Comparative Outcomes for Sclerotherapy of Head and Neck Venous Vascular Malformation between Alcohol and Bleomycin

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Objective: To assess and compare the effectiveness of the two sclerosing agents (95% alcohol and Bleomycin) for the treatment of head and neck venous malformation (VM).

Material and Method: The authors retrospectively reviewed our experience in treating VM of the head and neck region using two sclerosing agents, 95% alcohol (November 2001 to June 2008) and bleomycin (July 2008 to July 2010). Patients’ demography (age, sex), lesion number, location, type (focal/extensive), and characteristic features (cystic/tubular/mixed) were recorded. The treatment outcome was determined by decrease in size of VM in photographs taken at one month and at final clinical follow-up. These were analyzed by two radiologists using visual rating scale (worst or not improved, <50%, 50-75%, >75% of size reduction). One-way Anova test (p<0.1) was used to show the differences in treatment effectiveness of the two sclerosing agents at short- and long-term intervals.

Results: Thirty-three patients, age ranged from 11 to 62 years (mean 25.1 years), with 27 female and six male patients were included in this study. The majority of patients were less than 16 years (17 patients, 51%). The 43 lesions were categorized as 28 VMs were focal (65.1%), 15 (34.9%) diffuse, and 30 (69.7%) were of the mixed type. Sixteen lesions were treated with 95% alcohol, 23 lesions with bleomycin, and four lesions with a combination of the two sclerosants. The range of number of procedures was 1 to 16 (mean 3.76 procedures per patient) for alcohol, and 1 to 5 (mean 2.27 procedures per patient) for bleomycin. The cumulative dose of sclerosant used was 101 ml for alcohol and 32.11 mg for bleomycin. Total follow-up at 1-month and at final was 43/43 (100%) and 35/43 (81.4%) respectively. Mean follow-up interval was 14.7 months. Differences in size reduction after treatment by different sclerosing agents were found. At more than 1-year follow-up, those treated with bleomycin gained graded 3 (>75%) size reduction more than treated by 95% alcohol. No VM treated with 95% alcohol obtained grade 3 of size reduction at 1-year follow-up. Multiple regression analysis showed VM’s favorable character for bleomycin treatment by decreasing mixed, cystic, and tubular. Pediatrics had relatively more benefit with bleomycin treatment.

Conclusion: Sclerotherapy using either alcohol or bleomycin is an effective treatment for VMs. Different treatment outcomes were significant at long-term with group of VM those treated with bleomycin but not at short-term (p<0.1).

Keywords: Sclerotherapy, Vascular Malformation, Alcohol, Bleomycin

Vascular anomalies have been biologically classified into two major groups, vascular tumors (e.g. infantile hemangioma), and vascular malformations based on their clinical behavior, histology, and histochemistry as proposed by Glowacki and Mulliken in 1982(1). Vascular malformations are further subdivided according to their channel content, or flow characteristics into slow flow (including capillary, lymphatic (LM), venous (VM) and combined) malformations, and fast flow (arteriovenous) malformations.

Sclerotherapy has been widely accepted as a primary treatment for VMs with several available sclerosants. Dehydrated (95%) alcohol is one of the most effective and widely used sclerosants. Recently, bleomycin has been reported to be effective in treating LMs and possibly VMs(2-6). Few articles have been published that compares the efficacy of the two agents(7,8).

Therefore, in the present study, our aim was to assess and compare the efficacy and safety of the
two sclerosants for the treatment of head and neck VM in children and adults.

**Material and Method**

Following the approval of the University Hospital Ethics Board, a retrospective analysis was performed on patients with VM of head and neck region who underwent percutaneous sclerotherapy from November 2001 to February 2010, using two sclerosing agents (95% alcohol and bleomycin). Alcohol was used from November 2001 to June 2008, and bleomycin from July 2008 to July 2010.

Patients’ demography (age, sex), clinical presentation, their VM lesion information either number, location, type (focal/diffuse), characteristic features (cystic/tubular/mixed), VM lesion color photography, and details of treatment procedure were recorded. Treatment results determined by changing in size of VM on color photography taken within 1 week before treatment, at one month and at final clinical follow-up were done by two interventional neuroradiologists using visual rating scale, that was categorized as worst or not improved, <50% (grade 1), 50-75% (grade 2), and >75% (grade 3) of size reduction. Cystic appearance was classified when at least 80% of cystic component was apparent in VM. Comparative clinical outcome was evaluated by asking the patients during their clinic visit, which was arranged at one month and every few months after treatment. All patients were scheduled for percutaneous sclerotherapy every eight to 10 weeks if the result was not satisfactory or only partially satisfactory.

