HUE UNIVERSITY

UNIVERSITY OF MEDICINE AND PHARMACY

NGUYEN DINH LUAN

STUDY FOR DIAGNOSIS AND MANAGEMENT BY ABSOLUTE ALCOHOL OF PERIPHERAL VASCULAR MALFORMATIONS

SUMMARY OF MEDICAL DOCTORAL DISSERTATION

HUE - 2022

This work is completed at

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Academic supervisors:

Assoc. Prof. HOANG MINH LOI, MD, PhD

NGUYEN SANH TUNG, MD, PhD

Reviewer 1:

Reviewer 1:

Reviewer 1:

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MAJOR: RADIOLOGY AND NUCLEAR MEDICINE

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PROPOSAL

Vascular malformations are localized or diffuse lesions that affect the vascular components. Lesions are characterized as an increase in the number and size of blood vessels, the absence of proliferation of endothelial cells. Vascular malformations tend to progress over time [1], [2], [3].

In the past, vascular malformations were diagnosed and used with inconsistent terminology, inappropriate to the histopathological essence leading to inappropriate, less effective treatment options and many complications [4], [5]. In 2014, the International Society for the Study of Vascular Anomalies (ISSVA) released a classification of vascular anomalies, unified diagnosis, but the treatment issue is still debated.

Currently, there are not many researches on the systematic treatment of vascular malformations, nor many studies that compares difference between treatments. Endovascular intervention is considered the most positive treatment method, if combined with other methods (surgery) can increase the likelihood of completed treatment. Of all the materials that are used for sclerosing and thrombosing, absolute alcohol (Ethanol 99.5%) has been proven the most effective, but few authors apply it due to the difficulty in use and related serious complications. Yakes and Do reported the lowest complication rates and the highest cure rates for a variety of peripheral vascular malformations with alcohol using [6], [7].

In Vietnam, there are not many systematic studies on peripheral vascular malformations, inconsistent of the terminology and mainly surgical management [8], [9], [10], [11], [12]. There is few researches related to endovascular treatment, particularly with absolute alcohol.

Although in the past, absolute alcohol has been used for sclerosing of venous malformations and thrombosing of arterio-venous malformations. However, there are various reports with diverse results, differences in severe complications and in success rates. Is the progress of diagnostic imaging, definite diagnostic identification according to ISSVA 2014, clear classification of malformations, can improve the treatment results, reduce the complications of absolute alcohol in treatment? Research on the diagnosis and treatment of peripheral vascular malformations with absolute alcohol is necessary, so we carry out the study: ***"The research on diagnosis of some peripheral vascular malformations and interventional treatment with absolute alcohol injection"*** with two objectives:

1. Survey of clinical features, imaging of arteriovenous malformations and venous malformations according to the classification of the International Society for the Study of Vascular Anomalies ISSVA 2014.

2. *Evaluate the results of treatment with absolute alcohol injection for certain peripheral vascular malformations.*

New contributions of the thesis:

The thesis has the following main contribution points:

- Combining clinical with imaging exams: computed tomography, magnetic resonance, and digital subtraction angiography to diagnose arteriovenous malformations and venous malformations. Based on the ISSVA 2014 classification, proper identification of the type of vascular malformations help to choose the right treatment modalities.
- Assessing the sensitivity of computed tomography and magnetic resonance imaging, advantages, and disadvantages of each method; a combination of both methods when needed. In addition, imaging surveys on three planes: axial, sagittal, coronal planes help interventional radiologist navigating the lesions. Applying the Yakes classification which is a classification of arteriovenous malformations for treatment.
- Demonstrating the use of absolute alcohol in the treatment of endovascular interventions of arteriovenous malformations, venous malformations with high effective response to treatment, low complication rate.

Structure of the thesis

The thesis is 106 pages. Proposal: 2 pages; overview: 29 pages; subjects and methods: 27 pages; result: 21 pages, discussion: 24 pages, conclusion: 2 pages; recommendations: 1 page.

Chapter 1
OVERVIEW

Peripheral vascular abnormalities account for one percent of the population, are classified according to the standards of the International Society for the Study of Vascular Anomalies (ISSVA) [13], [14]. Vascular malformations can be seen at any age, from infants to adults.

1.1. TERMS OF VASCULAR ANOMALIES

Mulliken and his colleagues, based on pathology, clinical characteristics, and imaging features, made definitive diagnoses and

differential diagnoses between hemangiomas and vascular malformations [4], [15], [16].

In 2014, the ISSVA agreed to release a detailed classification, [17], [18].

Table 1.1. ISSVA 2014 classification for vascular anomalies

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
Benign Locally aggressive or borderline Malignant	**Simple** - **Capillary malformations.** - **Vascular malformations.** - **Venous malformations.** - **Arteriovenous malformations.** - **Arteriovenous fistula.**	Combined Combination between all the malformations.	Of major named vessels	Associated with other anomalies

1.2. ANATOMY OF THE VASCULAR SYSTEM

1.2.1. Macroscopic anatomy

The vascular system in the body includes: the circulatory system (arteries, capillaries, veins); pulmonary circulatory system and lymphatic system.

1.2.2. Microscopic anatomy

1.2.2.1. Arteries

Composed of three layers (inner, middle, outer). In the outer layer may contain small blood vessels called vasa vasorum.

1.2.2.2. Capillaries

Only the endothelial cell layer (intima) and the basement membrane, about 5 to 10 micrometers thick, are where nutrition and oxygen are exchanged.

1.2.2.3. Veins

The vein has 3 layers, the middle layer is thinner due to containing less smooth muscle and less elastic tissue. The veins have

a valve system that helps to resist gravity, pushing blood to the heart.

1.2.2.4. Lymphatic vessels

Large lymphatic vessels consist of 3 layers similar to veins: endothelial layer, smooth muscle, outer coat. Small lymphatic vessels are structurally similar to capillaries: endothelial cells lining and outer layer.

