Systematic Review and Meta-Analysis

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Ulinastatin reduces postoperative bleeding and red blood cell transfusion in patients undergoing cardiac surgery

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Ulinastatin is a type of glycoprotein and a nonspecific wide-spectrum protease inhibitor like antifibrinolytic agent aprotinin. Whether Ulinastatin has similar beneficial effects on blood conservation in cardiac surgical patients as aprotinin remains undetermined. Therefore, a systematic review and meta-analysis were performed to evaluate the effects of Ulinastatin on perioperative bleeding and transfusion in patients who underwent cardiac surgery.

Methods: Electronic databases were searched to identify all clinical trials comparing Ulinastatin with placebo/blank on postoperative bleeding and transfusion in patients undergoing cardiac surgery. Primary outcomes included perioperative blood loss, blood transfusion, postoperative re-exploration for bleeding. Secondary outcomes include perioperative hemoglobin level, platelet counts and functions, coagulation tests, inflammatory cytokines level, and so on. For continuous variables, treatment effects were calculated as weighted mean difference (WMD) and 95% confidential interval (CI). For dichotomous data, treatment effects were calculated as odds ratio and 95% CI. Statistical significance was defined as $P < .05$.

Results: Our search yielded 21 studies including 1310 patients, and 617 patients were allocated into Ulinastatin group and 693 into Control (placebo/blank) group. There was no significant difference in intraoperative bleeding volume, postoperative re-exploration for bleeding incidence, intraoperative red blood cell transfusion units, postoperative fresh frozen plasma transfusion volumes and platelet concentrates transfusion units between the 2 groups (all $P > .05$). Ulinastatin reduces postoperative bleeding (WMD = −0.73, 95% CI: −1.17 to −0.28, $P = .001$) and red blood cell (RBC) transfusion (WMD = −0.70, 95% CI: −1.26 to −0.14, $P = .01$), inhibits hyperfibrinolysis as manifested by lower level of postoperative D-dimer (WMD = −0.87, 95% CI: −1.34 to −0.39, $P = .0003$).

Conclusion: This meta-analysis has found some evidence showing that Ulinastatin reduces postoperative bleeding and RBC transfusion 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 Ulinastatin.

Abbreviations: α2-AP = α2-antiplasmin, ACT = activated coagulation time, APTT = activated partial thromboplastin time, AT = antithrombin, AT-III:A = AT-III activity, CABG = coronary artery bypass grafting, CI = confidence interval, CPB = cardiopulmonary bypass, F1 + 2 = prothrombin fragment 1 + 2, FXI:C = factor XI pro-coagulant activity, IL = interleukin, MFI = mean fluorescence intensity, OR = odds ratio, PA = plasminogen activator, PAGM% = maximum platelet aggregation ratio, PMNE = polymorphonuclear elastase, TAT = thrombin-antithrombin complex, TEG = thromboelastography, TNF-α = tumor necrosis factor-α, TXB = thromboxane, WMD = weighted mean difference.

Keywords: bleeding, cardiac surgery, meta-analysis, transfusion, Ulinastatin

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The authors have no conflicts of interest to disclose.

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1. Introduction

The result of the blood conservation using antifibrinolytics in a randomized trial led to the suspension of aprotinin use in cardiac surgery by Food and Drug Administration in the USA in 2007 over concerns of increased mortality.[1] Subsequently, aprotinin was withdrawn from the Chinese market in December 2007.[2]

Ulinastatin or urinary trypsin inhibitor, is a type of glycoprotein and a nonspecific wide-spectrum protease inhibitor.[3,4] Currently, Ulinastatin is used in China, Korean, Japan, and India. A large body of convincing evidence has indicated that, Ulinastatin can not only reduce the release of pro-inflammatory cytokines, but also provide vital organ protection in patients undergoing cardiac surgery for coronary artery diseases, heart valve diseases, congenital heart diseases.[5–7] A previous study found that Ulinastatin normalized coagulation function and prevented changes in thromboelastography (TEG) during liver surgery.[8] Another study by Ji et al demonstrated that, Ulinastatin shortened activated partial thromboplastin time (APTT) and activated coagulation time (ACT) after systemic heparinization in patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB).[9] Whether Ulinastatin has similar beneficial effects on blood conservation in cardiac surgical patients as aprotinin remains undetermined.[5–7] Therefore, we performed this meta-analysis to evaluate the effects of Ulinastatin 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 (Supplement Table 1, http://links.lww.com/MD/D776).[10] The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42018115698. Relevant trials were identified by computerized searches of MEDLINE, Cochrane Library and EMBASE till January 6th, 2019, using different combination of search words as follows: (cardiopulmonary bypass OR heart OR cardiac surgery OR coronary artery bypass surgery) AND (Ulinastatin OR urinary trypsin inhibitor OR Miraclid OR Ulinase OR Bikunin OR Urinastatin) AND (bleeding OR blood loss OR transfusion) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial) (Appendix, http://links.lww.com/MD/D771). No language restriction was used. We also searched the Chinese BioMedical Literature & Retrieval System (from 1978 to January 6th, 2019). Additionally, we used the bibliography of retrieved articles to further identify relevant studies.

2.3. Inclusion and exclusion criteria

We included all clinical trials comparing Ulinastatin with placebo or blank with respect to bleeding and transfusion in patients undergoing cardiac surgery. In studies which also included other comparator drugs, only data of Ulinastatin and placebo/blank groups were abstracted. Primary outcomes of interest included intra- and postoperative blood loss, blood transfusion (red blood cells, plasma, platelet concentrates, cryoprecipitate), postoperative re-exploration for bleeding. Secondary outcomes of interest include perioperative hemoglobin level, platelet counts and functions, coagulation tests, inflammatory cytokines level, and so on.

Exclusion criteria included

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

The 2 authors (NXF and DHL) 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.

2.4. Study quality assessment

Two authors (NXF and DHL) independently assessed the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions.[11] The Jadad score was used independently by 2 authors (NXF and DHL) to evaluate the methodological quality of each included trial.

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.[12]

2.5. Data abstraction

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

(1) author, year of publication, and journal of included studies;
(2) total number of patients, number of patients in Ulinastatin and control groups, gender, age;
(3) type of surgical procedure, CPB time, and aortic cross-clamping time;
(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. For trials in which continuous outcomes were reported as median and range, mean and standard deviation were estimated by utilizing the O'Rourke method.[13] When the results of the trial were reported as median and quartile, the Stela Pudar-Hozo method was used to estimate the mean and standard deviation.[14]

2.6. Statistical analysis

All data were analyzed by utilizing RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Pooled odds ratio (OR) 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 ($I^2 > 50\%$). 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. The possible effects of patient age, gender, country, surgery type, and CPB on postoperative bleeding and transfusion were evaluated by meta-regression. Publication bias was explored through visual inspection of funnel plots of the outcomes, and evaluated by Begg test with STATA 14.0 (Stata Corp, College station, TX). 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 34 articles[9,15–47] for complete evaluation. Finally, 21 eligible trials[9,15–34] were included in the meta-analysis. Descriptive analyses of these articles were presented in Table 1. Of the 21 literatures, 9[15–23] were written in English, and the other 12[9,24–34] were in Chinese. Ulinastatin administration protocols (dosage, timing, and route) varied among included trials.

3.2. Included trials characteristics

As shown in Table 2, 5 studies[9,16,18,21,24] included only CABG patients (3 studies[9,16,21] for on-pump CABG and 2[18,24] for off-pump CABG), 6 studies[19,20,22,23,25,26] included only valve surgical patients, 2 studies[27,33] included only patients undergoing repair for congenital heart diseases, 1 study[17] included only aortic surgical patients, the other 7 studies[19,28–32,34] involving patients with mixed surgery procedures. The 21 eligible trials involved totally 1310 patients, and 617 patients were allocated into Ulinastatin group and 693 into Control (placebo/blank) group. Pre- and intraoperative data of these patients were presented in Table 2. The study by Shu et al[28] measured 2 doses of Ulinastatin, it was; therefore, considered as 2 independent groups.

