REVIEW

New Approaches to the Treatment of Congenital Vascular Malformations (CVMs)—A Single Centre Experience

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Objective. A retrospective review of the results of management of congenital vascular malformation (CVM) patients was made to assess the efficacy of newly introduced approaches.

Methods. CVMs were categorised according to the Hamburg classification on the basis of minimally invasive tests. Invasive studies such as angiography are used to provide a road map for treatment. A new multidisciplinary approach was adopted, which accepts the integration of embolisation and sclerotherapy with traditional surgical therapy. Embolo-sclerotherapy was used as an independent therapy and as an adjunctive therapy to surgery.

Results. Ninety-nine out of a total of 294 venous malformation patients underwent ethanol sclerotherapy with an immediate success rate of 98.8%, requiring 419 sessions of treatment. Interim results were excellent with no evidence of recurrence (mean follow-up 18.2 months). Most of the 25 patients treated surgically received pre-operative embolo-sclerotherapy, each with excellent interim results and minimum morbidity (mean follow-up 21.2 months). Forty-eight patients among 76 arteriovenous malformation patients underwent embolo-sclerotherapy independently (32/48) or adjunctively (16/48). Independent therapy on 32 produced excellent interim results (25/32) requiring a total of 171 sessions (mean follow-up 19.2 months).

Eighty-nine extratruncal (ET) forms of lymphatic malformations received multiple sessions of sclerotherapy with OK-432 (108/120 sessions) or ethanol (12/20 sessions). OK-432 was used in 51 paediatric patients with the ET form and produced an excellent response in cystic type lesions (40/45) requiring 61 sessions with no evidence of recurrence (mean follow-up 24.2 months), whereas a mixed result was obtained in the cavernous type (3/6). OK-432 sclerotherapy was used as a pre-operative adjunctive therapy in 7 patients requiring 21 sessions with 17 cavernous type of the ET form, and produced good to excellent results after surgical excision of 14 lesions.

Conclusion. New approaches to the treatment of CVMs based on a multidisciplinary approach can improve results by fully combined surgical treatment with embolo-sclerotherapy.

Keywords: Congenital vascular malformations; Hamburg classification; Surgical therapy; Embolo/sclerotherapy; Multidisciplinary team approach; Venous malformation; Arteriovenous malformation; Lymphatic malformation.

Introduction

Congenital vascular malformations (CVMs) remain difficult diagnostically and therapeutically despite continued efforts over the decades. CVMs have a notorious reputation due to their variety, with a wide range of clinical presentations from a simple birthmark to a life-threatening condition containing embryonic remnants of a developmental defect. The condition has been further complicated by an unpredictable clinical course, confusing nomenclature, erratic response to treatment, frequent recurrence, and high morbidity following conventional treatment.1–4

The poor results of treatment over the last decade, are partly the result of ill-planned treatment strategies and a cavalier approach based on limited knowledge of CVMs.5–6 Recurrence also plays a part as embryonic remnants of CVMs retain developmental potential.7 Disastrous surgical experiences have allowed ill
founded prejudice to develop concerning the treatment of CVMs. The Hamburg classification was introduced to provide proper information about the aetiology, anatomy, and pathophysiology of CVMs, and has become the basis for contemporary diagnosis and management. The new concept of a multidisciplinary approach integrates surgical and nonsurgical treatments. We organised the CVM (congenital vascular malformation) clinic at Samsung Medical Center, Seoul, Korea as a referral centre, based on a multidisciplinary approach in 1994. A retrospective review of interim results of the diagnosis and management of CVM patients (January 1995–December 2001), was made to assess the various issues raised by this new approach.

**Diagnosis**

**Definition (Classification)**

The classification of CVMs is difficult, since CVMs are a group of birth defects that occur as a consequence of developmental arrest at various stages of embryonic life. This affects the whole peripheral vascular (arterial, venous, lymphatic, and capillary) system. Traditional nomenclature of these various CVMs, based mainly on of name-based eponyms (e.g. Klippel–Trenaunay Syndrome, Parkes–Weber Syndrome) add further confusion, and therefore a proper classification of CVMs has been developed to provide proper aetiological, anatomical, pathophysiological, histological, and embryologic information in addition to haemodynamic information. Various classifications have been proposed, including the (high and low) flow-based classification, but have failed to fulfil this requirement.

A classification was published based on a consensus workshop for CVMs held in Hamburg, Germany, in 1988 by the ISSVA (International Society of Study of Vascular Anomaly). It classified CVMs according to the predominant vascular defect: arterial, venous, AV (arteriovenous) shunting, lymphatic and combined. Each vascular defect was further classified into truncal (T) and extratruncal (ET) forms, based on the embryonic stage of developmental arrest.

ET forms, develop from the earlier stages of embryonic life at the reticular stage. They possess embryonic characteristics of developmental potential originating from mesenchymal cells (angioblasts). This feature allows them to grow whenever stimulation (e.g. trauma, surgery, hormonal therapy, pregnancy, and menarche) is given. The ET form is further classified by its clinical presentation as diffuse and infiltrating or as limited and localised. T forms develop from a later stage of embryonic life along axial vessels and lack embryonic characteristics. The haemodynamic impact of the T forms is more severe in general than that of the ET form. A lesion is further classified by its clinically presentation as either an aplasia or as an obstruction type (e.g. hypoplasia, aplasia, hyperplasia, stenosis, membrane, and congenital spur), or as a dilatation type (e.g. localised-aneurysm and diffuse-ectasia). This concept fulfils most of the requirements to provide aetiological, anatomical and pathophysiological information required for clinical management of CVMs. The Hamburg classification further elucidated the unique relationship between vascular malformations and vascular tumours (infantile/neonatal haemangiomas) to remove confusion concerning these two different entities which produce similar vascular anomalies. We adopted this modified Hamburg classification as the basis of a new structure of contemporary CVM management at our clinic.

