Improvements of symptoms after sirolimus treatment in children with complex vascular malformations

Mohamed A. Abdelbaky[a], Iman A. Ragab[b], Amr A.H. AbouZeid[a], Shaimaa A. Mohammad[c], Mohamed M. Dahab[a], Mohammed Elsherbeny[a], Hatem A. Safaan[a]

Departments of [a]Pediatric Surgery, [b]Pediatrics, [c]Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence to Mohamed A. Abdelbaky, MSc, Faculty of Medicine, Ain Shams University, Abbasia Cairo, Zip Code 11517, Egypt. Tel: 0226837673; e-mail: mohali24@hotmail.com

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Background and objectives
Management of complex vascular malformations is really challenging. They usually present at birth and have different complications, including bleeding, pain, cosmetic disfigurement, and functional impairment. This study was to done to determine symptomatic relief and quality-of-life improvement after sirolimus.

Patients and methods
The intervention phase included sirolimus administered orally on a continuous dosing schedule at a starting dose of 0.8 mg/m^2, and its level was maintained between 4 and 12 ng/ml. Dose was rounded to the nearest 1-mg tablet form.
Assessment of response to sirolimus was done (usually 2 weeks after start of sirolimus) clinically by assessment of clinical improvement of the main complaints of the patients, for example, bleeding, pain, and cosmetic disfigurement. Improvement of patients' laboratory investigations was assessed after the start of sirolimus, for example, elevation of hemoglobin and mean cell volume. The administration of Arabic translation of pediatric quality-of-life PedsQL 4.0 was done again 6 months after the start of sirolimus.

Results
A total of 18 patients were enrolled. The age of the patients during the start of sirolimus ranged from 5 months to 13 years, with a median age of 3 years. Bleeding stopped in eight (100%) patients, cosmetic disfigurement improved in 10 (76.9%) patients, and perception of pain improved in two (66.6%) patients. Moreover, quality of life of the study patients improved significantly, as the mean of the score of the patients before sirolimus was 65.18 and improved after sirolimus to be 78.

Conclusions
Symptomatic relief in patients after sirolimus administration is evident, with better quality of life.

Keywords:
blue rubber bleb nevus syndrome, lymphatic malformations, sirolimus, vascular malformation, venous malformations

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Introduction

Vascular anomalies are now divided into vascular tumors and vascular malformations. They are common in infancy and childhood and represent 30% of all pediatric soft tissue tumors. The International Society for the Study of Vascular Anomalies has developed a method based on multidisciplinary pathogenesis, dividing benign vascular anomalies into tumors and malformations [1] (Table 1).

Inappropriate classification of these patients is common and can lead to improper management. This classification system helps us to correctly diagnose and treat vascular anomalies. Vascular malformations usually appear at birth but can become obvious after birth owing to various triggers, including injury, infection, hormones, or puberty. They are abnormal vascular channels lined by inactive endothelial cells [2].

Vascular malformations are classified into high-flow and low-flow malformations according to their flow dynamics. Low-flow lesions include capillary, venous, and lymphatic malformations. They are more common than high-flow malformations. According to reports, the prevalence of venous and lymphatic malformations in the general population is 1%, of which 40% affect the limbs [3]. Many syndromes are related to vascular malformations, which are usually low flow. Blue rubber vesicular nevus, Proteus, CLOVES, Maffucci, Sturge-Weber, and Klippel-Trenaunay are among these syndromes [4].

Table 1 The International Society for the Study of Vascular Anomalies classification for vascular anomalies

Vascular malformations	Vascular tumors
High flow	Hemangioma
Arteriovenous malformation	Infantile hemangioma
Arteriovenous fistula	Congenital hemangioma (rapidly involuting, noninvoluting, and partially involuting)
Low flow	Kaposi form hemangioendothelioma
Capillary, venous, lymphatic, and combined	
Overgrowth syndromes	Tufted angioma
Klippel-Trenaunay syndrome	
Proteus syndrome	
CLOVES syndrome	

Superficial vascular malformations can cause functional impairment because they are large, painful, related to overgrowth of underlying tissues, or may be complicated by bleeding. Moreover, visceral vascular malformations can be life-threatening when complicated by gastrointestinal bleeding or hematological abnormalities (anemia and thrombocytopenia) [5].