3.3. Study quality and risk bias

The risk of bias analysis was shown in Supplement Figures 1, http://links.lww.com/MD/D772 and 2, http://links.lww.com/MD/D773. Of the 21 included trials, 8 trials[16–19,20,22,24,29,30]

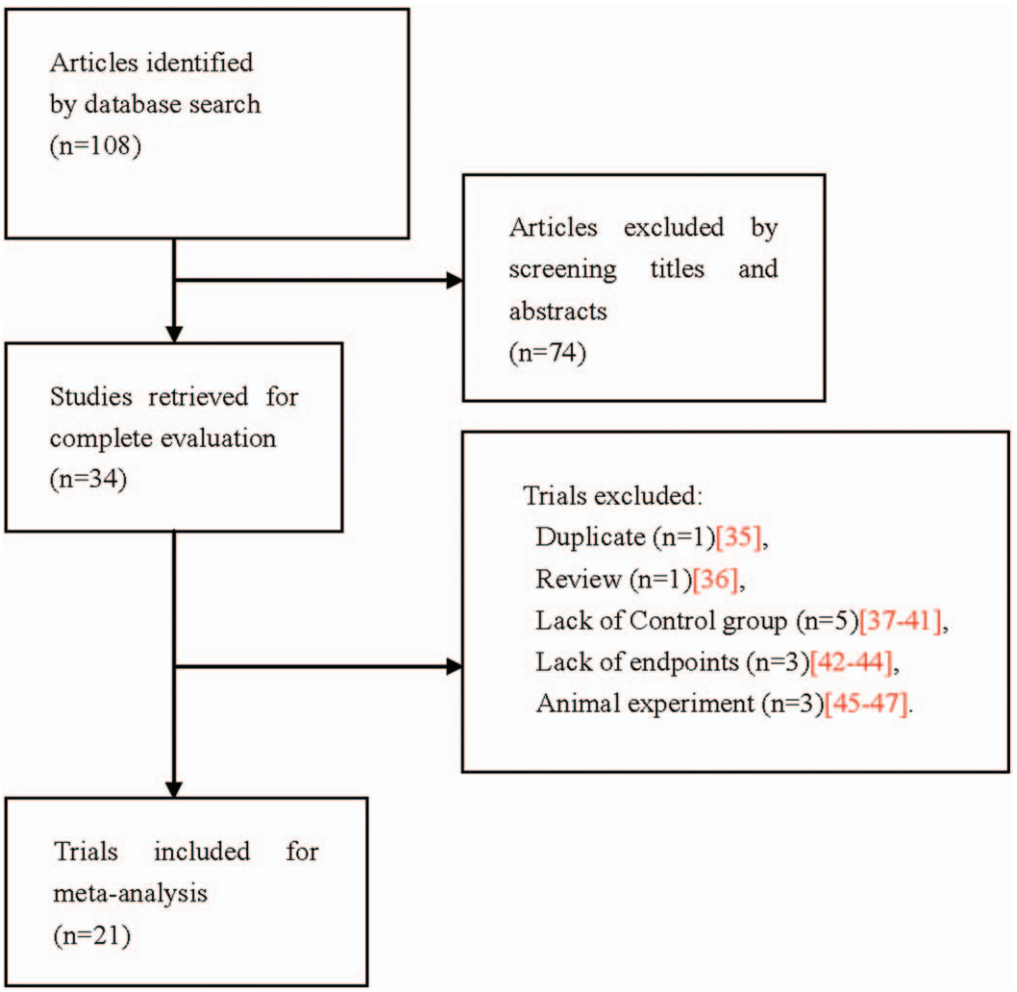

Figure 1. Flow chart.

Table 1

Included trials.

First author	Year	Journal	Country	Language	Ulinastatin administration	Control
Chen TT[22]	2013	*Heart Surg Forum*	China	English	12,000 U/kg iv. after AI 12,000 U/kg added to CPB prime	Saline
Ji BY[21]	2007	*J Cardiovasc Surg*	China	English	300,000 U iv. before CPB 300,000 U iv. before AXC release 400,000 U iv. after protamine	Saline
Ji HW[9]	2009	*Zhonghua Yi Xue Za Zhi*	China	Chinese	400,000 U iv. after AI 400,000 U added to CPB prime 200,000 U ivgtt. (40,000–60,000/h)	Saline
Jin XG[32]	2005	*Chin Pharm J*	China	Chinese	300,000 U iv. after AI 300,000 U added to CPB prime 300,000 U during CPB	Saline
Kim NY[18]	2013	*Korean J Anesthesiol*	Korea	English	300,000 U iv. after AI	Saline
Le HB[30]	2005	*Zhejiang Med*	China	Chinese	300,000 U iv. after AI 300,000 U added to CPB prime 300,000 U during CPB	Saline
Nakanishi K[16]	2006	*Crit Care Med*	Japan	English	5,000 U/kg iv. before CPB	Saline
Pang XY[15]	2016	*Am J Ther*	China	English	5,000 U/kg iv. after AI 5000 U/kg iv. after heparinizatioin 5000 U/kg iv. after protamine	Saline
Park JB[19]	2013	*Korean J Thorac Cardiovasc Surg*	Korea	English	5000 U/kg iv. before ACC	Saline
Qiu Y[23]	2015	*Chin Med J*	China	English	5000–10,000 U/kg iv. before incision 5000–10,000 U/kg added to CPB prime	No Uli
Shi J[34]	2010	*PUMC Doctorate Thesis*	China	Chinese	1,000,000 U iv. after AI 1,000,000 U iv. after heparinization 1,000,000 U iv. after protamine	Saline
Shi ZR[27]	2008	*Jiangsu Med J*	China	Chinese	20,000 U/kg added to CPB prime	Saline
Shu YZ[28]	2003	*Guizhou Med J*	China	Chinese	(1)30,000 U added to CPB prime (2)60,000 U added to CPB prime	No Uli
Song JE[20]	2011	*J Int Med Res*	Korea	English	5000 U/kg iv. before ACC	Saline
Tan RD[29]	2011	*Mod Hosp*	China	Chinese	300,000 U iv. after AI 300,000 U added to CPB prime	Saline
Wang GY[24]	2010	*Chin J ECC*	China	Chinese	6000 U/kg iv. after AI 1000 U/kg/h ivgtt. till end of surgery	Saline
Xu CE[17]	2013	*J Cardiothorac Vasc Anesth*	China	English	20,000 U/kg total, 1/3 after AI, 1/3 before ACC and 1/3 before ACC release	Saline
Yang WH[26]	2010	*Med Recap*	China	Chinese	12,000 U/kg iv. after AI 12,000 U/kg added to CPB prime	Saline
Yu JG[33]	2003	*Chin J Anesthesiol*	China	Chinese	6000 U/kg iv. after AI 6000 U/kg added to CPB prime	Saline
Zhang BJ[31]	2004	*J Cardiovasc Dis*	China	Chinese	300,000 U iv. after AI 300,000 U added to CPB prime 300,000 U during CPB	Saline
Zhai YJ[25]	2004	*Chin J ECC*	China	Chinese	12,000 U/kg iv. after AI 12,000 U/kg added to CPB prime	Saline

ACC = aortic cross-clamping, AI = anesthesia induction, CPB = cardiopulmonary bypass, Uli = Ulinastatin.

had Jadad scores ≥3 and were considered as high-quality randomized controlled trials (RCTs) (Supplement Table 2, http://links.lww.com/MD/D777).

3.4. Effects on intra- and postoperative bleeding

As shown in Figure 2 and Table 3, 3 trials[16,18,24] (118 patients) evaluated the effect of Ulinastatin on intraoperative bleeding, and 16 trials[9,16–22,24–29,33,34] (944 patients) reported blood loss in the first 24 hours postoperatively. Meta-regression suggested patient age, gender, country, surgery type, and CPB did not influence the result. Meta-analysis showed that, Ulinastatin administration did not significantly decrease intraoperative bleeding ([WMD = 0.13; 95% CI: −0.23 to 0.49; $P = .49$] without heterogeneity [$I^2 = 39\%$, $P = .19$]), but significantly reduced postoperative bleeding volume ([WMD = −0.73; 95% CI: −1.17 to −0.28; $P = .001$] with heterogeneity [$I^2 = 89\%$, $P < .00001$]).

As shown in Table 3, 4 trials[9,17,27,34] (302 patients) reported re-exploration for postoperative bleeding. Meta-analysis showed no difference in the rate of re-exploration for bleeding between Ulinastatin and Control groups (4/151[2.6%] vs 7/151 [4.6%], [OR = 0.59; 95% CI: 0.18–1.93; $P = .38$] without heterogeneity [$I^2 = 0\%$, $P = .60$]).

3.5. Effects on intra- and postoperative blood transfusion

As depicted in Table 3 and Figure 3, 3 trials[18–20] (208 patients) reported data on intraoperative RBC transfusion volume, 10 trials[9,18–21,25–28,34] (640 patients) reported postoperative RBC

Table 2

Grouping and patients data.

