

Sandwich method with or without lauromacrogol in the treatment of gastric variceal bleeding with liver cirrhosis

A meta-analysis

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Abstract

Background: To compare the efficacy and safety of the modified sandwich method with lauromacrogol in the treatment of gastric variceal bleeding (GVB) caused by liver cirrhosis with the traditional sandwich method no accompanied by lauromacrogol via a meta-analysis.

Methods: The Cochrane Library, Pubmed, the China National Knowledge Infrastructure (CNKI) database, the Chinese Wanfang database, and the Chongqing VIP database were searched to identify cohort studies comparing modified to traditional sandwich method in the treatment of GVB with liver cirrhosis. The relative risk for hemostasis rate, gastric varices (GV) remission rate, re-bleeding rate, the incidence of post-operative complications (pain, fever, ulcer or erosion, ectopic embolism), and all-cause mortality were calculated. The mean difference for average tissue adhesive dosage per case was calculated. Relevant data were analyzed with the Reviewer Manager 5.3.5.

Results: Four cohort studies with a total of 587 patients were included in this meta-analysis. In the treatment of GVB with liver cirrhosis, compared with the traditional sandwich method, the modified sandwich method was associated with a higher GV remission rate (RR: 1.24, 95% CI: 1.09–1.42; $P = .001$) according to the pooled results. There were no statistically significant differences between the 2 methods in the rate of hemostasis, re-bleeding, pain, fever, ulcer or erosion, ectopic embolism, and all-cause mortality ($P \geq .05$).

Conclusions: This meta-analysis indicated that the modified sandwich method with lauromacrogol is more effective than the traditional sandwich method without lauromacrogol. Due to the limited number of studies and samples, more RCT studies are needed to further validate the efficacy and safety of the modified sandwich method with lauromacrogol in the treatment of GVB with liver cirrhosis.

Abbreviations: CI = confidence interval, CNKI = China national knowledge infrastructure, EGV = esophageal and gastric varices, EGVB = esophageal gastric variceal bleeding, EV = esophageal varices, GV = gastric varices, GVB = gastric variceal bleeding, MD = mean difference, NOS = Newcastle-Ottawa Scale, RCT = randomized controlled trial, RR = relative risk.

Keywords: gastric variceal bleeding, lauromacrogol, liver cirrhosis, meta-analysis, sandwich method, tissue adhesive

1. Introduction

Esophageal and gastric varices (EGV) is a common and life-threatening complication in patients with liver cirrhosis along

with portal hypertension. The prevalence of gastric varices (GV) is less than esophageal varices (EV)'s, only found in 5% to 33% of patients with portal hypertension at any reason.^[1] The incidence of variceal bleeding is 5% to 15%, but the gastric variceal bleeding (GVB) is responsible for only 15% to 30% of the cases.^[1,2] GV are more difficult to break than EV, due to the presence of GV in the strata submucosum, and the thickness of the gastric mucosa. However, once the GV breaks, it is difficult to stop the bleeding because of its anatomical location. Moreover, compared with EV, the varicose veins of the stomach are thicker, the pressure in the vein is higher, GV are associated with more blood loss, and the mortality is about 45% to 55%.^[2–4] After the first esophageal gastric variceal bleeding (EGVB) stopped, the re-bleeding rate within 1 to 2 years is 60% to 70%, and the mortality can reach as high as 33%.^[1]

GV are divided into isolated GV (Lg type) and gastroesophageal varices (Leg type).^[2] Currently, the reported methods of prevention and treatment of GV in liver cirrhosis cases include: endoscopic treatment, administration of non-selective beta blockers, interventional therapy, and surgery.^[2] In endoscopic treatment, for isolated GV, tissue adhesive injection is recommended; for gastroesophageal varices, endoscopic treatment

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include injecting sclerosing agent into EV to achieve the goal of treating GV or injecting tissue adhesive into GV.^[2] Endoscopic tissue adhesive injection is recommended as a priority treatment for acute GVB,^[4] and is the first-line treatment to prevent gastric variceal re-bleeding in China for treating GV.^[2,5] N-2-butyl-cyanoacrylate has been extensively used for obturation of varices by endoscopic injection,^[6] and it is the most commonly used tissue adhesive in China with a “sandwich” injection.

