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Títol:

Gross Hemoglobinuria and Oliguria are Common Transient Complications of Sclerotherapy for Venous Malformations:
Review of 475 Procedures.

Director:

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ÍNDEX:

ABSTRACT

Purpose

To study the incidence, risk factors and treatment for gross hemoglobinuria and oliguria following sclerotherapy for venous malformations.

Materials and Methods

The clinical records and imaging studies of patients with venous malformations who underwent sclerotherapy at our institution between July 1993 and August 2007 were reviewed. Demographic data, location and estimated size of the malformation, type and dose of the sclerosing agents, development of post-procedural hemoglobinuria and the treatment given were documented and analyzed.

Results:

475 procedures were performed on 131 patients with venous malformations (57 males; 74 females, age range 2-58 years). The number of procedures ranged from 1 to 21 (mean 3.6 procedures) per patient.

Ethanol was used in 27 % of the procedures, sodium tetradecyl sulfate in 47 % and both agents in 26 %.

Transient hemoglobinuria occurred after 34 % of sclerotherapy procedures and 57 % of these were associated with transient oliguria with increased risk with higher adjusted doses (sclerosant's volume/ weight of patient) for both agents. Resolution of the hemoglobinuria and oliguria with hydration, alkalinization and diuretics was successful in all patients. The risk of hemoglobinuria increases with sclerotherapy of venous malformations affecting the lower extremities and multiple locations.

Conclusions:

Transient hemoglobinuria and oliguria are common complications of sclerotherapy for venous malformation. However, with proper fluid management, all the patients promptly recovered. The risk correlates with the volume of sclerosant (adjusted to patient's weight) and is higher for lower extremity and multiple locations.

INTRODUCTION

Venous malformations (VM) are developmental anomalies which can cause symptoms due to thrombosis, deformity and impairment of limb function. Treatment of venous malformations includes conservative measures (e.g. compression stockings), sclerotherapy, laser photocoagulation, anticoagulation and surgical resection. As many of these lesions are not surgically resectable, sclerotherapy has become the therapeutic mainstay [1]. Post-sclerotherapy hemoglobinuria is a known complication of sclerotherapy of venous malformation [2]. In this study, we evaluated the incidence, risk factors of developing this complication and treatment for this complication.

MATERIALS AND METHODS

This study was reviewed and approved by the Children's Hospital Boston Committee on Clinical Investigation. A retrospective review of the medical records and imaging Studies was performed on all patients with venous malformations who underwent sclerotherapy in the Division of Interventional Radiology at Children's Hospital Boston from July 1993 through August 2007. Patients with combined vascular malformation or overgrowth syndromes with complex vascular anomalies were excluded from this study. The patients were initially evaluated by our multidisciplinary Vascular Anomalies Center or by an experienced interventionalist and the diagnosis of VM was established clinically and radiologically.

For each procedure, demographic data, location and estimated size of the VM and type and dose of the sclerosant were documented. The locations of the VM included the cervicofacial, thoracic, pelviabdominal, upper extremity, lower extremity and multiple anatomical areas. Following sclerotherapy, the development of hemoglobinuria, oliguria and the treatment administered and outcome were also collected on all patients. For follow up, patients were contacted by telephone 1 day, 1 week, and 1 month after the procedure.

Assessment of the size of the venous malformation:

The size of the lesion was divided into two major groups: measurable and non-measurable based on the cross sectional

imaging studies (MRI and CT). Non-measurable lesions were either very small (subcentimetric) or very large (involving a wide area and several tissue planes).

Technique of Sclerotherapy

The treatment was performed under general anesthesia using an established protocol [3]. Based on the discretion of the interventionalist, the sclerosing agent used was either 98% ethanol, 3% sodium tetradecyl sulfate (STS) (Sotradecol, AngioDynamics, Inc. Queensbury, NY or Fibrovein, STD Pharmaceuticals, Hereford, UK) or both. Ethanol was opacified with oil-based contrast (Ethiodol, Savage Laboratories, Melville, NY) by mixing 10 ml of ethanol with 2 ml of Ethiodol. STS was made into foam by adding equal volume of air (or more) with or without Ethiodol. The dose of ethanol was limited to 1 ml/kg (not exceeding 60 ml) per procedure. The maximal dose of STS 3 % was 0.5 mL/kg (not exceeding 30 ml) per procedure.

Intra- operative and Post-operative Fluid Management

Prior to sclerotherapy, a Foley catheter was inserted in the urinary bladder to monitor urine output and to observe for gross hemoglobinuria. The patients were generously hydrated throughout the procedure and recovery period. Intraoperatively, the preoperative fluid deficit was replaced with intravenous crystalloid (lactated Ringer's) in the first 1-2 hours of the case, and fluids were then continued at 1 ½ - 2 times the maintenance rate.