	Sample size		Age, yr		Sex (M/F)		Surgery	CPB, min		ACC, min	
	Group Uli	Group C	Group Uli	Group C	Group Uli	Group C		Group Uli	Group C	Group Uli	Group C
Chen 2013	30	30	50±11	50±10	14/6	12/18	SVR/BVR	103±21	100±23	75±21	69±20
Ji 2007	15	15	57±7	57±6	11/4	11/4	CPB-CABG	108±29	117±34	60±22	67±23
Ji 2009	18	18	60±8	59±9	15/3	16/2	CPB-CABG	120±19	105±16	74±16	66±11
Jin 2005	15	12	37±14			NR	ASD/VSD/TOF/VR	123±58		67±30	
Kim 2013	25	25	67±10	63±9	19/6	17/8	OPCAB	NA	NA	NA	NA
Le 2005	20	18	36±12	34±10	9/11	8/10	ASD/VSD/SVR	111±58	107±53	66±42	66±40
Nakanishi 2006	14	14	62±9	61±10	12/2	11/3	CPB-CABG	150±37	135±39	118±32	104±32
Pang 2016	30	30	54±9	50±9	15/15	21/9	CPB-CABG/VR	NR	NR	NR	NR
Park 2013	41	69	55±14	48±14	10/31	27/42	VP/VR	126±38	117±32	78±28	71±27
Qiu 2015	70	138	48±10	47±9	18/52	51/87	VP/VR	129±37	111±33	86±30	74±29
Shi 2010	100	100	49±13	46±15	44/56	49/51	CHD-R/CABG/VR	115±134	108±48	75±36	78±37
Shi 2008	15	15	17±8*	17±8*	9/6	7/8	ASD/VSD	42±6	40±4	26±4	25±3
Shu 2003	Uli-1: 12	12	38±7	41±10	9/3	8/4	ASD/VSD/SVR	81±17	79±14	61±11	64±13
	Uli-2: 12		36±9		7/5			88±19		58±11	
Song 2011	24	24	52±17	53±19	8/16	9/15	AVR	164±32	173±28	99±24	105±26
Tan 2011	60	60	44±24	42±26	32/28	33/27	ASD/VSD/VR	93±16	91±17	56±14	56±14
Wang 2010	20	20	58±8	60±8	15/5	16/4	OPCAB	NA	NA	NA	NA
Xu 2013	18	18	55±9	53±7	16/2	15/3	Aortic surgery	236±26	247±20	60±22	58±17
Yang 2010	30	30	25-58	27-60	14/16	14/16	SVR/BVR	NR	NR	NR	NR
Yu 2003	10	10	12±7	11±6	7/3	6/4	ASD/VSD	57±24	50±18	37±24	30±11
Zhang 2004	18	15	36±12	35±10	NR	NR	ASD/VSD/VR	128±52	118±45	63±39	61±37
Zhai 2004	20	20	25–56	31–62	8/12	10/10	SVR/BVR	NR	NR	NR	NR

ACC = aortic cross-clamping, ASD/VSD = atrial septum defect/ventricular septum defect, AVR = aortic valve replacement, CPB = cardiopulmonary bypass, CPB-CABG = coronary artery bypass grafting with cardiopulmonary bypass, Group C = Group Control, Group Uli = Group Ulinastatin, NA = non-applicable, NR = not-reported, OPCAB = off-pump coronary artery bypass grafting, SVR/BVR = single valve replacement/bi- valve replacement, VP/VR = valve plasty/valve replacement.

* months.

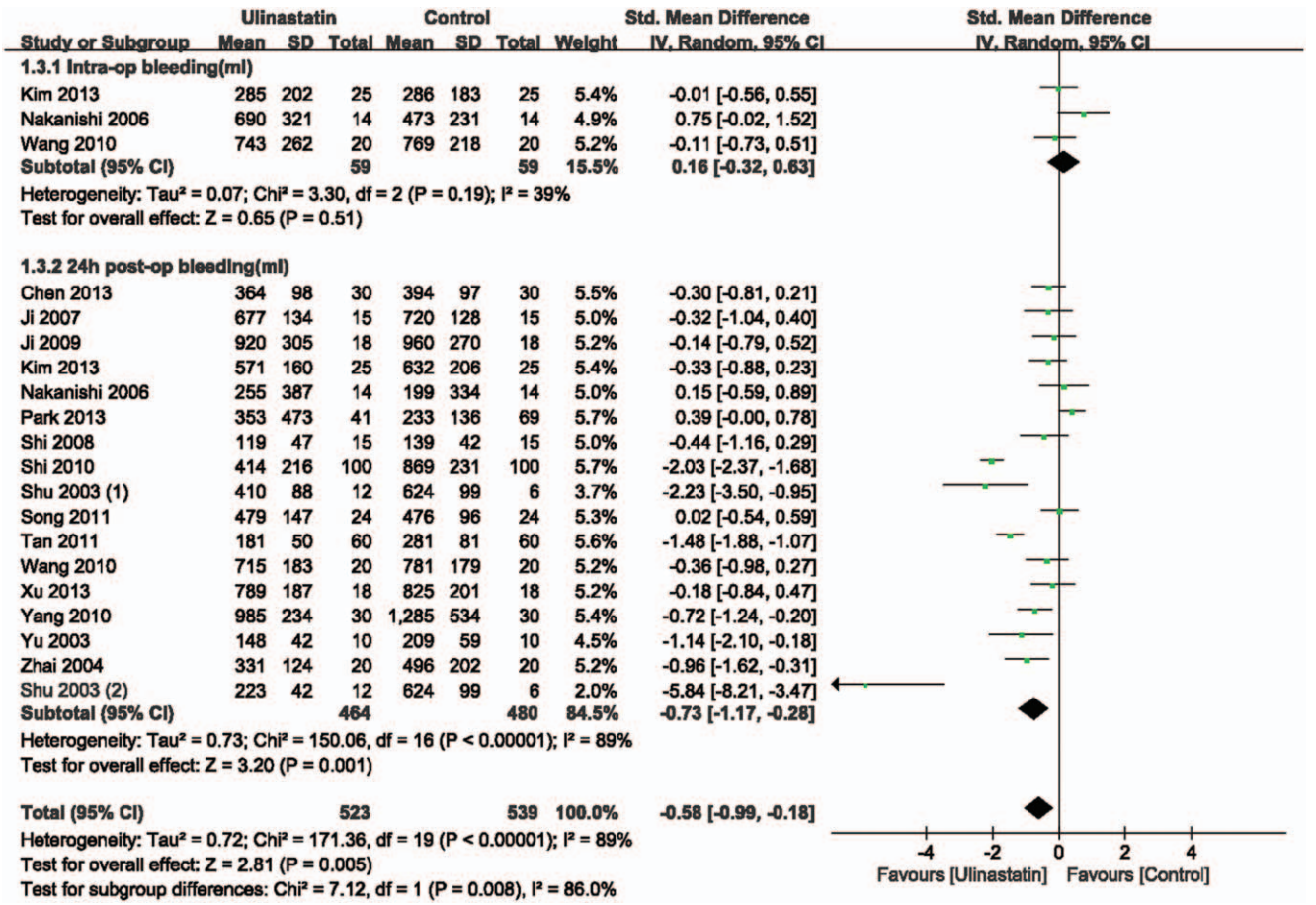

Figure 2. Forest plot of bleeding.

Table 3

Meta-analysis of outcomes.