1.3. ANATOMY OF VASCULAR ANOMALIES

Vascular malformations have normal vascular endothelial cells with flattened form, no endothelial cell proliferation and no increase in plasma cell size in nidus of malformation, dilated vascular structures [16], [19]. [20].

1.5. CLINICAL FEATURES OF VASCULAR MALFORMATIONS

Vascular malformations develop early from birth, however, clinical symptoms begin appearing when growing up. Mild symptoms: pain, bruises, heaviness at the site of the lesion; increased sweating in the lesion area, hirsutism; warmth; bleeding or fluid leakage. Severe symptoms of infection, muscular dystrophy, congestive heart failure, local symptoms associated with the lesion area, increased D-dimer [16], [36], [46], [47], [48], [49], [50], [51].

1.6. IMAGING APPEARANCE

Currently, diagnosing vascular malformations with high-precision imaging, according to ISSVA, it is agreed to consider diagnostic exams such as ultrasound (Doppler), computed tomography, magnetic resonance imaging, digital angiography as coordinated exams of diagnosis as alternatives to biopsy [33], [52], [53].

1.6.1. Ultrasound

Ultrasound is a simple diagnostic exam of screening, helping to diagnose the structures of vascular malformations [10], [54], [55].

1.6.2. Computed tomography

CT angiography is advantageous in cases of capillary malformations, direct arteriovenous fistula, arteriovenous fistula, related bone structure assessment, vascular malformation nidus assessment [4], [54], [56], [57], [58], [59].

1.6.3. Magnetic resonance

MRI helps to diagnose, assess the nature of the lesion and the blood supply characteristics (used for coordination lesions) [60]. Sensitivity and specificity of MRI in the diagnosis of vascular malformations are 95% and 83% respectively [17], [61], [62], [63], [64], [66].

1.6.4. Digital subtraction angiography

Digital subtraciton angiography is an invasive, gold standard procedure for diagnosing AVM [67]. Angiography, venous angiography, or angiography via direct puncture into the lesion. Indications for digital subtraction angiography include: fast-flow vascular malformations: direct arteriovenous shunt or arteriovenous malformations [55], [65], [68], [69].

1.7. DIAGNOSIS

Based on clinical symptoms and imaging, definitive diagnoses are divided by type: fast-flow vascular malformations (arteriovenous malformations, arteriovenous shunt) and slow-flow vascular malformations (capillary, lymphatic, venous malformations) [37], [70].

1.7.1. Slow-flow vascular malformations

These are types of vascular malformations that do not include arteriovenous connections, or are not present arterial lesions [65], [70].

1.7.1.1. Capillary malformations

Clinical diagnosis [71].

1.7.1.2. Lymphatic malformations

Diagnosis is based on clinical and imaging combination [72], [73].

1.7.1.3. Venous malformations

Venous malformations are the most common of all malformations [74], [75]. Diagnosis base on clinical and imaging exams, ultrasound is for screening, magnetic resonance imaging is for definitive diagnosis [26], [46], [53], [57], [76], [77], [78], [79].

1.7.2. Fast-flow vascular malformations:

There are two types but are grouped into arteriovenous malformations, and classified according to Schoebinger, according to Cho, or Yakes [58], [80], [81], [82].

Diagnosis by combination clinical with imaging, digital subtration angiography is the gold standard [6], [66], [82], [83], [84], [85], [86].

1.8. MODALITIES OF TREATMENT FOR VASCULAR MALFORMATIONS

Current treatments include: surgery, medical treatment, cryotherapy, laser ablation, endovascular intervention therapy [5], [63], [87], [88], [153].

1.8.1. Surgery

Today, the role of surgery is no longer the first-line treatment for vascular malformations [8], [89], [90], [91].

1.8.2. Laser treatments

Lasers are only valid in the treatment of capillary malformations, or some cases of superficial venous malformations [92], [93], [94], [95].

1.8.3. Medical treatments

Some drugs are used for medical treatment such as: ß blockers (venous malformations, capillaries); Bevacizumab, Tamoxifen (direct arteriovenous shunt in hemorrhagic hereditary vasodilation); Sirolimus (lymphatic malformation); Thalidomide (arteriovenous malformations) [96], [97], [98].

1.8.4. Endovascular intervention

Endovascular intervention therapy in vascular malformations is considered as the primary treatment [6].

There are two approaches to the nidus of vascular malformation: endovascular, direct puncture.

Vascular malformations nidus fibrosis, treatment of slow-flow vascular malformations. [6], [99], [100], [101], [102].

"Embolism" is a noun for a treatment of fast-flow vascular malformations (with artery involved) intended to reduce arterial flow, complete occlusion, partial occlusion of nidus [84], [85].

Of all materials, absolute 99.5% alcohol was considered as both fibrotic and embolistic treatment depending on the type of slow-flow or fast-flow vascular malformations [21], [103], [104], [105] [106], [107], [108].

1.9. CURRENT RESEARCH SITUATION

From 2018 to 2021:

Majewska and Hussein review diagnostic exams that help identify vascular malformations specifically for MRI 3 Tesla with TWIST sequences, distinguishing arteriovenous fistula existence [58], [67], [82], [109].

Molecular biology studies realting Vascular Endothelial Growth Factor, Al Olabi, Hoeger, Kangas synthesized gene mutations (GNAQ, KRAS, NRAS), mutations in intracellular signaling pathway PI3K, RAS, MAPK, helping to develop drugs for the treatment of Klippel Trenaunay , Cloves, FAVA syndromes [24], [110], [111].

Lenvitinib, Bevazumab and many Vascular Endothelial Growth Factor inhibitors are being tested for treatment [23], [42], [59], [94], [96], [97], [98], [111], [112], [113].

+ Evaluation of success rates and complications of some new materials such as EOI, onyx, fibrous materials such as

bleomycin, polidocanol have been studied, [102], [114], [115], [116], [117], [118].

