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ORIGINAL ARTICLE

Comparative Efficacy of High-Dose versus Low-Dose Bleomycin–Lipiodol Transarterial Chemoembolization in Adult Hepatic Hemangiomas: A Retrospective Cohort Analysis

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ABSTRACT

Background: Hepatic hemangiomas are the most common benign liver tumors and are usually detected incidentally; however, symptomatic or large lesions often require intervention. Surgical resection, while effective, is associated with substantial morbidity, prompting increasing use of minimally invasive therapies such as transarterial chemoembolization (TACE) with bleomycin.

Objective: To compare hemangioma response patterns reported in previous low-dose bleomycin interventions with outcomes observed in a cohort treated with high-dose (45 IU) transarterial bleomycin–Lipiodol TACE.

Methodology: This retrospective cohort study was conducted in 31 adult patients with hepatic hemangiomas at Pakistan Kidney and Liver Institute and Research Centre - PKLI, Lahore from January 2022 to December 2022. Hemangioma response was evaluated following single-session or limited-session transarterial chemoembolization using a cumulative bleomycin dose of 45 IU emulsified with Lipiodol. Radiological assessment was performed using contrast-enhanced CT or MRI, with standardized three-dimensional volumetric measurements.

Results: Technical success was achieved in all patients, with satisfactory intralesional Lipiodol deposition observed in 74%. No patient developed post-embolization syndrome. Only one patient (3%) developed a liver abscess, which was managed conservatively. Follow-up imaging was available for 26 patients, demonstrating a mean volumetric reduction of 71.4%. Clinical success (≥50% lesion regression) was achieved in 88% of patients, with 50% exhibiting ≥80% volumetric regression after a single treatment session. Only two patients (6%) required repeat embolization.

Conclusion: Compared with previously reported low-dose protocols, high-dose bleomycin–Lipiodol TACE demonstrated superior single-session efficacy, a markedly reduced need for repeat interventions, shorter hospitalization, and an excellent safety profile. These findings support high-dose TACE as a safe, effective, and durable minimally invasive treatment option for hepatic hemangiomas.

Keywords: Hepatic hemangioma; Bleomycin–Lipiodol; Transarterial chemoembolization; High-dose bleomycin; Radiological outcomes; Minimally invasive therapy

INTRODUCTION

Hepatic hemangiomas represent the most common benign tumors of the liver, with a prevalence ranging from 0.4% to 20% in the general population, often identified incidentally during imaging studies.[1,2] While most hemangiomas remain asymptomatic and require no intervention, large or symptomatic lesions can lead to abdominal discomfort, early satiety, or complications such as Kasabach-Merritt syndrome, necessitating therapeutic intervention.[3,4] Traditionally, surgical resection or enucleation was considered the definitive treatment; however, these procedures are associated with significant morbidity, risk of blood loss, and prolonged hospitalization.[5] Over the past two decades, minimally invasive strategies, including transarterial embolization and pharmacological therapy with agents such as corticosteroids, interferon-alpha, and bleomycin, have emerged as viable alternatives to surgery.

Bleomycin, a cytotoxic antibiotic with sclerosing properties, has been widely employed in the treatment of both cutaneous and visceral hemangiomas, administered via intralesional injection or transarterial routes.[6,7] Its mechanism of action involves endothelial damage, induction of apoptosis in proliferating vascular endothelial cells, and subsequent fibrosis, leading to lesion regression. Previous studies have predominantly utilized low-dose bleomycin (10–15 IU) delivered through super selective transarterial embolization, intralesional injection, or a combination approach, demonstrating clinical success rates of 70–80%, often necessitating multiple treatment sessions. While effective, these low-dose protocols are associated with variable volumetric regression, incomplete intralesional drug distribution, and a notable incidence of post-embolization syndrome, including pain, fever, and transient liver enzyme elevation.

