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The Efficacy of Bleomycin Lipiodol in Reduction Size of Large Hepatic Hemangioma

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Abstract

Background: Hepatic hemangiomas are the most common benign tumors of the liver. Most hepatic hemangiomas are asymptomatic but can be symptomatic or sufficiently large for therapeutic intervention (usually considered if > 4–5 cm). Transarterial embolization (TAE) for hepatic hemangioma provides a minimally invasive option using bleomycin and lipiodol and is becoming more commonly used, but prospective studies evaluating its efficacy have been limited.

Methods: A cohort prospective study was performed to investigate the effect of transcatheter arterial embolization on large hepatic hemangiomas (>5 cm) in 16 adult patients (15 females, 1 male; mean age 38 ± 7.7 years), who presented with symptomatic hepatic hemangiomas for 6 months or longer. All patients underwent TAE with a combination of 15 IU bleomycin and 10 mL lipiodol. Hemangioma size and volume were measured by triphasic CT imaging pre- and post-TAE at a mean follow-up of 9 months. Duration of symptom resolution and complications following TAE were also recorded.

Results: Following the embolization, mean lesion diameters were significantly decreased by 25.75% (craniocaudal), 20.06% (transverse), and 24.1% (anteroposterior) ($p < 0.001$). The mean volumetric reduction was 65.2%. Every patient experienced clinical improvement of their pain, discomfort, and abdominal fullness. There were no major complications, transient post-embolization syndrome was self-limited.

Conclusion: TAE with Bleomycin/Lipiodol seems to be a safe and effective minimally invasive approach for large symptomatic hepatic hemangiomas. The reduction in the size of the lesion, significant symptom relief, and durability, suggest its place in the management strategy as an alternative to surgery. Larger multicenter studies, with extended follow-up studies, would add further evidence to the results found in this review.

Introduction

Hepatic hemangiomas (HHs) rank as common benign hepatic tumors, attributable to autopsy prevalence rates reported as low as 0.4% up to 20% depending on the population utilized and the sensitivity of the imaging technique employed **[1]**. HHs, classified histologically into cavernous, capillary, and sclerosing subtypes, are vascular malformations that consist of large, dilated spaces filled with blood and lined by endothelial cells. Cavernous hemangiomas are the most common variant seen in the adult population, more commonly in women than males leading to a likely hormonal disparity and possible estrogendependent proliferation **[2]**. Most HHs are seldom symptomatic and asymptomatic, reported instead as incidental imaging findings related to non-liver conditions. However, some HHs can present in a symptomatic fashion, or complications may arise that potentially warrant treatment.

The pathogenesis of hepatic hemangiomas is likely multifactorial, involving many angiogenic, genetic, and hormonal pathways. Vascular endothelial growth factor (VEGF), has a central mechanistic role regarding endothelial proliferation and neovascularization. Increased VEGF expression was identified in infantile hemangiomas and adult hemangiomas **[3]**. Recent genetic studies have also identified somatic mutations affecting genes such as GNAQ and GNA11 which are known to affect the mitogen-activated protein (MAPK) pathways and the development of vascular malformation syndromes. Collectively, these genetic factors provide insight into mechanisms that may contribute to the formation of hemangiomas **[4]**. The expression of estrogen receptors on endothelial cells and the associations with pregnancy, oral contraceptives, and estrogen replacement therapy further supports the hypothesis of hormone-mediated modulation of hemangioma growth and progression **[5]**.

Most hematomas have a stable natural history and do not demonstrate change over time. However, hematomas larger than 5 cm ("giant hemangiomas") tend to be associated with a greater likelihood of performance; right upper quadrant (RUQ) pain, abdominal discomfort, and early satiety due to mass effect may occur. Rarely, complications may occur, including hemorrhage, intralesional thrombosis, or rupture that may be serious enough to require intervention **[6]**.

