## **Review** Article

# Traditional Chinese Medicine Yimucao Injection Combined with Western Medicine for Preventing Postpartum Hemorrhage after Cesarean Section: A Systematic Review and Meta-Analysis

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*Objective.* Yimucao injection combined with several contraction uterus drugs is in use for preventing postpartum hemorrhage after cesarean section. The present study is a meta-analysis comparing the efficacy and safety of these drugs. *Methods.* PubMed, Cochrane Library, Embase, the China National Knowledge Infrastructure (CNKI), the Chinese Biomedical Database (CBM), VIP, and Wanfang database were searched until June 2018. We selected RCTs of Yimucao injection combined with western medicine for preventing postpartum hemorrhage and study quality was assessed using the revised Cochrane risk of bias tool. Forty-eight RCTs are comprised of 7,330 participants. *Results.* The overall response rate of Yimucao injection combined with western medicine as a class (OR=4.19, 95%CI=2.83, 6.20, P<0.00001) was found to be significantly improved than western medicine alone. Yimucao injection combined with western medicine group could significantly reduce blood loss in intraoperative (SMD= -1.15, 95%CI= -1.43, -0.87, P<0.00001), compared with control group. The treatment group could significantly reduce postpartum blood loss within 2 hours (SMD= -1.73, 95%CI= -2.01, -1.46, P<0.00001) and had a significantly lower blood loss within 24 hours (SMD= -1.92, 95%CI= -2.21, -1.63, P<0.00001) than control group. Additionally, in terms of the safety, Yimucao injection group reduced the risk of adverse events in the course of prevention than the western medicine group. *Conclusions.* This study demonstrated that Yimucao injection combined with western medicine may be more effective for preventing postpartum hemorrhage after cesarean section. However, high-quality and large multicenter randomized clinical trials will be needed to prove the consequence in the further.

## 1. Introduction

Postpartum hemorrhage (PPH) is one of most common diseases of maternal death worldwide and severe morbidity during pregnancy [1]. Uterine atony, injury of birth canal, abnormal placenta, and dysfunction of blood coagulation were the leading cause of PPH in pregnant women with cesarean section, and the average blood loss during cesarean section is significantly higher than that during vaginal delivery [2, 3]. Currently, western medicine such as oxytocin [4], carboprost tromethamine [5], and misoprostol [6] can play an important role in addressing the issue of PPH during and after cesarean section. Oxytocin is an effective method to prevent uterine atony and PPH during cesarean section, and it is generally regarded that oxytocin is the first-line drug proposed by the world health organization (WHO) and other international guidelines [7]. However, the main characteristic of oxytocin is that the effect of contractile uterus was quick and short duration during the treatment of PPH, and it could be discontinues to contract uterine in certain dosage range and results in some side effects, such as tachycardia, hypotension, and arrhythmia [8].

A large number of studies confirmed that Yimucao injection as a traditional Chinese medicine is more effective for clinical prevention of postpartum hemorrhage. The main active components of Yimucao injection were alkaloids, and it has uterine contraction effects [9]. In addition, Yimucao injection combined with western medicine (oxytocin, carboprost tromethamine, and misoprostol) can not only prevent PPH during cesarean section and improve the curative effect, but also decrease the rate of adverse events. Even though several studies assessing the effect of Yimucao injection combined with western medicine increased dramatically in the decade, it is still lack of comprehensive systematic review to guidance. Therefore, our study included 48 RCTs with a total of 7330 pregnant women with cesarean section in order to investigate the effect of western medicine (oxytocin, carboprost tromethamine, and misoprostol) alone or combined with Yimucao injection in women after cesarean section, and we also performed subgroup analyses in order to acquire high-quality evidence, which comprehensive systematic review to assess the efficacy and safety of Yimucao injection as adjuvant treatment for preventing PPH during and after cesarean section.

#### 2. Methods

2.1. Search Strategy. We systematically searched Medical databases, including PubMed, Cochrane Library, Embase, the China National Knowledge Infrastructure (CNKI), the Chinese Biomedical Database (CBM), VIP database, and Wanfang for RCTs examining the effect of Yimucao injection combined with western medicine (oxytocin, carboprost tromethamine, and misoprostol) for preventing postpartum hemorrhage after cesarean section, from their inception until June 2018. The searched the terms of medical keywords: (1) "yimucao", "yimucao injection", "leonurus japonicus injection" connected with "OR"; (2) "cesarean section", "postpartum hemorrhage", "cesarean section", "abdominal delivery" connected with "OR"; (3) "randomized controlled" or "Clinical Trials". Then, the above search terms of (1), (2), and (3) were connected with "AND". We manually searched all research studies that are the references of the original and review articles for possible related studies.

2.2. Study Selection. This systematic review included 48 clinical studies that met the following criteria: (1) studies reported patients with cesarean section, (2) studies compared the effectiveness and safety of Yimucao injection combined with western medicine, (3) studies selected as randomized controlled trials (RCTs), and (4) studies included clinical outcomes which the estimated blood loss.

2.3. Data Abstraction. We collected relevant information including: study characteristics (publication year and sample size), participant characteristic (average age and cesarean section), interventions (type of administration, dose, treatment protocol, and duration of treatment), and outcomes (intraoperative blood loss, blood loss within 2 hours, blood loss within 24 hours, and adverse events). We assessed the clinical efficacy and safety of Yimucao injection combined with western medicine for preventing PPH according to the guideline on the information of extraction.

2.4. Quality Assessment. For eligible studies, data were extracted independently by the two authors and carried out a quality assessment process according to the predefined inclusion criteria. Disagreements were resolved by consensus or discussion with a third author. The methodological quality assessed the risk of bias of RCTs by the Cochrane risk of bias tool. We considered random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The modified instrument removed the "Low risk" option and added "Unclear risk" and "High risk".

2.5. Statistical Analysis. In this meta-analysis, RevMan 5.3 software provided by the Cochrane Collaboration was used to perform the data analysis. The analyses of dichotomous data were presented as the risk ratios (RR) or odds ratios (OR), and the continuous data were presented as mean difference (MD) or standardized mean difference (SMD) with 95% CI. All clinical studies were measured by the chi-square test, with the  $I^2$  test. If the  $I^2$  was less than 50%, we considered that the heterogeneity among studies was small, and we used the fixed effects model for data analysis. If heterogeneity was detected ( $I^2$  value >50%), we suggest severe heterogeneity between the studies by considering possible factors, such as the dose of medicine, treatment course, and disease type. If the heterogeneity was still significant, we chose the random effects model or used only qualitative descriptions.

#### 3. Results

*3.1. Search Results.* Through the seven medical database searches, we found 632 citations from all searches and excluded 353 duplicates. After screening the titles and abstracts, we retrieved 279 full texts for further assessment. Of these, 231 were excluded for the following reasons: duplicate publication as conference abstract, animal experimentation, basic studies of cells, trial without a control arm, the treatment of Yimucao injection combined with other medicine, the vaginal delivery of study, graduation thesis, and narrative reviews; 48 trials involving 7330 women delivered were finally included (Figure 1).

*3.2. Study Characteristics.* In the 48 trials included, a total of 7330 pregnant women participated: the treatment group of Yimucao injection combined with oxytocin and the control group with oxytocin (32 studies); the treatment group of Yimucao injection combined with carboprost tromethamine and the control group with carboprost tromethamine (12 studies); the treatment group of Yimucao injection combined with misoprostol and the control group with misoprostol (4 studies). All the studies were conducted in China and were published in Chinese. Baseline characteristics were summarized in Table 1.

