

UC Irvine

UC Irvine Previously Published Works

Title

Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in adult and teen patients

Permalink

<https://escholarship.org/uc/item/9bw1m5t1>

Journal

Journal of Vascular Surgery Venous and Lymphatic Disorders, 9(1)

ISSN

2213-333X

Authors

Nelson, Kari J
Antiquera, Pamela
Nelson, J Stuart
et al.

Publication Date

2021

DOI

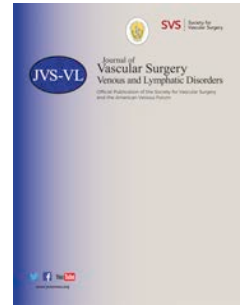
10.1016/j.jvsv.2020.04.001

Peer reviewed

Journal Pre-proof

Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in adult and teen patients

Kari J. Nelson, MD, Pamela Antiquera, FNP-BC, J. Stuart Nelson, MD PhD, Kristen M. Kelly, MD, Nadine Abi-Jaoudeh, MD



PII: S2213-333X(20)30210-9

DOI: <https://doi.org/10.1016/j.jvsv.2020.04.001>

Reference: JVSV 983

To appear in: *Journal of Vascular Surgery: Venous and Lymphatic Disorders*

Received Date: 5 January 2020

Accepted Date: 2 April 2020

Please cite this article as: K.J. Nelson, P. Antiquera, J.S. Nelson, K.M. Kelly, N. Abi-Jaoudeh, Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in adult and teen patients *Journal of Vascular Surgery: Venous and Lymphatic Disorders* (2020), doi: <https://doi.org/10.1016/j.jvsv.2020.04.001>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2020 Published by Elsevier Inc. on behalf of the Society for Vascular Surgery.

Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in adult and teen patients

Kari J. Nelson MD¹, Pamela Antiquera FNP-BC¹, J. Stuart Nelson MD PhD², Kristen M. Kelly MD³, Nadine Abi-Jaoudeh MD¹

¹ Department of Radiological Sciences, University of California Irvine

² Department of Surgery and Biomedical Engineering, University of California Irvine

³ Department of Dermatology, University of California Irvine

Corresponding author:

Kari J. Nelson MD

UC Irvine Medical Center

Department of Radiological Sciences

101 The City Drive South, Bldg 1

Orange, CA 92868

Abstract

Lymphatic malformations (LM) are rare congenital anomalies. LM are often refractory to standard treatments including surgical resection, debulking and sclerotherapy. Use of sildenafil, a phosphodiesterase-5 inhibitor (PDE-5i), for treatment of pediatric LM has been reported with demonstrated benefit to some patients. This case series reports treatment of three patients (ages 14-37 years) suffering from complicated or refractory LM with low dose oral PDE-5i resulting in significant clinical improvement.

Key words: lymphatic malformation, sildenafil, phosphodiesterase-5 inhibitor

Author conflict of interest: none

Lymphatic malformations (LM) are rare congenital anomalies^{1, 2} and are notoriously refractory to treatment. Conventional treatment options are invasive and include surgical resection, debulking and sclerotherapy. Despite these treatments, patients often remain plagued by LM. An initial report of LM improvement on sildenafil, a PDE-5i, in a pediatric patient undergoing treatment for pulmonary arterial hypertension³ prompted early studies involving the use of sildenafil for treatment of LM in pediatric patients^{4, 5}. Subsequent studies did not demonstrate similar success^{2, 6}. Sildenafil use for treatment of LM has been reported in patients from 12 days old to 16 years; however, even studies including teen patients had a median age under 10 years^{1, 2, 4, 5, 6}. The treatment of adult LM patients with sildenafil has not been published.

Following IRB approval, patients at a single institution with refractory lymphatic malformations treated with oral PDE-5i were retrospectively identified and reviewed. Consent to publish was obtained from each patient and/or from each patient's legal guardians.