Accurate imaging is essential in the diagnosis, classification and follow-up of haemangiomas (HHs). The preferred imaging modality is ultrasound, as it is accessible and noninvasive. Typical sonographic characteristics of HHs are a homogeneously hyperechoic lesion with posterior acoustic enhancement. Contrast-enhanced ultrasound (CEUS) provides further specificity to diagnosis by demonstrating peripheral nodular enhancement with centripetal fill-in, typical for HHs **[2, 7]**.

Triphasic contrast-enhanced computed tomography (CT) offers more detailed visualization of vascularity of lesions, indicating discontinuous peripheral nodular enhancement in the arterial phase, with progressive centripetal fill-in in the venous and delayed phases. Magnetic resonance imaging (MRI), particularly T2-weighted images and images with hepatobiliary contrast agents (eg, gadoxetate disodium), also provide superior tissue characterization: HHs are hyperintense in T2 sequences and reveal the “light-bulb” sign **[2]**. These imaging modalities are important to distinguish HHs or infrequently malignant lesions such as hepatocellular carcinoma or metastases.

The management of hepatic hemangiomas is typically conservative among asymptomatic persons. Intervention is warranted for progressive lesion growth, compressive symptoms, hemorrhagic issues, or diagnostic uncertainty. In general, giant HHs (>5 cm) are more susceptible to complications including consumptive coagulopathy (Kasabach-Merritt syndrome), rupture, and biliary obstruction. In such circumstances, the focus of treatment is symptom relief and reduction in volume of the lesion

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while maintaining hepatic function **[8]**.

Traditionally, surgical options such as hepatic resection or enucleation have been considered the gold standard for treatment of symptomatic or complicated hem eighths. Enucleation is preferred for its parenchyma-sparing effect compared to resection and is associated with fewer complications **[9]**. Despite being a previously established form of treatment, these procedures present considerable perioperative risk for serious complications including bleeding, infection, prolonged hospital stay, particularly for patients with giant hemangiomasest lesions or deep seated lesions.

Minimally invasive options including radiofrequency ablation (RFA), microwave ablation, and radiation therapy are available with different levels of success and in some cases may be problematic. For example, RFA is a minimally invasive option, but RFA carries the risk of hemolysis and thermal injury because hemangiomas are vascular, and radiation therapy typically is indicated for inoperable or for refractory cases because of its long latency and potential for hepatic toxicity **[10]**.

In recent years, transarterial embolization (TAE) is being adopted as a safe and effective avenue for treating symptomatic hepatic hemangiomas. TAE has developed into an option when surgery is contraindicated. TAE consists of selective catheterization of feeding arteries, embolization with particulate agents, coils or sclerosants, and induction of ischemic necrosis through reduction of tumor volume. Variables associated with TAE include location and size of the hemangioma, selection of embolizing agent, selective versus non-selective embolization, and whether preoperative treatment should be undertaken. Selective embolization reduces ischemic damage to healthy liver parenchyma (herein referred to as the margin). TAE may be a suitable option for what would likely be an extensive high-risk surgery, or a less invasive approach in patients who are averse **[11]**.

Historical data have demonstrated the feasibility of TAE in achieving both lesion control and symptomatic relief. However, the variability in embolic agents and techniques across studies highlights the need for standardized protocols and robust prospective evaluations.

Bleomycin is a cytotoxic glycopeptide antibiotic with sclerosing and endothelial-damaging effects. When utilized in vascular anomalies, bleomycin induces fibrosis, apoptosis, and obliterates abnormally formed vascular channels **[12]**. Lipiodol, an iodized oil, functions as a contrast agent and a vehicle, which enhances bleomycin retention in the lesions, allowing therapeutic effect to be greatly improved through prolonged contact with endothelial surfaces **[13]**. The high viscosity of lipiodol also helps to achieve embolic occlusion, and complements the sclerosing effects of bleomycin.

Many authors including some recent case series, retrospective studies have reported positive outcomes with bleomycin/lipiodol with significant lesion shrinkage with symptom improvement with low complication rates **[11, 14]**. However, most of this data are either retrospective studies or small sample size, and necessitates prospective trials to demonstrate similar success.