3.3. Quality Assessment. The methodological quality of included studies was estimated according to the bias risk assessment tools provided by the Cochrane Collaboration. All of the included trials mentioned randomized allocation and allocation concealment were unclear. Forty-six studies

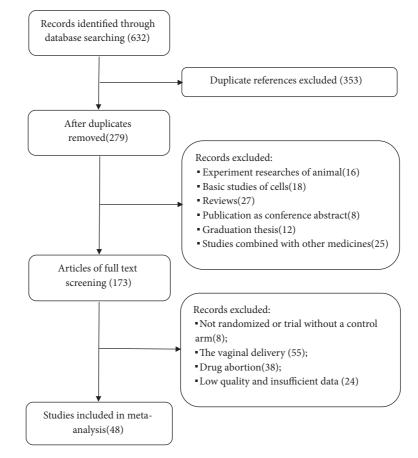


FIGURE 1: Flowchart and strategy of the meta-analysis.

were at an unclear risk of bias for blinding of participants and personnel, 12 trials [10–21] described in detail the method of random number table, and only 2 trials [12, 19] described as double-blind. All trials reported methods with a low risk of incomplete outcome data and thirty-eight studies were at low risk of bias. These results are summarized in Figure 2.

#### 3.4. Major Outcomes

3.4.1. The Total Effective Rate. The total effective rate was reported in seven studies [10, 14, 17, 22–25] in which 630 patients in the treatment group and 627 patients in the control group. The meta-analysis was conducted, as shown in Figure 3, Yimucao injection combined with western medicine showed a better effect on the prevention of PPH compared with the western medicine alone (OR=4.19, 95%CI=2.83, 6.20, P<0.00001).

3.4.2. Intraoperative Blood Loss. In total, thirty-three studies [10–14, 16–18, 22–46] reported the intraoperative blood loss during cesarean section. Decreased intraoperative blood loss in response to Yimucao injection combined with western medicine (oxytocin, carboprost tromethamine, and misoprostol) group than the western medicine group alone was observed by our analysis (SMD= -1.15, 95%CI= -1.43, -0.87,

P<0.00001). The result of this study further revealed that the treatment group performed better than the control group in improving PPH during cesarean section (Figure 4).

3.4.3. Blood Loss within 2 Hours after Delivery. Forty-six RCTs [10–27, 29–39, 41–57] (n=7042) reported the outcome of blood loss within 2 hours after delivery. The incidence of blood loss in the Yimucao injection combined with western medicine group significantly decreases compared to that in the control group (SMD= -1.73, 95%CI= -2.01, -1.46, P<0.00001) (Figure 5).

3.4.4. Blood Loss within 24 Hours after Delivery. In our analysis, there were forty-seven studies [10–25, 27–57] providing the data of blood loss within 24 hours after delivery. Our meta-analysis showed a significant difference in blood loss within 24 hours after delivery which was witnessed between the treatment group and control group (SMD= -1.92, 95%CI= -2.21, -1.63, P<0.00001). The result exhibited a significant efficacy in PPH in Yimucao injection combined with western medicine compared to the western medicine alone (Figure 6).

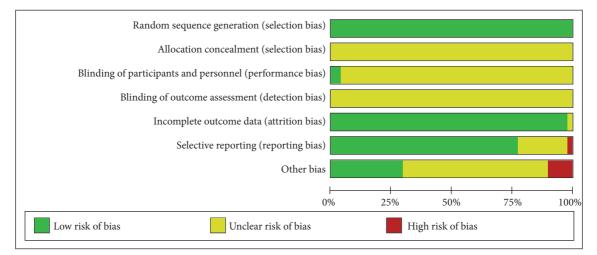
#### 3.5. Subgroup Analysis

3.5.1. Yimucao Injection + Oxytocin versus Oxytocin. Participants with PPH were treated with Yimucao injection and

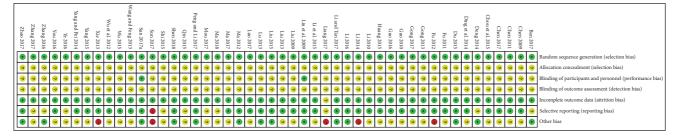
TABLE 1: Characteristics of included articles.

	Sample	Age	Interven	tion	2 11	
Study	(T/C)	(T/C)	Т	С	Follow-up	Evaluation
Peng and Li, 2017 [22]	250/250	28.32/27.45	YM+OT	OT	NR	1234
Ban, 2017 [26]	64/64	28.45/27.56	YM+OT	OT	4d	234
Sun, 2017 [47]	40/40	34.98/35.41	YM+OT	OT	3d	34
Li et al., 2015 [27]	75/75	25.2	YM+OT	OT	NR	234
Du, 2015 [10]	80/80	29.6/29.7	YM+OT	OT	3d	1234
Shi, 2015 [28]	34/34	NR	YM+OT	OT	3d	24
Ma, 2012 [11]	256/256	24.46/24.18	YM+OT	OT	NR	234
Chen, 2011 [29]	100/100	29	YM+OT	OT	3d	234
Fu, 2011 [30]	63/63	NR	YM+OT	OT	NR	234
Lin et al., 2009 [12]	144/149	NR	YM+OT	OT	NR	234
Shen, 2018 [13]	57/57	27.95/27.86	YM+CT	СТ	NR	234
Li and Tan, 2017 [14]	90/87	28.7/29.2	YM+CT	OT	3d	1234
Ye, 2016 [48]	98/98	28.89/29.56	YM+CT	СТ	2d	34
Yang, 2015 [49]	70/70	28.8/29.0	YM+CT	СТ	2d	34
Chou et al., 2015 [50]	52/52	26.6/27.3	YM+CT	OT	NR	34
Ding et al., 2014 [15]	60/60	NR	YM+CT	OT	NR	34
You, 2016 [31]	50/50	28	YM+OT	OT	NR	234
Zhang, 2016 [51]	37/37	26.3/27.9	YM+OT	OT	NR	34
Li, 2016 [16]	45/45	24.9/24.7	YM+OT	OT	NR	234
Liu, 2015 [23]	50/50	28.11/27.81	YM+OT	OT	NR	1234
Qin, 2015 [52]	59/59	28.3/28.5	YM+OT	OT	NR	34
Deng, 2014 [53]	68/68	28.4/29.3	YM+OT	OT	3d	34
Xie, 2013 [32]	100/100	NR	YM+OT	OT	3d	234
Lu, 2013 [45]	129/129	27.5/27.9	YM+OT	OT	NR	234
Liu, 2009 [33]	200/200	NR	YM+OT	OT	NR	234
Chen, 2009 [44]	100/100	NR	YM+OT	OT	NR	234
Ma, 2018 [54]	30/30	29.26/28.95	YM+CT	СТ	2d	34
Wang and Feng, 2013 [34]	40/40	25.2/27.4	YM+MS+OT	MS+OT	NR	234
Liu, 2013 [35]	65/65	25/25.2	YM+MS	OT	NR	234
Li, 2010 [36]	100/100	NR	YM+OT	OT	NR	234
Wu et al., 2012 [37]	30/30	NR	YM+OT	OT	NR	234
Yang and Pei, 2014 [24]	50/50	28.09/28.16	YM+OT	OT	NR	1234
Liang, 2017 [17]	50/50	29.6/29.3	YM+OT	OT	NR	1234
Luo, 2017 [38]	60/60	29.7/29.1	YM+OT	OT	NR	234
Guo, 2010 [39]	50/50	27.0/30.5	YM+OT	OT	NR	234
Guo, 2016 [25]	60/60	30.2/30.5	YM+OT	OT	NR	1234
Huang, 2015 [46]	36/36	27.2	YM+OT	OT	NR	234
Gong, 2013 [40]	110/110	NR	YM+OT	OT	NR	24
Wu, 2015 [41]	103/101	24.56	YM+OT	OT	NR	234
Zhang, 2017 [42]	100/100	22/23	YM+OT	OT	NR	234
Zhao, 2017 [18]	46/46	28.23/28.62	YM+OT	OT	NR	234
Sun, 2017 a[19]	53/53	28.09/28.21	YM+CT	СТ	2d	34
Mou, 2017 [43]	52/52	31.62/31.59	YM+CT	СТ	NR	234
Ma, 2017 [20]	40/40	28.13/28.46	YM+CT	CT	NR	34
Li, 2014 [55]	40/40	NR	YM+CT	CT	NR	34
Gong, 2017 [21]	51/51	29.03/28.47	YM+CT	CT	2d	34
Fu, 2012 [56]	46/46	26.6	YM+MS	OT	NR	34
Chen, 2017 [57]	84/84	24.3/24.7	YM+MS	MS	3d	34