Here's the “sandwich”, where the sandwich is tissue glue, and these 2 slices of bread are usually made of lipiodol, hypertonic glucose, or saline, the “sandwiches” made of these 3 kinds of bread are traditional sandwiches. The efficacy and safety of the traditional sandwich method in gastric varicose bleeding have been confirmed in several studies, but there are still some recurrence rates and complications in this method. Failure to meet the growing needs of patients and their families has led to continuous improvement and innovation among clinicians and researchers. There are now several researchers who have created modified sandwiches based on traditional sandwiches by using the lauromacrogol: these include replacing the traditional three kinds of bread with lauromacrogol (single or double replacement of bread), or add lauromacrogol to traditional sandwiches directly. These studies show that, compared to traditional sandwiches, modified sandwiches can improve the efficacy and safety of the method. Whereas, there is still inconsistency in the results obtained by various studies on the efficacy and safety of the modified sandwich method, relative to the traditional sandwich method. Therefore, we carried out this meta-analysis to provide reference for clinical application.

2. Materials and methods

2.1. Materials

2.1.1. Search strategies. The Cochrane Library, Pubmed, the China National Knowledge Infrastructure (CNKI) database, the Chinese Wanfang database, and the Chongqing VIP database were searched by 2 reviewers (from inception until July 2017). Search terms used in Pubmed were: (((((GV)) OR (gastric variceal))) AND ((cyanoacrylate) OR (tissue adhesive))) AND lauromacrogol. The language of studies was limited to English and Chinese. Reference lists of all eligible studies were manually searched for additional studies. This is a meta-analysis, thus no ethical approval is needed for this paper.

2.1.2. Eligibility criteria.

- (1) Participants: patients with GVB in liver cirrhosis;
- (2) Intervention: tissue adhesive combined with lauromacrogol (modified sandwich method);
- (3) Comparison: tissue adhesive combined only with lipiodol, or hypertonic glucose, or saline (traditional sandwich method);
- (4) Outcomes (each study reported at least 1 outcome): hemostasis rate: no active bleeding after treatment, GV remission rate: varicose veins disappear or become straighter or more anterior, re-bleeding rate: bleeding again after successful hemostasis, the incidence of post-operative complications (pain: posterior sternum pain and (or) abdominal pain, fever, ulcer or erosion, ectopic embolism), all-cause mortality, average tissue adhesive dosage per case;
- (5) Study types: cohort study;
- (6) The injection method: traditional sandwich method or the modified sandwich method.

2.1.3. Exclusion criteria.

- (1) Non-cirrhotic GVB;
- (2) Summary, uncontrolled case reports, no full-text studies;
- (3) Reports of the same data;
- (4) None-cohort studies.

2.2. Methods

2.2.1. Study selection and data extraction. Two reviewers independently screened all the studies, identified duplicated studies by EndNote X7 software (version 17.0.0.7072, Thomson Reuters) and manually, then excluded them. After reading the title and abstract of all the remaining studies, the full text of the studies was read and the articles were selected according to the eligibility and exclusion criteria. Disagreements were resolved by consultation of a third reviewer. After the study screening, we extracted the relevant data (authors' names, time of publication, type of study, treatment method, and sample size of the 2 methods, outcomes, follow-up time) from each study with a pregenerated standard table.

2.2.2. Quality assessment. Two reviewers independently appraised and summarized the risk of bias. A cohort study was appraised with the Newcastle–Ottawa Scale (NOS),^[7] which assesses three broad perspectives of each study, including the selection of the study population, the comparability between groups, and the exposure to measurement factors. A total of 9 points can be allocated to each study.