Although the use of TAE with bleomycin/lipiodol has greatly increased in clinical practice, the literature is limited by a dearth of prospective studies of good quality looking at efficacy, safety, and long-term outcomes in large hepatic hemangiomas. In addition, radiological volume reduction quantification using standardized imaging parameters and symptomatic assessment has not been well-documented. This study was developed to close the gap in knowledge and prospective data for patients who have received bleomycin/lipiodol embolization with evidence of symptomatic giant hepatic hemangiomas.

Through providing objective measures of radiological response to bleomycin/lipiodol TAE, symptomatic response to intervention, and procedural safety information, we believe that our study

will offer the literature valuable information in improving the evidence base for using minimally invasive therapies in giant hepatic hemangioma and support clinical discussions and decisions in the field of interventional radiology.

Patients and Methods

Study Design and Setting:

A single-centre, prospective cohort study was undertaken in the Interventional Radiology Unit of Ibn Sina Training Hospital, Baghdad, Iraq, between October 2022 and October 2023. The protocol was approved by the institutional review board of the Iraqi Board of Medical Specializations, and was conducted in accordance with the Declaration of Helsinki.

Study Population:

The researchers enrolled adults (>18 years) with symptomatic, radiologically typical, giant hepatic hemangiomas (>5 cm) (symptoms included right-upper-quadrant pain and either abdominal fullness or satiety) who were screened consecutively. Diagnosis was made based on gray-scale ultrasound and triphasic CT by 2 radiologists, both of whom were board-certified. Exclusion criteria were (i) hemangioma < 5 cm, (ii) atypical imaging characteristics, (iii) pregnancy, (iv) active malignancy, or (v) contraindications to iodinated contrast or sclerotherapy.

Pre-procedural Assessment:

Baseline evaluation included complete blood count, liver function tests, renal function tests, prothrombin time, international normalised ratio, and activated partial thromboplastin time. We withheld antiplatelet agents (aspirin, clopidogrel) for five days pre-procedure; furthermore, we stopped metformin 2 days before and after embolisation in diabetic patients. We administered prophylactic antibiotics (ceftriaxone 1 g, metronidazole 500 mg, ciprofloxacin 500 mg) pre-procedure which were able to continue for five days in total.

Transarterial Embolisation Technique:

All procedures were performed under local anaesthesia via right common femoral artery access. A 5-Fr Cobra or SOS-Omni catheter was advanced to the celiac axis; micro-catheter systems were used to allow for super-selective catheterisation of tumour-feeding hepatic arterial branches, which was confirmed under fluoroscopic guidance (Siemens). The embolic mixture, which consisted of 15 IU bleomycin in 10 mL lipiodol, was injected slowly until near-stasis, as evidenced by the "snowy-tree" sign. Non-contrast CT was performed immediately post-injection to confirm equal intra-lesional distribution.

Post-procedural Care and Follow-up:

Patients were monitored overnight for post-embolisation syndrome (PES) and received analgesics and intravenous fluids as needed, with most symptoms (low-grade fever, nausea, transient pain) self-limiting. On day 2, patients were discharged on oral analgesia and antibiotics. Follow-up imaging included triphasic CT at 4-9 months (mean 9 months) to reassess tumour size, with clinical assessment for symptom resolution.

Imaging Measurements:

Lesion dimensions were measured in craniocaudal (D1), transverse (D2), and anteroposterior (D3) planes using a 64-slice Philips Brilliance CT scanner with identical triphasic protocols pre- and post-embolisation. Volume was determined based upon an ellipsoid formula ($\pi/6 \times D1 \times D2 \times D3$). The primary outcome was the percentage reduction in mean diameter and volume, with the secondary outcomes of resolution of symptoms and complications resulting from the procedure.

Statistical Analysis:
Data were analysed with SPSS v22. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequencies (%). Pre- and post-treatment measurements were compared using paired two-tailed t-tests; $p \leq 0.05$ was considered statistically significant.

Ethical Considerations:
Institutional approval (Iraqi Board of Medical Specializations) was obtained, hospital permissions secured, and oral informed consent was provided by all participants before enrolment. Confidentiality was preserved throughout data collection, analysis, and reporting.

