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Dynamic Changes of Biochemical Indices and Prognosis of Insulin Therapy in Burn Shock Resuscitation

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Abstract: This study aims to conduct a preliminary exploration on the application value and prognosis of the insulin therapy in the burn shock resuscitation by observing the impact of insulin on the shock resuscitation fluid requirement, urine output and organ function of patients with major burns during the shock stage. Fifty eight patients with major burns including 31 males and 27 females admitted to the Burn Department of the hospital during the period from February, 2012 to December, 2012 were randomly arranged in an insulin treatment group and a control group, each consisting of 29 patients. The initial resuscitation fluid replacement was calculated based on the Ruijin formula, i.e., the total volumes of the colloid (plasma) and crystal (lactated Ringer's solution) were calculated on a 1.5 mL/kg/1% TBSA basis and the ratio of crystal to colloid was between 1:1 and 2:1. The shock resuscitation indicators and platelet changes were tested. The unit colloid volume of the treatment group in the first 24 h was 0.98±0.29 mL/kg/1% TBSA which was significantly lower than (1.16±0.32) mL/kg/1% TBSA in the control group. Meanwhile, the unit urine outputs during the shock stage for the treatment group and the control group were 1.90±0.68 and 1.37±0.61 mL/kg/h, respectively. The treatment group showed significantly higher unit urine output than the control group. The differences between the two groups were statistically significant ($p<0.05$). The TBIL, DBIL, BUN and Cr levels between the patients in the two groups had no significant difference one day after burn. Since day 2 after burn, the treatment group showed lower levels of these indicators than the control group at various time points and the difference had statistical significance ($p<0.05$) at most time points. Platelet counting of the control group was higher than the treatment group on day 3, 6, 9 and 12. The platelet counting between the two groups showed statistical significance ($p<0.05$). The APACHE II score of the control group (6.49±2.18) was significantly lower than that of the treatment group (16.25±3.81) in the first 24 h after the admission. The APACHE II scores of the two groups had statistical significance ($p<0.05$). The application of insulin during the shock stage can reduce the colloid/crystal fluid requirement for resuscitation and increase the urine output of the patient with major burns. This therapy can also extenuate tissue damage and protect organ function. The study shows potential promise of the application of insulin in the shock resuscitation from severe burns.

Key words: Insulin, burn shock, biochemical index, dynamic change, clinical analysis

INTRODUCTION

Systemic Inflammatory Response Syndrome (SIRS) is a common complication occurring on severely burned patients. This syndrome can further develop into Multiple Organ Dysfunction Syndrome (MODS) or even lead to multiple organ failure and shock which are the main cause for death in patients with severe burns. Burn shock is one of the causes of early death in the burn patients and the treatment during the shock stage of the severe burn is of vital importance. The smooth transition of this stage will create good conditions for future wound treatment and reduce the occurrence of sepsis or multiple organ failure (Fioramonti *et al*., 2012; Goertz *et al*., 2012; Samuelsson *et al*., 2012).

Since, the non-diabetic efficacy of insulin was discovered in early 1920s, there have been many studies exploring the regulation and mechanism of insulin on various cytobiological behaviors through non-metabolic means. Multiple stages of wound healing are involved in the role of insulin in regulating the wound repair. Insulin can stimulate the proliferation and migration of the epidermal keratinocytes and vascular endothelial cells so as to promote re-epithelialization and angiogenesis and the wound healing. Insulin can also directly regulate systemic and wound local inflammatory response (Lee *et al*., 2012; Sugita *et al*., 2012; Wang *et al*., 2012). It has been found by some researchers that insulin is also involved in the regulation of vascular permeability. The role of insulin in regulating the wound inflammatory

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response and vascular permeability may be helpful in the shock resuscitation of patients with major burns (Carter *et al*., 2011).

By observing the impact of insulin application on the fluid volume required for resuscitation and the urine output and organ function of the patients with major burns during the shock stage this study aims to conduct a preliminary exploration on the application value of insulin therapy in the resuscitation from burn shock, determine the severity of the major burns and its significance in the prognosis.

