

## What is popular may no longer be popular: Cyanoacrylate and other alternatives in surgical treatment of chronic venous insufficiency

*Popüler olan, artık popüler olmayabilir: Kronik venöz yetmezliğin cerrahi tedavisinde siyanoakrilat ve diğer alternatifler*

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### ABSTRACT

With the beginning of 21<sup>st</sup> century, great advances in surgical treatment of venous insufficiency have been achieved including endovenous laser ablation and radiofrequency ablation methods. These methods became first line therapy alternatives also recommended by guidelines. Despite satisfactory results, the thermal nature and tumescent anesthesia requirement of the techniques initiated a search for a better technique with increasing expectations in society. The method closest to ideal seems to be cyanoacrylate ablation therapy that is non-thermal and non-tumescent. Having easy applicability and comparable satisfactory results with first line therapeutic methods with the longest follow-up of two years, cyanoacrylate ablation therapy may be the future for surgical treatment of venous insufficiency. Still, studies with long-term follow-up are needed to be conducted.

**Keywords:** Cyanoacrylates; endovenous thermal ablation; venous insufficiency.

Considering the high incidence of chronic venous insufficiency reported in series as 164/1000,<sup>[1]</sup> not much has progressed in its treatment in the 20<sup>th</sup> century. The surgical therapy mainly focused on high ligation and stripping (HLS) defined by Myers in 1947.<sup>[2]</sup> With the beginning of 21<sup>st</sup> century, great developments have been achieved including endovenous laser ablation (EVLA) first reported by Navarro and Min in 2001<sup>[3]</sup> and radiofrequency ablation (RFA) by Weiss and Weiss in 2002.<sup>[4]</sup> Those two methods defined as endovenous thermal ablation (EVTA) have become the treatment of choice as first line therapy recommended

### ÖZ

Yirmi birinci yüzyılın başlangıcı ile beraber, venöz yetmezliğin cerrahi tedavisinde endovenöz lazer ablasyon ve radyofrekans ablasyon yöntemlerini içeren büyük gelişmeler yaşandı. Bu yöntemler, klavuzlarda da önerilen birinci seçenek terapi alternatifleri haline geldi. Tatmin edici sonuçlara rağmen, tekniklerin termal doğası ve tümesan anestezi gereksinimi, toplumda artan beklentilerle beraber daha iyi bir teknik arayışına yol açtı. İdeale en yakın yöntem, non-termal ve non-tümesan olan siyanoakrilat ablasyon terapisi gibi gözükmemektedir. Kolay uygulanabilirliği ve en uzun takip süresi iki yıl olmak üzere, birinci seçenek terapötik yöntemlerle karşılaştırılabilir tatmin edici sonuçlara sahip olması ile siyanoakrilat ablasyon terapisi venöz yetmezliğin cerrahi tedavisinin geleceği olabilir. Yine de uzun takip süreli çalışmaların yapılması gereklidir.

**Anahtar sözcükler:** Siyanoakrilatlar; endovenöz termal ablasyon; venöz yetmezlik.

by American Venous Forum and United Kingdom recommendations.<sup>[5,6]</sup> However, a search for a better technique has continued with mechanicochemical ablation (MOCA) first reported by Elias and Raines in 2012<sup>[7]</sup> and finally cyanoacrylate ablation (CAA) by Almeida in 2013.<sup>[8]</sup>

### What is the current state of surgical treatment strategies and why do we need alternatives?

All available treatment strategies have been compared with the conventional HLS in many randomized studies and meta-analyses. One-year



Available online at  
www.tgkdc.dergisi.org  
doi: 10.5606/tgkdc.dergisi.2017.13526  
QR (Quick Response) Code

Received: May 30, 2016 Accepted: July 23, 2016

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occlusion rates were statistically comparable: 94.2% for EVLA, 95.2% for RFA and also 95.2% for HLS. These results were better compared to the 83.7% rate for ultrasound guided foam sclerotherapy (UGFS). When five-year results were explored, saphenous vein patency rates were again statistically equivalent: 17.9% for EVLA and 10.1% for HLS.<sup>[9]</sup> In a meta-analysis exploring 31 randomized controlled trials, in two years, in comparison with HLS, recurrence on greater saphenous vein (GSV) was lowest with EVLA (hazard ratio: 0.84) than RFA (hazard ratio: 0.94) and UGFS (hazard ratio: 0.92). Venous Clinical Severity Score (VCSS) was lower for EVLA and RFA compared to HLS in one year, whereas pain scores were lowest with UGFS and RFA. When cost-effectiveness was a measure, UGFS was the most effective option where EVLA, RFA, and HLS did not differ significantly.<sup>[10]</sup>

As we look at the whole picture, the first line treatment strategies seem to be quite effective compared to HLS and follow-up results are satisfactory, but there are drawbacks. Especially, EVTA requires tumescent anesthesia (TA), which is the major concern for postoperative pain and discomfort. The tip of the catheter produces over 700 °C heat in EVLA and 120 °C heat in RFA which makes the TA inevitable.<sup>[11]</sup> The TA aims to protect surrounding tissues from the heat produced, but still paresthesia and even nerve damage are great issues. Superficial veins are not suitable and skin burns may form if EVTA is performed.<sup>[11,12]</sup> Compression stockings are also recommended following EVTA; however, three-day and one-month periods of use were documented to be comparable.<sup>[13]</sup> Moreover, there are still unsatisfactory results due to recanalization in EVTA and the expectations are increasing among the population.

