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REVIEW

The Effect of Baihu Decoction (白虎汤) on Blood Glucose Levels in Treating Systemic Inflammatory Response Syndrome

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ABSTRACT In this paper we investigated the mechanisms of Baihu Decoction (白虎汤, BH) and Baihu with *Radix Ginseng* (BHG) in treating systemic inflammatory response syndrome (SIRS) and sepsis in humans and animals. By reviewing published data on the effects of BH and BHG and the control of blood glucose in treating SIRS and sepsis, we found that (1) BH and BHG were beneficial in the treatment of SIRS and sepsis in humans and animals; (2) BH and BHG also had great effect in lowering blood glucose level; and (3) the tight control of blood glucose during critical illness substantially improved the outcome. Considering these data together, we hypothesize that one of the major mechanisms of BH and BHG in treating SIRS and sepsis is to lower the blood glucose level. The findings also suggest that the application of BH and BHG can extend to many acute illnesses and injuries, which commonly cause hyperglycemia.

KEYWORDS Baihu Decoction, mechanism, hyperglycemia, critical illness, blood glucose control

Baihu Decoction (白虎汤, BH), documented in the "*Shang Han Lun*" (伤寒论, Treatise on Febrile Disease)(1), composed of *Rhizoma Anemarrhenae* (Windweed Rhizome) 9 g, *Gypsum Fibrosum* (Gypsum) 30 g, Prepared *Radix Glycyrrhizae* (Prepared Licorice Root) 3 g, and *Semen Oryzae Nonglutinosae* (Polished Round-grained Nonglutinous Rice) 9 g, is a curative for the syndrome with interior excessive heat. The typical symptoms that BH treats are high fever and big and strong pulse(2). The following symptoms and signs are also often seen in the syndromes, which can be eliminated by BH: flushed face, fear of heat, great thirst for water, restlessness, profuse perspiration, and parched tongue(1-3).

Baihu Decoction with *Radix Ginseng* (BHG) consists of the components in BH and *Radix Ginseng*. In Chinese medicine, many syndromes that can be treated by BH and BHG are similar. One of the major differences is that dehydration is more severe in the syndromes treated with BHG(2). Besides the syndromes treated with BH, if a patient has a faster respiratory rate, a weaker pulse, or if the patient is very weak or elderly, then BHG is suitable(1).

In Chinese medicine terminology, high fever often refers to body temperature of > 39 ℃ and big and strong pulse often refers to a heart rate of > 100 beats/min(2). The descriptions of BH and BHG in the historical documents show that the syndromes treated with BH and BHG fit the modern definition of the systemic inflammatory response syndrome (SIRS) and sepsis. SIRS is triggered by localized or generalized infection, trauma, thermal injury, or sterile inflammatory processes. According to the definition by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) in 1991, SIRS is present when patients have more than one of the following clinical findings: body temperature of >38 ℃ or <36 ℃, heart rate of >90 beats/min, hyperventilation evidenced by a respiratory rate of >20 times/min or a $PaCO_2$ of <32 mm Hg, and a white blood cell (WBC) count of >12 000 cells/μL or <4 000 cells/μL(4). The manifestations of sepsis are the same as those previously defined for SIRS, and sepsis is a result of SIRS from documented infection. It is a complex morbid state typically initiated by an infectious insult and associated with elevated levels of cytokines and other humoral/cellular mediators of inflammation, coagulation, and metabolic dysfunction(5-8). The prevalence of sepsis and related syndromes in intensive care unit (ICU) patients is very high and is a principal cause of multiple organ failure and death in these patients(9-11).

In the past decade it has been repeatedly reported

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that BH and BHG could reduce or heal the syndromes of SIRS or sepsis in humans and mammals[12-16]. Some studies were conducted to explain the mechanism of BH and BHG in treating SIRS and sepsis[17]. Most of them focused on BH and BHG's function of adjusting the body's thermoregulatory set-point, and their anti-bacterial properties. However, researchers have not come to an agreement on the mechanism of BH and BHG to treat SIRS and sepsis, and the results of some studies exclude each other. Although BH and BHG have significant benefit in treating SIRS and sepsis patients, the lack of a clear explanation of their mechanism has hindered their application in clinics.