*Note.* T: treatment group; C: control group; d: days; NR: not report; YM: Yimucao injection; OT: oxytocin; CT: carboprost tromethamine; MS: misoprostol; ①: the total effective rate; ②: intraoperative blood loss; ③: blood loss within 2 hours; ④: blood loss within 24 hours.



(a) Summary of RCTs quality showing the percentage of RCTs satisfying each risk of bias graph



(b) Detailed item-by-item analysis of the risk of bias summary

Figure 2

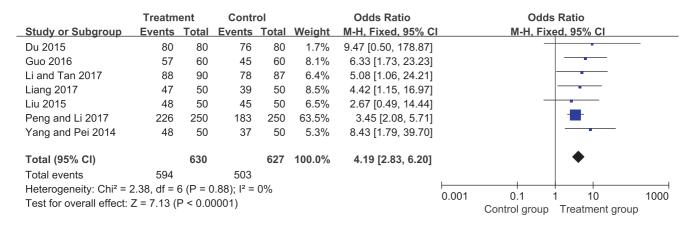


FIGURE 3: Forest plot of the meta-analysis with the total effective rate.

oxytocin in the treatment group and with oxytocin in the control group. Results of subgroup analysis showed that Yimucao injection combined with oxytocin may be effectively reduces the intraoperative blood loss (SMD= -1.06, 95%CI= -1.34, -0.77, P<0.00001), blood loss within 2 hours (SMD= - 1.33, 95%CI= -1.60, -1.06, P<0.00001), and blood loss within 24 hours after delivery (SMD= -1.46, 95%CI= -1.74, -1.19, P<0.00001) for preventing PPH compared with the oxytocin alone.

3.5.2. Yimucao Injection + Carboprost Tromethamine versus Carboprost Tromethamine. Patients with PPH were treated with Yimucao injection and carboprost tromethamine in the treatment group and with carboprost tromethamine in the control group. Results of subgroup analysis demonstrated that the treatment group could significantly reduce the intraoperative blood loss (SMD= -1.28, 95%CI= -2.78, 0.22, P=0.09), blood loss within 2 hours (SMD= -2.50, 95%CI= -3.23, -1.76, P<0.00001), and blood loss within 24 hours

	Tre	eatment		c	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.2.1 Yimucao injectio	on combi	ned with	n oxyto	ocin.					
Ban 2017	185.63	4.03	64	190.26	5.24	64	3.1%	-0.98 [-1.35, -0.62]	
Chen 2009	240.5	55.3	100	248.3	52.6	100	3.1%	-0.14 [-0.42, 0.13]	-
Chen 2011	268.5	51.2	100	293.6	52.2	100	3.1%	-0.48 [-0.76, -0.20]	
Du 2015	123.8	55.2	80	185.4	54.3	80	3.1%	-1.12 [-1.45, -0.79]	
Fu 2011	185	30.9	63	219	50.4	63	3.1%	-0.81 [-1.17, -0.44]	
Gong 2013	170	45.35	110	290	33.65	110	3.0%	-2.99 [-3.38, -2.61]	
Guo 2010	215.6	95.3	50	258.5	85.1	50	3.0%	-0.47 [-0.87, -0.07]	
Guo 2016	157.5	10.31	60	180.6	11.4	60	3.0%	-2.11 [-2.56, -1.66]	
Huang 2015	142.1	48.1	36	253.9	55.7	36	2.8%	-2.13 [-2.71, -1.54]	
Li 2010	313	210	100	350	258	100	3.1%	-0.16 [-0.43, 0.12]	
Li 2016	182.5	21.5	45	189.4	29.5	45	3.0%	-0.27 [-0.68, 0.15]	
Li et al. 2015	236.7	42.6	75	297.5	57.8	75	3.1%	-1.19 [-1.54, -0.84]	
Liang 2017	232.5	26.8	50	289.6	27.6	50	2.9%	-2.08 [-2.57, -1.59]	
Lin et al.2009	255	114	144	269	141	149	3.2%	-0.11 [-0.34, 0.12]	-
Liu 2009	202	52.8	200	278	53.6	200	3.2%	-1.43 [-1.65, -1.21]	
Liu 2015	117.32	75.23	50	162.35	53.23	50	3.0%	-0.69 [-1.09, -0.28]	
Lu 2013	269.5	52.7	129	292.4	51.2	129	3.1%	-0.44 [-0.69, -0.19]	
Luo 2017	139.7	46.6	60	231.5	52.8	60	3.0%	-1.83 [-2.26, -1.40]	
Ma 2012	210.43	50.38	256	234.14	16.91	256	3.2%	-0.63 [-0.81, -0.45]	-
Peng and Li 2017	232.26	43.58	250	298.15	54.23	250	3.2%	-1.34 [-1.53, -1.14]	-
Shi 2015	246.5	54.5	34	323.4	48.2	34	2.9%	-1.48 [-2.02, -0.94]	
Wu 2015	186.6	25.88	103	274.65	35.7	101	3.0%	-2.82 [-3.21, -2.43]	
Wu et al. 2012	300.3	67.1	30	373.1	57.6	30	2.9%	-1.15 [-1.70, -0.60]	
Xie 2013	281.51	34.74	100	283.35	154.89	100	3.1%	-0.02 [-0.29, 0.26]	+
Yang and Pei 2014	232.4	27.1	50	289.9	51.3	50	3.0%	-1.39 [-1.83, -0.95]	
You 2016	126.6	39.5	50	186.5	42.6	50	3.0%	-1.45 [-1.89, -1.00]	_ <del></del>
Zhang 2017	23.2	9.9	100	22.3	10.2	100	3.1%	0.09 [-0.19, 0.37]	
Zhao 2017	159.09	53.67	46	182.36	55.45	46	3.0%	-0.42 [-0.84, -0.01]	
Subtotal (95% CI)			2535			2538	85.2%	-1.06 [-1.34, -0.77]	◆
Heterogeneity: Tau <sup>2</sup> = 0	0.55; Chi²	= 592.3	4, df =	27 (P < 0	).00001);	l² = 95	%		
Test for overall effect: 2	Z = 7.32 (I	> < 0.00	001)						
2.2.2 Yimucao injectio	on combi	ned with	1 Carb	oprost tr	ometha	mine.			
Li and Tan 2017	134.7	44.6	90	179.2	53.2	87	3.1%	-0.90 [-1.21, -0.59]	
Mou 2017	196.31	22.58	52	279.72	30.36	52	2.8%	-3.09 [-3.67, -2.52]	
Shen 2018	316.35	61.74	57	309.89	63.05	57	3.1%	0.10 [-0.26, 0.47]	
Subtotal (95% CI)			199			196	9.0%	-1.28 [-2.78, 0.22]	
Heterogeneity: Tau <sup>2</sup> =	1.70; Chi²	= 84.31	, df = 2	(P < 0.0	0001); l²	= 98%			
Test for overall effect: 2	Z = 1.68 (ł	<b>-</b> = 0.09	)						
2.2.3 Yimucao injectio				-					
Liu 2013		12.33		150.21	13.82	65	2.9%	-3.41 [-3.95, -2.87]	
Wang and Feng 2013	235.6	27.1	40	268.5	31.6	40	2.9%	-1.11 [-1.58, -0.63]	
Subtotal (95% CI)			105			105	5.8%	-2.25 [-4.51, 0.00]	
Heterogeneity: Tau <sup>2</sup> = 2	2.58; Chi²	= 39.28	, df = 1	(P < 0.0	0001); l²	= 97%			
Test for overall effect: 2	Z = 1.96 (I	⊃ = 0.05	)						
Total (95% CI)			2839				100.0%	-1.15 [-1.43, -0.87]	
Heterogeneity: Tau <sup>2</sup> =				32 (P < 0	).00001);	$I^2 = 96$	%		-4 -2 0 2 4
Test for overall effect: 2	•								Treatment group Control group
Test for subgroup diffe	rences: Cl	hi² = 1.1:	3, df =	2 (P = 0.	57), l² = (	0%			5 i