MATERIALS AND METHODS

Subjects: Fifty eight patients aging between 16 and 60 with major burns including 31 males and 27 females admitted to the Burn Department of the hospital during the period from February, 2012 to December, 2012 were enrolled for this study. Their total burn areas were between 10 and 80% TBSA and their third degree burn areas ranged between 30 and 70% TBSA. The 58 patients were randomly arranged in an insulin treatment group and a control group, each consisting of 29 patients.

Excluded cases: Patients who had severe primary cardiac, hepatic, renal or endocrine diseases (including diabetes) burns combined with inhalation damage and had been subject to tracheotomy or burns due to electric shock, explosion, chemical poisoning and other special causes and delayed resuscitation patients with evident shock symptom upon admission.

Fluid replacement: The initial resuscitation fluid replacement was calculated based on the Ruijin formula, i.e., the total volumes of the colloid (plasma) and crystal (lactated Ringer's solution) were calculated on a 1.5 mL/kg/1% TBSA basis and the ratio of crystal to colloid was between 1:1 and 2:1. The initial resuscitation fluid replacement was calculated based on the Ruijin formula, i.e., the total volumes of the colloid (plasma) and crystal (lactated Ringer's solution) were calculated on a 1.5 mL/kg/1% TBSA basis and the ratio of crystal to colloid was between 1:1 and 2:1. During the resuscitation stage, the volumes of the colloid and crystal fluids were adjusted according to the vital signs and urine output of the patients. The target was to ensure that the patients were conscious and quiet with warm limbs, well filled peripheral circulation and urine output of 1-2 mL kg^{-1}. The crystal and colloid fluid volumes during the second 24 h were half of the actual intake during the first 24 h and the colloid of the same volume as the second 24 h was given and no crystal was infused in the third 24 h (Arrandale and Ng, 2009).

In addition to the above crystal and colloidal fluids, 3,000 mL day^{-1} of water should be supplemented on a daily basis. The water supplementation may be increased to 5,000 mL day^{-1} according to the body weight of the patient, the ambient temperature and humidity and other conditions. The treatment group was given water supplementation in the form of GIKC solution which was prepared with 1,000 mL of 0.9% NaCl solution+30u of regular insulin+10 mL of 10% KCl solution+1 g of vitamin C while the water supplementation of the control group was given as 0.9% NaCl solution with the same amount of vitamin C, i.e., 1 g of vitamin C per 1,000 mL of NaCl solution. There was no difference in other aspects of the treatments for the two groups.

Shock resuscitation indices: Record the volumes of the actually infused colloid and crystal of the patient in the first 24 h and calculate the unit colloid (or crystal) volume of the first 24 h according to the body weight and burn area: Unit colloid (or crystal) volume of the first 24 h (mL/kg/1% TBSA) = Volume of the actually infused colloid (or crystal) in the first 24 h (mL)/body weight (kg)/1% TBSA.

Record the urine output of the first 24 h and the total urine output in the shock stage (72 h after burn) and calculate the unit urine output: Unit urine output of the first 24 h (mL/kg/h) = Urine output of the first 24 h (mL)/body weight (kg)/24 (h), Unit urine output in the shock stage (mL/kg/h) = Urine output in the shock stage (mL)/body weight (kg)/72 (h).

Biochemical indices: Record the hematocrit indicators in the routine blood tests as well as liver and kidney function related biochemical indicators of the two groups on days 1, 2 and 3 including albumin, prealbumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, Total Bilirubin (TBIL), Direct Bilirubin (DBIL), Blood Urea Nitrogen (BUN) and Creatinine (Cr).

Platelet counting: Test the platelet counting of the peripheral venous blood on the day of admission and monitor the change of platelet counts at 5 time points, i.e., on days 1, 3, 6, 9 and 12 after the admission. Record as well the poorest value of the physiological indicators in the first 24 h after admission (the higher the score, the worse the illness state) and calculate the APACHE II score accordingly.

