Efficacy of Xuebijing for coagulopathy in patients with sepsis

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ABSTRACT

الأهداف: يقوم هذا التحليل البعدي بدراسة البراهين المرتبطة بمدى فعالية زوبيجينغ (Xuebijing) على عملية تخثر الدم لدى المرضى المصابين بإنتان الدم (تسمم الدم).

الطريقة: أُجريت هذه الدراسة في مستشفى بمقاطعة ليونينغ، شينيانغ، الصين وذلك خلال الفترة من ديسمبر 2013م إلى مايو 2014م. لقد قمنا بالبحث في عدد من قاعدات البيانات وذلك عن الدراسات العشوائية المتحكم بها والتي تناولت البحث عن كل من زوبيجينغ، التخثر، والإنتان، والتي تم نشرها قبل ديسمبر 2013م. ولقد استند التحليل الإحصائي على استخدام Review Manager 5.2 من مجموعة كوكرين.

النتائج: شمل هذا التحليل على 14 دراسة عشوائية متحكم بها والتي تضمنت 867 مريضاً. وقد أشارت نتائج الدراسة بأن حقن زوبيجينغ قد قامت وبفعالية واضحة بتحسين نتائج الصفائح الدموية (MD = 42.14, 95% CI: 22.42 - 61.86, p<0.00001) وتقليل زمن الثرمبوبلاستين المفعل الجزئي (MD = -4.81, 95% CI: -7.86 - [-1.76], p=0.002) ، وتقليل زمن البروثرومبين (MD = -2.33, 95% CI: -4.15 - [-0.51], p=0.01)، وتقليل زمن الثرومبين (MD = -2.05, 95% CI: -3.52 - [-0.58], p=0.006) وذلك عند المقارنة مع المجموعات التي حُقنت بالعلاج المُموه. غير أنه لم يكن هناك اختلاف واضح من الناحية الإحصائية بين المجموعات التي حُقنت بحقن زوبيجينغ و المجموعات التي حُقنت بالعلاج المُموه وذلك فيما يخص الفيبرينوجين (MD = 0.21, 95% CI: -0.38 - 0.81, p=0.48).

الخاتمة: أظهر هذا التحليل بأنه قد يكون لحقن زوبيجينغ فعالية في تحسين نتائج التخثر لدى المرضى المصابين بإنتان الدم. لذلك ننصح بعمل المزيد من الدراسات ذات الجودة والعينات الإحصائية العالية من أجل تأكيد مثل هذا النتائج التي توصل لها هذا التحليل.

Objectives: To provide evidence of the clinical efficacy of Xuebijing (XBJ) on blood coagulation in patients with sepsis.

Methods: We conducted this meta-analysis in The People's Hospital of Liaoning Province, Shenyang, China between December 2013 and May 2014. We searched a number of databases for relevant randomized controlled trials (RCTs) published before December 2013 using the keywords 'Xuebijing', 'coagulation' and 'sepsis'. Statistical analysis was performed with Review Manager 5.2 from the Cochrane Collaboration.

Results: Fourteen RCTs involving 867 patients were included. Compared with placebo, XBJ injection significantly improved platelets (mean differences [MD] = 42.14, 95% confidence interval [CI]: 22.42 - 61.86, p<0.00001), shortened the activated partial thromboplastin time (MD = -4.81, 95% CI: -7.86 - [-1.76], p=0.002), shortened the prothrombin time (MD = -2.33, 95% CI: -4.15 - [-0.51], p=0.01), and shortened the thrombin time (MD = -2.05, 95% CI: -3.52 - [-0.58], p=0.006). However, no significant difference was found between the XBJ injection and the placebo group for fibrinogen (MD = 0.21, 95% CI: -0.38 - 0.81, p=0.48).

Conclusion: Xuebijing injection may improve coagulopathy in patients with sepsis. High-quality and large sample clinical trials are needed for confirmation.