+ Studies comparing other materials with absolute alcohol [119], [120], [121].

+ Other studies apply new techniques such as cryotherapy.

Chapter 2
SUBJECTS AND METHODS

2.1. RESEARCH SUBJECTS

Including 85 patients with AVMs and VMs at Nhan Dan Gia Dinh Hospital from 06/2016 to 06/2020.

2.1.1. Criteria of Patient Selection:

- Patients have no age limit, regardless of gender.
- The patients have definitive diagnosis of AVM, VM and is indicated for endovascular intervention.
- Agree to participate in the study after being clearly explained the purpose and process of the study.

2.1.2. Exclusion criteria

- Patients with comorbidities that affected the follow-up during the study.
- Pregnant patients.
- Patients with contraindications to treatment of AVMs and VMs.
- The patients agreed to treatment but did not re-examine or follow up with clinical and diagnostic imaging after treatment at least 1 cycle after the intervention.

2.2. RESEARCH METHODS

2.2.1. Research Methods

We carried out a prospective interventional non-controlled study, follow-up from June 2016 to June 2020 at Nhan Dan Gia Dinh Hospital.

2.2.2. Sample size and sampling methods:

Appropriate sample size, based on the number of patients satisfying the criteria for patient selection, exclusion criteria, and indications for interventional treatment during the study period.

2.2.2. Research Diagram

2.2.3. Diagnostic processes, therapeutic procedures and measurements, definition of variables

2.2.3.1. Diagnostic processes

2.2.3.1.1. Clinical symptoms

2.2.3.1.2. Diagnostic imaging

- Diagnostic imaging such as computed tomography, magnetic resonance imaging, help confirm vascular malformations. [61], [76], [78], [124].

Computerized tomography:

- *Indications:*

+ Injuries of direct arteriovenous fistula, arteriovenous malformation.

+ Injuries of the skeletal system.

+ Injuries of chest wall and lungs.

+Contraindications to magnetic resonance imaging.

Magnetic Resonance Imaging:

- Indications:

+ Vascular malformations of the the head, face, neck, soft tissues, limbs and abdomen – pelvis regions.

+ Venous malformations.

+ AVM associated with soft tissue injuries (clinical assessment and screening ultrasound).

- There are no contraindications to MRI. Some limitations related to MRI: chest wall, lung, bone.

Digital subtraction angiography

- Digital subtraction angiography is performed for all types of malformations as the gold standard.

- Indications:

+ Arteriovenous, capillary malformations: angiography.

+ Venous and lymphatic malformations: direct needle puncture.

2.2.3.1.3. Laboratory testing:

Pre-operative laboratory tests. Other tests are performed only when there are clinical abnormalities, or other laboratory tests are abnormal.

2.2.3.2. Diagnosis

Based on ISSVA classification 2014

2.2.3.2.1. Venous malformations:

- Diagnosis is based on clinical, diagnostic imaging (MRI).

- The definitive diagnosis of venous malformation is a sign of blood reflux when the needle is directly punctured into the nidus (specific sign).

2.2.3.2.2. Arteriovenous malformations:

- Arteriovenous malformations are diagnosed based on clinical evidence, CT and/or MRI.

- Digital subtraction angiography: gold standard in diagnosis, imaging of nidus and structural components of arteriovenous malformations were classified according to Yakes.

2.2.3.2.3. Mixed vascular malformations

- In case there are more than two types of vascular malformations in a patient, we classify as mixed vascular malformations including fast - slow flow or slow-slow flow.

- However, when treating patients, we will classify these cases as malformation that cause symptoms on admission.

2.2.4. Interventional treatment process

2.2.3.1. *Indications for interventional treatment*

2.2.3.1.1 Indications and contraindications for the treatment of vascular malformations (According to Burrows and Lee)[117]:

- **Absolute indications:**

+ Venous malformations is bleeding.

+ Secondary complications caused by venous congestion.

+ Malformations located in a life-threatening location (airway, natural body cavities).

- **Relative indications:**

+ Pain or heaviness in the affected area.

+ Injuries that affect daily movement or quality of life.

+ Injuries cause serious disfigurement and unsightliness, affecting the patient's psychology and quality of life.

+ VMs affect bone growth, causing hypertrophy and abnormal bone growth.

+ VMs are located at a site with a risk of bleeding or complications.

+ VMs are located at a site where there is a risk of recurrent infection or sepsis.

Relative contraindications:

+ Injuries near the nerve plexus, or lesions causing focal neurologic signs.

+ VMs located all over the surface of the skin.

+ VMs associated with deep vein injuries.

+ Blood clotting disorder.

+ Chronic obstructive pulmonary disease.

2.2.3.1.2 Indications and contraindications for the treatment of AVM (Based on the Schobinger Classification)[123]:

Indications for treatment:

- There are symptoms, or complications caused by the malformations.

- Aesthetics: deformation, color change.

- Locations of intervention: right at the lesion. In the case of diffuse malformation, interventional therapy is performed at the site of symptom presentation.

- All cases of treatment are used absolute alcohol as the main material for artetial embolization and nidus malformations.

- Coils are used to support in case of need to reduce the amount of alcohol, especially used to block the vein near the arteriovenous fistula in AVMs.

- NBCA glue is used when the microcatheter position cannot reach a secure position.

There are no contraindications to the treatment of AVMs.

2.2.3.2. Patient Preparation

The patient will be examined before anesthesia. Prepare the patient 24 hours prior to treatment as a surgical treatment under general anesthesia.

2.2.3.3. Interventional treatment techniques

*** Instruments – materials:**

* **Patient Positions:**

- Depending on the location of the malformations that need intervention.

* Interventional techniques:

- All treatment cases are under general anesthesia.

- For AVMs, the diagnosis is confirmed by digital angiography with Sheldinger technique, the location of the entrance is the right femoral artery.