2.3. Statistical analysis

Data were analyzed by the Reviewer Manager 5.3. software (Version:5.3.5; The Cochrane Collaboration). Relative risk (RR) and its 95% confidence interval (CI) were calculated for dichotomous data. The mean difference (MD) and its 95% CI were calculated for continuous data. A 2-tailed *P* value of <.05 was used to determine statistical significance. Statistical heterogeneity was assessed and quantified by the I^2 index; when $I^2 > 50\%$ it represents substantial heterogeneity. Since the 2 groups used different reagents in the four cohort studies, we used a random effect model. when $P < .10$ and $I^2 > 50\%$, we assessed the source of heterogeneity, since there were only 4 included studies, no further subgroup analysis was conducted.

3. Results

3.1. Search results and general characteristics

A total of 20 English and 240 Chinese studies were identified in the initial search of the electronic databases. EndNote and manually screening were used to remove duplicate studies (a total of 50 studies). A total of 210 studies were reviewed and 189 studies were removed after reading the title and abstract. The 2 reviewers screened out the full text of the remaining 21 related studies, and 3 Chinese studies were included. In addition, 1 Chinese study, acquired from searching the references of the included 3 studies, conformed to the eligibility and exclusion criteria. A total of 4 Chinese studies^[8–11] with a total of 587 patients were finally included in this meta-analysis. The workflow of the selection process of the included studies is shown in the diagram in Fig. 1. The general characteristics of the included studies are shown in Table 1.

