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Review Article

Role of Scelerotherapy in Arteriovenous Malformations: An Overview

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Abstract

Vascular malformations comprise a group of lesions characterized by the presence of normal mature endothelial lining. They can affect a patient's appearance and function and even cause life-threatening bleeding or respiratory tract obstruction. The current methods of treatment include surgery, laser therapy, sclerotherapy, or a combined. Sclerotherapy for arteriovenous malformations has to be performed under general anaesthesia because of the pain during injection and the need of careful monitoring. It can be used in the outpatient clinic to treat arteriovenous malformations that have a slow flow or a venous outflow that can be compressed to artificially slow the flow during injection. The purpose of this study was to review the role of sclerotherapy in management of arteriovenous malformations.

Keywords: Sclerotherapy; Malformations; Angiography

Introduction

Arteriovenous Malformations (AVMs) comprise a group of lesions characterized by the presence of normal mature endothelial lining [1,2]. These lesions are usually present at birth, although not always noticed, and commensurate with the child's development. They are characterized by an arteriovenous shunt through a nidus. They present as a pulsatile mass that is frequently associated with signs of venous congestion in the skin, with possible skin breakdown and massive bleeding [3].

Sign and Symptoms

They most commonly occur in young adults, with morbidity and death occurring in 30-50% and 10-15% of patients, respectively. The incidence of venous malformation is approximately 1:5,000-10,000; approximately 40% of them occur in the head and neck regions. The vast majority of these malformations are sporadic and more commonly occur in the mouth, airway tract and muscle [4]. The appearance of the AVM depends on the size of the blood vessel involved. The affected area may have a pink-blue tint, which can darken over time. You may feel some warmth in the area and it may also pulse. It is not only disfiguring but is also usually associated with complications, such as pain, ulcers, bleeding, and the compression or invasion of adjacent structures. These complications have severe impact on speech, swallowing, and respiratory function and may even lead to death due to bleeding and suffocation [5].

Classification

Jackson et al differentiated vascular malformations according to their flow features (ie, low- and high-flow lesions) [6]. Low-flow vascular malformations include lymphatic, venous, and capillary malformations. The high-flow lesions are arteriovenous malformations (AVMs)/fistulas. [2,7]

Schobinger gave the classification of AVMs as:

Schobinger classification of AVMs.

Stage;Features

1. Cutaneous blush/warmth
2. Bruit, audible pulsations, expanding lesion
3. Pain, ulceration, bleeding, infection
4. Cardiac failure

Diagnosis

Diagnosis is usually based on physical examination and one or more of the following diagnostic imaging tests.

- A Duplex or Doppler ultrasound to image blood vessels and measure the blood-flow speed.
- Computed Tomography Angiogram (CTA) using a contrast agent (dye), which is injected into the vessels, to look for abnormalities. CT scans that do not use dye may also be taken for head and neck.
- Magnetic Resonance Angiography (MRA) combines an injected contrast agent (dye) with magnetic and radio waves to create 3-D cross-sections of the arteries in the neck and brain. An MRI (without dye) to create images of head and neck.
- In a catheter angiogram, the surgeon inserts a thin catheter through the groin and threads it into the carotid arteries; a contrast agent (dye) is injected to help clinicians visualize the arteries on X-rays.

Management

Various methods have been used to treat arteriovenous malformations, including conservative treatment such as head position elevation, sclerotherapy, laser therapy, and surgery. Due to the variety of treatment methods and different manifestations in individual patient, it is suggested that multidisciplinary approach should be performed in patients with complicated lesions. Treatment should be delivered by a team of experts in vascular malformations.

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Conservative treatment is primarily suitable for small, isolated, asymptomatic venous malformations. Head elevation is very important in alleviating the hydrostatic pressure that leads to expansion of the deformity and can reduce airway obstruction, swelling and pain. Other beneficial conservative treatments include local compression, anti-infection therapy, pain control, etc.

