

Hemocoagulase reduces postoperative bleeding and blood transfusion in cardiac surgical patients

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Hemocoagulase is isolated and purified from snake venoms. Hemocoagulase agents have been widely used in the prevention and treatment of surgical bleeding. A systematic review was performed to evaluate the effects of hemocoagulase on postoperative bleeding and transfusion in patients who underwent cardiac surgery.

Methods: Electronic databases were searched to identify all clinical trials comparing hemocoagulase with placebo/blank on postoperative bleeding and transfusion in patients undergoing cardiac surgery. Two authors independently extracted perioperative data and outcome data. For continuous variables, treatment effects were calculated as weighted mean difference and 95% confidential interval (CI). For dichotomous data, treatment effects were calculated as odds ratio and 95% CI. Each outcome was tested for heterogeneity, and randomized-effects or fixed-effects model was used in the presence or absence of significant heterogeneity. Sensitivity analyses were done by examining the influence of statistical model and individual trial on estimated treatment effects. Publication bias was explored through visual inspection of funnel plots of the outcomes. Statistical significance was defined as $P < .05$.

Results: Our search yielded 12 studies including 900 patients, and 510 patients were allocated into hemocoagulase group and 390 into control group. Meta-analysis suggested that, hemocoagulase-treated patients had less bleeding volume, reduced red blood cells and fresh frozen plasma transfusion, and higher hemoglobin level than those of controlled patients postoperatively. Meta-analysis also showed that, hemocoagulase did not influence intraoperative heparin or protamine dosages and postoperative platelet counts. Meta-analysis demonstrated that, hemocoagulase-treated patients had significantly shorter postoperative prothrombin time, activated partial thromboplastin time, and thrombin time, higher fibrinogen level and similar D-dimer level when compared to control patients.

Conclusion: This meta-analysis has found some evidence showing that hemocoagulase reduces postoperative bleeding, and blood transfusion requirement in patients undergoing cardiac surgery. However, these findings should be interpreted rigorously. Further well-conducted trials are required to assess the blood-saving effects and mechanisms of Hemocoagulase.

Abbreviations: ACT = activated coagulation time, APTT = activated partial thromboplastin time, CI = confidence interval, DD = D-dimer, FFP = fresh frozen plasma, Fg = fibrinogen, GPs = glycoproteins, Hb = hemoglobin, HCA = hemocoagulase agkistrodon, PC = platelet concentrate, PT = prothrombin time, RBC = red blood cells, RCT = randomized clinical trials, TLEs = thrombin-like enzymes, TT = thrombin time, VSD = ventricular septal defect, WMD = weighted mean difference.

Keywords: cardiac surgery, hemocoagulase, meta-analysis

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1. Introduction

Systemic heparinization, hemodilution, and hypothermia applied during cardiac surgery with cardiopulmonary bypass (CPB) significantly influence coagulation and fibrinolysis systems, resulting in excessive bleeding and increased requirement of blood transfusion.^[1]

Traditional hemostatic drugs (eg, anti-fibrinolytic agents) have hemostatic effects and side effects as well. Snake venom thrombin-like enzymes (TLEs) accelerate the formation of fibrin monomers and hastens fibrin clot formation.^[2–6] TLEs have drawn attention due to their outstanding features of low toxicity, fast onset of action, long-lasting efficacy, and no intravascular embolism.^[7–15] Hemocoagulase is a TLE isolated and purified from snake venoms.^[2–6] Hemocoagulase agents (reptilase, batroxobin, hemocoagulase agkistrodon [HCA]) have been widely used in the prevention and treatment of surgical bleeding.^[7–15] Evidence has accumulated that, hemocoagulase significantly reduces bleeding in patients undergoing abdominal, urological, thyroid, orthopedic, obstetric, and gynecological surgeries.^[8–15] A meta-analysis suggested that, topical hemocoagulase was significantly effective in reducing bleeding, pain and

swelling and promoting wound healing after tooth extraction.^[7] However, another meta-analysis of 5 randomized clinical trials (RCTs) concluded that it was not evident enough to support the efficacy of hemocoagulase for hemorrhage during thoracic surgery.^[8] Whether hemocoagulase has beneficial effects on blood conservation in cardiac surgical patients remains undetermined. Therefore, we performed this meta-analysis to evaluate the efficacy and safety of hemocoagulase on bleeding and transfusion in patients undergoing cardiac surgery.

2. Methods

2.1. Ethical approval

This study was a meta-analysis of previously published literatures, ethical approval was not necessary under the ethical committee of Fuwai Hospital.

