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Risk Factors for Macroscopic Haemoglobinuria After Sclerotherapy Using Ethanolamine Oleate for Venous Malformations

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WHAT THIS PAPER ADDS

This study identified a total injected dose of 5% ethanolamine oleate (EO) $\geq$ 0.18 mL/kg as an independent contributing factor for the risk of macroscopic haemoglobinuria (MH) after sclerotherapy for venous malformations. Moreover, MH is a reversible complication if immediate and appropriate interventions are performed with aggressive hydration and haptoglobin administration. Hence, MH should be closely monitored following sclerotherapy, especially when using 5% EO $\geq$ 0.18 mL/kg.

Objectives: Sclerotherapy is an essential component of the treatment for venous malformations, and ethanolamine oleate (EO) is known as a useful sclerosing agent. However, macroscopic haemoglobinuria (MH) and subsequent renal impairment are severe complications after sclerotherapy using EO. The present study aimed to clarify the MH risk factors for better peri-operative management of venous malformations.

Methods: Data collected during 130 procedures involving 94 patients who were undergoing sclerotherapy using EO for venous malformation were retrospectively analysed. Pre-operative and operative variables, including sex, age, pre-operative body mass index, location, depth, type of lesion, size, number of procedures, type of drainage vein, ratio of sclerosant to air, and injected total dose of 5% EO per body weight (BW), were examined. Univariable analysis and multivariable logistic regression were performed to determine the possible risk factors for MH.

Results: Following sclerotherapy, MH occurred in 27.7% of patients, but no patient developed post-operative renal impairment because of aggressive hydration and haptoglobin administration. On univariable analysis, diffuse lesion, lesion size $\geq$50 cm^2, and total injected dose of 5% EO $\geq$ 0.18 mL/kg were found to be the MH risk factors. Multivariable logistic regression analysis identified a total injected dose of 5% EO $\geq$ 0.18 mL/kg as the significant independent factor contributing to MH risk.

Conclusions: Macroscopic haemoglobinuria is a reversible complication if immediate and appropriate interventions with aggressive hydration and haptoglobin administration are performed; therefore, it should be closely monitored following sclerotherapy, especially when using 5% EO $\geq$ 0.18 mL/kg.

Keywords: Macroscopic haemoglobinuria, Sclerotherapy, Ethanolamine oleate

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INTRODUCTION

Venous malformation is the most common type of vascular malformation and enlarges gradually without spontaneous regression. Small and localised lesions are usually treated by surgical excision; however surgical excision of diffuse or extensive lesions is often difficult because of risks such as haemorrhage, musculoskeletal impairment, and conspicuous scar. Conversely, percutaneous sclerotherapy, which leads to vessel obliteration by damaging the endothelium with subsequent inflammation and fibrosis, can reduce the lesion size with fewer risks than surgical excision,[1–3] and its utility is described in the Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS).[4] Accordingly, sclerotherapy is an essential component of treatment for venous malformation.

Ethanolamine oleate (EO) is one of the most widely used sclerosing agents for sclerotherapy of oesophageal varices,[5–7] and several studies have reported its usefulness for treating venous malformations.[1,8–12] EO has an equivalent or superior clinical effect to other sclerosants, such absolute ethanol, on volumetric reduction of venous malformation, with few systemic complications.[1,8] The effect of EO can be preserved even after dilution; therefore, EO can be mixed with contrast to confirm that the sclerosant has been

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injected into the vascular lumen of the venous malformation and to achieve proper diffusion and retention.[1] On the other hand, macroscopic haemoglobinuria (MH) is a common, but serious, complication following sclerotherapy using EO for venous malformation.[1,8,13,14] EO is known to act on red blood cell membranes to induce intravascular haemolysis and release of free haemoglobin; subsequently, MH occurs when the levels of free haemoglobin in the circulating blood exceed 22–35 mg/dL.[5,15,16] Under normal conditions, free haemoglobin is excreted by the glomerulus and reabsorbed in the renal tubules. However, renal impairment can occur if free haemoglobin exceeds the amount that can be reabsorbed.[6,17] Indeed, case series have reported patients who developed acute renal failure followed by MH after sclerotherapy using EO,[15,18] implying that MH is a corresponding condition requiring immediate intervention; therefore, predicting MH after sclerotherapy using EO for venous malformation is important and beneficial. However, the MH risk factors have not been identified. The present study aimed to clarify the factors contributing to MH with statistical analysis to enable more effective peri-operative management of venous malformations.