FIGURE 4: Forest plot of the meta-analysis of effects of Yimucao injection combined with western medicine versus western medicine alone for the prevention of PPH on the intraoperative blood loss.

(SMD= -2.64, 95%CI= -3.31, -1.97, P<0.00001) compared to the control group. Although carboprost tromethamine appeared to decrease intraoperative blood loss, the difference was not statistically significant.

3.5.3. Yimucao Injection + Misoprostol versus Misoprostol. Parturient women with PPH were treated with Yimucao injection and misoprostol in the treatment group and with misoprostol in the control group. The results of subgroup analysis indicated that Yimucao injection combined with misoprostol therapy was significantly decrease compared to misoprostol alone in the intraoperative blood loss (SMD= - 2.25, 95%CI= -4.51, 0.00, P=0.05), blood loss within 2 hours (SMD= -2.52, 95%CI= -3.42, -1.62, P<0.00001), and blood loss within 24 hours (SMD= -3.37, 95%CI= -5.14, -1.60, P=0.0002).

3.6. Heterogeneity and Publication Bias. During the metaanalysis, we found high heterogeneity among studies. Consequently, we performed a sensitivity analysis by Egger's test

## Evidence-Based Complementary and Alternative Medicine

Study or Subaraun		eatment	Total		ontrol	Total		td. Mean Difference	Std. Mean Difference
<u>Study or Subgroup</u> 3.1 Yimucao injectio	Mean			Mean	50	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
an 2017	205.36	62.33		280.56	71.24	64	2.2%	-1.12 [-1.49, -0.74]	
Chen 2009	200.00 46	51.9	100	59	70.5	100	2.3%	-0.21 [-0.49, 0.07]	
Chen 2011	50.1	15.4	100	62.8	16.3	100	2.3%	-0.80 [-1.09, -0.51]	-
Deng 2014	114	42	68	226	78	68	2.2%	-1.78 [-2.18, -1.38]	
Du 2015	239.2	34.6	80	283.4	45.9	80	2.2%	-1.08 [-1.41, -0.75]	
Fu 2011	72	20.4	63	95	25.9	63	2.2%	-0.98 [-1.35, -0.61]	
Guo 2010	101.3	15.6	50	129.2	18.5	50	2.2%	-1.62 [-2.07, -1.16]	
Guo 2016	59.3	8.7	60	80.4	7.3	60	2.2%	-2.61 [-3.10, -2.12]	
Huang 2015	219.3	48.9	36	336.8	59.9	36	2.1%	-2.13 [-2.71, -1.54]	
_i 2010	48	49	100	52	47	100	2.3%	-0.08 [-0.36, 0.19]	1
_i 2016	202.3	61.2	45	280.2	69.5	45	2.2%	-1.18 [-1.63, -0.73]	
_i et al. 2015	46.3	11.4	75	75.2	16.2	75	2.2%	-2.05 [-2.45, -1.66]	
₋iang 2017 ∟in et al.2009	35.7 46	7.3 78	50 144	57.6 50	6.2 51	50 149	2.1% 2.3%	-3.21 [-3.81, -2.61]	+
_in et al.2009 _iu 2009	40 35	54.9	200	60	71.5	200	2.3%	-0.06 [-0.29, 0.17] -0.39 [-0.59, -0.19]	
_iu 2005	188.57	60.03		250.23	80.84	50	2.2%	-0.86 [-1.27, -0.45]	
_u 2013	51.6	15.8	129	66.3	14.5	129	2.3%	-0.97 [-1.22, -0.71]	-
_uo 2017	196.3	49.2	60	318	57.5	60	2.2%	-2.26 [-2.72, -1.80]	
Ma 2012	35.84	29.24	256	52.37	32.15	256	2.3%	-0.54 [-0.71, -0.36]	-
Peng and Li 2017	45.12	23.25	250	78.23	26.43	250	2.3%	-1.33 [-1.52, -1.13]	
Qin 2015	44.9	10.4	59	53.3	13.3	59	2.2%	-0.70 [-1.07, -0.33]	
Sun 2017	225.7	42.5	40	261.8	48.9	40	2.2%	-0.78 [-1.24, -0.32]	
Wu 2015	47.86	10.2	103	78.43	15.82	101	2.2%	-2.29 [-2.65, -1.94]	
Wu et al. 2012	46.9	9.9	30	64.1	10.8	30	2.1%	-1.64 [-2.23, -1.05]	
Xie 2013	49.91	47.1	100	60.54	7.5	100	2.3%	-0.31 [-0.59, -0.04]	
Yang and Pei 2014	35.5	7.4	50	57.8	6.7	50	2.1%	-3.13 [-3.73, -2.54]	
You 2016	210.3	41.2	50	274	51.8	50	2.2%	-1.35 [-1.79, -0.91]	
Zhang 2016 Zhang 2017	115.6 35.2	43 14.4	37 100	226.8 70.2	78 28.6	37 100	2.1% 2.2%	-1.75 [-2.29, -1.21] -1.54 [-1.86, -1.22]	<u> </u>
Zhao 2017	219.27	48.93		336.76	59.94	46	2.2%	-2.13 [-2.65, -1.61]	
Subtotal (95% CI)	210.27	40.00	2595	000.70	00.04	2598	66.1%	-1.33 [-1.60, -1.06]	•
est for overall effect: 2	(.		,						
	on combin	ned with	Carbo	prost tro	metham	ine.			
Chou et al. 2015	on combin 272.5	ned with 56.2	Carbo 52	p <b>rost tro</b> 301.6	<b>metham</b> 70.6	ine. 52	2.2%	-0.45 [-0.84, -0.06]	
Chou et al. 2015		56.2	52		70.6		2.2% 2.2%	-0.45 [-0.84, -0.06] -0.58 [-0.94, -0.21]	
Chou et al. 2015 Ding et al. 2014	272.5	56.2	52 60	301.6	70.6	52			<del></del>
Chou et al. 2015 Ding et al. 2014 Gong 2017	272.5 422.41	56.2 213.49	52 60	301.6 589.64 378.32 425	70.6 345.21	52 60	2.2% 2.0% 2.1%	-0.58 [-0.94, -0.21]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017	272.5 422.41 209.38 356 242.6	56.2 213.49 34.15 30.5 45.7	52 60 51 40 90	301.6 589.64 378.32 425 287.5	70.6 345.21 51.24 28 48.3	52 60 51 40 87	2.2% 2.0% 2.1% 2.2%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017	272.5 422.41 209.38 356 242.6 290.56	56.2 213.49 34.15 30.5 45.7 9.31	52 60 51 40 90 40	301.6 589.64 378.32 425 287.5 334.85	70.6 345.21 51.24 28 48.3 9.47	52 60 51 40 87 40	2.2% 2.0% 2.1% 2.2% 1.9%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81]	 
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018	272.5 422.41 209.38 356 242.6 290.56 241.26	56.2 213.49 34.15 30.5 45.7 9.31 36.51	52 60 51 40 90 40 30	301.6 589.64 378.32 425 287.5 334.85 362.32	70.6 345.21 51.24 28 48.3 9.47 48.25	52 60 51 40 87 40 30	2.2% 2.0% 2.1% 2.2% 1.9% 2.0%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07]	 