Patient 1

18-year-old woman with congenital microcystic LM of the pelvis with trans spatial involvement presented to our institution with daily bleeding, oozing, pain and intermittent infection of the LM at the gluteal cleft (Figure 1a). The patient was prescribed a 10-week course of oral sildenafil given the severity of her condition. The insurer would not authorize sildenafil, but approved an alternate PDE-5i, tadalafil 5 mg by mouth taken at bedtime (po QHS). After 3 weeks of PDE-5i, all bleeding and drainage had resolved. After completion of 10-weeks of PDE-5i, the patient

underwent initial sclerotherapy using doxycycline. Four weeks post-treatment, the patient reported mild oozing of the malformation but decreased tenseness and discoloration. PDE-5i was again prescribed but denied by her new insurer. The patient underwent 5 additional image-guided sclerotherapy treatments over 18 months using doxycycline, sodium tetradecyl sulfate and bleomycin. After each treatment, components would slough and regrow; the malformation would dry up and then resume mild oozing and bleeding, remaining stable or slightly decreased in size (Figure 1b). Given diminishing improvement with sclerotherapy and concern for cumulative radiation dose, appeal for PDE-5i use was resubmitted and approved. The patient began taking sildenafil 20 mg po QHS. Within 4 weeks, all oozing and bleeding had resolved, pain decreased and LM appeared smaller. Continued shrinkage of LM was experienced with ongoing use of the PDE-5i, except for a large, sessile component along the right gluteal cleft. Trial of topical rapamycin to this area was initiated but resulted in bleeding and oozing and was discontinued. The patient chose to continue PDE-5i use. The patient has been on continuous PDE-5i use for 35 months with ongoing improvement (Figure 1c). At no time during the course of PDE-5i use has the patient experienced adverse effects of the drug nor has she experienced genital swelling or arousal related to taking the drug.

Patient 2

37-year-old woman with congenital right neck/supraclavicular mixed LM with trans-spatial involvement presented with worsening right neck and arm pain. The congenital lesion had been quiescent and was believed to be a lipoma until her first pregnancy, at which time it acutely enlarged, causing pain and mass effect. The patient was refused surgical resection or debulking given involvement of the right brachial plexus. Sclerotherapy was performed, followed by a decrease in lesion size and symptoms for 1 year. When symptoms recurred, the patient

established care at our institution and underwent 7 additional percutaneous sclerotherapy treatments over 6 years using doxycycline and sodium tetradecyl sulfate. Each treatment was triggered by increased size and mass effect resulting in right arm pain and intermittent right hand tremor. Alternative treatments were discussed. The patient was started on a PDE-5i (sildenafil 20 mg po QHS) (Figure 2a). At 3 months, the patient reported stable lesion size and no tremor recurrence. At 5 months, the patient reported decreased size and swelling of the LM. At 20 months, the lesion was further decreased in size and asymptomatic (Figure 2b). Patient has denied adverse effects of the PDE-5i throughout treatment and denied genital swelling or arousal related to taking the drug.

Patient 3

14-year-old male with congenital right neck mixed LM with trans-spatial involvement presented with bleeding from his LM following initiation of topical imiquimod. The patient's LM was noticed at 12 months of age, but remained clinically silent until 13 years when it began to intermittently bleed. The patient was started on topical imiquimod, which caused increased bleeding, and was then discontinued. Following interdisciplinary evaluation, patient underwent percutaneous sclerotherapy using doxycycline with subsequent improvement in appearance and decreased bleeding. Patient and his family desired treatment but wished to avoid repeat sclerotherapy. After lengthy discussion, the patient was started on a trial of PDE-5i (sildenafil 20 mg po QHS). After 6 weeks, the patient's parents reported a "drastic improvement" in the malformation. After 5 months of PDE-5i, the LM is asymptomatic and has lightened in coloration. Patient continues to deny adverse effects of the drug (such as flushing, changes in vision or hearing, dizziness, nausea) and has not experienced erection related to taking the drug.

Discussion

All 3 patients in our series presented with complications of their LM. Two were refractory to traditional treatments, and two demonstrated acute worsening with topical immune modulator treatment. Initial improvement with low dose PDE-5i was seen between 3 weeks and 5 months.

All patients experienced sustained improvement over time with use of PDE-5i. Duration of continuous PDE-5i for 2 patients has significantly exceeded treatment durations previously reported for pediatric LM^{1, 2, 3, 4, 5, 6}.

PDE-5i lead to smooth muscle relaxation in blood vessels causing dilation and may similarly affect lymphatic vessel smooth muscle. The mechanism by which PDE-5i act upon lymphatic malformations is extrapolated from in vitro study in which a relationship between nitric oxide and lymphatic vessel growth via production of cyclic guanosine monophosphate (cGMP) was demonstrated⁷. cGMP mediates lymphatic endothelial cell proliferation⁷. PDE-5i prevents degradation of cGMP by inhibiting PDE-5, prolonging the presence of cGMP which may facilitate lymphatic vessel growth and improve drainage of lymphatic malformations⁷ (Figure 3). Further investigation is needed.