Management of complex vascular malformations and overgrowth syndromes requires dedicated multispecialty care. We have no guidelines for treatment, and management may include just observation, compression with a physical bandage, sclerotherapy, resection (when feasible), anti-inflammatory or anti-coagulation drugs, or interferon or anti-proliferative drugs [5].

Rapamycin was discovered in 1975 and is an inhibitor of the mTOR pathway, which has been extensively studied. Excessive activation of this pathway is essential for tumorigenesis, cell proliferation, and survival. These indicate the potential of sirolimus use in the medical treatment of patients with overgrowth of somatic cells related to the PI3K/AKT/mTOR pathway [6].

Sirolimus (or rapamycin) has the advantage to be given through oral route in either tablet or liquid suspension form. It has a rapid curative effect on vascular malformations and is generally well tolerated. However, the dose, follow-up, and results of sirolimus are heterogeneous [5].

Most of the previous studies emphasized the need for more clinical trials to better describe sirolimus indications, dose, and efficacy in the management of complex vascular malformation.

Patients and methods

A cohort study was conducted at the combined vascular anomalies clinic of Ain Shams University Children's Hospital from November 2018 to June 2021. The study included patients with low-flow vascular malformations.

Pediatric patients younger than 15 years with complex vascular malformation, including microcystic, mixed, and macrocystic lymphatic vascular malformations; venous malformations; and combined venolymphatic malformations, were included in the study. Patients with small vascular malformations amenable to surgical intervention and injection, those with a history of cancer in the previous 2 years, those on immunosuppressive, and those having chronic infectious diseases and liver insufficiencies were excluded. Moreover, patients with overgrowth syndromes, for example, Klippel-Trenaunay and CLOVES syndromes, were excluded. The study was approved by the ethical committee of Ain Shams University Hospitals, Faculty of Medicine, in August 2018. Informed consents were taken from the children's caregivers.

Data collection from clinic records included patients' age, sex, age of first presentation, main complaint, and previous treatments including medical, interventional radiology, or surgical treatment. The study included initial evaluation, intervention phase, and postintervention evaluation. Initial clinical data of the vascular malformations of the patients included type, site, size, distribution, percent of skin involvement, and complications. The percent of skin involvement was done using severity scoring of atopic dermatitis: the SCORAD index (Severity Scoring of Atopic Dermatitis: the SCORAD index, 1993). The initial radiological data of vascular malformations included type, size, site, visceral organ involvement, and pattern of contrast enhancement using MRI vascular anomaly protocol.

Initial laboratory assessments included complete blood count, coagulation profile (prothrombin time and activated partial thromboplastin time), ferritin, and liver and kidney function tests. Initial assessment

of quality of life was done for children more than 2 years of age using Arabic-translated and validated version of pediatric quality-of-life questionnaire for those in the prospective evaluation group [7].

The PedsQL 4.0 Generic Core Scales (Mapi Research Trust, Lyon, France) include 23 items, which comprise (a) physical functioning (eight items), (b) emotional functioning (five items), (c) social functioning (five items), and (d) school functioning (five items). A five-point Likert response scale is utilized ranging from 'never a problem' to 'almost always a problem.' Items are reverse scored and linearly transformed to a 0–100 scale, so that higher scores indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed [7].

The intervention phase included sirolimus administered orally on a continuous dosing schedule at a starting dose of 0.8 mg/m^2, and its level was maintained between 4 and 12 ng/ml. The dose was rounded to the nearest 1-mg tablet form. In case of nonavailability of a solution form and small dose, a once-daily 1-mg tablet form was used. Fixed time and relations to meals with the sirolimus dose were maintained.

Assessment of response to sirolimus was done (usually 2 weeks after start of sirolimus) clinically by assessment of clinical improvement of the main complaint of the patient, for example, bleeding, pain, cosmetic disfigurement, and functional impairment. Moreover, assessment of decrease in size for superficial lesions was done by photography. Improvement of patients' laboratory investigations was assessed after the start of sirolimus, for example, elevation of hemoglobin and mean cell volume. Arabic translation of pediatric quality-of-life PedsQL 4.0 was done again 6 months after the start of sirolimus.

