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SCIENTIFIC PAPER (OTHER) EMBOLISATION (ARTERIAL)

Effectiveness of Transarterial Embolization in Treatment of Symptomatic Hepatic Hemangiomas: Systematic Review and Meta-analysis

Pooya Torkian[1] · Jianjun Li[2,3] · John A. Kaufman[3] · Younes Jahangiri[3]

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Abstract

Purpose To evaluate the current evidence for the effectiveness of transarterial embolization (TAE) in treatment of symptomatic hepatic hemangiomas.

Materials and Methods A systematic literature review was conducted in PubMed, CINAHL and Scopus databases to identify studies of hepatic hemangiomas treated with transarterial embolization. Main outcome was defined as the mean difference between pre- and post-TAE hemangioma diameters. Treatment agents were categorized as Lipiodol based [bleomycin (L + BE), pingyangmycin (L + PYG) or ethanol (L + ethanol)] and non-Lipiodol based (polyvinyl-alcohol-only). Conventional random-effect meta-analysis technique was applied to analyze data.

Results Of 3080 initially inspected publications, 21 studies were included in the meta-analysis comprising of 1450 patients with total of 1871 hemangiomas (36.2% male, mean age: 46.3 ± 3.6 years). One hundred and twenty-six, 1666, 41 and 38 lesions were treated with L + BE, L + PYG, L + ethanol and PVA, respectively. Median follow-up time after embolization was 12 months. Lipiodol-based treatments showed significant effect in reducing hemangioma size after TAE compared to PVA ($P < 0.001$). Pooled diameter reduction (cm) (95% confidence interval) was − 4.37(− 5.32, − 3.42), − 4.70(− 5.70, − 3.71), − 0.93(− 2.02, 0.16) for overall TAE treatment, Lipiodol-based and non-Lipiodol-based treatments, respectively. Main complications included post-embolization syndrome and transient liver enzyme elevation (pooled incidence for Lipiodol-based and non-Lipiodol-based techniques: 36% and 33%; and 37% and 0, respectively). No fatal complications were reported. Symptomatic improvement was reported in 63.3%–100% of the cases with majority of studies (15/21) reporting improvement in all cases (pooled response rate: 98%).

Conclusions Transarterial embolization with bleomycin, pingyangmycin or ethanol in combination with Lipiodol is safe and associated with reduced size of hemangiomas resulting in symptoms alleviation.

Keywords Hepatic hemangioma · Transarterial embolization · Lipiodol · Bleomycin · Pingyangmycin

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✉ Younes Jahangiri
jahangiy@ohsu.edu

[1] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

[3] Dotter Department of Interventional Radiology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97239, USA

Introduction

Hepatic hemangiomas are the most common benign tumors of the liver with the reported prevalence of 2–7% [12]. Large hemangiomas (> 5 cm) lead to a decrease in overall

quality of life and risk of rupture in peripherally located lesions [6, 40]. Appropriate treatment of hepatic hemangiomas has been controversial. Although surgical intervention has been recommended for large symptomatic hemangiomas and is considered as the gold standard in most centers [21], minimally invasive techniques, including transarterial embolization, have shown acceptable efficacy with lower rates of post-procedure morbidity and mortality [5, 33, 48, 53]. Studies regarding effectiveness of transarterial embolization techniques have demonstrated contradictory results [1], mainly due to small sample size and differences in the applied embolization materials. The purpose of this study is to systematically review and summarize the currently available evidence using meta-analysis techniques.

Materials and Methods

Search Strategy

A systematic search in PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Scopus databases was conducted to identify relevant studies until October 2018. The applied keywords included: ["hemangioma" or "hepatic hemangioma"] combined with ["Transarterial Embolization," "TACE" or "embolization"]. No language restriction was applied.

Selection of the Studies and Data Extraction

Study selection process is demonstrated in Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart [24] (Fig. 1). Initial search revealed a total of 3080 publications with 2899 unique publications. Titles and abstracts of 2899 studies were screened for their relatedness to the topic of interest, out of which 62 publications regarding treatment of hepatic hemangiomas with transarterial embolization were identified for further screening. After excluding duplicate publications (2), single case reports (7), review articles (1), reports of no treatment or treatment other than embolization such as percutaneous ethanol injection (2), embolization of malignant tumor (2) or non-hepatic hemangiomas (2), combination of embolization with medical treatment (beta blocker; 1), infantile population (2), no report of hemangioma size (1), 42 articles were selected for in-depth review of their full report. At this stage, studies with missing hemangioma size information (15), infantile target population (1) and case reports not identifiable from abstract (5) were excluded from further review. Finally, 21 studies were included in meta-analysis. Two studies reported comparison of different embolization modalities: one study compared two Lipiodol-based embolization methods (pingyangmycin + Lipiodol + gelfoam versus pingyangmycin + Lipiodol without gelfoam) [30] and another one reported a comparison of embolization with pingyangmycin + Lipiodol at room temperature and after heating the solution to 110 °C [50]. Due to significant differences reported in the post-embolization lesion diameters, the study groups were recorded separately for a total of 23 treatment cohorts.

Selection of the studies was done independently by two investigators (PT, YJ), and in case of differences, consensus was achieved by a meeting discussion. Data regarding type of the study (prospective, case control study or case series), publication year, country/region of the study, number of patients and lesions, patients' demographics, pre- and post-operative largest diameter of hemangioma, type of chemotherapeutic agents, perioperative complications, length of clinical follow-up and clinical outcomes were extracted.

