ORIGINAL ARTICLE

Comparison of different therapeutic approaches for children with common lymphatic malformation

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ABSTRACT

Background: Our study compared the outcomes of three different therapies: surgery (Group I), bleomycin sclerotherapy (Group II), and a combination of both (Group III), for children with common (cystic) lymphatic malformation (LM) at a paediatric surgical centre in Yogyakarta, Indonesia.

Methods: Medical records of patients who were treated for LM in the Paediatric Surgical Centre Universitas Gadjah Mada from January 2015 to January 2019 were reviewed. Scoring systems were used to assess the outcomes, including reduction of size, problems of aesthetics, functional problems, complications, necessity of further interventions, and interventions' frequencies.

Results: During the four-year study, we included 31 children, consisting of 6, 5, and 20 patients in Groups I, II, and III, respectively. The total score did not significantly differ between Groups I, II, and III (14.67±2.80 vs. 13.40±2.07 vs. 12.50±1.47, respectively; *p*=0.056). Group II scored better in aesthetic problems than other groups (*p*=0.001), Group III scored higher in necessity of further interventions compared to the other groups (*p*=0.026), and Group I was higher in interventions' frequencies than the other groups (*p*<0.001). However, there were no significant differences in reduction of size, functional problems, and complications among groups (*p*=0.554, 0.151, and 0.076, respectively).

Conclusions: There is no significant different effect of the three modalities treatment for LM, although one group might have more beneficial effects compared with the other groups due to different scoring system parameters. Further multicentre and prospective cohort studies with a larger number of patients are necessary to establish the existence and extent of our findings.

KEY WORDS:
Bleomycin sclerotherapy; children; combination therapy; lymphatic malformation; surgery

INTRODUCTION

Common (cystic) lymphatic malformation (LM) is a congenital malformation of the lymphatic system, characterised by differently dilated lymphatic cysts, marked by endothelial cells with a lymphatic phenotype.[1] The International Society for the Study of Vascular Anomalies (ISSVA) classified LM, capillary malformation, venous malformation, arteriovenous fistula, and arteriovenous malformation into one group, named as simple vascular malformations.[1] LM can be classified as three subgroups: a) microcystic, b) macrocystic, and c) mixed.[1] LM occurs frequently in the cervicofacial and axillary region, of infants and young children.[1,2] Although considered benign, large masses in the cervicofacial can cause aesthetic and functional problems or can even cause airway disorders such as airway compression by the mass. Surgery with excision has been done as the standard management, but LM in the cervicofacial region are often near vital structures, and total excision is difficult to do. The main disadvantages of surgery are the difficulty in achieving total LM surgery with narrow margins, risk of injury to vital structures, high recurrence rates, and unacceptable cosmetic results. Therefore, many types of sclerotherapy (ST) agents, including bleomycin, have been used as an alternative to surgery.[3]

ST with bleomycin has been shown to be effective for the treatment of cervical LM,[2] but is still has not routinely used.4 There is little previous data comparing the output of each treatment modality to treat LM in children. Therefore, we aimed to compare the outcomes of three different therapies, surgery (group I), bleomycin sclerotherapy (group II), and a combination of both (group III), for children with LM at a paediatric surgical centre in Indonesia.

MATERIALS AND METHODS

Subjects

The authors collected data retrospectively from the medical records of patients diagnosed with LM in the Paediatric Surgical Centre Universitas Gadjah Mada, from January 2015 until January 2019. The medical records of patients were obtained: the age, sex, initial symptoms, mass size, location, diagnosis method used, and treatment modalities, including therapeutic response quantitative scores, consisting of mass size reduction, aesthetics problem, functional problem, post treatment complications, further interventions needed and interventions' frequency.[5] The follow-up of patients after the treatment was performed only based on the medical records of the outpatient clinic.

