






Intralesional bleomycin injection treatment of intra-abdominal lymphangiomas presenting with acute abdomen in children

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ABSTRACT

BACKGROUND: We evaluated the results of urgent intralesional bleomycin injection (IBI) treatment of intra-abdominal lymphangiomas (IAL) presenting with acute abdomen in children.

METHODS: The records of patients who underwent urgent IBI due to acutely presenting IAL between January 2013 and January 2020 were reviewed retrospectively in terms of age, presenting symptoms, cyst type, number of injections, pre- and post-treatment cyst volume, clinical response, complications, and follow-up.

RESULTS: Six patients with a mean age of 4.3 years (2–13 years) were treated. Presenting symptoms were acute abdominal pain (n=4), abdominal distention (n=1), hypoproteinemia and chylous ascites (n=1). Lesions were of macrocystic type in four and macro and micro cystic in two patients. The median number of injections performed was 2 (1–11). Mean cyst volume reduced dramatically from 567 cm³ (range 117–1656) to 3.4 cm³ (range 0–13.8) after treatment (p=0.028). Treatment response was excellent in four patients with complete resolution of the cysts, while good in the remaining two. No early or late complications or recurrence was observed in a mean follow-up period of 40 months (16–56 months).

CONCLUSION: IBI is a safe, fast, and easily applicable method with satisfactory results in the treatment of acutely presenting IAL. It may be recommended in primary as well as recurrent lesions.

Keywords: Bleomycin; cystic lymphatic malformation; lymphangioma; sclerotherapy; surgery.

INTRODUCTION

Lymphatic malformations (LM) are congenital vascular abnormalities caused by the abnormal development of lymphatic channels. They are observed all over the body, with the most frequent locations being the head and neck regions. The term intra-abdominal lymphangioma (IAL) refers to lymphangiomas located in the retroperitoneum, mesentery, and omentum.^[1]

LM are of three types: macrocystic, microcystic, and combined. IALs are generally macrocystic.^[2,3] Clinical findings

can vary depending on the location and size of the lesion (abdominal pain, intestinal obstruction, chylous ascites, hypoproteinemia, etc.).^[4] Abdominal pain and other gastrointestinal symptoms may be acute or chronic. In the pediatric age group, admissions with acute abdominal findings (volvulus, intestinal obstruction, or peritonitis) are more common than in adults.^[5]

Surgical excision, medical treatment (propranolol, sirolimus, etc.), and sclerotherapy (tetracycline, ethanol, doxycycline, bleomycin, OK-432, etc.) are recommended methods in the

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treatment of IAL.^[2-7] Intralesional sclerosing therapy has recently become an important tool as an alternative for surgery, as surgical therapy is often complex with a high rate of complications and recurrence.^[1]

The present study aimed to evaluate the results of urgent intralesional bleomycin injection (IBI) treatment of IAL presenting with acute abdomen in children.

MATERIALS AND METHODS

This study was approved by the institutional review board (decision/protocol No. 83045809/604.01.02) and informed consent was obtained based on the retrospective nature of the study. Children who underwent urgent IBI due to IALs presenting with acute abdomen between January 2013 and January 2020, were reviewed retrospectively. The patients were evaluated in terms of age, gender, presenting symptoms, radiological imaging methods, cyst location and LM classification, prior therapy before IBI, number of injections, pre- and post-injection cyst volumes, complications, and clinical outcomes.

Pre-procedure first imaging modality in all children was ultrasound (US) (Fig. 1). In addition, magnetic resonance imaging (MRI) was used in four and computerized tomography (CT) in two. Pre- and post-procedure volumes were calculated using the formula Length \times width \times depth \times 0.52 cc (0.52 correction factor) with measurements obtained by the US.^[8]

IBI was performed by a team of interventional radiologists and pediatric surgeons. The procedure was performed under general anesthesia or sedation, in the operating room or interventional radiology department.