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Recent advancements in interventional radiology have allowed for the safe escalation of bleomycin doses and refinement of transarterial chemoembolization (TACE) techniques, particularly the combination of bleomycin with Lipiodol as an embolic carrier.[8] Lipiodol, an iodized oil, enhances intralesional drug deposition, prolongs local retention, and facilitates radiological visualization, enabling more precise assessment of treatment coverage and efficacy.[9] High-dose bleomycin–Lipiodol TACE protocols have been explored in small adult cohorts, suggesting improved single-session efficacy, higher volumetric reduction, and reduced need for repeat interventions, while maintaining an acceptable safety profile. Nevertheless, heterogeneity in study designs, dosing regimens, and imaging follow-up criteria has limited direct comparison across studies, underscoring the need for systematic evaluation of response patterns relative to historical low-dose protocols.

In clinical practice, radiological response is typically measured as the percentage reduction in lesion volume on follow-up imaging, using either contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).[10] Clinical success is conventionally defined as ≥50% lesion regression, often accompanied by symptomatic improvement such as reduction in abdominal pain or discomfort. While pediatric and non-hepatic hemangioma studies frequently focus on time to complete resolution or cure rates, adult hepatic hemangioma research emphasizes durable volumetric regression and minimization of procedural morbidity. Standardization of response assessment, including volumetric measurements and uniform reporting of Lipiodol deposition, is essential for meaningful comparison of therapeutic outcomes.

Given these considerations, the present study was designed to compare hemangioma response patterns reported in previous low-dose bleomycin interventions with outcomes observed in a cohort treated with high-dose (45 IU) transarterial bleomycin–Lipiodol TACE. By evaluating both radiological and clinical

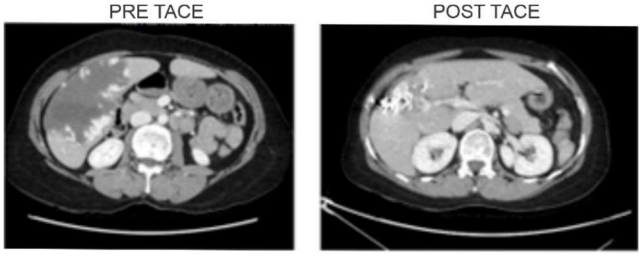
outcomes, including volumetric regression, distribution of embolic agent, and the need for repeat procedures, this study aims to provide comprehensive evidence regarding the efficacy and safety of high-dose TACE for hepatic hemangiomas, while harmonizing response criteria with historical literature. This approach enables clinicians and researchers to contextualize high-dose protocols within the broader therapeutic landscape, offering insights into optimization of minimally invasive strategies for managing symptomatic hepatic hemangiomas.

MATERIAL & METHODS

This study was conducted at Pakistan Kidney and Liver Institute and Research Centre - PKLI, Lahore from January 2022 to December 2022 and designed to compare hemangioma response patterns reported in previous bleomycin-based interventions with those observed in a cohort treated using high-dose (45 IU) transarterial bleomycin–lipiodol chemoembolization. The primary objective was to evaluate radiological and clinical response as well as durability of treatment effect, rather than performing direct statistical pooling, due to heterogeneity among published studies in terms of bleomycin dosage, embolization techniques, and follow-up protocols. Prior studies predominantly assessed treatment response through reduction in lesion size or volume on follow-up imaging after administration of low-dose bleomycin (10–15 IU) via super selective transarterial, intralesional, or combined approaches. Clinical success in these reports was commonly defined as a ≥50% reduction in lesion volume, accompanied by improvement in symptoms such as abdominal pain, distension, or early satiety. Follow-up imaging generally ranged from six to twelve months, and multiple treatment sessions were frequently required to achieve optimal lesion regression.

In the present cohort, hemangioma response was evaluated following single-session or limited-session transarterial chemoembolization using a cumulative bleomycin dose of 45 IU emulsified with Lipiodol. Radiological assessment was performed using contrast-enhanced CT or MRI, with standardized three-dimensional volumetric measurements. Clinical success was defined in alignment with prior hepatic hemangioma studies as a ≥50% reduction in lesion volume; however, additional parameters including the extent of volumetric regression, uniformity of intralesional Lipiodol distribution, and reduction in the requirement for repeat embolization were also considered. In patients with multiple hemangiomas, lesion-wise analysis was performed to avoid underestimation of treatment effect. Follow-up imaging was conducted between one and twelve months to evaluate early and intermediate treatment responses.

