Intralesional copper wire retention and pingyangmycin injection: an effective combinational therapy for complex venous malformation in soft tissue

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Abstract
Objectives: Complex venous malformations (VMs) may extensively involve the soft tissue. The treatment remains a challenge till now. Here we introduce a combinational therapy of copper wires and pingyangmycin (bleomycin A5,PYM).
Methods: Copper wires were retained in VMs by repeated penetration with a straight needle. Subsequently, PYM solution was injected into the lesion. Eight to 10 days later, copper wires were removed. The dressing was changed every day until the puncture pores healed. Magnetic resonance imaging scanning was performed to observe the change of VMs.
Results: From January 2001 to December 2011, 56 patients were treated. During the follow-up period, most of the VMs shrunk obviously. The symptoms were relieved or disappeared. The complications included local pain, temporary paraesthesia and moderate fever, which disappeared quickly after the removal of copper wires.
Conclusions: This combinational therapy is a safe and effective approach for the complex VMs in soft tissue.

Keywords: venous malformation; copper wire; pingyangmycin

Introduction
Venous malformations (VMs) are common congenital low-flow vascular malformations in soft tissue. Complex VMs may infiltrate into the spatium intermusculare, surround the nerves and vessels and lead to severe symptoms, such as local pain, hyperalgesia, dyskinesia or even physical disability. Owing to the indefinite boundary and the complicated anatomical relation, the treatment of complex VMs remains a challenge till now.

Copper needles retention has been reported to be an effective approach for VMs. In 1974, Mullan first reported copper needle retention in treatment of carotid artery and fistula. In 1992, Ogawa and Inoue treated angioma in the face and scalpel varicosis in the leg with copper needles and Li observed the coagulation and thrombosis induced by copper needles both in vitro and in vivo. In 2008, Yin confirmed that copper needles lead to the denaturalization, fibrosis and disappearance of the blood vessel in an animal model. Clinical studies have demonstrated the effectiveness of copper needles retention in VMs. However, in the follow-up period, the recurrence of VMs was observed in some patients. The major cause of the recurrence was residual VMs without the retention of copper needles.

Intralesional injection of low-dosage pingyangmycin (PYM), also called bleomycin A5, is a good choice for the small and well-defined superficial VMs. However, when used in complex VMs with abundant draining veins, the drug would...
flow quickly into systemic circulation. The drug concentration in the lesion decreases quickly, which reduces the action time of the drug in VMs. In these cases, low-dosage of PYM cannot achieve a sufficient concentration to effectively injure the vessel wall and high dosage of PYM may lead to phlebitis, pulmonary or skin fibrosis.\textsuperscript{10,11} Hence, how to acquire high drug concentration for enough time and reduce the outflow of drug to avoid non-specific injury is the key point to improve the effect of PYM injection in complex VMs.

Here, we introduce a combinational therapy of intralesional copper wire retention and PYM injection. Copper wires may injure the malformed veins, lead to bleeding and subsequent thrombus in the lesion, and thus slow the blood flow in the lesion. Ideally, this may increase the concentration of PYM in VM and prolong its action time. PYM also can injure the malformed veins without copper wire retention. Hence, copper wire retention and PYM injection may have a co-acting effect and achieve better results in VMs. The procedures and results are summarized in this paper.

**Methods**

This study was approved by the Committee on Clinical Investigation of Jinling Hospital. Informed consent was provided for the patients, according to the Declaration of Helsinki. From January 2001 to December 2011, 56 patients with VMs in soft tissue were included in this study, 25 of whom were males. The average age of the patients was 19.7 years (age range, 5–61 years old). VMs were located in the head (\(n = 1\)), shoulders (\(n = 4\)), trunk (\(n = 8\)) and lower extremities (\(n = 27\)). A portion of VMs in the extremities infiltrated into the spatium intermusculare and surrounded the nerves and vessels. Magnetic resonance imaging (MRI) scanning was performed before the treatment. Before admitting into our department, 10 patients had undergone sclerotherapy with absolute ethanol and six patients had undergone unsuccessful operations.