- With AVMs: Insert the needle into the malformations with a needle with the size from 18G to 23G, the length from 100mm to 200mm depending on the depth of the lesion.

- The maximum amount of alcohol that can be used for each time is 1mg/kg.

2.2.3.4. Postprocedural treament

Symptomatic treatment after the procedure with anti-inflammatory, analgesic, antibiotics if infections occur.

2.2.4. Clinical assessment and postprocedural follow-up

Assess response to treatment according to 3 criteria:

+ Clinical response (symptoms and signs).

+ Diagnostic imaging.

+ Synthesize clinical responses, diagnostic imaging and complications as a results of treatment.

Treatment outcomes are divided into clinical response and imaging response and overall treatment outcome.

2.2.4.1. Clinical response assessment

Complete clinical response [125].

Near – complete clinical response: complaints persist, aesthetic index decreases by 2 steps on the scale.

Partial response: complaint symptoms improved, aesthetic index decreased by 1 level or remained.

Severe complications (death, severe permanent sequelae, *Require intensive intervention, Inpatient hospitalization > 48h).*

Mild complications *(temporary sequelae such as neurapraxia, reversible skin lesions, muscle injuries, motor impairment).*

2.2.4.2. Imaging response assessment

Treatment results were assessed by the degree of hypoperfusion in the malformation (100%; 76 - 99%, 50-75%, <50%).

For VMs, the malformation cavity is calculated by the formula:

$$V = (N \times TS \times D)/2$$

V: volume of venous malformation cavity.

N: maximum width on one or three three-dimensional splanes.

TS: maximum height on one or three three-dimensional planes.

D: maximum length on one or three three-dimensional planes [118].

AVMs are effectively evaluated based on DSA imaging of arteriovenous malformations.

2.2.4.3. Treatment results

Evaluate the results of treatment as follows:

+ **Complete response**: complete improvement of clinical symptoms and 100*% reduction of perfusion on imaging.*

+ **Near – complete response:** *improve clinical symptoms completely or almost completely and improve imaging from 76% - 99%.*

+ **Partial response**: partial clinical improvement and imaging improvement from 50 to 75% or < 50% *perfusion in malformation on imaging.*

+ **Treatment failure**: when causing severe complications, amputation or removal of malformed organs or aggravation of clinical symptoms.

+ Evaluate the radiation dose for each case and the total dose.

Finally, evaluate the overall outcome of the treatment method when the treatment result from partial response to complete response or ineffectiveness.

2.2.5. Data collection and deviation management process

The collected data are put into the research sample medical record, then entered into Excel software for management and monitoring. Data from Excel were converted and processed using R-statistical software.

2.2.6. Research variables

2.2.6.1. Common variables

2.2.6.2. Laboratory and imaging variables

2.2.6.3. Treatment variables

2.3. RESEARCH ETHICS

The research outline was approved by the Ethics Committee in biomedical research at Nhan Dan Gia Dinh Hospital and the Medical Ethics Committee in biomedical research at Hue University of Medicine and Pharmacy (Decision No. 54 /QD-NDGD 15/01/2016).

Chapter 3
RESEARCH RESULTS

85 patients, including 16 cases of AVMs and 69 cases of VMs were diagnosed according to ISSVA 2014 criteria and treated with absolute alcohol injection.

3.1. General features

Bảng 3.1. General characteristics of the study distributed by age (n=85)

Features	Quantity (n = 85)
Median (Q1-Q3)	18 (14-32)
Mean (Standard Deviation)	23,4 (13,7)
Youngest age – oldest age	5-64

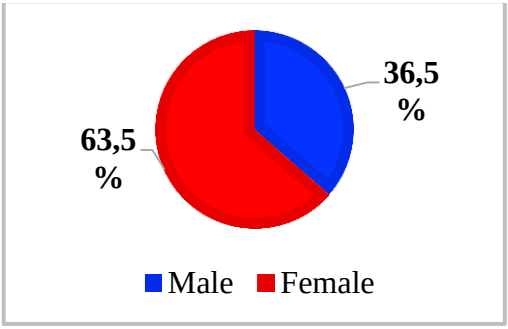

Chart 3.1. Distribution by sex of the study population

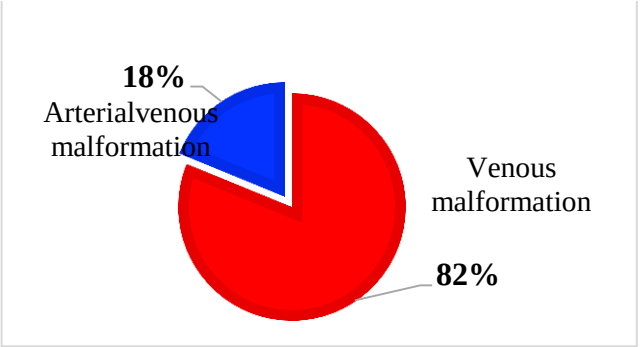

Chart 3.3. Proportion by type of malformation

Table 3.2. Classification of malformation by sex and age (n=85)

		Vascular malformation		p
		VMs (n=69)	AVMs (n=16)	
		n (%)	n (%)	
Age group (years)	< 7	3 (4,3%)	1 (6,2%)	**0,039**
	7 – 18	36 (52,2%)	3 (18,8%)	
	>18	30 (43,5%)	12 (75,0%)	
Age (years)	Mean /Standard Deviation	21,9 (12,8)	29,9 (15,9)	**0,033**
	Median (Q1-Q3)	17 (13-27)	25,5 (21- 41,8)	

Table 3.5. Signs at site by type of malformation (n = 85)

