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Comparison of Two Fluid Therapy Methods with and Without Lasix in Crash Injured Patients with Lung Contusion: A Randomized Clinical Trial

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Abstract

Introduction: There are various approaches to fluid therapy for patients with lung contusions, and managing fluid levels can be crucial to the recovery of these patients. This study was conducted from January to June 2022 to determine the effectiveness of two methods of fluid therapy with and without Lasix in patients with crash injury accompanied by lung contusion.

Methods: This clinical trial, conducted at Bahonar Hospital, Kerman, randomly divided patients with crush injury into two groups: recipients of normal saline and recipients of crystalloid plus Lasix. Clinical parameters, including blood pressure, respiratory function, and biochemical markers, were monitored at baseline and every 3 hours for a period of 96 hours.

Results: The Lasix group showed a significantly reduced need for intubation (22.2% vs 43.8%, $p = 0.02$) and shorter NIV duration ($p = 0.008$) compared to the control group. Intra-abdominal pressure and PF ratio demonstrated favorable trends in the intervention group ($p<0.01$). Significant improvements in CPK, phosphorus, and potassium levels were observed with diuretic therapy ($p<0.05$).

Conclusion: The addition of Lasix to standard fluid therapy improved respiratory outcomes and metabolic parameters in patients with crush injuries and pulmonary contusions. This combined approach warrants further investigation in larger clinical trials.

Keywords: Crush Injuries, Contusion, Trauma, Fluid Therapy, Furosemide.

Introduction

Crush injury results from external compression, causing direct tissue trauma and reperfusion ischemia. Releasing the pressure can lead to muscle damage, swelling, necrosis, and nerve dysfunction[1]. Crush syndrome, the systemic manifestation of this injury, may result in organ failure or death. Early detection and aggressive fluid resuscitation are critical to preventing acute kidney injury [2]. This syndrome can also occur in non-traumatic settings, such as prolonged immobilization due to intoxication or unconsciousness[3], and may progress to kidney failure, multi-organ dysfunction, or death [4–6]. Notably, it is the second leading cause of death in earthquakes [7]. Pulmonary contusion involves vascular lung damage without tissue rupture and accounts for over 25% of fatalities in blunt chest trauma [8]. Severe cases requiring mechanical ventilation are often associated with significant chest wall injury [9]. Respiratory distress is a key symptom, and clinical worsening may occur within the first 24 hours, necessitating close monitoring [10, 11]. Management focuses on respiratory support and fluid balance, although optimal fluid therapy remains a topic of debate[12]. In unstable patients, shock treatment takes priority, even if it exacerbates pulmonary fluid accumulation and hypoxia [12]. Initial resuscitation typically involves crystalloids (normal saline or Ringer's lactate), but blood products are recommended if initial efforts fail [13]. Animal and human studies suggest hypertonic saline (7.5%) may reduce mortality[5]. However, the lack of standardized guidelines and conflicting approaches to fluid management and respiratory support highlight the need for further research. This study aims to compare the efficacy and safety of two fluid resuscitation strategies in patients with crush injuries and concomitant pulmonary contusions, evaluating their impact on clinical outcomes, including respiratory parameters, hemodynamic stability, and complication rates.

Methods

Study Design and Setting

This study was conducted as a clinical trial. The study population consisted of patients aged 18-50 years with stroke or injury who were referred to Bahnerkerman Hospital during the first six months of 2022. The study protocol was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics code: IR.KMU.AH.REC.1401.250) and registered in the Iranian Registry of Clinical Trials (IRCTID: IRCT20101220005426N14). Informed consent procedures were carefully adapted for critically ill patients with pulmonary contusions, utilizing simplified forms for conscious patients and obtaining consent from legally authorized representatives for incapacitated individuals. In emergencies where family members were unavailable, deferred consent was implemented under strict ethical oversight, with thorough documentation, independent witnessing, and the option to withdraw at any time. Written informed consent was ultimately obtained from all participants or their representatives, with all procedures complying with the Helsinki Declaration and national clinical research regulations to ensure complete protection of patients' rights.

Participants

Considering that an article similar to the current work was not found to determine the sample size, a pilot study was conducted first, and the number of 26 people in each group was considered based on the following formula.