Outcome Definition

Main outcome was defined as the mean difference between pre- and post-embolization hemangioma diameters. Cochrane equation [15] was used to calculate pooled standard deviation of the differences. Additionally, to assess the embolic effect of Lipiodol, treatment agents were categorized as Lipiodol based [bleomycin (L + BE), pingyangmycin (L + PYG), ethanol (L + ethanol)] and non-Lipiodol based [polyvinyl alcohol (PVA)].

Clinical response was defined as "resolution or improvement" of the pre-embolization clinical symptoms attributed to the hepatic hemangioma or "Clinical success" as reported by the studies.

Reported complications were categorized to grade 1–2 or grade 3 according to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) standards for classification of complications [8]. Post-embolization syndrome was defined as report of fever and right upper abdominal pain [3].

Institutional review board (IRB) review was not required for the study since no human subjects were involved, and no individual patient information was used to conduct meta-analysis [36].

Statistical Analysis

Stata for Windows version 14.2 (StataCorp, College Station, TX) was used for data analysis. A random-effect model was employed to calculate study weights. Presence of publication bias was evaluated using the Funnel plot and tested using the Egger's test. One large study including about 60% of the patient population (1120 lesions in 836

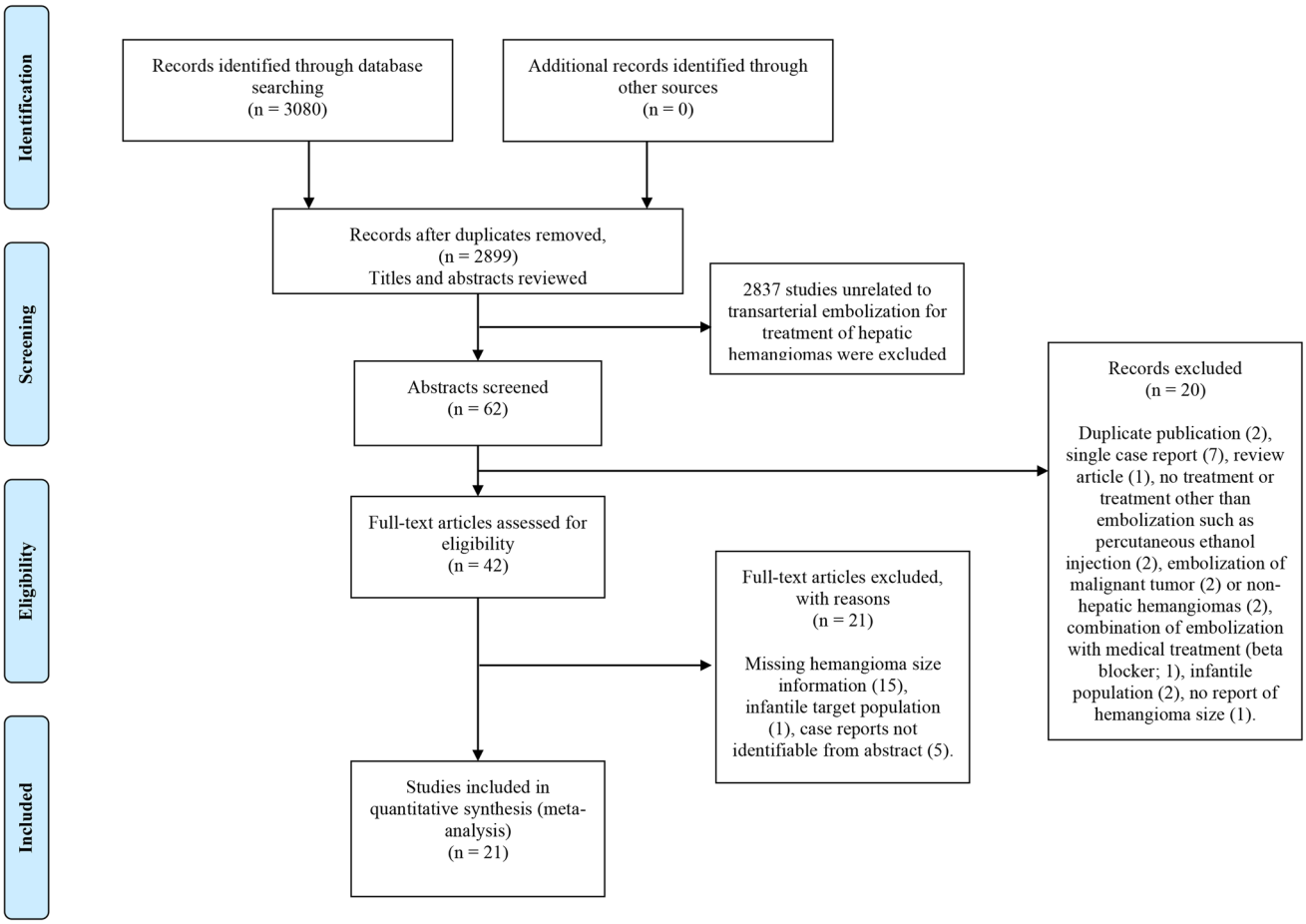

Fig. 1 Flow diagram demonstrating study selection process for meta-analysis

patients) [23] was excluded from assessment of publication bias to avoid single study effect. Differences between pooled effect sizes of embolization agents were tested with the Wald test.

A random-effect meta-regression analysis with restricted maximum likelihood (REML) estimation of between-study variances was applied to evaluate whether decrease in hemangioma diameter is associated with the length of follow-up in the studies. Stata "metan," "metaprop" and "metareg" packages were used for meta-analysis and meta-regression, respectively. P values < 0.05 were considered statistically significant in all analyses.