Outcomes	Trials (n)	Group Uli (n)	Group Ctrl (n)	Heterogeneity		Analysis model	WMD/OR	95% CI	Overall effect *P*
				I^2 (%)	*P*				
Bleeding									
Intraop (mL)	3	59	59	39	.19	IV, Fixed	0.13	–0.23, 0.49	.49
24 h post-op (mL)	17	464	480	89	<.00001	IV, Random	–0.73	–1.17, –0.28	.001*
Re-exploration for bleeding (%)	4	151	151	0	.60	M-H, Fixed	0.59	0.18, 1.93	.38
Blood transfusion									
Intra-op RBC (U)	3	90	118	0	.74	IV, Fixed	0.04	–0.21, 0.30	.75
Post-op RBC (%)	3	140	140	0	.47	M-H, Fixed	0.78	0.42, 1.45	.43
Post-op RBC (U)	11	312	328	95	<.00001	IV, Random	–0.70	–1.26, -0.14	.01*
Post-op FFP (mL)	3	165	193	45	.16	IV, Fixed	–12.11	–56.19, 31.97	.59
Post-op PC (U)	2	141	169	Not applicable	IV, Random	0.40	–1.00, 1.80	0.58	
Post-op Cryo (mL)	1	24	24	Not applicable		IV, Random	Not estimable		Not applicable
Hemoglobin									
Pre-op (g/dL)	5	153	153	0	.83	IV, Fixed	–1.70	–5.43, 2.04	.37
End-of-op (g/dL)	3	115	115	91	<.00001	IV, Random	11.80	–1.15, 24.75	.07
24 h post-op (g/dL)	5	153	153	91	<.00001	IV, Random	9.17	0.17, 18.17	.05
Heparin (mg)	4	114	142	89	<.00001	IV, Random	21.02	–6.46, 48.49	.13
Protamine (mg)	4	114	142	83	.0006	IV, Random	10.56	–11.17, 32.28	.34
ACT									
Baseline (s)	2	43	43	40	.20	IV, Fixed	2.69	–3.35, 8.73	.38
Post-heparinization (sec)	2	43	43	95	<.00001	IV, Random	–31.60	–58.17, –5.02	.02*
End-of-op ACT (s)	2	43	43	0	.77	IV, Fixed	–3.08	–12.32, 6.16	.51
Platelet count									
Pre-op ($\times 10^9$/L)	14	383	474	0	.90	IV, Fixed	–0.75	–7.93, 6.43	.84
24 h post-op ($\times 10^9$/L)	10	298	391	81	<.00001	IV, Random	9.07	–4.44, 22.58	.19
Post-op PAGM (%)	2	35	32	0	1.00	IV, Fixed	9.20	4.72, 13.68	<.00001*
Post-op CD62p (%)	3	53	50	97	<.00001	IV, Random	–7.04	–15.16, 1.09	.09
Post-op CD62p (MFI)	6	93	90	66	.01	IV, Random	–0.59	–3.29, 2.11	.67
PT									
Pre-op (s)	4	108	136	58	.07	IV, Random	0.01	–0.34, 0.36	.95
End-of-op (s)	2	43	43	0	.85	IV, Fixed	–0.06	–0.58, 0.46	.82
24 h post-op (s)	4	108	136	0	.40	IV, Fixed	–0.01	–0.25, 0.23	.94
APPT									
Pre-op (s)	4	108	136	0	.40	IV, Fixed	–0.92	–1.96, 0.12	.08
End-of-op (s)	2	43	43	78	.03	IV, Random	–3.79	–9.64, 2.06	.20
24 h post-op (s)	3	84	112	0	.42	IV, Fixed	–1.18	–3.47, 1.12	.31
Fibrinogen									
Pre-op (mg/dL)	4	108	136	49	.12	IV, Fixed	8.43	–12.45, 29.31	.43
End-of-op (mg/dL)	1	18	18	Not applicable		IV, Random	6.00	–43.34, 55.34	.81
24 h post-op (mg/dL)	3	83	111	0	.48	IV, Fixed	2.48	–15.01, 19.97	.78
D-dimer									
Pre-op (mg/dL)	5	76	61	0	.85	IV, Fixed	–0.03	–0.07, 0.01	.12
End-of-op (mg/dL)	4	52	37	94	<.00001	IV, Random	–1.07	–1.66, –0.49	.0003*
24 h post-op (mg/dL)	6	106	91	98	<.00001	IV, Random	–0.87	–1.34, –0.39	.0003*
Leukocyte count									
Pre-op ($\times 10^9$/L)	4	140	208	0	.93	IV, Fixed	0.07	–0.29, 0.43	.71
End-of-op ($\times 10^9$/L)	4	140	208	39	.18	IV, Fixed	–0.27	–1.08, 0.54	.52
24 h post-op ($\times 10^9$/L)	4	140	208	0	.66	IV, Fixed	–0.00	–0.79, 0.78	.99
Neutrophil count									
Pre-op ($\times 10^9$/L)	2	95	163	0	.98	IV, Fixed	–0.01	–0.39, 0.36	.95
End-of-op ($\times 10^9$/L)	2	95	163	0	.89	IV, Fixed	–0.04	–0.91, 0.83	.92
24 h post-op ($\times 10^9$/L)	2	95	163	0	.88	IV, Fixed	0.30	–0.60, 1.20	.89
TNF-α									
Pre-op (pg/mL)	5	193	193	0	.44	IV, Fixed	0.11	–0.24, 0.47	.52
End-of-op (pg/mL)	5	193	193	93	<.00001	IV, Random	–35.16	–56.47, –13.85	.001*
24 h post-op (pg/mL)	5	193	193	99	<.00001	IV, Random	–39.25	–73.00, –5.51	.02*
PMNE									
Pre-op (ng/mL)	5	193	193	13	.33	IV, Fixed	0.78	–0.86, 2.42	.35
End-of-op (ng/mL)	5	193	193	98	<.00001	IV, Random	–104.28	–166.53, –42.04	.001*
24 h post-op (ng/mL)	5	193	193	99	<.00001	IV, Random	–98.90	–149.14, –48.67	.0001*
IL-6									
Pre-op (pg/mL)	6	213	213	0	.89	IV, Fixed	–0.05	–0.38, 0.27	.75
End-of-op (pg/mL)	6	213	213	97	<.00001	IV, Random	–44.46	–60.48, –28.44	<.00001*
24 h post-op (pg/mL)	6	213	213	98	<.00001	IV, Random	–19.35	–32.35, –6.35	.004*
IL-8									
Pre-op (pg/mL)	4	163	163	0	.93	IV, Fixed	–0.08	–1.85, 1.70	.93
End-of-op (pg/mL)	4	163	163	93	<.00001	IV, Random	–50.31	–86.76, –13.85	.007*
24 h post-op (pg/mL)	4	163	163	96	<.00001	IV, Random	–46.90	–78.36, –15.45	.003*
IL-10									
Pre-op (pg/mL)	3	150	150	23	.27	IV, Fixed	3.59	1.80, 5.38	<.0001*
End-of-op (pg/mL)	3	150	150	98	<.00001	IV, Random	–8.97	–61.88, 43.93	.74
24 h post-op (pg/mL)	3	150	150	97	<.00001	IV, Random	11.91	–11.08, 34.90	.31

95%CI = 95%confidence interval, ACT = activated clotting time, APPT = activated partial thromboplastin time, Cryo = cryoprecipate, Ctrl = control, End-of-op = end of operation, FFP = fresh frozen plasma, IL = interleukin, Intra-op = intraoperative, IV = inverse variance, MFI = mean fluorescence intensity, M–H = Mantel–Haenszel, OR = odds ratio, PAGM = platelet aggregation maximum, PC = platelet concentrates, PMNE = polymorphonuclear elastase, Post-op = postoperative, Pre-op = preoperative, PT = prothrombin time, RBC = red blood cell, TNF = tumor necrosis factor, Uli = Ulinastatin, WMD = weighted mean difference.

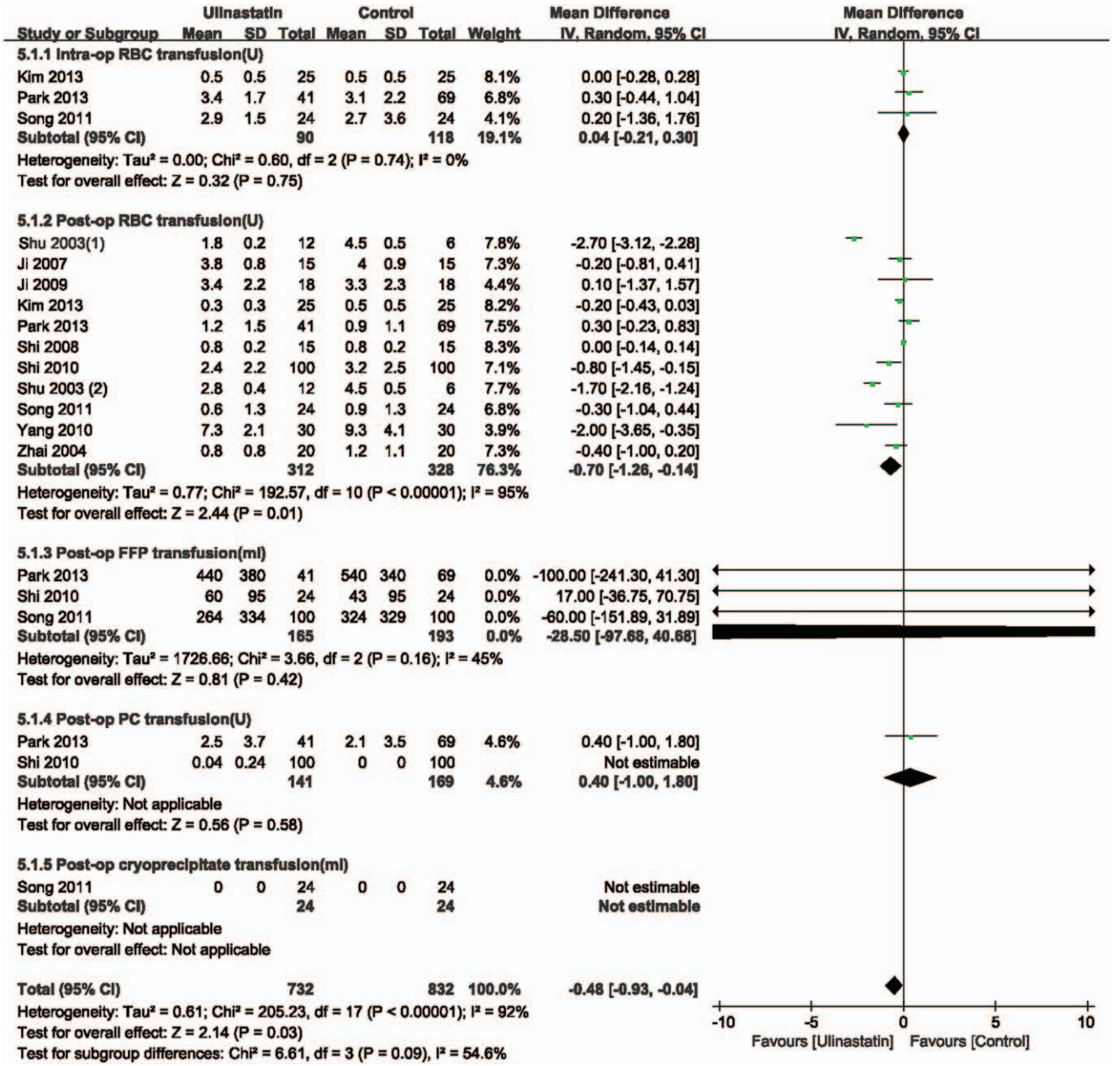

Figure 3. Forest plot of RBC transfusion. RBC = red blood cells.