- Z_1-α/2 = 1.96 (for α=0.05)
- Z_1-β = 0.84 (for 80% power)
- $\sigma_1 = 5.2$, $\sigma_2 = 4.8$ (SD from pilot study)
- $\mu_1 - \mu_2 = 4.0$ (clinically important difference in CPK levels)

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

Inclusion criteria:

- Crash injury patients with lung congestion and need oxygen therapy
- CPK greater than 5000 during two measurements 6 hours apart
- Consent to participate in the study
- Age 18-50 years
- Absence of respiratory distress at the beginning of arrival
- No need for intubation
- No history of known disease under treatment
- Absence of myocardial contusion

Exclusion criteria:

- Myocardial contusion
- organ failure
- chronic pulmonary disease
- pulmonary embolism
- need for massive transfusion
- Complications of blood transfusion
- spinal cord injury
- Acute kidney injury
- not willing to participate in the study
- death within the first 48 hours.
- After obtaining the ethics code and the clinical trial code, the researcher began to conduct the study. In the initial stage, after sampling and explaining the research objectives to the patients and their families and obtaining informed

consent, the patients were randomly assigned to one of two groups: a) liquid therapy or b) fluid therapy + Furosemide. A block randomization method with four blocks was used to assign people to two intervention groups.

- **Randomization:** The block random assignment method was used to assign people to two groups randomly. For this purpose, blocks of four were used, with two people in the control group and two people in the intervention group. R Statistical software was used for this work.
- **Blinding:** This study was conducted in a double-blinded manner, and the participants were unaware of the allocation of the study groups. The individuals who collected the data during the study were also unaware of the study groups.

To ensure rigorous blinding despite furosemide administration in the intervention group, identical IV solutions were prepared by an independent pharmacy team (furosemide-added crystalloids for the intervention group vs. normal saline for the control group), with all infusion pumps pre-programmed and screens covered by opaque labels. A double-blind design was maintained for participants, treating clinicians, and outcome assessors, while diuresis monitoring was performed by unblinded ICU staff who were not involved in data collection.

2.3. Procedure

Therapeutic intervention

1. Control group: Patients received one liter of crystalloid solution per hour as a bolus for two hours, under monitoring, and then received six liters of liquid daily until they were unable to tolerate oral intake.
2. Intervention group: Similar to the control group, fluid therapy was initiated. After three hours of receiving fluids, a bolus of 40 mg furosemide was administered via an ampule, followed by a continuous infusion of 2 mg per hour using an infusion pump and a Lasix ampule. The Lasix ampule was manufactured by the Caspian company and contained 20 milligrams per 2 milliliters.

Data gathering

A study checklist was prepared to record the desired variables (systolic pressure, diastolic pressure, mean arterial pressure, heart rate, respiration rate, Pao2, arterial blood gases, serum electrolytes, and CPK). Systolic pressure, diastolic pressure, mean arterial pressure, heart rate, respiratory rate, Pao2, before the intervention and every hour after the intervention for up to 24 hours and arterial blood gases, serum electrolytes and CPK before the intervention and every 6 hours up to It was measured 24 hours after the intervention ALPK2 mercury sphygmomanometer made in Japan was used to measure systolic and diastolic blood pressure. In each patient, pressure was measured from one arm. Heart rate and breathing rate were measured visually by the researcher using a pulse oximeter. Also, to measure electrolytes, five cc of venous blood samples were taken at the desired times and sent to the central laboratory of Shahid Bahonar Hospital, Kerman. Arterial blood gases were also taken with a heparinized insulin syringe and measured in the central laboratory of Shahid Bahonar Hospital, Kerman. In cases of hypotension or electrolyte imbalance, appropriate measures, including fluid adjustment and electrolyte correction, were implemented, with furosemide discontinued in severe cases. For patients experiencing worsening respiratory distress, oxygen support was escalated according to clinical conditions, potentially progressing to HFNC or intubation if necessary. If acute kidney injury occurred, immediate consultation with a nephrologist was obtained, with renal-dose dopamine considered when indicated. For anaphylaxis or transfusion reactions, the causative agent was immediately discontinued, and epinephrine, along with corticosteroids, was administered.

Statistical analysis

After collecting the data, it was entered into SPSS 22 software, and descriptive statistics, including frequency, percentage, mean, and standard deviation, were used to analyze the data. Repeated-measure ANOVA statistical analysis was used to compare the desired variables between the two intervention groups. If the data distribution was not normal, non-parametric tests such as the Friedman test were used, and the significance level was set at 0.05.