2.2. Search strategy

We conducted a systemic review according to the preferred reporting items for systemic reviews and meta-analysis quality of reporting of meta-analysis guidelines^[16] (Supplemental Digital Content [Supplemental Table 1, <http://links.lww.com/MD/D547>]). The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42019127918. Relevant trials were identified by computerized searches of MEDLINE, Cochrane Library and Ovid till February 14th, 2019, using different combination of medical subject headings and text words (Supplemental Digital Content [Appendix, <http://links.lww.com/MD/D543>]). No language restriction was used. We also searched the Chinese BioMedical Literature & Retrieval System, China National Knowledge Infrastructure, VIP Database and Wangfang Database (from inception to February 14th, 2019). Additionally, we used the bibliography of retrieved articles to further identify relevant studies. We included all RCTs comparing hemocoagulase with control (placebo/blank) with respect to postoperative bleeding and transfusion in patients undergoing cardiac surgery. In studies which also included other comparator drugs (aprotinin, ulinastatin, tranexamic acid, etc), only data of hemocoagulase and placebo/blank groups were abstracted. Primary outcomes included postoperative blood loss, blood transfusion of red blood cells (RBC), fresh frozen plasma (FFP) and platelet concentrates (PC). Secondary outcomes include hemoglobin (Hb) level, platelet counts and functions, coagulation tests, and so on. Exclusion criteria included

- (1) studies published as review, case report, or abstract;
- (2) animal studies;
- (3) duplicate publications;
- (4) studies only comparing hemocoagulase with aprotinin, tranexamic acid, and ulinastatin;
- (5) studies lacking information about outcomes of interest.

The 2 authors (XY and NXF) independently reviewed the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion was further determined by reading the full text.

2.3. Study quality assessment

Risk of bias for the included trials was assessed by 2 authors (XY and NXF) independently based on the consort criteria.^[7,17] Trial

was assessed to have a “high” risk of bias if it did not record a “yes” in 3 or more of the 4 main categories; “moderate” if 2 out of 4 categories did not record a “yes” and “low” if randomization, assessor blinding, and completeness of follow-up was considered adequate. The Jadad score was also used to evaluate the methodological quality of each included trial.^[18] The Jadad scoring system (ranging from 0 to 5) includes:

- (1) randomization process;
- (2) blindedness assessment; and
- (3) reporting of withdrawals/dropouts.

Higher scores indicate excellent methodologic qualities, and lower scores suggest poor qualities.^[18]

2.4. Data abstraction

The following data were abstracted from the included studies to a data collection form by 2 authors (XY and NXF) independently:

- (1) author and year of publication;
- (2) total number of patients, number of patients in hemocoagulase and control groups;
- (3) type of surgical procedure;
- (4) data regarding outcomes of interest in both groups.

Disagreements were resolved by discussion among all authors during the process of data abstraction. The authors of the included studies were contacted if necessary.

2.5. Statistical analysis

All data were analyzed by utilizing RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Pooled odds ratio and 95% confidence interval (CI) were estimated for dichotomous data, and weighted mean difference (WMD) and 95% CI for continuous data, respectively. Each outcome was tested for heterogeneity, and randomized-effects or fixed-effects model was used in the presence or absence of significant heterogeneity (Q -statistical test $P < .05$). Sensitivity analyses were done by examining the influence of statistical model on estimated treatment effects, and analyses which adopted the fixed-effects model were repeated again by using randomized-effects model and vice versa. In addition to that, sensitivity analysis was also performed to evaluate the influence of individual study on the overall effects. Publication bias was explored through visual inspection of funnel plots of the outcomes. All P -values were 2-sided and statistical significance was defined as $P < .05$.

3. Results

3.1. Search results

As depicted in the flow chart (Fig. 1), database search identified 26 articles for complete evaluation. Finally, 12 eligible trials (10 published literatures^[19,20,22–27,29,30] and 2 master degree dissertations^[21,28]), all written in Chinese, were included in the meta-analysis. Patients and surgery data were presented in Table 1. Out of the 12 trials, 5^[23–25,28,29] included only adult patients, 5^[20,21,26,27,30] included only pediatric patients, the other 2^[19,22] included both adult and pediatric patients. As shown in Table 1, surgical procedures varied among the 12 trials. Two RCTs^[25,28] involved patients undergoing valve replacement, 1 RCT^[23] involved only patients undergoing off-pump coronary surgery, 2 RCT^[20,30] involved only patients undergoing