The inclusion criteria for this study were patients aged less than 18 years who were diagnosed with LM in the Paediatric

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Table I: Baseline characteristics of subjects with LM

	Surgery (I) N (%); mean ± SD	Sclerotherapy with bleomycin (II) N (%); mean ± SD	Combination (III) N (%); mean ± SD	*p*
Subjects	6 (19.4)	5 (16.1)	20 (64.5)	
Gender				
Male	3 (50)	3 (60)	14 (70)	
Female	3 (50)	2 (40)	6 (30)	
Age (months)	62.5 ± 33.96	32.8 ± 23.36	23.55 ± 23.96	
Treatment frequency (times)	5.33 ± 0.82	10.0 ± 0.85	16.65 ± 7.18	0.01*
Location				0.15
Frontalis	-	-	1 (5)	
Auricula	-	-	1 (5)	
Buccal	1 (16.7)	1 (20)	4 (20)	
Lower jaw	-	1 (20)	1 (5)	
Neck	2 (33.3)	2 (40)	5 (25)	
Shoulder	-	1 (20)	-	
Axilla	-	-	3 (15)	
Upper arm	2 (33.3)	-	1 (5)	
Waist	-	-	1 (5)	
Scrotum	1 (16.7)	-	-	
Thigh	-	-	2 (10)	
Hand	-	-	1 (5)	
Surgical frequency	1.17 ± 0.41	-	1.05 ± 0.22	0.00*
Sclerotherapy frequency	-	3.60 ± 1.95	4.95 ± 2.01	0.03*
Complications				
Scars	3 (50)	1 (20)	13 (65)	0.03*
Anemia	-	-	3 (15)	
Surgical site infection	-	-	3 (15)	
Nerve injury	1 (16.67)	-	-	
No Complications	2 (33.33)	4 (80)	5 (25)	

*, significant (p<0.05); LM, lymphatic malformation; SD, standard deviation

Table II: Therapeutic response quantitative score between three modalities of therapy for LM patients

		Total score (mean ± SD)	*p*
Therapeutic method	Surgery (I)	14.67 ± 2.80	0.056
	Sclerotherapy with bleomycin (II)	13.40 ± 2.07	
	Combination (III)	12.50 ± 1.47	

*, significant (p<0.05)

Table III: Comparison of each variable within scoring system among three therapy groups

Variable	Therapy	Score	*p*
Size decrease	Surgery (I)	17.83	0.554
	Sclerotherapy with bleomycin (II)	12.60	
	Combination (III)	16.30	
Esthetic problem	Surgery (I)	14.50	0.001*
	Sclerotherapy with bleomycin (II)	26.10	
	Combination (III)	13.93	
Functional problem	Surgery (I)	14.33	0.151
	Sclerotherapy with bleomycin (II)	14.00	
	Combination (III)	17.00	
Postoperative complications	Surgery (I)	16.33	0.076
	Sclerotherapy with bleomycin (II)	23.10	
	Combination (III)	14.13	
Necessity for further intervention	Surgery (I)	14.33	0.026*
	Sclerotherapy with bleomycin (II)	8.00	
	Combination (III)	18.50	
Times of intervention	Surgery (I)	27.25	0.000*
	Sclerotherapy with bleomycin (II)	18.00	
	Combination (III)	12.13	

*, significant (p<0.05)

Surgical Centre Universitas Gadjah Mada and underwent cyst excision (surgery), ST with bleomycin or combination; while the exclusion criteria were LM patients who were deceased, untreated, with other pre-existing comorbid disorder, and/or incomplete data.

The Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital gave approval for this study (Ref. #KE/FK/0943/EC/2018).