Statistical analysis: All the data were analyzed by SPSS 12.0. The measurement data were expressed as (±S). The groups were compared by the non-paired t-test. $p<0.05$ was considered statistically significant.

Table 1: General data of the two groups

Groups	Case No.	Male/female (%)	Age (years)	Body weight (kg)	Total burn area	Third degree burn area
Control	29	17 (58.63)/12 (41.38)	46.7±14.6	67.5±12.5	43.9±24.9	51.3±18.4
Insulin treatment	29	14 (48.28)/15 (51.72)	48.2±15.1	65.9±14.9	44.8±26.2	49.8±17.9

Table 2: Comparison between shock resuscitation indices

Groups	First 24 h unit colloid volume (mL/kg/1% TBSA)	First 24 h unit crystal volume (mL/kg/1% TBSA)	First 24 h urine output (mL/kg/h)	Urine output during shock (mL/kg/h)
Control	1.16±0.32	1.08±0.41	1.26±0.62	1.37±0.61
Insulin treatment	0.98±0.29*	1.02±0.37	1.30±0.59	1.90±0.68*

Compared with the control group, *p<0.05

RESULTS AND DISCUSSION

General data: The two groups had no statistically significant difference (p>0.05) in sex ratio, age composition, body weight, burn area and third degree burn area (Table 1).

Comparison between shock resuscitation indices: The treatment group showed a first 24 h unit crystal volume of 1.02±0.37 mL/kg/1% TBSA which was lower than that of the control group 1.08±0.41 mL/kg/1% TBSA. Meanwhile, the treatment group showed a first 24 h unit urine output of 1.30±0.59 mL/kg/h greater than that of the control group 1.26±0.62 mL/kg/h. No significant difference (p>0.05) was found between the two groups. The unit colloid volume of the treatment group in the first 24 h was 0.98±0.29 mL/kg/1% TBSA which was significantly lower than 1.16±0.32 mL/kg/1% TBSA in the control group. Meanwhile, the unit urine outputs during the shock stage for the treatment group and the control group were 1.90±0.68 and 1.37±0.61 mL/kg/h, respectively. The treatment group showed significantly higher unit urine output than the control group. The differences between the two groups were statistically significant (p<0.05) (Table 2). It is suggested that the insulin therapy can reduce the colloidal dosage and increase the urine output in the shock resuscitation.

Hematocrit results of the two groups: On days 1, 2 and 3 after burn, the hematocrit of the treatment group were lower than that of the control group but no significant difference (p>0.05) was found between the two groups (Table 3).

Liver and renal functions-relating biochemical indices: On the first 3 days after burn, two groups had no statistically significant difference (p>0.05) in prealbumin, albumin, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase levels.

The TBIL, DBIL, BUN and Cr levels between the patients in the two groups had no significant difference one day after burn. Since, day 2 after burn, the treatment group showed lower levels of these indicators than the control group at various time points and the difference had statistical significance (p<0.05) at most time points (Table 4).

Table 3: Hematocrit results of the two groups (%)

Groups	1st day	2nd day	3rd day
Control	0.56±0.07	0.53±0.05	0.50±0.05
Insulin treatment	0.51±0.06	0.47±0.07	0.45±0.06

Dynamic changes of platelet count after admission: The platelet counts of the treatment group and the control group on day 1 after admission had no statistically significant (p>0.05) difference with each other. The platelet counts of the two groups dropped significantly on day 4 compared with day 1 and the differences were statistically significant (p<0.05). On days 6, 9 and 12, the platelet counts of the two groups grew from low levels to the normal range (100×10^9/L~300×10^9/L) or even became higher than the normal value. The platelet count of the control group was higher than the treatment group on days 3, 6, 9 and 12. The platelet counting of the two groups showed statistical significance (p<0.05) (Table 5).