Aspiration of the cyst was performed using a 20–22 G Chiba needle under US guidance. In large volume lesions (cases

1–3–5), the cyst was drained with an 8 F percutaneous drainage catheter. An appropriate dose of bleomycin (<10 kg: 0.6 mg/kg, >10 kg: 1 mg/kg, not exceeding a total dose of 15 mg at one injection) was diluted to approximately the volume of aspirated fluid and administered into the cyst. During the procedure, the distribution of bleomycin within the cyst and whether there was intraperitoneal spread was monitored under US guidance.

Antibiotics were not routinely given before or after sclerotherapy. The patients were hospitalized and their vital signs were monitored for 24 h following IBI. The first clinical evaluation and radiological imaging (US) were performed 1 month after the procedure. The lesion volume was followed every 3 months with the US and the procedure was repeated for residual lesions.

The response was evaluated according to clinical and radiological examinations as stated in the literature:^[8]

- Excellent – complete regression
- Good – >50% regression
- Poor – <50% regression.

Statistical analysis was done with SPSS 15.0 for the Windows program. Wilcoxon Signed Ranks Test was used to determine the difference between pre- and post-injection volume. “Statistical significance” was accepted as $p < 0.05$.

RESULTS

Six patients with a mean age of 4,3 yrs (range: 2–13 years) were treated. Male to female ratio was 3/3. The most common presenting symptom was acute abdominal pain (n=4). Two patients had previously undergone surgical treatment in other institutions and presented with recurrence (Table

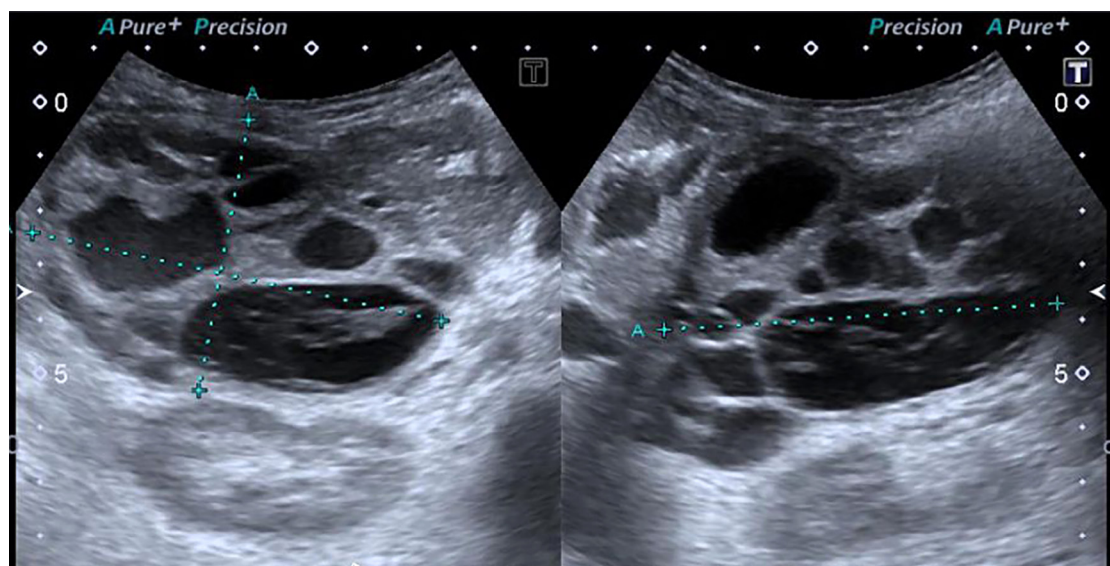


Figure 1. USG image of macrocystic lymphangioma separated by septa in the retroperitoneal space.