Quantitative Scoring System for Treatment of LM
We adapted the scoring system by Jin et al.[5] The scoring system was developed because the existing scoring system was not consistent for assessing and reporting treatment responses of LM (i.e. good, satisfactory and poor response). It did not define the treatment outcomes into good, satisfactory and poor response. However, it quantified the treatment outcomes using six variables, consisting of decrease in LM size, aesthetic problem, functional problem, postoperative complications, necessity for further intervention, and times of intervention. Each variable was given scored from 0 (worse) to 3 (better). It compared the total score between treatment groups.[5]

The functional problem was defined as problem in the breathing, eating, or speech, while the postoperative complications consisted of fever and swelling (score 2), serious infections, hematoma, temporal facial paralysis, Horner syndrome (score 1), or permanent facial paralysis and other nerve injuries (score 0).[5]

Statistical Analysis
Data was analysed by ANOVA if the data were normally distributed and Kruskal-Wallis if the data were not normally distributed, followed by a multivariate analysis using linear regression.

RESULTS

Baseline Characteristics of the Subjects
We collected 59 medical records of LM patients but excluded in all 28 patients due to incomplete data (19), deceased (2), final diagnosis was not LM (4), different treatment (2), and existing comorbid disorder (1). Therefore, this four-year study involved 31 research subjects divided into three groups, six in group I, five in group II and 20 in group III. The baseline characteristics of the subjects are presented in Table I.

Shapiro-Wilk test showed that the data was not normally distributed among three groups ($p<0.05$). The selection of therapy was in accordance to the preferences of the attending paediatric surgeons' and the condition of patients, so that the distribution of the number of each group was not comparable.

In addition, there were significant differences in surgical and sclerotherapy frequencies, but not location of LM, among all groups (Table I). For the complication category, group II had 80% percentage free from complications, followed by group I with 33.33% and group III with 25%. These differences were statistically significant ($p=0.03$) (Table I).

Therapeutic Response Quantitative Score
We compared the total score between three methods: 14.67±2.80 vs. 13.40±2.07 vs. 12.50±1.47 for group I, II, and III, respectively. These differences did not reach a significant level ($p=0.056$) (Table II).

Next, we compared each variable within the scoring system between groups (Table III). Group II showed better scores in aesthetic problems than other groups ($p=0.001$), Group III had better scores in necessity of further interventions than other groups ($p=0.026$), and Group I revealed better scores in intervention's frequencies than other groups ($p<0.001$). However, there were no significant differences in reduction of size, functional problems, and complications among groups ($p=0.554$, 0.151, and 0.076, respectively).

DISCUSSION

In this study, we are unable to reveal the different impacts of three modalities therapy for LM. Previous studies showed that there is no evidence supporting which therapy is the most effective treatment for LM.[3,6] Although the surgical procedures have been shown to be superior to bleomycin sclerotherapy to cure LM,[5] due to intraoperative complications such as facial nerve damage[3], bleomycin sclerotherapy has more favourable outcomes as the first line therapy for LM, especially in the cervicofacial region.[6-8] In addition, therapeutic responses after sclerotherapy are usually delayed three months after the first attempt and therefore, multiple procedures are needed for most patients.[9] It should be noted that sclerotherapy in the excised cavity after surgery can reduce recurrence rates.[10]

Another sclerotherapy has been reported to be effective for LM treatment, including sirolimus and OK-432.[9,11] Sirolimus is an immunosuppressive drug that is able to reduce abnormal vascular proliferation by inhibiting the mTOR/PI3K pathway and diminishing the VEGF level and responsiveness of its receptors;[11] while OK-432 is an immunopotentiating anticancer agent that causes LM reduction due to the lymphatic vessel endothelial cells destruction induced by OK-432 itself and might involve the cellular and cytokine mediated pathway.[9]

The mean age of our patients in the surgical therapy, sclerotherapy with bleomycin and combination groups were 62.5±33.96 months, 32.8±23.36 months, and 23.55±23.96 months, respectively. This result is compatible with a previous report, indicating that the mean age of patients undergoing initial therapy was two years old.[5] Patients with LM are usually diagnosed at birth and most of them are diagnosed before two years of age.[10] However, our study showed that the mean age of patients undergoing therapy was approximately two years of age. This delay might be due to some socioeconomic differences, such as educational level and health insurance coverage of parents.