Neodymium (Nd)

YAG laser is most commonly used, but Potassium Titanyl Phosphate (KTP) laser can also be used [8]. The Nd: YAG laser is a 1064 nm wavelength laser that utilizes invisible light from the infrared portion of the spectrum, which can be transmitted through the thin optic fiber to targeted sites from the mouth to the larynx. The absorption of laser energy by hemoglobin generates a high localized temperature, which results in coagulation and immediate shrinkage of the lesions. It should be pointed that lasers can only penetrate 1-3 mm. AVMs often are much larger and thicker than 3 mm and can never be affected by laser treatment. Thus, the superiority of ethanol and liquid sclerosants to flow throughout AVMs is distinct and thus be treated. Thermal injuries to nerves and skin scarring due to laser treatments of superficial lesions are to be avoided.

In most cases, surgical treatment is considered primarily as an adjuvant to improve the function and appearance [9]. Localized or limited venous malformations can be removed surgically [10]. For large lesions, partial excision can be considered after sclerotherapy to improve cosmetics Before operation, MRI should be performed to define the extent of the lesion and venous drainage. Blood transfusion should be prepared because blood loss can be significant. In cases with extensive tissue defects caused by surgical removal, a skin graft or flap should be transplanted for reconstruction.

Sclerotherapy consists of a percutaneous (through skin) injection of a substance into the abnormal veins of the venous malformation. The substance can be one of many that are able to irritate the wall of the vessel which results in the formation of a blood clot within the vessel. The blood clot will effectively stop the flow of blood through the blood vessel and if the irritation is severe enough, the blood vessel will be destroyed and replaced with scar tissue. These procedures are usually performed in an angiography suite, with the assistance of ultrasound guidance and "fluoroscopy" or real-time x-ray monitoring. It has become the current mainstream treatment for venous malformation [11,12]. It can be used alone or combined with surgery and/or laser therapy. For large lesions, multiple treatments are necessary. Recurrence is seen, this may possibly happen with some sclerosing agents that incompletely treat the AVMs being injected.

Sclerotherapy

Percutaneous sclerotherapy has been developed as a minimally invasive treatment modality and usually employed in low-flow venous malformations and macrocystic lymphatic malformations [13]. On the other hand, AVMs have a rapid flow and are, therefore, not usually candidates for percutaneous sclerotherapy. They are usually better treated by a combination of endovascular embolization with liquid adhesives or other embolic agents, with or without surgical excision of the remaining malformation [3,14,15]. However, if the arterial feeder and the venous drainage can be temporarily compressed during the injection of the scrolosant to ensure exposure of the nidus to the agent for a sufficient time, the arterial feeder, the nidus, or the draining vein can be punctured and those cases may be candidates for percutaneous sclerotherapy.

The sclerosants commonly used are 5% sodium morrhuate, pingyangmycin (PYM), anhydrous ethanol and lauromacrogol. They work by destroying the endothelial cells of blood vessels, accelerating protein coagulation in the blood of the lesions, promoting platelet adhesion to the vascular wall during thrombosis formation and causing vascular occlusion through thrombotic mechanisms. After treatment with sclerosing agents recurrence is common. The possible reasons include insufficient doses and the presence of residual lesions. In addition, after injection, the thrombus formed is absorbed or dissolved, which leads to lumen recanalization and eventually, recurrence [16].

Common sclerosing agents used are:

Sodium morrhuate

5% sodium morrhuate was historically the sclerosing agent used most commonly in the treatment of arteriovenous malformations.

Because sodium morrhuate is irritating, can induce severe reactions or even tissue necrosis, it is seldom used nowadays.

Pingyangmycin (PYM)

PYM is an anticancer drug extracted from gram-positive Streptococcus, which has a chemical structure similar to that of bleomycin A5. The major histological changes observed after intralesional injection of PYM include injured vascular endothelial cells, various degrees of vascular wall thickening and luminal occlusion16, while thrombosis formed within the lumen and inflammatory response outside the lumen are not as obvious as after injection of sodium morrhuate. Therefore, the side effects (e.g., local swelling and pain after treatment) are mild.