transfusion volume, and 3 trials[9,18,34] (280 patients) reported data on postoperative RBC transfusion incidence. Meta-analysis showed that, Ulinastatin did not reduce postoperative RBC transfusion incidence as compared to control (90/140 [64.3%] vs 95/140 [67.9%], [OR = 0.78; 95% CI: 0.42–1.45; $P = .43$] without heterogeneity [$I^2 = 0\%$, $P = .47$]), but significantly reduced postoperative RBC transfusion volume ([WMD = −0.70; 95% CI: −1.26 to −0.14; $P = .01$] with heterogeneity [$I^2 = 95\%$, $P < .00001$]). Meta-regression suggested patient age, gender, country, surgery type, and CPB did not influence the result. In addition to that, 3 trials[19,20,34] (358 patients) reported postoperative fresh frozen plasma transfusion, which were all comparable between Ulinastatin and Control groups ([WMD = −12.11; 95% CI: −56.19 to 31.97; $P = .59$] without heterogeneity [$I^2 = 45\%$, $P = .16$]). In addition to that, 2 trials[19,34] (310 patients) reported postoperative PC transfusion, and 1 trials[20] (48 patients) reported postoperative cryoprecipitate transfusion.

3.6. Effects on hemoglobin levels

As shown in Table 3, 5 trials[9,18,25,26,29] (306 patients), 3 trials[18,26,29] (230 patients) and 5 trials[9,18,25,26,29] (306 patients) reported respective hemoglobin level before operation, at the end of operation and 24 hours postoperatively. Meta-analysis showed that, Ulinastatin-treated patients and Control patients had similar hemoglobin levels at all the 3 time points (Pre-op: WMD = −1.70; 95% CI: −5.43 to 2.04; $P = .37$ without heterogeneity [$I^2 = 0\%$, $P = .83$]; End-of-op: WMD = 11.80; 95%

CI: −1.15 to 24.75; $P=.07$ with heterogeneity [$I^2=91\%$, $P<.00001$]; 24 hours post-op: WMD = 9.17; 95% CI: 0.17–18.17; $P=.05$ with heterogeneity [$I^2=91\%$, $P<.00001$]).

3.7. Effects on heparin and protamine dosages, ACT values

As shown in Table 3, 4 trials[9,15,18,19] (256 patients) reported intraoperative heparin dose and protamine dose for heparinization reversal, 2 trials[9,18] (86 patients) reported ACT values at baseline, after heparinization and at the end of operation. There was no difference in intra-operative heparin ([WMD = 21.02; 95% CI: −6.46 to 48.49; $P=.13$] with heterogeneity [$I^2=89\%$, $P<.00001$]) and protamine doses ([WMD = 10.56; 95% CI: −11.17 to 32.28; $P=.34$] with heterogeneity [$I^2=83\%$, $P=.0006$]). However, Ji et al[9]reported that post-heparinization ACT in Group Ulinastatin was significantly shorter than that in Group Control ([602 ± 126] s vs [824 ± 146] s, $P<.05$).

3.8. Effects on coagulation functions

As shown in Table 3, 4 trials[9,18–20] (244 patients), 2 trials[9,18] (86 patients) and 4 trials[9,18–20] (244 patients), reported Prothrombin time (PT) and activated partial thromboplastin time (APTT) values at baseline, at the end of operation, and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups with respect to PT (Pre-op: WMD = 0.01; 95% CI: −0.34 to 0.36; $P=.95$ without heterogeneity [$I^2=40\%$, $P=.20$]; End-of-op: WMD = −0.06; 95% CI: −0.58 to 0.46; $P=.82$ with heterogeneity [$I^2=95\%$, $P<.00001$]; 24 hours post-op: WMD = −0.01; 95% CI: −0.25 to 0.23; $P=.94$ without heterogeneity [$I^2=0\%$, $P=.77$]) and APTT values perioperatively (Pre-op: WMD = −0.92; 95% CI: −1.96 to 0.12; $P=.08$ with heterogeneity [$I^2=58\%$, $P=.07$]; End-of-op: WMD = −3.79; 95% CI: −9.64 to 2.06; $P=.20$ without heterogeneity [$I^2=0\%$, $P=.85$]; 24 hours post-op: WMD = −1.18; 95% CI: −3.47 to 1.12; $P=.31$ without heterogeneity [$I^2=0\%$, $P=.40$]). Four trials[9,18,19,20] (244 patients), 1 trial[9] (36 patients) and 3 trials[9,19,20] (194 patients), reported fibrinogen levels at baseline, at the end of operation, and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups, either (Pre-op: WMD = 8.43; 95% CI: −12.45 to 29.31 without heterogeneity [$I^2=49\%$, $P=.12$]; $P=.43$; 24 hours post-op: WMD = 2.48; 95% CI: −15.01 to 19.97; $P=.78$ without heterogeneity [$I^2=0\%$, $P=.48$]).

Antithrombin (AT) is a small protein molecule that inactivates several enzymes of the coagulation system.[28] Shu and colleagues compared the influence of 2 doses of Ulinastatin and blank control on AT-III activity (AT-III:A) and Factor XI pro-coagulant activity (FXI:C) in patients undergoing cardiac surgery with CPB, and they found that there was no intergroup difference in AT-III: A, but patients receiving larger dose of Ulinastatin had highest FXI:C at the end of CPB and 6 hours later.[28]

Thrombin-antithrombin complex (TAT) and prothrombin fragment 1 + 2 (F1 + 2), are 2 indices of in vivo thrombin generation.[48] The trial by Kim et al[18] investigated the influence of Ulinastatin versus saline on TAT and F1 + 2 in off-pump CABG patients, and suggested that Ulinastatin did not attenuate increased thrombin generation peri-operatively.

3.9. Effects on platelet count and functions

As shown in Table 3, 14 trials[9,18–21,23–27,29,30,32,33] (857 patients) and 10 trials[9,19–21,23,26,27,29,32,33] (689 patients) reported platelet count preoperatively and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups (Pre-op: WMD = −0.75; 95% CI: −7.93 to 6.43; $P=.84$ without heterogeneity [$I^2=0\%$, $P=.90$]; 24 hours post-op: WMD = 9.07; 95% CI: −4.44 to 22.58; $P=.19$ with heterogeneity [$I^2=81\%$, $P=P<.00001$]).

As shown in Table 3, platelet aggregation function was evaluated by examining maximum platelet aggregation ratio (PAGM%) in 2 included trials[30,32] which both indicated that Ulinastatin preserved postoperative platelet aggregation function better than control. CD62P, also known as P-selectin, is released from α-granules upon platelet activation and promotes platelet aggregation through platelet-fibrin and platelet-platelet binding.[49] Three trials[9,30,32] (103 patients) and 6 trial[9,21,24,27,32,33] (183 patients) reported postoperative CD62P expression percentage (%) and mean fluorescence intensity (MFI), respectively. Meta-analysis showed that there was no intergroup difference in either CD62P expression percentage ([WMD = −7.04; 95% CI: −15.16 to 1.09; $P=.09$] with heterogeneity [$I^2=97\%$, $P<.00001$]) or MFI (WMD = −0.59; 95% CI: −3.29 to 2.11; $P=.67$ with heterogeneity [$I^2=66\%$, $P=.01$]). Platelet factor-4 (PF-4), also a marker of platelet activation released from α-granules of platelets during aggregation.[18] No difference in PF-4 level was found between Ulinastation group and Control group throughout the study period by Kim and colleagues.[18] Thromboxane B_2 (TXB_2) is an inactive metabolite of thromboxane-A_2, the latter is involved in platelet activation and aggregation.[33] Yu et al demonstrated that Ulinastatin, as compared to saline, significantly lowered TXB_2 levels in patients undergoing on-pump repair operation for congenital heart diseases.[33]

3.10. Effects on fibrionlysis

As shown in Table 3, 4 trials[20,28,31,33] (137 patients), 3 trial[28,31,33] (89 patients) and 5 trials[20,22,28,31,33] (197 patients), reported D-dimer levels at baseline, at the end of operation, and 24 hours postoperatively. Meta-analysis indicated that Ulinastatin-treated patients had lower D-dimer levels at the end of operation ([WMD = −1.07; 95% CI: −1.66 to −0.49; $P=.0003$] with heterogeneity [$I^2=94\%$, $P<.00001$]), and 24 hours postoperatively when compared to those in Control patients ([WMD = −0.87; 95% CI: −1.34 to −0.39; $P=.0003$] with heterogeneity [$I^2=98\%$, $P<.00001$]).