Signs	Vascular malformation		p
	VMs (n=69)	AVMs (n=16)	
	n (%)	n (%)	
Lump	67 (97,1)	16 (100)	1,0
Painful	36 (52,1)	6 (37,5)	0,435
Color change	2 (2,9)	5 (31,3)	**0,001**
Bleeding	1 (1,4)	5 (31,3)	**<0,001**
Pulse	0 (0)	9 (56,3)	**<0,001**
Others (Dysphagia , hand numbness)	22 (31,9)	6 (37,5)	0,892

Table 3.8. Features of computed tomography images of arteriovenous malformations (n=13)

Features	**AVMs (n=13)**
Invasion	
-Epidermis/epithelium	1 (7,7%)
- Subcutaneous tissue	11 (84,6%)
- Bone	0
- Muscles	1 (7,7%)
Locality	
- Local	11 (84,6%)
- Diffuse	2 (15,4%)
Grayscale density	
- *Soft tissue*	13 (100)
Contrast agents absorption	
- *Strong*	12 (92,3%)
- *Medium*	1 (7,7%)

Table 3.9. Features of isointense lessions on T1, T2 and STIR for each type of vascular malformation (n=74)

Feature		**Classification of vascular malformations**			
		(AVM) (n=5)	**(VM) (n=67)**	**(VM-LM) (n=2)**	**P**
		n (%)	**n (%)**	**n (%)**	
T1 isointense	No	3 (60,0)	7 (10,4)	0	**0,006**
	Yes	2 (40,0)	60 (89,6)	2 (100)	
T2 isointense	No	3 (60,0)	3 (4,5)	0	**<0,001**
	Yes	2 (40,0)	64 (95,5)	2 (100)	
STIR isointense	No	3(60,0)	4 (6,0)	0	**<0,001**
	Yes	2 (40,0)	63 (94,0)	2 (100)	
T1	Hyperintense	2 (40,0)	9 (13,4)	0	0,237
	Isointense	1 (20,0)	8 (11,9)	0	
	Hypointense	2 (40,0)	50 (74,6)	2 (100)	
T2	Hyperintense	4 (80,0)	65 (97,0)	2 (100)	0,261
	Isointense	1 (20,0)	1 (1,5)	0	
	Hypointense	0	1 (1,5)	0	
STIR	Hyperintense	5(100)	67 (100)	2(100)	NA
	Hypointense	0	0	0	

Table 3.10. Features of flow-void, Phleboliths on T2 by type of malformation and contrast enhancement on T1 FS (n=74)

Features		Classification of vascular malformations			
		AVMs (n=5)	**VMs (n=67)**	**VM-LMs (n=2)**	**P**
		n (%)	**n (%)**	**n (%)**	
Flow-void	No	1 (20,0)	26 (38,8)	1 (50,0)	0,661
	Yes	4 (80,0)	41 (61,2)	1 (50,0)	
Phleboliths	No	5 (100)	25 (37,3)	2 (100)	**0,006**
	Yes	0	42 (62,7)	0	
Intensity of enhancement on T1FS	Strong	5 (100)	66 (98,5)	2 (100)	0,948
	Weak	0	1 (1,5)	0	

Table 3.13. Imaging Features of digital subtraction angiography with direct needle puncture before intervention in the group of venous malformations, lymphatic malformations (n = 69)

Features	**Venous malformation (n=67)**	**Venous – lymphatic malformation (n=2)**	**p**
Types of fluid Blood Lymph Blood + Lymph	 67 (100) 0 0	 1 (50,0) 0 1 (50,0)	**0,029**
Connection to the cardiovascular system	61 (91,0)	2 (100)	**1**

Table 3.15. Value of computed tomography in the diagnosis of arteriovenous malformations (n=16)

Total cases	**Number of correct diagnoses**	**Sensitivity**	**Specificity**	Positive Predictive Value **(**PPV**)**
16	15	93,8 (69,8-99,9)	NA	100%

Table 3.16. Value of magnetic resonance imaging in the diagnosis of venous malformations (n=69)

Total cases	**Number of correct diagnoses**	**Sensitivity**	**Specificity**	Positive Predictive Value **(**PPV**)**
69	67	97,1 (89,9-99,7)	NA	100%

3.2. TREATMENT RESULTS

Table 3.18. Treatment features between the two groups: AVMs and VMs (n=85)

Features	**AVMs (n = 16)**	**VMs (n = 69)**	**p**
Intervention times	3,0 ± 2,1	2.2 ± 1,2	0,048
Approach Direct needle puncture Intravascular Both	 9 (56,3) 5 (31,2) 2 (12,5)	 69 (100) 0 0	**<0,001**
Number of injection sites	5,1 ± 3,8	5,0 ± 3,5	0,971
Total alcohol volume (ml)	50,5 ± 49,7	24,8 ± 18,7	**<0,001**
Compression of draining veins	8 (50,0)	45 (65,2)	0,398
Supportive treatment No Coils Surgery Others Combination (NBCA+surgery)	 10 (62,5) 3 (28,8) 1 (6,2) 1 (6,2) 1 (6.3)	 64 (92,8) 0 2 (2,9) 3 (4,3) 0	**0,002**
Total radiation dose (uGym2)	47329,1 ± 51414,2	7741,7 ± 7051,0	**<0,001**

Table 3.19. Results of treatment of vascular malformations (n=85)

Treament response		**Classification of vascular malformations**		**p**
		AVMs (n=16)	**VMs (n=69)**	
Cosmetic improvement	Yes	8 (50,0)	62 (89,9)	**<0,001**
	No	8 (50,0)	7 (10,1)	
clinical response	Complete response	1 (6,3)	0	0,116
	Near – complete response	10 (62,5)	36 (52,2)	
	Partial response	5 (31,2)	33 (47,8)	
Imaging response	100%	4 (25,0)	0	**<0,001**
	>75%-<100%	2 (12,5)	25 (36,2)	
	50%-75%	9 (56,3)	44 (63,8)	
	<50%	1 (6,2)	0	
Overall treatment outcome	Complete response	2 (12,5)	0	**0,015**
	Near – complete response	3 (18,8)	19 (27,5)	
	Partial response	9 (56,3)	48 (69,6)	
	None response	2 (12,4)	2 (2,9)	
Effective treatment	Yes	14 (87,5)	66 (95,7)	0,510
	No	2 (12,5)	3 (4,3)	