Injection procedures: PYM injection at a concentration of 2 mg/ml is prepared by diluting 8 mg PYM powder with normal saline, adding 2% lidocaine and dexamethasone and then mixing uniformly. The dosage for each injection should not exceed 8 mg. For large lesions, PYM injection can be repeated at an interval of 2 to 3 weeks [17].

For superficial lesions, a 25 gauze needle is inserted into the normal tissue adjacent to the lesion and enters the lesion horizontally. The drug is injected into the lesion until the lesion turns pale and swells. The injection should not begin from the surface of the lesions to avoid bleeding or drug effusion, which might reduce the treatment effects. For deep malformations, direct puncture should be performed first to confirm that blood can be withdrawn and the needle is in the lesions rather in normal tissues using ultrasonography guidance or fluoroscope. For lesions localized in the eyelids and lips and superficial lesions, each injection dosage should not exceed 4 mg at a concentration ≤ 1 mg/mL to avoid local tissue necrosis. After injection, effusion of solution should be avoided by applying pressure to the injection sites with sterile cottons for 2 to 3 min. For large or multiple lesions, injection should be conducted in multiple sessions. Generally, the periphery lesion is injected first, followed by injection of solution into the central part of the lesion, to prevent further expansion of the lesion during treatment.

For malformations with a diameter less than 1.5 cm, one injection is usually sufficient; but for larger lesions or multiple lesions, 3 or more injections are needed to achieve acceptable outcomes. The treatment effect can be observed 7-30 days after injection.

Absolute ethanol

Absolute ethanol is a strong sclerosant with a long history of clinical application [18], and it is used due to its ability to destroy vascular endothelial cells, which induces hemoglobin denaturation, intravascular thrombosis and fibrosis, thus leading to occlusion of the vessel and formation of embolisms within the lesions. Because of its lower cost, quick metabolism, good results and low recurrence rate when used in the sclerotherapy of venous malformations, absolute ethanol has been used widely to treat any types of venous malformations under fluoroscope, especially extensive or complicated lesions. Preoperative percutaneous venogram can be used to confirm the diagnosis, determine the size and compartments of the lesion, number of draining veins and return velocity, thereby providing important information for estimating the sclerosant dosage and prevention of complications. Absolute ethanol can be used alone or in combination with other sclerosants, such as PYM or lauromacrogol, to reduce the dose and improve the efficacy [19].

Absolute ethanol is strongly irritating to tissue; therefore, a minor mistake may lead to serious complications. The injection should be implemented under Digital Substraction Angiography (DSA) direct visualization [20]. After proper sterilization, a butterfly needle is used percutaneously and the needle is advanced into the AVM via US or fluoroscopic guidance. Blindly burying needles of varying lengths to the hub in the vicinity of the AVM is never tried. Accurate placement of the needle is advocated. The needle's depth and direction should be adjusted until automatic outflow of blood through the connecting tube of the butterfly needle. Contrast medium is then injected until the draining vein is demonstrated. The dosage of absolute ethanol is approximately 1/2 to 2/3 of the amount of the contrast used. For large malformations involving multiple anatomical sites, injection can be done simultaneously in different areas. The cumulative total dose of serial injections of ethanol in a single procedure should not exceed 1 ml ethanol/ kg body weight of the patient [21]. After quick injection of ethanol into the compartments, the patient's blood pressure and heart rate should be monitored. If the venous return velocity is fast, compression should be applied to the draining veins during injection to prevent a great quantity of ethanol flowing into the pulmonary circulation in a short time and minimize complications, such as pulmonary artery spasm, pulmonary hypertension and pulmonary embolism. Preoperative and postoperative injection of dexamethasone can ease tissue edema. For patients undergoing injection at a dose more than 0.5 ml/kg, the blood pressure and the amount of urine after operation should be observed. A balanced salt solution and sodium bicarbonate should be given intravenously to alkalinize urine to prevent acute renal failure caused by hemoglobinuria. Antibiotics are given when necessary.