Previous studies on the mechanism of BH and BHG in treating SIRS have ignored an important function of these formulas: BH and BHG could lower the blood glucose concentration. It is very common in SIRS and sepsis patients to have hyperglycemia. Hyperglycemia used to be considered beneficial for survival in critical illness until a clinical study in 2001 showed that preventing even moderate hyperglycemia during critical illness substantially improved the outcome[18,19]. Since then, numerous reports have shown that tight blood glucose control yielded favorable results in septic patients. In this paper, we review the studies of BH and BHG and the studies of contemporary treatment of SIRS and sepsis, and we try to explain the mechanism of BH and BHG from a new perspective. Considering the fact that BH and BHG are beneficial in the treatment of SIRS and sepsis and that they have great effect in lowering the blood glucose level, we hypothesize that one of the major roles that BH and BHG have in treating SIRS and sepsis is to maintain the blood glucose at the normal level.

To verify our hypothesis, we conducted a published literatures search, and collected data from all publication types, in both the Chinese and English languages. A broad variety of search terms, including glucose, hyperglycemia, SIRS, sepsis, critical ill, Baihu, *Radix Ginseng*, *Rhizoma Anemarrhenae*, *Gypsum Fibrosum*, and Chinese medicine inflammation, in combination with the individual search terms was used, followed by manual cross-referencing. We focused on the following aspects: (1) modern clinical and animal studies on BH in treating SIRS and sepsis, (2) previous studies on the mechanism of BH in healing SIRS, (3) modern clinical and animal studies on the effects of blood glucose control in treating critically ill patients, and (4) modern clinical and animal studies on BH's function of lowering the blood glucose concentration.

Contemporary Studies of BH Treating SIRS and Sepsis

Besides the historical documents, which recorded numerous cases of BH treating the conditions similar to SIRS and sepsis, some contemporary animal and human studies showed that BH exerts beneficial effects on the outcome of SIRS and sepsis. Here we give several examples.

In an animal study, 38 rabbits were randomized to receive an injection of lipopolysaccharide (LPS, *E. coli* 0111:B4) 15 μg/kg at marginal ear veins (n=30) and the normal saline (n=8). LPS significantly increased the body temperature and WBC counts (P<0.01). The LPS-injected rabbits were randomized to receive BH injection or the normal saline injection (control). Body temperature, WBC, superoxide dismutase (SOD) concentration, endothelin concentration (ET), and concentrations of IgG and IgM were measured two hours later. The results showed that compared with the control group, in the BH group the body temperature, WBC, ET, and IgG significantly decreased (P<0.05 or P<0.01), SOD increased (P<0.05). There was no significant difference in the concentration of IgM. Because the body temperature and WBC increased after the injection of LPS, the results of this study showed that BH produced a favorable outcome on LPS-induced SIRS for rabbits[15].

In the early phase of epidemic encephalitis B, patients have typical symptoms of SIRS—fever and increased WBC[20]. Many historical and contemporary reports have shown the benefit of BH in treating epidemic encephaletis B[21]. Shu[14] reported that of 78 outpatients who received BH therapy, 69 were healed, four had reduced symptoms, and five died. Thus, the healing rate was 92.6%.

Jiang[13] conducted a clinical study to investigate the clinical effect of BH on SIRS. Forty-four patients with SIRS were randomized to receive BH (21 patients) and the conventional therapy (23 patients). The clinical symptoms were significantly improved in those in the Chinese medicine group compared with those in the conventional therapy group. After seven days of treatment in the two groups the respiratory rate, heart rate, and WBC counts were decreased significantly (P<0.05). The recovery time of temperature, respiratory rate, heart rate, and WBC were shorter in the Chinese medicine group than in the conventional therapy group (P<0.05). The cases of multiple organ dysfunction syndrome were less in the Chinese medicne group than in the conventional therapy group (P<0.05)[13].