Table 3.20. Relationship between complications and type of vascular malformation (n=85)

Complication		Classification of vascular malformations		p
		AVMs (n=16)	VMs (n=69)	
Severe	No	15 (93,8)	66 (95,7)	0,573
	Severe permanent sequelae	1 (6,2)	1 (1,4)	
	Intensive care	0	2 (2,9)	
Mild	No	1 (6,2)	3 (4,3)	1
	Neurapraxia	0	1 (1,4)	1
	reversible skin lesions	8 (50,0)	20 (29,0)	0,188
	Swelling	13 (81,3)	60 (87,0)	0,848
	Pain	13 (81,3)	55 (79,7)	1
	Dry skin	1 (6,2)	0	0,422
Pain level after intervention		4,3 ± 1,7	4,2 ± 1,4	0,855

Table 3.24. Prognostic factors for cosmetic improvement after treatment for malformation (n = 85)

Prognostic variable	Comparative variable	OR	95%CI	p
Type of malformation	AVMs	8,57	2,17– 33,93	**0,002**
Yakes Classification	AVMs	Type II 0,03 Type IV 0,11	0 – 0,29 0,02 – 0,67	**0,003** **0,016**
Dubois classification	VMs	Type II 8,25	1,98 – 34,38	**0,004**
Number of treatments	1 times	0,49	0,32 – 0,76	**0,001**
Number of alcohol injection sites	1 site	0,77	0,65 – 0,91	**0,002**
Alcohol volume	1 ml	0,98	0,96 – 0,99	**0,011**

Chapter 4
DISCUSSION

4.1.CLINICAL CHARACTERISTICS AND IMAGINGS OF VASCULAR ANOMALIES DISEASES

4.1.1 Clinical characteristics

There are 54 females (63.5%) and 31 males (36.1%) in 85 patients (Fig 3.1), mean age 23,4 ± 13,7, the youngest and the oldest is 5 and 64 years old, respectively. Median age is 18 (14 to 32), comparable to other studies. The under 6-year-old group is 4.7%, the 7 to 18-year-old group is 45.9% and the over 18-year-old group is 49.4%.

Fig 3.3 – gender and age differences in the AVM and VM group; demonstrates the greater number of AVM in the over 18-year-old group, which is 75%, compared to 43.8% VM in the same one, p = 0,039; whilst the frequent age of VM is 7 to 18. Mean age of AVM is 29.9, while that of VM is 21.9, p = 0.033. In terms of age in vascular anomalies diseases, Lee et al reported the female predominance, with a female to male ratio of 60:40 in all types and 2:1 in AVM group exclusively. Our study shows age divergence between AVM and VM group, that 75% of AVM is above 18 when admitted, mean age 29,9 ± 15,9, p = 0.039 and 0.033 respectively. Regarding AVM, the disease progression is related to hormonal changes or secondary impact (trauma, e.g.) leading to the late onset opposed to VM.

A study of 3573 under 3-year-old children diagnosed with vascular anomalies disease publicized by Tansdi et al (1993) demonstrates 1.2% cases of vascular anomalies (43/3573). Additionally, VM and AVM account for 16 cases (30.7%). According to Akita et al in a study of 123 patients, 69.9% is female, 69,1% is VM, 15.44% is AVM and mixed type is 6.69%.

Lee B.B. et al reported 32.8% VM, 12% AVM, 43.2% others and 10% unidentified type in their study. However, in the unidentified group, VM is later defined.

In the matter of functional symptoms, including swell, pain, deformity, hemorrhage and discoloration of the lesions, it is more frequently seen in AVM (25% and 18,8%) than VM (4,3% and 1,4%), p = 0.022, similar to other studies.

There are many specific signs of AVM including discoloration, hemorrhage and blood pulsing, with p = 0.005, 0.001 and <0.001, respectively, which is in accordance with literature.

Concerning the lesional locations, there are 9/16 (56.2%) AVM and 33/69 (47.8%) VM in the head and neck. The second most popular site is limb, with 5/16 (31.3%) AVM and 32/67 (46.4%) VM.

According to Lee, lower limb, head and neck, upper limb and body account for 38.6%, 22.9%, 11.5% and 6.5%, each in order, comparable to our study.

4.1.2. Imaging characteristics

Most AVM are diagnosed with CT (68.8%), while most VM are done with MRI (100%), $p<0.001$; corresponding to other study by Arnold, Bashir, Darrow, Dubois, Fayad, Gunelyi, Wang. With the exception of contraindications, MRI is preferential modality for diagnosing vascular anomalies diseases.

However, in some instances, both MRI and CT are necessary for diagnosis.

There are various characteristics of AVM on CT, including subcutaneous invasion (84.6%), regional lesion (84.6%), tissue density values (100%) and hyperenhancement (92.3%). The AVM which is slightly enhanced are mostly Yakes type IV.

Fig 3.10, on T1W, T2W, STIR images, the heterogenous lesions are more frequently seen in AVM than in VM, p=0,006, <0,001, <0,001, respectively.

Fig 3.11; our study confirms that hyperenhancement is specific feature of vascular anomalies disease (100% AVM, 98% VM). One of the diagnosis features of vascular anomalies disease is flow-void, specific for high-flow AVM. Additionally, flow-void is observed in 39.1% VM in our study, which is higher than others (31.25%, Rak et al.). It is because of the anstomosis to central venous system, though the flow is not as quick as it is in AVM. Phlebolith is a specific characteristic of VM, due to slow flow leading to calcification (60.9%), $p<0.001$.

DSA features of AVM including dilatation of feeding arteries (87,5%), early venous filling (93,8%), dilatation of venous drainage (75%) are all key features in accordance with ISSVA 2014.