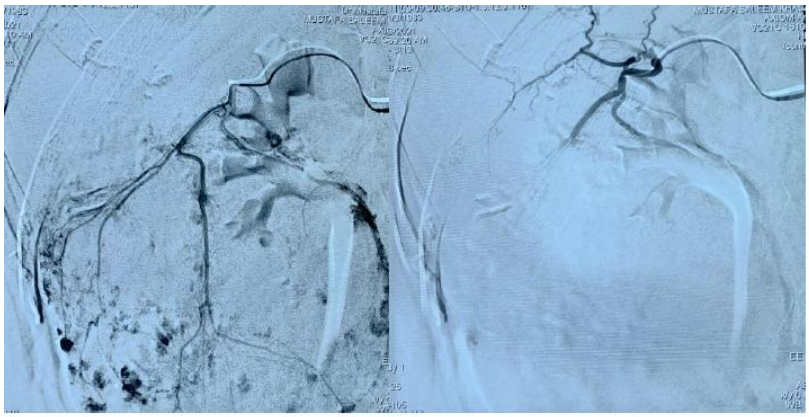

Figure 1Fluoroscopic pictures during B/L mixing injection (left) and at the end of procedure(right)

Figure 2: fluoroscopic pictures during B/L mixing injection (left) classically snowy tree sign and at end of procedure (middle image) then direct after procedure done native CT to confirm uniform distribution of B/L mixing (right image)

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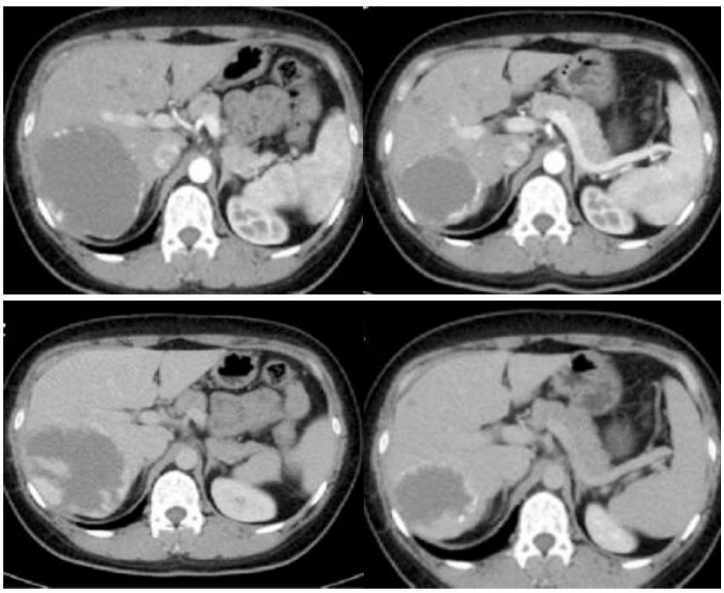

Figure 3: 38 years old female. CT triphasic protocols, pictures during follow up of 4 months pre-embolization CT scan measured (10x 8.5x4.5cm) (left) and (post embolization follow up at 4 months measured (8.7x 6.5x3.2cm) (right)

