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EXPERIENCE IN TREATING VENOUS MALFORMATIONS OF THE EXTERNAL GENITALIA IN CHILDREN

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Resume:

Objective. To improve the efficacy of treating children with isolated and diffuse venous malformations of the external genitalia, as well as Klippel-Trénaunay syndrome involving the genitalia in addition to the lower limb, using minimally invasive bleomycin sclerotherapy and systemic treatment with rapamycin.

Keywords: *venous malformation, sclerotherapy, bleomycin, Klippel-Trénaunay syndrome, ISSVA classification, rapamycin*

Materials and methods. The study included 30 patients stratified into two groups based on the volume and extent of the vascular malformation. The first group consisted of male patients with isolated penile venous malformations and female patients with lesions affecting the labia majora. The second group comprised patients with diffuse venous malformations of the perineum/scrotum or lower extremities, including patients with Klippel-Trénaunay syndrome. Patients in the first group underwent staged sclerotherapy with bleomycin. Patients in the second group received systemic therapy with rapamycin.

Results. In the first group of patients, bleomycin sclerotherapy demonstrated high efficacy, characterized by a reduction in the volume of the venous conglomerate by 60% or more. In the second group of patients treated with rapamycin, positive changes were observed as early as one month after the start of therapy: reduction of pain, a decrease in plasma D-dimer concentration, and inhibition of neovascularization in the pathological veins.

Research purpose. To enhance treatment outcomes in children with isolated and diffuse venous malformations of the external genitalia and Klippel-Trenaunay syndrome by utilizing minimally invasive procedures and systemic rapamycin administration.

Materials and Methods. The study included 30 patients stratified into two groups based on the volume and extent of the vascular malformation. Group 1 consisted of male patients with isolated venous malformations of the penis and female patients with involvement of the labia majora. Group 2 included patients with diffuse venous malformations of the perineum/scrotum, lower extremity, including patients with Klippel-Trenaunay syndrome. Group 1 patients underwent staged sclerotherapy using bleomycin. Group 2 patients were prescribed systemic therapy with rapamycin.

Results. In Group 1 patients, bleomycin sclerotherapy demonstrated high efficacy, characterized by a reduction in venous conglomerate volume of 60% or more. In Group 2 patients receiving rapamycin, positive dynamics were observed as early as one month after the start of therapy: reduction of pain syndrome, decrease in plasma concentration of D-dimer, and inhibition of neovascularization of pathological veins.

Relevance. Due to their specific nature, low prevalence, and diagnostic complexity, vascular malformations often fall outside the scope of priority scientific research. Currently, the overall incidence of congenital vascular anomalies in newborns is estimated at 10–13%, with venous malformations (VMs) constituting the predominant group and exhibiting an estimated prevalence of 1 in 5,000–10,000 [1].

Venous malformations are characterized by significant clinical heterogeneity, ranging from localized nodular lesions to extensive deep-seated lesions that infiltrate adjacent anatomical regions and–in the absence of adequate and timely therapeutic intervention—can potentially lead to life-threatening conditions.

Objective. To improve the efficacy of treating children with localized and diffuse venous malformations of the external genitalia, as well as Klippel-Trenaunay syndrome, using minimally invasive treatment methods and systemic therapy with rapamycin.

Materials and Methods. This study included 132 patients with various forms of venous malformations (VMs) who presented to our center between 2021 and 2024; from this group, 30 patients were selected who had either isolated venous malformations of the external genitalia or diffuse lesions involving the perineum, genitalia, and lower limbs. We applied the following selection criteria:

1. Age (≤16 years); we chose 16 years as the cutoff, as it represented the upper age limit among our patient cohort.

2. Lesion location (external genitalia–either as an isolated lesion or in conjunction with adjacent sites in cases of diffuse disease, as well as a manifestation of Klippel-Trénaunay syndrome).

3. Lesion size (mean cross-sectional diameter of the venous conglomerate on ultrasound/MRI: 0.8 cm for boys, 3 cm for girls) [3].