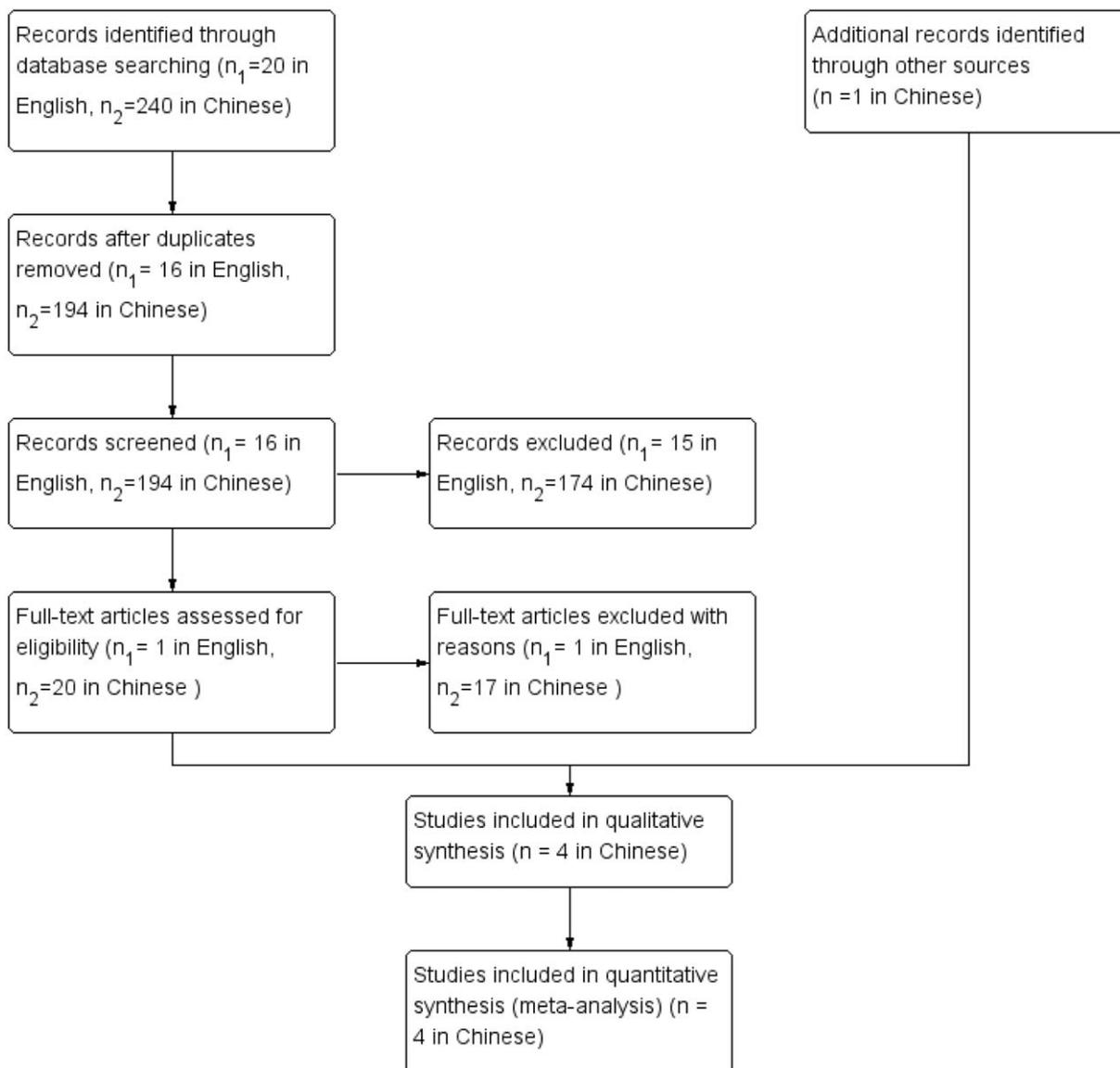


Figure 1. Flow diagram of the included studies.

3.2. Quality assessment

A summary of the risk of bias is shown in Fig. 2. In the 4 studies included in this meta-analysis, the basic condition of patients was analyzed and reported; baseline characteristics were comparable.

3.3. Results of the meta-analysis

3.3.1. Hemostasis rate. Three studies completely reported the hemostasis rate between the modified method with the traditional method.^[9-11] A total of 341 patients were included, 183 patients were allocated with the modified method, and 158 patients with

Table 1
Summary of the general characteristics of the included studies.

Reference	Study design	Intervention		Control		Outcomes	Follow up time (months)
		ModifiedMethod	No. of patients	TraditionalMethod	No. of patients		
Bian 2016 ^[8]	Cohort	A-B-A	142	C-B-C	104	<u>abc</u> defghi	13 ± 8/ 12 ± 7
Zhang 2016 ^[9]	Cohort	A-B-A	41	C-B-C	43	abcde <u>fg</u> h	6
Liu 2014 ^[10]	Cohort	A-D-B-D	41	D-B-D	45	<u>abc</u> defghi	12
Hou 2014 ^[11]	Cohort	C-A-B-C	101	C-B-C	70	abc <u>ef</u> ghi	7.47 ± 6.04/ 12.17 ± 8.01

A = lauromacrogol; B = tissue adhesive (cyanoacrylate); C = lipiodol; D = normal saline.
a = hemostasis rate; b = gastric varices total effective rate; c = re-bleeding rate; d = pain; e = fever; f = ulcer or erosion; g = ectopic embolism; h = all-cause mortality; i = average tissue adhesive dosage per case (the underlined letters indicate that the data of this outcome is incomplete).

	Representativeness of the exposed cohort	New Item Selection of the non exposed cohort	Ascertainment of exposure to implants	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
Bian 2016	+	+	+	+	+	+	+	+
Hou 2015	+	+	+	+	+	+	+	+
Liu 2014	+	+	+	+	+	+	+	+
Zhang 2016	+	+	+	+	+	+	+	+

Figure 2. Quality assessment of the included studies by the Newcastle–Ottawa Scale. (The ⊖ stands for 0 point; the ⊕ stands for 1 point; the question mark inside the circle stands for 2 point).

the traditional method. There was no substantial heterogeneity between the studies in this outcome ($P = .42, I^2 = 0\%$). Random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the hemostasis rate (RR: 1.00, 95% CI: 0.98–1.02; $P = .77$; Fig. 3).