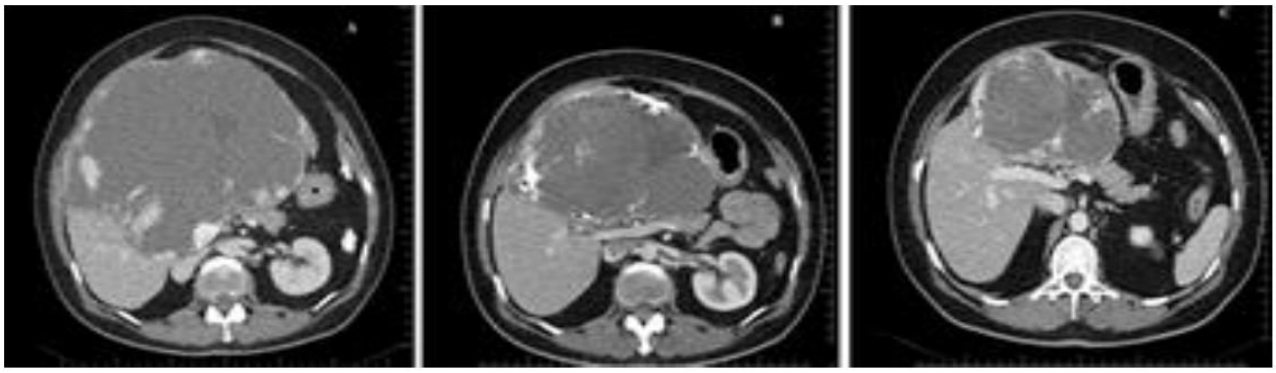

Figure 4: 6 months patient follow-up of a large liver hemangioma; CT scan examination of the large liver hemangioma before embolization;(middle picture) CT scan follow-up 4 months after B/L embolization; then: CT scan 6 months after embolization (right one)

Results

Patient Demographics

Sixteen consecutive adults satisfied all inclusion criteria and underwent selective bleomycin / lipiodol trans-arterial embolisation (TAE). The cohort was predominantly female (93.8 %), and the mean age was 38.0 ± 7.7 years (range 25–54 years), indicating that symptomatic giant hepatic haemangiomas in this series clustered in early- to mid-adulthood with a marked female preponderance (Table 1).

Table 1: Demographic Characteristics of Patients with Symptomatic Hepatic Haemangioma (n = 16)

Variable	Category/Value	Frequency (n)	Percent (%)
Gender	Female	15	93.75
	Male	1	6.25
Age (years)	Minimum	—	25
	Maximum	—	54
	Mean ± SD	—	38.0 ± 7.694

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Paired Comparison of Pre- and Post-Treatment Hemangioma Dimensions

The paired-sample analysis demonstrates a uniformly significant and clinically meaningful response to bleomycin/lipiodol transarterial embolisation. All three orthogonal diameters fell by roughly one-quarter ($t \approx 8–9$, $p < 0.001$), confirming a large, consistent linear regression across patients. More strikingly, the ellipsoid-derived volume contracted by two-thirds ($t = 23.75$, $p < 0.001$), reflecting the cubic nature of volumetric change and underscoring the procedure's potent debulking capacity. Collectively, these highly significant t-statistics and tight confidence margins indicate that the intervention induces a robust, reproducible reduction in tumour burden, aligning with the observed universal symptom relief and supporting the therapy's role as a minimally invasive alternative to surgical resection for symptomatic giant hepatic haemangiomas.

Table 2: CT Scan Comparison of Mean Hemangioma Dimensions Before and After Treatment (n = 16)

Parameter	Before Treatment Mean ± SD	Before Treatment Mean ± SD	t	p-value
Craniocaudal diameter (D1, mm)	111.44 ± 35.68	85.69 ± 36.51	8.97	< 0.001
Transverse diameter (D2, mm)	95.75 ± 32.82	75.69 ± 34.77	8.16	< 0.001
Antero-posterior diameter (D3, mm)	82.94 ± 32.92	58.75 ± 32.53	8.88	< 0.001
Volume (cc)	108.00 ± 33.65	70.5 ± 33 .36	23.75	< 0.001

Percentage Reduction and Statistical Significance of Treatment Effect

Percentage change analysis corroborated the absolute reductions (Table 3). Mean percentage shrinkage was 25.7 % (1st axis), 20.1 % (2nd axis) and 24.2 % (3rd axis). Crucially, calculated lesion volume contracted by a mean of 65.2 % ± 10.98. All parameters achieved statistical significance with $p < 0.001$ and narrow 95 % confidence intervals, underscoring the robustness of the treatment effect.