Additionally, Chen et al[22] demonstrated that, Ulinastatin had no effect on concentrations of 2 fibrinolytic indexes, plasminogen activator (PA) and α2-antiplasmin (α2-AP), in patients undergoing heart valve replacement surgery.

3.11. Effects on TEG profiles

Park and colleagues[19] failed to detect any significant differences between Ulinastatin and saline with respect to postoperative TEG profiles including R (clotting time), K (clot formation time), and MA (maximum clot firmness) values in cardiac surgical patients. That is contrary to previous study by Okida et al reporting that Ulinastatin normalized the coagulation function and prevented changes in TEG during liver resection surgery.[8]

3.12. Effects on leukocyte and neutrophil counts

As shown in Table 3, 4 trials[15,18,21,23] (348 patients) and 2 trials[18,23] (258 patients) reported leukocyte count and neutrophil

count preoperatively, at the end of operation, and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups in either leukocyte count (Pre-op: WMD = 0.07; 95% CI: −0.29 to 0.43; $P = .71$ without heterogeneity [$I^2 = 0\%$, $P = .93$]; End-of-op: WMD = −0.27; 95% CI: −1.08 to 0.54; $P = .52$ without heterogeneity [$I^2 = 39\%$, $P = .18$]; 24 hours post-op: WMD = −0.00; 95% CI: −0.79 to 0.78; $P = .99$ without heterogeneity [$I^2 = 0\%$, $P = .66$]) or neutrophil count (Pre-op: WMD = −0.01; 95% CI: −0.39 to 0.36; $P = .95$ without heterogeneity [$I^2 = 0\%$, $P = .98$]; End-of-op: WMD = −0.04; 95% CI: −0.91 to 0.83; $P = .92$ without heterogeneity [$I^2 = 0\%$, $P = .89$]; 24 hours post-op: WMD = 0.30; 95% CI: −0.60 to 1.20; $P = .89$ without heterogeneity [$I^2 = 0\%$, $P = .88$]).

3.13. Effects on polymorphonuclear elastase (PMNE) and interleukins

As shown in Table 3, 5 trials[15,17,21,22,34] (386 patients) reported PMNE and tumor necrosis factor-α (TNF-α) preoperatively, at the end of operation, and 24 hours postoperatively. Six trials[9,15,17,22,24,34] (426 patients) reported interleukin-6 (IL-6) preoperatively, at the end of operation, and 24 hours postoperatively. Four trials[15,17,21,34] (326 patients) reported IL-8 preoperatively, at the end of operation, and 24 hours postoperatively. The present meta-analysis indicated that, Ulinastatin-treated patients had lower levels of PMNE, TNF-α, IL-6, and IL-8 both at the end of operation and 24 hours postoperatively when compared to those in control patients (Table 3). Three trials[15,24,34] (300 patients) reported IL-10 preoperatively, at the end of operation, and 24 hours postoperatively. Meta-analysis showed that, Ulinastatin-treated patients had higher baseline IL-10 value than that of control patients, and that they had comparable levels of IL-10 at the end of operation and 24 hours postoperatively (Table 3).

3.14. Sensitivity analyses and publication bias

Sensitivity analysis showed that treatment effects on all the outcomes were not affected by the choice of statistical model (Supplement Table 3, http://links.lww.com/MD/D778). Sensitivity tests were also performed by exclusion of some studies to analyze the influence of the overall treatment effect on high heterogeneity outcomes (Supplement Table 4, http://links.lww.com/MD/D779 but no contradictory results were found. No significant publication bias was detected by funnels plot examination for postoperative bleeding (Fig. 4) and RBC transfusion (Fig. 5). The symmetry of funnel plots of both outcomes were further evaluated by Begg test ($P = .436$ and .266 for postoperative bleeding and RBC transfusion, respectively) (Supplement Figs. 3, http://links.lww.com/MD/D774 and 4, http://links.lww.com/MD/D775).

4. Discussion

To our knowledge, this is the first meta-analysis dedicated to evaluate whether Ulinastatin could reduce blood loss and transfusion requirements. The present meta-analysis suggested that, Ulinastatin administration could reduce postoperative bleeding and RBC transfusion requirement, preserve platelet function, inhibit hyperfibrinolysis, and attenuate systemic inflammation in cardiac surgical patients.

Systemic heparinization, hemodilution, and hypothermia applied during cardiac surgery with CPB significantly influence coagulation and fibrinolysis systems. The present meta-analysis showed that Ulinastatin did not influence coagulation parameters such as PT and APTT values, fibrinogen levels, AT-III:A, and in vivo thrombin generation. CPB-induced fibrinolysis activation is associated with increased postoperative bleeding volume.[49] D-dimer is an index for measurement of fibrinolytic activity in cardiac surgery. The present meta-analysis confirmed the anti-fibrinolytic effect of Ulinastatin, as manifested by lowering postoperative D-dimer levels without influence on PA and α2-AP concentrations.

Platelets play an important role in hemastasis by means of adhesion, activation, and aggregation. CPB and hypothermia can result in significant changes in platelet function.[50] Upon platelet activation, CD62P (also known as P-selection) was rapidly

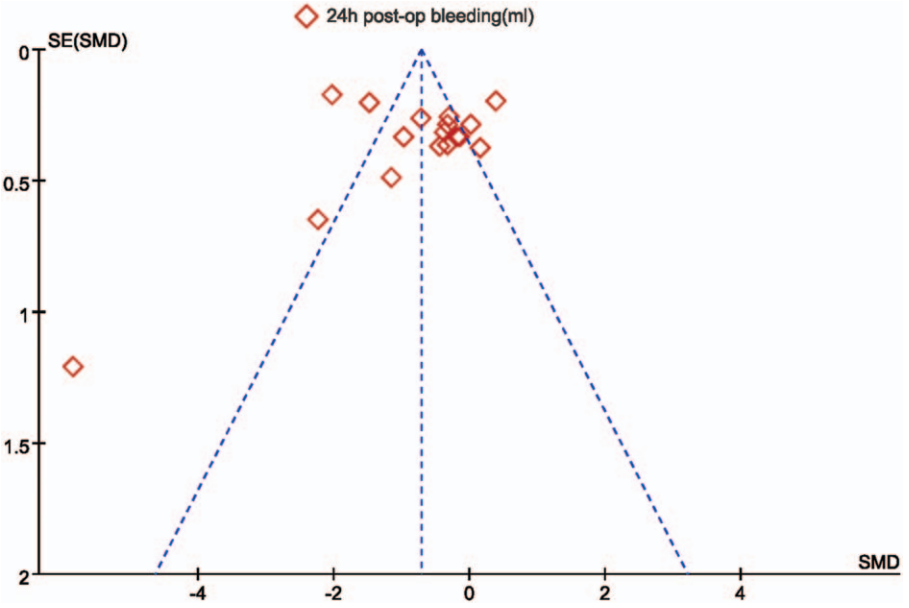

Figure 4. Funnel plot for postoperative bleeding.