We also showed the therapeutic duration of surgery was significantly shorter than other groups (Table I). These findings were not compatible with the study by Ardıçlı et al.[4] that found the duration of sclerotherapy therapy was significantly shorter than surgery regardless of repetition of

the therapy. In addition, surgery is still the main modality of therapy for LM, especially superficial lesions as in our study, because it is relatively easy to avoid injurious complications of vital structures. Surgical therapy is also more flexible to remove as much mass as possible in superficial lesions, while taking care not to injure nerve tissue and other vital structures.[5]

There was no significant difference in functional problems between the three groups (Table III), although there was one patient who suffered nerve injury in the surgical group (Table I). Boardman et al.[12] reported that an ongoing nerve injury was found in 7% of surgical therapy for LM, especially in the thoracic operation, while only 4% in the other surgical group without a thoracic component.

Interestingly, each therapeutic option has its own advantages, as follows: sclerotherapy with bleomycin group showed better scores in aesthetic problems, while the combination group had better scores in necessity of further interventions, and the surgical group revealed better scores in interventions' frequencies (Table III). The scar complication was higher in the combination (65%) than the surgical (50%) and sclerotherapy (33%) groups. These differences were statistically significant (p=0.03) (Table I). To the best of our knowledge, our study is the first report of these findings. Previous studies reported that the highest scar complication frequency is in the surgical group.[4,13,14] Further study is needed to clarify and confirm our findings, especially to explain the highest scar rate in the combination group. Furthermore, Boardman et al.[12] showed that the complications following surgical treatment for neck LM are mostly minor and temporary, while the complications of sclerotherapy are pain and swelling in 20% of patients. Ardıçlı et al.[4] revealed that the complications were significantly lower in the sclerotherapy treatment than surgical therapy. In addition, patients in the surgical group may have a complete therapy, with a short duration of therapy and allow a histopathological diagnosis, however, they might have an incision scar and potential for nerve injury. Patients with sclerotherapy are do not usually have scar tissue, which is less invasive, while avoiding nerve trauma and having shorter length of stay, however, they may have swelling in the lesion after therapy and need longer time for size reduction of tumour. Therefore, the therapy might be delayed and have an impact on significant airway obstruction, possible recurrence, problems in histopathological diagnosis and also unknown presence of long-term toxic effects.[9,12] It should be noted that the use of bleomycin might have a risk for pulmonary toxicity. However, its risk is significantly associated with bleomycin dosage.8 The higher risk of pulmonary toxicity is correlated with a total dose exceeding 400IU given intravenously to malignant tumour patients.[8] Fortunately, the dosage given in sclerotherapy are much lower than those given for oncology treatment. To the best of our knowledge, there is no report of pulmonary fibrosis as a complication of intralesional bleomycin for LM.[8,9]

LIMITATIONS

Finally, our research certainly has several weaknesses. The number of samples is relatively small and the number for each group is not comparable. This limitation is due to the cohort of patients and the treatment modalities based on the preferences of the attending paediatric surgeon considering the location of the lesion and severity. Our report was a retrospective study; therefore, we performed a follow-up of patients only according to the medical records of the outpatients' clinic and we did not have any data on the income and education background of parents to support our hypothesis that the treatment delay for our patients might be due to some socioeconomic differences, such as' educational level and health insurance coverage of parents. We also did not divide LM based on the severity of the disease due to the incomplete recording of' medical records of patients concerning the type of lesion (i.e., macrocystic, microcystic, or mixed) and the lack of detailed supporting imaging in classifying the type of lesion, which is a limitation of our study. Notably, we used the scoring system that consisted of six variables; however, we compared each variable within the scoring system to other studies not as a total score. These facts should be considered during the interpretation of our findings.

CONCLUSIONS

There was no significant different effect of three modalities treatment for LM, although one group might have more beneficial effects than other groups due to different scoring system parameters. Further multicentred and prospective cohort studies with a larger number of patients are necessary to establish the existence and extent of our findings.

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