Percutaneous sclerotherapy with 95% alcohol or bleomycin was done by two interventional neuroradiologists according to previously reported techniques. All procedures were carried out under general anesthesia. In general, the VM was cannulated with a 20-gauge needle and the needle position was confirmed by free blood returning and injection with contrast media. Sclerosant volume injected was determined by estimating the volume of lesion related to appearance seen on the venogram. Whenever possible, compression of the outflow veins was performed. The maximal volume of alcohol injected was limited to 1mL/Kg (not exceeding 40 mL) per session. For bleomycin, the dose did not exceed 0.5 mg/Kg for infants <1 year and 15 mg for older patients. Bleomycin was prepared with normal saline at 1mg/1mL concentration.

SPSS 11.0.4 was used for all statistical calculations. Descriptive statistics were obtained. One-way Anova test ($p<0.1$) was used to show the differences in treatment efficacy of the two sclerosing agents at short- and long-term intervals. Multiple regression analysis was used for predicting the alcohol and bleomycin’s favorable VM lesion characteristic (cystic/tubular/mixed) and expected excellent outcome (>75% reduction of size).

**Results**

Thirty-three patients with ages ranging from 1 to 62 years (mean 25 years and median 15 years), female/male (27/6) with 43 VMs were included in the present study. Seventeen patients (51%) were children, defined as age less than 16 years. Mean VM lesion/patient is 43/33 (1.3). Twenty-eight VMs were focal, 15 were diffuse. Most of VMs (30/43, 69.8%) were mixed type. Sixteen VMs were treated with 95% alcohol, 23 with bleomycin, and four with a combination of both agents. The latter was indicated if initial treatment with ethanol was unsuccessful.

The number of procedures per patient was 1 to 16 (mean 3.76) sessions for alcohol and 1 to 5 (mean 2.27) sessions for bleomycin. The cumulative dose used per patient was 101 mL for alcohol and 32.11 mg for bleomycin. Data from the 1-month follow-up was available on all patients (100%). Long-term follow-up was available on 35/43 (81.4%) for a period range of 1 to 48 months (mean 15.9 months) for alcohol, and 1 to 24 months (mean = 13.5 months) for bleomycin.

Subjective clinical and objective color photography follow-up results confirmed the effectiveness of percutaneous sclerotherapy for head and neck VM with these two sclerosant drugs were found on the present study.

All patients were satisfied with the result even though there were differences in VM size reduction.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number or mean (n = 33)</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>25±19.1</td>
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<tr>
<td>Range</td>
<td>1-62</td>
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<tr>
<td>Median</td>
<td>15</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>6</td>
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<tr>
<td>Female</td>
<td>27</td>
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<tr>
<td>Type of treatment</td>
<td></td>
</tr>
<tr>
<td>95% alcohol</td>
<td>15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>16</td>
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<tr>
<td>Combine</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
</tr>
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after treatment. In the group of 15 VM patients treated with 95% alcohol, our data showed that most of the lesions slightly decreased in size (grade 1) (15/15, 100%) at one month follow-up, and continued further reduction in size (grade 2) (12/15, 80%) at mean follow-up interval. No response at 1-year follow-up has been found in a minority of this group, who showed no response at 1-month. The patients treated with bleomycin (16 patients), all patients (100%) achieved grade 1-size reduction at 1-month follow-up, and grade 3 (15/16, 93.8%) at mean follow-up interval. Only one patient (1/16, 6.3%) of this group had a constant size VM. There were four VMs in four patients where alcohol treatment was ineffective, so they were further treated with bleomycin. All four patients (100%) were getting better and achieved grade 2 size reduction. This result illustrated that changing sclerosant agent to bleomycin for patients whose VM was unresponsive to alcohol was reasonable and recommended by the present study.

Grade 3 (>75%) of VM size reduction was found in 19 out of 33 patients (57.6%) in the present study, at mean follow-up interval of each group and irrelevant to VM character. Twelve of these patients were treated with bleomycin, five with alcohol, and two with combined drugs. However, it should be noted that no patient treated with alcohol achieved grade 3 of size reduction at 1-year follow-up.