**CVMs and haemangiomas**

CVMs and haemangioma are both categorised as ‘vascular anomalies’, but the conditions are entirely different, so a precise understanding of their differences is essential for the proper diagnosis and management of these conditions.

Haemangioma (infantile/neonatal) is the most common tumour of infancy. It is a rapidly growing, but self-limiting vascular tumour that usually appears during the first 4 weeks of life. Explosive growth is common, and is generally triggered postnatally, but almost invariably undergoes spontaneous regression before the age 5–7 years. The rapid growth of haemangiomas is the result of endothelial proliferation with increased mitotic activity. In contrast CVMs are not hypercellular and have a ‘mature’ endothelium with normal endothelial mitotic activity, and grow pari passu with the child. The differentiation of haemangioma and CVM is generally possible given the clinical history and the physical examination alone. However, a deeply seated haemangioma in subcutaneous tissue or muscle without involvement of the papillary dermis can be confusing, and occasionally needs histological confirmation. In addition to their differentiation from haemangiomas, CVMs need to be differentiated from other vascular/non-vascular conditions involving soft tissue (e.g. haematoma, neurofibroma, and sarcoma). The proper differentiation of CVMs from various malignant
tumours is critical in view of the potentially serious consequences when overlooked. If any doubt exists, a tissue biopsy should be obtained.

**Modalities of investigation (invasive and non-invasive)**

A careful physical examination and detailed history taking are most important for clinical diagnosis. The clinical impression should be further confirmed by laboratory evaluation to identify the characteristics of the CVM, and its extent and degree of involvement. This initial evaluation is based on minimally invasive tests. Duplex ultrasonography (colour Doppler imaging and spectral waveform analysis) is excellent for haemodynamic assessment. It provides information about blood flow, velocity, and volume along the lesion as well as demonstrating its feeding artery and draining vein. Airplethysmography (APG) or venous photoplethysmography (PPG) is also essential to determine the functional status of the venous system. Infrared limb volumetry is indispensable for general investigation of swellings of extremities with CVM involvement. Transarterial lung perfusion scintigraphy (TLPS), utilising Tc-99m macroaggregated albumin, can provide essential information on the arteriovenous (AV) shunting status through an AV malformation (AVM), when it is located in an extremity. This technique is extremely informative not only for the initial evaluation, but also for assessing result of treatment. Tc-99m RBC whole body blood pool scintigraphy (WBBPS), known as ‘transvenous angioscan’, is able to detect abnormal blood pooling throughout the body, and is excellent at detecting VM, and AVM, and also for ruling out lymphatic malformation (LM), though it cannot differentiate CVMs from haemangiomas. TLPS is excellent for the initial work-up of all CVMs and for follow-up. Standard T1 and T2 weighted magnetic resonance imaging (MRI) studies of CVMs are essential to differentiate high flow from low flow status. This technique has excellent ability to identify VM, although some difficulty is experienced differentiating haemangioma and LM. MR arteriography (MRA) and MR venography (MRV) can be used as options when standard MRI is insufficient (e.g. CVM in the trunk). Computerised tomographic (CT) contrast studies including three-dimensional reconstruction are excellent at delineating AVM lesions. Tc-99m antimony sulphide colloid lymphoscintigraphy is also essential for the assessment of lymphatic function, mostly for LMs and haemo-lymphatic malformation (HLMs). Ultrasonographic lymphangiography and MR lymphangiography can be used, mostly to evaluate candidates for venolymphatic reconstructive surgery with the T form of LM, although this is still in the investigational stage. A comparative venous oxygen saturation study of the affected extremity is occasionally added given a differential diagnosis of AVM.

Bone X-ray studies to assess long bone growth discrepancies secondary to an intra- or extra-osseous CVM are included to rule out vascular-bone syndrome by any CVM involving the lower extremity. Such studies are often combined with an assessment of the spine and pelvic tilt.

Invasive studies remain the reference standard for the management of all CVMs. However, they are generally used to decide upon the treatment plan, as ‘road maps’, though they may be used for the differential diagnosis of a complex form of CVM. Ascending, descending, and multilevel regional venography, and percutaneous direct puncture phlebography are used mainly to assess VM lesions and the deep vein system. Standard selective and super-selective arteriography are used for arterial malformations (AMs) or AVMs; and direct puncture lymphangiography for LMs. Detailed information from each test, related to the investigation of various CVMs, has been thoroughly assessed for findings, role, indication, morbidity, and for technical information for each test. Every test mentioned above has a special role (e.g. WBBPS, TLPS) for the diagnosis and for the management of the various CVMs, as reviewed previously. Therefore, the precise understanding of each test, is mandatory to ensure that a proper combination of tests is used to achieve synergism effect and a precise assessment.

The initial diagnostic (laboratory) procedure for a CVM, following proper history taking and physical examination should include a duplex scan, MRI, and WBBPS as a basic test set. TLPS, lymphoscintigraphy, CT contrast study and/or airplethysmography can be added depending upon the kind of CVM (e.g. VM, AVM, LM or HLM) and/or its type (e.g. T form or ET form).