Safety outcomes were prospectively assessed, with specific attention to post-embolization syndrome and procedure-related complications. Notably, no patient developed post-embolization syndrome in the present cohort. Only one patient developed a liver abscess**,** which was managed conservatively, and no treatment-related mortality was observed. These safety findings were incorporated into the overall evaluation of treatment tolerability.



To enable meaningful comparison with previous studies, response criteria were harmonized by considering radiological lesion measurements, clinical success (≥50% volumetric regression), symptom improvement, and the need for additional treatment sessions. Variations in bleomycin dosage, embolization technique, and follow-up duration were acknowledged as key modifiers of response and were analyzed descriptively. Hemangioma response in the present cohort was interpreted in relation to previously reported outcomes, focusing on volumetric reduction, proportion of patients achieving clinical success, durability of response, and safety in relation to treatment intensity. All quantitative comparisons are presented in the Results section using structured tables. The study was conducted in accordance with institutional ethical standards for retrospective research, with strict adherence to patient confidentiality.

RESULTS

A total of 31 patients underwent high-dose bleomycin–lipiodoltransarterial chemoembolization (TACE) for hepatic hemangiomas. The mean age was 44.9 ± 9.1 years (range: 29–68 years), with a female predominance (71%, n = 22). Single hemangiomas were observed in 45% of patients, while 35% had 2–4 lesions and 19% had ≥5 hemangiomas. Right-lobe involvement was the most frequent distribution (52%). Baseline hematological and coagulation parameters were within normal limits for all patients (Table 1).

Technical success was achieved in all cases (100%), with satisfactory intralesional lipiodol deposition; Grade 3–4 coverage was observed in 74% of patients. No patient developed post-embolization syndrome, including pain, fever, nausea, or fatigue. One patient (3%) developed a liver abscess during follow-up, which was managed conservatively without the need for surgical intervention. No procedure-related mortality or other major complications were recorded. The mean hospital stay was 1.2 ± 0.6 days (Table 2).

Follow-up imaging was available for 26 patients (84%), with a mean follow-up duration of 4.8 ± 2.1 months. The mean volumetric reduction of treated hemangiomas was 71.4%. Clinical success, defined as ≥50% lesion regression, was achieved in 23 patients (88%). Notably, 50% of patients demonstrated ≥80% volumetric regression following a single TACE session. Only two patients (6%) required repeat embolization due to suboptimal initial response (Table 3).

Table 1. Baseline Characteristics of Patients (n = 31)

Variable	Value
Mean age (years)	44.9 ± 9.1
Female sex	22 (71%)
Single hemangioma	14 (45%)
≥5 hemangiomas	6 (19%)
Right-lobe involvement	16 (52%)
Mean combined diameter (cm)	12.6 ± 5.4
Hemoglobin (g/dL)	12.3 ± 1.6
Platelets (×10⁹/L)	275 ± 84
INR	0.89 ± 0.12

Table 2. Procedural and Early Outcomes

Variable	Value
Bleomycin dose	45 IU (100%)
Lipiodol volume	10 mL
Technical success	31/31 (100%)
Grade 3–4 lipiodol coverage	23 (74%)
Post-embolization syndrome	0 (0%)
Liver abscess	1 (3%)
Mean hospital stay (days)	1.2 ± 0.6
Repeat TACE	2 (6%)
Mortality	0

Table 3. Radiological Response (n = 26)

Outcome	Patients (%)
Mean follow-up duration	4.8 ± 2.1 months
Mean volumetric reduction	71.4%
≥80% reduction	13 (50%)
60–79% reduction	7 (27%)
50–59% reduction	3 (11%)
<50% reduction	3 (12%)
Clinical success (≥50%)	23 (88%)

When compared with previously reported low-dose bleomycin TACE protocols (10–15 IU), the high-dose 45 IU regimen demonstrated superior single-session efficacy, a markedly reduced requirement for repeat procedures, and comparable or improved volumetric reduction, without an increased incidence of post-embolization syndrome or major complications (Table 4).