Particular attention should be paid during ethanol injection listed as follows [22]. (1) It is of outmost importance to inject ethanol into the compartments rather than into the surrounding tissues or major blood vessels under DSA guidance; (2) When performing ethanol injection in the upper 1/3 of the face, the possibility of accidental embolization of the cavernous sinus should always be considered. Facial venous connections may connect to the angular vein. This in turn drains superiorly to connections to the Superior Ophthalmic Vein (SOV). This then drains into the cavernous sinus. Merely manually compressing the angular vein against the maxilla to prevent upward flow to the eye, or compressing the vein connections around the glabella of the upper nasal area will simply and effectively prevent flow into the cavernous sinus. While doing either compression maneuver they should repeat the AVM direct puncture angiographs to prove that the maneuver is successful in preventing flow into the cavernous sinus; (3) Caution should be taken when the injection is near the parotid gland to avoid damaging the facial nerve and subsequent facial paralysis. It is in the medial third of the parotid gland that the 7th nerve traverses. Not all areas are dangerous. Further, large doses in this area are to be avoided. Small doses with repeated procedures, rather than large injections with few procedures greatly reduce the chances of facial palsy. An alternative is using ethanol to occlude the draining veins, followed by administration of PYM to eliminate the compartments; (4) For type III or IV venous malformations, the draining veins should be compressed to prolong the staying time of the sclerosis agent within the compartments and prevent pulmonary complications; (5) For patients with venous malformations in the tongue, floor of the mouth, parapharyngeal area and soft palate, the airway may be compromised postoperatively. If necessary, a prophylactic tracheotomy may be performed, or prolonged endotracheal intubation considered.

Polidocanol

Also known as lauromacrogol or aethoxysclerol (chemical name: lauryl alcohol polyoxyethylene), is a more moderate form of ethanol [23] most commonly used in European countries. It is an effective sclerosing agent that consists of 95% hydroxypolyethoxydodecane and 5% ethyl alcohol and is known to have a low risk of complications. Injection of lauromacrogol can damage vascular endothelium cells, promote thrombosis, occlude blood vessels and induce aseptic inflammation and subsequent fibrosis, resulting in obliteration of the vascular channels and elimination of the compartments.

After proper disinfection, a 25 gauze needle is inserted into the lesion from the adjacent normal tissue until blood can be withdrawn. For larger lesions, multiple injections will ensure uniform distribution of the drug within the lesion. The injection should continue until the lesion surface turns pale and swells. After injection, compression is applied to the insertion sites with sterile cottons for 2-3 min to prevent effusion of the drug. The total dosage is determined by the location and size of the lesions and the patient's age, with no more than 3 ml at each injection (less than 1 ml for children). For patients with lesions that fail to complete response, injection is repeated at an interval of 1 to 2 weeks but not more than 5 consecutive sessions.

Lauromacrogol injection is a simple, time-saving, safe and effective way for venous malformations. Lauromacrogol has definite anesthetic effect; the injection is painless and well-tolerated by the patients. Furthermore, allergic reactions are rare, and hemolysis seldom occurs, which largely reduces the possibility of pigmentation. Therefore, it is suitable for treating head and neck arteriovenous malformations. The main disadvantage is necrosis and ulceration may occur if the solution leaks out into the skin or mucosa.

Lauromacrogol can also be mixed with a certain amount of air (the most commonly used liquid-to-air ratio is 1:4) as sclerosing foam, [24], which reduces the dosage and concentration of the sclerosant. Additionally, the selectivity of action on endothelium of the foam reduces the risk of tissue damage while the sclerosant runs off the vessels. However, the rate of relapse after treatment with sclerosing foam is higher compared with liquid sclerosant [25], and the complication may occur with use of "foam" VM embolization causing strokes by flowing foam bubbles going through Patent Ductus Arteriosus (PDA) and the like.