The risk and morbidity involved for the various tests, should also be evaluated especially for paediatric patients of less than 2 years old. Unless an accurate diagnosis is immediately needed to allow urgent treatment (e.g. a life or limb-threatening lesion, or a lesion hampering vital functions), morbidity associated with diagnostic procedures may be deferred until the child is old enough to tolerate them. Various minimally invasive studies (e.g. MRI, duplex scan, TLPS, and WBBPS) were sufficient to diagnose the majority of CVMs at our clinic, and selective invasive study (e.g. super-selective arteriography,
percutaneous direct puncture lymphangiography), was generally deferred until needed for treatment purposes. The less invasive investigations are the mainstay of our diagnostic strategy. Selective invasive studies are reserved for treatment planning purposes. Our multidisciplinary approach allowed the integration of diagnostic specialties and the sharing of critical information obtained using the advanced diagnostic techniques.1,32,33

**Management**

**Care system**

Our multidisciplinary approach promotes the role of embolo-sclerotherapy as an independent as well as an adjunctive therapy to surgery. The clinic has become efficient by acting as a ‘referral centre’ facilitating the efficient management of CVM problems by coordinating the work of 15 clinical specialists, including:11 Departments of Vascular Surgery, Paediatric Surgery, Interventional, and Diagnostic Radiology, Plastic and Reconstructive Surgery, Nuclear Medicine, Orthopaedic Surgery, Head and Neck Surgery, Oral-maxillary Surgery, Anaesthesiology, Vascular Medicine, Pathology, Physical Medicine and Rehabilitation, Psychiatry and Dermatology.

The majority of the CVMs treated require the involvement of most of the 15 specialists. This team is led by vascular surgery and interventional radiology specialists. Social service staff have played a crucial role to solicit active involvement by patients and their families through a self-help club.

The clinical management of the T form of lymphatic malformation (LM) is performed through the Lymphoedema Clinic, along with primary and secondary lymphoedemas of various aetiologies. The ET form of LM, often called cystic or cavernous lymphangioma, is treated at our CVM Clinic, as are other ET and T forms of vascular malformation.

**Multidisciplinary approach**

Each CVM patient needs to be thoroughly evaluated by each clinic team member individually.1 The summed results of the individual assessments are fully discussed by the clinical board and the final decision on management strategy arrived at by consensus.9–12 The treatment plan may be adjusted whenever a treatment strategy can be improved to deal with morbidity or recurrence.1,10,11 The clinic limits the treatment of a small number of conditions to an ‘absolute’ indication for treatment, but a ‘relative’ indication is more liberal and includes various conditions which can be managed without significant risk of morbidity (Table 1). Therefore, not all CVMs warrant treatment nor is treatment feasible in some cases within the resources of our clinic. Treatment is commenced only when the benefit of treatment exceeds the risks involved.1,11,13

The first decision made by the clinic team following the confirmation of a diagnosis of CVM is whether the patient needs treatment. Treatment decisions are made when the patient has one absolute indication or two relative indications (Table 1). Once the decision to treat is made a treatment plan is devised. The best option for management is selected from the available treatment modalities.31 Multi-session embolo-sclerotherapy is in general conducted with intervals of 1 month between sessions, with assessment following each treatment. The treatment plan is reviewed regularly to assess efficacy and complications. The clinic team will modify the plan is necessary. A regular review of the course of treated and untreated lesions is also made periodically in addition, to provide further optimum control and reinforce a life-time commitment.10,34

**Outcome assessment**

Clinical assessments are based on the subjective improvement of clinical symptoms on a scale of 0–10 after the completion of multisession therapy. Each symptom and sign, (e.g. pain, discomfort, ache, stiffness, or limited joint motion or gait) the patient has before starting the treatment is documented based on descriptions by the patient, or by the patient’s family members, and include medical photographs. Objective evidence of improved clinical signs, e.g. reduction in the size of a lesion or swelling, or an improved range of motion of the joint on a scale 0–5, or the classification of response as ‘excellent’, ‘good,’ or ‘fair’.1,13

Laboratory assessments are based on combinations of minimally invasive tests, such as duplex scanning, WBBPS, TLPS, and MRI, especially for interim assessment during multisession therapy. Angiographic findings remain the reference standard for the assessment of the treatment response, especially of an AVM. At the conclusion of each treatment, and at the completion of multisession therapy, ‘excellent’ describes complete control (disappearance), ‘good’ for near complete control with negligible evidence of residual lesion, and ‘fair’ for substantial control with significant residual lesion. Similar criteria are applied.

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to the results of tests used for treatment assessment. For example, duplex ultrasonography assesses the blood flow in a lesion. Complete cessation of flow at the treated nidus is ‘excellent’. Near complete cessation, but with some suspicion along the feeding artery and draining veins is ‘good’. Drastic reduction, but with substantial evidence of residual activity of the treated nidus is ‘fair’. Similar criteria are applied for WBBPS, TLPS, and MRI. WBBPS provides more quantitative measurement of outcome. On serial tests, a reduction of 50% or more in the isotope label is interpreted as ‘good’, and a reduction of 30–50% as ‘fair’. Periodical follow-up evaluations of treatment results are made every 6 months by the multidisciplinary team. A proper combination of these tests replaces classical angiography in monitoring progress of treatment. Arteriography must be included in the final confirmation of treatment results, and during subsequent biannual follow-up as a routine protocol for AVMs.

### Treatment

#### Indications

Treatment in principle is aimed at correction of haemodynamic disturbances caused by CVM lesions. Treatment strategies for the ‘primary malformation’ and for ‘secondary disorders’, especially of musculoskeletal and soft tissue systems are quite different. Individual tailoring of the treatment strategy should be made to meet the patient’s functional needs and those of the specific underlying pathology.\(^ {10,11}\)

Absolute indications for treatment include: haemorrhage; lymphatic leakage with recurrent local or systemic sepsis by LM or HLM; high output heart failure or a secondary ischemic complications of an AVM and chronic venous insufficiency secondary to VM or HLM. CVM lesions located in a potentially life-threatening region (e.g. adjacent to an airway), lesions located in a limb threatening region and lesions jeopardizing vital functions (e.g. seeing, hearing, eating and breathing) are also considered to be absolute indications for treatment (Table 1).