Results

Characteristics of the Included Studies and Study Population

A summary of the studies and detailed baseline and follow-up data is presented in Tables 1 and 2. Studies were published between 2001 and 2018. A total of 1871 hemangiomatous lesions in 1450 patients (36.2% male, mean age: 46.3 ± 3.6 years) were treated. One hundred and twenty-six, 1666, 41 and 38 lesions were treated with L + BE (4 studies), L + PYG (12 studies), L + ethanol (2 study) and PVA-only (3 studies), respectively.

Reported pre-treatment clinical and radiological symptoms are right upper quadrant (RUQ) pain and distension, early satiety or asymptomatic hemangioma with tumor enlargement of more than 1.0 cm during 2 years as detected incidentally or by imaging surveillance. Median follow-up time after embolization was 12 months (range 2.5–90 months).

Effectiveness of Transarterial Embolization for Hepatic Hemangiomas

Mean pre- and post-embolization lesion diameters were 9.8 ± 2.6 and 6.0 ± 1.4 cm, respectively. Pooled differences (95% confidence interval) were − 4.37 (− 5.32, − 3.42), − 4.70 (− 5.70, − 3.71), − 0.93 − 2.02, 0.16) for overall TAE treatment, embolization with

Table 1 Characteristics of the included studies

References	Country	Study design	Embolic agent	Diagnostic imaging modality
Lipiodol based				
Zeng et al. [48]	China	R/MC	L + PYG	CT + US
Li et al. [22]	China	R/SC	L + PYG	CT + US + DSA
Zhang et al. [49]	China	R/SC	L + PYG	CT + US
Tian et al. [39]	China	R/SC	L + PYG	CT + MRI
Wang et al. [44]	China	R/SC	L + Ethanol	CT + MRI + US
Zhu et al. [55]	China	R/SC	L + PYG	CT + MRI + US
Jiang et al. [18]	China	R/SC	L + PYG	CT + MRI + US + DSA
Fan et al. [7]	China	R/SC	L + BE	CT + MRI + DSA
Bozkaya et al. [4]	Turkey	R/SC	L + BE	CT + MRI
Wang et al. [43]	China	R/SC	L + PYG	CT + MRI + DSA
Season et al.[a] [30]	China	R/SC	L + PYG; L + PYG + Gelfoam	CT + US
Li et al. [23]	China	R/MC	L + PYG	CT + MRI
Sun et al. [37]	China	R/SC	L + PYG	CT + MRI + US
Szejnfeld et al. [38]	Brazil	R/SC	L + ethanol	CT + MRI
Zhang et al.[a] [50]	China	R/SC	L + PYG at 25 °C; L + PYG at 110 °C	CT + MRI + US
Zhang et al. [52]	China	R/SC	L + PYG + Gelfoam	CT + MRI
Akhlaghpoor et al. [1]	Iran	R/SC	L + BE	CT + MRI + US
Kirnap et al. [20]	Turkey	R/SC	L + BE	CT + US
Non-Lipiodol based				
Srivastava et al. [34]	India	P/SC	PVA + Gelfoam	CT + MRI + US
Giavroglou et al. [12]	Greece	R/SC	PVA	CT + MRI
Firouznia et al. [9]	Iran	R/SC	PVA	CT + MRI + US

[a]Comparative studies of two embolic agents, reporting two patient populations. The populations are included in the analysis separately

R retrospective, *MC* multicenter, *SC* single-center, *L* Lipiodol, *PYG* pingyangmycin, *BE* bleomycin, *PVA* polyvinyl alcohol, *CT* computed tomography, *MRI* magnetic resonance imaging, *US* ultrasonography, *DSA* digital subtraction angiography

Lipiodol-based and non-Lipiodol-based treatments, respectively (Fig. 2).

On two-by-two comparison of the embolic agents, Lipiodol-based embolization demonstrated a significantly higher pooled effect size in decreasing hemangioma diameters compared to non-Lipiodol-based treatment ($P < 0.001$). Among Lipiodol-based agents, no significant differences were detected in the effect sizes of none of the agents (L + PYG vs. L + BE; P = 0.778; L + PYG vs. L + ethanol: P = 0.710; and L + BE vs. L + ethanol: P = 1.000) (Supplemental Figure S1).

On meta-regression analysis, there was no statistically significant association between decrease in hemangioma size and length of follow-up ($\beta \pm SE$: -0.04 ± 0.02, P = 0.077) (Fig. 3).

One study included a large number of patients (about 60% of the patient population; 1120 lesions in 836 patients). This study reported a significant decrease in the lesion diameter from 9.6 ± 0.8 cm (pre-embolization) to 3.6 ± 0.5 cm after TAE (mean calculated diameter decrease: -6.0 ± 0.5 cm, mean follow-up duration: 4.4 ± 1.8 years) [23]. The calculated pooled effect size in the rest of the studies was -4.29 (-5.30, -3.28), -4.63 (-5.71, -3.65) and -0.93 (-2.02, 0.16) for overall TAE effect, embolization with Lipiodol-based and non-Lipiodol-based treatments, respectively (Supplemental Figure S2).

No significant publication bias was detected (Fig. 4) [Egger's bias coefficient: -2.48 (95% confidence interval: -8.27 to -3.31); $P = 0.383$] (Supplemental Figure S3).

Clinical response to embolization as improvement of hemangioma-related symptoms was reported in 63.3–100% of the cases with majority of the studies (15/21) reporting 100% response rate. Pooled clinical response rate was 98% (95% confidence interval: 94–100%) with no significant difference between Lipiodol-based and non-Lipiodol-based embolization methods (98% vs. 100%, respectively) (Fig. 5).