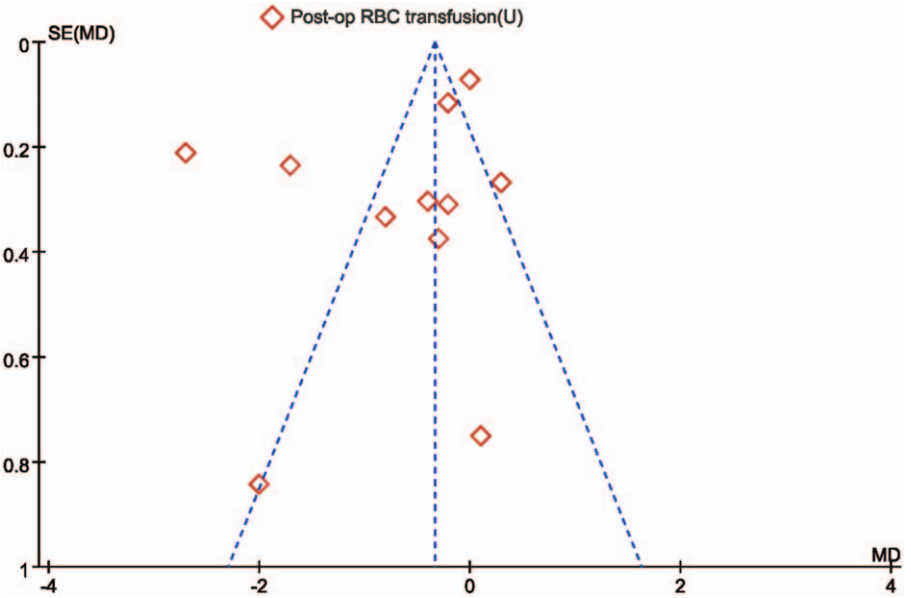

Figure 5. Funnel plot for postoperative RBC transfusion. RBC = red blood cells.

released from α-granules to external surface.[36] Therefore, CPB-induced platelet activation could be evidenced by increases in CD62P expression.[36] The present meta-analysis suggested that, Ulinastatin did not influence platelet count, but PAGM% was better preserved post-operatively in Ulinastatin-treated patients.

Inflammation contributes to thrombotic response and influence the initiation and propagation of blood coagulation.[51] Evidence has suggested that, Ulinastatin can reduce pro-inflammatory cytokines, elevate anti-inflammatory cytokines, and provide organ protection in patients undergoing cardiac surgery.[5–7] The conclusion is further confirmed by our meta-analysis which indicated that Ulinastatin not only reduced postoperative bleeding and transfusion requirement, but also inhibited the release of inflammatory mediators such as TNF-α, PMNE, IL-6, and IL-8. Open heart surgery triggers systemic inflammatory response syndrome via the action of leukocytes, especially polymorphonuclear neutrophils (PMNs). PMNs degrade or inhibit the activity of fibrin, fibrinogen, platelets and coagulation factors, and lead to increased blood loss and transfusion requirements.[19,52] The inhibitory effect of Ulinastatin on inflammatory cytokines may be related to the activity inhibition of the widely distributed serine proteases, inhibition of migration and activation of leukocytes, reduction in inflammatory cell infiltration and release of tissue toxic substances.[53,54] It has also been proved that Ulinastatin is effective in lowering allogeneic blood transfusion induced PMNE and cytokines release.[55–57] Interestingly, it has been indicated that Ulinastatin addition could attenuate in vitro storage lesion (eg, hemolysis, erythroptosis) of human red blood cells.[58,59]

Notably, the administration strategy of Ulinastatin could significantly affect the outcomes of interests. The maximum recommended daily dosage of Ulinastatin in its product instructions is 30×10^4U (Guangdong Techpool Bio-pharma Co. Ltd., Guangdong, China). However, the doses required to treat severe acute diseases (eg, sepsis, acute pancreatitis) is much higher. In a recent randomized, double-blinded, placebo-controlled and single-dose escalation study, Chen et al[60] demonstrated that, 2 hours of intravenous infusion of Ulinastatin ranging from 30×10^4U to 800×10^4U was well tolerated in healthy volunteers. The effects of Ulinastatin on blood loss reduction might be dose-dependent. In our meta-analysis, larger doses (eg, above 1.2×10^4U/kg or 300×10^4U) of Ulinastatin tended to reduce bleeding and blood transfusion requirement, while smaller doses (eg, 5000 U/kg) might not be sufficient to be effective. Ulinastatin administration only by intravenous bolus were unable to reduce bleeding in 5 trials,[16,17,19–21] while 5 included trials[25,27–29,33] demonstrated that adding Ulinastatin to CBP prime could significantly reduce blood loss. The half-life of Ulinastatin in healthy adults is only 40 minutes,[61,62] which is shorter than the duration of cardiac surgery or CPB. It is also possible that CPB-induced hemodilution could reduce the effectiveness of Ulinastatin.[20] Therefore, it is highly possible that, larger doses and longer period of Ulinastatin infusion may be necessary to be effective in reducing bleeding in cardiac surgical patients. It is also possible that, there are different effective Ulinastatin concentrations for different therapeutic purposes, such as anti-fibrinolysis, anti-inflammation, and so on. The optimal doses of Ulinastatin for different therapeutic purposes remain to be investigated. Notably, both Ulinastatin and aprotinin are trypsin inhibitors although derived from different sources. Whether ulinastatin have any effect on short- and long-term outcomes of cardiac surgical patients remains to be examined in adequately powered RCTs.

This study has some limitations. Meta-analysis can increase the power of analysis by pooling many small low-quality studies, but varied Ulinastatin dosages and surgical operation types, different clinical practices, quality and heterogeneity issues of included studies may limit the certainty of the findings of meta-analysis. To clarify the hemostatic effectiveness of Ulinastatin in cardiac surgical patients, a prospective randomized, placebo-controlled, triple-blinded trial is ongoing in our center (ClinicalTrials.gov Identifier: NCT01060189).

To conclude, Ulinastatin reduces postoperative bleeding and transfusion requirement in cardiac surgical patients, possibly by inhibiting hyperfibrinolysis, preserving platelet function, and

alleviating inflammation. To confirm this, more well-designed and adequately-powered randomized trials are needed.