Table 1. Patient characteristics

Patient	Age (years)	Sex	Symptom	Cyst location	Pre-injection surgical interventions		Bleomycin Injection (n)
					In other institution	In our department	
1	2	F	Abdominal distension	Intraabdominal/Retroperitoneal	Laparotomy/Cystectomy-Partial pancreatectomy-Roux-en-Y anastomosis	Partial pancreatectomy Cholecystectomy Extrahepatic bile duct resection Hepaticojejunostomy	11
2	2	F	Hypoproteinemia, chylous ascites	Intraabdominal/Mesentery	Laparotomy/Partial Cystectomy/Cyst aspiration	–	1
3	4	M	Abdominal pain	Intraabdominal	–	–	2
4	13	F	Abdominal pain	Intraabdominal	–	–	2
5	3	M	Abdominal pain	Intraabdominal	–	–	4
6	2	M	Abdominal pain	Intraabdominal	–	–	2

Table 2. Volume of LM before and after IBI

Patient	LM classification	Pre-injection volume (cm ³)	Post-injection volume (cm ³)
1	Combined	431	13.8
2	Macrocytic	140	0,7
3	Macrocytic	635	0
4	Macrocytic	421	0
5	Combined	1656	5.7
6	Macrocytic	117	0
Mean volume (cm ³)		567	3.4 (p=0.028)

LM: Lymphatic malformations; IBI: Intralesional bleomycin injection.

1). Macrocytic lymphangioma was identified in four patients, while two patients had macro and microcytic lymphangiomas.

The mean number of procedures performed in all cases was 2 (1–11 procedures) (Table 1). In our early experience, the first patient with prior surgical therapy was reoperated, and partial pancreatectomy, extrahepatic bile duct resection, and hepaticojejunostomy were done. Despite extensive surgery, the cyst recurred in the early post-operative period causing severe abdominal distension and limiting physical activity. In this patient, clinical and radiological improvement was achieved by reducing the cyst size from 431 cm³ to 13.8 cm³ in a total of 11 IBI procedures.

Mean pre-injection cyst volume was 567 cm³ (range 117–1656) which reduced dramatically to mean 3.4 cm³ (range 0–13.8) after treatment (p=0.028). Treatment response was

excellent in three patients with complete resolution of the cysts, while it was good in the remaining three (Table 2). Complete clinical response was obtained in all cases, radiological disappearance of the cyst was achieved in three cases, and all of them were macrocytic.

A significant reduction was observed after injection as shown in Figures 2a and b.

The mean duration of follow-up was 40 months (16–56 months). No recurrence or early or late complications have occurred due to treatment.

DISCUSSION

IAL constitutes <10% of all cases of lymphangiomas.^[1] In total, 5% of IALs are located in the mesentery and 1% in the retroperitoneum and can reach massive dimensions. There are very few reports in the English literature with more than five patients treated for IALs.^[9]

IALs usually present with acute abdominal pain and distention, vomiting, constipation, diarrhea, or a palpable mass. Complications requiring emergency surgery such as intestinal obstruction, volvulus, rupture, infection, and bleeding can also occur.^[4] Although rare, hypoalbuminemia may also be a presenting symptom.^[10] In our series, urgent IBI was effective in avoiding these possible complications in all patients who presented with acute abdomen.

Radiological differentiation between cystic lesions in the abdomen and lymphangioma may be difficult. Although the final diagnosis is made by histopathological examination, radiological imaging is very helpful. The most commonly used first-line imaging method is the US. In the US, solitary or