3.3.2. GV remission rate. Three studies completely reported the GV remission rate between the 2 methods.^[8–9,11] A total of 501 patients were selected; 284 patients were allocated with the modified method and 217 with the traditional method. There was no substantial heterogeneity between the studies in this outcome ($P = .48, I^2 = 0\%$). Random effect model analysis was used. The result showed that the GV remission rate of the modified method was significantly higher than that of the traditional method (RR: 1.24, 95% CI: 1.09–1.42; $P = .001$; Fig. 4).

3.3.3. Re-bleeding rate. Three studies completely reported the re-bleeding rate between the two methods.^[8–9,11] A total of 501 patients were selected; 284 patients were allocated with the modified method and 217 with the traditional method. There was no significant heterogeneity between the studies in this outcome ($P = .19, I^2 = 39\%$). Random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the re-bleeding rate (RR: 0.69, 95% CI: 0.46–1.02; $P = .06$; Fig. 5).

3.3.4. Pain. Three studies reported the incidence of chest or abdominal pain between the 2 methods.^[8–10] A total of 416 patients were included; 224 patients were allocated with the modified method, 192 patients with the traditional method. There was no significant heterogeneity between the studies in this outcome ($P = .99, I^2 = 0\%$). Random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the incidence of chest or abdominal pain after treatment (RR: 0.72, 95% CI: 0.44–1.17; $P = .18$; Fig. 6).

3.3.5. Ulcer or erosion. Four studies reported the incidence of ulcer or erosion between the 2 methods.^[8–11] A total of 587 patients were included; 325 patients were allocated with the

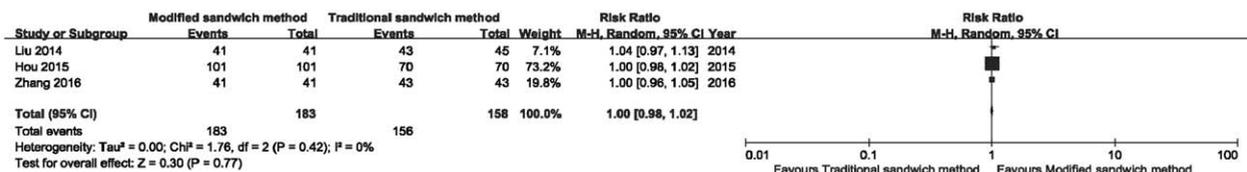


Figure 3. Forest plot of the hemostasis rate between the two methods. (A=lauroacrogol; B=tissue adhesive (cyanoacrylate); C=lipiodol; D=normal saline).

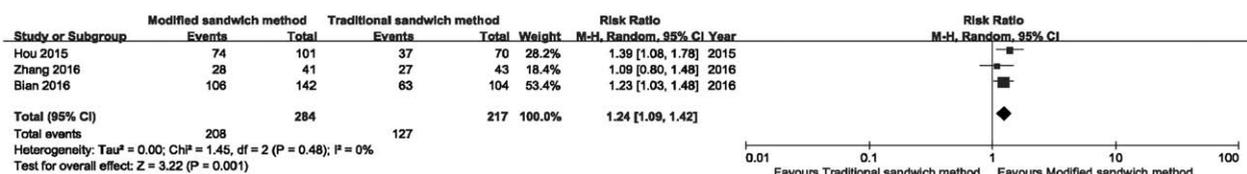


Figure 4. Forest plot of the gastric varices total effective rate between the 2 methods. (A=lauroacrogol; B=tissue adhesive (cyanoacrylate); C=lipiodol).

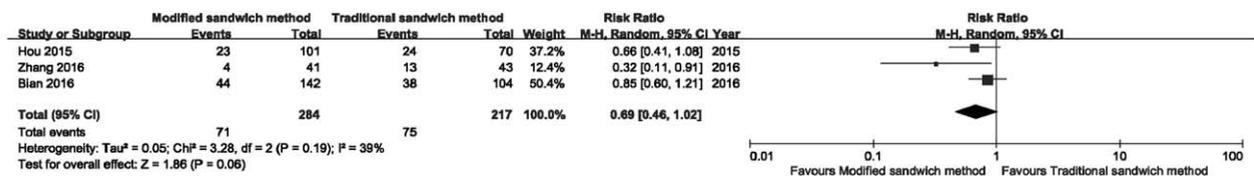


Figure 5. Forest plot of the re-bleeding rate between the 2 methods. (A=lauromacrogol; B=tissue adhesive (cyanoacrylate); C=lipiodol).

