INTRODUCTION

Arteriovenous malformations (AVMs) are congenital lesions consisted of abnormal connections of the hypertrophied inflow arteries and shunting through a primitive vascular nidus into tortuous dilated outflow veins. AVM has the strong potential of residual mesenchymal cells evolving into malformed embryonal tissue so that extreme care should be required not to overlook its eruption like a volcano. AVM surgery proved extremely difficult and hazardous, so sclerotherapy with alcohol has emerged as a main therapeutic choice (1).

In most cases, sclerotherapy have been done under general anesthesia because of severe pain, headache, nausea, vomiting, tachycardia, and fever in an awake patient (2). Various complications can occur such as skin and nerve injury, tissue necrosis, elevation of pulmonary artery pressure, pulmonary embolism, hemoglobinuria, and cardiovascular collapse. Total dose 1.0 mL/kg of the maximum volume of ethanol used in treating patients with AVM in most clinic is based on the clinical experience, but the safety of this dose has not been confirmed (3, 4). Exceeding doses can cause ethanol toxicity which elicit the possibility of various central nervous system effects (5), arrhythmias (6), spasms of coronary (7) and cerebral (8) vessels, and elevation of pulmonary artery pressure (1). It is important to predict the serum ethanol levels for the prevention of excessive alcohol intoxication after injection of alcohol into the vascular nidus during sclerotherapy. In the AVMs, systemic serum ethanol level may rise more easily than in other vascular malformations because of high blood flow and large draining veins. But few reports have been published about the serum ethanol levels after alcohol sclerotherapy in the AVMs.

We analyzed the effects of several factors on the serum ethanol levels after alcohol sclerotherapy in the arteriovenous malformations (AVMs) retrospectively. Blood ethanol level, amounts of given alcohol, location of lesions, methods of flow control, and Doppler resistive index (RI) were analyzed. The results of linear regression analysis showed that the amount of alcohol administered was the predictor of serum ethanol level (r²=0.75, p<0.001). The average amount of injected alcohol was 0.89 mL/kg in the patients with the serum levels above the legal intoxication level (>80 mg/dL). Location of the lesions was not related with the serum ethanol level (p=0.643), and other variables such as forms of flow control and RI were not related to the serum ethanol level after controlling for injected amounts of alcohol (analysis of covariance). It is recommended to keep an eye on the possibility of intoxication when using the amounts of alcohol exceeding 0.89 mL/kg in the sclerotherapy of AVMs.

Materials and Methods

Patients

Because of concerns regarding possible cardiac and central nervous system effects, serum ethanol levels have been routinely obtained after all sclerotherapy. Between January 1998 and December 2001, ninety patients with AVM over the age of 18 yr, ASA class I-II physical status were enrolled (M:F=51:39). Exclusion criteria were abnormal liver or renal function test and history of drug or alcohol abuse. Average age was 29.7 ±10.4 yr, and body weight was 57.8 ±12.8 kg. The following locations were treated: upper extremities (n=30), lower extremities (n=34), head and neck (n=20), and others (n=6).

Procedure

All procedures were performed by two radiologists under general anesthesia. Sclerotherapy of AVMs involved cannulation of femoral or radial artery and selective catheterization.
of supplying arteries with a guiding catheter. After angiography, a microcatheter was inserted into the feeding arteries and advanced as close to the nidus as possible. Ethanol was injected into superselected appropriate vessels during inflow occlusion and various vascular occlusion techniques such as tourniquet, occlusion balloon catheter, and external manual compression were employed for the stasis of the flow. Radiologist determined the amount and the rate of injection of ethanol by the flow-volume characteristics of the malformations. The maximum volume of pure ethanol used did not exceed 1.0 mL/kg in 80% patients. The same procedure was done repeatedly when necessary. At the end of the procedure, patients were transferred to the recovery room and blood was sampled for immediate measurement of plasma ethanol level. The duration from the first ethanol injection to blood sampling was 72.5 ± 21.0 min. Ethanol concentrations were determined by using gas chromatography (Hewlett-Packard 5890, Wallingford, MA, U.S.A.).

Anesthesia

Preanesthetic medication was not done, and anesthesia was induced with thiopental sodium 4-5 mg/kg, vecuronium 0.1-0.15 mg/kg, and maintained with O2 1 L/min, medical air 1 L/min, and enflurane 1-3.5 vol%. We monitored radial artery pressure, pulmonary artery pressure via Swan-Ganz catheter inserted into the internal jugular vein, EKG, peripheral oxygen saturation, end-tidal carbon dioxide level, body temperature and urine output. After procedures, patients were transferred to the recovery room in the intubated state.

Variables

Total amounts of alcohol injected, the methods of the flow occlusion, and locations of the malformations were examined. Resistive indices of the feeding artery (RI=V_{maxsys}-V_{enddias}/V_{maxsys}, described by Pourcelot (9), where V_{maxsys} is the maximum systolic velocity and V_{enddias} is end diastolic velocity) were obtained by using Duplex Doppler image in patients with AVMs in the extremities (n=30).

Statistical Analysis

The relationship between the volume of ethanol administered and the serum ethanol level was determined by linear regression. And location of lesions, forms of the flow control, and RI ratio were tested as predicting variables with being evaluated the influences on the serum ethanol levels after controlling for amounts of ethanol (analysis of covariance). The probability value for significance was set at $p<0.05$. All tests were performed using SPSS 4.0 version for Windows.

RESULTS

The relationship between plasma ethanol level and amount of injected ethanol was significant. The model of simple regression yielded a linear regression with a significant Spearman’s correlation coefficient ($r^2=0.75, p<0.001$, Fig. 1).