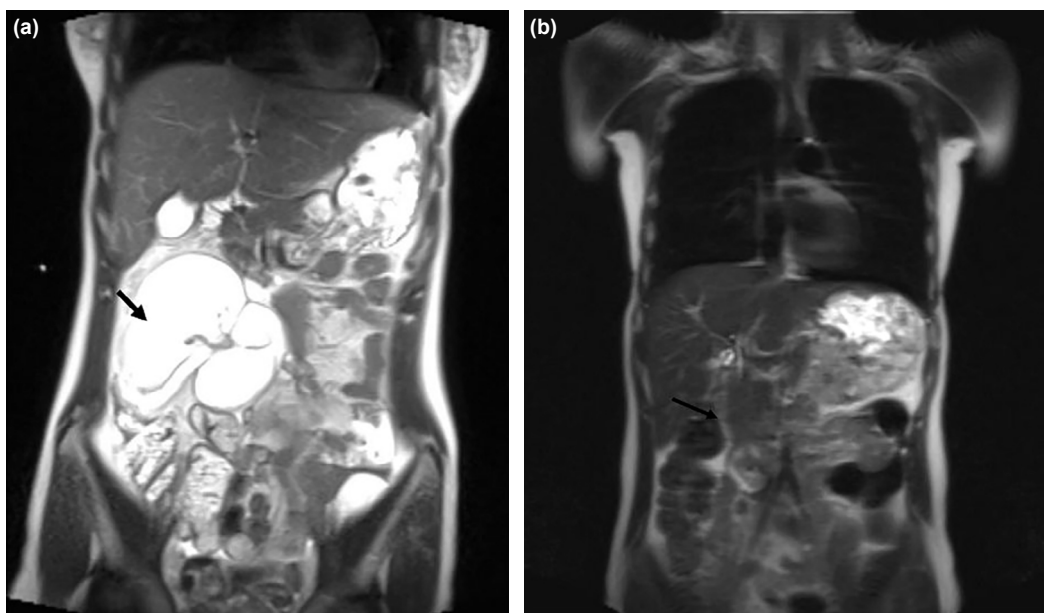


Figure 2. The appearance of IAL at the beginning of the treatment (a) and end of the treatment (b).

more commonly multiloculated macro-or microcystic lesions with thin walls and thin septations that are characteristically avascular and without solid components suggest lymphangioma.^[9,11] Particularly in lesions located in the mesentery, typical US findings are round-shaped hypoechoic cystic masses containing echogenic septations. CT and MRI show similar findings and better delineate the relationship with the surrounding organs and structures.^[11–13] In particular, MRI is the best radiological method in the diagnosis of IAL and helps to exclude potential malignant lesions.^[14] In this series, IBI was performed in patients whose diagnosis of lymphangiomas was confirmed by radiological imaging, including two patients who had previous surgery with histopathological confirmation of the lesion.

In the past, surgical excision has been the most recommended treatment for IAL. However, large bowel resection, lymphatic leakage, and recurrence are undesired complications of surgery. In a large series of 186 patients, recurrence was observed in 29%.^[9] Intralesional sclerotherapy is an effective and easily applicable treatment modality for IAL patients presenting with acute abdomen and those that may require large bowel resection or extensive surgery due to invasion of the surrounding tissues and retroperitoneal space. The reasons precluding widespread acceptance of sclerotherapy were diagnostic uncertainties, technical difficulties, and lack of knowledge regarding the effects of the sclerosing agent in the peritoneal cavity. Few articles have reported favorable results in reducing symptoms and size of abdominal lymphangiomas with doxycycline and a case report with OK-432.^[2,3,7,15] Elbaaly et al.^[16] also recommend sclerotherapy alone or as part of combined treatment in the treatment of IAL.

Bleomycin was first used in Japan in 1977 in the treatment of lymphangioma and has become a widely preferred agent in

lymphangiomas located in the head and neck regions.^[17] Studies have reported its efficacy, safety, and successful clinical and cosmetic results in the treatment of lymphangioma and vascular malformations.^[18–20] Some studies reported systemic effects of locally applied bleomycin in hemangiomas and vascular malformations. Muir et al.^[21] reported that the amount of locally administered bleomycin in the systemic circulation is negligible and does not cause pulmonary fibrosis. In the study of Ionescu et al.,^[22] the plasma concentration of bleomycin administered intralesionally to hemangioma patients was shown to be 100 times lower than in cancer patients with IV administration of the same agent. Baskin^[23] and colleagues argued that performing the procedure under USG control will prevent potential trauma to other organs and that direct intralesional injection may reduce systemic effects. Bleomycin has been used routinely in our clinic in the treatment of lymphangiomas since 2000. Between 2000 and 2010, 32 cases with lymphangiomas in various locations were injected with bleomycin, and significant regression was detected in 75%.^[24] No hematological or pulmonary side effects were encountered. Our unreported series reached a total of 120 cases by 2022 with similar results and no side effects except for flagellate pigmentation in three patients. Therefore, the use of IBI in this small series of IALs has followed extensive experience with this method in the treatment of cystic lymphangiomas in our department.