Relative indication for treatment include disabling pain, usually attributable to non-healing ulcers, lesions accompanied by functional impairment, lesions located at regions with a high-risk of complication (e.g. haemarthrosis, deep vein thrombosis and/or pulmonary embolism) and lesions causing a cosmetically severe deformity reducing the quality of life (Table 1).\(^ {11}\)

#### Surgical therapy

We now use surgery in combination with embolo-sclerotherapy rather than as an independent treatment in the management of the ET form of various CVMs,\(^ {13}\) reducing surgical morbidity. Pre- and post-operative embolo-sclerotherapy can increase scope of surgical therapy to various other ET forms. This strategy allows treatment of complex forms of CVM which was beyond the conventional approach.\(^ {35,36}\)

Surgical treatment alone or in conjunction with pre-operative embolo-sclerotherapy, is still the best method for the T form of various CVMs, especially of VM (e.g. venous aneurysm and marginal vein) where there is no risk of recurrence.\(^ {37,38}\) Surgery is more practical for the localised type of infiltrating Et although there is a risk of recurrence. Surgical procedures aimed at reducing the haemodynamic impact of vascular defects must be given priority in the management of CVMs.\(^ {11}\) Reconstructive surgery such as venous bypass to restore normal haemodynamics, and ablative (excisional) surgery to remove the vascular defect itself may be combined. These haemodynamic operations are performed before

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**Table 1. Treatment indication for congenital vascular malformations**

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<th>Absolute indication</th>
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<tr>
<td>Haemorrhage—mostly from the VM or AVM</td>
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<tr>
<td>Increasing or progressing risk of high-output heart failure—AVM</td>
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<tr>
<td>Secondary complication of chronic venous hypertension—AVM or VM</td>
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<tr>
<td>Lesions located at a life and/or limb threatening region (e.g. proximity to the airway)—VM or AVM</td>
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<tr>
<td>Lesions threatening vital functions (e.g. seeing, hearing, eating or breathing)—various CVMs</td>
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<tr>
<th>Relative indication</th>
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<tr>
<td>Disabling pain and/or discomfort of a progressive nature</td>
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<tr>
<td>Functional disability or impairment affecting daily activity and the quality of life</td>
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<tr>
<td>Cosmetically severe deformity accompanying physical and/or psychological disability and severe negative impact on the quality of life</td>
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<tr>
<td>Vascular-bone syndrome with rapid progress of long bone growth discrepancy accompanied by significant pelvic tilt and/or compensatory scoliosis</td>
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<tr>
<td>Lesions located at a region with a high risk of complication (e.g. haemarthrosis; deep vein thrombosis)</td>
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<tr>
<td>Lesions with recurrent infection and sepsis</td>
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*The consensus among multidisciplinary team of the CVM Clinic, Samsung Medical Center, Seoul, Korea.*
undertaking reconstructive procedures to address the secondary affects of primary CVM lesions. Most reconstructive surgery is required to restore arterial supply and venous outflow and is usually required to manage the T form of VM (e.g. femoro-popliteal venous bypass or the repair of femoral or popliteal vein ectasia or aneurysm). Ablative surgery includes excision of vascular defects either of the ET or T forms (e.g. the removal of the marginal-lateral embryonic vein for the HLM) to eradicate the primary lesion and does not need additional reconstructive surgery. Once haemodynamic surgery has been completed, non-haemodynamic operations can be commenced. These aim at correcting the consequence of a CVM, either caused by CVM treatment (e.g. Achilles tendon contracture) or as a consequence of progression of CVM lesions. These operations include orthopaedic surgery to improve the function (e.g. Achilles tendon lengthening) or plastic surgery to improve a cosmetic deformity.

Complete resection of CVMs should be limited to the isolated superficial lesion without extension into the contiguous structure in order to minimise surgical morbidity. An extensive lesion beyond the deep fascia with the involvement of muscle, tendon or bone or extending into the pelvis or gluteal region from the extremity is not ideal for excisional surgery. Embolo-sclerotherapy is used as the first line of treatment in these cases and may be followed by surgery. Extreme lesions with gross deformity and poor functional status, especially of a lower limb, are considered for early amputation and followed by fitting with a proper prosthesis. This allows more rapid rehabilitation rather than persisting with futile treatment.

The excisional surgery occasionally requires preparation for large blood loss, although pre-operative embolo-sclerotherapy has substantially reduced this requirement. We use several techniques for minimising blood loss including intraoperative hypotensive anaesthesia, autotransfusion, rapid infusion, the use of a proximal tourniquet, intraoperative embolo-sclerotherapy, and even complete circulatory arrest under deep hypothermia and an extra-corporeal bypass procedure.

**Embolo-sclerotherapy**

We use absolute ethanol, N-butyl cyanoacrylate (NBCA), contour particles and coils for the embolo-sclerotherapy of CVMs at our clinic. These materials are safe, effective and reduce morbidity and recurrence, particular in the diffuse infiltrating extratruncal (ET) forms of VMs. This treatment is useful where surgery would be difficult due to extensive involvement beyond the deep fascia to muscle, tendon, bone and joints. The diffuse infiltrating type of the extratruncal form of CVM is therefore appropriately managed by this treatment. Pre-operative embolo-sclerotherapy improves the overall safety and efficacy of surgery, reducing morbidity and complications.