4. Tissue involvement in female patients–Type I (Type I: involvement limited to skin and subcutaneous tissue; Type II: involvement of muscle, bone, or joints, with or without skin and subcutaneous tissue involvement). The pattern of tissue involvement observed on MRI was categorized into two types according to the Birmingham classification [4].

5. Phleboliths (presence or absence). These appear as high-density granular formations on MRI or MSCT.

Patients with combined lymphatic-venous malformations or isolated capillary malformations were excluded from the study. The diagnosis of venous malformation was based on clinical and instrumental examinations.

Patients were divided into two groups: Group 1 consisted of boys with isolated venous malformations of the penis and girls with lesions of the labia majora, without diffuse involvement of the adjacent tissues of the perineum or scrotum; Group 2 comprised patients with diffuse venous malformations affecting the genitals, perineum, and lower limbs, including patients with Klippel-Trénaunay syndrome. The patients ranged in age from 3 to 16 years, with children of preschool and early school age predominating (70%). Isolated genital venous malformations were diagnosed in 16 boys and 9 girls, while diffuse systemic forms were observed in 5 children (3 boys and 2 girls).

The primary complaint of patients and their parents was the presence of visibly prominent, dilated, and pathologically deformed veins. In three cases, phlebectasias located on the glans penis near the urethral meatus distorted its shape, thereby affecting the urinary stream. In instances where the venous malformation involved not only the genitalia but also the pelvic region and extremities, the patients' chief complaints were pain and a sensation of heaviness in the lower limbs, particularly in the evening. This symptom was the primary reason for seeking medical attention and was observed in all patients with diffuse involvement.

The clinical criterion was the early appearance of a lesion that progressively enlarged with age. In three boys, the pathological phlebectasias on the penis extended to the soft tissues of the scrotum. In all girls, the dilated capillary network and phlebectasias were unilateral and located in the soft tissues of the labia majora; in 30% of cases, they also extended to the perineum or the upper third of the thigh. In one girl, the capillary network extended upward from the genitalia, infiltrating the soft tissues of the pubic region and the inguinal fold.

Pain was assessed using a verbal numerical rating scale (NRS) ranging from 0 to 10 (0 = no pain, 10 = unbearable pain) during the patient's initial visit. Parent ratings were shown to correlate well with child ratings. If the young patient was unable to rate their pain, a parent's assessment was obtained. For isolated venous malformations (VMs) of the external genitalia, pain scores ranged from 0 to 1, whereas patients with syndromic and diffuse venous malformations of the lower extremities involving the genitalia rated their pain at an average of 7–8. Three patients exhibited functional impairments associated with lower-extremity muscle hypotrophy resulting from the infiltration of pathological structures into the muscle tissue.

All patients underwent mandatory ultrasound imaging with Doppler mapping to evaluate the structure of the venous system, the nature of blood flow in the deep and superficial veins of the lower extremities, and the presence of thrombosis or phlebitis; involvement of adjacent organs and the presence of associated anomalies were also assessed. To clarify the nature, extent, and volume of the lesion, MRI (using T1, T2, and STIR sequences) or MSCT angiography was performed. The MRI criterion was the presence of a mass demonstrating a high signal on fat-suppressed T2-weighted (T2-W) images, characterized by extensive venous pools [5]. Regarding laboratory tests, an elevated blood

