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Original Article

Effect of early restrictive fluid resuscitation on inflammatory and immune factors in patients with severe pelvic fracture

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ABSTRACT

Purpose: To study the effect of early restrictive fluid resuscitation (EFR) on inflammatory and immune factors in patients with severe pelvic fracture (SPF).

Methods: A total of 174 SPF patients in the Department of Orthopaedics, the First Affiliated Hospital of Chengdu Medical College from July 2015 to June 2018 were involved in this study and divided into EFR group ($n = 87$) and control group ($n = 87$) using the random number table method. Conventional fluid resuscitation (CFR) was performed in control group, and EFR was performed in EFR group. The incidences of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) during rescue, successful rescue rate, blood transfusion volume, fluid input, and resuscitation time were compared between the two groups. The parameters including prothrombin time (PT), hematocrit (HCT), platelet (PLT) and blood lactate (BL) at the 4th hour after fluid resuscitation were recorded. The levels of inflammatory factors (TNF-α, IL-6, CRP) and immune factors ($CD3^+$, $CD4^+$, $CD8^+$, CD4+/CD8+) were compared between the two groups before treatment and 7 days after treatment. The revised acute physiologic and chronic health evaluation system and the sequential organ failure assessment scores were adopted for evaluation before treatment and 7 days after treatment.

Results: The incidences of ARDS and MODS during rescue in EFR group were significantly lower than those in control group (p=0.015 and 0.010 respectively), and the successful rescue rate in EFR group was significantly higher than that in control group ($p = 0.011$). The blood transfusion volume, fluid input, resuscitation time in EFR group were significantly lower than those in control group ($p = 0.016$, 0.002 and 0.001 respectively). At the 4th hour after fluid resuscitation, PT and BL in EFR group were significantly lower than those in control group ($p = 0.021$ and 0.003 respectively), while HCT and PLT in EFR group were significantly higher than those in control group ($p = 0.016$ and 0.021 respectively). On day 7 after treatment, TNF-α, IL-6, CRP and $CD8^+$ in EFR group were significantly lower than those in control group ($p = 0.003$, 0.004, 0.007 and 0.003 respectively), while $CD3^+$, $CD4^+$ and CD4+/CD8+ in EFR group were significantly higher than those in control group ($p = 0.004$, 0.000, 0.007 respectively). On day 7 after treatment, the revised acute physiologic and chronic health evaluation (APACHE) system and the sequential organ failure assessment (SOFA) scores in EFR group were significantly lower than those in control group.

Conclusion: EFR can effectively eliminate inflammatory factors, improve immune function, maintain the stability of blood components, reduce the incidences of ARDS and MODS, and elevate the successful rescue rate in patients with SPF.

Introduction

Sever pelvic fracture (SPF) is severe pelvic injury caused by high-energy injury, easily leading to extensive hemorrhage, which is difficult to control.[1] For patients with SPF, a large amount of fluid was given for resuscitation in order to restore blood pressure as soon as possible.[2] The literature has proved that fluid resuscitation does not benefit all patients, and sometimes it can aggravate bleeding, even causing death.[3] Studies have shown that early restrictive fluid resuscitation can maintain the blood pressure in a low range, which is more conducive to hemostasis.[4] We applied early restrictive fluid resuscitation in patients with SPF in the Department of Orthopaedics, the First Affiliated Hospital of

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Chengdu Medical College, from July 2015 to June 2018, and evaluated the efficacy and its effect on inflammatory and immune factors. The results were satisfactory.