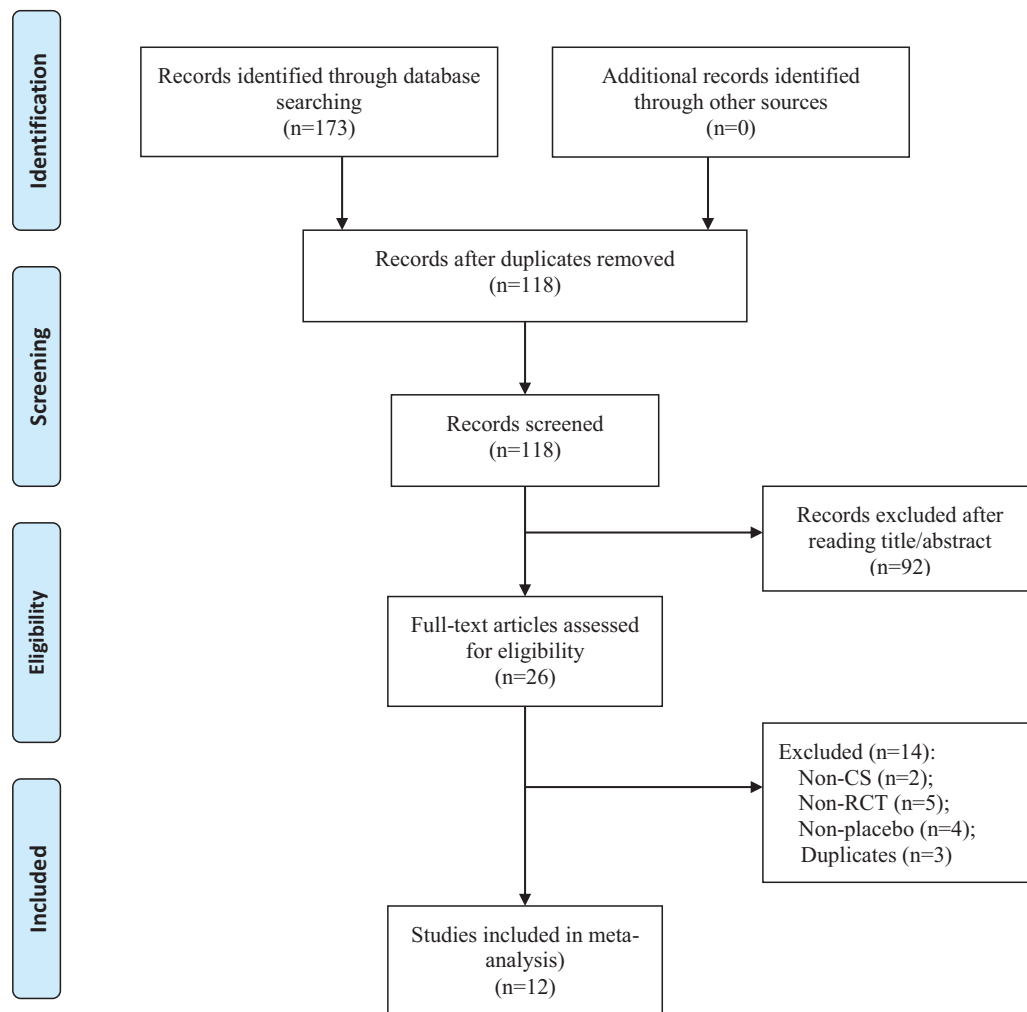


Figure 1. PRISMA flow diagram. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

ventricular septal defect (VSD) repair, 3 RCTs^[21,24,26] included patients undergoing mixed spectrum of ventricular or atrial septal defect repair and tetralogy of Fallot or pulmonary stenosis correction, 4 RCTs^[19,22,27,29] did not specify the surgical type. The 12 eligible trials involved total 900 patients, and 510 patients were allocated into group hemocoagulase, 390 into group control. Among the 12 trials, hemocoagulase was specified as HCA in 3 trials,^[19,27,28] as batroxobin in 1 trial,^[22] as reptilase in 3 trials,^[24,26,30] 1 trial^[29] included both groups of batroxobin and reptilase, the other 4 trials^[20,21,23,25] only mentioned hemocoagulase without specification. Hemocoagulase administration protocols (eg, dosage, timing, and route) of the included trials were shown in Table 1.

3.2. Study quality

As shown in Table 2, 4 main methodological studies were assessed for quality. All 12 trials claimed randomized allocation but did not mention concealment of allocation and blinding, all 12 included trials are of moderate risk of bias. None of these trials reported sample size calculation before the trial was established. None of the included studies used intention-to-treat analysis. Five trials^[19,20,23–25] had a Jadad score of 3 and were considered as

high-quality RCTs, and the other 7 trials^[21,22,26–30] were scored at 2.

3.3. Effects on postoperative bleeding

All 12 trials^[19–30] reported bleeding volume during the first 24 hours postoperatively. As shown in Figure 2 and Table 3, all 12 trials (900 patients) evaluated the effect of hemocoagulase on blood loss in the first 24 hours postoperatively. Meta-analysis showed that, hemocoagulase significantly reduced postoperative bleeding volume (WMD = -64.82; 95% CI: -87.74 to -41.90; $P < .00001$) with possible publication bias (Supplemental Digital Content [Supplemental Fig. 1, <http://links.lww.com/MD/D544>]).

3.4. Effects on postoperative blood transfusion

As depicted in Figure 3 and Table 3, 5 trials (303 patients)^[23,25,26,28,29] reported postoperative transfusion of RBC. Meta-analysis showed that, hemocoagulase significantly reduced postoperative RBC transfusion (WMD = -137.39; 95% CI: -213.18 to -61.60; $P = .0004$) without publication bias (Supplemental Digital Content [Supplemental Fig. 2, <http://links.lww.com/MD/D544>]).

Table 1
Included trials.