Industrial pure copper wires with a diameter of 0.2 mm were buffed by sandpaper to remove the oxidation layer, cut into pieces of 50 cm length and submerged in 75% ethanol solution for more than 12 hours to be sterilized. PYM solution (8 mg PYM diluted by 5 mL normal saline) was prepared during the procedure. General or block anaesthesia was used according to location of the VM, patient’s age and other conditions.

The outline of the surface of the VMs was drawn with methylene based on the clinical examination and the MRI images. Furthermore, a 5-mL syringe was used to withdraw blood from the sinuses to confirm the position of the VMs, and the pinpoints were marked with methylene as the guidance of subsequent procedure. In cases in which the VMs were very close to the major nerves and blood vessels, ultrasonography was used to guide the puncture. Then, an 8-cm straight steel needle was used to take the copper wires (Figure 1), and penetrate through the lesion from one side of the VM to the other side. The end (about 2 cm) of the copper wire remained outside the skin and contorted like a circle (Figure 2). Then the penetration was repeated. The interval between the puncture pores was about 5 mm. The times of puncture were decided by the location and volume of VM. Finally, copper wires were retained in VM like a meshwork. Subsequently, PYM solution was injected into the lesion with a 5-mL syringe. The dosage of the PYM was decided by the volume of VMs and the age and body weight of the patient. In children less than 12 years old, we injected 4–8 mg PYM. In adults, we injected 8–16 mg PYM.

After the treatment, the puncture pores were cleaned by 75% ethanol solution every other day. The VMs would be swelling and painful. Oral tramadol was administrated. Eight to 10 days later, necrotic tissue, coagulated blood and inflammatory secretion extravasated from the puncture pores. Then, we drew out the copper wires. The dressing

![Figure 1 Needle with copper wire. Length of the needle is 8 cm](image-url)
was changed every day until the puncture pores healed. The patients were followed up for one to five years. MRI scanning was performed periodically to evaluate the changes of VMs.

Statistics Microsoft® Office Excel was used to statistically analyse the clinical data.

Results

From January 2001 to December 2011, 56 patients were treated by this method. Among them, 36 patients underwent the treatment once and the remaining patients twice. The length of the copper wires used in one procedure ranged from 2 to 12 m. The dosage of the PYM ranged from 4 to 16 mg. The complications included local ache, temporary paraesthesia and moderate fever. Local ache was the frequent complaint, and persisted for several days to two weeks, which could be relieved by oral tramadol effectively. Nine of the 56 patients (16.07%) had temporary paraesthesia over the VMs in the extremities, which disappeared several days after the removal of copper wires. Moderate fever occurred in most of the patients. No local infection or delayed wound healing was observed in our patients. The scar at the puncture pores was slight.

To evaluate the therapeutic effect of the treatment, we rated the follow-up results as ‘excellent’, ‘good’ or ‘poor’, according to the images of MRI scanning and the clinical outcomes. Excellent results meant obvious shrinkage of the lesion, and complete relief of the symptoms caused by VMs. Good results meant some shrinkage of the lesion and partial relief of the symptoms. Poor results meant no obvious change of the lesion and the symptoms. In one to five years follow-up period, 55.4% (31/56) of the patients were rated as ‘excellent’, 37.5% (21/56) were rated as ‘good’ and 7.1% (4/56) were rated as ‘poor’.

Typical cases

Case 1: A six-year-old boy had a painful VM in the lateral side of his right leg (Figure 3A). MRI scanning showed an ill-defined VM in the soft tissue and spatium intermusculare, with many abnormal veins (Figure 3B). He underwent the treatment once (Figures 3C and D). MRI scanning 14 months later showed obvious shrinkage of VM (Figure 3E). The function of the right leg was normal. The scar at the puncture pores was slight (Figure 3F) and the pain caused by the VM disappeared. The results were rated as ‘excellent’.

Case 2: A 26-year-old man had a painful VM in the right leg (Figure 4A). MRI scanning showed a VM extensively infiltrating the soft tissue and
spatium intermusculare (Figure 4B). He accepted the treatment once (Figures 4C and D). Six months later, MRI scanning showed that the volume of VM decreased obviously (Figure 4E). The scar at the puncture pores was slight (Figure 4F). The pain caused by the VM was totally relieved. The results were rated as ‘excellent’.