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In 2012, the international guidelines for the management of severe sepsis and septic shock conference defined sepsis as the presence (probable or documented) of infection together with systemic manifestations of infection.[1] Ranging from the systemic inflammatory response syndrome and its complications, septic shock, and multiple organ dysfunction syndrome (MODS), sepsis represents the leading cause of death in intensive care patients. A significant cause of infective systemic manifestations in sepsis is the uncontrolled release of inflammatory mediators and cytokines.[2] A variety of inflammatory mediators and cytokines may directly or indirectly confuse the body's coagulation, and result in an abnormal clotting mechanism.[3] Xuebijing (XBJ), which has been extensively used for treating sepsis in China, is an intravenous injection consisting of 5 traditional Chinese medicines (safflower, *Radix Paeoniae Rubra*, angelica, Chuanxiong, salvia miltiorrhiza).[4] It can improve microcirculation and blood coagulation dysfunction based on the theory of anti-endotoxin, anti-inflammatory, regulating immune function, scavenging oxygen free radicals and stabilizing vascular endothelial cells simultaneously.[5-8] Previous studies have showed that XBJ is effective for sepsis,[9] and this drug has been approved by the State Food and Drug Administration of China for clinical use. We conducted this meta-analysis to provide an up-to-date and comprehensive picture of the clinical efficacy of XBJ on blood coagulation in patients with sepsis.

Methods. This meta-analysis was conducted in the People's Hospital of Liaoning Province, Shenyang, China, between December 2013 and May 2014. We included all relevant studies published before December 2013 in the China National Knowledge Infrastructure, Wanfang database, MEDLINE, Embase and Cochrane Library based on the following search terms: 1) "xuebijing" [Supplement Concept]; 2) "blood coagulation", or "coagulation", or "clotting"; 3)'sepsis'; 4) "blood platelets", "partial thromboplastin time", "prothrombin time", "thrombin time", or "fibrinogen".

We included studies in this meta-analysis if: 1) they were randomized controlled trials (RCTs); 2) used a parallel design or crossover design of XBJ versus placebo treatment; 3) duration of treatment was ≥ 72 hours; 4) reported data on platelet (PLT), activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), and fibrinogen (FIB); 5) excluded the factors that can cause changes in PLT and coagulation (for example, original thrombotic diseases, cancer, hematological disorders, connective tissue disease and use of anticoagulants); 6) These studies were published in English or Chinese.

Abstracts of cited articles were reviewed by 2 independent investigators to determine their relevance. Discrepancies were resolved by consensus or, as needed, with a third investigator and confirmed by consensus. When there were multiple reports from the same trial, the most complete and recently reported data was chosen. The quality of included articles was further assessed using the Jadad criteria.[10] The scores ranged from 0 to 5 (a high score indicating high quality).

The statistical analysis was performed with Review Manager 5.2 (RevMan, The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark), 2013. For efficacy measures, mean changes in PLT, APTT, PT, TT, and FIB as continuous variables were assessed. For these continuous variables, weighted mean differences (MD) and 95% confidence interval (CI) for changes from baseline were calculated. A p-value <0.05 was considered to be statically significant. Heterogeneity was tested by the Q statistic (significance level at p<0.10) and the I^2 statistic (significance level at I^2>50%).[11] A random-effects model was used if the Q or I^2 statistic was significant. Otherwise, a fixed-effects model was used.

Results. The initial literature search retrieved 1236 relevant articles. Nine hundred and sixty-four articles were excluded after scanning the titles. Two hundred and nineteen articles were excluded after carefully reading the abstracts. Then, 39 articles were excluded for various reasons (duplicate, review, case report, no required data), and finally 14 RCTs[12-25] were retained for meta-analysis. Pooled analysis included 867 patients. Overall, the included studies were of adequate methodologic quality (mean Jadad score 3.429 for included studies, all studies had a score ≥3). Included studies, basic characteristics of enrolled patients, and details of drug therapy are presented in **Table 1**.

Analysis of risk of bias showed that 6 trials reported the detailed methods of sequence generation and allocation concealment.[14,18,19,21,23,25] Blinding was performed properly in all included trials. All trials were free from incomplete outcome data and free from selective outcome reporting as well as other sources of bias. A total of 14 trials had a low or moderate risk of bias. The risk of bias is summarized in **Table 1**.

