hospital stay that were not remarkably different between the two groups. Therefore, they concluded the inefficiency of this combination and recommended further investigations (20).

The evaluation of the efficacy of the albumin and furosemide combination among mechanically-ventilated children in PICUs and achievement of significant results in reducing pleural effusion in mechanically-ventilated ill children within 4 days can be regarded as the strengths of the present study. However, it is of great importance to note that as we had a short-term follow-up of patients, this study could not assess the secondary outcomes and the length of hospital or PICU stay, which can be regarded as the limitations of the present study. Significant results obtained from the used combination can encourage other researchers to perform similar studies with a longer follow-up period.

Conclusion

In conclusion, as the first study worldwide, considerable benefits were found in the use of albumin and furosemide combination among PICU-admitted children under mechanical ventilation who required negative fluid balance. No hemodynamic instability or death was reported in this study. During this short follow-up period, a satisfactory percentage of children were separated from the ventilator and transferred to the ward. In order to generalize the outcomes, further studies with a larger study population are recommended.

Acknowledgments

This study was supported by a grant from Isfahan University of Medical Sciences.

Authors' contributions

MR. H and A. SH: Conceptualization; data collection; Investigation; writing the original draft; review and editing. A. SH.: Conceptualization; methodology; project administration; supervision; writing the original draft; review and editing. H. ZA and MR. H: Conceptualization; methodology; writing, review and editing.

Funding

Non

Conflict of interests

The authors declare they have no conflict of interests.

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