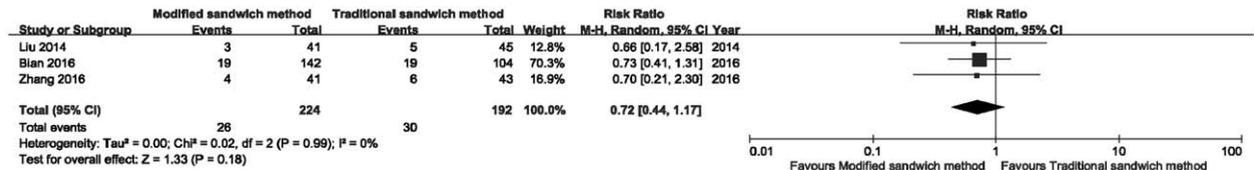


Figure 6. Forest plot of the incidence of pain between the 2 methods. (A=lauromacrogol; B=tissue adhesive (cyanoacrylate); C=lipiodol; D=normal saline).

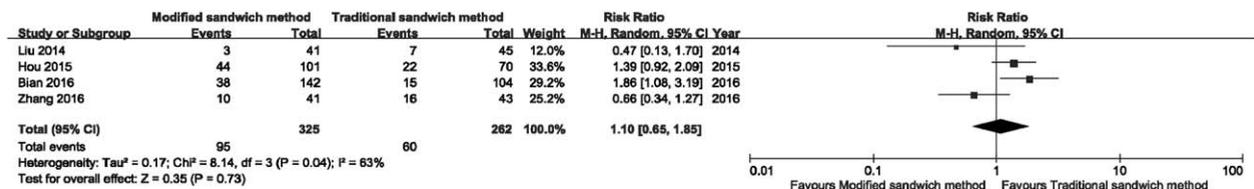


Figure 7. Forest plot of the incidence of ulcer or erosion between the 2 methods. (A=lauromacrogol; B=tissue adhesive (cyanoacrylate); C=lipiodol; D=normal saline).

modified method and 262 with the traditional method. There was significant heterogeneity between the studies in this outcome ($P = .04$, $I^2 = 63\%$), which we assumed to have been derived from the different dosage of lauromacrogol used or the different number of participants in each study. The random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the incidence of ulcer or erosion after treatment (RR: 1.10, 95% CI: 0.65–1.85, $P = .73$; Fig. 7).

3.3.6. Fever. Four studies reported the incidence of fever between the 2 methods.^[8–11] A total of 587 patients were included; 325 patients were allocated with the modified method and 262 patients with the traditional method. There was no substantial heterogeneity between the studies in this outcome ($P = .44$, $I^2 = 0\%$). Random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the incidence of fever after treatment (RR: 1.43, 95% CI: 0.96–2.11; $P = .08$; Fig. 8).

3.3.7. Ectopic embolism. Four studies reported the incidence of ectopic embolism between the 2 methods.^[8–11] A total of 587 patients were included; 325 patients were allocated with the modified method and 262 with the traditional method. There was no substantial heterogeneity between the studies in this outcome ($P = .97$, $I^2 = 0\%$). Random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the incidence of ectopic embolism (RR: 0.18, 95% CI: 0.03–1.00; $P = .05$; Fig. 9).