The results of meta-analysis showed that XBJ injection can significantly improve PLT (MD = 42.14,

95% CI: 22.42 - 61.86, $p<0.00001$, **Figure 1**), shorten the APTT (MD = -4.81, 95% CI: -7.86 - [-1.76], $p=0.002$, **Figure 2**), shorten the PT (MD = -2.33, 95% CI: -4.15 - [-0.51], $p=0.01$, **Figure 3**), shorten the TT (MD = -2.05, 95% CI: -3.52 - [-0.58], $p=0.006$, **Figure 4**). However, no significant difference was found between the Xuebijing injection and the placebo group in FIB change (MD = 0.21, 95% CI: -0.38 - 0.81, $p=0.48$, **Figure 5**).

Discussion. The pathogenesis of sepsis is not yet entirely clear, but endotoxin, inflammatory mediators/cytokines, and/or endothelial cell damage are more reliable reasons.[26] Most patients with sepsis

Table 1 - Basic characteristics of included studies of enrolled patients with sepsis and details of drug therapy.

	Age (years)		Gender (m/f)				TD	Study	Jadad	Risk of bias					
Author, year of study	XBJ	PL	XBJ	PL	Outcome measures	XBJ dose	(days)	size	score	SG	AC	B	IOD	SOR	OSB
Liu et al 2006[12]	40±6		27/14		PLT, APTT, PT, TT, FIB	100ml q.d.	10	41	3	?	?	√	√	√	√
Ming et al 2007[13]	43±25		40/20		PLT, APTT, PT, TT, FIB	200ml q.d.	7	60	3	?	?	√	√	√	√
Zhang et al 2008[14]	48.6±15.2	50.1±16.8	Unclear		PLT, APTT, PT	50ml b.i.d.	14	60	4	√	√	√	√	√	√
Jin & Li 2009[15]	58±16	52±12	14/10	16/12	PLT, APTT, PT, TT, FIB	100ml q.d.	7	52	3	?	?	√	√	√	√
Wang 2009[16]	70±11		13/10		PLT, APTT, PT, TT, FIB	100ml b.i.d.	7	23	3	?	?	√	√	√	√
Zhang et al 2009[17]	20~80		32/28		PLT, APTT, PT, FIB	100ml q12h	7	60	3	?	?	√	√	√	√
Liu et al 2010[18]	44.3±12.7	42.8±13.5	44/28	39/31	PLT, APTT, PT, TT	50ml q12h	7	142	4	√	√	√	√	√	√
Zhang et al 2010[19]	65.25±15.33	64.81±16.85	9/7	11/5	PLT, APTT, PT	100ml b.i.d.	5	32	4	√	√	√	√	√	√
Su et al 2011[20]	58.55±12.43	58.35±11.14	12/8	10/10	PLT, APTT, PT, TT, FIB	50ml b.i.d.	7	40	3	?	?	√	√	√	√
Yao et al 2011[21]	59.04±18.32	52.13±22.21	21/19	27/11	PLT, APTT, PT, FIB	100ml b.i.d.	7	78	4	√	√	√	√	√	√
Ge et al 2012[22]	62±12		114/46		APTT, PT, FIB	100ml b.i.d.	5	160	3	?	?	√	√	√	√
Yang et al 2012[23]	60.15±14.93	61.08±16.01	20/13	21/11	PLT, APTT, PT	50ml b.i.d.	6	65	4	√	√	√	√	√	√
Zhang et al 2012[24]	58±24	60±22	8/12	10/12	PLT, APTT, PT, FIB	100ml q12h	7	42	3	?	?	√	√	√	√
Zhang & Ma 2013[25]	63.5±15.23	64.58±17.7	9/7	11/5	APTT, PT	50ml b.i.d.	7	32	4	√	√	√	√	√	√

q.d. - once a day, b.i.d. - twice a day, q12h - once every 12 hours, XBJ - Xuebijing injection, PL - placebo, PLT - platelet, APTT - activated partial thromboplastin time, PT - prothrombin time, TT - thrombin time, FIB - fibrinogen, √ - low risk of bias, ? - unclear risk of bias, ! - high risk of bias, TD - treatment duration, SG - sequence generation, AC - Allocation concealment, B - blinding, IOD - incomplete outcome data, SOR - selective outcome reporting, OSB - other sources of bias