MATERIALS AND METHODS

A retrospective analysis was performed of a prospectively collected database of 129 consecutive Japanese patients who underwent sclerotherapy using EO for venous malformation at the Kyorin University Hospital from 2012 to 2017. Exclusions included twenty-eight patients undergoing combined therapy with surgery and sclerotherapy and seven patients undergoing sclerotherapy using EO combined with other sclerosants, such as absolute ethanol or polidocanol. Therefore, a total of 94 patients were included. The study was approved by the institution's ethics committee, and all patients provided informed consent.

Pre-operative evaluation

Venous malformation was diagnosed using magnetic resonance imaging (MRI) and ultrasonography. Venous malformations were divided into isolated or diffuse type lesions (Fig. 1). The size was determined by the product of the largest diameter and the perpendicular maximum width measured on pre-operative MRI.[8] The size of diffuse lesions was evaluated in the lesion targeted for sclerotherapy. Pre-operative variables such as sex, age, pre-operative body mass index (BMI), location, depth, type of lesion, and size were recorded. Pre-operative renal function with a measure of estimated glomerular filtration rate (eGFR)[19,20] and serum albumin level, which influence renal impairment induced by haemolysis,[6] were evaluated using blood examinations in all patients.

Procedure

Sclerotherapy was performed in accordance with the institution's established protocol, as previously reported.[1,8] Most procedures were performed under general anaesthesia. A Foley catheter was inserted to monitor urine output and MH in all patients prior to sclerotherapy. During sclerotherapy, a trial injection of contrast medium was used until the lesion opacified prior to the appearance of the draining vein to confirm the accurate placement of the injection into the cavernous lesion and to estimate the volume for subsequent sclerosant injection; additionally, a foaming sclerosant mixture of 5% liquid EO with air in the ratio of 1:2, 1:3, or 1:4 was used.

Post-operative monitoring

Hydration was maintained in all patients throughout the procedure and until the next morning to maintain a urine volume of 1 mL × body weight (BW) per hour for at least 3 h after the procedure, while patients were observed for the

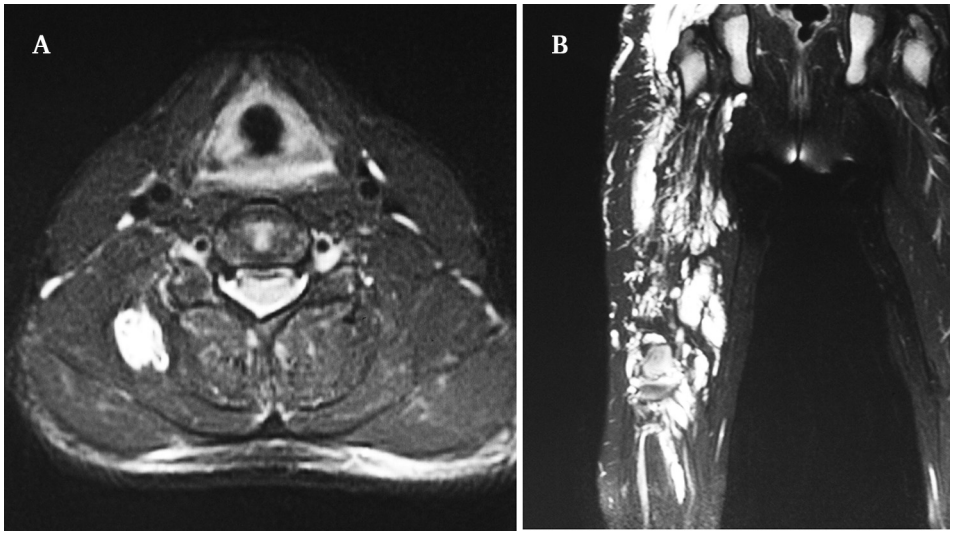

Figure 1. Types of venous malformations. (A) Isolated type of venous malformation in the right cervix. (B) Diffuse type of venous malformation in the right thigh.