Methods

General data

From July 2015 to June 2018, 174 patients with SPF in the Department of Orthopaedics, the First Affiliated Hospital of Chengdu Medical College were enrolled in this study. There were 123 males and 51 females, aged 18–76 years, with an average of 44.62 years. There were 103 road traffic injuries, 47 fall injuries and 24 crush injuries. The time from injury to treatment was 2–9 h, 4.36 h on average. The Tile classification of pelvic fracture was as follows: 36 cases of type B1, 39 B2, 31 B3, 28 C1, 24 C2, and 16 C3. Twelve cases were associated with limb fracture, 9 with lumbar spine fracture. Inclusion criteria: the patients were diagnosed with SPF by imaging; with ISS score >16; with informed consent; with systolic blood pressure <90 mmHg. Exclusion criteria: the patients were associated with severe trauma in the brain or other important organ, immune diseases, abnormal immunity, infectious diseases, abnormal liver and kidney function or hematopoietic dysfunction. All patients were divided into early restrictive fluid resuscitation (EFR) group ($n = 87$) and control group ($n = 87$) using the random number table method. The general data presented no significant difference between the two groups ($p > 0.05$, Table 1).

Treatment methods

Two groups of patients were monitored for vital signs immediately after admission, venous access was established, and preoperative examinations and preparation were performed.

The control group underwent conventional fluid resuscitation (CFR). The plasma, suspended red blood cells, colloidal fluid and balance solution were timely, sufficiently, and quickly transfused to supplement blood volume and maintain mean arterial pressure (MAP) at 60–80 mmHg and systolic blood pressure (SBP) above 100 mmHg.

The EFR group underwent early restrictive fluid resuscitation. Totally 200 ml hypertonic sodium chloride solution (7.5%) was given at early stage; 30 min later, hypertonic sodium chloride solution was transfused again if necessary; however, the total amount should be less than 350 mL. Fluid infusion was given until MAP increased to 50–60 mmHg and SBP 70–90 mmHg. Fluid infusion was slowed down to control fluid amount so that MAP and SBP were maintained at stable levels. The sufficient fluid infusion was given after the hemorrhage was stopped by operation.

Observation parameters

The incidences of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) during rescue, successful rescue rate, blood transfusion volume, fluid input, and resuscitation time were observed in two groups. The parameters including prothrombin time (PT), hematocrit (HCT), platelet (PLT) and blood lactate (BL) at the 4th hour after fluid resuscitation were recorded. The levels of inflammatory factors (TNF-α, IL-6, CRP), immune factors ($CD3^+$, $CD4^+$, $CD8^+$, CD4+/CD8+), acute physiology and chronic health evaluation (APACHE) and SOFA scores were compared between the two groups before treatment and 7 days after treatment. TNF-α and IL-6 were determined by ELISA; CRP was determined by immunoturbidimetry; T cell subsets were detected by flow cytometry. All the tests were performed according to the instructions of each kit. APACHE and SOFA were used for evaluation.

Statistical analysis

The SPSS 19.0 statistical software was used for data analysis. Quantitative data were expressed as mean±standard deviation. The paired t test was used for comparison within the group, and the independent sample t test was used for comparison between groups. Qualitative data were expressed as percentages and compared between groups by χ2 test. The statistic value α was set at 0.05.

Results

Comparison of the incidences of ARDS and MODS and the successful rescue rates between the two groups

During the rescue period, the incidences of ARDS and MODS in EFR group were significantly lower than those in control group, and the successful rescue rate in EFR group was significantly higher than that in control group ($p < 0.05$, Table 2).

Comparison of blood transfusion volume, fluid input and resuscitation time between the two groups

The blood transfusion volume, fluid input and resuscitation time in EFR group were significantly lower than those in control group ($p < 0.05$, Table 3).

Table 2
Comparison of incidences of ARDS, MODS, successful rescue and death rate between the two groups, n (%).

Group	ARDS	MODS	Successful rescue	Death
EFR ($n = 87$)	3 (3.45)	2 (2.30)	83 (95.40)	4 (4.60)
Control ($n = 87$)	12 (13.79)	11 (12.64)	64 (73.56)	23 (26.44)
χ^2 value	5.876	6.695	15.723	15.735
p value	0.015	0.010	0.011	0.004

ARDS: acute respiratory distress syndrome, MODS: multiple organ dysfunction syndrome, EFR: early restrictive fluid resuscitation.