Trials	Age	Surgery	Group hemocoagulase	Group control	Reported outcomes										
					Post-op transfusion					Coagulation function					
					POB	Hb	RBC	FFP	PC	PTC	PT	APTT	TT	Fg	DD
Chen 2011 ^[19]	A, P	CPB-CS	HCA: 1U iv after AI, 1U in CPB prime (n=60)	Saline (n=60)	✓		✓		✓	✓	✓	✓	✓	✓	✓
Di 2015 ^[20]	P	VSD-R	H: 0.5U iv. after CPB (n=25)	Blank (n=25)	✓										
Han 2015 ^[21]	P	VSD-, ASD-R	H: 0.3U for BW <10 kg or 0.5U for BW >10 kg, iv after CPB (n=20)	Blank (n=20)	✓	✓					✓	✓			✓
Li 2004 ^[22]	A, P	CPB-CS	B: 1U for BW <40 kg, 2U for BW >40 kg, iv after CPB (n=27)	Blank (n=25)	✓					✓	✓	✓	✓	✓	✓
Liu 2012 ^[23]	A	OPCAB	H: 0.04 U/kg iv BI, 2U iv after CPB, 2U iv per 2 h till EOS (n=20)	Blank (n=20)	✓		✓	✓							
Tan 2011 ^[24]	A	ASD-, VSD-R, VR	R: 1.5KU iv. after AI, 1.5KU in CPB prime (n=60)	Saline (n=60)	✓	✓				✓					
Wang 2015 ^[25]	A	VR	H: 2U iv. BI (n=20); 2U iv during CPB (n=20); 2U iv after CPB (n=20).	Saline (n=20)	✓		✓			✓	✓	✓	✓	✓	✓
Yu 2008 ^[26]	P	ASD-, VSD-R, TOF-, PS-CR	R: 2KU iv after CPB (n=28) 4KU iv after CPB (n=28)	Blank (n=28)	✓	✓	✓	✓/✓							
Zhang 2012 ^[27]	P	CPB-CS	HCA: 1U iv after CPB (n=30)	Saline (n=30)	✓					✓	✓	✓	✓	✓	✓
Zhang 2015 ^[28]	A	VR	HCA: 1U in CPB prime (n=25)	Saline (n=25)	✓		✓			✓	✓	✓	✓	✓	✓
Zhao 2004 ^[29]	A	CPB-CS	R: 1U iv + 1U im after CPB (n=55) B: 1U iv +1U im. after CPB (n=57)	Blank (n=62)	✓		✓			✓	✓	✓	✓	✓	✓
Zhou 2009 ^[30]	P	VSD-R	R: 1KU iv after AI, 1 KU in CPB prime (n=15)	Saline (n=15)	✓	✓				✓	✓	✓			✓

A = adults, AI = anesthesia induction, APTT = activated partial thromboplastin time, ASD = atrial septal defect, B = batroxobin, BI = before incision, CPB = cardiopulmonary bypass, CR = correction, CS = cardiac surgery, DD = D-dimer, EOS = end of surgery, FFP = fresh frozen plasma, Fg = fibrinogen, H = hemocoagulase, Hb = hemoglobin, HCA = hemocoagulase agkistrodon, im = intramuscularly, iv = intravenously, P = pediatrics, PC = platelet concentrates, PLT = platelet count, POB = postoperative bleeding, PS = pulmonic stenosis, PT = prothrombin time, R = reptilase, RBC = red blood cell, TOF = tetralogy of fallot, TT = thrombin time, VR = valve replacement, VSD = ventricular septal defect.

lww.com/MD/D545]). As shown in Figure 4 and Table 3, 3 trials (174 patients)^[19,23,26] reported postoperative FFP transfusion. Meta-analysis showed that, hemocoagulase significantly reduced postoperative FFP transfusion (WMD = -37.90; 95% CI: -57.28 to -18.51; P = .0001) without publication bias (Supplemental Digital Content [Supplemental Fig. 3, <http://links.lww.com/MD/D546>]). No trials reported postoperative PC transfusion.

3.5. Effects on Hb levels

As shown in Table 3, 3 trials (364 patients)^[21,24,30] and 4 trials (448 patients)^[21,24,26,30] reported pre- and postoperative Hb level, respectively. Meta-analysis showed that, 2 groups of patients had similar Hb levels preoperatively (WMD = 0.57; 95% CI: -2.43 to 3.56; P = .71), but hemocoagulase-treated patients had higher postoperative Hb level than that of controlled patients (WMD = 8.00; 95% CI: 1.79-14.21; P = .01).

Table 2
Quality assessment of included studies.