occurrence of MH. The diagnosis of MH was primarily based on the macroscopic findings (Fig. 2), but the urine dipstick test was used to accurately distinguish and diagnose MH from choluria. Hydration was maintained until the urine became completely clear if MH occurred post-operatively. Maintenance hydration was continued even after the disappearance of MH to further maintain the urine volume at $\geq$ 0.5 mL $\times$ BW per hour. In the presence of MH and a positive fluid balance, furosemide was administered.[21] In addition, for post-operative MH, haptoglobin was intravenously administered as soon as possible. In adult cases, haptoglobin was initially administered at a dose of 2000 units. If the MH persisted, additional doses of 2000 units each and a maximum dose of up to 8000 units were administered until MH was treated. In paediatric cases, a first dose of 1000 units was administered followed by an additional dose 1000 units each and a maximum dose of up to 4000 units.[1] In patients who developed MH, post-operative renal function was evaluated by measuring eGFR with blood examination the morning after the procedure.

The medical records and operative notes of patients were reviewed for operative variables including number of procedures, type of drainage vein, ratio of sclerosant to air, and the injected total dose of 5% EO per BW. Draining veins were categorised into three groups with reference to previous reports:[22,23] no draining vein, draining vein into a normal vein, and draining vein into a dilated vein (Fig. 3). The amount of 5% EO injected was estimated by the initial amount of 5% liquid EO before preparing foam.

Statistical analysis

All independent variables were subjected to univariable analysis to establish their relationship with MH, and the results were evaluated using Fisher exact test. The receiver operating characteristic (ROC) curve was used to determine the cut off point of the injected total dose of 5% EO per BW, and the most appropriate cut off point was defined in a way that it presented the best trade off between high sensitivity and high specificity. Variables with $p < .10$ on univariable analysis were subjected to multivariable logistic regression analysis to identify the variables independently associated with MH. All analyses were performed using SPSS Ver. 24 statistical software (SPSS Inc., Chicago, IL, USA).

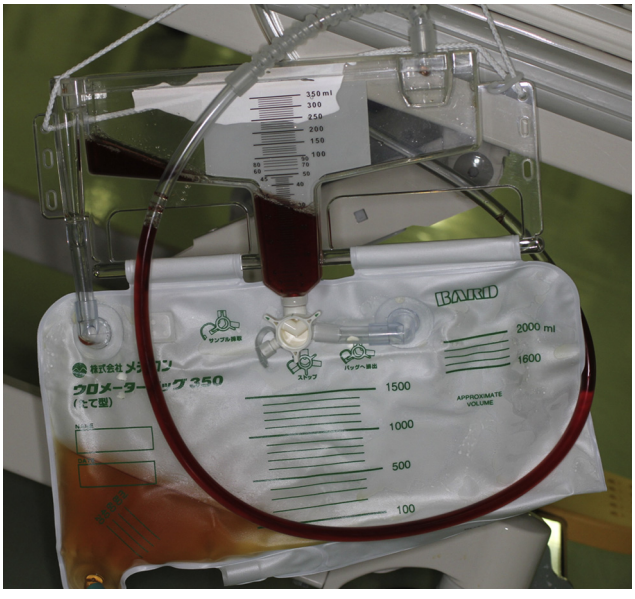

Figure 2. Macroscopic haemoglobinuria following sclerotherapy using ethanolamine oleate.

RESULTS

The patient characteristics included in the present study are summarised in Table 1. Twenty-nine males and 65 females were evaluated with a median age of 22 (range 2—78) years at the time of first sclerotherapy. There was a total of 130 procedures with an average of 1.4 $\pm$ 0.9 (range 1—6) procedures per patient. In all patients, pre-operative renal function (pre-operative mean eGFR, 135.7 $\pm$ 56.9 mL/min/1.73 m^2) and serum albumin level were within the normal limits. Macroscopic haemoglobinuria occurred in 36 procedures (27.7%) following sclerotherapy. Aggressive hydration and administration of haptoglobin were used to manage all patients who developed MH. Post-operative eGFR in all these patients was within the normal limits (post-operative mean eGFR, 133.3 $\pm$ 64.3 mL/min/1.73 m^2). The mean dose of haptoglobin administered was 2842 $\pm$ 882 and 1941 $\pm$ 1044 units in adults and children respectively, which resolved MH within 3 h of initiating the treatment.