Severe acute respiratory syndrome (SARS) has typical SIRS syndromes. In the "Scheme of diagnosis and treatment of SARS", issued by the Chinese Medical Association and China Association for Traditional Chinese Medicine (2003)[22], BH is one of the major therapies. In the treatment of SARS, however, BH is always used with other herbs and medicines, so there is no report of the function of BH alone in treating SARS. In a clinical study, Zhao, et al[16] compared the treatments of SARS with conventional therapy adding Chinese medicine (treatment group) and conventional therapy alone (control group). Seventy-seven patients with SARS were randomized to a treatment group (37 patients) and a control group (40 patients). The Chinese herbs used in the treatment group were *Rhizoma Anemarrhenae*, *Gypsum Fibrosum*, *Radix Glycyrrhizae*, *Semen Pruni Armeniacae*, *Herba Ephedrae*, *Flos Lonicerae, Radix Ginseng*, and *Radix Salviae Miltiorrhizae*, among which *Rhizoma Anemarrhenae*, *Gypsum Fibrosum*, and *Radix Glycyrrhizae* are the major components in BH. The results reported that the healing rate in the treatment group was 100%. In the control group, one patient died, and 39 patients were healed. After seven days of treatment, among the patients in the acute phase, in the control group, the average CD_4^+ T cell count of 27 patients was lowered from 497 $\pm$ 262 cells /μL to 377 $\pm$ 190 cells/μL. In the treatment group, the average CD_4^+ T cell count of 24 patients after seven days of treatment was increased from 584 $\pm$ 440 cells/μL to 662 $\pm$ 316 cells/μL. The difference was significant (P<0.05).

Patients who have hemorrhagic fever with renal syndrome (HFRS) develop typical SIRS three to four days after the syndrome occurs[20]. In Chinese medicine, BH has been a major formula for HFRS[21]. In a clinical study, in addition to the conventional therapy (ribovirin 1 g, dexamethasone 10 mg, added to 500 mL 5% glucose by intravenous dripping every day), 47 patients with HFRS received BH therapy (adding *Lophatheri gracilis*, *Radix Isatidis* and *Radix Sophora tonkinensis*)[12]. It was found that 80.9% of the patients (38 patients) were healed. The symptoms of 17% of the patients (8 patients) were relieved and 2.1% (1 patient) had no beneficial effect. The total effective rate was 97.1%[12].

From the historical case records and the contemporary studies, we can see that BH has some benefits in treating SIRS and sepsis.

Previous Studies on the Mechanism of BH in Healing SIRS

Several studies have been conducted to investigate the mechanism of BH in treating SIRS and sepsis[17] and most of them have focused on the function of BH of adjusting the body's thermoregulatory set-point, and its anti-bacterial properties.

Researchers have not come to an agreement on BH's mechanisms for lowering the body temperature. Several experimental results even gave exclusive conclusions. It was believed that calcium sulfate ($CaSO_4$) plays the major role in lowering the body temperature and Ca^{2+} has the function of adjusting the thermoregulatory set-point[2,17]. In the 1980s, SHI Jun-hua reported that Ca^{2+}-free BH did not have the function of lowering body temperature on rabbits and there was a high correlation between the concentration of Ca^{2+} and body temperature decreasing[17]. However, MA You-du in the 1960s, GUO Rui-chao in the1980s, and XU Hong-chun in the 1990s reported that the Ca^{2+} concentration had little to do with lowering the body temperature[17]. They concluded that the components in *Gypsum Fibrosum*, which have this function, were the other unidentified micro-minerals[17].

Most researchers believe that *Mangifera Indic* in *Rhizoma Anemarrhenae* has the effect of lowering the body temperature[17]. However, SHI Jun-hua, in the 1980s, reported that Ca^{2+}-free *Rhizoma Anemarrhenae* and prepared *Radix Glycyrrhizae* decoction had no favorable outcome in lowering body temperature, but *Gypsum Fibrosum* decoction alone without *Rhizoma Anemarrhenae* lowered the body temperature in rabbits[17].