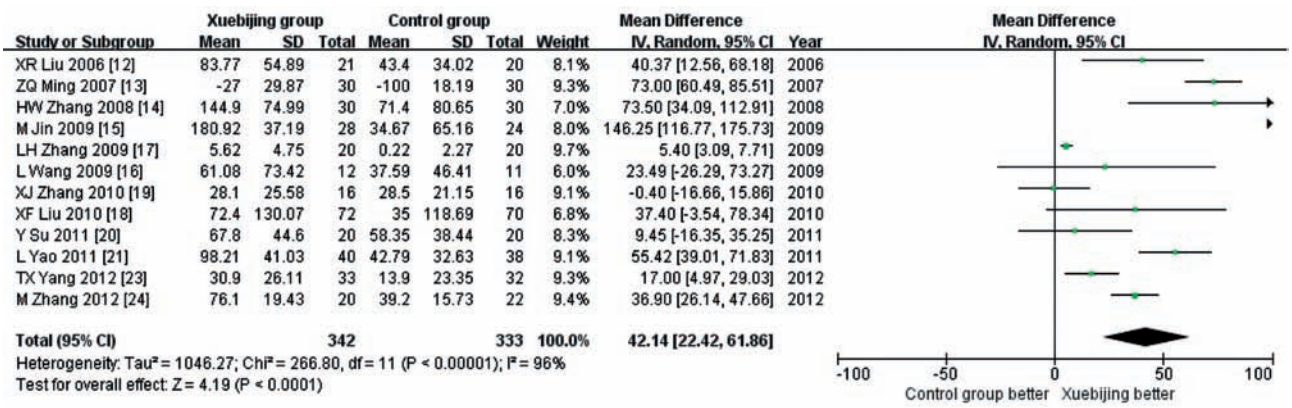

Figure 1 - Meta-analysis of platelet change of Xuebijing injection for sepsis. IV - inverse variance, CI - confidence interval

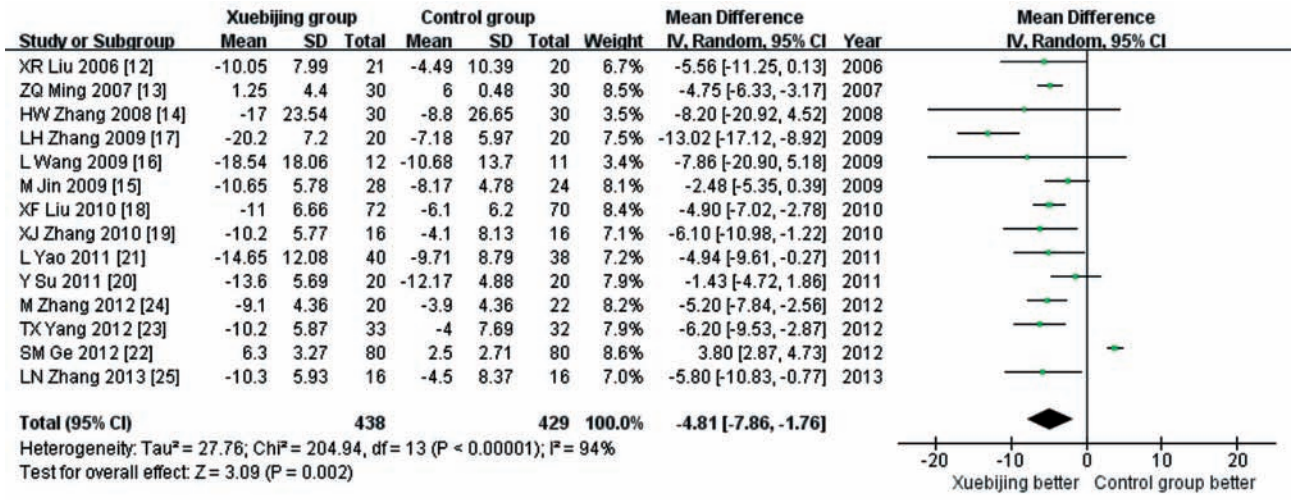

Figure 2 - Meta-analysis of activated partial thromboplastin time change of Xuebijing injection for sepsis. IV - inverse variance, CI - confidence interval