The color of the urine and the urine output were observed for the development of hemoglobinuria (pink to brown discoloration of urine) [Fig. 1]. If gross hemoglobinuria developed, the intravenous fluid was modified to D5W with 75 mEq/L sodium bicarbonate running at the maintenance rate to alkalinize the urine. Any additional fluid was administered as lactated Ringers or normal saline. During the recovery period, patients were kept on D5W with 75 mEq/L sodium bicarbonate running at 2 times maintenance until the urine was clear. Blood pH was not routinely checked. Oliguria (defined as urine output less than 1 ml/kg/hour) was treated with a bolus of IV normal saline (10-20 ml/kg) and a single small dose of intravenous furosemide (0.25 mg/kg).

Statistical analysis:

Since gross hemoglobinuria is a binary outcome, we used a logistic regression model to analyze the relationship between the dose of agent (adjusted for weight) and the development of hemoglobinuria. Similarly, the effect of the anatomical locations of the malformation was studied. P value < 0.05 was considered statistically significant.

RESULTS

A total of 131 patients were included in the study with 57 males and 74 females. The age of the subjects ranged from 2 to 58 years (median 8 years). A total of 475 procedures were performed with an average of 3.6 procedures per patient (range 1-21 procedures).

The following anatomical locations were treated: lower extremity (n=46, 35.1 %), head and neck (n=44, 33.6 %), upper extremity (n=18, 13.7 %), thorax (n=8, 6.1%), abdomenpelvis (n=8, 6.1 %) and multiple locations (n=7, 5.3 %). 57 patients had a measurable lesion and 62 patients had non-measurable lesions (very small in 16 and very large in 46) and data was not available on 12.

Ethanol was used in 128 procedures (27%) of the procedures with a dose range of 3 to 60 ml. 3% STS was used in 224 procedures (47%) with a dose range of 1-30 ml. A combination of both agents was used in 123 procedures (26%) with the same maximal doses. Post-sclerotherapy gross hemoglobinuria was noted towards the end of the procedure and/or during the recovery period in 162 procedures (34%). Ninety-two of these 162 procedures (57%) (or 19% of total number of procedures) were associated

with transient oliguria. In all cases of oliguria, there was concomitant hemoglobinuria. The corrected dose (volume of agent/weight of patient) of both ethanol and STS 3% is a significant predictor of the development of hemoglobinuria. The odds of developing hemoglobinuria increased by 193 and 665 times for each volume/weight unit (ml/kg) increase for STS 3% and ethanol, respectively.

As only a fraction of the subjects had measurable malformations, the statistical power to detect a difference was negatively affected. However, in our practice, the dose of sclerosant seems to correlates with the size of the venous malformation. Hence, after the

dose effect was included in the analysis, the effect of the size of the malformation was marginalized. For the anatomical location of the VM, only the lower extremity (P=0029) and multiple anatomical areas (P=0.0120) were associated with increase risk of hemoglobinuria.

Treatment with adequate hydration, alkalinization of urine and diuretics was successful in all patients.

DISCUSSION

Venous malformations are the most common type of vascular anomalies. These malformations are present at birth, commonly symptomatic, grow proportionately with the patient and do not spontaneously regress (4). Since many VMs are not fully resectable and medical therapies are not predicted to have an effect in the absence of cellular proliferation or angiogenesis, sclerotherapy has emerged as the primary treatment option for venous malformations. Ideally, sclerotherapy of VMs is achieved with the controlled delivery of a toxic agent (sclerosant) which damages the endothelial lining of the malformation. The goal of this endothelial damage is the formation of irreversible occlusive thrombi to obliterate the slow-flow, dilated venous channels in these malformations. Recanalization after sclerotherapy or expansion of adjacent channels frequently requires repeated treatments, especially in larger malformations. The toxic effects of sclerosants at the biochemical and cellular level are significant. Buchta et al. reported tissue findings following infusion of ethanol into the renal artery in dogs (5). Electron microscopy showed that degeneration of the glomerular Basement membrane occurred in 2 minutes with necrosis of endothelial, epithelial, and mesangial cells and loss of nuclear structure. Detergent sclerosants (such as STS, sodium morrhuate, ethanolamine and polidocanol) produce endothelial damage, decreasing the endotelial cell surface tension, interfering with cell surface lipids, disrupting intercellular adhesión molecules, and extracting cell surface proteins (6). While not targeted by sclerotherapy, circulating erythrocytes are lysed, leading to significant release of free hemoglobina through at least two distinct mechanisms. First, direct membrane damage by sclerosants may lyse erythrocytes. Erythrocytes are significant components of venous thrombi, perhaps more so in slow-flow VMs, and prolonged exposure to sclerosant at the site of injury may enhance this mechanism of hemolysis.