Conclusion

The main limitation of this study was the small number of cases. A larger series and longer follow-up are needed to better define the role of IBI in IAL. Nevertheless, IBI is a promising minimally invasive treatment alternative for patients with primary or recurrent IAL presenting with acute abdomen, in whom surgical treatment is demanding and carries a high re-

current risk. We recommend it as a life-saving treatment, especially in intra-abdominal lymphangiomas that require extensive surgical resection at primary presentation or in those that do not allow resection due to its location in the mesentery. Evaluation and treatment of these patients should be conducted in collaboration with interventional radiologists.

Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Clinical Research Ethics Committee (Date: 02.11.2016, Decision No: 396163).

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Authorship Contributions: Concept: R.Ö., G.T., O.F.Ş.; Design: R.Ö., G.T., F.G., Ş.E.; Supervision: G.T., O.F.Ş., F.G., R.Ö.; Resource: Ş.E., A.E.H., S.A.; Materials: A.E.H., R.Ö., S.A., F.G., G.T., O.F.Ş.; Data: A.E.H., A.C.B., Ş.E., S.A.; Analysis: A.C.B., S.A., Ş.E., R.Ö.; Literature search: A.E.H., R.Ö., S.E., A.C.B., S.A.; Writing: R.Ö., G.T., A.E.H.; Critical revision: G.T., O.F.Ş., F.A., A.E.H.

Conflict of Interest: None declared.

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ORIJİNAL ÇALIŞMA - ÖZ

Çocuklarda akut karın ile başvuran karın içi lenfanjiyomların intralezyonel bleomisin enjeksiyonu tedavisi**Dr. Raşan Özcan,¹ Dr. Ali Ekber Hakalmaz,¹ Dr. Şenol Emre,¹ Dr. Ayten Ceren Bakır,¹ Dr. Süreyya Aydın,¹ Dr. Fatih Gulsen,² Dr. Osman Faruk Senyuz,¹ Dr. Gonca Topuzlu Tekant¹**¹Istanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, Çocuk Cerrahisi Anabilim Dalı, İstanbul
²Istanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, Radyoloji Anabilim Dalı, İstanbul**AMAÇ:** Çocuklarda akut karın ile başvuran intraabdominal lenfanjiyomların (IAL) acil intralezyonel bleomisin enjeksiyonu (İBİ) tedavisinin sonuçlarını değerlendirdik.**GEREÇ VE YÖNTEM:** Ocak 2013 ile Ocak 2020 arasında akut İAL nedeniyle acil İBİ yapılan hastaların kayıtları geriye dönük olarak yaş, başvuru semptomları, kist tipi, enjeksiyon sayısı, tedavi öncesi ve sonrası kist hacmi, klinik yanıt, komplikasyonlar ve takip açısından değerlendirildi.**BULGULAR:** Ortalama yaşı 4.3 (2–13 yıl) olan altı hasta tedavi edildi. Başvuru semptomları akut karın ağrısı (n=4), karın şişliği (n=1), hipoproteiniemi ve şilöz asit (n=1) idi. Lezyonlar dört hastada makrokistik, iki hastada makro ve mikro kistik tipteydi. Enjeksiyon sayısı ortalama 2 (1–11) idi. Ortalama kist hacmi tedaviden sonra 567 cm³'ten (117–1656 aralığı) 3.4 cm³'e (0–13.8 aralığı) dramatik bir şekilde azaldı (p=0.028). Tedavi yanıtı, kistlerin tamamen kaybolduğu dört hastada mükemmelken, geri kalan iki hastada iyiydi. Ortalama 40 aylık (16–56 ay) takip döneminde erken veya geç komplikasyon veya nüks gözlenmedi.**TARTIŞMA:** İBİ, akut başvuran IAL tedavisinde tatmin edici sonuçlar veren güvenli, hızlı ve kolay uygulanabilir bir yöntemdir. Primer ve tekrarlayan lezyonlarda önerilebilir.**Anahtar sözcükler:** Bleomisin; cerrahi; kistik lenfatik malformasyon; lenfanjiom; skleroterapi.

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