Lymphology 57 (2024) 104-106

LETTER TO THE EDITOR

BIOBRIDGE™ COLLAGEN MATRIX FOR LYMPHEDEMA THERAPY

M. Paukshto, G. King

We read with interest the recently published article by Dr. M. Witt and Dr. A. Ring "Handley's Thread Lymphangioplasty Vs. BioBridge™ Collagen Matrix for Lymphedema Therapy–Old Wine in New Bottles?" (1). The article presents a thorough summary of the history of lymphangioplasty as a method to treat lymphedema over the course of history, which is fascinating. We have tremendous respect for Dr. Witt and this work. However, we respectfully found some areas which we do not believe may be correct.

While the title of the paper is clever, it is, respectfully, somewhat misleading. The BioBridge device was not related to the Handley's efforts using threads in treatment of lymphedema, but it was developed from a tissue engineering research effort to promote and direct the formation of lymphatic vessels (2,3) and based on a fundamental discovery of the mechanisms that regulate lymphangiogenesis (4,5).

The authors state that "lymphangioplasty is a technique of re-constructive lymphatic surgery where subcutaneous lymphatic neocollectors are created, using surgical threads, nanofibrillar collagen threads, plastic tubes or autologous tissue flaps." However, the term "neocollectors" is clearly introduced here in the context of "neo-lymphangiogenesis" presented in (6) and reflects the possibility of new lymphatic collector creation through neolymphangiogenesis induced by subdermal dissection. We are not aware of, nor has the authors presented any evidence of, the formation of new lymphatic collectors after implantation of plastic tubes or surgical threads. Therefore, the statement is lacking basis.

The authors validate throughout this paper the claims of success made in historic papers but without providing specific data or criteria. While this is challenging, this lacks scientific rigor because how one author in 1913 defines success could be quite different from another author in 1965 or some other year. Is it limb volume reduction? (by how much is considered successful?), What is the duration of efficacy? (6 months? one year?), complications rate? (0%? 50%?) At the time of many of these papers longevity of treatment was not front of mind (life expectancy in the United States was 51 years in 1913 vs 77 years today). This is an important point because the author appears to accept these claims at face value that such techniques have merit and have been proven to be successful, even though there is no evidence presented that these historic approaches have induced a repair to the lymphatics or just provide some rudimentary level of temporary lymphatic drainage. One must ask if any of these simple techniques indeed do have merit, why have none of them been adopted and used today in the treatment of lymphedema? This is a fundamental question that has not been answered in this paper.

One might conclude that these earlier techniques simply do not work or create risk of other complications that have been known (such as silk threads inducing foreign body reactions). The paper makes only one critical comment in the discussion that "There has always been criticism that thread and tube lymphangioplasties create static fluid col-

umns, but do not provide any motor force for draining the lymph." Respectfully, this should have been further explored. As the authors have summarized, BioBridge has been shown to promote and direct lymphangiogenesis. This provides an entirely different mechanism of action than historic thread lymphangioplasty approaches.

To criticize the numerous preclinical studies conducted using existing and established lymphedema animal models for not comparing BioBridge to a suture or other material – which are not being used clinically today – does not seem fair. These studies, conducted by independent and leading researchers in US, Spain, Taiwan, and Japan, each evaluated BioBridge as a therapeutic target against a surgical control group because the control group in these models are well established and were used to quantify the therapeutic benefit of the treatment. If the authors wish to conduct such comparison studies they can, but it does not seem appropriate to criticize all the other studies that have been published in peer-reviewed journals as having a problem. There are a number of different surgical threads, how many of them should be tested?

There are a few statements that are not exactly correct, and we would like to address them too. Concerning the references (4,5) that "prove that simple collagen (not aligned nanofibrillar one) promotes directed lymphangiogenesis as well". Actually, in the studies by Boardman and Swartz the injected type I collagen solution formed at least partially aligned fibrillar collagen gel during the gelation under the directional flow of interstitial fluid (1-dimentional model). These experiments have been repeated in VA Palo Alto and also used BioBridge scaffold.