Trials	PN	GN	Groups	Randomization	Allocation concealed	Blindness	Withdrawals	Risk of bias	Jadad score
Chen 2011 ^[19]	120	2	H, C	Yes	No	No	Yes	Moderate	3
Di 2015 ^[20]	100	4	H, T, H + T, C	Yes	No	No	Yes	Moderate	3
Han 2015 ^[21]	60	3	H, T, C	Yes	No	No	Yes	Moderate	2
Li 2004 ^[22]	52	2	H, C	Yes	No	No	Yes	Moderate	2
Liu 2012 ^[23]	80	4	H, T, H + T, C	Yes	No	No	Yes	Moderate	3
Tan 2011 ^[24]	180	3	H, U, C	Yes	No	No	Yes	Moderate	3
Wang 2015 ^[25]	80	4	H1, H2, H3, C	Yes	No	No	Yes	Moderate	3
Yu 2008 ^[26]	84	3	H1, H2, C	Yes	No	No	Yes	Moderate	2
Zhang 2012 ^[27]	60	2	H, C	Yes	No	No	Yes	Moderate	2
Zhang 2015 ^[28]	100	4	H, U, H + U, C	Yes	No	No	Yes	Moderate	2
Zhao 2004 ^[29]	174	3	H1, H2, C	Yes	No	No	Yes	Moderate	2
Zhou 2009 ^[30]	30	2	H, C	Yes	No	No	Yes	Moderate	2

C = control, GN = group number, H = hemocoagulase, PN = patient number, T = tranexamic acid, U = ulinastatin.

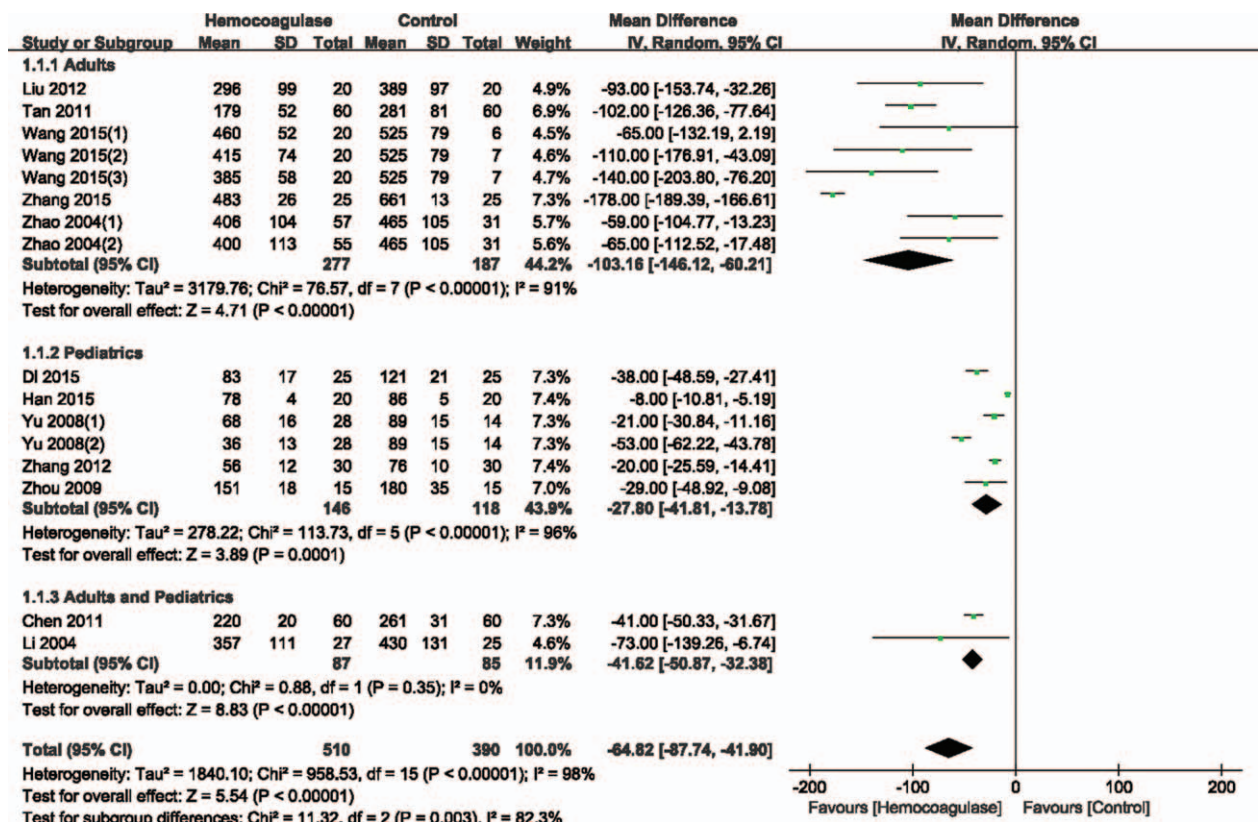


Figure 2. Forest plot of postoperative bleeding.

Table 3

Meta-analysis of outcomes.