Concerning lesion character and treatment outcome at 1-year follow-up interval, multiple regression analysis revealed that in the group of mixed appearance, which constituted the majority of our patients (26/33, 78.8%), there were five, eight and two patients with VM treated with alcohol, bleomycin, and combined drugs respectively, accomplished grade 3 size reduction. Of six patients with cystic VM, three (50%) treated with bleomycin accomplished size reduction grade 3, but the other three (50%) treated with alcohol achieved only size reduction grade 1 and 2 at 1-year follow-up. Of three patients with tubular appearance of VM, one (33%) treated with bleomycin accomplished size reduction grade 3, but other two treated with alcohol achieved only size reduction grade 1 and 2 at 1-year follow-up. Therefore, our results indicated that mixed type VM can be treated with either drug but bleomycin was preferable. Treating cystic type VM with bleomycin led to the most favorable results.

At 1-year follow-up, treatment with bleomycin proved more effective than treatment with alcohol as most of the patients (9/16, 56.3%) especially children (5/9, 55.6%) treated with this drug obtained size reduction grade 3 at 1-year interval. This was in contrast to treatment with alcohol, which achieved grade 1 or more than grade 1 size reduction, 8/15 patients (53.3%), two of which were children (2/15, 13.3%), at or later than 1 year. One-way Anova test ($p<0.1$) showed the differences in treatment effectiveness of the two sclerosing agents at short- and long-term intervals.

**Discussion**

Treatment of VM is sometimes difficult. Part of the problem is due to our (as yet) poor understanding of the underlying mechanisms of VM development. Recently, supporting clinical observations that VM does not represent tumors or a simple collection of abnormal channels that can be removed, but rather indicates developmental defects that usually involve an entire anatomic area. Defects in genes that control the endothelial-cell specific receptor tyrosine kinase (TIE-2 mutations)$^{10}$ have been found to be associated

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>95% alcohol (n = 15)</th>
<th>Bleomycin (n = 16)</th>
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<tbody>
<tr>
<td>Mean of VM per patient</td>
<td>1.1 (16/15)</td>
<td>1.4 (23/16)</td>
</tr>
<tr>
<td>Mean of procedures per patient</td>
<td>3.76</td>
<td>2.27</td>
</tr>
<tr>
<td>Cumulative dose used per patient</td>
<td>101 ml</td>
<td>32.11 mg</td>
</tr>
<tr>
<td>Mean of long-term follow-up</td>
<td>15.9 months</td>
<td>13.5 months</td>
</tr>
<tr>
<td>No. of patient decreased in size of VM</td>
<td></td>
<td></td>
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<tr>
<td>1 month follow-up</td>
<td>Grade 1 (15/15, 100.0%)</td>
<td>Grade 1 (16/16, 100.0%)</td>
</tr>
<tr>
<td>1 year follow-up</td>
<td>Grade 3 (5/15, 33.3%)</td>
<td>Grade 3 (15/16, 93.8%)</td>
</tr>
<tr>
<td>Mean follow-up interval</td>
<td>Grade 3 (0/15, 0.0%)</td>
<td>Grade 3 (12/16, 75.0%)</td>
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VM = venous malformation

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Table 2. Comparison of patients were treated with 95% alcohol and bleomycin
with defective formation of the smooth muscle and endothelial layers of the vein walls in group of patients with familial vascular malformation. Thus, treatment with alcohol and bleomycin, which affect the dysmorphic endothelial cells lining the venous channels of VM, is reasonable. Bleomycin seems to be more fascinating as it also has antitumoral effect that alcohol does not have. Dual effects of bleomycin as antitumor and sclerosant drugs may be responsible. To date, we know of no randomized trial that clearly shows the best choice of sclerosant agents.

Generally, VM is congenital, and symptoms manifest when they enlarge as the child grows, typically during puberty, or during pregnancy and after surgery or trauma.

Biological factors that influence the progression of vessel dilation are still not well understood. Postnatal angiogenesis does not appear to be responsible for the evolution of these lesions, so pharmacological management with angiogenesis inhibitors is ineffective.