The authors state that "An ongoing study in Stanford and Chicago is examining the therapeutic benefits of LVAs alone versus LVAs plus lymphangioplasty with BioBridge™, in a group of approximately 80 patients". Actually, the prospective study in Stanford and Chicago is examining the therapeutic benefits of VLNTs alone versus VLNTs in combination with BioBridge. In addition, "According to a recent metanalysis, such combined BioBridge™ lymphangioplasties lead to an average excess limb volume reduction of 1-10.7% [47]". But the study analyzed in [47] did not use the BioBridge and presented results related to silicone tubing treatment only (Note: [47] is referenced in the original article and it is also noted here as (7)).

Additionally, the authors state that "To date, BioBridge™ has only been implanted subcutaneously. The effect and benefit of BioBridge™ used in the sense of a subfascial lymphangioplasty according to Handley-Lexer still needs to be investigated." Actually, there are clinical cases where BioBridge has been implanted in the deep lymphatic region in the surgical treatment of lymphedema. Also, there are clinical cases of head and neck lymphedema treatments.

The authors also propose that "Whether the same effect of a lymphangioplasty with BioBridge™ or at least a similar one can be achieved using cheaper materials, such as surgical sutures (as in historical lymphangioplasties), and whether BioBridge™ is significantly superior to simple suture materials has not yet been investigated. Such studies would however be highly desirable." This statement again assumes these other historic materials have been proven suitable for use today in clinical treatment of lymphedema. The authors are speculating that these cheaper materials work the same way as BioBridge or might be able to work together in some fashion, but this has not been supported with meaningful evidence.

Finally, the authors state that "This can hardly ever be achieved with BioBridge™ alone, for mere financial reasons." While the authors may feel BioBridge is expensive, we believe this statement is not accurate since BioBridge has been used in over one hundred clinical cases to date for the treatment of lower limb lymphedema, where several devices have been implanted along the entire leg and foot. Financial justification has been made for these cases based on the quality-of-life impact and reduced long term medical cost burden. Specifically regarding BioBridge, the current price in the US is $3,000 per 5-pack, not $1,500 and BioBridge is a registered trademark (® not ™).

REFERENCES

1. Witt, M, A Ring: Handley's Thread Lymphangioplasty Vs. BioBridgeTM Collagen Matrix for Lymphedema Therapy–Old Wine in New Bottles? Lymphology 56 (2023) 110-120.
2. Paukshto, M, G Martin, D McMurtry, et al: Control of cellular migration, survival, gene expression on patterned collagen fibers. Collagen GRC. 2013.
3. Nakayama, KH, G Hong, JC Lee, et al: Aligned-braided nanofibrillar scaffold with endothelial cells enhances arteriogenesis. ACS Nano. 9 (2015 Jul 28), 6900-6908.
4. Boardman, KC, MA Swartz: Interstitial flow as a guide for lymphangiogenesis. Circ. Res. 92 (2003), 801-808.
5. Rutkowski, JM, KC Boardman, MA Swartz: Characterization of lymphangiogenesis in a model of adult skin regeneration. Am. J. Physiol. Heart Circ. Physiol. 291 (2006), H1402-H1410.
6. Yamamoto, T, N Yamamoto: Possibility of new lymphatic pathway creation through neo-lymphangiogenesis induced by subdermal dissection. Lymphology 54 (2021), 154-163.
7. Reyes Valdivia, A, Á Duque Santos, C de Miguel, et al: Midterm outcomes of silicone tubing for treatment of moderate and severe limb lymphoedema. Eur. J. Vasc. Endovasc. 67 (2024), 687-688.

Michael Paukshto, PhD, CTO & Co-founder
Greg King, CEO
Fibralign Corp.
32930 Alvarado-Niles Rd., Suite 350
Union City, CA 94587
Tel: 650-492-1440
www.fibralignbio.com