3.3.8. All-cause mortality. Four studies completely reported the all-cause mortality between the 2 methods.^[8–11] A total of 587 patients were included; 323 patients were allocated with the modified method and 262 with the traditional method. There was no significant heterogeneity between the studies in this outcome ($P = .37$, $I^2 = 4\%$). Random effect model analysis was used. The result showed that there was no statistically difference between the modified method with the traditional method in the all-cause mortality (RR: 1.00, 95% CI: 0.55–1.85; $P = .99$; Fig. 10). Only

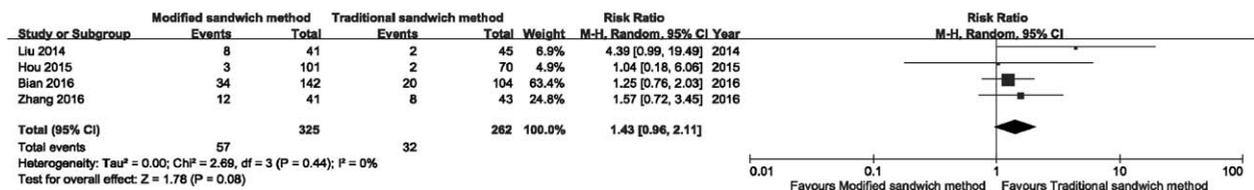


Figure 8. Forest plot of the incidence of fever between the 2 methods. (A=lauromacrogol; B=tissue adhesive (cyanoacrylate); C=lipiodol; D=normal saline).

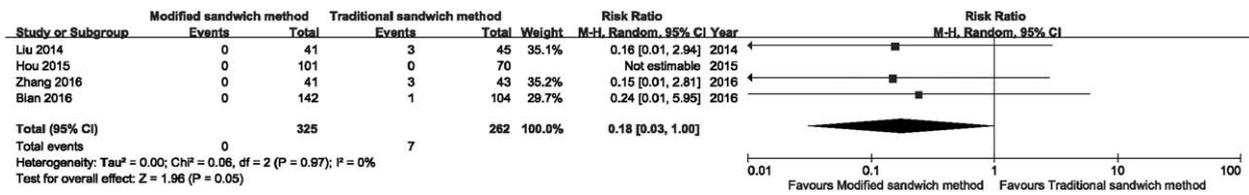


Figure 9. Forest plot of the incidence of ectopic embolism between the 2 methods. (A = lauromacrogol; B = tissue adhesive (cyanoacrylate); C = lipiodol; D = normal saline).

Hou et al included the bleeding-related mortality after all,^[11] therefore no bleeding specific mortality analysis was performed.

3.3.9. Average tissue adhesive dosage per case. Only 2 studies completely reported the average tissue adhesive dosage per case between the 2 methods.^[8,11] A total of 417 patients were included; 243 patients were allocated with the modified method and 147 with the traditional method. The results of both studies were no statistically significant for the average tissue adhesive dosage per case between the 2 methods.

4. Discussion

GVB is one of the main causes of death of cirrhotic portal hypertension patients. Once the GV break and bleed, it leads to high mortality.^[3] At present for the endoscopic treatment of GVB, either isolated or leg-operated, Sandwich injection with tissue adhesive is recommended.^[2]

The traditional sandwich method usually combines tissue adhesive with lipiodol, or hypertonic glucose, or saline. Tissue adhesive is commonly used in the medical practice, it is polymerized within few seconds after contact with blood, and forms a solid exterior membrane, which can completely separate an area from the vessels, and eventually cause occlusion of vessels.^[12] However, it can easily clog syringes and endoscopic biopsy channels and can even stick on the surgical needle during operation. Although tissue adhesive-induced ulceration, vascular remodeling, and occlusion of GV are rare and they mainly occur on the submucosal vessels, there is still a little effect on the muscular layer and serosa vessels, which prevents the disappearance of GV and the formation of new varicose veins.^[13,14] Because it cannot be absorbed by the body and is excreted in about 14 days after injection,^[11] dumping the material from the body can lead to re-bleeding in the not well occluded GV.^[14-16] In addition, the excessive dosage can lead to ectopic embolism.^[14] At the same time, because the GV are larger in diameter,^[13,14] and have higher venous pressure than EV, the thrombus formed during treatment is easily washed away by blood,^[14] which is not only a potential risk for ectopic embolism, but also for reducing

the method's efficacy. Lipiodol or hypertonic glucose acts as diluent. Mix production of lipiodol and tissue adhesive can cause ectopic embolism by collateral circulation,^[13] and this may also be related to the condensation delay of lipiodol.^[17]