In all locations, there was a positive correlation between serum ethanol levels and injected alcohol amounts ($p<0.001$), and the strength of the relationship was not different according to the locations ($p=0.939$, Table 1). After controlling for the amounts of injected alcohol, there was no significant difference in serum ethanol levels according to the locations of lesions ($p=0.643$, Table 1).

And the methods of flow occlusion did not relate to serum ethanol levels ($p=0.720$).

The Doppler RI was lower in the involved extremities with AVMs compared to that in the contralateral side. The RI of the feeding artery was $0.67 \pm 0.14$ in the involved side and $1.08 \pm 0.23$ in the contralateral side. The ratio of RI of the feeding artery to the contralateral side was $0.61 \pm 0.18$. The RI value was not the predictor of serum ethanol level ($p=0.760, r^2=0.01$).

DISCUSSION

The results of this study demonstrated a strong correlation between the serum ethanol level and the amount of ethanol

![Fig. 1. Relationship between amounts of injected ethanol and serum ethanol levels in all 90 patients ($y=101.4x-0.76, r^2=0.75$).](image-url)
injected during sclerotherapy of AVMs. Correlation of the amount of ethanol administered with the serum ethanol level indicates to carefully monitor the ethanol dose during the sclerotherapy of AVMs. Ninety to 98% of injected alcohol is removed in the liver by alcohol dehydrogenase. There are no pharmacokinetic studies during alcohol sclerotherapy, but we can assume that elimination process is similar to that after oral intake. Elimination proceeds at a constant rate (zero-order kinetics) of 20 mg/dL/hr in adults and 18.6 mg/dL/hr in adolescents and children after oral intake (10). In most cases, alcohol injection was done repeatedly during the procedure and the serum ethanol levels were measured in the recovery room between 52 min and 93 min (72.5 ± 21.0 min) after the first ethanol injection. The difference of sampling timing, maximum 40 min, can theoretically induce the difference of serum ethanol levels by about 14 mg/dL, which value is within the range of standard deviation of serum levels (56.6 ± 36.5 mg/dL). So, the serum ethanol level measured in the recovery room may not reflect the peak serum ethanol level but may reflect the cumulative serum ethanol level. Further studies are warranted to estimate the peak serum ethanol level after every alcohol injection during the procedure.

When alcohol is injected into the vessel, ethanol induces thrombosis by denaturing proteins, dehydrating vascular endothelial cells, precipitating their protoplasm, and denuding the vascular wall. And thrombus formation is promoted by the vascular spasm, perivascular necrosis, and stagnations of red blood cells in the arteriole (11). Since ethanol completely destroys the endothelial cells, the phenomenon of recanalization and neovascular recruitment are noticeably absent (12). In our study, the average amount of alcohol injected was higher than 0.89 mL/kg in the patients with serum levels above the legal intoxication level (>80 mg/dL). Yakes et al. reported complication rates of 10-30% related to alcohol sclerotherapy (1). In our study, there were no specific complications in patients with the serum ethanol levels below 20 mg/dL. However, elevation of pulmonary artery pressure (n=3) during procedure, pulmonary edema (n=1) after procedure, and hemoglobinuria (n=2) occurred among the 12 cases with the serum ethanol levels above the 100 mg/dL. Pulmonary artery catheterization and arterial blood pressure monitoring are essential to minimize the possibility of cardiopulmonary complication during the procedure (1). Once pulmonary artery pressure begin to rise, it is best not to inject any more ethanol and wait until the pulmonary artery pressures return to normal. If pulmonary artery pressures become pathologically high, the infusion of nitroglycerin or prostaglandin E: through the Swan-Ganz line lowers the pulmonary artery pressure. We did not observe the complication of neurology such as the change of speech, mood, and ataxia after the procedure because of anesthesia and narcotics used for analgesia.

We expected that serum ethanol level should be influenced by the locations of malformations because of different venous return according to the locations of lesions. In our study, the amounts of alcohol injected in the lower extremities were larger than other sites (0.76 mL/kg : 0.39 mL/kg), it might reflect the common idea of the radiologists that extremity is safer than other sites. Contrary to our expectation, the location of malformations was not the predictor of serum ethanol levels. First, this result may reflect the appropriate effects of the occlusion techniques before injecting alcohol. Second, when alcohol is injected into the nidus during sclerotherapy, absorption of the alcohol may occur both at the damaged vessel wall itself and by the draining veins. Our result implies the absorption of alcohol through the damaged endothelial vessel wall plays an important role on the serum ethanol levels.

Kusano and Ohta reported the average serum ethanol levels of 58.2 mg/dL (average amounts of alcohol, 0.17 mL/kg) in the transcatheter obliteration of renal artery without balloon occlusion in 11 dogs, which value is higher compared with our results (13). But, three ways for the stasis of blood did not have any influence on the serum ethanol levels. We used torniquet in extremities, manual compression in the head and neck, and occlusive balloon in other sites. This result shows that manual compression is as effective as other techniques.

Duplex Doppler image is an essential tool in the diagnosis and the follow-up of AVMs. AVMs demonstrate high velocity and low resistance waveforms. In our study, the average RI ratio to the contralateral side in the cases of extremities was 0.61, but showed no relationship with serum ethanol levels. This study showed that the RI ratio was not an important factor on the systemic washout of injected alcohol. As the malformations serially become ablated, the RI and the flow volumes become normalized (14).

In conclusion, the serum ethanol levels related to the amounts of injected alcohol, not to the locations of malformations, forms of flow occlusion and characteristics of the flow in the AVMs during sclerotherapy. It is prudent to keep an eye on the possibility of intoxication when using the amounts of alcohol exceeding 0.89 mL/kg in the sclerotherapy of AVMs.

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