Primary Surgery vs Primary Sclerotherapy for Head and Neck Lymphatic Malformations

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**IMPORTANCE** The optimal treatment for head and neck lymphatic malformations (LMs) is unknown. To our knowledge, this is the first head-to-head comparison of primary surgery and sclerotherapy for this condition.

**OBJECTIVE** To compare surgery and sclerotherapy as initial treatment for head and neck LMs.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective cohort study including patients in 2 pediatric vascular anomaly programs receiving treatment for head and neck LMs.

**INTERVENTIONS** Primary surgery or primary sclerotherapy and any subsequent therapy within 1 year.

**MAIN OUTCOMES AND MEASURES** Treatment effectiveness was measured by (1) need for further therapy after first treatment and within 1 year and (2) change in Cologne Disease Score (CDS). Resource utilization was reflected by total intervention number, hospital and intensive care unit (ICU) days, and tracheostomy placement.

**RESULTS** A total of 174 patients were studied. Their mean (SD) age at presentation was 4.2 (4.7) years; 45.1% were female. The initial treatment was surgery in 55.8%, sclerotherapy in 35.1%, and other interventions in 9.1%. The LM stage ranged from 1 to 5, with similar distributions ($P = .15$) across initial treatment types; 31.2% of LMs were macrocystic, 34.8% were microcystic, and 33.9% were mixed, with similar distributions across treatment types. Patients receiving sclerotherapy had worse pretreatment CDS subscores for respiration, nutrition, and speech ($all P = .02$). In univariate analysis, initial surgery and initial sclerotherapy had similar effectiveness after the first intervention ($P = .21$) and at 1 year ($P = .30$). In multivariate analysis controlling for lesion stage and type, initial surgery and sclerotherapy did not differ in effectiveness after the first intervention ($P = .28$) or at 1 year ($P = .97$). Total CDS and subscale changes were similar between treatment types except for the nutrition subscale. Treatment type did not predict total number of interventions ($P = .64$), total hospital days ($P = .34$), total ICU days ($P = .59$), or higher likelihood of subsequent tracheostomy ($P = .36$). Higher LM stage predicted more hospital and ICU days and higher likelihood of tracheostomy ($all P = .02$).

**CONCLUSIONS AND RELEVANCE** In this multisite comparison, initial surgery and sclerotherapy for head and neck LMs were similar in effectiveness and resource utilization. Higher stage predicted greater resource utilization.
lymphatic malformations (LMs) occur most commonly in the head and neck\textsuperscript{1-3} and can have a significant effect on the health and function of children.\textsuperscript{4} The International Society for the Study of Vascular Anomalies classifies LMs as low-flow vascular malformations\textsuperscript{5} that can be described radiographically as macrocystic (loculation volume \( \geq 2 \text{ cm}^3 \)), microcystic (loculation volume \(< 2 \text{ cm}^3 \)), or mixed, but this broad description was not designed to (nor does it) capture the variability on these lesions in extent, impact, and treatment response.\textsuperscript{6} Indeed, the histological appearances of macrocystic and microcystic LMs are identical.\textsuperscript{7}

Lymphatic malformations have been recognized as a disease entity for more than 100 years,\textsuperscript{1} but a detailed classification or staging system correlated with treatment outcomes has not yet been described, largely owing to a poor understanding of the natural history of LMs and differing treatment techniques.\textsuperscript{4,6} In general, more extensive lesions are thought to respond poorly to therapy and can be categorized with an existing staging system that is not widely used. This system classifies lesions by laterality and relationship to the hyoid and predicts treatment outcomes and complications.\textsuperscript{8,9} Because descriptive head and neck LM classification systems are not commonly used to plan therapy, it has been impossible to compare the efficacy and cost-effectiveness of existing therapies,\textsuperscript{6} which are usually primary surgical resection or primary sclerotherapy as recommended in contemporary studies and reviews of this disease.\textsuperscript{3,5,6,8} Although these modalities have been well described, to our knowledge, no published studies have directly compared surgery and sclerotherapy as first-line treatment for head and neck LMs, and existing literature on LM treatment does not report pretherapy and posttherapy LM assessment or treatment outcomes in a standardized manner.\textsuperscript{8}

The treatment philosophy for LMs at our institutions is primarily to improve function and symptom burden; objective reduction of malformation size is a secondary consideration.\textsuperscript{3,4} The size of LMs, although often used clinically as a proxy for disease burden, does not reflect disease burden in a validated or consistent way. Similarly, complete LM resolution is not a useful treatment end point because, in our experience, many patients are satisfied and fully functional with some residual disease, some LMs spontaneously regress,\textsuperscript{10} and there is no clinically relevant standardized method for measuring persistent malformation.