While the modified sandwich method add the lauromacrogol. Lauromacrogol can be absorbed by the human body; and it can damage the endangium, cause aseptic chemical inflammation, promote thrombogenesis,^[15] gradually block the varicose veins on the mucosa surface and the deep layer.^[13] But at high dosage, it can lead to ulcer formation, perforation, hemorrhage and so on; at low dosage, it has a low occlusion efficiency.^[10] Meanwhile, because its action is slow and the pressure in the varicose vein is high, blood surges at the time of injection and bleeding can occur through the injection orifice, when the needles are withdrawn.^[14,15]

Lauromacrogol and tissue adhesive can complement each other. Lauromacrogol injection can induce local inflammation, ulceration, and thrombosis in the mucosa and the deep layer varicose veins; whilst the injected tissue adhesive is quickly polymerized and localized. Thus the modified sandwich method can effectively occlude varicose veins and injection orifices, as we showed in this meta-analysis that the modified method had a significantly higher GV remission rate than that of the traditional method (RR: 1.24, 95% CI: 1.09-1.42; P = .001). In addition, lauromacrogol can induce fibrosis in the mucosal surfaces and the deep layer varicose veins, while the result showed that there was no statistically difference between the modified method with the traditional method in the re-bleeding rate (RR: 0.69, 95% CI: 0.46-1.02; P = .06; Fig. 5). Pooled results also indicated that there were no statistically significant differences between the 2 methods in the incidence of hemostasis, pain, fever, ulcer erosion, ectopic embolism, all-cause mortality. As to July 2017, no similar meta-analysis had been published.

There are some limitations to this meta-analysis. First, this meta-analysis included only cohort studies, and the strength of evidence is weaker than in randomized controlled trials (RCTs), but the quality of the included cohort study is high. Second, only 4 studies were included, and the sample size of each study was relatively small. Third, because we limited the language of studies to English and Chinese, as well as the lauromacrogol is made in China, so there are selective bias and publication bias that may

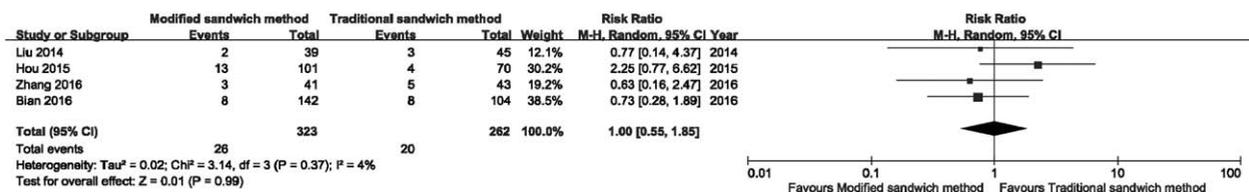


Figure 10. Forest plot of the all-cause mortality between the 2 methods. (A = lauromacrogol; B = tissue adhesive (cyanoacrylate); C = lipiodol; D = normal saline).

affect the cumulative evidence. Fourth, the sensitivity analysis was not conducted because only 4 studies were included in this meta-analysis.

5. Conclusion

In the treatment of GVB with liver cirrhosis, the modified sandwich method with lauromacrogol is more effective in eradicating the GV compared with the traditional sandwich method without lauromacrogol. No significant differences between the 2 methods were seen in the incidence of hemostasis, re-bleeding, pain, fever, ulcer erosion, ectopic embolism, and all-cause mortality. However, prolonged follow-up periods, multicenter, and large sample size randomized controlled trials are needed to illustrate the efficacy and safety of the modified sandwich method in the treatment of GVB due to liver cirrhosis.

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