Case 3: A 19-year-old girl had a painful VM above the left knee joint (Figure 5A). She underwent the treatment once (Figures 5B and C). Seventeen months later, the VM shrunk and the scar at the puncture pores was slight (Figure 5D). MRI scanning also showed that the volume of the VM decreased (Figure 5E, pretreatment; Figure 5F 17 months after the treatment). The pain caused by the VM was relieved. The results were rated as ‘good’.

**Discussion**

VMs, common vascular malformations in soft tissue, are simple, sporadic or familial (cutaneomucosal VMs), combined (e.g. capillaro-lymphatico-venous malformations) or syndromic (Klippel–Trenaunay, blue rubber bleb naevus and Maffucci). For small and well-defined VMs, both surgery and intralesional injection of sclerosing agents, such as ethanol and polidocanol foam can get good results. However, for complex VMs involving large areas of soft tissue and extensively infiltrating spatium intermusculare, it is always difficult or even impossible to make a complete removal of the lesion and high-dosage injection of sclerosing agents may lead to some worrying complications, such as venous thrombosis,
tissue necrosis, haemoglobinuria, paradoxical embolism or even stroke, although they are rare.17–20

From the first report of copper needle retention in the treatment of carotid artery and fistula by Mullan,2 a series of experimental and clinical studies3–6 were carried out to investigate the application of this procedure in vascular malformations. Li4 performed an in vitro test to compare the coagulative ability of copper needles, stainless steel and bamboo needles. The results showed that copper needles had the most coagulative ability. In vivo animal study4 further observed coagulation and thrombus in the vein with copper needle retention, and the inflammatory reaction in the surrounding tissue. In Yin et al.’s5 study, the thrombus, fibrosis and necrosis of the veins with copper needle retention were observed in both the animal model and the clinical samples. In these studies,4–6 copper needle retention was used in more than 300 patients. The results demonstrated the effects of this procedure in VMs.

However, this procedure still has some limitations. First, there are still a portion of malformed veins without the retention of copper needles, which may enlarge continuously and lead to the recurrence of the remnant lesion. Second, the scar at the puncture pores is obvious. In this study, we used copper wires instead of copper needles. The diameter of the copper wire was much smaller than that of the copper needle. We could puncture VMs by copper wires for much more times, even more than 100 times in one case. Therefore, copper wires can be retained in VMs in a much larger number than copper needles. More malformed veins could be penetrated and more blood would contact with the copper wires. More thrombus, fibrosis and necrosis of malformed

Figure 4 Typical case 2: A 26-year-old man with a painful VM in the right leg (A), which extensively infiltrated the soft tissue and spatum intermusculare (B). He underwent the treatment once (C and D). Six months later, the volume of VM in MRI scanning decreased obviously (E) and the scar at the puncture pores was slight (F)
veins could be achieved. Furthermore, the scar in the puncture pores caused by copper wires was slighter than that caused by copper needles.

Soon after the retention of the copper wires, we injected PYM solution into the lesion. For the malformed veins with copper wire retention, PYM can enhance the injury of the vessel wall and for the malformed veins without copper wire retention, PYM can injure the vessel wall by itself. Furthermore, as mentioned in the Introduction, the slowness of blood flow caused by copper wire retention can increase the concentration of PYM in the lesion, prolong its action time, slow down the outflow of PYM and then reduce the possibility of complications. We therefore believe that copper wire retention and PYM injection have a co-acting effect and compensate for each other’s disadvantages.

Nevertheless, some patients in our study did not get satisfactory results. Maybe the second or third treatment was needed for them to get better results. In our study, temporary paraesthesia occurred in a few of the patients. VMs always infiltrate into the spatium intermusculare, or even surround the nerves. Thus, it is possible for copper wires to puncture a few of the small nerve branches. After the removal of the copper wires, the paraesthesia always disappeared in several days. We did not observe severe bleeding in our cases. Comprehensive reading of MRI images and sufficient review of the local anatomy before treatment were necessary for us to locate VMs exactly and avoid the possible puncture of larger blood vessels or nerves.

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Contributorship: S-MY, Z-JH and H-QJ conceived the study, performed most of the treatments and wrote the manuscript. JW and X-BH were involved in patient recruitment. All the authors reviewed and approved the final version of the manuscript.

References