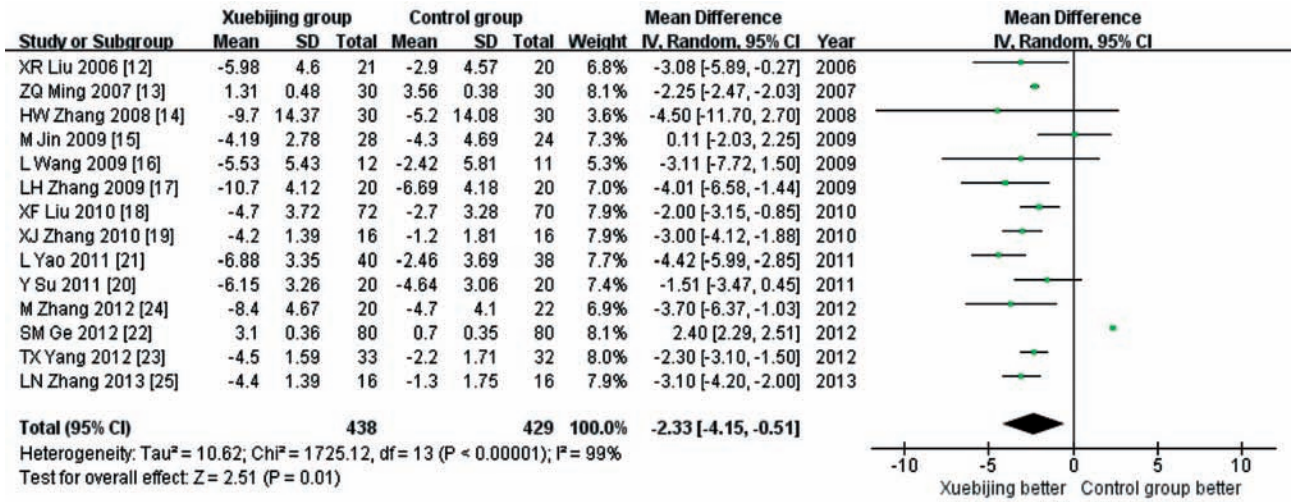

Figure 3 - Meta-analysis of prothrombin time change of Xuebijing injection for sepsis. IV - inverse variance, CI - confidence interval

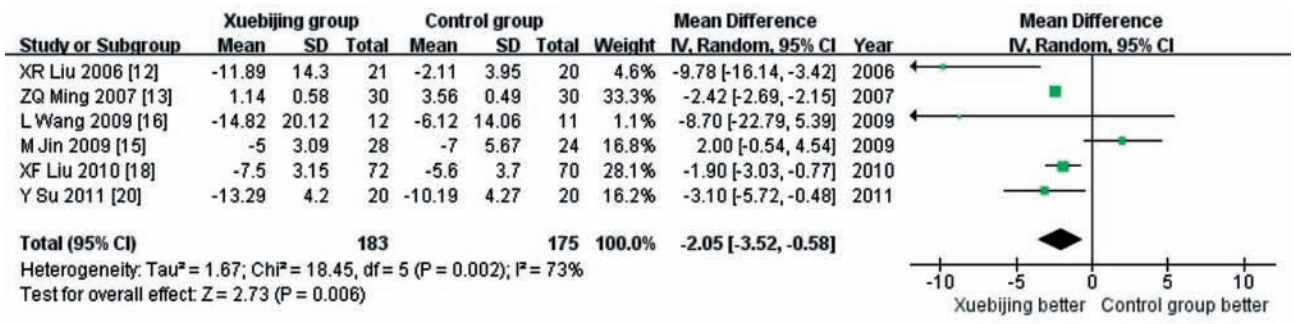

Figure 4 - Meta-analysis of thrombin time change of Xuebijing injection for sepsis. IV - inverse variance, CI - confidence interval