The concentration of lauromacrogol used to produce foam sclerosing agent is 0.25% to 4%, depending on the size of the malformation and hemodynamic characteristics of the lesions. A higher concentration (3% to 4%) is used for intramuscular venous malformations, and lower concentrations (0.25% to 0.5%) for the peripheral portions of huge malformations. 1% to 2% lauromacrogol is chosen for residual lesions after treatment [25] .

Sclerotherapy can also be combined with other treatment modalities. For large malformations or lesions with a fast drainage, selective ligation of the connecting veins, suture around the lesions and mixing the agents with tissue glue may [26] help to increase local drug concentration and prolong the sclerosing effect. Preoperative sclerotherapy is often used to create thrombosis of the lesions and reduce blood loss during operation. Sclerotherapy is used for treating residual lesions after laser therapy or surgical excision.

Other drugs used as sclerosing agents in the treatment of venous malformations include sodium tetradecyl sulfate, ethanolamine, gliadin, diatrizoate acid, quinoline, poppy oil, hypertonic glucose, tetracycline or doxycycline, Ethibloc, urea and OK-432 [26].

These drugs are presently used less frequently or used as a combination [27].

Sclerotherapy of venous malformations is a relatively safe and reliable treatment modality, and its efficacy is related to the type and dose of sclerosing agent, as well as type and extent of the lesion.

Complications of sclerotherapy include allergic reactions, cutaneous or mucosal necrosis, and sensory nerve or motor nerve injuries such as facial paralysis. These complications occur more often after injection of absolute ethanol and sodium morrhuate but seldom PYM injection [28,29]. Thus, PYM is suitable and usually selected for the treatment of superficial lesions. In addition, patients may develop more severe swelling after sodium morrhuate or absolute ethanol injection. Airway obstruction caused by postoperative swelling should be considered when treating lesions on the base of the tongue, floor of mouth, soft palate, pharynx and larynx, and the patients are usually hospitalized for treatment and observation for 2 to 3 days.

Absolute ethanol injection can be extremely painful; therefore, it is recommended that the injection be administered under general anesthesia or sedation to alleviate patients' suffering. By adding radiopacity agent into the sclerosing agent, the puncture site can be monitored through the fluorescent screen to determine whether the sclerosing agent was injected into the lesions and how it was distributed within the lesions, which is helpful to minimize complications. Because ethanol sclerotherapy can give rise to serious complications, although rarely encountered in head and neck cases, such as pulmonary artery spasm or pulmonary embolism, it should only be performed by physicians with significant clinical experience and excellent skills and in specialize medical centers or hospitals with adequate equipment and technical capability. In addition, ethanol injection of less than 0.14 ml/kg body weight every ten minutes obviates the occurrence of cardio-pulmonary collapse [21].

Fever often occurs after PYM injection; this can be alleviated with symptomatic treatment. The main side effects of PYM injection are interstitial pneumonitis and pulmonary fibrosis related to endothelial cell damage in pulmonary capillaries. These complications are closely related to the total amount of drug used. No reports on the use of PYM to treat venous malformations leading to pulmonary fibrosis have been published that we are aware of. Very rare patients may experience acute allergic shock during injection. Therefore, care must be taken to prevent this fatal complication, and first aid treatment must be available on the spot, including intravenous infusion, and anti-shock treatment, anti-allergy treatment [17].

Conclusion

When AVMs are treated by direct puncture, it may be more effective than a sclerosing agent for occluding these lesions [30]. To the best of our knowledge, very little has been reported about the effectiveness of foam sclerotherapy for AVMs. The small AVMs that can be compressed, to artificially decrease the flow during injection, are curable with sclerotherapy using 1% polidocanol liquid.

Percutaneous sclerotherapy can be used in the outpatient clinic to treat AVMs that have a slow flow or have a venous outflow that can be compressed to artificially decrease the flow during the injection. Diagnosis and management of AVMs by a multidisciplinary approach that integrates surgical therapy with embolism and sclerotherapy appears to improve the results and management with limited morbidity and no recurrence during early follow-up.

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