Combinations of sclerosant drugs and embolisation materials can be used to improve efficacy. Absolute ethanol sclerotherapy is the preferred method of treatment at our clinic for the infiltrating type of the ET form, though this is accompanied by significant morbidity. Absolute ethanol has given excellent interim results with no evidence of recurrence during the limited follow-up after more than 400 sessions of treatment. Ethanol can be delivered percutaneously directly into the nidus of the VM lesion by using the direct puncture technique. N-butyl cyanoacrylate (NBCA) embolotherapy also has been incorporated into the management of extensive VM lesions prior to surgery in order to minimise bleeding.

It is important to treat the nidus of an AVM lesion in any type of AVM. The nidus should be reached via a transarterial, transvenous, or direct puncture route independently or simultaneously for precise control. The old concept of ligating or blocking feeding vessels must be condemned since, it may result in a rebound phenomenon and unintentionally stimulate the nidus into rapid growth with further deterioration.

Pre-operative NBCA embolisation has key role in the management of AVMs. This treatment enhances complete removal of the lesion and minimises bleeding complications. However, NBCA is not an ideal agent for the control of surgically-inaccessible diffuse infiltrating ET forms of AVM as an independent therapy. When a glue-filled lesion cannot be excised the long-term effect on the endothelium of the AVM nidus is uncertain as permanent means of preventing recurrence. Absolute ethanol is better for non-resectable AVMs than glue, though the short-term risk of morbidity and complications is increased. Ethanol can be used alone using a multisession approach, in conjunction with any other modalities. We have recently used NBCA in combination with ethanol and coils, especially for the fistulous type of AVM. In the case of LMs the indications for ethanol sclerotherapy at our clinic are limited to the ET form, which fail to respond to or is unsuitable for OK-432 sclerotherapy. OK-432 is recommended as a substitute for absolute ethanol in the primary therapy of LMs, especially for the cystic ET form, since, most LMs are not life or limb-threatening, and therefore less powerful, safer drugs may be tried first.
OK-432 sclerotherapy as pre-operative adjunctive therapy for LMs has shown limited success at reducing the surgical morbidity of the cavernous ET form.\(^\text{30}\) Interstitial laser therapy of the cavernous ET form of LM is under clinical trial for surgically unresectable lesions, with mixed results.

For the HLM(s) representing the combined form of CVM, which include VM, LM, CM (capillary malformation), and micro-AVM, each component has to be managed separately as indicated for each CVM type and form (T form or ET form).

### Drugs used for embolo-sclerotherapy

Numerous attempts have been made to develop reliable, less dangerous drugs to fulfil the requirement that they permanently destroy endothelial cells of CVM ET forms and prevent recurrence. ET forms of CVMs retain developmental potential from mesenchymal cells and can grow when stimulated by incomplete destruction.

Drugs using successfully for the management of varicose veins, such as polidocanol, tetracetyl sulphate, sodium morrhuate, and ethanolamine, have been investigated for efficacy in CVM sclerotherapy.\(^\text{39–43,45–47}\) Absolute ethanol remains the most reliable substance for permanently occluding peripheral arteries and veins although the risk of major adverse effects (e.g. skin and soft tissue necrosis, nerve damage, deep vein thrombosis) is significant.\(^\text{1,13,41,42,45,46}\) Absolute ethanol permanently obliterates the vessel lumen and provides the least chance of recanalisation because it denatures blood protein, dehydrates vascular endothelia cells, and precipitates protoplasm.\(^\text{41,42,50,51}\) The majority of its complications are minor and include skin erythema or bullae.\(^\text{1,13}\) The severity of local complications is related to the location of a lesion, i.e. close enough to the skin dermis to allow the ethanol to influence the skin resulting in vesicles, bullae, necrosis and ulceration. Major complications include deep venous thrombosis, pulmonary embolisation, peripheral nerve palsy, and cartilage necrosis.\(^\text{1,13}\) Precautions should be taken to avoid these whenever possible.\(^\text{10,31}\) Complications are generally accepted by patients and physicians as justifiable morbidities to obtain minimum recurrence. However, the balance of benefit over anticipated complications should be properly weighed. Transient elevation of pulmonary arterial pressure is the most common acute morbidity associated with ethanol sclerotherapy, especially for high-flow lesions, due to the reaction between the applied ethanol and the pulmonary circulation. This is easily detected and controlled with proper medication under close cardiopulmonary monitoring during general anaesthesia.

The successful control of the extensive infiltrating types of VM within calf muscles by ethanol sclerotherapy is often accompanied by calf muscle contracture. This can be successfully managed with vigorous physical therapy sometimes necessitating surgical Achilles tendon lengthening.

Absolute ethanol should only be used by experienced personnel. The smallest dose possible should be administered, based on the dose calculated for the individual’s body weight. The total used in a session should not exceed 1.0 ml of absolute ethanol per kg of body weight. Increased risk of pulmonary hypertension is associated with repeated treatment sessions. This should must be managed by nitro-glycerine administration rather than calcium channel blockers, because of its selective action on the venous system, including the pulmonary artery, and its reduced systemic effect.\(^\text{32–34}\)

### Results

#### CVMs in general: demographic data

Seven hundred and ninety seven patients (females: 446, males: 351, mean age of 22.1 years: range 14 days–81 years) with various CVMs were registered at the CVM clinic during the period January 1995–December 2001. Three hundred and fifteen patients were confirmed as LM (T form: 226 and ET form: 89); 294 patients as VM; 76 as AVM; and 66 as having the combined form as HLM. The site of predilection of CVMs was along the extremity (404/797: 324 lower limbs and 80 upper limbs) followed by the head and neck (179/797), though multiple locations was also prevalent (163/797). Of these 797 patients, 327 (124 VM, 48 AVM, 127 LM and 28 HLM) were considered appropriate for interventional treatment. The lesions treated were located mostly in the head and neck region (117/329), followed by the extremities (88/329) and multiple (63/329) lesions.