Table 2 A summary of the studies included in meta-analysis of effectiveness of transarterial embolization for hepatic hemangiomas

References	Population/ lesion/male	Location of hemangiomas	Mean age (years)	Embolic agent	Agents dose and volume	Pre-operative diameter (cm)	Post-operative diameter (cm)	Hemangioma diameter change (cm)	Follow-up duration (months)	Number with severe complications[b]
Zeng et al. [22, 48]	98/98/72	61:Rt, 16:Lt, and 21: Rt&Lt	41.6	L + PYG	8–24 mg PYG + L in a 1–1.5 ratio	9.7 ± 2.3	3 ± 1.2	− 6.7 ± 1.6	9	2
Li et al. [22]	32/44/19	NA	39	L + PYG	24 mg of PYG + 10 ml L	6.8 ± 2.2	4.6 ± 1.5	− 2.2 ± 1.5	6	0
Zhang et al. [49]	23/31/7	14:Rt, 5:Lt, 4: Rt&Lt	42.6	L + PYG	8–24 mg PYG + 5–20 ml L	8.1 ± 2.2	3.4 ± 1.2	− 4.7 ± 1.5	12	0
Tian et al. [39]	37/59/12	NA	44	L + PYG	8 mg PYG + 10 ml L	4.4 ± 3.1	NA	− 2.4 ± 1.6	6	0
Wang et al. [44]	25/38/10	15:Rt, 10: Lt	46	L + ethanol	ETOH:L ratio = 2:1 Mixture volume: 8–25 ml	8.15 ± 2.03	2.8 ± 1.2	− 5.35 ± 1.38	12	0
Zhu et al. [55]	49/66/11	30:Rt, 8:Lt, 11: Rt&Lt	44	L + PYG	8 mg PYG + 10–20 ml L	9.3 ± 2.2	2.0 ± 1.3	− 7.3 ± 1.5	12	0
Jiang et al. [18]	28/28/NA	NA	46	L + PYG	8–24 mg PYG + 5–20 ml L	10.67 ± 9.3	4.69 ± 4.4	− 5.98 ± 6.7	90	0
Fan et al. [7]	46/46/17	NA	46.6	L + BE	5-25 mg BE + 4-20 ml L	9.2 ± 3.5	4.0 ± 3.0	− 5.2 ± 2.3	43.4	0
Bozkaya et al. [4]	26/32/5	24:Rt, 4:Lt, 4:Rt&Lt	49.83	L + BE	15 mg BE + 10 ml L in a 1:2 ratio	9.72 ± 0.8	7.63 ± 0.76	− 2.09 ± .55	7.4	1
Wang et al. [43]	18/21/7	11:Rt, 4:Lt, 3: Rt&Lt	48	L + PYG	8–24 mg PYG + 5–20 ml L	10.2 ± 3.24	4.44 ± 2.16	− 5.76 ± 2.16	16.7	0
Season et al.[a] [30]	30/37/8	13:Rt, 12:Lt, 5: Rt&Lt	44.5	L + PYG	1.5 mg PYG + 1 ml L	8.0 ± 1.9	6.8 ± 1.5	− 1.2 ± 1.3	6	0
Season et al.[a] [30]	30/35/6	13:Rt, 13:Lt, 4: Rt&Lt	43.8	L + PYG + Gelfoam	1.5 mg PYG + 1 ml L	8.1 ± 2.2	4.2 ± 1.1	− 3.9 ± 1.5	6	0
Li et al. [23]	836/1120/ 301	NA	42.83	L + PYG	24 mg PYG + 10 ml L	9.6 ± 0.8	3.6 ± 0.5	− 6 ± 0.5	52.8	2
Sun et al. [37]	27/27/6	13:Rt, 1:Lt, 13:Rt&Lt	47.7	L + PYG	8 mg (21 patients) or 16 mg (6 patients) PYG + 2–26 ml L in a 1:3 ratio	11.2 ± 5.1	7.6 ± 3.9	− 3.6 ± 3.4	9.58	0
Szejnfeld et al. [38]	3/3/1	NA	57	L + ethanol	8 mL ethanol + 2 ml L	17.33 ± 4.35	14.2 ± 4.7	− 3.13 ± 3.21	2.5	0

Table 2 continued

References	Population/ lesion/male	Location of hemangiomas	Mean age (years)	Embolic agent	Agents dose and volume	Pre-operative diameter (cm)	Post-operative diameter (cm)	Hemangioma diameter change (cm)	Follow-up duration (months)	Number with severe complications[b]
Zhang et al. [50]	24/38/8	NA	47.2	L + PYG at 25 °C	8–24 mg PYG + L in a 1.5:1 ratio	6.8 ± 3.42	NA	− 6.23 ± 5.78	36	0
Zhang et al. [50]	24/32/8	NA	49.3	L + PYG at 110 °C	8–24 mg PYG + L in a 1.5:1 ratio	6.55 ± 2.84	NA	− 4.77 ± 3.64	36	0
Zhang et al. [52]	22/30/7	NA	46	L + PYG + Gelfoam	8 mg PYG + 10 ml L + 350–560 μm gelatin sponge particles	14.4 ± 4.7	9.5 ± 4.1	− 4.9 ± 3.2	6	0
Akhlaghpoor et al. [1]	23/29/3	20: Rt, 9:Lt	46.7	L + BE	30–45 IU BE + 7–15 ml L in a 1:1.5–2 ratio	10.41 ± 5.17	3.5 ± 1.4	− 6.91 ± 4.22	7.5	0
Kirnap et al. [20]	17/19/7	7:Rt, 2:Lt, 8;Rt&Lt	46.41	L + BE	15 mg BE + 10 ml L in a 1:2 ratio	14.72 ± 12.8	7.63 ± 4.76	− 7.09 ± 9.75	14.47	1
Srivastava et al. [34]	8/9/5	5:Rt, 1:Lt, 3:Rt&Lt	47.75	PVA + Gelfoam	NA	9.28 ± 5.13	8.62 ± 2.77	− 0.66 ± 3.56	13	0
Giavroglou et al. [12]	4/4/1	2: Rt, 2:Lt	51.25	PVA (Ivalon)	150–250 μ	13.1 ± 6.6	8.5 ± 1.8	− 4.6 ± 5.4	21.5	0
Firouznia et al. [9]	20/25/4	NA	46.8	PVA	300–400 μ	9.7 ± 4.785	8.9 ± 4.327	− 0.8 ± 3.24	6	0
Total	1450/1871/ 525	NA	46.3	18 L based;3 non-L based		9.8 ± 2.6	6.0 ± 1.4	− 4.37 ± 2.02	12	6