Fig. 4 shows the ROC curve for the injected total dose of 5% EO per BW; 0.18 mL/kg (sensitivity 72%, specificity 67%) was established as the cut off point for subsequent analysis. Table 2 shows the results of pre-operative and operative variables on univariable analysis. Diffuse lesion ($p = .08$), size $\geq$ 50 cm^2 ($p = .006$), and total injected dose of 5% EO per BW $\geq$ 0.18 mL/kg ($p = .0001$) were significantly related to MH. There was no significant correlation between age and MH ($p = .15$). The results of the multivariable logistic regression analysis are shown in Table 3. Total injected dose of 5% EO per BW $\geq$ 0.18 mL/kg (odds ratio [OR] = 3.830; $p = .005$) was an independent factor contributing to MH after sclerotherapy using EO for venous malformation.

DISCUSSION

In the present study, MH occurred in 27.7% following sclerotherapy using EO for venous malformation, and the independent factor contributing to MH risk was an injection of 5% EO $\geq$ 0.18 mL/kg.

The incidence of MH following sclerotherapy for venous malformation is reported to vary from 28% to 50%.[1,8,13,14] An intravascular injection of EO can trigger haemolysis followed by the release of free haemoglobin;[5,15,16] Barranco-Pons[14] reported two distinct mechanisms of haemolysis: direct membrane damage caused by a sclerosant and micro-angiopathic shearing of circulating red blood cells with fibrin generation triggered by sclerotherapy. Therefore,

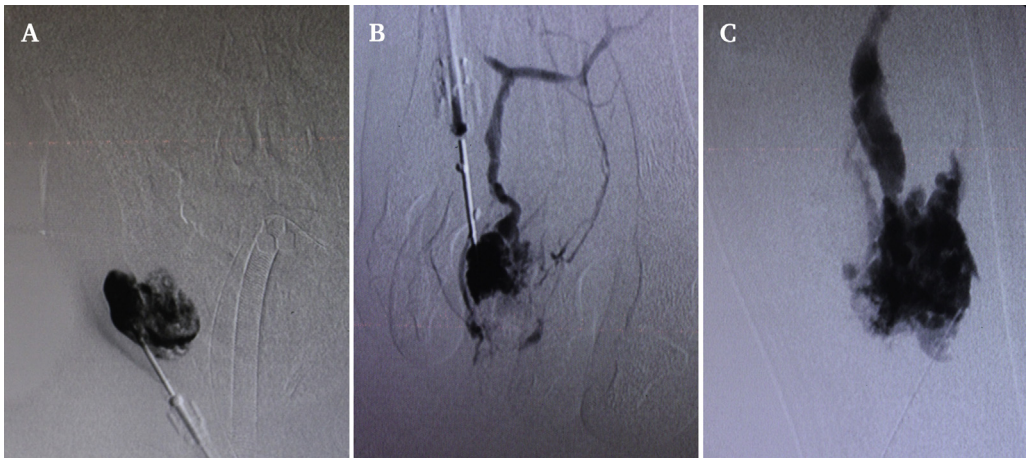

Figure 3. Following injection of contrast prior to ethanolamine oleate injection. (A) Isolated malformation without draining vein. (B) Malformation that drains into normal vein. (C) Malformation that drains into dilated vein.

intravascular haemolysis followed by MH would be an inevitable adverse event after intravascular injection of high dose EO. In addition, a previous study on the treatment of oesophageal varices reported that haemolysis increases in an EO concentration dependent manner,[6] which emphasises the importance of closely monitoring MH after sclerotherapy using high dose EO per BW (≥0.18 mL/kg). On the other hand, in the current series, no cases progressed to renal failure thanks to aggressive hydration and haptoglobin administration. This result indicates that MH is a reversible complication if immediate and appropriate interventions are performed. Therefore notably, the study result does not necessarily suggest restricting the use of EO ≥ 0.18 mL/kg for venous malformations in the clinical setting in patients with sclerotherapy provided that adequate post-operative monitoring is performed. As an alternative, the combined use of other sclerosants such as polidocanol, which has not been reported to influence post-operative renal function,[24] should be considered.