Results

This study included 18 patients; 12 (66.7%) of them were males and six (33.3%) were females. Regarding the type of vascular malformations, nine (50%) patients had venous malformations, six (33.3%) had lymphatic malformations, and three (16.7%) had mixed venolymphatic malformations.

Vascular malformations are widely distributed in various organs throughout the body. A total of seven (38.9%) patients had vascular malformations involving upper and lower limbs, seven (38.9%) in the head and neck, six (33.3%) in internal organs, and three (16.7%) involving the main trunk of the body. The most common complication was cosmetic disfigurement, which affected 13 (72.2%) patients, followed by functional impairment in 11 (61.1%) patients and then bleeding in eight (44.4%) patients (Fig. 1).

Patients underwent different treatment modalities before the start of sirolimus, but their symptoms were not alleviated. These treatment modalities included surgery in four (22.2%) patients, sclerotherapy in other four (22.2%) patients, and laser in one (5.5%) patient.

Sirolimus was started for different indications such as bleeding in eight (44.4%) patients, cosmetic disfigurement in 13 (72.2%), visceral organ involvement in six (33.3%), and pain in three (16.6%) patients.

The age of the patients during the start of sirolimus ranged from 5 months to 13 years, with a median age of 3 years.

Bleeding stopped after sirolimus in eight (100%) patients, with no further need for blood transfusion. Cosmetic disfigurement improved in 10 (76.9%) patients, whereas three (23.1%) patients still had cosmetic problems. Pain perception improved in two (66.6%) of three patients (Table 2).

Functional impairment was a serious problem in 11 (61.1%) patients as complications of vascular malformations interfered with their daily activities. There was a significant improvement in functional impairment in nine (81.9%) patients.

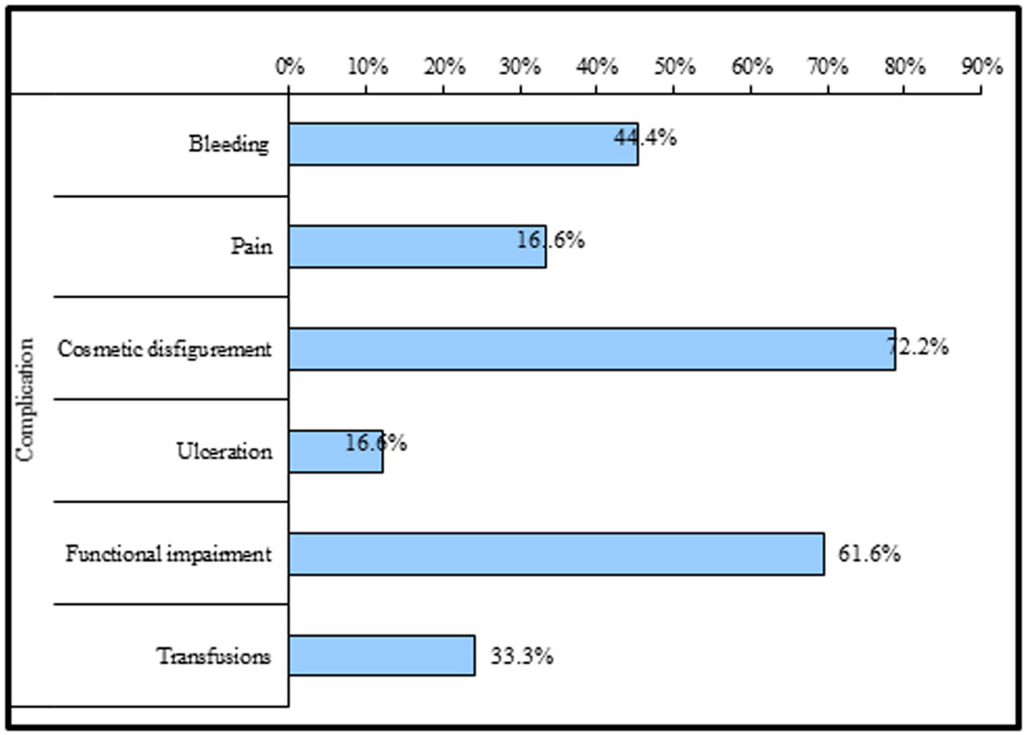
Moreover, quality of life of the studied patients improved significantly after the start of sirolimus as the mean score of the patients before the start of sirolimus was 65.18 and improved after sirolimus administration to be 78 (Table 3).