Our multicenter retrospective cohort study compared the effectiveness of primary surgery and primary sclerotherapy in patients with head and neck LMs, including patients from a center providing almost entirely surgical therapy and another center focusing on sclerotherapy. Our hypothesis was that primary surgery and primary sclerotherapy differ in effectiveness and resource utilization. \textit{Effectiveness} was defined in 2 ways. First, treatment caused a clinical improvement such that no further treatment was needed either after the first intervention or within 1 year of initial intervention. This definition reflected the desire of patients and health care providers to improve LM disease burden, including but not limited to LM size reduction, within a reasonable time. Second, we measured changes in Cologne Disease Score (CDS), a nonvalidated composite system that reflects LM disease burden.\textsuperscript{11,12} Resource utilization associated with initial surgery and sclerotherapy was compared in exploratory analysis through treatment-associated intensive care unit (ICU) and hospital days, total number of procedures, and tracheostomy placement.

**Methods**

This study was approved by the institutional review boards at Seattle Children’s Hospital and Rady Children’s Hospital San Diego. Consecutive patients undergoing treatment for head and neck LMs were accrued in vascular anomaly patient databases at these hospitals. To allow maximum power to detect treatment differences and because of the lack of published data to guide the choice of effect size a priori, all eligible patients were included for the duration of these databases from 1995 through 2012. Inclusion criteria were treatment for head and neck LM, written parental consent for inclusion in the patient databases, and at least 1 follow-up appointment within 1 year of the first treatment. There were no specific exclusion criteria. Owing to the relative rarity of LMs, a retrospective cohort design was selected to allow study sample accrual.

All LMs were assessed and staged prior to treatment initiation using the de Serres staging system described by de Serres et al\textsuperscript{16} (de Serres staging system). The CDS values were determined in an attempt to assess functional effects of head and neck LMs, at initial evaluation and at posttreatment evaluation, in a subset of patients with these data.\textsuperscript{11} This scoring system incorporates an “observer statement” describing disease progression, but owing to the retrospective nature of this study, observer statement data were not collected or analyzed. Other available data collected included radiographic LM characterization (macrocystic, microcystic, or mixed), treatment modalities used during the study period, LM treatments before study center evaluation, number of posttreatment ICU and hospital days, total number of LM treatments at study centers, and tracheotomies performed. Each intervention within a staged LM treatment plan was considered a separate treatment.

Data analysis included both univariate analysis for simple comparisons and multivariate analysis to account for the effects of possible confounders. We used the \( \chi^2 \) test for univariate comparison of proportions, \( t \) test for univariate comparison of means, Spearman rank correlation for tests of correlation, analysis of variance (ANOVA) for tests of association, and the Kruskal-Wallis test for comparisons of distribution. Multivariate analysis was performed with ANOVA and multivariate linear regression using dummy variables for regression with categorical variables. No correction was made for multiple testing because multiple testing did not occur in the evaluation of any single question addressed in this study; the above statistical tests were identified as appropriate for specific hypotheses or questions to be addressed. Data were entered into Microsoft Excel (Microsoft), converted to Stata format using StatTransfer software (Circle Systems), and analyzed with Stata/SE 9.2 software (StataCorp).
Results

Descriptive Data
The analysis included 174 patients (Table 1). No patient had more than 1 lesion. The mean ages did not differ between the surgery and sclerotherapy groups (P = .41). The initial stage distributions were similar between treatment groups (P = .15) but differed between LM types, with macrocystic and mixed lesions tending to be higher stage (P = .04) (Figure).

Pretreatment CDS was calculated for 138 patients (Table 3). There was no difference in mean CDS subscores (P = .24), distribution of de Serres stage (P = .15), or LM type (P = .31) between treatment groups. Patients undergoing initial sclerotherapy had higher mean CDS subscores for airway (P = .02), oral nutrition (P = .008), and speech (P = .01) impairment. Each increase in de Serres stage was also associated with worse scores in all CDS categories (all P < .001).

During the study period, 133 of 174 patients (76.4%) had a single treatment or intervention, 21 (12.1%) had 2 interventions, 8 (4.6%) had 3, 6 (3.4%) had 4, and 6 (3.4%) had 5 or more (Figure).