Previous studies have reported that MH typically occurs in large lesions,[2,14] although this was not statistically significant on multivariable analysis in the present study. Lesion size is an important clinical factor in effective sclerotherapy, and more sclerosant is necessary for larger lesions,[13,23] which may possibly explain why the present study results found that the incidence of MH is significantly higher after sclerotherapy for large lesions on univariable analysis. There is currently no high quality evidence of a

Table 1. Clinical characteristics of patients who underwent sclerotherapy using ethanolamine oleate for venous malformation (total number = 94)

Patient characteristics	
Sex	
Male	30 (31.9%)
Female	64 (68.1%)
Median age, range (years)	22 (2–78)
Location	
Head and neck	35 (37.2%)
Trunk	10 (10.6%)
Upper extremity	15 (16.0%)
Lower extremity	34 (36.2%)
Depth	
Subcutaneous	6 (6.4%)
Musculoskeletal	50 (53.2%)
Both	38 (40.4%)
Lesion type	
Isolated	47 (50.0%)
Diffuse	47 (50.0%)

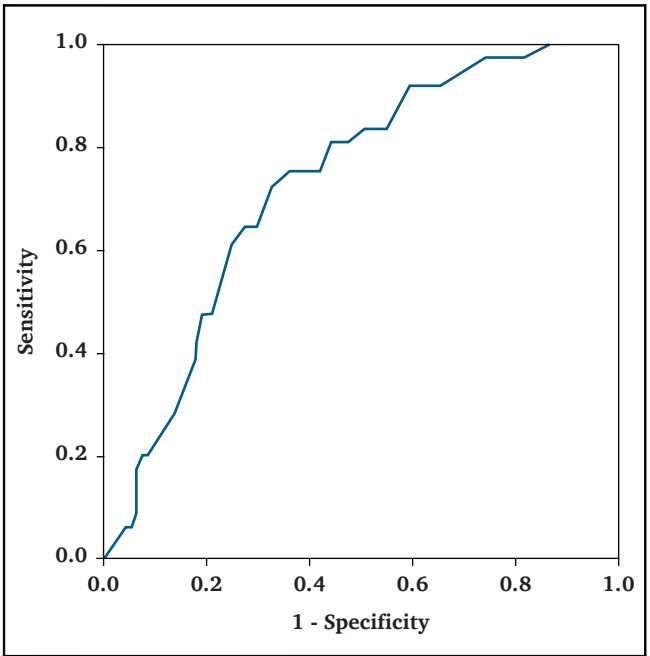

Figure 4. Receiver operating characteristic curve: the total injected dose of 5% ethanolamine oleate per body weight and macroscopic haemoglobinuria; area under the curve = 0.72.

higher incidence of MH following sclerotherapy for larger venous malformations. Based on the limited experience so far, it is obvious that multiple treatment sessions may be required for large venous malformations and that 5% EO should be used in a dose of 0.4 mL/kg for adults and not exceed a total of 20 mL, and in a decreased dose according to BW for children (0.3 mL/kg) at each treatment.[1,8,10] In addition, the risk of MH should be evaluated based on the dose of injected EO and not the lesion size.

Macroscopic haemoglobinuria following sclerotherapy is a corresponding condition requiring immediate intervention, and preventive approaches against renal impairment have been reported.[5,6,15,21,25] The distinct mechanism of renal damage, other than that caused by free haemoglobin, includes a decrease in renal arterial flow following injection of 5% EO.[25] Therefore, hydration is particularly crucial during the peri-operative period, and it is important to carefully balance the fluid administered, along with the urine output. Administration of haptoglobin, a protein produced by the liver, is also important for the treatment of MH.[15] Haptoglobin combines with excess free haemoglobin to form a haptoglobin—haemoglobin complex, which is metabolised by the liver rather than being excreted through the kidney.[5,25] Consequently, MH severity is markedly reduced following haptoglobin administration.[5,25] The policy of the institution is that haptoglobin should be administered immediately once MH has occurred post-operatively even if there are no signs of renal impairment. Further, the utility of albumin administration for MH has been reported following endoscopic injection sclerotherapy using EO for

Table 2. Results of univariable analysis assessing pre-operative and operative variables of macroscopic haemoglobinuria following sclerotherapy using ethanolamine oleate for venous malformation