Outcomes	Trials (n)	Group Hemo (n)	Group Ctrl (n)	Heterogeneity		Analysis model	WMD	95% CI	Overall effect P
				I ² (%)	P				
Post-op bleeding (mL)	12	510	390	98	<.00001	IV, Random	-64.82	-87.74, -41.90	<.00001*
Blood transfusion									
Post-op RBC (mL)	5	186	118	66	.005	IV, Random	-137.39	-213.18, -61.60	.0004*
Post-op FFP (mL)	3	101	73	39	.18	IV, Fixed	-37.90	-57.28, -18.51	.0001*
Hemoglobin									
Pre-op (g/dL)	4	207	157	52	.08	IV, Random	0.57	-2.43, 3.56	.71
Post-op (g/dL)	5	263	185	95	<.00001	IV, Random	8.00	1.79, 14.21	.01*
Heparin (mg)	3	152	102	0	.76	IV, Fixed	4.17	-4.06, 12.41	.32
Protamine (mg)	2	40	40	0	.84	IV, Fixed	-3.33	-40.94, 34.28	.86
Platelet count									
Pre-op (×10 ⁹ /L)	8	389	297	0	.87	IV, Fixed	-3.33	-7.87, 1.21	.15
Post-op (×10 ⁹ /L)	8	389	297	94	<.00001	IV, Random	26.36	9.88, 42.84	.22
PT									
Pre-op (s)	8	349	257	88	<.00001	IV, Random	-0.07	-0.40, 0.25	.66
Post-op (s)	8	349	257	41	.08	IV, Fixed	-0.73	-0.88, -0.59	<.00001*
APPT									
Pre-op (s)	8	349	257	25	.21	IV, Fixed	-0.52	-0.91, -0.12	.01*
Post-op (s)	8	349	257	89	<.00001	IV, Random	-2.96	-4.40, -1.52	<.00001*
TT									
Pre-op (s)	5	202	160	57	.03	IV, Random	0.03	-0.28, 0.34	.86
Post-op (s)	5	202	160	85	<.00001	IV, Random	-0.96	-1.62, -0.30	.004*
Fibrinogen									
Pre-op (mg/dL)	6	314	222	0	.96	IV, Fixed	0.01	-0.09, 0.11	.85
Post-op (mg/dL)	6	314	222	90	<.00001	IV, Random	0.23	0.01, 0.44	.04*
D-dimer									
Pre-op (mg/dL)	4	120	120	0	.82	IV, Fixed	0.00	-0.02, 0.02	.99
Post-op (mg/dL)	4	120	120			IV, Random	-0.05	-0.15, 0.06	.37

95% CI = 95% confidence interval, APPT = activated partial thromboplastin time, Ctrl = control, FFP = fresh frozen plasma, Hemo = hemocoagulase, IV = inverse variance, M-H = Mantel-Haenszel, Post-op = postoperative, Pre-op = preoperative, PT = prothrombin time, RBC = red blood cell, TT = thrombin time, WMD = weighted mean difference.

* P < .05.

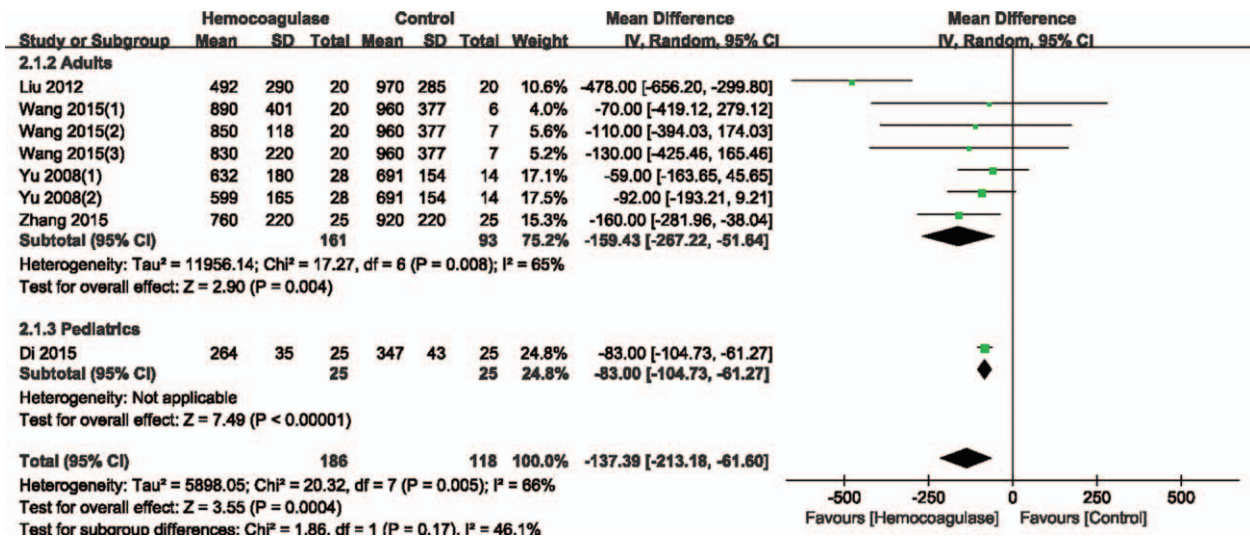


Figure 3. Forest plot of RBC transfusion. RBC = reduced red blood cells.