First 24 h APACHE II scores after admission: The APACHE II score of the control group (6.49±2.18) was significantly lower than that of the treatment group (16.25±3.81) in the first 24 h after the admission. The APACHE II scores of the two groups had statistical significance (p<0.05).

Correlation between prognosis and clinical indices of the insulin treatment group: For severely burned patients in the treatment group, logistic regression is done with survival or death prognosis after the admission as the dependent variable and age, sex, APACHE II score, presence of platelet counting reduction (defined as the presence of platelet count <100×10^9/L at two or more time points, 29 cases in total) and the length of hospital stay as the independent variables (Table 6).

It is shown in the logistic regression analysis that APACHE II score and presence of platelet counting reduction were closely related to the prognosis after

Table 4: Liver and renal functions-relating biochemical indices

Groups	Time (day)	TBIL (μmol L^{-1})	DBIL (μmol L^{-1})	BUN (mmol L^{-1})	Cr (μmol L^{-1})
Control	1st	31.25±12.67	6.28±3.45	6.18±2.16	117.15±29.14
	2nd	29.44±11.94	6.16±3.48	5.68±2.19	104.52±24.80
	3rd	28.62±11.61	5.82±2.49	5.62±2.17	97.81±22.91
Insulin treatment	1st	30.58±12.53	6.24±3.28	6.09±2.17	115.9±28.450
	2nd	27.49±11.78	4.25±1.81*	3.15±1.05*	71.39±16.81*
	3rd	18.41±9.150*	4.16±1.62*	2.98±0.98*	65.91±17.61*

Compared with the control group, *p<0.05

Table 5: Dynamic changes of platelet count after admission ($\times 10^9$ L^{-1})

Groups	1st day	3rd day	6th day	9th day	12th day
Control	172.2±38.1	99.4±26.8	183.6±49.5	216.9±54.8	273.3±61.9
Insulin treatment	169.1±40.2	82.5±28.4*	161.5±42.9*	198.4±51.6*	254.5±62.8*

Compared with the control group, *p<0.05

Table 6: Correlation between prognosis and clinical indices of the insulin treatment group

Variables	Value set method
Age (X1)	Actual age
Sex (X2)	Male = 1, female = 2
APACHE II score (X3)	Actual score
Platelet decrease or not (X4)	Decrease = 1, not decrease = 2
Length of hospital stay (X5)	Actual length of hospital stay

severe burn (the OR values were 1.484 and 0.013, respectively and the p values were 0.026 and 0.041, respectively) and the regression equation was Logit (p) = 1.281+0.519×3-3.956×4. It is suggested that the non-presence of platelet counting reduction existed as a protective factor and the APACHE II score was the risk factor.

After burn, the organism was in a stringent state and might have glucose metabolism disorders and insulin resistance. The stringency could lead to hyperglycemia but insulin secretion and function in the organism were still relatively insufficient due to the reduction of insulin/pancreatic glucagon ratio. The early application of insulin with glucose after burn could increase the utilization ratio of glucose to maintain stable blood glucose and overcome the impact of insulin resistance (Zhang *et al*., 2011). Insulin has been widely known as a synthetic hormones involved in the regulation of carbohydrates, fat and protein metabolism after severe burns. In recent years, researchers have discovered insulin receptor-mediated and non-metabolism dependent regulation capacity of the insulin for various cells of the organism. For instance, insulin can promote the proliferation and migration of the epidermal keratinocytes, vascular endothelial cells and other wound repair cells. Insulin can also regulate the time phases and function of the appearance and extinction of the neutrophils and wound macrophages on the wound surface (Chen *et al*., 2011; Tuvdendorj *et al*., 2011). By exploring the non-diabetic application of insulin, the clinical application indications of insulin were broadened and new solutions were provided for some difficult clinical problems.