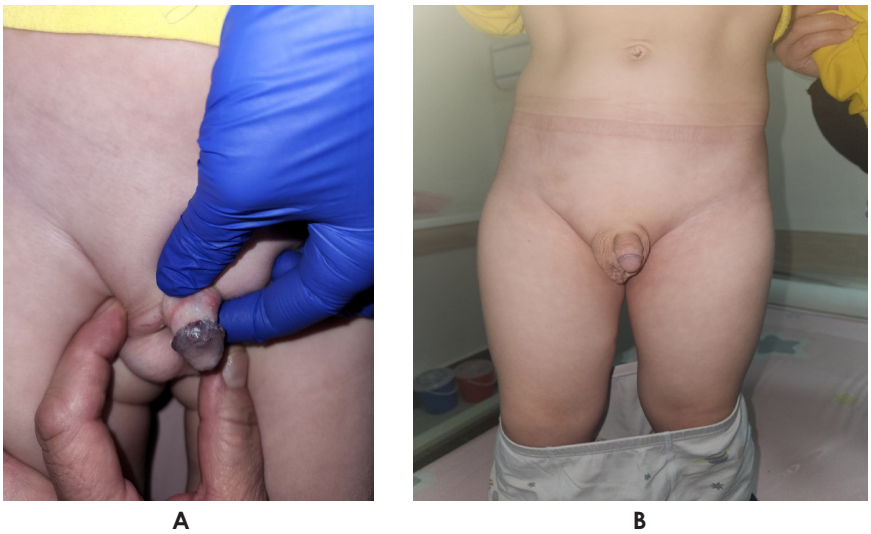
D-dimer level–measured in all patients with diffuse venous system involvement–indicates the presence of or risk for thrombus formation.

Based on the principle of determining the number of planned sessions required to maximize treatment efficacy for localized lesions–while accounting for their extent–we selected a staged bleomycin sclerotherapy regimen for both boys and girls in Group 1. The calculated single dose of the drug was 0.5 mg/kg of body weight [6]. The maximum theoretical dosage exceeds the actual volume of bleomycin required for a single procedure. For penile malformations, an average of 1 ml of sclerosant was administered per session; this volume was chosen to prevent compression of the urethral lumen caused by potential reactive postoperative edema. For girls, the dose was increased to 2 ml, taking into account anatomical and physiological differences.

Results. To evaluate the efficacy of sclerotherapy in patients with isolated forms of venous malformations, we used the following categories: 1) High efficacy–reduction in the volume of the venous conglomerate by 60% or more; 2) Satisfactory efficacy–reduction in the volume of the venous conglomerate by 30–60%; 3) Unsatisfactory efficacy–reduction in the volume of the venous conglomerate by less than 30%. In cases of unsatisfactory results, a decision was made to adjust the drug dosage [7].

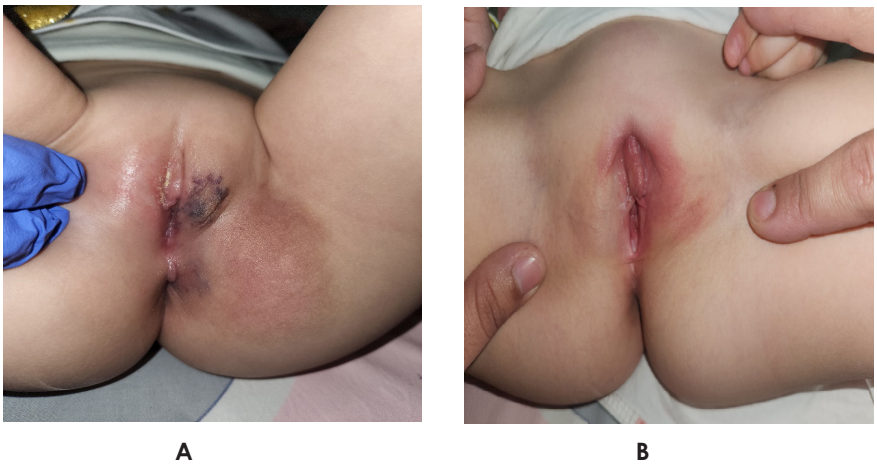
These criteria were used both to evaluate each individual procedure 3–6 months after it was performed and to assess the overall efficacy of the chosen therapy upon completion of treatment.