[a]Comparative studies of two embolic agents, reporting two patient populations. The populations are included in the analysis separately

[b]Severe complications included persistent pain, ischemic cholecystitis, hepatic abscess, hemoglobin drop requiring transfusion

L Lipiodol, *PYG* pingyangmycin, *BE* bleomycin, *PVA* polyvinyl alcohol, *Rt* right, *Lt* left, *NA* not available

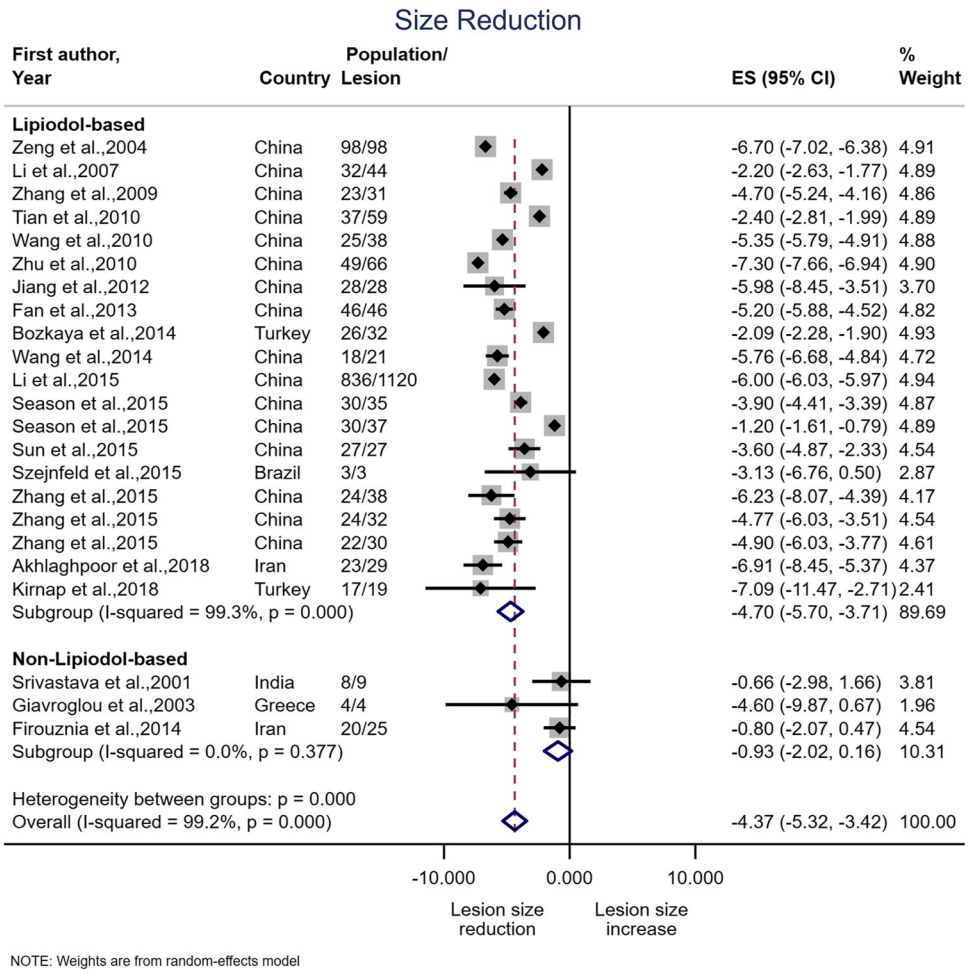

Fig. 2 Forest plot summarizing decreases in hepatic hemangioma diameters (cm) in response to transarterial embolization with Lipiodol-based and non-Lipiodol-based agents. (Data in parentheses demonstrate 95% confidence intervals (CIs). Solid squares show risk estimates for the individual studies with the size of the squares proportional to the sample size and the number of events. The horizontal lines represent the 95% CIs, and the diamonds show the pooled effect sizes. ES effect size.)