Discoloration and pain are two main problems for patients. Pain from VM is considered to relate with expansion of VM and stagnation of VM flow. Many management methods of VM have been described, for example, compression, resection, and obliteration of the channel lumens by sclerosant injection or laser photocoagulation. Surgical resection may be hazardous and can lead to major blood loss and/or incomplete resection. Recurrent and cosmetic problems are common after surgical resection. Burrows and Mason reported success in treating VM by percutaneous intraliesional injection of sclerosants drugs(11). In their series, 75 to 90% of patients with VM who underwent serial sclerotherapy mainly with alcohol reached good to excellent results. The present study was actually designed to answer some specific clinical questions regarding the method of treatment. Firstly, we really wanted to know the efficacy of these two drugs for treatment of both our child and adult VM patients, when VM character was taken into account. Secondly, we wanted to know at what point should we consider to be the end point of this treatment. To answer the second question, we compared patients’ satisfaction and VM changes on color photography related to treatment procedure.

Although the present study involved a relative small group of patients (33, which 17 were children) and evaluation of the treatment results were limited, we used only lesion color photography. However, the efficacy of alcohol and bleomycin in the present study were in accordance with other published results(2,7,10-13). It was also clear when comparing treatment results that bleomycin seemed to be more effective at long-term (1-year) follow-up interval than alcohol as many more grade 3 size reduction after treatment was obtained. The effect of alcohol was relatively slow but prolonged on the present study when compared to bleomycin as most of alcohol-treated VMs reached only grade 2 size reduction at 1-year, and continued minimal changes after 1 year of treatment. Another piece of evidence supporting the higher potency of bleomycin over alcohol was found in our combined treatment group, and in the pediatric segment of the present study. The authors recommended that those patients who had been unsuccessfully-treated with alcohol, and pediatric patients with head and neck VM, should be treated with bleomycin.

The authors had found the characteristics of VM types seemed to be predictors for favorable treatment responses with each sclerosant. Despite being unable to say for sure about the different biological effects of both sclerosants that determined our study result (and this was clearly another limitation of our study), we can still conclude that sequential treatment with bleomycin every few months should be stopped at 1 year after the first treatment. Reduction of treatment efficacy relative to its obtainable maximal effect was found in more than half of our patients, as the main reason. A long-term study is encouraged to both validate and expand on our findings.

Conclusion

Sclerotherapy using either alcohol or bleomycin is an effective treatment for VMs. Different treatment outcomes were significant at long-term follow-up for the VM patients treated with bleomycin, but not at short term ($p<0.1$).

What is already known on this topic?

Dehydrated (95%) alcohol is one of the most effective and widely used sclerosants. Recently, bleomycin has been reported to be effective in treating LMs and possibly VMs.

What this study adds?

Sclerotherapy using either alcohol or bleomycin is an effective treatment for VMs. Different treatment outcomes were significant at long-term follow-up for the VM patients treated with bleomycin, but not at short-term.
Potential of conflicts of interest
None.

References
การเปรียบเทียบประสิทธิผลของการรักษาโรคหลอดเลือดดําผิดปกติด้วยการฉีดสารทำลายโดยตรง ระหว่างสารทำลายออกฤทธิ์ 95% และยา bleomycin

พิศิษฐ์ ล่อมแสง, อัญชลี ชูเวียง, รุจิมาส ลู่ทอง, ลักษณวัฒน์ มหิวรรณ

วัตถุประสงค์: เพื่อประเมินและเปรียบเทียบประสิทธิผลของการรักษาโรคหลอดเลือดดําผิดปกติด้วยการฉีดสารทำลายโดยตรง (sclerotherapy) ระหว่างสารทำลาย (sclerosing agent) 2 ชนิด ได้แก่ ยาออกฤทธิ์ 95% และยา bleomycin

วัตถุประสงค์และวิธีการ: การศึกษาเป็นการศึกษาแบบย้อนหลัง (retrospective research) เพื่อประเมินผลการรักษาด้วยการฉีดสารทำลายของโรคหลอดเลือดดําผิดปกติในศัลยแพทย์และสังเวียนทางการแพทย์ที่ใช้สารทำลายอย่างกัน 2 ชนิด คือ ทั้งการฉีดสารทำลายออกฤทธิ์ 95% (percutaneous alcohol injection) และการฉีดยา bleomycin (percutaneous bleomycin injection)