It has been shown that glycyrrhizic acid in prepared *Radix Glycyrrhizae* has glucocorticoid-like effects. It suppresses an organism's LPS response and inflammatory response[2,17]. *Rhizoma Anemarrhenae* also has anti-bacterial effects on staphylococcus and almonella typhi, Escherichia coli, and Shigella dysenteriae. The anti-bacterial effects of the components of BH are believed to contribute to BH's treatment of SIRS[23].

We hypothesize that, in addition to the functions of lowering the body temperature and its anti-bacterial properties, one of the major functions of BH in treating SIRS is controlling the blood glucose level. Hyperglycemia is common in SIRS and sepsis patients with and without diabetes. In the past few years, it has been repeatedly shown that strict glucose control exerted a beneficial effect on the outcome of critical illness. To reveal the importance of lowering blood glucose level in the BH and BHG treatment of SIRS and sepsis, we will briefly review the relationship among hyperglycemia, blood glucose control, and critical illness, including SIRS and sepsis.

Blood Glucose Control Saves Lives of Critically Ill Patients

Hyperglycemia is a common occurrence in patients with severe sepsis and in critical care patients in general, independent of a previous diabetic condition(24-27). According to van den Berghe, "Today, it is well known that any type of acute illness or injury results in insulin resistance, glucose intolerance, and hyperglycemia, a constellation termed 'diabetes of injury'"(19). High blood glucose levels are associated with more severe organ damage in nondiabetic ICU patients(28) and have harmful effects on cellular and organ function(29,30). Hyperglycemia has been noted to be associated with higher mortality and a poor clinical outcome after burns, surgery, stroke, myocardial infarction, and head trauma(31-41). It increases the risk of infectious complications in surgical patients, and indirect evidence indicates that maintenance of euglycemia can reduce the risk of infection(42).

Elevations in blood glucose became a major therapeutic target after a study in 2001 indicated a mortality benefit of intensive insulin therapy among patients in an ICU(43). Since then, aggressive control of blood sugar levels has been reported to decrease the mortality and morbidity of the critically ill patient(18,36,44). To some extent, it became a benchmark for the quality of ICU care(43).

In a prospective, randomized, controlled study, van den Berghe, et al(18) investigated the value of insulin therapy directed at maintaining strict glucose control in 1 500 patients admitted to ICU. The patients were randomized to receive intensive insulin therapy (continuous infusions to maintain blood glucose concentrations at 80-110 mg/dL) or conventional insulin therapy (infusion of insulin only if the blood glucose level exceeded 215 mg/dL and maintenance of glucose at a level between 180 and 200 mg/dL). Interim analysis at one year demonstrated a significant reduction in ICU mortality (4.6% *vs* 8.0%, P=0.036, with adjustment for sequential analysis) with continuous infusion. The mortality benefit was especially evident among patients requiring intensive care for >5 days (10.6 *vs* 20.2%, P=0.005). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50%, and critical-illness polyneuropathy by 44%. Patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care(18).

An analysis of the van den Berghe, et al(45) study in 2003 showed a linear correlation between the degree of hyperglycemia and the risk of death. It also showed that strict blood glucose control (<110 mg/dL) prevents morbidity effects such as acute renal failure, bacteremia, and anemia. Multivariate logistic regression analysis confirmed the independent role of blood glucose control in achieving most of the clinical benefits of intensive insulin therapy and underscored the importance of lowering the blood glucose level to strict normoglycemia(19).

Similar results were reported in a retrospective review of >1 800 critically ill medical and surgical patients. Patients whose mean glucose concentrations were maintained between 80 and 99 mg/dL had the lowest hospital mortality (9.6%). Mortality increased progressively with increases in mean glucose concentrations, and patients with mean blood glucose concentrations >300 mg/dL had the highest mortality (42.5%, P<0.001)(36).

Although the underlying mechanisms of strictly controlling hyperglycemia with insulin therapy are yet unclear, the researches in the past decade clearly show that it substantially improves the outcome of critical illness. "The days of ignoring blood sugar levels or tolerating marked hyperglycemia in the ICU (which was commonplace even five years ago, 2001) are over"(43).