Univariate Analysis
Of patients undergoing surgery, 75.3% needed no further treatment after the first intervention compared with 83.6% of those undergoing sclerotherapy. These proportions were not significantly different (P = .21). Similarly, the probability of effective treatment within 1 year did not differ between these treatment groups (P = .30). None of the CDS values, total scores, or scores for individual categories differed between the initial surgery or sclerotherapy groups (P = .10-.93), nor did the mean number of subsequent interventions (P = .64). However, higher de Serres stage predicted a greater total number of interventions in univariate analysis (P = .04 by ANOVA) (Figure).

Multivariate Analysis
Results of multivariate analysis are presented in Table 4. Patients undergoing surgery and those undergoing sclerotherapy were equally likely to need no further treatment after the first intervention and within 1 year. Predominantly, macrocystic LMs were more likely than microcystic LMs to require no further treatment within 1 year. Initial surgery was associated with significantly better improvement in nutrition CDS than initial sclerotherapy. However, this difference was small because the multivariate regression model estimated the mean nutrition CDS change to be 0.17 greater in the surgery than in the sclerotherapy group.

The malformation stage at treatment initiation was the only predictor of resource utilization as measured by ICU days, hospital days, and need for tracheostomy. Not enough patients were decannulated to allow multivariate analysis of this outcome. However, in univariate analysis, higher LM stage was associated with a lower probability of decannulation (P = .01), whereas neither initial treatment type (P = .90) nor LM type (P = .59) predicted decannulation.

Discussion
This study directly compared treatment effectiveness of primary surgery and primary sclerotherapy for head and neck LMs in a large cohort, and several key findings emerged. First, initial treatment type does not affect the probability of needing any further treatment after the first intervention or at 1 year. Second, macrocystic malformations are more likely than microcystic lesions to have been treated successfully within 1 year. Third, malformation stage at treatment initiation is a significant predictor of resource utilization. Fourth, high-stage LMs were uncommon in this cohort.

In this study, initial surgery and initial sclerotherapy showed no statistically significant difference in effectiveness as measured by the proportion of patients requiring no further treatment after the first intervention or at 1 year. This lack of difference persisted after adjustment for lesion stage and lesion type. However, with the predominance of stage 2 and 3...
lesions in this study, this finding may be more generalizable for patients with unilateral malformations. Use of staged treatment plans, not considered in our analysis, may explain this lack of differences after the first intervention. However, the lack of difference between initial surgery and initial sclerotherapy persists at 1 year, suggesting that this explanation is incomplete.

In contrast to initial treatment type, lesion type predicted the need for further treatment at 1 year in multivariate analysis. This finding is in keeping with previous publications suggesting that macrocystic LMs are often easier to treat than microcystic LMs.6 On the other hand, de Serres stage did not predict treatment effectiveness after the first intervention or at 1 year, probably because this limited staging system does not fully capture the complexity of head and neck LMs. These findings occurred despite a tendency for macrocystic lesions to be higher stage, suggesting a possible interaction of these variables. To clarify this relationship, more comprehen-

Table 3. Summary of Initial CDS for a Subset of the Study Sample (138 Patients) in Whom Pretreatment CDS Data Were Availablea

<table>
<thead>
<tr>
<th>Initial CDS</th>
<th>Airway Subscale</th>
<th>Oral Nutrition Subscale</th>
<th>Speech Subscale</th>
<th>Appearance Subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>91.7 (normal)</td>
<td>88.2 (normal)</td>
<td>91.3 (regular speech development)</td>
<td>4.2 (no lesion visible)</td>
</tr>
<tr>
<td>1</td>
<td>2.1 (impaired)</td>
<td>6.9 (impaired)</td>
<td>5.1 (impaired)</td>
<td>79.9 (asymmetric)</td>
</tr>
<tr>
<td>0</td>
<td>6.3 (tracheostomy)</td>
<td>4.9 (feeding tube)</td>
<td>3.6 (mute)</td>
<td>16.0 (mulitizing)</td>
</tr>
<tr>
<td>Proportion of 0 score group presenting with stage 4 or 5 LMsb</td>
<td>88.9</td>
<td>85.7</td>
<td>80.0</td>
<td>60.9</td>
</tr>
</tbody>
</table>

Abbreviations: CDS, Cologne Disease Score; LMs, lymphatic malformations.

a Parenthetical descriptions for each scoring category are drawn from the original publication of the CDS by Wittekindt et al.11

b See Table 2 for description of the staging system.