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References

[1] Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–31.
[2] Wang X, Zheng Z, Ao H, et al. A comparison before and after aprotinin was suspended in cardiac surgery: different results in the real world from a single cardiac center in China. J Thorac Cardiovasc Surg 2009;138:897–903.
[3] Pugia MJ, Lott JA. Pathophysiology and diagnostic value of urinary trypsin inhibitors. Clin Chem Lab Med 2005;43:1–6.
[4] Pugia MJ, Valdes RJr, Jortani SA. Bikunin (urinary trypsin inhibitor): structure, biological relevance, and measurement. Adv Clin Chem 2007;44:223–45.
[5] He S, Lin K, Ma R, et al. Effect of the urinary tryptin inhibitor ulinastatin on cardiopulmonary bypass-related inflammatory response and clinical outcomes: a meta-analysis of randomized controlled trials. Clin Ther 2015;37:643–53.
[6] Zhang Y, Zeng Z, Cao Y, et al. Effect of urinary protease inhibitor (ulinastatin) on cardiopulmonary bypass: a meta-analysis for China and Japan. PLoS One 2014;9:e113973.
[7] He QL, Zhong F, Ye F, et al. Does intraoperative ulinastatin improve postoperative clinical outcomes in patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. Biomed Res Int 2014;2014:630835.
[8] Okida M, Masako O, Maruya H, et al. Intraoperative changes in blood coagulation and the effectiveness of ulinastatin during liver resection. J Anesth 1991;5:43–7.
[9] Ji HW, Chen L. Effects of ulinastatin on coagulation and platelet function in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Zhonghua Yi Xue Za Zhi 2009;89:175–8.
[10] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
[11] Higgins JP, Altman DG, Gøtzsche PC, et al. Cochrane bias methods group; cochrane statistical methods group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[12] Clark HD, Wells GA, Huët C, et al. Assessing the quality of randomized trials: reliability of the Jadad scale. Control Clin Trials 1999;20:448–52.
[13] O'Rourke K. Mixed Means and Medians: A Unified Approach to Deal With Disparate Outcome Summaries. Proceedings of the 4th Symposium on Systematic Reviews: Pushing the Boundaries. Oxford: Cochrane Methodol Register; 2002. 49.
[14] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
[15] Pang XY, Fang CC, Chen YY, et al. Effects of ulinastatin on perioperative inflammatory response and pulmonary function in cardiopulmonary bypass patients. Am J Ther 2016;23:e1680–9.
[16] Nakanishi K, Takeda S, Sakamoto A, et al. Effects of ulinastatin treatment on the cardiopulmonary bypass-induced hemodynamic instability and pulmonary dysfunction. Crit Care Med 2006;34:1351–7.
[17] Xu CE, Zou CW, Zhang MY, et al. Effects of high-dose ulinastatin on inflammatory response and pulmonary function in patients with type-a aortic dissection after cardiopulmonary bypass under deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 2013;27:479–84.
[18] Kim NY, Shim JK, Bang SO, et al. Effects of ulinastatin on coagulation in high-risk patients undergoing off-pump coronary artery bypass graft surgery. Korean J Anesthesiol 2013;64:105–11.
[19] Park JB, Kim SH, Lee SA, et al. Effects of ulinastatin on postoperative blood loss and hemostasis in atrioventricular valve surgery with cardiopulmonary bypass. Korean J Thorac Cardiovasc Surg 2013;46:185–91.
[20] Song JE, Kang WS, Kim DK, et al. The effect of ulinastatin on postoperative blood loss in patients undergoing open heart surgery with cardiopulmonary bypass. J Int Med Res 2011;39:1201–10.
[21] Bingyang J, Jinping L, Mingzheng L, et al. Effects of urinary protease inhibitor on inflammatory response during on-pump coronary revascularisation. Effect of ulinastatin on inflammatory response. J Cardiovasc Surg 2007;48:497–503.
[22] Chen TT, Liu JD, Wang G, et al. Combined treatment of ulinastatin and tranexamic acid provides beneficial effects by inhibiting inflammatory and fibrinolytic response in patients undergoing heart valve replacement surgery. Heart Surg Forum 2013;16:E38–47.
[23] Qiu Y, Lin J, Yang Y, et al. Lack of efficacy of ulinastatin therapy during cardiopulmonary bypass surgery. Chin Med J 2015;128:3138–42.
[24] Wang GY, Ji BY, Liu NN, et al. Effect of ulinastatin on thrombin and platelet activation in the patients during off-pump coronary artery bypass graft surgery. Chin J ECC 2010;8: 100-2, 21.
[25] Zhai YJ, Wang XL. The protection of ulinastatin and aprotinin on blood fibrinolytic system during cardiopulmonary bypass. Chin J ECC 2004;2:84–6.
[26] Yang WH, Zhang H, Shang BJ. Ulinastatin and aprotinin to blood protection of operation on vessels of heart. Med Recapitulate 2010;16:2374–6.
[27] Shi ZR, Jiang ZF, Li JD, et al. Protective effects of ulinastatin on thrombocytic function in infants and children undergoing open heart surgery under cardiopulmonary bypass. Jiangsu Med J 2008;34:795–7.
[28] Shu YZ, Xiang DK, Zhou T. Effects of ulinstatin on blood coagulative function at cardiopulomonary bypass patients. Guizhou Med J 2003;27:883–4.
[29] Tan RD, Liang RQ, Chen HM. The effect of ulinastatin and reptilase on safeguard of blood in patients undergoing cardiac surgery under extracorporeal circulation. Mod Hosp 2011;11:26–8.
[30] Le HB, Zhang YQ, Zhang BJ. Platelet protective effect of ulinastatin during cardiopulmonary bypass. Zhejiang Med 2005;27:84–6.
[31] Zhang BJ, Zhang YQ, Le HB, et al. The effects of ulinastatin and tranexamic acid on D-dimer during cardiopulmonary bypass. J Cardiovasc Dis 2004;23:32–3.
[32] Jin XG, Fang GA, Liu B, et al. Effects of ulinastatin and tranexamic acid on platelet during cardiopulmonary bypass. Chin Pharm J 2005;993-5:998.
[33] Yu JG, Shuai XJ, Zhou GL, et al. The effect of ulinastatin on blood fibrinolytic system and platelet function during cardiopulmonary bypass. Chin J Anesthesiol 2003;23:7–10.
[34] Shi J, Li LH. Effects of Ulinastatin and Tranexamic Acid on Hemostasis and Inflammatory Mediators in Cardiac Surgical Procedures (Doctorate Thesis). Beijing, China: Peking Union Medical College; 2010.
[35] Liu MZ, Ji BY, Wang GY, et al. Effects of urinary protease inhibitor on activated leukocytes and platelets during extracorporeal circulation. Chin J ECC 2008;6:75–7.
[36] Ji BY, Long C. The proactive effect of ulinastatin on the organs during extracorporeal circulation. Chin J Clin Thorac Cardiovasc Surg 2002;9:51–3.
[37] Chen HL, Li H. The effect of Ulinastatin combined with hemocoagulase on coagulation function in patients undergoing cardiac surgery with cardiopulmonary bypass. Chin J Mod Drug Appl 2010;4:153–4.
[38] Lu T, He ZF. The effect of large dose Ulinastatin on coagulation function in patients undergoing cardiac surgery with cardiopulmonary bypass. Xibei Yaoxue Zazhi 2004;19:180–1.
[39] Mao GZ, Ji H, Wu LG, et al. Effects of tranexamic acid and Ulinastatin on inflammatory cytokines coagulation function and cognitive function in patients with cardiac surgery. Chin J Rational Drug Use 2017;14:10–3.
[40] Wang ZL. Comparison of the effects among tranexamic acid, Ulinastatin and aprotinin in coronary surgical patients. Heibei Med 2014;36:2214–6.
[41] Wu T, Wen QX. Study on the effects of ulinastatin plus tranexamic acid and aprotinin on cardiopulmonary bypass. Tianjin Med J 2005;33:767–9.

[42] Ren TY, Yang XW, Ma Y, et al. Myocardial protective effect of ulinastatin against ischemia/reperfusion injury during open heart surgery with cardiopulmonary bypass. Zhonghua Yi Xue Za Zhi 2003;83:1391–3.
[43] Wang GY, Qiu HB, Zhan SG, et al. Protection of ulinastatin against myocardial injury induced by off-pump coronary artery bypass graft surgery: report of 24 cases. Zhonghua Yi Xue Za Zhi 2007;87:2502–4.
[44] Gao L, Yang BX, Li F, et al. Advantages of ulinastatin in off-pump coronary artery bypass surgery. Chin J New Drugs 2005;14:470–2.
[45] Chang KQ, Yang DX, Wang GY, et al. Effects of large dose of ulinastatin on coagulation-fibrinolysis system during normothermia extracorporeal circulation in rabbits. Chin J ECC 2008;6:247–50.
[46] Chang KQ, Yang DX, Wang GY, et al. Effects of different doses of ulinastatin on coagulation-fibrinolysis system during normothermia cardiopulmonary bypass in rabbits. Mol Cardio Chin 2009;9:310–3.
[47] Chang KQ, Yang DX, Wang GY, et al. Effects of large dose of ulinastatin on coagulation-fibrinolysis system during normothermia cardiopulmonary bypass in rabbits. Chin Mol Cardio 2009;9:310–3.
[48] Ikeda U, Yamamoto K, Shimada K. Biochemical markers of coagulation activation in mitral stenosis, atrial fibrillation, and cardiomyopathy. Clin Cardiol 1997;20:7–10.
[49] Jimenez JJ, Iribarren JL, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. Crit Care 2007;11:R117.
[50] Bønding Andreasen J, Hvas AM, Ravn HB. Marked changes in platelet count and function following pediatric congenital heart surgery. Paediatr Anaesth 2014;24:386–92.
[51] Esmon CT. Crosstalk between inflammation and thrombosis. Maturitas 2004;47:305–14.
[52] Manfredi AA, Rovere-Querini P, Maugeri N. Dangerous connections: neutrophils and the phagocytic clearance of activated platelets. Curr Opin Hematol 2010;17:3–8.
[53] Despotis GJ, Avidan MS, Hogue CWJr. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg 2001;72:S1821–31.
[54] Nakatani K, Takeshita S, Tsujimoto H, et al. Inhibitory effect of serine protease inhibitors on neutrophil-mediated endothelial cell injury. J Leukoc Biol 2001;69:241–7.
[55] Shu H, Liu K, He Q, et al. Ulinastatin, a protease inhibitor, may inhibit allogeneic blood transfusion-associated pro-inflammatory cytokines and systemic inflammatory response syndrome and improve postoperative recovery. Blood Transfus 2014;12 Suppl 1:s109–18.
[56] Nishiyama T, Hanaoka K. Do the effects of a protease inhibitor, ulinastatin, on elastase release by blood transfusion depend on interleukin 6? Crit Care Med 2001;29:2106–10.
[57] Nishiyama T, Aibiki M, Hanaoka K. The effect of ulinastatin, a human protease inhibitor, on the transfusion-induced increase of plasma polymorphonuclear granulocyte elastase. Anesth Analg 1996;82: 108–12.
[58] Nishiyama T, Hanaoka K. Hemolysis in stored red blood cell concentrates: modulation by haptoglobin or ulinastatin, a protease inhibitor. Crit Care Med 2001;29:1979–82.
[59] Liu DH, Yao YT, Li LH, et al. Effects of ulinastatin on in vitro storage lesions of human red blood cells. Clin Lab 2017;63:833–8.
[60] Chen Q, Hu C, Liu Y, et al. Safety and tolerability of high-dose ulinastatin after 2-hour intravenous infusion in adult healthy Chinese volunteers: a randomized, double-blind, placebo-controlled, ascending-dose study. PLoS One 2017;12:e0177425.
[61] Jönsson-Berling BM, Ohlsson K. Distribution and elimination of intravenously injected urinary trypsin inhibitor. Scand J Clin Lab Invest 1991;51:549–57.
[62] Enzan K, Mitsuhata H, Masaki Y, et al. Effects of ulinastatin on granulocyte elastase and fibronectin in patients undergoing cardiopulmonary bypass. Masui 1991;40:1625–31.