BHG Lowers the Blood Glucose Concentration

In Chinese medicine, the syndromes treated with BH and BHG are similar. One of the major differences is that the degree of dehydration in BHG is higher than that in BH[2]. Due to this slight difference, there are very few contemporary researches on the treatment of SIRS and sepsis with BHG, since BH and BHG have a similar effect on SIRS and sepsis.

Besides treating SIRS or sepsis, BHG has been used in Chinese medicine to treat diabetes for a long time (e.g., see Synopsis of Prescriptions of the "*Jin Gui Yao Lue*" (金匮要略, Gold Chamber)[46]. Some contemporary clinical studies show that lowering the blood glucose concentration plays a role in BHG treatment of diabetes. For example, Chen, et al[47] reported 54 cases of treatment of type Ⅱ diabetes with BHG. The results showed that blood glucose level and blood lipid level were lowered significantly after four weeks of treatment (P<0.05). Chen, et al[48] reported that among 60 patients with type Ⅱ diabetes, 30 accepted BHG and 30 accepted the conventional therapy. Fourteen weeks later, the blood glucose levels of the BHG group were significantly lower than those of the control group (P<0.05)[48]. Other research groups reported similar results[49,50].

Unfortunately, only few clinical studies on the treatment of diabetes with BHG had rigorously designed blood glucose concentration sampling plans, and most of them only showed that BHG had a favorable effect on the outcome of diabetes. For example, Wu, et al[51] reported that of 128 patients with type Ⅱ diabetes treated by BHG, 39 patients (30.47%) recovered in a short time, 16 markedly effective and 56 effective, the total effective rate being 86.70%. Based on clinical studies only, it remains unclear whether the favorable effect of BHG on diabetes is to lower the blood glucose levels or other mechanisms.

However, many animal studies directly show that BHG lowers the blood glucose level. Dai, et al[52] reported that BHG obviously reduced the levels of blood glucose in alloxan-induced diabetic mice. Kimura, et al reported that BHG had the effect of significantly lowering the blood glucose level on KK-CAy diabetes mice and alloxan-induced diabetes mice[53]. Okumura, et al[54] reported that BHG could lower the blood glucose level in a non-insulin-dependent diabetes mellitus model using KK-Ay mice, and the optimal dose was 500 mg/kg. The authors concluded that BHG had the significant and continuous function of lowering the blood glucose level and it was the major mechanism for BHG to have a favorable effect on the outcome of diabetes.

Rhizoma Anemarrhenae, the main component of BH and BHG, has been proven to have the effect of lowering the blood glucose[59, 60]. Miura, et al. reported that the water extract of *Rhizoma Anemarrhenae* (90 mg/kg) reduced blood glucose levels from 570 ± 29 to 401 ± 59 mg/dL 7 h after oral administration (P<0.05) and also tended to reduce serum insulin levels in KK-Ay mice[61].

It was shown that BHG's effect of lowering the blood glucose was related to the combination of its components. Each of the components, except for *Semen Oryzae Nonglutinosae*, was shown to have the effect of lowering the blood glucose[53]. The effect was reduced when one of the components was removed. Interestingly, it was shown that the combination of *Rhizoma Anemarrhenae* and *Radix Ginseng* had less effect of lowering the blood glucose than each of them alone. However, after adding *Gypsum Fibrosum*, the effect of the combination was increased. For the combination of *Rhizoma Anemarrhenae*, *Radix Ginseng*, and prepared *Radix Glycyrrhizae*, the effect of lowering the blood glucose without Ca^{2+} was significantly lower than the one with Ca^{2+}[53,58,59].

Hypotheses and Future Research Directions

In the last several decades, many studies have been conducted to clarify the mechanisms of Chinese herbs. The successful cases, for example, recognizing the antibiotic function of *Radix Bupleuri* and *Rhizoma Coptidis*, promoted the application of those herbs in modern clinics on a large scale. In the case of BH or BHG treating SIRS and sepsis, however, no explanation has been satisfactory, and researchers have not reached a consensus. The lack of a clear explanation of the mechanism of BH and BHG has hindered the application of these formulas.