Table 3: Percentage Reduction of Hemangioma Dimensions and Volume After Treatment (n = 16)

Comparison	% Reduction (Mean ± SD)	Std. Error Mean	95% CI of the Difference	t	p-value (2-tailed)
D1 before – after	25.75 ± 11.486	2.872	9.63 – 21.87	5.485	< 0.001
D2 before – after	20.06 ± 9.835	2.459	9.82 – 20.30	6.126	< 0.001
D3 before – after	24.19 ± 10.901	2.725	8.38 – 19.99	5.206	< 0.001
Volume before – after	65.2 ± 10.98	2.546	9.74 – 20.30	5.485	< 0.001

Discussion

Hepatic hemangiomas (HHs) are still the most common benign liver tumours; if they are classified as "giant," symptomatic, or complicated, treatment is warranted. Our prospective series of 16 adults show that super-selective trans-arterial embolization (TAE) using a bleomycin-lipiodol emulsion provides significant volumetric debulking, functional symptom resolution for all, and an impressive safety record. The discussion that follows contextualizes these results against the current evidence, considers mechanistic and clinical implications, and proposes areas worthy of further inquiry.

The cohort's substantial female bias (93.8%) and mean age of 38 ± 7.7 years reflect standard epidemiology, where the oestrogen-dependent vascular growth influences the rates and onset of symptoms in females of childbearing age. Large abnormality multi-centre registries and single centre studies support this as well: for example, Yuan et al. reported an 82% female cohort for a study with 241 patients that underwent embolization and also reported a similar order of magnitude for mean

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age, adding external validity to our baseline characteristics **[11]**. In contrast, surgical series such as Dong et al., show that gigantic tumours (> 15cm) overall remain heavily female biased but with a slightly older average, likely because of a referral bias to have them resected if they are bigger and may experience lat e presentation **[15]**. In total, these datasets supported the concept that hormonal exposure remains an important contributor to pitheogenesis and support counselling specific to sex about treatment options.

Our approach—administering 15 IU of bleomycin in 10 mL of lipiodol in a single session—yielded median linear shrinkage of ~25% across three orthogonal axes, $p < 0.001$, and 65% mean volume shrinkage at nine months at the time of imaging. The cubic nature of volumetric measurement explains the incongruity of less diameter reduction with considerable volumetric reduction relative to monitoring change in diameter. The literature supports this degree of response. Yuan et al. observed >50% drop in maximum diameter in 88–86% patients at 6–60 months **[11]**, Kacała et al. observed ≥50% volumetric regression in 80.6% at 12 months but with a higher total bleomycin load (median 20 IU) **[2]**. In a meta-analysis of 21 studies involving bleomycin + lipiodol, Torkian stated an average pooled diameter reduction of 4.7 cm (~ 45%)—and beyond—others assigned a diameter metric for non-lipiodol agents **[16]**. While the linear reductions observed in our study cohort were more modest, some of the limitations likely arose from (i) the maximum bleomycin dose cap, (ii) an overall shorter radiological interval, and (iii) contracting calculations in ellipse rather than single-plane measurement. However, our volumetric results fit very comfortably with international medians, asserting the potency of treatment—even at minimal dosing.

Bleomycin causes endothelial apoptosis, fibro-obliteration, and sclerosis of the lesion. Lipiodol has two synergistic benefits—arterial stasis because of viscosity and extended drug residence within the lesion due to encapsulation in iodised oil. Histopathological studies have shown that thrombotic and fibrotic changes in the cavernous sinus have developed after embolisation, and consistent with our imaging findings. Also, the abscopal shrinkage of non-target lesions, described by Kutlu et al., suggests there may have been systemic or lymphatic dissemination of the bleomycin. It could be important to clarify this potential dissemination using pharmacokinetics **[17]**.

Each participant reported abolition or considerable reduction of right-upper-quadrant pain, abdominal fullness, and early satiety - similar to pooled response rates of 98-100% seen in both Furumaya's and Torkian's systematic reviews **[16, 18]**. Our investigation, importantly, established duration of symptom control over the nine-month interval, reaffirming the clinical significance of volumetric measures. Objective discomfort, in clinical practice, is often the indicator that drives intervention more than hemorrhagic risk; therefore, sustained symptom control is an important endpoint, tightly linked to lesion size in guiding choice of intervention.