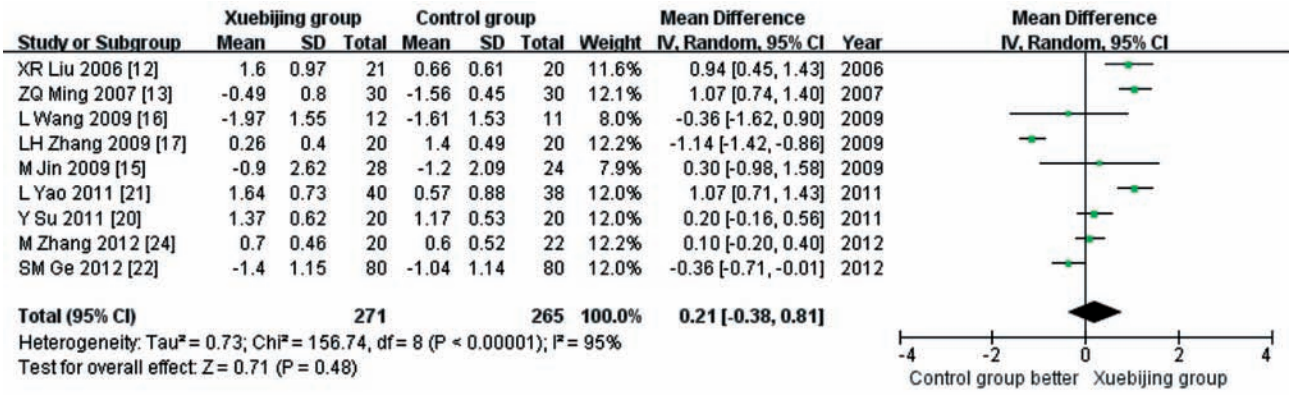

Figure 5 - Meta-analysis of fibrinogen change of Xuebijing injection for sepsis. IV - inverse variance, CI - confidence interval

have coagulation dysfunction,[27] and pathological manifestations show a large number of micro thrombus formation in microcirculation. Some scholars have inferred sepsis-induced organ dysfunction essentially due to microcirculation.[28] If we can antagonize endotoxins, remove inflammatory mediators, repair endothelial cells, block the coagulation dysfunction and improve microcirculation in patients with sepsis, we may relieve the development of sepsis to severe sepsis, septic shock, and even MODS.

The examination of coagulation disorders in patients with sepsis showed prolonged TT, PT, and APTT, with decreased FIB or PLT, even the occurrence of disseminated intravascular coagulation. By observing the changes of TT, PT, APTT, FIB, and PLT, we can conclude the efficacy of XBJ for coagulopathy in patients with sepsis. In this study, we found that, compared with the control group, coagulation function was significantly better in the XBJ group.

The meta-analysis showed XBJ can significantly improve blood coagulation dysfunction in patients with sepsis based on active anti-infective and other supportive symptomatic treatment. But, XBJ itself can not directly inhibit and kill pathogenic microorganisms. When sepsis occurs, only based on active anti-infective and other support symptomatic treatment, XBJ can exert its protective function of organs and improve blood coagulation dysfunction. Therefore, we do not recommend the application XBJ alone in the treatment of sepsis.

In conclusion, the present study evaluated the clinical efficacy of XBJ could be a credible alternative for sepsis patients who have abnormal blood coagulation. We included 14 RCT's in the meta analysis, with a mean Jadad score 3.429, making the conclusions of this systematic analysis reliable. More high-quality, large sample, randomized, multicenter clinical trails are needed to confirm clinical efficacy of XBJ on blood coagulation in patients with sepsis.

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