Table 4. Comparative Outcomes: Low-Dose vs High-Dose Bleomycin TACE

Parameter	Low-Dose (10–15 IU)	High-Dose (45 IU, Present Study)
Clinical success	80–81%	88%
Mean volumetric reduction	65–76%	71.4%
≥80% regression	30–40%	50%
Repeat TACE	Up to 54%	6%
Post-embolization syndrome	~50%	0%
Mean hospital stay (days)	2–4	1.2
Major complications	Rare	Liver abscess (3%)

Figure: 1

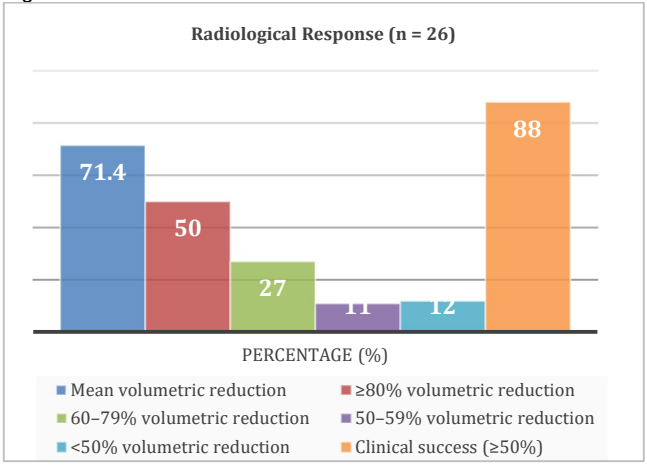
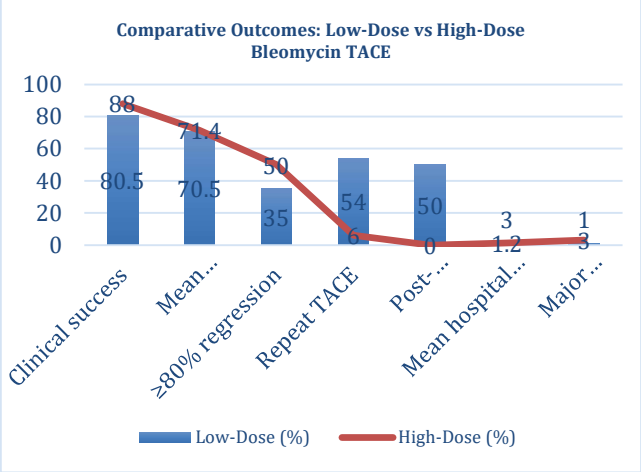


Figure: 2



DISCUSSION

The present study demonstrates that high-dose (45 IU) transarterialbleomycin–lipiodol chemoembolization (TACE) is a highly effective and well-tolerated treatment for hepatic hemangiomas, providing superior single-session outcomes compared with previously reported low-dose protocols. Earlier studies utilizing low-dose bleomycin (10–15 IU) reported clinical success rates of approximately 80–81% and frequently required multiple treatment sessions to achieve optimal lesion regression.[11-13] These protocols were associated with higher rates of repeat embolization, longer hospital stays, and a post-embolization syndrome incidence approaching 50%. In contrast, the present high-dose protocol achieved clinical success in 88% of patients after predominantly single-session treatment, with half of the cohort demonstrating ≥80% volumetric regression and only 6% requiring repeat embolization. Importantly, no patient in our cohort developed post-embolization syndrome, and the mean hospital stay was limited to 1.2 ± 0.6 days, underscoring the favorable tolerability of this intensified regimen.