Table 4. Results of Multivariate Analysis Including Treatment Type, LM Type, and Increasing LM Staged

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
<th>Effect of Initial Treatment Type (Surgery vs Sclerotherapy)</th>
<th>Effect of LM Type (Macrocystic vs Microcystic)</th>
<th>Effect of Each Increase in LM Stageb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No further treatment after first intervention</td>
<td>.28</td>
<td>.09</td>
<td>.11</td>
</tr>
<tr>
<td>No further treatment within 1 year of first intervention (all patients)</td>
<td>.97</td>
<td>.04</td>
<td>.11</td>
</tr>
<tr>
<td>Mean change in total CDS</td>
<td>.68</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean change in CDS airway subscale</td>
<td>.054</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean change in CDS oral nutrition subscale</td>
<td>.006</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean change in CDS speech subscale</td>
<td>.64</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean change in CDS appearance subscale</td>
<td>.35</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean posttreatment ICU days</td>
<td>.59</td>
<td>...</td>
<td>.005</td>
</tr>
<tr>
<td>Mean posttreatment hospital days</td>
<td>.34</td>
<td>...</td>
<td>.02</td>
</tr>
</tbody>
</table>
| Mean No. of subsequent interventions | .08 | ... | ...
| Need for tracheostomy | .36 | .27 | <.001 |

Abbreviations: CDS, Cologne Disease Score; ICU, intensive care unit; LM, lymphatic malformation.

a Each variable was analyzed while controlling for the other 2. Ellipses indicate comparisons not included in a priori or exploratory analyses.

b See Table 2 for description of the staging system.
tive staging systems and treatment algorithms must be developed based on prospective multisite data collection.

The initial surgery and sclerotherapy groups did not show significant differences in resource utilization, specifically total procedures, ICU days, and hospital days. Sclerotherapy is often seen as a staged, minimally invasive modality requiring multiple rounds of outpatient treatment, whereas surgery is seen as complex, requiring prolonged hospital stays. This view was not borne out in our data. Patients undergoing sclerotherapy may have been less likely to seek further treatment, or treatments may have been provided at other institutions and therefore not captured in our data. An alternative explanation is the use of staged surgical procedures, as discussed earlier. The similarity in hospital and ICU days between initial treatment types may reflect the need for inpatient management after both sclerotherapy and surgery. An important related observation, demonstrated in the Figure, was that most patients whose LM had a lower de Serres stage were treated with a single intervention. This finding suggests that good outcomes with either surgery or sclerotherapy can be achieved relatively quickly in lower-stage head and neck LMs, which in turn underscores the need to develop validated disease burden staging systems. It may also reflect spontaneous regression, which is more likely in stage 1 macrocystic lesions.

Overall mean CDS change and subscale mean changes apart from nutrition did not differ significantly between surgery and sclerotherapy groups. Although changes in CDS were not statistically significant for either treatment group, the mean total change was 0.5. This change may be clinically important given that CDS subscales range only from 0 to 2 and the total possible score range is 0 to 8. Further study of the CDS is necessary to determine whether it provides clinically relevant information as a treatment outcome measure.

This study’s strengths are that it directly compares primary surgery and primary sclerotherapy for LM treatment and that it analyzes a large sample, with the full range of lesion types and stages represented. Analyses controlled for well-accepted covariates, and distributions of these covariates were similar within treatment groups. Resource utilization, an important issue to be considered in any comparison of treatment outcomes, is also addressed in an exploratory fashion. The study also had several limitations. First, it was retrospective, with inherent limitations in data quality and availability. Second, the decision to not use lesion size or complete resolution as outcome measures might increase false-positive classifications—unsatisfied patients not pursuing treatment for other reasons. We attempted to prevent misclassification by ensuring that all included patients had adequate follow-up of at least 1 year. Third, neither de Serres stage nor LM type is validated as a long-term prognostic factor for treatment outcomes. Fourth, we were unable to adjust for lesion location or epicenter, as there is not currently a way to stratify these locations in a consistent manner. Finally, the CDS has not been validated as a measure of treatment outcomes.

In conclusion, this study is the first to directly compare primary surgery and primary sclerotherapy for head and neck LMs. It suggests that these 2 major treatment modalities do not differ in effectiveness after the first intervention or at 1 year. Lower-stage LMs were often treated successfully after a single intervention with either treatment type. Higher-stage LMs are less common than lower-stage LMs and require intensive therapy. Such therapy might be best performed at a center experienced in LM management. Surgery and sclerotherapy did not lead to significantly different resource utilization in our exploratory analysis. Although prospective studies are necessary, these results suggest that providers must continue to individualize treatment decisions until a comprehensive prognostic and staging system becomes available.

REFERENCES


ARTICLE INFORMATION

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Study concept and design: Balakrishnan, Magit, Perkins.

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