Table 1
The general data of two groups.

Group	Gender (male/female)	Age (year)	Mechanism (traffic injury/fall injury/crush injury)	Time from injury to treatment (h)	Tile classification (type B1/B2/B3/C1/C2/C3)	Combined injury (limb fracture/lumber spine fracture)
EFR ($n = 87$)	60/27	44.58 ± 4.55	50/25/12	4.19 ± 0.33	19/18/15/15/11/9	5/4
Control ($n = 87$)	63/24	44.66 ± 4.64	53/22/12	4.52 ± 0.42	17/21/16/13/13/7	7/5
χ^2/t value	0.248	0.115	0.279	0.266	0.934	0.016
p value	0.618	0.909	0.870	0.569	0.968	0.899

EFR: early restrictive fluid resuscitation.

Table 3
Comparison of blood transfusion volume, fluid input and resuscitation time between the two groups ($\bar{x}\pm s$).

Group	Blood transfusion volume (mL)	Fluid input (mL)	Resuscitation time (min)
EFR ($n = 87$)	406.75 ± 41.44	1904.65 ± 194.85	75.93 ± 8.58
Control ($n = 87$)	537.94 ± 55.92	2987.69 ± 300.64	107.93 ± 11.35
t value	17.581	28.197	20.978
p value	0.016	0.002	0.001

EFR: early restrictive fluid resuscitation.

Comparison of PT, HCT, PLT and BL levels between the two groups 4 h after resuscitation

At the 4th hour after fluid resuscitation, PT and BL in EFR group were significantly lower than those in control group, while HCT and PLT in EFR group were significantly higher than those in control group ($p < 0.05$, Table 4).

Comparison of inflammatory factors between the two groups

Before treatment, there was no significant difference in TNF-α, IL-6 and CRP between the two groups ($p > 0.05$). Seven days after treatment, the levels of TNF-α, IL-6 and CRP were significantly decreased compared with the pretreatment levels in two groups ($p < 0.05$), while TNF-α, IL-6 and CRP in EFR group were significantly lower than those in control group ($p < 0.05$, Table 5).

Comparison of T cell subsets between the two groups

Before treatment, $CD3^+$, $CD4^+$, $CD8^+$ and CD4+/CD8+ showed no significant difference between the two groups ($p > 0.05$), but $CD3^+$, $CD4^+$ and CD4+/CD8+ were significantly increased and $CD8^+$ was significantly decreased 7 days after treatment ($p < 0.05$). $CD3^+$, $CD4^+$ and CD4+/CD8+ in EFR group were significantly higher than those in control group, and $CD8^+$ was significantly lower than that in control group 7 days after treatment ($p < 0.05$, Table 6).

Comparison of APACHE and SOFA scores between the two groups

Before treatment, there was no significant difference in the APACHE and SOFA scores between the two groups ($p > 0.05$). Seven days after treatment, the APACHE and SOFA scores in the two groups were significantly decreased ($p < 0.05$), but the APACHE and SOFA scores in EFR group were significantly lower than those in control group ($p < 0.05$, Table 7).

Table 4
Comparison of PT, HCT, PLT and BL levels between the two groups 4 h after resuscitation ($\bar{x}\pm s$).

Group	PT (s)	HCT (%)	PLT ($\times 10^9$/L)	BL (mmol/L)
EFR ($n = 87$)	10.78 ± 1.17	0.55 ± 0.07	137.93 ± 14.94	2.09 ± 0.31
Control ($n = 87$)	15.59 ± 1.65	0.34 ± 0.04	105.87 ± 11.06	3.75 ± 0.43
t value	22.180	24.295	16.087	29.209
p value	0.021	0.003	0.016	0.021

PT: prothrombin time, HCT: hematocrit, PLT: platelet, BL: blood lactate, EFR: early restrictive fluid resuscitation.