The enhanced efficacy observed in the present study can be attributed to multiple technical and biological factors. Administration of a higher cumulative bleomycin dose emulsified with Lipiodol likely promoted more homogeneous intralesional drug delivery and prolonged local drug retention, as reflected by satisfactory Grade 3–4 lipiodol coverage in 74% of patients. This may explain the substantial volumetric regression achieved after a single treatment session. Furthermore, use of standardized three-dimensional volumetric imaging allowed precise quantification of lesion regression, offering a more robust assessment of therapeutic response than the two-dimensional measurements commonly employed in prior studies.[14-16] Lesion-wise analysis in patients with multiple hemangiomas further minimized underestimation of treatment effect, strengthening the validity of our response estimates.

From a safety perspective, the high-dose protocol demonstrated an excellent tolerability profile. No cases of post-embolization syndrome were observed, and only one patient developed a liver abscess, which was managed conservatively without long-term sequelae. The absence of systemic toxicity, major complications, or procedure-related mortality indicates that dose escalation to 45 IU does not compromise safety when performed using super selective embolization techniques. These findings challenge the conventional concern that higher bleomycin doses inherently increase adverse event risk and suggest that optimized delivery methods may permit safer dose intensification.[17,18]

Compared with pediatric and non-hepatic hemangioma studies, which often prioritize time to resolution or cure, the present study emphasizes both the magnitude and durability of volumetric regression, highlighting the capacity of high-dose TACE to achieve rapid and sustained lesion shrinkage in adult hepatic hemangiomas.[19-20] The markedly reduced need for repeat procedures further suggests a potential health-economic advantage by minimizing cumulative procedural exposure, hospital stay, and overall treatment cost.

In summary, high-dose bleomycin–lipiodol TACE offers a safe, effective, and durable minimally invasive treatment strategy for hepatic hemangiomas, delivering superior single-session efficacy with an exceptionally favorable safety profile compared with previously reported low-dose protocols. Future prospective, multicenter studies with extended follow-up are warranted to confirm long-term outcomes, refine optimal dosing strategies, and establish standardized volumetric imaging criteria for response assessment in this patient population.

CONCLUSION

High-dose (45 IU) bleomycin–Lipiodoltransarterial chemoembolization represents a safe, well-tolerated, and highly effective minimally invasive treatment for hepatic hemangiomas. This approach provides superior single-session volumetric regression, significantly reduces the need for repeat interventions, and achieves durable clinical response compared with conventional low-dose protocols. The technique facilitates uniform intralesional drug distribution while maintaining an excellent safety profile, with no observed post-embolization syndrome and only a single minor infective complication in the present cohort. These findings support high-dose TACE as a promising first-line therapeutic option for patients with symptomatic or large hepatic hemangiomas, offering both clinical and logistical advantages. Prospective multicenter studies with longer follow-up are warranted to further refine optimal dosing strategies and to validate

standardized volumetric imaging as a routine assessment tool for treatment response.