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15	52 60 51 40 90 40 30 52	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18	52 60 51 40 87 40 30 52	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.1%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 18.15	52 60 51 40 90 40 30 52 57	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84	52 60 51 40 87 40 30 52 57	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.1% 2.2%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 18.15 32.51	52 60 51 40 90 40 30 52 57 53	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58	52 60 51 40 87 40 30 52 57 53	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.1% 2.2% 2.0%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2017 Shen 2018 Sun 2017a Yang 2015	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68 234.5	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 18.15 32.51 50.2	52 60 51 40 90 40 30 52 57 53 70	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69 356.2	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5	52 60 51 40 87 40 30 52 57 53 70	2.2% 2.0% 2.1% 2.2% 2.0% 2.0% 2.1% 2.2% 2.0% 2.2%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 18.15 32.51	52 60 51 40 90 40 30 52 57 53 70	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58	52 60 51 40 87 40 30 52 57 53	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.1% 2.2% 2.0%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45]	
-	272.5 422.41 209.38 356 242.6 242.6 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup>	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 18.15 32.51 50.2 36.52 = 306.61	52 60 51 40 90 40 30 52 57 53 70 96 <b>691</b> , df = 1	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69 356.2 362.34	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b>	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.1% 2.2% 2.2% 2.2% 2.2% <b>25.4%</b>	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Yang 2015 Yag 2015 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 7 Fest for overall effect: 2 2.3.3 Yimucao injectio	272.5 422.41 209.38 356 242.6 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> z = 6.67 (F	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 32.51 50.2 36.52 = 306.61 2 < 0.000 med with	52 60 51 40 90 40 30 52 57 53 70 96 <b>691</b> , df = 1 01) <b>misop</b>	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69 356.2 362.34 1 (P < 0.	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b>	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.1% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 7 Fest for overall effect: 2 <b>2.3.3 Yimucao injectic</b> Chen 2017	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> c = 6.67 (F on combin 216.56	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 32.51 50.2 36.52 = 306.61 2 < 0.000 med with 32.39	52 60 51 40 90 40 30 52 57 53 7 53 7 96 <b>691</b> , df = 1 01) <b>misop</b> 84	301.6 589.64 378.32 425 287.5 334.85 362.32 193.71 368.69 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 000001); I	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b> 2 = 96%	2.2% 2.0% 2.1% 2.2% 2.0% 2.1% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 7 Test for overall effect: 2 <b>2.3.3 Yimucao injectio</b> Chen 2017 Fu 2012	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> 2 = 6.67 (F on combin 216.56 158.2	56.2 213.49 34.15 30.5 45.7 9.31 36.51 18.15 32.51 50.2 36.52 = 306.61 > < 0.000 med with 32.39 16.4	52 60 51 40 90 40 30 52 57 53 70 <b>691</b> , df = 1 01) <b>misop</b> 84 46	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 000001); I	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b> 2 = 96% 84 46	2.2% 2.0% 2.1% 2.2% 2.0% 2.1% 2.0% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 7 Test for overall effect: 2 <b>2.3.3 Yimucao injectio</b> Chen 2017 Fu 2012 Liu 2013	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> 2 = 6.67 (P on combin 216.56 158.2 198.28	56.2 213.49 34.15 30.5 45.7 9.31 38.15 18.15 32.51 50.2 36.52 = 306.61 > < 0.000 med with 32.39 16.4 20.34	52 60 51 40 90 40 30 52 57 53 70 96 <b>691</b> , df = 1 01) <b>misop</b> 84 46 65	301.6 589.64 378.32 425 287.5 362.32 386.29 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4 240.65	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 000001); I	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b> 2 = 96% 84 46 65	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.2% 2.0% 2.2% 2.2% 2.2% 2.2% 2.1% 2.1% 2.1% 2.2%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67] -1.75 [-2.16, -1.35]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = $\frac{1}{2}$ Test for overall effect: 2 2.3.3 Yimucao injectio Chen 2017 Fu 2012 Liu 2013 Wang and Feng 2013	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> 2 = 6.67 (F on combin 216.56 158.2	56.2 213.49 34.15 30.5 45.7 9.31 36.51 18.15 32.51 50.2 36.52 = 306.61 > < 0.000 med with 32.39 16.4	52 60 51 40 90 40 30 57 57 53 70 96 <b>691</b> , df = 1 01) misop 84 46 65 40	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 000001); I	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b> $e^2 = 96\%$ 84 46 65 40	2.2% 2.0% 2.1% 2.2% 2.0% 2.1% 2.0% 2.2% 2.2% 2.2% 2.2% 2.2% 2.1%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67] -1.75 [-2.16, -1.35] -2.36 [-2.93, -1.78]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2017 Ma 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 7 <b>Cast for overall effect: 2</b> <b>2.3.3 Yimucao injectic</b> Chen 2017 Fu 2012 Liu 2013 Wang and Feng 2013 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0	272.5 422.41 209.38 356 242.6 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> : <b>c</b> = 6.67 (F <b>c n combin</b> 216.56 158.2 198.28 42.4	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 32.51 50.2 36.52 = 306.61 > < 0.000 ned with 32.39 16.4 20.34 11.7 = 39.22,	52 60 51 40 90 40 30 52 57 53 70 96 <b>691</b> 01) misop 84 46 65 40 <b>235</b> 40 <b>235</b>	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4 240.65 68.5	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 00001); I 24.57 18.2 27.24 10.2	52 60 51 40 87 40 30 52 57 53 70 96 <b>688</b> 2 = 96% 84 46 65 40 <b>235</b>	2.2% 2.0% 2.1% 2.2% 1.9% 2.0% 2.2% 2.0% 2.2% 2.2% 2.2% 2.2% 2.1% 2.1% 2.1% 2.2%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67] -1.75 [-2.16, -1.35]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = $-7$ Test for overall effect: 2 <b>2.3.3 Yimucao injectic</b> Chen 2017 Fu 2012 Liu 2013 Wang and Feng 2013 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0 Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2	272.5 422.41 209.38 356 242.6 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> : <b>c</b> = 6.67 (F <b>c n combin</b> 216.56 158.2 198.28 42.4	56.2 213.49 34.15 30.5 45.7 9.31 36.51 38.15 32.51 50.2 36.52 = 306.61 > < 0.000 ned with 32.39 16.4 20.34 11.7 = 39.22,	52 60 51 40 90 40 30 52 57 53 70 96 691 101) misop 84 46 65 540 0235 67 = 3 ( 01)	301.6 589.64 378.32 425 287.5 334.85 362.32 386.29 193.71 368.69 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4 240.65 68.5	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 00001); I 24.57 18.2 27.24 10.2	52 60 51 40 87 40 52 57 53 70 96 <b>688</b> 2 = 96% 84 46 65 40 <b>235</b> 92%	2.2% 2.0% 2.1% 2.2% 2.0% 2.2% 2.2% 2.2% 2.2% 2.2% 2.2	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67] -1.75 [-2.16, -1.35] -2.36 [-2.93, -1.78] -2.52 [-3.42, -1.62]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = $-7$ Test for overall effect: 2 2.3.3 Yimucao injectic Chen 2017 Fu 2012 Liu 2013 Wang and Feng 2013 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Chest for overa	272.5 422.41 209.38 356 242.6 290.56 241.26 212.45 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> : 2 = 6.67 (F <b>on combin</b> 216.56 158.2 198.28 42.4 0.78; Chi <sup>2</sup> : 2 = 5.48 (F	56.2 213.49 34.15 30.5 45.7 9.31 36.51 18.15 32.51 50.2 36.52 = 306.61 0 < 0.000 ned with 32.39 16.4 20.34 11.7 = 39.22, 0 < 0.000	52 60 51 40 90 40 30 52 57 53 70 96 <b>691</b> , df = 1 01) misop 84 46 65 235 57 53 70 96 691 , df = 1 01) 352 46 52 57 53 70 96 691 90 96 96 91 90 90 90 90 90 90 90 90 90 90 90 90 90	301.6 589.64 378.32 425 287.5 334.85 362.32 193.71 368.69 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4 240.65 68.5 P < 0.00	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 000001); I 24.57 18.2 27.24 10.2 001); I <sup>2</sup> =	52 60 51 40 87 40 52 57 53 70 96 <b>688</b> 2 = 96% 84 46 65 40 <b>235</b> 92% <b>3521</b>	2.2% 2.0% 2.1% 2.2% 2.0% 2.2% 2.0% 2.2% 2.2% 2.2% 2.4% 2.1% 2.2% 2.1% 8.6%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67] -1.75 [-2.16, -1.35] -2.36 [-2.93, -1.78]	
Chou et al. 2015 Ding et al. 2014 Gong 2017 Li 2014 Li and Tan 2017 Ma 2017 Ma 2018 Mou 2017 Shen 2018 Sun 2017a Yang 2015 Ye 2016 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = $-7$ Test for overall effect: 2 <b>2.3.3 Yimucao injectic</b> Chen 2017 Fu 2012 Liu 2013 Wang and Feng 2013 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0 Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2	272.5 422.41 209.38 356 242.6 290.56 241.26 152.68 208.68 234.5 241.27 1.60; Chi <sup>2</sup> 2 = 6.67 (F on combin 216.56 158.2 198.28 42.4 0.78; Chi <sup>2</sup> 2 = 5.48 (F	56.2 213.49 34.15 30.5 45.7 9.31 36.51 18.15 32.51 50.2 36.52 = 306.61 2 < 0.000 ned with 32.39 16.4 20.34 11.7 = 39.22, $2 < 0.000$ = 1168.0	52 60 51 40 90 40 30 52 57 53 70 96 <b>691</b> , df = 1 01) <b>misop</b> 84 46 65 40 02 <b>235</b> 4f = 3 (01) <b>3521</b> 6, df =	301.6 589.64 378.32 425 287.5 334.85 362.32 193.71 368.69 356.2 362.34 1 (P < 0. <b>rostol.</b> 326.24 196.4 240.65 68.5 P < 0.00	70.6 345.21 51.24 28 48.3 9.47 48.25 64.18 20.84 43.58 51.5 48.26 000001); I 24.57 18.2 27.24 10.2 001); I <sup>2</sup> =	52 60 51 40 87 40 52 57 53 70 96 <b>688</b> 2 = 96% 84 46 65 40 <b>235</b> 92% <b>3521</b>	2.2% 2.0% 2.1% 2.2% 2.0% 2.2% 2.0% 2.2% 2.2% 2.2% 2.4% 2.1% 2.2% 2.1% 8.6%	-0.58 [-0.94, -0.21] -3.85 [-4.51, -3.19] -2.33 [-2.91, -1.76] -0.95 [-1.26, -0.64] -4.67 [-5.53, -3.81] -2.79 [-3.52, -2.07] -3.27 [-3.86, -2.67] -2.09 [-2.54, -1.63] -4.13 [-4.81, -3.45] -2.38 [-2.82, -1.94] -2.82 [-3.22, -2.42] -2.50 [-3.23, -1.76] -3.80 [-4.31, -3.29] -2.19 [-2.71, -1.67] -1.75 [-2.16, -1.35] -2.36 [-2.93, -1.78] -2.52 [-3.42, -1.62]	