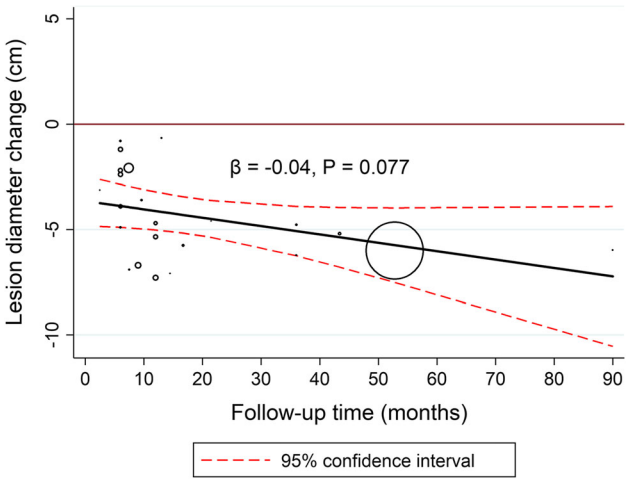

Fig. 3 The association between post-embolization lesion diameter change and follow-up time. Markers pertain to individual studies, and their size relates to the individual study weights

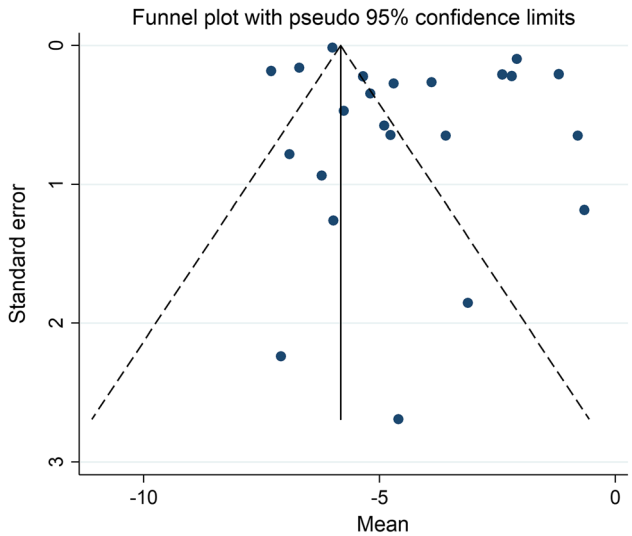

Fig. 4 Funnel plot assessing the publication bias

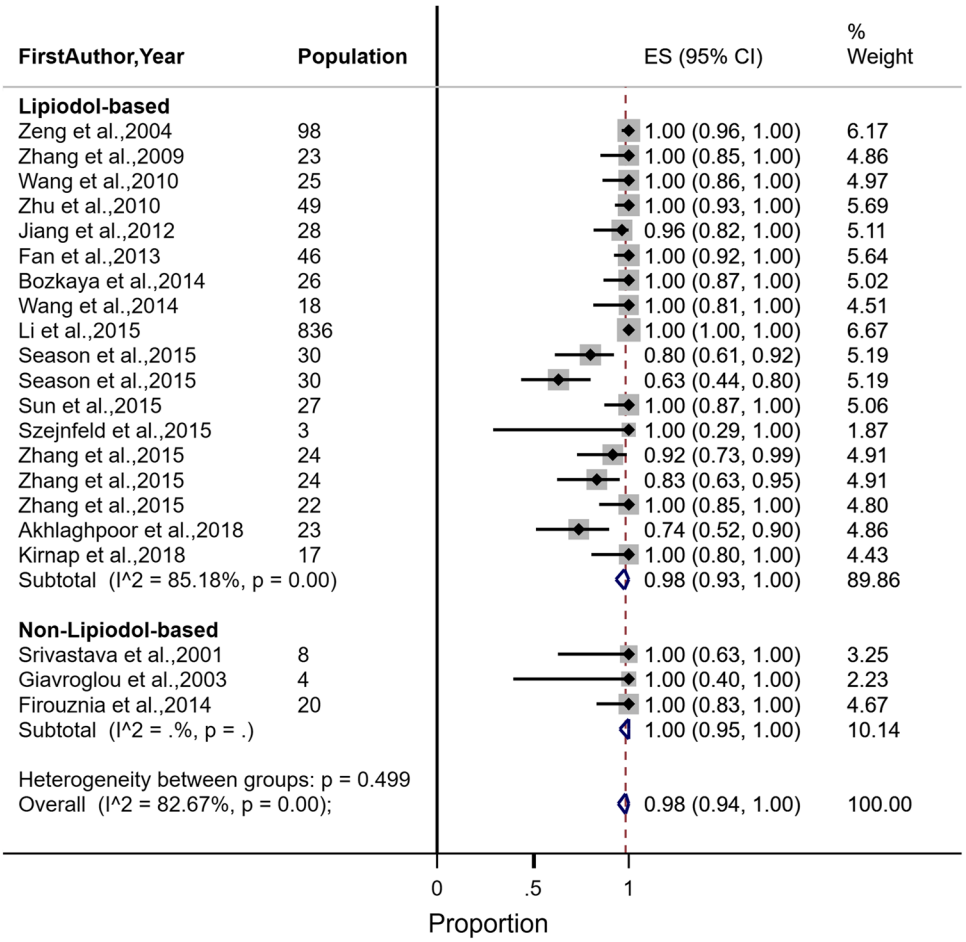

Fig. 5 Forrest plot demonstrating overall reported symptomatic improvement after transarterial embolization of hepatic hemangiomas