The effect of BH and BHG of lowering the blood glucose has been ignored in previous studies of these formulas' effects in treating SIRS and sepsis. As far as we know, no previous studies of BH and BHG have made the connection between their functions of lowering the blood glucose and treating SIRS and sepsis. As we addressed above, the acute illness (e.g., SIRS or sepsis) often causes hyperglycemia, and hyperglycemia in turn slows down the process of healing or in some cases even leads to a more severe situation, e.g., sepsis-associated organ failure via such mechanisms as impairing the immune function and worsening the inflammation. Recent clinical studies have shown that, in this vicious circle, hyperglycemia plays a pivotal role, and rigorous blood glucose control is a possible way to break through this vicious circle. All these suggest that one of the major functions of BH and BHG in treating SIRS and sepsis is its effect of controlling the blood glucose.

The mechanism of BH and BHG for lowering the blood glucose level remains unclear. It is believed that in critically ill patients, stress causes the increase of the level of counter-regulatory hormones (i.e. glucagons, growth hormone, catecholamine, and glucocorticoid), as well as the levels of cytokines (i.e., tumor necrosis factor-α, interleukin-1, interleukin-6)(60). The increased counter-regulatory hormones and cytokines cause an increase in insulin resistance(61), which is believed to be the major cause of hyperglycemia in septic and critically ill patients(42, 60, 62). Since many studies have reported that BHG had obvious favorable outcomes in type Ⅱ diabetes, which was caused by insulin resistance, it is possible that BHG lowers the blood glucose level through its effect of regulating the counter-regulatory hormone and the inflammatory cytokines, therefore, suppressing insulin resistance. This hypothesis and the detailed mechanism are yet to be investigated by future studies.

Considering the fact that any type of acute illness or injury results in glucose intolerance, hyperglycemia, and insulin resistance(19); that many studies after 2001 have indicated the favorable effects of blood glucose control among patients in the surgical ICU(43); and that BHG has been proven to have substantial effect in controlling the blood glucose level, we hypothesize that the application of BH and BHG may not be limited to their traditional description in the "*Shang Han Lun*"(1). For example, they could be used as a major component in the treatment of acute illness or injury.

There is some clinical evidence supporting this idea. In a clinical study, Chen, et al(63) investigated the effect of BH in the treatment of high fever caused by infection after renal transplantation. Thirty-two patients after renal transplantation were assigned to two groups. The treatment group was administered BH, hormone, anti-virus, and anti-germ treatment. At the same time the dosage of cyclosporine was reduced, cellular toxic medicine was stopped, and whole body support treatment was used. The control group received exactly the same therapy except that they were not treated with BH. The results showed that among 15 cases in the treatment group, 14 cases were recovered, one case improved, and the cure rate was 93%, and among 17 cases in the control group, nine cases were recovered, one case improved, seven cases died, and the cure rate was 53%. The cure rate of the two groups had a significant difference (P<0.05). The authors concluded that BH had the effect of eliminating fever and agitation, producing fluids and preventing thirst, and reducing temperature and inflammation(66). After renal transplantation, the fever caused by low immunity can be effectively improved by BH along with other therapies.

Increasing evidence suggests that hyperglycemia impedes normal physiologic responses to infection. *In vitro* and *in vivo* studies have reported substantial impairment in immune function and wound healing associated with hyperglycemia(64-67). Weekers's study showed that strict blood glucose control with insulin infusion after trauma significantly improved innate immunity in the fed rabbit model(68). Thus, in the treatment of high fever caused by infection after renal transplantation, it is possible that one major function of BH and BHG is to control the blood glucose level, therefore improving the hyperglycemic-damaged immune system.

With its mechanism−blood glucose control clarified, the main components of BH or BHG may be used in the treatment of acute illness or injury. We suggest that researchers conduct more clinical and animal studies to further investigate this idea.

In summary, by reviewing the studies of BH and BHG and the studies of contemporary treatment of critical illnesses, including SIRS and sepsis, we hypothesize that one of the major functions of BH and BHG in treating SIRS and sepsis is to lower the blood glucose level. Based on our findings, we suggest that future researches investigate whether BH and BHG can be applied to other acute illnesses and injuries other than their traditional description in the "*Shang Han Lun*"(1).

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