FIGURE 5: Forest plot of the meta-analysis of effects of Yimucao injection combined with western medicine versus western medicine alone for the prevention of PPH on the blood loss within 2 hours after delivery.

	Tre	eatment		с	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean		Total		SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.4.1 Yimucao injectio	on combi	ned with	n oxyto	ocin.					
Chen 2009	411	60.5	100	448	63.2	100	2.2%	-0.60 [-0.88, -0.31]	-
Chen 2011	382.2	50.1	100	432.7	56.3	100	2.2%	-0.94 [-1.24, -0.65]	
Deng 2014	363	87	68	478	88	68	2.2%	-1.31 [-1.68, -0.94]	÷
Du 2015 Fu 2011	301.4 25	39.8 12.4	80 63	360.2 46	45.9 14.5	80 63	2.2% 2.2%	-1.36 [-1.71, -1.02] -1.55 [-1.95, -1.15]	
Gong 2013	285	45.2	110	400	48.5	110	2.2%	-2.44 [-2.80, -2.09]	-
Guo 2010	225.1	12.5	50	281.5	15.1	50	2.0%	-4.04 [-4.73, -3.35]	
Guo 2016	35.2	4.3	60	50.3	5.4	60	2.1%	-3.07 [-3.61, -2.54]	
Huang 2015	261.6	49.2	36	391.7	63.9	36	2.1%	-2.26 [-2.85, -1.66]	
Li 2010	27	25	100	28	23	100	2.2%	-0.04 [-0.32, 0.24]	+
Li 2016	265.8	60.3	45	342.5	71.6	45	2.2%	-1.15 [-1.60, -0.70]	
Li et al. 2015	63.3	24.5	75	78.3	26.4	75	2.2%	-0.59 [-0.91, -0.26]	
Liang 2017	46.3	6.5 24	50 144	73.4 29	13.3 28	50 149	2.1% 2.2%	-2.57 [-3.10, -2.03]	4
Lin et al.2009 Liu 2009	26 365	24 56.5	200	449	62.2	200	2.2%	-0.11 [-0.34, 0.11] -1.41 [-1.63, -1.19]	
Liu 2015	266.75			331.32	86.23	50	2.2%	-0.79 [-1.20, -0.38]	
Lu 2013	384.7	38.9	129	423	45.6	129	2.2%	-0.90 [-1.16, -0.64]	-
Luo 2017	254.8	51.6	60	393.5	61.1	60	2.1%	-2.44 [-2.91, -1.96]	
Ma 2012	61.62	35.32	256	86.18	36.67	256	2.3%	-0.68 [-0.86, -0.50]	÷
Peng and Li 2017		24.56	250	79.42		250	2.2%	-0.80 [-0.98, -0.62]	<b>-</b>
Qin 2015	104.3	31.5	59	122.6	42.4	59	2.2%	-0.49 [-0.85, -0.12]	
Shi 2015	366.8	38.5	34	423.6	42.6	34	2.1%	-1.38 [-1.92, -0.85]	
Sun 2017	294.8	40.2	40	341.8	38.6	40	2.1%	-1.18 [-1.66, -0.70]	
Wu 2015	24.33	7.5	103	37.5	8.63	101	2.2%	-1.62 [-1.94, -1.31]	
Wu et al. 2012 Xie 2013	406 22 34	19 20.78	30 100	498.9 30.01	24.6 6.78	30 100	1.8% 2.2%	-4.17 [-5.10, -3.25] -0.49 [-0.78, -0.21]	-
Yang and Pei 2014	31.5	6.3	50	73.8	11.2	50	2.0%	-4.62 [-5.38, -3.86]	<u> </u>
You 2016	255.6	42.8	50	307.9	45.5	50	2.2%	-1.17 [-1.60, -0.75]	
Zhang 2016	325.6	82	37	479.8	86	37	2.1%	-1.82 [-2.36, -1.27]	
Zhang 2017	273.3	116.2	100	379.6	182.5	100	2.2%	-0.69 [-0.98, -0.41]	
Zhao 2017	407.92	60.48		448.09	63.01	46	2.2%	-0.65 [-1.06, -0.23]	
Subtotal (95% CI)			2675			2678	66.9%	-1.46 [-1.74, -1.19]	•
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z				30 (P < 0	.00001	);  ² = 9	5%		
2.4.2 Yimucao injectio	on combi	ned with	n Carb	oprost tr	ometha	amine			
Chou et al. 2015	319.5	67.3	52	353.2	73.1	52	2.2%	-0.48 [-0.87, -0.09]	
Ding et al. 2014		16.44	60	69.31		60	2.2%	-1.42 [-1.82, -1.02]	
Gong 2017	287.52			464.13		51	2.0%	-3.49 [-4.11, -2.86]	
Li 2014	420	26.1	40	550	27.5	40	1.9%	-4.80 [-5.68, -3.92]	
Li and Tan 2017	323.5	43.2	90	377.9	50.5	87	2.2%	-1.15 [-1.47, -0.84]	-
Ma 2017	400.03	10.48	40		11.12	40	1.8%	-5.66 [-6.66, -4.66]	
Ma 2018	312.28			456.83		30	2.0%	-2.41 [-3.08, -1.73]	
Mou 2017	115.28			191.68		52	2.1%	-3.03 [-3.60, -2.46]	
Shen 2018	267.24			310.07		57 52	2.1%	-2.06 [-2.52, -1.61]	
Sun 2017a Yang 2015	282.73 309.7		53 70	484.35 443.3	69.36 68.6	53 70	2.1% 2.2%	-3.51 [-4.12, -2.89] -2.00 [-2.40, -1.59]	- I
Ye 2016	312.28			445.3		96	2.2%	-2.43 [-2.80, -2.05]	-
Subtotal (95% CI)	012.20	01.27	691	100.00	51.00	688	24.9%		◆
Heterogeneity: Tau <sup>2</sup> = 1				11 (P < 0	.00001	); I² = 9			
Test for overall effect: Z	<u>2</u> = 7.75 (F	ا0.00 > ~	UU1)						
2.4.3 Yimucao injectio					00.04	<u>.</u>	0.40/		
Chen 2017 Fu 2012	296.32			424.28		84 46	2.1%	-4.92 [-5.53, -4.31]	
Fu 2012 Liu 2013	191.4 289.12		46 65	297.4 348.36	21.4	46 65	1.9% 2.2%	-5.22 [-6.09, -4.35] -1.76 [-2.16, -1.35]	
Wang and Feng 2013	113.4		65 40	348.36 172.8	35.62	65 40	2.2%	-1.67 [-2.18, -1.35] -1.67 [-2.18, -1.16]	
Subtotal (95% CI)	110.4	51.1	235	.12.0	52.0	235	8.2%		
Heterogeneity: Tau <sup>2</sup> = 3	3.17; Chi <sup>2</sup>	= 118.6		3 (P < 0.	00001):			,	
Test for overall effect: 2					,				
Total (95% CI)			3601			3601	100.0%	-1.92 [-2.21, -1.63]	•
Heterogeneity: Tau <sup>2</sup> = 0	),94: Chi²	= 1280		= 46 (P <	0.0000				
Test for overall effect: Z						.,, .	/ -		-4 -2 0 2 4
Test for subgroup differ				= 2 (P = 0	.001), I	² = 85.5	5%		Treatment group Control group

FIGURE 6: Forest plot of the meta-analysis of effects of Yimucao injection combined with western medicine versus western medicine alone for the prevention of PPH on the blood loss within 24 hours after delivery.

	treatment group (n=1669)	control group (n=1664)
blood pressure elevation	24 (1.44%)	38 (2.23%)
facial flushing	22 (1.32%)	30 (1.80%)
nausea and vomiting	29 (1.74%)	82 (4.93%)
abdominal discomfort	5 (0.30%)	7 (0.42%)
chest discomfort	15 (0.90%)	34 (2.04%)
arrhythmia	11 (0.66%)	20 (1.20%)
allergic reaction	1 (0.06%)	0 (0.00%)

TABLE 2: The incidence of adverse reactions between the treatment group and control group.

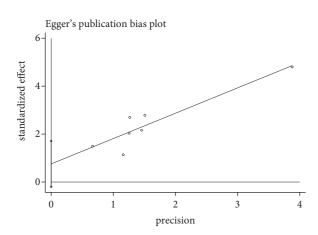


FIGURE 7: Egger's funnel plot of total effective rate.

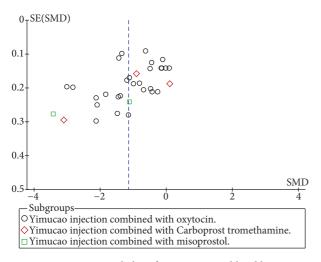


FIGURE 8: Funnel plot of intraoperative blood loss.

of the total effective rate (Figure 7). A significant symmetry was noted for distribution in funnel plots of the intraoperative blood loss (Figure 8). These results did not demonstrate any evidence of publication bias (P>0.098).