#### Venous malformation (VM)

A total of 294 patients (males: 138, females: 156, mean age 18.6 years: range 3 months–59 years) were confirmed as having VM mostly located in the extremities (128/294: upper limbs: 30 and lower limbs: 98), and often as a multiple lesions (73/294). One hundred and twenty four of the 294, were selected for treatment. Ninety-nine infiltrating ET forms,
unsuitable for surgical therapy, received a total of 419 sessions of ethanol sclerotherapy. Twenty-five limited ET forms were excised surgically, though most underwent pre-operative embolo-sclerotherapy (16/25) with N-butyl cyanoacrylate (NBCA). Thirty-six sessions of NBCA embolotherapy were given independently or in conjunction with ethanol sclerotherapy as pre-operative adjunct therapy for the subsequent surgical excision of 16 ET forms. Nine T forms (e.g. venectasia, or venous aneurysm) underwent haemodynamic operations to ligate and remove large vessels.

The 99 ET forms treated with ethanol sclerotherapy showed an immediate success rate of 98.8% (414 sessions among 419 sessions). Failures were due to direct connection between the lesion and the main venous outflow, the close proximity of the lesion to the skin and the consequent risk of skin necrosis (e.g., eyelid, face), technical difficulty in reaching the residual nidus of the lesion, and the proximity of a nerve. The interim results of ethanol sclerotherapy were also excellent in the majority (89/99) with a fair to good response and no evidence of recurrence of the treated lesions during the limited average follow-up period of 18.2 months. On average 3.2 sessions per patient were required. (Fig. 1).

Sixteen ET forms, which underwent pre-operative embolo-sclerotherapy and subsequent surgical excision showed excellent results in all with minimum morbidity and no recurrence during the follow-up period (average 21.2 months) (Fig. 2). Nine T forms, underwent surgery with excellent results in all. There were no chronic sequelae due to the toxic effect of absolute ethanol on the pulmonary vasculature.

Fig. 1. Management of venous malformation (VM) with absolute ethanol as an independent sclerotherapy. (A) and (B): Clinical appearance of VM-affected right cheek, pre-operative (A) and post-operative (B). (C) and (D): Whole body blood pool scan finding of a VM lesion over the right cheek lesion, pre-operative (C) and post-operative (D). (E): Phlebographic finding of VM lesion in the cheek region via direct puncture. (F): Phlebographic finding of immediate sclerotherapy success via an absolute ethanol injection into the nidus of the lesion. (G): Duplex scan finding of the haemodynamic condition at the internal jugular vein draining the VM lesion-increased blood volume and vein diameter of IJV before the treatment (top two photos), and decreased blood volume and vein diameter following treatment (bottom two photos). (H) and (I): MRI findings of a VM lesion in the cheek and in the sublingual region, before treatment (H) and after treatment (I).
The 99 VM patients developed 101 ‘acute’ complications during 98 of 419 sessions (23.4% of sessions and 50.5% of patients). Most were minor, and were confined to skin and subcutaneous tissue injury, due to the proximity of lesions to the skin (87/101). These healed with standard wound care. Since, they were mainly predictable (68/87) patients were forewarned, and they were accepted in most cases as unavoidable minor morbidities of the treatment. However, 9 with skin complications involved deeper tissue injury (e.g. muscle and/or tendon injury), which required subsequent plastic reconstructive work (e.g. split-thickness skin graft, etc.) to obtain healing.

Deep vein thrombosis (DVT) developed in 8 sessions; one was complicated by an acute pulmonary embolism (PE), and another by superficial thrombophlebitis. All lesions were located near the normal deep vein system of the lower extremity, with direct drainage of the VM lesion by connecting vessels into the deep system. The transient elevation of pulmonary artery pressure (PAP) as a signal of spilled ethanol entering the systemic circulation did not occur in all 8 of these cases. Two DVTs complicated by PE developed more than 24 h after the third sessions had been completed, but were accompanied by abnormal coagulation profiles including protein C and protein S deficiency. The DVTs were treated with low molecular weight heparin and oral anticoagulation.

Fig. 2. Management of a venous malformation (VM) by pre-operative embolisation and subsequent surgical excision. (A): Clinical appearance of the VM lesion along the left buttock in a massively swollen condition. (B): WBBPS* finding of the lesion involving the entire buttock. (C): TLPS* finding of the lesion without evidence of hidden AV-shunting condition. (D) and (E): MRI finding of diffuse infiltrating extratruncal form of the VM lesion throughout the soft tissues and gluteal muscles. (F): Angiographic finding of the pure venous nature of the lesion (AV shunting condition was ruled out). (G): Angiographic finding of the pre-operative embolisation with N-butyl cyanoacrylate (NBCA) glue. (H): Pre-operative CT scan finding of the glue-filled lesion as a road-map for subsequent surgical excision. (I): Pre-operative preparation status with volume expanders along the massive lesion to achieve wound expansion. (J): Operative finding of the glue-filled lesion to reduce bleeding-related morbidity. (K): Surgical specimen of the lesion safely resected with minimum morbidity. (L): Surgical wound, feasible for primary closure without additional skin graft and/or flap rotation. *WBBPS, whole body blood pool scan; TLPS, transarterial lung perfusion scan.