Increased vascular permeability is the main pathophysiological basis of burns and septic shock. It is mediated by thrombin, interleukin-8, tumor necrosis factor-α and other inflammatory mediators and there has been so far no targeted therapy. Although, there are reports on the application of the signaling molecule Src inhibitor against the change of the vascular permeability but Src can be widely involved in cell function which limits its clinical application as an inhibitor (Gauglitz *et al*., 2010a, b; Xin-Long *et al*., 2011). The current therapies, such as burn shock resuscitation or septic shock Early Goal-Directed Therapy (EGDT) are all stopgap measures after the circulatory body fluid has been greatly leaked, lost or transferred to the interstitial space. Researchers discovered that early insulin intervention could reduce damage to endothelial cells and reduce granulocyte infiltration which suggested indirect regulatory capacity of insulin on vascular permeability (Rabiee *et al*., 2009). These findings suggest that with its capacity mediated by the antagonistic inflammatory mediators to increase the vascular permeability and reduce damage to the vascular endothelial cells, insulin used in the shock stage can reduce body fluid leakage for patients with major burns in shock stage and their fluid requirements in the shock resuscitation. This is conducive to fundamentally improving or correcting the burn shock (Ballian *et al*., 2010; Gauglitz *et al*., 2010a, b). The group of patients treated with insulin (treatment group) had first 24 h unit colloid volume lower than that of the control group. However, the treatment group had significantly increased unit urine output in the shock stage. This suggested that the insulin therapy can reduce the colloidal dosage and increase the urine output in the shock resuscitation. The relatively high hematocrit in the control group also suggested that the control group had more concentrated blood and more evident circulatory fluid loss than the treatment group.

Under the stimulation of the infection, trauma, shock and other risk factors, macrophages were activated and a large number of pro-inflammatory cytokines were released,

such as Tumor Necrosis Factor-α (TNF-α), Interleukin-1 (IL-1), etc. These cytokines promoted the further release of other inflammatory cytokines and induced the synthesis of Tissue Factor (TF) and its expression on the cell surface causing damage to endothelial cells and activation of the platelets. The activated platelets aggregated and had abnormal distribution on the damaged endothelial cells (Maciel *et al*., 2012). The inflammatory cells and damaged endothelial cells were activated at the same time, releasing a large number of Platelet-Activating Factors (PAFs) and von Willebrand Factors (vWFs) and further increasing the aggregation of platelets. Massive destruction of platelets can result in the release of the high concentrations of 5-Hydroxytryptamine (5-HT) and Prostaglandin (PGH) further mediating the massive release of inflammatory mediators. Platelet-activating factors play an important role in the inflammation of the organism and damage to important organs after burn, especially damage to the lungs, gastrointestinal tracts and kidney (Kostina and Peretiagin, 2011). Furthermore, the activation of platelets was positively correlated with the high expression of the proinflammatory cytokines. Both of them were related to the disease condition and prognosis. More severe disease condition would increase the platelet activation and shorten the life expectancy of the platelets. The platelet counting would decrease as a result of excessive consumption (Chen and Zheng, 2012).

Dynamic monitoring of the peripheral blood platelet counting of severely burned patients can reflect the change of disease condition of the patients with high sensitivity and can combined with the APACHE II score after admission, accurately reflect the prognosis. It can serve as a relatively reliable indicator to determine the severity and prognosis of the patients with severe burns. For patients with significantly decreased platelet counting in addition to the treatment of the primary disease, thrombopoietin drugs should be applied promptly and platelets should be transfused to improve the prognosis.

CONCLUSION

The application of insulin therapy together with the colloid and crystal resuscitation in the shock stage can reduce the volume of resuscitation fluids required in the shock stage. The insulin therapy can also protect the function of the cells, tissues and organs and is conducive to the treatment of patients with severe burns (Kasper *et al*., 2011). Besides, randomized and controlled experiments with larger sample sizes and testing of more indicators including the blood sugar and urine sugar will be conducive to the comprehensive and clear illustration of the function and working mechanism of insulin. They are what researchers are going to do in the near future.

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