Based on Yakes AVM classification, the most frequent type is type IV (37.5%), followed by type II (31.3%), type I (12.55), type IIIb (12.5%) and type IIIa (6.2%). This classification is certainly applicable to treatment as it assist in the analysis of venous features of AVM, which is the target of embolotherapy.

Fig 3.14, the fluid suctioned is consistent with primary diagnosis, meaning accuracy 100%, p=0.029. DSA images established the difference in central venous connection of VM and LM, p=1; there are 91% VM cases having central venous anastomosis specifically.

Fig 3.15, the most common VM type is type II Dubois – Puig (53.6%, followed by type III (18.8%).

Tropp et al reported that 23/51 VM definitively diagnosed with venography by DSA, which is distinct from our study as 100% vascular anomalies diseases are determined by DSA during the process of diagnosis or treatment.

We made the comparision between CT, MRI and DSA to determine the sensitivity and positive prediction value in AVM diagnosis. Concerning CT, the sensitivity is 93.8%, the positive prediction value (PPV) is 100%, while the sensitivity and positive prediction value of MRI is 97.1% and 100%, respectively.

4.2. THE RESULT OF TREATMENT BY ABSOLUTE ALCOHOL SCLEROSIS

46.4% VM have under 1-year follow-up. There are 73.3% AVM having over 1-year follow-up, which is disticnt from other groups, p=0.042 (fig 3.18), similar to studies from other authors who reported follow-up period ranging from 6 to 32 months. In addition, Do et al describes the follow-up time of AVM reaching 48 months, mean 14.6 months. This distinction may be due to the complexity of AVM, requiring multiple treatment sessions.

There are two approaches of vascular anomalies disease: endovascular and direct puncture; p<0.001. The total volume used in AVM and VM intervention is different, p<0.001, which are 50,5 ± 49,7 mL and 24,8 ± 18,7 mL, respectively. Due to the pathologic anastomosis between artery and vein, the injected alcohol quickly flows from the puncture site to the venous drainage, results in more alcohol volume needed and different assisted techniques to slow the flow including compression, coling, p=0.002. Long flouroscopy time for each AVM treatment session is needed, leading to more radiation dose, which is 47.329 ± 51.414,2 uGym2 compared to 7741,7 ± 7051 uGym2 for each one of VM, p<0.001. Regarding VM treatment, venous drainage compression to prevent deep venous thrombosis has been reported in many studies.

In a study by Do et al concerning AVM, there are 32/40 patients going through over 2 sessions of alcohol sclerosis. In terms of VM,

Koo et al reported a majority of cases having under 2 treatment sessions. However, Koo perform sclerosis by using a combination of alchol and radiofrequency ablation under ultrasound guidance, which is distinct from our way. Furthermore, Wang et Su believe that regarding treatment of VM in the head and neck region, the more volume of alcohol used (under 1ml/kg), the more effective the treatment is.

In the matter of treatment assesment, 1/16 (6,3%) AVM has complete clinical response and 4/16 (25%) have complete radiological response, $p=0.116$ and <0.001, respectively. 89.9% VM have better asthetical response than AVM (50%), $p<0.001$. Despite the treatment response of VM (95.7%) is superior to AVM (87.5%), AVM can be radically managed not only clinically but also radiologically.

With reagard to VM, there are multiple treatment complications including pain (79.7%), swollen (87%), neurological pain due to inflammation (1.4%). Most of them are self-limited, some may require topical antibiotics or anti-inflammatory drugs. There are 4 cases of severe complication, including 3 VM (4.3%), 1 AVM (6.2%). All of them are large surface infected necrosis requiring surgery and strong antibiotics. One case of permanent complication is distal index finger necrosis after AVM treatment, resulting in dactylectomy. In spite of different complication rate, there is no distinction between severe and minor complication of VM and AVM.

There is no difference of pain level between AVM ($4,3 \pm 1,7$) and VM ($4,2 \pm 1,4$), $p = 0,855$. Paracetamol is sufficient in the first 24 hour.

The extent of VM treatment response following Dubois – Puis includes type I (100%), type II (97.3%), type IV (80%). Regarding AVM, treatment response in agreement with Yakes classification shows perfect response in type II and type III (100%). Type I, however, has 50% response rate.

Cho et al in a study of AVM indicated that 48% cases having minor complications such as blister, skin necrosis. About severe complication: 2/66 ulnar paralysis, one case of severe infection requiring amputaion.

Surgery is only compatible with small, localized lesion. It depends on Schobinger classification, emphasizing the importance of clinical aspects which demonstrate the natural progress of peripheral vascular anomalies. A study by Kang shows the results of surgery management of VM: 6% great, 72% good and 22% insignificant change.

Nevertheless, concerning AVM, the results are much better, with 29% great, 57% good and 14% insignificant change. Nguyen Cong Minh reported 67 cases of vascular anomalies surgery management; however majority of cases (48 cases) is under 3cm, single and shallow. Apart from that, 19 cases are above 3cm, extensive, deep, and 68% have bad surgery outcome, 16% have recurrent lesion, mostly in group having extensive nidus. 81% undergo bad surgery outcome comparing to 4.1% severe complcation in our study. In terms of distinctive vascular anomalies types, surgery achieves some limited results according to some studies by Steiner (VM), Visser (AVM), Monterio (lower mandibular AVM), Giuseppe (hand AVM), Lee (LM); however the results are not better than other studies', with low rate of complete response, high rate of complication.

In comparision with surgery, our study attains 95.5% VM and 86.7% AVM. The rate of severe complication is 4.5% VM and 6.7% AVM. The most frequent complications are pain and swollen. Based on the pain scale, the average pain level is 4 and it decreases with time or with pain relief.