VM complications and morbidity

Deep vein thrombosis (DVT) developed in 8 sessions; one was complicated by an acute pulmonary embolism (PE), and another by superficial thrombophlebitis. All lesions were located near the normal deep vein system of the lower extremity, with direct drainage of the VM lesion by connecting vessels into the deep system. The transient elevation of pulmonary artery pressure (PAP) as a signal of spilled ethanol entering the systemic circulation did not occur in all 8 of these cases. Two DVTs complicated by PE developed more than 24 h after the third sessions had been completed, but were accompanied by abnormal coagulation profiles including protein C and protein S deficiency. The DVTs were treated with low molecular weight heparin and oral anticoagulation.
with coumadin. No further complication or sequelae occurred, and anticoagulation treatment was maintained for an average of 6 months.

Peripheral nerve damage, mostly peroneal, ulnar, median or facial nerves, either as transient or permanent damage, developed following 9 sessions of treatment. Two were permanent, but the other 6 were transient and recovered within 2 weeks–2 months.

Chronic complications and morbidities developed in 11 of 99 VM patients, 3–12 months after successful sclerotherapy. Seven of these 11 patients had fibrosis of the calf muscles and subsequently developed contracture of the ankle, requiring aggressive physical therapy to improve an abnormal gait. Five of these 7 achieved satisfactory compensation with physical therapy and two patients required an early Achilles tendon lengthening procedure to increase the efficacy of physical therapy.

Transient pulmonary hypertension and transient haematuria are reported as acute complications of ethanol sclerotherapy. These developed in more than two-thirds of the 419 sessions, but were all managed safely using vasodilators. Nitroglycerine given through the intravenous port of a Swan-Ganz catheter (0.3–1.5 μg/kg of body weight/min) was considered to be superior to calcium channel blockers as it has less effect on the systemic circulation.

Fig. 3. Management of the AVM by combination embolo-sclerotherapy using coils and ethanol simultaneously. (A): Clinical appearance of a rapidly expanding AVM lesion with a painful swelling at the right forearm. (B): WBBPS* finding of a haemodynamically active AVM lesion with a large abnormal blood pool at the right forearm. (C): TLPS* finding of AV shunting status through the lesion nidus—25.45%. (D): Angiographic finding of the AVM lesion with rapid flow-accompanying nidus. (E): Angiographic finding of the preliminary coil embolization (transarterial) to reduce the blood flow through a nidus planned for subsequent ethanol treatment. (F): Angiographic finding of the lesion following the priming of the nidus by coil embolisation for subsequent ethanol sclerotherapy. (G): Angiographic finding of the satisfactory result following the completion of simultaneous embolo-sclerotherapy with coil and ethanol.*WBBPS, whole body blood pool scan; TLPS, transarterial lung perfusion scan.
flow fistulous lesions (Fig. 3). Ethanol was utilised (in 158/162 of the successful sessions) mainly for high combined with coils, glues and/or contour particles were 171 sessions with nine failures. Ethanol was used alone in 132 sessions with no further treatment. One patient had a pulmonary embolism following the use of NBCA glue. All 16 patients had excellent interim results with no evidence of recurrence, during a follow-up averaging 24.3 months.

Thirty-two patients (extratruncal: 28; truncal: 4) with surgically inaccessible lesions, mostly diffuse infiltrating AVMs (buttck; thigh, and calf muscles) were managed by embolo-sclerotherapy alone. There were 171 sessions with nine failures. Ethanol was combined with coils, glues and/or contour particles (in 158/162 of the successful sessions) mainly for high flow fistulous lesions (Fig. 3). Ethanol was utilised alone in 132 sessions. The majority (25/32 patients) were considered to have an excellent result at an average follow-up of 19.2 months. Good to fair control of the activity of the nidus was observed among the remaining seven. All had angiographic follow-up. No evidence of recurrence was found during the follow-up period of 19.2 months.

AVM complications and morbidity

There were 31 complications, the majority (27/31) of which were minor and involved the skin. This usually followed ethanol treatment. Three of four major complications developed after ethanol therapy: 1 transient facial nerve palsy, 1 deep vein thrombosis and 1 massive ear cartilage necrosis. One pulmonary embolism followed NBCA glue embolisation of an AVM of the fistulous type. These major complications developed in high-flow conditions, while the majority of minor complications developed among extratruncal AVMs. Treatment was stopped for one patient with a high-flow AVM fistula involving bone, despite what was considered good progress. Subsequently, the patient required a forearm amputation to arrest recurrent massive bleeding and high-output cardiac failure as a life-saving procedure. Unfortunately, the patient eventually committed suicide.

Two hundred and twenty six cases of the T form of LM clinically presented as chronic lymphoedema of the congenital type (40/226), precox type (138/226), or tarda type (48/226). They were affected by chronic lymphoedema: 32 at stage I; 104 at stage II; 48 at stage III; 18 at stage IV; and 24 at an undetermined stage.

The clinical response of the T form in clinical stages I and II to manual lymphatic drainage (MLD)-based complex decongestive physiotherapy (CDP) was excellent to good, following initial in-hospital care in the majority of cases (121/136). Some improvement also occurred in stages III and IV (31/66), with a good to fair response, despite additional SIPC-based compression therapy (38/66). The long-term maintenance of the initial treatment results with excellent to good to fair responses in a total of 152 cases (stages I through IV), was found to be totally dependent on patient compliance. In most cases (102/152), good compliance with home-maintenance care was achieved for up to 48 months, the end-point of the follow-up assessment. In addition to this, CDP-based conservative therapy as a basic therapy for all 315 T forms, 15 patients with 19 T form limbs received further surgical therapy, either reconstructive (10/19) or ablative (9/19).