Variables	Procedures with post-operative haemoglobinuria (n = 36)	Procedures without post-operative haemoglobinuria (n = 94)	p
Sex			
Male	14 (38.8%)	27 (28.7%)	.29
Female	22 (61.1%)	67 (71.3%)	
Age (years)			
≤ 15	17 (47.2%)	30 (31.9%)	.15
> 15	19 (52.8%)	64 (68.1%)	
Pre-operative BMI (kg/m^2)			
≤ 18.5	14 (38.9%)	28 (29.8%)	.31
> 18.5, ≤25	19 (52.8%)	62 (66.0%)	
> 25	3 (8.3%)	4 (4.3%)	
Location			
Head and neck	9 (25.0%)	34 (36.2%)	.66
Trunk	5 (13.9%)	10 (10.6%)	
Upper extremity	6 (16.7%)	13 (13.8%)	
Lower extremity	16 (44.4%)	37 (39.4%)	
Depth			
Subcutaneous	0	7 (7.4%)	.28
Musculoskeletal	18 (50.0%)	46 (48.9%)	
Both	18 (50.0%)	41 (43.6%)	
Lesion type			
Isolated	11 (30.6%)	46 (48.9%)	.08
Diffuse	25 (69.4%)	48 (51.1%)	
Size (cm^2)			
< 50	20 (55.6%)	76 (80.9%)	.006
≥ 50	16 (44.4%)	18 (19.1%)	
Number of procedures			
One	26 (72.2%)	68 (72.3%)	1.00
Two or more	10 (27.8%)	26 (27.7%)	
Type of draining vein			
No draining vein	10 (27.8%)	40 (42.6%)	.27
Drainage into normal vein	13 (36.1%)	29 (30.9%)	
Drainage into enlarged vein	13 (36.1%)	25 (26.6%)	
Ratio sclerosant/air			
1/2	10 (27.8%)	20 (21.3%)	.74
1/3	22 (61.1%)	61 (64.9%)	
1/4	4 (11.1%)	13 (13.8%)	
Total dose of 5% EO per BW (mL/kg)			
< 0.18	11 (30.6%)	64 (68.1%)	.0001
≥ 0.18	25 (69.4%)	30 (31.9%)	

BMI = body mass index; EO = ethanolamine oleate; BW = body weight.

Table 3. Results of multivariable logistic regression analysis assessing independent factors for macroscopic haemoglobinuria following sclerotherapy using ethanolamine oleate for venous malformation

Variables	Odds ratio	95% confidence interval	*p*
Diffuse lesion	0.977	0.3520–2.710	.96
size ≥50 cm^2	1.890	0.6720–5.300	.23
Total dose of 5% EO per BW ≥ 0.18 mL/kg	3.830	1.5100–9.700	.005

EO = ethanolamine oleate; BW = body weight.

eradicating oesophageal varices,[6] suggesting that EO splits into oleic acid and ethanolamine after entering the systemic circulation and that oleic acid combines with serum albumin in the blood.[26] Approximately 50% of oleic acid combines with serum albumin within 30 min.[26] Oleic acid activity is lost as a result of the complex, and erythrocyte haemolysis induced by EO is inhibited by albumin. However, in this report, the subjects were cirrhotic patients with low serum albumin levels. Patients undergoing sclerotherapy for venous malformation were typically healthy with normal albumin levels; therefore, no interventions, apart from aggressive hydration and haptoglobin, were necessary in these patients.

The present study had several limitations. First, it was a retrospective study with a limited sample size; hence, the operative procedure and post-operative management were not entirely standardised and statistical analysis showed limited reliability. However, this is the first report to statistically analyse the factors contributing to MH solely in patients undergoing sclerotherapy using EO for venous malformation, although more investigation with a larger number of patients is needed to definitively prove the MH risk factors. Second, the laboratory blood levels relating to renal function were not routinely evaluated in patients not developing MH after treatment; hence occult renal impairment cannot be excluded. However, no previous literature has reported a case developing acute renal failure without MH. In addition, in the current series, no patient presented with symptoms associated with renal failure, such as acute anuria or severe oliguria not responding to intervention.

CONCLUSION

Injecting 5% EO per BW ≥ 0.18 mL/kg was the independent factor contributing to the risk of developing MH after sclerotherapy for venous malformation. If immediate and appropriate intervention with aggressive hydration and haptoglobin administration are adopted, MH can be reversed; therefore, MH should be closely monitored for following sclerotherapy, especially when using 5% EO ≥ 0.18 mL/kg.

CONFLICT OF INTEREST

None.

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