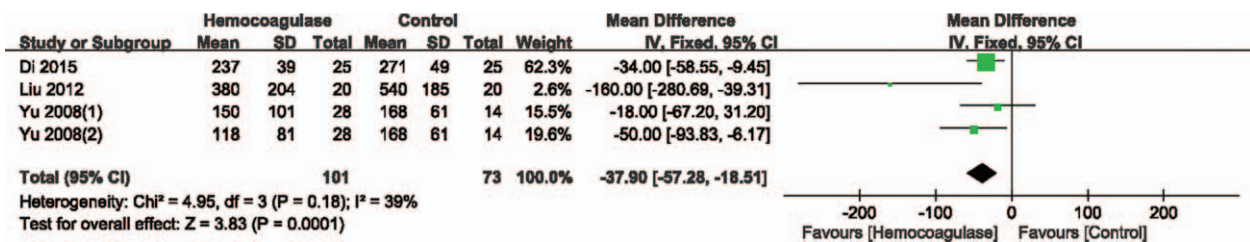


Figure 4. Forest plot of FFP transfusion. FFP = fresh frozen plasma.

3.6. Effects on intraoperative coagulation

As shown in Table 3, 3 trials (254 patients)^[28–30] and 2 trials (80 patients)^[28,30] reported intraoperative heparin and protamine dosages, respectively. Meta-analysis showed that, heparin and protamine dosages in 2 groups were comparable (WMD=4.17; 95% CI: -4.06 to 12.41; P=.32 for heparin, WMD=-3.33; 95% CI: -40.94 to 34.28; P=.86 for protamine). Li et al^[22] observed the effect of hemocoagulase on activated clotting time (ACT). They reported hemocoagulase significantly shortened ACT as compared to placebo after heparin reversal by protamine ([112±15] seconds vs [132±16] seconds, P<.01), which were comparable during systemic heparinization ([796±158] seconds vs [750±209] seconds, P>.05).

3.7. Effects on platelet count and function

As shown in Table 3, 8 trials (686 patients)^[19,22,24,25,27–30] reported pre- and postoperative platelet counts. Meta-analysis demonstrated that, platelet counts in 2 groups of patients were similar both preoperatively (WMD=-3.33; 95% CI: -7.87 to 1.21; P=.15) and postoperatively (WMD=26.36; 95% CI: 9.88–42.84; P=.22). Additionally, Zhou et al^[30] investigated the impact of hemocoagulase on platelet membrane glycoproteins (GPs). Thirty pediatric patients undergoing VSD repair with CPB were randomized to receive hemocoagulase or placebo. They demonstrated hemocoagulase had protective effects on platelets

as manifested by lower granule membrane protein-140 level and higher GPIb level, while GPIIb/IIIa level was comparable between 2 groups perioperatively.

3.8. Effects on coagulation functions

As shown in Table 3, 8 trials (606 patients)^[19,21,22,25,27–30] reported pre- and postoperative prothrombin time (PT) values. Meta-analysis demonstrated that, preoperative PT values in 2 groups of patients were similar (WMD=-0.07; 95% CI: -0.40 to 0.25; P=.66), hemocoagulase significantly shortened PT values when compared to placebo (WMD=-0.73; 95% CI: -0.88 to -0.59; P<.00001). As shown in Table 3, 8 trials (606 patients)^[19,21,22,25,27–30] reported pre- and postoperative activated partial thromboplastin time (APTT) values. Meta-analysis demonstrated that, APPT values in hemocoagulase group were shorter than control group both preoperatively (WMD=-0.52; 95% CI: -0.91 to -0.12; P=.01) and postoperatively (WMD=-2.96; 95% CI: -4.40 to -1.52; P<.00001). After excluding 1 trial,^[19] Meta-analysis demonstrated that, preoperative APPT values were comparable in both groups (WMD=-0.36; 95% CI: -0.82 to 0.09; P=.12), while postoperative APPT values were shorter in hemocoagulase group than control group (WMD=-3.30; 95% CI: -4.70 to -1.89; P<.00001). Five trials (362 patients)^[19,22,25,27,28] reported pre- and postoperative thrombin time (TT), respectively. Meta-analysis demonstrated that, TT

values in 2 groups of patients were similar preoperatively (WMD=0.03; 95% CI: -0.28 to 0.34; $P=.86$), Hemocoagulase significantly shortened TT when compared to placebo (WMD = -0.96; 95% CI: -1.62 to -0.30; $P=.004$). As shown in Table 3, 6 trials (536 patients)^[19,22,25,27-29] reported pre- and postoperative fibrinogen (Fg) levels. Meta-analysis demonstrated that, Fg levels in 2 groups of patients were similar preoperatively (WMD=0.01; 95% CI: -0.09 to 0.11; $P=.85$), hemocoagulase group had higher postoperative Fg levels than control group (WMD=0.23; 95% CI: 0.01-0.44; $P=.04$).