Results

The age in the group receiving Lasix was 43.28 ± 13.12 years, and in the control group it was 42.72 ± 12.43 years. The frequency of gender in the group receiving Lasix was 16 (35.6%) women and 29 (64.4%) men, and in the control group, 20 (41.7%) women and 28 (58.3%) men, respectively. No statistically significant difference was found between the two groups in terms of age (P = 0.833) or gender (P = 0.545).

The average levels of calcium (P = 0.967), potassium (P = 0.637), and phosphorus (P = 0.42) showed no statistically significant differences between the two groups before the intervention (Table 1).

In the Lazix 10 (22.2%) group, intubation was required, whereas in the control group, 21 (43.8%) patients required intubation. This difference was statistically significant (P = 0.02). In the Lazix group, the number of days on NIV was significantly lower compared to the control group, and this difference was statistically significant (P = 0.008). (Table 2)

Table 1: Investigation of the mean electrolyte levels in patients in the two groups of Lasix and control before intervention.

variable	Group	Mean ± SD	t	P value
Ca	Lasix	3.28 ± 0.33	-0.041	0.967
	Control	3.29 ± 0.31		
K	Lasix	5.38 ± 0.58	-0.474	0.637
	Control	5.43 ± 0.54		
P	Lasix	5.55 ± 0.47	-0.813	0.418
	Control	5.63 ± 0.44		

Table 2: Assessment of the need for intubation and the number of days of NIV in patients in the two groups of Lasix and control before intervention

Variable	Group	Lasix (n=45)	Control (n=48)	χ^2	p-value
Need for intubation	Yes	10 (22.2%)	21 (43.8%)	4.84	0.02
	No	35 (77.8%)	27 (56.2%)		
Duration of NIV use	0 days	35 (77.8%)	27 (56.2%)	4.22	0.008
	1 day	4 (8.9%)	7 (14.6%)		
	2 days	3 (6.7%)	8 (16.7%)		
	≥3 days	3 (6.7%)	6 (12.5%)		

There was no significant difference between the two groups in intra-abdominal pressure before the intervention (P = 0.895). There was a significant difference in intra-abdominal pressure between the two groups at different times, such that in the Lasix group, this value decreased. In contrast, in the control group, it increased. In both groups, the temporal trend of intra-abdominal pressure was statistically significant (P < 0.00) (Table 3). According to the repeated measures ANOVA test, it can be observed that there is a significant difference between the two groups in terms of abdominal pressure, and a significant time trend is also present for both groups (Time: F = 2.48, P = 0.03; Group: F = 24.98, P < 0.001).

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According to the repeated measures ANOVA test, it can be observed that there is a significant difference between the two groups in terms of abdominal pressure, and a significant time trend is also present for both groups (Time: F = 2.48, P = 0.03; Group: F = 24.98, P < 0.001).

Overall, there was a significant difference in PF ratio between the two groups, Lasix and control (P = 0.00). Additionally, at different hours, except for the sixth hour, where there was no significant difference, the average PF RATIO had a significant difference between them, increasing over time (Table 4). According to the repeated measures ANOVA test, it is observed that there is a significant difference between the two groups in PF ratio, and the temporal trend is also significant for both groups. Time (F=2.35, P=0.02), group (F=32.7, P<0.001).

Table 3: Investigating the average intra-abdominal pressure in the two groups of patients, one receiving Lasix and the other serving as a control, at different time intervals

Intra-abdominal pressure at different hours		Mean ± SD	t	P value
zero	Lasix	6.71 ± 3.85	0.13	0.89
	Control	6.81 ± 3.56		
six	Lasix	9.35 ± 4.25	1.65	0.10
	Control	10.29 ± 4.14		
Twenty-four	Lasix	8.97 ± 5.08	3.7	0.00
	Control	11.75 ± 4.61		
forty eight	Lasix	7.75 ± 4.72	6.43	0.00
	Control	12.47 ± 5.9		
Ninety six	Lasix	6.2 ± 4.75	6.2	0.00
	Control	12.2 ± 6.72		

Table 4: Investigating the average PF RATIO in patients in the two groups of Lasix and control at different times

PF RATIO at different hours		Mean ± SD	t	P value
six	Lasix	139.77 ± 28.3	1.24	0.21
	Control	137.16 ± 27.2		
Twenty-four	Lasix	154.28 ± 29.8	3.95	0.00
	Control	136.6 ± 30.13		
forty eight	Lasix	187.2 ± 33.2	6.46	0.00
	Control	146.9 ± 40.8		
Ninety six	Lasix	219.6 ± 39.3	6.18	0.00
	Control	168.93 ± 51.8		

Since the CPK test is not normally distributed, the Whitney test, a non-parametric test, was used for each time point. The results in the above table show that, according to the Whitney test, there was no significant difference in the mean CPK between the two groups before the intervention, and also no significant difference at the sixth hour. However, at 24, 48, and 96 hours, this difference is statistically significant (P < 0.00). It is also evident that from the sixth hour after the intervention, this trend has been decreasing.