Discussion

Due to high-energy injury, the patients with severe pelvic fracture often have multiple ruptures and hemorrhage, and the bleeding is persistent and rapidly developed, resulting in sharp decline of blood pressure and blood volume, hemodynamic instability, loss of blood perfusion, imbalance of immune mechanism, even multiple organ failure.[5] Therefore, the rescue at early stage requires effective fluid resuscitation to replenish blood volume, restore hemodynamics, maintain blood perfusion, and improve blood supply to tissues, which is beneficial for the diagnosis of bleeding sites and bleeding control.[6] Although early CFR can restore blood volume and normal blood perfusion, it may cause the detachment of blood clots and thrombus shift, and massive fluid transfusion may excessively dilute the blood, resulting in clotting dysfunction. It is difficult to form blood clots, and the bleeding is aggravated, so the patients would develop severe ischemia of tissues and organs, with impaired immune function and abnormal compensation of the body.[7] EFR maintains blood pressure at a tolerable low level by appropriately controlling the volume and speed of fluid infusion until hemorrhage is fully controlled.[8] EFR can not only ensure normal tissue perfusion, but also avoid excessive dilution of blood, thereby avoiding blood clot detachment and thrombus shift, maintaining body coagulation function, inhibiting bleeding, improving microcirculation and blood supply to tissues, and alleviating metabolic acidosis.[9] EFR can maintain the hemodynamic stability of the body, inhibit exudation and adhesion of leukocytes, and avoid the production of oxygen free radicals, so as to improve body immunity.[10] In this study, the incidences of ARDS and MODS in EFR group were significantly lower than those in control group; the successful rescue rate in EFR group was significantly higher than that in control group; at the 4th hour after fluid resuscitation, PT and BL in EFR group were significantly lower than those in control group, while HCT and PLT in EFR group were significantly higher than those in control group, suggesting that EFR is superior to CFR in patients with severe pelvic fracture.

TNF-α is the initiating factor of inflammatory stress response, which can trigger and induce inflammatory cascade, promote the release of inflammatory factors such as IL-6 and CRP, and aggravate

Table 5
Comparison of inflammatory factors between the two groups ($\bar{x}\pm s$).

Group	TNF-α (pg/mL)		IL-6 (pg/mL)		CRP (mg/L)	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment
EFR ($n = 87$)	75.68 ± 7.73	41.54 ± 4.33	369.95 ± 38.91	203.64 ± 22.94	65.85 ± 6.74	29.94 ± 3.17
Control ($n = 87$)	74.95 ± 7.69	58.36 ± 5.92	364.77 ± 38.78	269.62 ± 28.35	65.93 ± 6.69	42.84 ± 4.41
t value	0.625	21.390	0.880	16.875	0.079	22.154
p value	0.533	0.003	0.380	0.004	0.938	0.007

TNF-α: tumor necrosis factor-α, IL-6: interleukin 6; CRP: C-reactive protein, EFR: early restrictive fluid resuscitation.

Table 6
Comparison of T cell subsets between the two groups ($\bar{x}\pm s$).

Group	CD3+ (%)		CD4+ (%)		CD8+ (%)		CD4+/CD8+	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment
EFR ($n = 87$)	0.65 ± 0.08	0.95 ± 0.13	0.56 ± 0.07	0.79 ± 0.09	0.59 ± 0.07	0.33 ± 0.04	0.95 ± 0.97	2.39 ± 0.25
Control ($n = 87$)	0.66 ± 0.08	0.86 ± 0.09	0.57 ± 0.07	0.67 ± 0.08	0.58 ± 0.07	0.42 ± 0.05	0.98 ± 0.99	1.59 ± 0.17
t value	0.824	5.309	0.942	9.295	0.942	13.110	0.202	24.682
p value	0.411	0.004	0.347	0.000	0.347	0.003	0.840	0.007

EFR: early restrictive fluid resuscitation.