สำหรับยาออกฤทธิ์ 95% (alcohol injection) ทั้งหลอดเลือดดําผิดปกติที่ทำการรักษาระหว่างเดือนกรกฎาคม พ.ศ. 2551 ถึง กรกฎาคม พ.ศ. 2553 โดยรวบรวมข้อมูลได้แก่ อาการและลักษณะของโรค ตัวแหน่ง ชนิดของโรค (focal/extensive) และลักษณะของโรค (tubular/mix) และผลประเมินการรักษา (ผลลดลงของขนาดของโรคจากภาพถ่ายที่มีที่กดดันที่มีผลการรักษา 1 เดือนหลังการรักษาแล้วครั้ง แต่ผลการรักษาแบบแตกต่าง และผลการติดตามผลการรักษาครั้งสุดท้าย โดยรังสีแพทย์ 2 คน ทำการวิเคราะห์ด้วยวิเคราะห์สถิติ visual rating scale โดยแบ่งเป็นเกรด 0-3 คือ 0 = ไม่เห็น, 1 = เห็นน้อยกว่าร้อยละ 50, 2 = เห็นร้อยละ 50-75, 3 = เห็นมากกว่าร้อยละ 75 และใช้วิเคราะห์แบบสถิติ one-way ANOVA เพื่อแสดงความแตกต่างของผลการรักษาของยาทำลายทั้ง 2 ชนิด และระยะเวลาในการรักษา

ผลการศึกษา: ผู้ป่วยจำนวน 33 ราย ประกอบด้วยเพศหญิง 27 ราย เพศชาย 6 ราย อายุระหว่าง 1-62 ปี อายุเฉลี่ย 25.1 ปี ระหว่างผู้ป่วยที่อายุน้อยกว่า 16 ปี มีจำนวน 17 ราย (51.5) การศึกษาเรียนเพื่อผลการรักษาโรคหลอดเลือดดําผิดปกติด้วยยา bleomycin 32.11 แปลง (percutaneous bleomycin injection) ออกฤทธิ์ 95% จำนวน 23 ตัวแหน่ง และเป็นการรักษาครั้งที่ 2 ครั้ง 4 ตัวแหน่ง ผู้ป่วยรักษาที่มีการฉีดยาออกฤทธิ์ 95% ระหว่าง 1-6 ครั้ง เฉลี่ย 3.76 ครั้ง คือยา bleomycin 1-5 ครั้ง เฉลี่ย 2.27 ครั้ง คือยา bleomycin ปริมาณเฉลี่ยของยาทำลายเพื่อใช้คือตัดการได้แก่ ยาออกฤทธิ์ 95% ปริมาณเฉลี่ย 101 มก. และ bleomycin ปริมาณเฉลี่ย 32.11 มก. ผู้ป่วยทุกรายได้รับการติดตามผลการรักษาที่ 1 เดือน และติดตามอาการทางคลินิกครั้งสุดท้าย (final clinical follow-up) 35 ตัวแหน่ง จากทั้งหมด 43 ตัวแหน่ง ระยะเวลาติดตามการเฉลี่ย 14.7 เดือน การลดลงของขนาดของโรคผิดปกติหลังการรักษาด้วยยาทำลายหลอดเลือดดําผิดปกติทั้ง 2 ชนิด มีความแตกต่างกันอย่างมีนัยสัมพัทธ์ทางสถิติ (p<0.1) สำหรับการติดตามอาการหลังการรักษาที่ 1 เดือน โดยผู้ป่วยโรคหลอดเลือดดําผิดปกติที่รักษาด้วยยา bleomycin มีความแตกต่างกันเป็นระดับนัยสำคัญที่ 3 คือ ตลอดเวลากรของร้อยละ 75 ในขณะที่การรักษาด้วยยาออกฤทธิ์ 95% ไม่มีผู้ป่วยที่ผลการรักษาได้ผลเป็นเกณฑ์ 3 การวิเคราะห์ของข้อมูลพบว่าลักษณะของโรคผิดปกติของโรคหลอดเลือดดําผิดปกติมีความสัมพันธ์กับผลการรักษาด้วยยา bleomycin ทั้ง 3 ประเภท (mixed, cystic และ tubular) สำหรับผู้ป่วยเดินการรักษาที่มีอาการกล้าต้านยา bleomycin เช่นกัน

สรุป: การรักษาโรคหลอดเลือดดําผิดปกติด้วยการฉีดสารทำลายโดยตรงไม่จะเป็นยาออกฤทธิ์ 95% และยา bleomycin ดังนั้นผลการรักษาที่มีประสิทธิผล ความแตกต่างระหว่างผลการรักษาอย่างมีนัยสัมพัทธ์จะต้องติดตามอาการเร็วมากกว่า 1 ปี (p<0.1)