VIn the table above, we can see that the average phosphorus level during different hours is significantly different between the two groups (P = 0.0001). Additionally, the phosphorus level in both groups decreased over time. (Table 6). Based on the repeated-measures ANOVA test, it is observed that there is a significant difference between the two groups in terms of phosphorus, and the time trend is also significant for both groups. Time (F=0.78, P<0.001) and group (F=17.87, P<0.001).

The results of the table above also indicate that, from 6 pm onwards, there was a significant statistical difference in the average potassium levels between the two groups (P = 0.00). It is also evident that this trend has been decreasing in both groups. (Table 7). According to the repeated measures ANOVA test, it can be observed that there is a significant difference between the two groups in terms of potassium. Also, the temporal trend is significant for both groups. Time (F=7.98, P<0.001) and group (F=33.15, P<0.001).

Table 5: Investigation of mean CPK in patients in the two groups of Lasix and control at different times.

CPK at different hours		Mean ± SD	P value
zero	Lasix	13537.7 ± 3545.5	0.817
	Control	13572.9 ± 3413.2	
six	Lasix	17175.5 ± 17641.8	0.192
	Control	15366.6 ± 4132.5	
Twenty-four	Lasix	16196.6 ± 5075	0.010
	Control	17620.8 ± 4461.5	
forty eight	Lasix	7496.8 ± 7489	0.001
	Control	10889.3 ± 9727	
Ninety six	Lasix	2136.8 ± 3524.6	0.000
	Control	4766.7 ± 5428.6	

Table 6: Investigation of mean P in patients in the two groups of Lasix and control at different times.

	P	Mean ± SD	P value
six	Lasix	5.25 ± 0.5	<0.0001
	Control	5.40 ± 0.47	
Twenty-four	Lasix	4.98 ± 0.56	<0.0001
	Control	5.28 ± 0.53	
forty eight	Lasix	4.62 ± 0.5	<0.0001
	Control	5.03 ± 0.45	
Ninety six	Lasix	4.36 ± 0.45	<0.0001
	Control	4.78 ± 0.55	

Table 7: Investigation of mean P in patients in the two groups of Lasix and control at different times.

K		Mean ± SD	P value
six	Lasix	5.08 ± 0.45	<0.0001
	Control	5.31 ± 0.46	
Twenty-four	Lasix	4.79 ± 0.48	<0.0001
	Control	5.1 ± 0.45	
forty eight	Lasix	4.39 ± 0.45	<0.0001
	Control	4.89 ± 0.45	
Ninety six	Lasix	4.18 ± 0.31	<0.0001
	Control	4.68 ± 0.52	

Discussion

Currently, there are therapeutic contradictions, especially in the field of fluid therapy and respiratory support, in patients with pulmonary contagion. For this purpose, the present study was conducted to compare two fluid therapy methods in patients with crash injury accompanied by lung contusion. The study's key findings revealed that the group receiving both fluid therapy and diuretics required fewer intubations, had shorter mechanical ventilation durations, and experienced a reduction in intra-abdominal pressure. Additionally, we observed a significant difference in electrolytes (phosphorus, potassium, and creatine kinase) in the group that received diuretics. Therefore, this study identified that the use of diuretics in patients with concomitant pulmonary contusion leads to better outcomes in terms of fluid resuscitation. In other studies, conducted on this subject, Gryth et al. (2010) conducted a study in which 29 pigs, all wearing body armor, were shot with a 7.62 mm assault rifle to induce a standard lung injury. These animals were divided into three groups: a saline hypertonic with dextran group, a Ringer's lactate group, and an untreated control group.