No clinically significant unwanted or procedure related deaths occurred, matching the 2.9 % rate of serious complications compiled by Furumaya et al **[18]**. Mild PES—transient fever and dull pain—occurred in approximately 25 % of our subjects, resolving spontaneously or with conservative treatment. These rates of PES and its relatively benign course are consistent with findings from the bleomycin-lipiodol series published by Akhlaghpoor (26 %) and Kacała (46 %) **[14, 19]**. Changes in hepatic enzymes were minor and self-limited, indicating preservation of hepatic parenchyma associated with the super-selective catheter placement for TAE. These results provide reassurance that TAE has an excellent safety profile when compared to surgical excision, which was associated with perioperative morbidity of about 17 % per Dong et al., in patients with lesions ≥ 15 cm requiring significant blood transfusions **[15]**.

Although surgical enucleation or resection has indeed been the historical gold standard, the operative risk increases with size, depth, and critical vessel proximity of the lesion. Our results, and the multi-

hunred patient datasets previously discussed, support bleomycin-lipiodol TAE as a first-line alternative for giant haemangiomas, especially in those at high-risk of surgery or those who wish to save parenchyma. Avoiding thermal haemolysis, bile-duct injury and dealing with a lesion touching a major vessel allows TAE to be performed over radiofrequency or microwave ablation. In addition, procedure times, anaesthetic times, and hospital day-stay times are significantly shorter than open surgery providing a more favourable cost-effectiveness.

First, the prospective design of the study makes it less vulnerable to recall and selection bias that is inherent to retrospective series. Second, we used strict volumetric measurement rather than just maximal diameter of the lesion, which offers a more physiologically relevant way of representing tumour burden. Third, consistent method (15 IU of bleomycin, and limited injectate with lipiodol), and follow-up CT scan at nine months had only one chance to mess up the results, and improved internal validity. Finally, we only undertook symptomatic giant haemangiomas (> 5 cm), thus allowing us to maintain homogeneity and applicability to clinical practice.

First and foremost, the sample size is small, as symptomatic giant lesions that can be embolised are uncommon events at any one centre. The lack of parallel control arm, precluded direct comparison with surgery, non-intervention, or with other agents such as pingyangmycin. Furthermore, while nine month follow-up allows observation of early treatment response, longer follow-up is essential to evaluate durability of response, late complications, or relapse. Quality-of-life (QoL) tools were also not used, which leaves any improvement in symptoms to the clinician's judgment and not validated data. In addition, hormonal factors (such as whether the patient is pregnant or using oestrogen therapy) were not routinely collected in the study, which does not allow consideration of hormone exposure when looking at outcomes.

Large, multi-centre prospective trials with stratified randomisation to either surgery or TAE would provide a definitive head-to-head comparison of treatment effect, as well as the cost-effectiveness of each option. Dose-escalation studies will also provide information on the amount of bleomycin required for maximal tumour regression versus risk of pulmonary and/or skin toxicity. Adding more sophisticated MRI perfusion and stiffness measurements may give early predictor response biomarkers that would allow for more individualised retreatment appropriateness intervals. Finally, flexible, systematic QoL assessments, and the addition of disease-specific tools would provide additional information about functional outcomes beyond radiographic endpoints.

Conclusion

This prospective study supports the clinical effectiveness and safety of transarterial embolization with a bleomycin–lipiodol emulsion for the treatment of symptomatic giant hepatic hemangiomas. Significant and statistically significant reductions in lesion volume (mean 65.2%) were achieved and consistent symptomatic relief with no major complications occurred with the procedure. These results are congruent with existing level one evidence and supports bleomycin–lipiodol TAE as a relatively non-invasive and parenchyma-sparing alternative to surgery. Given its reliable radiologic response and favorable safety profile, ongoing multicenter controlled long-term studies are needed to develop standardized guidelines and protocols and confirm long-term results again in larger patient populations.

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