Among the 25 patients in Group 1, 90% clearance of the pathological lesion was achieved in 11 boys and 6 girls over an average of 3–4 sessions; the remaining 10% consisted of stable telangiectasias and small venous areas (up to 0.7 cm in diameter) that showed no signs of progressive growth during



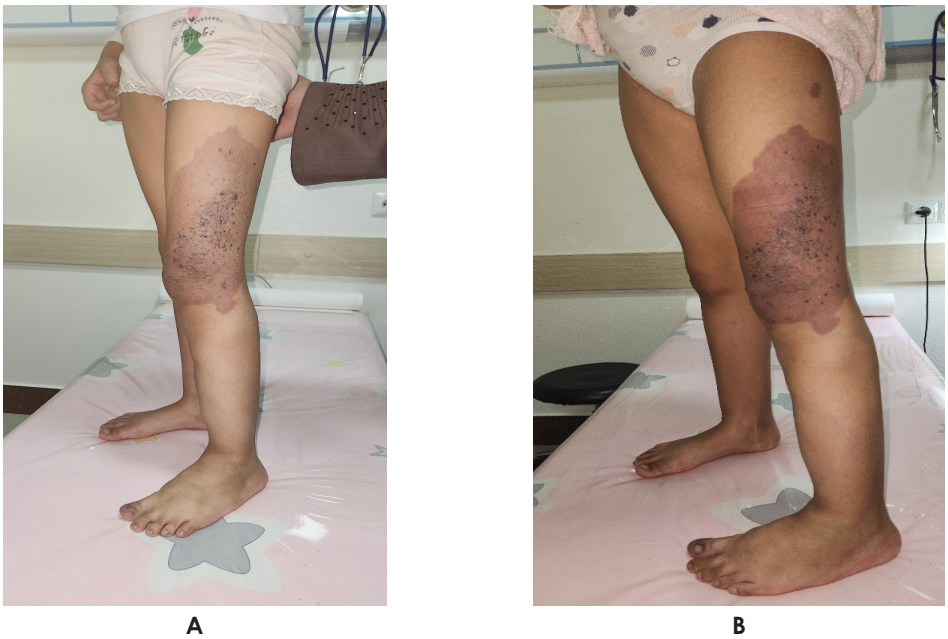
A B

Photo 1. A – 6-year-old patient with a venous malformation of the glans penis before treatment; B – after three sclerotherapy sessions



A B

Photo 2. A – 3-year-old female patient, venous malformation of the left labium majus before treatment; B – after two sclerotherapy sessions



A B

Photo 3. Klippel-Trénaunay syndrome in a 9-year-old girl. A – before treatment, B – 6 months after the start of rapamycin therapy

the 6-month follow-up period (Photos 1A, B and 2A, B). All children were advised to continue follow-up monitoring with their attending physician.

The remaining 8 patients are continuing staged treatment with good interim results.

The condition of the five patients undergoing systemic treatment was assessed based on the resolution and/or disappearance of characteristic symptoms—pain, edema, impaired functional activity, and the volume and mass of the affected limb—as well as laboratory monitoring of D-dimer levels. All patients showed clinical improvement as early as one month after starting the medication; the most immediate changes were a reduction in pain and a decrease in D-dimer levels. After six months, the volume and mass of the affected limb had decreased, leading to a partial restoration of functional activity (Photo 3 A, B). Wearing compression garments is an essential component of the comprehensive treatment for patients with Klippel-Trénaunay syndrome [8]; however, not all children readily comply with this recommendation. In our experience, children who incorporated a Class 2 compression stocking into their daily routine experienced less discomfort and pain during everyday activities and reported no episodes of thrombosis.

Discussion. In this study, we present our experience in treating children with venous malformations (VMs) affecting the genitalia and perineum, as well as those involving adjacent areas in cases of diffuse disease. To ensure a highly homogeneous study cohort, we focused our analysis exclusively on patients with isolated diffuse VMs and those with Klippel-Trénaunay syndrome involving the genitalia. Our results demonstrate the efficacy of minimally invasive sclerotherapy for patients with isolated VMs and of systemic treatment with the immunosuppressant rapamycin for patients with Klippel-Trénaunay syndrome. We also emphasize the importance of high-quality preoperative imaging, as an accurate diagnosis and the selection of an appropriate treatment strategy depend directly on the precise characterization of the local or systemic venous system involvement.