Regarding laboratory investigation follow-up, there was a highly significant increase in hemoglobin, in which the mean hemoglobin of the patients increased from 7.78 to 10.86. Moreover, there was a significant decrease in neutrophils in which the median decreased from 3.73 to 2.77 (Table 4).

Discussion

Management of vascular malformation is usually challenging. As there are different types of vascular

Figure 1



Complications of vascular malformations; the most common complication was cosmetic disfigurement, followed by functional impairment and then bleeding and pain.

Table 2 Highly significant improvement in bleeding and cosmetic disfigurement after sirolimus

	Post [*n* (%)]	Test value	*P* value	Significance
Bleeding				
No	8 (100)	24.500	0.000	HS
Yes	0			
Pain				
No	2 (66.6)	3.010	0.083	NS
Yes	1 (33.3)			
Cosmetic disfigurement				
No	10 (76.9)	16.425	0.000	HS
Yes	3 (23.1)			

Table 3 Significant improvement of quality of life of patients after sirolimus (*P*=0.038)

QOL	Pre	Post	Test value	*P* value	Significance
Mean ±SD	65.18 ±21.09	78.69 ±24.22	2.289	0.038	S
Range	31–97.5	30–100			

QOL, quality of life.

malformations and they occur in different sites, this leads to diverse presentations, which makes management of vascular malformations and assessment of response to different treatment modalities extremely difficult. Management of vascular malformations needs a multidisciplinary team, including pediatric hematology, pediatric surgery, diagnostic radiology, interventional radiology, dermatology, and child psychiatry.

So, we aimed to study the effect of sirolimus on complex vascular malformations regarding symptomatic improvement and quality-of-life improvement.

In our study, the median age to start sirolimus was 3 years, with the least age being 5 months. The age of start of sirolimus depends upon the age of patient presentation and maximum symptoms. We tried to delay the start of sirolimus in young infants to complete vaccination schedule and avoid sirolimus adverse effects; however, two patients started before the age of 6 months as one of them had a huge arm venous malformation that presented with disseminated intravascular coagulopathy and the other had a huge intra-abdominal lymphatic malformation with marked abdominal distension.

We usually start sirolimus orally on a continuous dosing schedule at a starting dose of 0.8 mg/m^2, with the level to be maintained between 4 and 12 ng/ml. The dose was rounded to the nearest 1-mg tablet form.

Overall, five cases reported a previous use of sirolimus in early age, which was started in the neonatal period for the management of massive cardiac rhabdomyoma but at a lower dose of 0.125 mg daily, because when

Table 4 Highly significant rise in hemoglobin level (*P*=0.002) and significant decline in neutrophil number (*P*=0.043) after sirolimus

	Pre	Post	Test value	*P* value	Significance
TLC					
Median (IQR)	11 (6.8–11.3)	8.1 (7.4–9)	–0.980	0.327	NS
Range	5.5–28	4.1–13.2			
NE					
Median (IQR)	3.73 (3.55–6.15)	2.77 (2.4–4.5)	–2.023	0.043	S
Range	3.3–24	1.1–5			
LYM					
Median (IQR)	2.8 (2.2–5.89)	3.43 (2.6–4.7)	–0.730	0.465	NS
Range	1–6.4	1.8–8			
Hg					
Mean±SD	7.78±1.88	10.86±1.37	4.565	0.002	HS
Range	5.1–11	8.6–13.1			
MCV					
Mean±SD	66.19±18.98	70.29±8.86	0.687	0.518	NS
Range	29.7–90	57–85			
PLT					
Median (IQR)	233 (173–325)	404.23±172.72	–0.420	0.674	NS
Range	48–1130	143–661			

Hg, hemoglobin; IQR, interquartile range; LYM, lymphocyte; MCV, mean corpuscular volume; PLT, platelet; TLC, total leukocyte count.

they were started on 0.25-mg daily sirolimus, the trough level was significantly high, but there were no reported adverse effects even with a high trough level [8].

It seems that the sirolimus trough level is extremely important not just for toxicity of the drug but also for efficacy. In our study, we have a case of blue rubber bleb nevus syndrome that was on sirolimus, and the dose was adjusted to the body surface area, but the patient still had persistent gastrointestinal bleeding and anemia. When the sirolimus trough level was repeated, it was subtherapeutic, so the dose was increased and consequently bleeding stopped and hemoglobin increased.