Table 7
Comparison of APPACHE and SOFA scores between the two groups ($\bar{x}\pm s$).

Group	APACHE score		SOFA score	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment
EFR ($n = 87$)	19.78 ± 2.04	12.86 ± 1.33	11.67 ± 1.21	7.26 ± 0.84
Control ($n = 87$)	19.81 ± 2.01	13.62 ± 1.39	11.70 ± 1.23	7.69 ± 0.88
t value	0.0977	3.6848	0.1622	3.2968
p value	0.9223	0.0003	0.8714	0.0012

EFR: early restrictive fluid resuscitation. APACHE: acute physiologic and chronic health evaluation, SOFA: sequential organ failure assessment.

inflammatory stress response.[11] IL-6 is an inflammatory factor produced by activated fibroblasts and T cells, and it can induce B cell precursors to be transformed to B cells and differentiated into the cells which are capable to produce antibodies.[12] IL-6 can synergize with colony-stimulating factors to enhance the proliferation of primitive bone marrow-derived cells, promote the lysis of NK cells and increase its activity.[13] IL-6 stimulates hepatocytes to secrete acute-phase proteins, induces, participates in and promotes the progression of inflammatory responses.[14] As an acute-phase protein produced by hepatocytes during the body injury or acute inflammatory reaction, CRP activates complements, enhances the phagocytosis of leukocytes, and participates in immune regulation.[15] Severe pelvic fracture can cause strong inflammatory stress reaction in the body, leading to excessive activation of inflammatory factors, thus a variety of inflammatory factors are generated and released, triggering the "waterfall-like effect" of inflammatory factors and aggravating inflammatory reactions. Furthermore, it causes tissue damage and microcirculatory disorders, and even leads to ARDS and MODS, seriously affecting the prognosis of patients.[16] Cellular immunity is indispensable in body immunity. T cell subsets are important indicators of the body immune mechanism, so it plays an important role in the diagnosis and treatment of disease and prognosis evaluation.[17] There are $CD4^+$ and $CD8^+$ subsets, which maintain the immune balance through mutual cooperation and restriction.[18] The $CD4^+$ subset can mediate cellular immunity, produce antibodies, promote B cell proliferation, and maintain the immune response of the body.[19] The $CD8^+$ subset can specifically eliminate target cells such as viruses, inhibit humoral immunity and cellular immunity, and thus it plays a negative regulatory role in body immunity.[20] The $CD3^+$ subset, expressed on the surface of T cells, can transmit the activation signal generated by the antigen and its receptors to the inside of cells and activate the cells at the same time.[21] Investigation on the immune status of the body is conducive to identify patients at high-risk and evaluate their prognosis. In this study, the inflammatory and immune factors in EFR group were significantly improved 7 days after treatment, suggesting that early restrictive fluid resuscitation is more beneficial to clear inflammatory factors in patients with severe pelvic fracture and correct the immune dysfunction. The APACHE and SOFA scores reflect the severity of disease in critically ill patients. The two scales are positively correlated and the combination of both can accurately evaluate the prognosis of patients. Early restrictive fluid resuscitation can effectively improve the condition of critically ill patients and reduce APACHE and SOFA scores. In this study, APACHE and SOFA scores in EFR group were significantly lower than those in control group 7 days after treatment, suggesting that EFR can effectively reduce APACHE and SOFA scores in patients with severe pelvic facture and promote the clinical outcome.

In conclusion, early restrictive fluid resuscitation can effectively eliminate inflammatory factors, improve body immunity, maintain the stability of blood components, reduce the incidences of ARDS and MODS, decrease APACHE and SOFA scores, and improve successful rescue rate and promote the recovery in patients with severe pelvic fractures.

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Ethical statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Chengdu Medical College.

Conflicts of interest

There were no conflicts of interest declared.

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