*3.7. Adverse Events.* In the 48 included studies, twenty-six trials [10, 13–16, 19, 22, 23, 25–30, 32–34, 36, 41, 43–45, 49–51, 53] reported on adverse events. No adverse effects of Yimucao injection combined with western medicine group were identified in 4 trials. Only one trial reported allergic

reaction in the Yimucao treatment group. However, all of these twenty-two trials reported blood pressure elevation, facial flushing, nausea, and vomiting in both the control group and treatment groups, in which 3 trials reported arrhythmia, 3 studies reported abdominal discomfort, and 2 trials reported chest discomfort. The side-effect incidence rates of the treatment group and the control group of blood pressure elevation were 1.44% and 2.23%, facial flushing 1.32% and 1.80%, nausea and vomiting 1.74% and 4.93%, abdominal discomfort 0.30% and 0.42%, chest discomfort 0.90% and 2.04%, arrhythmia 0.66% and 1.20%, and allergic reaction 0.06% and 0.00%, respectively. But all of these adverse events were not severe. No serious adverse events were reported. Symptoms of patients disappeared or significantly improved in the short term without provided treatment. In our analysis of adverse events it was suggested that the treatment group has less adverse effects than the control group (Table 2).

#### 4. Discussion

4.1. Main Outcome. Postpartum hemorrhage (PPH) continues to be the most important cause of maternal mortality and morbidity worldwide. Therefore, in women during delivery, we should give priority to the care of the prevention and treatment of PPH. Yimucao is a Chinese herbal medicine of the genus Leonurus Lamiaceae and the main active ingredient of alkaloid. It has antithrombosis, anticoagulation, improving microcirculation, antioxygen free radical, and excited uterine smooth muscle strips and maintains the stability of intracellular calcium. Yimucao injection has been widely used in the treatment of obstetric and gynecologic disease such as abnormal menstruation, promoting gestation, postpartum hemorrhage, uterine involution, and so on. In 48 RCTs in our study, a total of 7,330 women were included in order to acquire high-quality evidence for the clinical efficacy and safety of Yimucao injection therapy in PPH. The results showed that Yimucao injection which is combined with western medicine for the treatment of PPH and significantly improved the total effective rate compares control group. Our meta-analysis shows that, compared with control group, Yimucao injection combined with western medicine has the more significant effect on the blood loss during the intraoperative, delivery hours of 2 hours and 24 hours, and it effectively reduced the amount of blood loss and risk of adverse events.

4.2. Subgroup Analysis. Oxytocin is one of the naturally occurring hormones, which can initiate oxytocin receptors

and maintain adequate uterine tone resulting in rhythmic uterine contractions and thereby minimise blood loss [58]. Moreover, oxytocin is first-line uterotonics for prevent uterine atony and PPH during delivery [7]. The metaanalysis results showed that oxytocin combined with Yimucao injection was effective agent than oxytocin alone in reducing the blood loss during the intraoperative, 2 hours and 24 hours during cesarean section in our subgroup analysis.

Although oxytocin was found to be the most commonly used uterotonic agent for the prevention of PPH and has been reported to reduce blood loss during cesarean section [59]. However, it has a half-life of <10 min (short duration of action), negative inotropic, antiplatelet, and antidiuretic effects. The study [24] found that the effect of traditional Chinese medicine Yimucao contractile uterus was slow and lasted more than 6 hours. Thus, Yimucao injection and oxytocin have synergistic effect. Moreover, most of the studies have reported other uterotonic agents and also showed the prevention of PPH, including carboprost tromethamine and misoprostol [60–62].

Carboprost tromethamine is the synthetic 15-methyl analogue of prostaglandin F2 $\alpha$ , and it was reported [5] that carboprost tromethamine for the treatment of persistent hemorrhage due to uterine atony significantly improved the effective rate by 84-96%. A study [63] reported that 237 patients were used to PPH with carboprost tromethamine, and the result showed that the improvement rate of PPH was 87.8%. This study was to compare carboprost tromethamine combined with Yimucao injection with carboprost tromethamine alone for the prevention of PPH in high-risk females undergoing cesarean delivery. Results of subgroup analysis indicated that carboprost tromethamine combined with Yimucao injection group could significantly enhance the uterine contraction for preventing PPH compared with carboprost tromethamine group.

Misoprostol is a PGE1 analogue of the strong effect on the uterus, which has been widely used for the prevention of PPH during cesarean delivery especially in developing countries [64]. Most of the studies [65–68] were suggested that misoprostol to be effective in reducing blood loss during cesarean section and it is regarded as an effective drug could substitute for other uterotonic agents. In addition, the advantages of misoprostol were inexpensive and thermostable. A few studies [34, 57] have reported the efficacy of Yimucao injection combined with misoprostol versus misoprostol alone. According to the above analysis it was demonstrated that the clinical efficacy of Yimucao injection combined with misoprostol for preventing PPH was significantly better than that of misoprostol.

This study systematically reviewed that the effect of Yimucao injection combined with western medicine for preventing PPH during cesarean section. In forty-eight RCTs in our study, a total of 26 trials reported adverse events. However, all trials did not show abnormal changes and severe adverse drug reactions during the course of treatment. Therefore, in the aspect of safety analysis, it could be judged that Yimucao injection combined with western medicine has better safety in the prevention of PPH. 4.3. Limitations of This Study. Although, we have comprehensive analysis and evaluate all studies, it still has limitations. First, the review includes 48 RCTs, with 7,330 women, which were published in Chinese and lacked relevant foreign experiments; the results of this study were regional and there may be publication bias. Secondly, most of the studies showed only the randomized trials, but no specific methods of random sequence generation, RCTs of allocation concealment, and blinding of outcome assessment. There were only two studies which reported double blinding. The methodological quality of many of the included RCTs was generally low and might have a high risk of bias. Third, we found that the outcome indicator of PPH in some trials was high heterogeneity. There was the difference in the doses of Yimucao injection combined with western medicine and western medicine alone in the treatment group and the control group. Furthermore, the control group was the use of different drugs in varied regimens. We considered different methods of administration in subgroup analyses, and there was still a very high heterogeneity. The source of high heterogeneity may be inconsistent with the method used to measure the amount of bleeding in clinical studies. We also found that the doses of drugs and methods of administration were different between study groups. In our meta-analysis, reporting bias is an important section. The funnel plot of the intraoperative blood loss showed symmetry and the quantitation of Egger's test with the total effective rate (P>0.098). The results indicated that publication bias was possibly low and partly reliable, but it could not show the whole publication biases.

## 5. Conclusions

In summary, this meta-analysis of RCTs suggested the use of Yimucao injection for the effective prevention PPH during and after cesarean section. It can effectively prevent of PPH and reduce the risk of adverse events. Subgroup analyses indicated that the clinical efficacy of Yimucao injection combined with western medicine such as oxytocin, carboprost tromethamine, and misoprostol could significantly improve PPH compared with western medicine alone. However, the methodological quality of these trials was relatively low and the significant intergroup heterogeneity in this study. Trials of larger scale or long-term, double-blind RCTs and high methodological standards are needed to provide more evidence to demonstrate the efficacy of Yimucao injection in preventing PPH during and after cesarean section.

#### **Conflicts of Interest**

The authors declare that there are no conflicts of interest.

## **Authors' Contributions**

Shichun Chen and Baocheng Xie contributed equally to this work. Shichun Chen, Baocheng Xie, and Hao Tian comprehensively searched the medical database and collected and extracted consistent randomized clinical trials; Shichun Chen, Baocheng Xie, and Hao Tian discussed and analyzed Evidence-Based Complementary and Alternative Medicine

data together; Shichun Chen and Baocheng Xie wrote papers; Hao Tian provided suggestions for writing preparation; Chengyu Lu conceived the idea for this paper and revised the paper. The final version of the article is determined after review by all authors.

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