Sirolimus seemed to be effective in decreasing the size and symptoms of vascular malformations for which previous invasive techniques had unsatisfactory results or were associated with recurrence. This was seen not only in simple but also in complex malformations and in those being part of a syndrome. A relief in symptoms, improved function, and quality of life as well as effects on the lesion size have been described [9,10].

In our study, symptomatic relief occurred in most of the patients. Bleeding stopped after sirolimus in eight (100%) patients, with no further need for blood transfusion. Overall, three cases were diagnosed as blue rubber bleb nevus syndrome, and they suffered from severe gastrointestinal bleeding which required hospital admission and blood transfusion. After sirolimus, bleeding stopped, with no required blood transfusion.

Surgery and endoscopy seem to be ineffective in management of young children with blue rubber bleb nevus syndrome. Sirolimus can be considered a good choice for young patients, which can control massive bleeding and delay surgery or endoscopic treatment until the lesions appear completely, and for patients with multiple organ involvement [11].

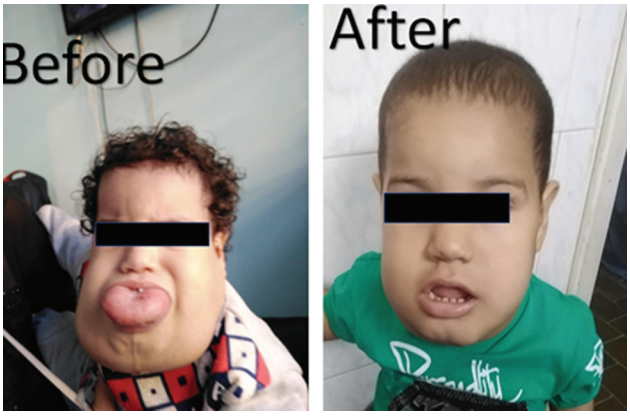
Cosmetic disfigurement usually is a common complaint as it is present in superficial lesions either venous, lymphatic, and venolymphatic malformations but hopefully in 10 (76.9%) patients (Fig. 2), whereas three (23.1%) patients still had their cosmetic problem. Pain perception improved in two (66.6%) of three patients.Assessment of quality of life in patients with vascular malformations is extremely important before and after treatment. In our study, we used the Arabic translation of pediatric quality-of-life PedsQL 4.0 questionnaire to assess outcomes before and 6 months after the start of sirolimus. There was significant improvement in the patients' quality of life, especially in patients who presented with bleeding or had internal organ involvement. Some studies also recommended a specific questionnaire designed for each type of vascular malformation to predict accurately the main concern of the patient and assess accurately the degree of improvement [12].

Regarding hematological parameters, hemoglobin rise was highly significant in patients after sirolimus. This

Figure 2

A patient with extensive venous malformation 3 and 6 months after sirolimus.

Figure 3



A patient with huge lymphatic malformation of the head and neck 6 months after the start of sirolimus.

rise in hemoglobin level in addition to bleeding stoppage and improvement in quality of life proves the important role of sirolimus in patients whose main complaint is bleeding, especially patients with blue rubber bleb nevus syndrome.

Response of lymphatic malformation to sirolimus is extremely heterogeneous. Dramatic improvement occurred in four (66.7%) patients (Fig. 3), whereas the other two patients did not show any improvement. It seems that macrocystic has a better response than microcystic malformations. Initial reduction in size by sirolimus can be followed by bleomycin injection or surgical resection if it could be done. More specific studies are needed for lymphatic malformations.

Conclusion

Symptomatic relief in patients after sirolimus is evident regarding different parameters, for example, bleeding, cosmetic disfigurement, and pain. Moreover, sirolimus seems to be a rescue drug in cases of blue rubber bleb nevus with refractory massive gastrointestinal bleeding.

Limitations

After the study of sirolimus in our patients, we encountered some limitations. Oral suspension is needed for patients less than 1 year, but unfortunately, it is usually unavailable. A separate study for each type of vascular malformations with adequate number of cases will be needed. Longer follow-up is needed for patients on sirolimus to know the long-term adverse effects and for patients who stopped sirolimus to know the incidence of recurrence.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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