Endovascular intervention can be single treatment, or in combination with surgery or multidisciplinary approaches. It is divided into two types based on types of vascular anomalies disease: VM and AVM. AVM is often approached by transarterial or percutaneous technique. There are multiple studies by Muller Willie, Akita, Lidsky, BB Lee, which mention the management of vascular anomalies preferring multidisciplinary approaches.

A study concerning direct alcohol punture of VM by Wang et al demonstrates good result in 28.6% cases and 33% achieve great outcome. If all cases having definite improvement are combined, our study shows better results than Wang's study. Other sclerosing agents such as STS, Picibanil (OK32), Doxycyline, Bleomycine, acid acetic, pingyangmycin, Polidocanol are normally employed in VM treatment. According to Defnet, Donovan, Giurazza, though they do not give as good outcome as alcohol does, they contribute to lower complication rate.

In a meta-analysis by Li – Ming Sun (2020) comparing absolute alcohol and polidocanol in VM treatment, there are 7 studies using alcohol, including total 331 patients, treatment response ranging from 70-95%. Complete response are observerd in 6 studies, vary from 5% to 68%. In those studies using polidocanol in VM treatment, there are

117 patients in 4 studies, the treatment reponse is from 44% to 90%; complete reponse is ranging from 21% to 76%. In the author's opinion, absolute alcohol is considered stronger and more effective sclerosant than polidocanol, though it could lead to higher complication rate.

Besides endovascular treatments, some drugs have been utilised in vascular anomalies disease treatment, including corticoid, beta blocker, some under-development drugs such as Sirolimus, Bevacizumab

Based on the results of our study, we make assesment of the association between variables, treatment response and complications. If the pain level on the pain scale increases 1 point, risk of complication increases by 2.97 fold, p=0.017

In terms of aesthetic improvement, VM is superior to AVM by 8.57 fold, p=0.002

Type II and type IV Yakes AVM have the worst aesthetic improvement compared to VM, p=0.003 and 0.016, respectively.

Type II Dubois VM have the greatest aesthetic improvement in comparision with AVM by 8.25 fold, p=0.004.

CONCLUSION

1. Clinical characteristics, diagnostic imagings for peripheral vascular malformations following ISSVA 2014:

Gender distribution: male 36.5%, female 63.5%; over 18-year-old group is 49.4% and the youngest and the oldest is 5 and 64 years old, respectively; Median age is 18 (14 to 32), comparable to other studies. Vascular malformations's distribution: AVMs 18%; VMs 82%.

Clinical signs: specific symptoms for AVMS are haemorrhage and discolorations, p = 0,022 và 0,020. Specific physical examinations for AVMs is, p <0,001. Most position seen in AVMs (56,2%) and VMs (47,8%) is head and neck.

Diagnostic Imagings:

MSCT and MRI are chosen for definite diagnostic and therapeutic plan. MRI is advantage to diagnose all vascular malformations except for contraindications and limitations in thoracique wall, lung, bone where MSCT is better exploration. In some difficult situation, both MSCT and MRI are used to increase capacity of accuracy. MSCT's

sensitivity is about 93.8%, positive predicted value about 100%, meanwhile, MRI is about 97.1% and 100% respectively.

2. Therapeutic results of vascular malformations managed by absolute alcohol:

All of VMs procedure is direct puncture, while 68.8% of AVMs is used it, p <0,001. Therapeutic sum of alcohol, material assisted and radioactive dose is used more in AVMs rather than VMs statistically p<0.001. Aesthetic improvement is better in VMs (89.9%) compared in AVMs (50%), p <0,001.

Clinical and imaging completed therapeutic results, there are 2 cases of AVMs, 13,3%, p = 0,013. Following Dupois Puig classification, response of type I is 100%, type II (97,3%), p = 0,383. Following Yakes classification, response of type II and III is 100%, p = 0,432.

There are 3 seriously complications in VMs, rates 4.3%; including 2 cases specific treated requirement. Minor complications are swollen (87%), painful (79.9%), reversible skin lesions (29%), glimpse nerve damage (1.4%). In AVMs, there is 1 severe complication, rate 6.2%, minor complications are included swollen (81.3%), painful (81.3%), reversible skin lesions (50%), dry skin (6.2%).

Following guidance from ISSVA 2014, standard diagonstic imagings (evaluation for 3 axials), management of peripheral vascular malformations is proved effectively excelent success with 87.5% for AVMs and 95.7% for VMs, complicated rates is quite low 1.4%.

Recomendations

Absolute alcohol (99.5%) is effective, cheap agent which is useful for management of peripheral vascular malformations. But, complications are still matter which physician shold be awared of, so should be trained well before use it.

Management of peripheral vascular malformations should require multiple discipline (IR, vascular surgeon, dermatologist, radiologist, reconstructive surgeon), multiple methods for increasing successful rate.

Our research has limitations because of lacking of quantity of cases and limit of follow up time. In future, research should focus on every single of malformations in field of diagnostic and management (VMs, AVMs, LM, CM). We need to launch comparaison of every agent so that we can find out best solutions for treating them.

PUBLICATIONS OF RESEARCH RESULTS OF THE THESIS

1. Nguyen Dinh Luan, Hoang Minh Loi, Nguyen Sanh Tung (2019), Primary results for diagnosis and management of peripheral vascular malformations by using absolute alcohol, *Journal of Medicine and Pharmacy - Hue University of Medicine and Pharmacy*, 9 (06+07), pp.173-180.

2. Luan N. D., Hien T. M., Tai N. T., Kinh B. T., et al (2021), Diagnosis and management of calcaneal Yakes type IV AVM: Two case reports, *Radiology Case Reports*, *16*(12), pp.3621-3627.

3. Nguyen Dinh Luan, Nguyen Sanh Tung, Hoang Minh Loi, (2021) , Management of peripheral vascular malformations by absolute alcohol, *Journal of Medicine and Pharmacy - Hue University of Medicine and Pharmacy*, 12 (01), pp. 118-125.