Complications after transarterial embolization for hepatic hemangiomas

Details of reported complications are presented in Supplemental Table S1. No mortality attributable to the TAE treatment was reported. Transient post-embolization syndrome (CIRSE grade 1–2) including abdominal pain, fever and nausea and vomiting after the procedure as well as transient rise in the liver enzymes were reported with a pooled incidences of 35% (95% CI 18%–55%) [36% and 33% for Lipiodol-based and non-Lipiodol-based embolization, respectively; P = 0.766] and 30% (95% CI 12%–52%) [37% and 0% for Lipiodol-based and non-Lipiodol-based embolization, respectively; $P < 0.001$] (Fig. 6). Reports of complications after L + ethanol were available from one study regarding PES (none of the 3 reported cases) [38] and from two studies regarding liver enzyme elevation (0/3 cases in one study and 20/25 cases in another study) [38, 44] (pooled liver enzyme elevation rate: 74%, Supplemental Figure S4). CIRSE grade 3 complications were reported in 6/1450 cases. Hemoglobin drop requiring transfusion of 2 packs of red blood cell suspension was reported after embolization with Lipiodol + bleomycin in 1/17 cases in one study [20]. The hemoglobin levels were stabilized after transfusion. Ultrasound examination did not reveal any source of extravasation and the patient was discharged 72 h after the procedure with no further complications. One other study reported ischemic cholecystitis in 1/26 cases after embolization with Lipiodol + bleomycin [4] which improved after 72 h of observation with intravenous fluid and antibiotic therapy. Continued abdominal pain after embolization with Lipiodol + pingyangmycin resulted in surgical resection of the hemangioma in 2/98 patients in one report [48]; and liver abscess found in 2/836 cases after embolization with Lipiodol + pingyangmycin were treated with 15 and 18 days of percutaneous drainage [23].

Discussion

The results of this meta-analysis indicate that transarterial embolization with a combination of Lipiodol with bleomycin, pingyangmycin or ethanol is safe and effective in shrinking symptomatic hepatic hemangiomas.

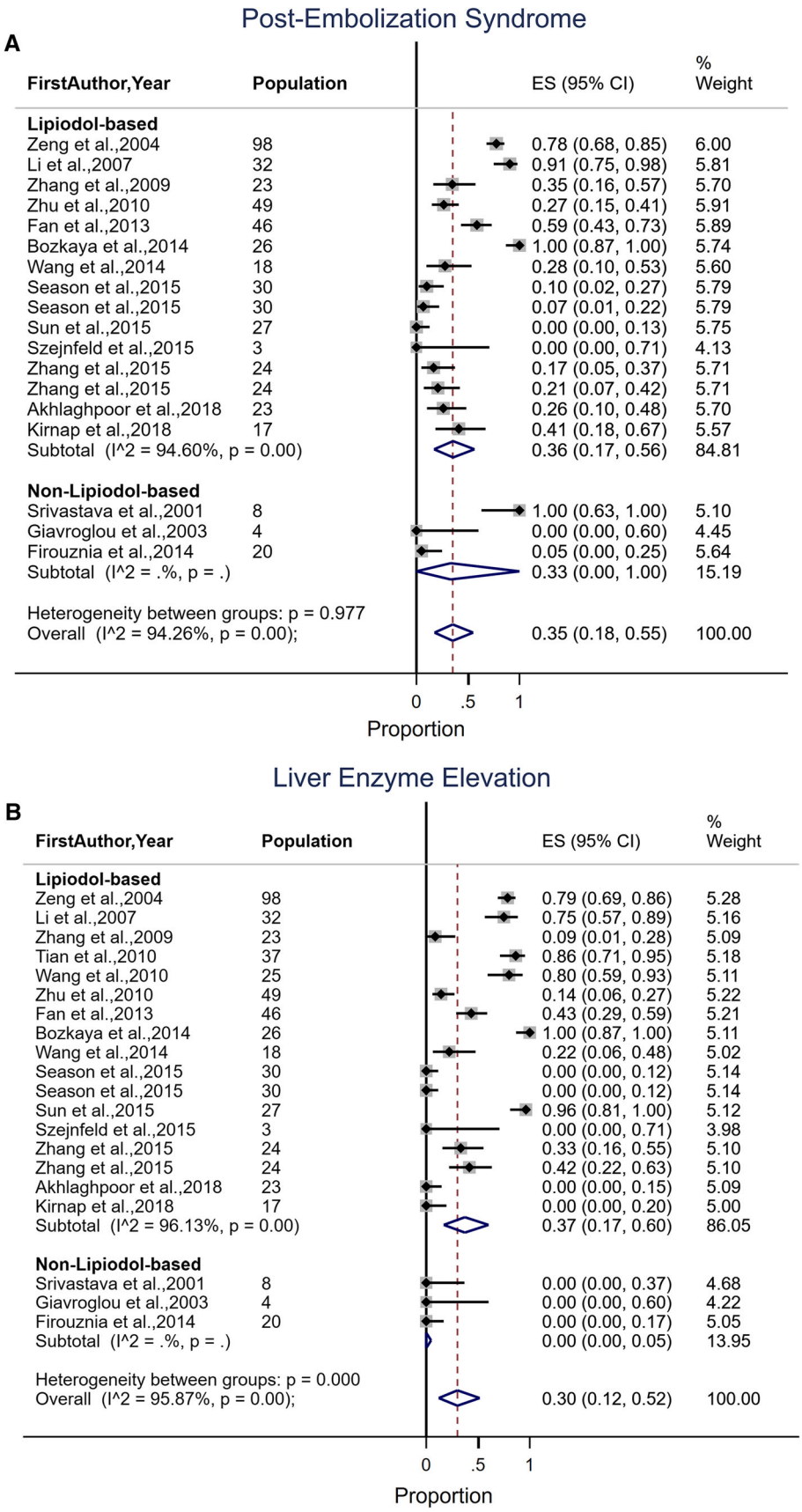

Fig. 6 Forest plot summarizing reported complications including post-embolization syndrome (**A**) and hepatic enzymes elevation (**B**) after transarterial embolization of hepatic hemangiomas

Additionally, transarterial embolization with PVA did not show significant effect in decreasing the hemangioma size.

Management of giant hepatic hemangiomas with transarterial embolization has not been well defined and no general agreement exists on treatment indications and selection of chemotherapeutic emulsion.