3.9. Effects on fibrinolysis

Four trials (240 patients)^[19,21,28,30] reported pre- and postoperative D-dimer (DD). Meta-analysis demonstrated that, DD levels in 2 groups of patients were similar both preoperatively (WMD = 0.00; 95% CI: -0.02 to 0.02; $P=.99$) and postoperatively (WMD = -0.05; 95% CI: -0.15 to 0.06; $P=.37$).

3.10. Adverse effects

Six trials^[22,23,25-27,29] observed possible side effects of hemocoagulase, no adverse events of anaphylactic reaction,^[22,25,29] thrombosis,^[23,25,26] cardiorespiratory dysfunction,^[26,27] or hepato-renal dysfunction^[25,27] were reported.

3.11. Sensitivity analyses

Sensitivity analysis showed that treatment effects on postoperative bleeding, RBC and FFP transfusion were not affected by the choice of statistical model (Supplemental Digital Content [Supplemental Table 2, <http://links.lww.com/MD/D548>]). Sensitivity tests were also performed by exclusion of some studies to analyze the influence of the overall treatment effect on high heterogeneity outcomes (Supplemental Digital Content [Supplemental Table 3, <http://links.lww.com/MD/D549>]), but no contradictory results were found.

4. Discussion

Snake venoms contain a large number of proteins that affect the hemostatic system,^[2-6] considerable efforts have been made to develop pro- and anticoagulants from them. The snake venom TLEs comprise a number of serine proteases functionally and structurally related to thrombin.^[2-6] Hemocoagulase, the TLE isolated from venoms in several snake species, could accelerate the formation of fibrin monomers and hastens fibrin clot formation.^[2-6] Batroxobin (reptilase), the TLE from *Bothrops atrox* (common lancehead) venom, has anticoagulant ability by cleaving Arg16-Gly17 bond of A α -chain of Fg which spontaneously converts into loose fibrin clots.^[2-6] Since the coagulation studies on Batroxobin (reptilase) in 1957, over 40 TLEs had been isolated and characterized.^[2-6] For example, HCA is a double chain TLE obtained from *Deinagkistrodon acutus* (Chinese moccasin). HCA is a national class 1 drug in China and is known for its hemostatic efficacy.^[10-13,31,32]

Hemocoagulase agents (such as reptilase, batroxobin, HCA) have been widely used for the prevention and treatment of hemorrhage in non-cardiac surgeries.^[9-15,31] To our knowledge, this is the first meta-analysis dedicated to evaluate whether hemocoagulase could reduce blood loss and transfusion requirements in cardiac surgical patients. The present

meta-analysis suggested that, hemocoagulase-treated patients had less bleeding, reduced RBC and FFP transfusion, and higher Hb level postoperatively than those of controlled patients. The current meta-analysis also showed that, hemocoagulase did not influence intraoperative dosages of heparin and protamine and postoperative platelet counts in 2 groups of patients. Hemocoagulase-treated patients had significantly shorter postoperative PT, APTT, and TT values. Perioperative Fg level is a predictor of postoperative bleeding in patients undergoing cardiac surgery with CPB. The current meta-analysis demonstrated that, hemocoagulase-treated patients had higher Fg level than controlled patients. Fibrinolysis activation induced by CPB is also associated with increased postoperative bleeding. DD is a measurement index for fibrinolytic activity in cardiac surgery. The current meta-analysis demonstrated that, hemocoagulase-treated patients had similar DD level when compared to controlled patients. Hemocoagulase agents have been widely used for surgical and nonsurgical bleeding, and proved to be relatively safe. However, rare but disastrous side effects of hemocoagulase (eg, severe anaphylactic reactions^[33] and hypofibrinogenemia^[34]) need further investigation.

This study has some limitations. Meta-analysis can increase the power of analysis by pooling many small low-quality studies, but different administration modalities of hemocoagulase (eg, agent, dose, route, timing), varied quality and heterogeneity of the included studies, and possible biases may limit the certainty of the findings of meta-analysis. It is noteworthy that although the thrombotic event associated with Hemocoagulase was very rarely reported, it should be contraindicated in patients with venous/arterial thrombosis and a tendency for intravascular coagulation. Whether hemocoagulase agents (especially when administered early in cardiac surgical patients) increase the risk of thromboembolism is unknown. Current evidence suggested that early administration (after anesthesia induction or before surgical incision) of hemocoagulase agents was both effective and safe in noncardiac surgical patients. The rationale of using hemocoagulase agents to prevent hemorrhage in cardiac surgical patients needs further investigation. To clarify the hemostatic efficacy and safety of hemocoagulase in cardiac surgical patients, adequately-powered prospective randomized, placebo-controlled, double-blinded trials are needed.

To conclude, hemocoagulase reduces postoperative bleeding and blood transfusion requirement in cardiac surgical patients by preserving coagulation functions. To further confirm this, more well-designed and adequately-powered randomized trials are needed.

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