PDE-5i have been commercially available since 1998⁸. Chronic use of PDE-5i has not demonstrated chronic side effects although data is limited⁸. Side effects related to sildenafil use for pediatric LM have been limited and mild, most commonly involving flushing, dizziness and nausea.

The treatment of non-pediatric LM population with sildenafil has not been published. The prescription of PDE-5i in a sexually maturing or mature patient raises concern for side effects including unwanted erection or genital swelling/arousal. For this reason, the patients in this series were treated with low-dose PDE-5i at bedtime, with significantly lower dosing compared to the pediatric studies published to date^{1,2,4,5,6}. In our series, there were no reports of side effects

with the low dose regimen which may be related to the dose or to the bedtime administration of the medication. Despite the low dose, all patients demonstrated significant clinical response. Based upon the relatively benign safety profile, the clinical response and lack of side effects, all patients have elected to continue PDE-5i use for now. Given paucity of data on long-term PDE-5i use and lack of randomized controlled trials on treatment of LM with PDE-5i, caution with use of PDE-5i for treatment of LM and careful patient screening are needed.

References

1. Tu JH, Tafoya E, Jeng M, Teng JM. Long-term follow-up of lymphatic malformations in children treated with sildenafil. *Pediatr Dermatol* 2017;34(5):559-565.
2. Koshy J, Eisemann B, Agrawal N, Pimpalwar S, Edmonds JS. Sildenafil for microcystic lymphatic malformations of the head and neck: a prospective study. *Int J Pediatr Otorhinolaryngol* 2015;79(7):980-982.
3. Swetman GL, Berk DR, Vasanawala SS, Bruckner AL. Sildenafil for severe lymphatic malformations. *N Engl J Med* 2012;366:384-386.
4. Danial C, Tichy AL, Tariq U, Swetman GL, Khuu P, Leung TH, et al. An open-label study to evaluate sildenafil for the treatment of lymphatic malformations. *J Am Acad Dermatol* 2014;70(6):1050-1057.
5. Wang S, Zhang J, Ge W, Liu Y, Guo Y, Liu Y, et al. Efficacy and safety of oral sildenafil in treatment of pediatric head and neck lymphatic malformations. *Acta Otolaryngol* 2017;137(6):674-678.
6. Rankin H, Zwicker K, Trenor CC. Caution is recommended prior to sildenafil use in vascular anomalies. *Pediatr Blood Cancer* 2015;62:2015-2017.

- 1 7. Malleske DT, Yoder BA. Congenital chylothorax treated with oral sildenafil: a case
2 report and review of the literature. *J Perinatol* 2015;35:384-386.
- 3 8. Schwarz ER, Kapur V, Rodriguez J, Rosanio S. The effects of chronic
4 phosphodiesterase-5 inhibitor use on different organ systems. *Int J Impot Res* 2007;19(2):139-
5 148.

6

7

8

9

Figure Legend

Figure 1. Cutaneous component of the congenital microcystic lymphatic malformation: 1a.

Appearance at initial presentation, with evidence of ongoing bleeding and oozing; 1b.

Appearance after 6 sclerotherapy sessions, with stable or slightly decreased size of the majority

of the malformation and evidence of decreased bleeding and oozing; 1c. Appearance after 35

months of PDE-5 inhibitor use with decreased size of the malformation, lightened coloration and

resolution of all bleeding and oozing.

Figure 2. Contour abnormality of the right lower cervical region related to underlying mixed type

lymphatic malformation: 2a. Appearance following 8 sclerotherapy sessions; 2b. Appearance

after 20 months PDE-5 inhibitor use with decreased contour abnormality and decreased

displacement of the patient's necklace.

Figure 3. Potential mechanism of action for PDE-5 inhibitors on lymphatic malformations: Nitric

oxide interacts with the enzyme guanylate cyclase to enable conversion of GTP to cGMP; PDE-

5i prevents breakdown of cGMP by inhibiting PDE-5, resulting in prolonged activation of

cGMP; cGMP may then cause smooth muscle relaxation in lymphatic vessels decreasing

pressure within lymphatic structures and may contribute to generation of new lymphatic vessels.

GTP= guanosine triphosphate; cGMP= cyclic guanosine monophosphate; GMP= guanosine

monophosphate; PDE-5= phosphodiesterase; PDE-5i= phosphodiesterase-5 inhibitor.