Although surgical resection or enucleation is the accepted treatment modality for large symptomatic or enlarging hepatic hemangiomas in some centers [27, 42], complications associated with surgery prohibit considering these techniques as the first line treatments. These complications include 0.5–2% mortality rate [16], massive blood loss, protracted length of hospital stay and moderate to severe perioperative complications such as hepatic insufficiency, bile leakage and wound infection [16, 32]. Recently, laparoscopic resection followed by cool-tip cluster radio frequency (RF) ablation of hepatic hemangiomas showed low intraoperative blood loss, less pain and insignificant rates of complications [53]. However, this technique also remains in a point of controversy due to the complexity of technique, and associated potential complications including kidney dysfunction, acute respiratory distress syndrome and about 40% technical failure rate in ablating hemangiomas with the maximal diameter > 10 cm [10, 11, 28, 45].

Transarterial embolization of hepatic hemangiomas was reported for the first time by Yamamoto et al. [46].

Embolization with polyvinyl alcohol particles (PVA) or a combination of Lipiodol (as the drug-delivery agent) with bleomycin, pingyangmycin or ethanol has been shown to have intrahepatic arterial sclerosant effects [13, 26].

Pingyangmycin (also known as bleomycin A5 hydrochloride) is a member of the bleomycin family. It was extracted from soil in China in 1969 and was approved for clinical use by the Chinese Food and Drug Administration in 1978 [14]. Although pingyangmycin has been associated with lower rates of lung injury compared to bleomycin [54], it has been shown to expedite apoptosis and cause irreparable defects to the vascular endothelium [47], endothelial cell necrosis [25] and fibroblast hyperplasia by similar cellular signaling pathways as bleomycin such as increasing the caspase-3 activity, inducing p53 pathway and inhibiting telomerase activity [17], and proapoptotic effects for sclerotherapy and obliteration of vascular lumen and destruction of the endothelial cells through activation of mTOR pathway and suppression of bcl-2 in venous malformations and hemangiomas [51].

Pooled analysis results in this study did not show significant difference in the effectiveness of the combination of L + BE with that of L + PYG based on changes in hemangioma diameters. Therefore, since pingyangmycin is not approved by the Food and Drug Administrations (FDA) of Western countries, L + bleomycin seems to be an equivalent embolic material for patients in these regions.

Pulmonary fibrosis through destroying the alveolar capillaries [19] is one of the most dreaded complications of bleomycin and pingyangmycin [17, 29, 48]. Among the studies included in this meta-analysis, pulmonary fibrosis with bleomycin was not reported mainly due to the fact that maximum administered dose did not exceed the maximum safe dose of 450 mg [2]. Furthermore, the maximum administered dose of PYG (40 mg) in selected studies was much lower than the toxic dose [17].

Embolization with PVA can provide permanent embolic effect by adhering to the vascular wall and inducing inflammatory cascade reaction and angionecrosis [41]. However, embolization with PVA particles alone did not show significant pooled effect on hemangioma size in this meta-analysis. The irregular shape of the PVA particles promotes their aggregation. This can be problematic when they lodge in proximal branches and as a result lead to incomplete embolization or promoting collateral circulation of the distal embolization target triggering the need for re-embolization. The possibility of incomplete embolization increases with using bigger particle sizes [41]. Although the studies in this meta-analysis used 150–400 μ particles, it seems that smaller particles might be needed for this procedure to decrease chance of incomplete embolization.

Significantly higher effectiveness in shrinking hemangioma diameters with Lipiodol-based agents compared with non-Lipiodol-based PVA suggests that proper results by transarterial embolization can be achieved by using chemical agents accompanied by Lipiodol as a drug-delivery system to initiate and bolster a destruction process. Emulsifying sclerosant agents in Lipiodol helps carry them into the smaller diameter vessels through drug-carrying and microembolic characteristics of Lipiodol [31]. Also, its entrapment in the microvascular spaces causes flow stagnation optimizing sclerosing agents effectiveness [35]. Additionally, radiopaque properties of Lipiodol help visualize intra-procedural flow status as well as monitor hemangioma size changes on post-procedure follow-up. Despite the expectation that the embolized lesions will shrink over time after embolization progressively, in our analysis there was a weak evidence that lesion diameter change is associated with follow-up time. This might signal that the initial decrease in lesion size during first year after transarterial embolization remains stable over the course of several years. This finding however, should be interpreted with caution since there are several limitations into this observation. The limitations including large heterogeneity in follow-up time with most of the studies having less than 1 year follow-up and only one study having about 4 years follow-up, small weight of most of the studies in the meta-

regression due to their high standard error in their reported lesion diameter changes and low sample size, and lower power of meta-regression analysis in general [15].

As far as general limitations of the study, available studies lack comparison with a control group (other treatment modality). Additionally, the studies have been reported from a limited number of geographical regions likely due to skepticism around serious clinical sequelae of hepatic hemangiomas (pain or rupture) and effectiveness of embolization in decreasing lesion size. Therefore, further studies with larger samples sizes, a control group and longer duration of follow-up will help improve quality of evidence.

Conclusion

Transarterial embolization with bleomycin/Lipiodol, pingyangmycin/Lipiodol or ethanol/Lipiodol is safe and effective in decreasing lesion size and resolution of symptoms in large hepatic hemangiomas. Lipiodol-based embolization demonstrated higher effectiveness compared to non-Lipiodol-based embolization. Further studies with larger sample sizes, comparison group and longer follow-up durations are needed to improve quality of evidence.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, consent for publication is not required.

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