Of a total of 32 cases who underwent reconstructive surgery 10 patients (limbs) with primary lymphoedema due to the T form of LM were treated by a venolymphatic anastomosis (4/10) or a free lymph node transplant (6/10), as a supplementary surgical therapy when the clinical stage of the lymphoedema progressed. Of 4 veno-lymphatic anastomotic reconstructions performed for primary lymphoedema, only 2 showed good to fair maintenance of the initially good results (6–12 months) at the end-point of the follow-up (48 months). There was an accompanying compatible improvement of lymphatic function by lymphoscintigraphic evaluation, with reduced dermal backflow and higher tracer clearance.

Four of 6 patients who underwent free lymph node transplant surgery showed a good to fair response on the initial evaluation (12 months), together with viable lymph nodes (3/4) by ultrasound evaluation, and functioning lymph nodes by lymphoscintigraphy (2/4). Subsequently, 3 patients maintained a good to excellent clinical response at the 24 month follow-up assessment.

Of 22 patients at the end stage of chronic lymphoedema who received ablative (excisional) surgery on 33 limbs, 9 limbs of 5 patients with primary lymphoedema as a result of the T form of LM were included, together with 24 limbs of secondary lymphoedema, where the disease had progressed from stage III to IV...
with an increased incidence of local and/or systemic sepsis. This causes a rapid deterioration in the quality of life, and/or an inability to apply CDP due to massive swelling of the limb.

In 9 limbs, where excisional surgery for primary lymphoedema was undertaken, only 6 were able to maintain a good result for 48 months. However, all 6 cases that complied well with post-operative CDP and/or compressotherapy maintained an acceptable outcome. None showed improved lymphatic function by follow-up lymphoscintigraphic evaluation.

Of 89 patients with the ET form of LM, 73 patients were treated by sclerotherapy (62/73) or surgically (11/73). Sixty-two patients, including most with the cystic type, were treated by 120 sessions of sclerotherapy with OK-432 (108/120) and absolute ethanol (12/120) (Fig. 4). Eleven patients, including most of the cavernous type, were treated by surgical excision; 7 patients were treated using combined pre-operative OK-432 sclerotherapy prior to the surgical excision, and 4 patients were treated independently.

Of 62 patients, 51 patients selected from the paediatric age group were treated only by OK-432 sclerotherapy over 108 sessions. Complete to marked shrinkage was obtained in 88.9% of the limited cystic type (40/45) and of 50% (3/6) of the diffuse infiltrating cavernous type. There was only one recurrence during the minimum follow-up period of 24 months.

Seventeen lesions (9-diffuse; 8-limited) of 7 patients underwent pre-operative OK-432 sclerotherapy to reduce the magnitude of the subsequent surgical excision. Fourteen of 17 lesions showed good to excellent results with much reduced morbidity and complications. There was no evidence of recurrence during the minimum follow-up period of 24 months.

Fig. 4. Management of a lymphatic malformation (LM) with OK-432 and/or ethanol as an independent sclerotherapy. (A): Clinical appearance of an LM-affected upper anterior-lateral-chest wall with recurrent local cellulitis, following an ill-managed lesion surgically. (B): MRI finding of a primarily cystic type of an extratruncal form of an LM lesion. (C): Angiographic findings of the superficial and/or de-novo lesion (neck) lesion treated with OK-432 and of the recurrent and/or deep-seated lesion (chest wall) treated with ethanol.
Discussion

Recommendations

A new strategy based on the multi-disciplinary concept has achieved significant improvements in the management of CVMs, although this success has created new problems of acute and chronic morbidity following treatment. All presently available treatment modalities have been carefully integrated to reduce the risk of complications. No single treatment modality presently available fulfills all treatment and cost requirements.

We adopted absolute ethanol as the main drug for sclerotherapy despite the risk, because it can destroy endothelial cells permanently minimising recurrence. The use of absolute ethanol for the management of CVM is acceptable if complications of treatment are managed properly. We encountered a previously unknown risk of ethanol sclerotherapy, when treating the infiltrating type of VM lesion within the calf muscle.\(^1\) The treatment was effective but progressive muscle fibrosis with a subsequent contracture of the calf muscles was more serious than expected. We cannot over emphasise the need for continuous attention and maximum effort to reduce both the acute and chronic complications of absolute ethanol. We do not recommend absolute ethanol for ‘routine’ use unless a specialised team approach is taken, especially in the case of high flow AVM lesions.

The new strategy of combining embolisation materials (e.g. coils, contour particles, N-butyl cyanoacrylate) with absolute ethanol was introduced recently to achieve synergistic effects and to reduce the morbidity associated with absolute ethanol. This new strategy seems to work well with the extensive forms of VM and AVM, especially of the fistulous type with high flow, which lacks an adequate nidus to attack with ethanol alone. The strategy of converting a fistulous lesion to a non-fistulous lesion by preliminary embolisation can substantially reduce the risks of ethanol sclerotherapy.

In an attempt to replace ethanol, a trial with polidocanol and tetradecyl sulphate foam has been started for VM. This is delivered under duplex ultrasound control. VMs involving the dermis or critical areas (e.g. the face) were selected for this trial since, ethanol would carry a considerable risk of complications. Similar efforts have been made to treat the less dangerous LM, or HLM with OK-432, also known as picibanil, which is a streptococcal exotoxin with LM specificity. This sclerosant seems to have a reasonable future for LM as it provides the same success rate as ethanol for the limited (cystic) type of the LM ET form, though its results are mixed for in recurrent and diffuse (cavernous) types.

Conclusion

A multidisciplinary team approach to CVMs has been developed improving results of treatment, with reduced morbidity and recurrence compared to conventional approaches. New strategies that fully integrate traditional surgical therapies with combinations of embolisation and sclerotherapy are effective in lesions, which once would have been impossible to treat. This system of treatment aims to improve the quality of life from this ever-miserable disease.

Acknowledgements


References


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