Venous malformations (VMs) are congenital anomalies classified based on the type of vessels involved (purely venous forms and combined types: arteriovenous, capillary-venous, and venolymphatic) and rheological characteristics (low-flow). They occur sporadically in 92% of cases, and their etiology remains unclear. However, a somatic mutation in TIE-2–a tyrosine kinase receptor that plays a crucial role in angiogenesis and cardiovascular development—can be detected in nearly half of affected patients [9]. This genetic determinant allows for potential treatment with an mTOR inhibitor, such as rapamycin, which suppresses vascular proliferation [10].

The presence and progressive growth of venous malformations (VMs) are genetically determined from birth, and the visualization of pathological lesions is linked to the patient's growth and physical development. VMs typically remain asymptomatic until the first clinical manifestation–such as an episode of thrombosis, thrombophlebitis, or significant compression of adjacent structures causing pain (which is the most common reason for seeking medical attention), or, less frequently, hemor-

rhage. These events are precipitated by the dilation of deformed veins–driven by the exhaustion of the compensatory capacity of the weak, malformed vessel wall (a process that intensifies during puberty)–alongside localized intravascular coagulation, a phenomenon that frequently accompanies VMs [11]. In our case series, however, we observed no correlation between the onset of pain and the period of puberty.

Traditionally, the primary evidence-based treatments for venous malformations (VMs) are the use of compression garments and transcutaneous sclerotherapy. Wearing compression garments on affected limbs prevents structural insufficiency of the venous wall, facilitates venous outflow, provides symptomatic relief, and prevents thrombophlebitis and ulceration. However, in children, their effectiveness is often limited by poor treatment adherence. Moreover, growing children require adjustments to their garments at least twice a year [12]. The principle of sclerotherapy involves damaging the walls of deformed veins, leading to their subsequent collapse. Good efficacy in controlling symptoms and malformation progression has been reported with the use of several sclerosing agents, such as tetradecyl sulfate, bleomycin, and lauromacrogol [13]. Regardless of the specific substance, sclerosing agents injected near nerves or thin muscles can damage these structures. Complication rates of up to 12% have been reported, including skin necrosis, transient or permanent neurological damage, muscle or fascial fibrosis, and renal failure [14]. However, none of our patients developed the aforementioned post-procedural complications.

Venous malformations also occur as a component of Klippel-Trénaunay syndrome, defined by the International Society for the Study of Vascular Anomalies as a combination of varicose veins and/or venous malformations, capillary malformation, and bony and/or soft-tissue malformation of the limbs (Photo 4 A, B, C) [15].

Treatment options for the syndrome are currently very limited and supportive in nature. For the treatment of extensive and syndromic CM, we have chosen the tactics of systemic treatment with the drug rapamycin. Oral administration of the drug has a beneficial effect on patients with extensive or complex low-flow vascular malformations, patients with syndromic lesions that are refractory to



A



B



C

Photos 4 A, B, C. Clinical variants of the Klippel-Trénaunay syndrome triad in children of different ages: vascular nevus, phlebectasia, and limb hypertrophy

traditional therapy. Many clinicians are now considering the use of rapamycin based on its significant effect and activation of the PI3K/AKT/mTOR pathway in angiogenesis and lymphangiogenesis [16]. However, the optimal dose and blood level, in addition to the duration of treatment, have not yet been established. In addition, safety is a major concern, especially for pediatric patients when long-term treatment is required. Follow-up requires careful monitoring of possible side effects in addition to infectious complications. Therefore, further studies are needed to determine the safety, efficacy, optimal dosage, and long-term side effects to establish the long-term benefits of sirolimus treatment [17].

Conclusions. Our experience has demonstrated the successful use of sclerotherapy for treating isolated venous malformations of the penis and labia majora, as well as systemic rapamycin therapy for patients with diffuse venous malformations and Klippel-Trenaunay syndrome, without the occurrence of serious complications**.**

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