Second, fibrin generation triggered by sclerotherapy may contribute to microangiopathic shearing of circulating erythrocytes.

We have seen evidence of this on peripheral blood smears in some patients.

Hemoglobin freed into the plasma is bound to haptoglobin (a protein produced by the liver). The halflife of haptoglobin-hemoglobin complexes is minutes, leading to rapid depletion of haptoglobin levels (7, 8). If haptoglobin is depleted by accelerated intravascular hemolysis, the resulting free hemoglobin is filtered by the kidneys and degraded by the renal tubular epithelium (9).

Free plasma hemoglobin also depletes nitric oxide, which may consequently cause dystonias involving the gastrointestinal, cardiovascular,

pulmonary and urogenital systems, as well as clotting disorders (10).

The plasma ethanol level is directly proportional to the amount of ethanol injected and not dependent on the VM morphology, venous drainage, or injection technique (11). Nevertheless, none of our patients developed any clinically significant systemic hemolysis despite the fact that some of the received relatively large doses of two sclerosants. Despite some patients receiving relatively large doses of the two sclerosants, no patient developed complication of hemolysis beyond transient hemoglobinuria and oliguria. Gardner and Brooks studied the hematologic and coagulating parameters During endoscopic sclerotherapy of esophageal varices and found no evidence of disseminated intravascular coagulation (12). Despite some patients receiving relatively large doses of the two sclerosants, no patient in our study developed complication of hemolysis beyond transient hemoglobinuria and oliguria.

It has been demonstrated that injection of sclerosants into the superior vena cava results in marked hemolysis and a significant decrease in creatinine clearance (13). Berenguer and colleagues reported gross hemoglobinuria in 28% of patients who underwent sclerotherapy for craniofacial venous malformations (2). The acute adverse effects of hemolysis on renal function following sclerotherapy were also common in our cohort. More than half of the patients with hemoglobinuria also developed oliguria. If evaluated with more sensitive measures - such as urine analysis for heme, circulating lactate dehydrogenase or haptoglobin levels – we would predict that the majority of patients have measurable hemolysis; though microscopic hemoglobinuria would not require intervention.

Our study showed an increased probability of the development of hemoglobinuria

following sclerotherapy for VMs in the lower extremity and multiple locations. A plausible explanation for this result may be that lower extremity VMs tend to be large and require a larger volume of the sclerosants for effective sclerotherapy.

Various measures have been advocated as prophylaxis against renal damage by free hemoglobin. Miyoshi and colleagues reported that haptoglobin prevents renal dysfunction associated with intravariceal infusion of ethanolamine oleate; a sclerosing agent similar to STS (14). Renal tubular function indices increased following sclerotherapy while glomerular filtration rate remained normal. Ohta et al. reported that albumin inhibits hemolysis induced by sclerotherapy for esophageal varices in a dose-dependent manner (15). Our patients were typically healthy children with normal albumin, renal and liver function, and no interventions beyond hydration and alkalinization were necessary. None of them clinically developed any sequela of their transient hemoglobinuria and oliguria.

We believe generous IV hydration is particularly crucial as patients have had a prolongad fast prior to the procedure and are likely to be dehydrated. While initiation of intravenous fluids prior to the start of the case would be ideal, it is not always possible in the pediatric population. Thus, it is our practice to quickly replace the preoperative deficit once intravenous access is obtained. We recommend the placement of a Foley catheter for observation of the color and volume of urine. Gross hematuria developed during or immediately following the procedure, and patients were not discharged home until they had fully recovered from general anesthesia and had resumed the production of clear urine.

This study is not without limitations: the retrospective nature, the heterogenous size and location of the VMs, the variable doses and combinations used and lack of information about the systemic levels of the sclerosants made it difficult to quantify the effect of sclerosants on the erythrocytes and the subsequent biochemical and clinical sequelae.

In conclusion, our study demonstrated that gross hemoglobinuria and oliguria are common, transient sequelae of sclerotherapy for venous malformations using ethanol and sodium tetradecyl sulfate. The lower extremity and multiregional venous malformation are more likely to develop this complication. The higher dose (ml/kg) of the sclerosants is a strong predictor of these complications and treatment with hydration and diuresis is effective.

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CAPTIONS

Figure 1. Early development of hemoglobinuria during sclerotherapy for VM. Note the faint reddish-brownish discoloration of the urine which occurred after the injection of the sclerosant, compared to the clear urine obtained earlier.