REFERENCES

1. Aziz H, Brown ZJ, Baghdadi A, Kamel IR, Pawlik TM. A comprehensive review of hepatic hemangioma management. Journal of Gastrointestinal Surgery. 2022 Sep 1;26(9):1998-2007.
2. Jia K, Gao Z, Li M, Yu C. Interventional treatments for hepatic hemangioma: A state-of-the-art review. Journal of Interventional Medicine. 2022 Feb 1;5(1):6-9.
3. Guido LP, Garcia-Buitrago MT. Benign hepatocellular lesions and neoplasms: a comprehensive review. Diagnostic Histopathology. 2021 Feb 1;27(2):85-95.
4. Bergasa NV. Tumors of the Liver. InClinical Cases in Hepatology 2021 Oct 26 (pp. 391-410). London: Springer London.
5. Ghosh NK, Rahul R, Singh A, Malage S, Sharma S, Kumar A, Singh RK, Behari A, Saxena R. Surgery for symptomatic hepatic hemangioma: Resection vs. enucleation, an experience over two decades. Annals of hepato-biliary-pancreatic surgery. 2023 Aug 31;27(3):258-63.
6. Farhat W, Ammar H, Said MA, Mizouni A, Ghabry L, Hammami E, Gupta R, ben Mabrouk M, ben Ali A. Surgical management of giant hepatic hemangioma: A 10-year single center experience. Annals of Medicine and Surgery. 2021 Sep 1;69:102542.
7. Xie QS, Chen ZX, Zhao YJ, Gu H, Geng XP, Liu FB. Outcomes of surgery for giant hepatic hemangioma. BMC surgery. 2021 Apr 8;21(1):186.
8. Rajakannu M, Pascal G, Castaing D, Vibert E, Ducerf C, Mabrut JY, Baulieux J, Adam R. Revisiting the surgical management of giant hepatic hemangiomas: enucleation versus anatomical resection?. Journal of Clinical and Experimental Hepatology. 2021 May 1;11(3):321-6.
9. Jiang B, Shen ZC, Fang XS, Wang XM. Enucleation versus hepatectomy for hepatic hemangiomas: A meta-analysis. Frontiers in Surgery. 2022 Jul 28;9:960768.
10. Zhang W, Liu J, Zhang Z, Wang Y, Xiang S, Chen L, Zhu P, Zhang W, Shu C, Lau WY, Zhang B. Perioperative outcomes of robot-assisted versus laparoscopic liver resection for cavernous hemangioma: a propensity score matching study. Surgical Endoscopy. 2023 Jun;37(6):4505-16.
11. Jan I, Shah A, Beigh SH. Therapeutic effects of intralesional bleomycin sclerotherapy for non-invasive management of low flow vascular malformations-A prospective clinical study. Annals of Maxillofacial Surgery. 2022 Jul 1;12(2):151-6.
12. Sachan P, Singh SK, Pandey AK, Gupta AK, Kumar R. A Prospective Comparative Study of Efficacy of Intralesional Bleomycin Injection with Intralesional 5-FU Injection in Resistant Palmo-Plantar Warts. Clinical Dermatology Review. 2023 Jul 1;7(3):258-65.
13. Searle T, Al-Niaimi F, Ali FR. 5-fluorouracil in dermatology: the diverse uses beyond malignant and premalignant skin disease. Dermatologic Surgery. 2021 Mar 1;47(3):e66-70.
14. Sharma S, Vinay K, Bassi R. Treatment of small keloids using intralesional 5-fluorouracil and triamcinolone acetonide versus intralesional bleomycin and triamcinolone acetonide. The Journal of Clinical and Aesthetic Dermatology. 2021 Mar 1;14(3):17.
15. Kacała A, Dorochowicz M, Patrzałek D, Janczak D, Guziński M. Safety and feasibility of transarterial bleomycin–lipiodol embolization in patients with giant hepatic hemangiomas. Medicina. 2023 Jul 25;59(8):1358.
16. Hodeib AA, Al-Sharkawy BG, Hegab DS, Talaat RA. A comparative study of intralesional injection of Candida albicans antigen, bleomycin and 5-fluorouracil for treatment of plane warts. Journal of Dermatological Treatment. 2021 Aug 18;32(6):663-8.
17. Yuan B, Zhang JL, Duan F, Wang MQ. Medium and long-term outcome of superselective transcatheter arterial embolization with lipiodol–bleomycin emulsion for giant hepatic hemangiomas: results in 241 patients. Journal of Clinical Medicine. 2022 Aug 15;11(16):4762.
18. Gao X, Ren E, Chu C, Zeng Y, Liu G. Nanomedicine-lipiodol formulations for transcatheter arterial chemoembolization. InAdvances in Smart Nanomaterials and their Applications 2023 Jan 1 (pp. 51-72). Elsevier.
19. Ko CC, Yeh LR, Kuo YT, Chen JH. Imaging biomarkers for evaluating tumor response: RECIST and beyond. Biomarker research. 2021 Jul 2;9(1):52.
20. Pepe A, Crimì F, Vernuccio F, Cabrelle G, Lupi A, Zanon C, Gambato S, Perazzolo A, Quaia E. Medical radiology: current progress. Diagnostics. 2023 Jul 21;13(14):2439.

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