The results showed that the impact caused pulmonary contusion, desaturation, hypotension, increased heart rate, and an inflammatory response. No change in blood pressure was observed after fluid therapy. The treatment with hypertonic saline and dextran led to a significant decrease in lung water and a better tendency to achieve a higher PaO2 compared to the treatment with Ringer's lactate. The dissemination of tumor necrosis factor-alpha and heart rate in animals that were given fluids was significantly lower. Overall, the results of this study showed that fluid administration has no effect on blood pressure or mortality in this non-hemorrhagic shock model caused by lung contusion. However, the data from this study indicate that hypertonic saline with dextran has advantages over Ringer's lactate for damaged lungs [14]. In the study by Prunet et al. (2014), anesthetized female pigs (n=5 groups) were shot with five small bullets to the right side of the chest. The researchers allowed them to bleed for 30 minutes, resulting in a loss of 25 to 30 milliliters per kilogram of body weight. The pigs were randomly divided into resuscitation groups, in which mean arterial blood pressure was maintained at a minimum of 70 millimeters of mercury using one of three methods: A) normal saline, B) normal saline without restriction, C) normal saline with low volume plus norepinephrine or hypertonic saline with hydroxyethyl starch. The control pigs were anesthetized but did not receive any injury or treatment. After 20 hours, the animals were euthanized for measurement of extravascular lung water by gravimetry. The results showed that the fluid loading in each group was significantly different. All three treatment groups had higher extravascular lung water compared to the control group. Bilateral pulmonary edema was observed in the normal saline and hypertonic saline with hydroxyethyl starch groups. The three treatment groups showed similar decreases in oxygen delivery. Pulmonary static compliance decreased in both the normal saline and hypertonic saline groups, regardless of the use of hydroxyethyl starch. However, compliance in the low-volume normal saline group with norepinephrine and the control group remained similar. The normal saline low volume group with norepinephrine had pathological lactate levels [15].

In a similar study, Prunet et al. (2018) investigated the short-term effects of hypertonic saline and hydroxyethyl starch in an experimental model of lung contusion and hemorrhagic shock. Lung contusion resulting from blunt chest trauma was induced in 28 anesthetized female pigs with five screw impacts to the right chest wall, followed by hemorrhagic shock and fluid resuscitation.The results showed that traumatic blunt chest injury was accompanied by transient collapse and hypoxemia in both groups. Post-mortem weighing assessment showed a significant difference in EVLW between the normal saline group and the HS/HES group. Based on the pathological threshold of EVLW exceeding ml/kg7, the results showed that only the normal saline group, unlike the HS/HES group, experienced pulmonary edema. After hemorrhagic shock, infusion of HS/HES provided the possibility of restoring mean arterial pressure and effective cardiac index. The pulmonary shunt increased transiently after fluid resuscitation, but there was no significant impairment in oxygen delivery. In this study, an animal model of lung injury following hemorrhagic shock was used to evaluate the short-term effectiveness of fluid resuscitation with 4 milliliters per kilogram of HS/HES in preventing pulmonary edema, which was more effective than therapeutic fluid with 10 milliliters per kilogram of normal saline [16]. Given the reference to the above studies, it can be said that prescribing liquid therapy in individuals with pulmonary edema is controversial [17]. However, measuring pulmonary artery pressure enables the doctor to administer sufficient fluids to prevent shock without exacerbating edema [18]. The primary focus of our approach to these patients was prescribing diuretics to reduce fluid overload. This is because it may be used in the treatment of pulmonary edema to relax the smooth muscle of the pulmonary veins, thereby decreasing pulmonary venous resistance and pressure in the pulmon.

Conclusion

Considering that there are therapeutic contradictions, especially in the field of fluid therapy and respiratory support in patients with pulmonary contusion due to crash injury. The results of the present study showed that fluid therapy with diuretics had favorable outcomes in patients with crash injuries and lung contusion. Therefore, this method can improve patient conditions and save lives. In the future, more studies can be conducted in this field.

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None.

Conflict of Interest Disclosures

The authors had no conflicts of interest.

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None.

Authors' Contributions

MA, ST, MT*, YJ, and EN conceived the study, designed the trial, supervised the conduct of the trial, and data collection. MA and ST undertook recruitment of participating centers and patients and managed the data, including quality control. YJ and EN provided statistical advice on study design and analyzed the data. MT drafted the manuscript, and all authors contributed substantially to its revision. MT takes responsibility for the paper as a whole. All authors read and approved the final version of the manuscript.

Ethical Statement

The study protocol was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics code: IR.KMU.AH.REC.1401.250) and registered in the Iranian Registry of Clinical Trials (IRCTID: IRCT20101220005426N14).

Declaration of Generative AI and AI-assisted technologies

Not cleared.

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