#### **What are the new alternative strategies other than cyanoacrylate?**

Since the first line treatment recommended by guidelines is EVTA, all studies aim to compare the alternatives with either EVLA or RFA.

### **MECHANOCHEMICAL ABLATION**

Mechanochemical ablation is a non-thermal, non-tumescent method that consists of a wire that rotates 3500 rpm, simultaneously injecting sclerotherapy agents. The main strategy is to cause mechanical damage in the endothelium and also increase shear stress.<sup>[7]</sup> It does not require TA. The main drawback is the possibility of the wire to get stuck on vein wall or even cause perforation which is not very hardly resolved by pulling back the catheter, but may cause substantial postoperative pain and discomfort. van

Eekeren et al.<sup>[14]</sup> documented their one year results in 92 patients and 106 limbs and reported GSV occlusion rates as 93.2% in six months and 88.2% at one year. One-month to six-month occlusion rates of >90% were documented in other series.<sup>[15,16]</sup> When compared to RFA, it was reported that MOCA caused lesser postoperative pain and discomfort.<sup>[17]</sup>

To document the non-inferiority of MOCA compared to RFA, Mechanochemical Endovenous Ablation versus RADiOfrequeNcy Ablation (MARADONA) Trial for GSV and Mechanochemical Endovenous Ablation versus Radiofrequency Ablation (MESSI) Trial for lesser saphenous vein (LSV) are still ongoing.

### **STEAM ABLATION**

Despite its thermal nature, steam ablation (SA) was presented as a new alternative to EVTA methods. It produces 120 °C heat on the catheter, measured as 60 °C on the tip and still requires TA. Six-month and one-year GSV occlusion rates were reported to be 96.1% and 83%, respectively.<sup>[18]</sup> In the endovenous Laser Ablation versus Steam Ablation (LAST) Trial, one-year occlusion rates for SA and RFA were 96% and 92%, respectively.<sup>[19]</sup> Despite these satisfactory results, SA does not seem to bring advantages over current EVTA methods.<sup>[20]</sup>

### **CYANOACRYLATE ABLATION**

The commercially available ethyl-2-cyanoacrylate known as the “crazy glue” or “superglue” is chemically similar to N-buthyl-cyanoacrylate (NBCA) and 2-buthyl-cyanoacrylate which are available for medical and veterinary applications. Cyanoacrylate has been used for embolization of arteriovenous malformations as well as treatment of bleeding from gastric and esophageal varices for many decades.<sup>[21]</sup> Following injection, NBCA rapidly solidifies via a polymerization reaction and causes a strong inflammatory reaction on the vein wall followed by obliteration of the vein.<sup>[22]</sup> The main advantage of CAA therapy is its non-thermal nature that does not require TA (non-thermal, non-tumescent). Besides, no compression stockings following CAA is recommended.

The first human use of cyanoacrylate in GSV incompetency was documented by Almeida et al.<sup>[23]</sup> in 2013<sup>[8]</sup> and two-year results were then published. They included 38 patients in C2-C4 class where GSV diameter ranged between 3 to 12 mm (mean 6.7 mm) and presented >0.5 second reflux. The length of the treated vein segment was 33.8±9.1 cm. The mean procedural time was 21 minutes (quite shorter compared to EVTA). The 24-month occlusion rate

was 92.2% which is comparable to EVTA methods. The VCSS, pain and edema were decreased during follow-up and no paresthesia was observed. In the first eight cases (21.1%), glue or thrombi extension across the saphenofemoral junction (SFJ) was observed which resolved spontaneously in three months. However, it was no longer an issue as soon as the initial injection was made 3-5 cm below the SFJ in the following cases. Compression stockings were not employed following CAA.

Proebstle et al.<sup>[24]</sup> documented the results of the first prospective study on CAA in 70 C2-C4 class patients where GSV diameter ranged between 3 to 10 mm (mean 7.8 mm) and presented >0.5 second reflux. The mean length of the treated vein segment was 37.6 cm. The mean procedural time was 18.6 minutes. The 12-month GSV occlusion rate was 92.9%. The VCSS, Aberdeen Varicose Vein Questionnaire (AVVQ) score, pain and edema decreased over time and no paresthesia was documented. The rate of glue extension across SFJ was 1.4% in one year despite the fact that proximal injection site was 5 cm away from SFJ. The results were quite satisfactory and comparable to EVTA. Compression stockings were not employed following CAA.

Chan et al.<sup>[25]</sup> published inferior results in a similar group of 29 patients and 57 legs. The 12-month occlusion rate was 78.5%. Toonder et al.<sup>[26]</sup> documented 76% success rate in CAA for perforator venous incompetency.

In the VeClose Trial, which is a non-inferiority trial, 222 patients were included and CAA (n=108) was compared with RFA (n=114). The patients were in class C2-C4b and the GSV diameter was in 3-10 mm range. The mean diameter was 4.9 vs. 5.1 mm and the mean length of treated vein segment was 32.8 cm vs. 35.1 cm for CAA and RFA, respectively. The three-month occlusion rate was 99.5% for CAA and 96% for RFA. The decrease in VCSS and AVVQ score was comparable.<sup>[27]</sup> The two-year occlusion rates were documented as 94% for both.<sup>[28]</sup>

The largest series comparing cyanoacrylate use (n=154) with EVLA (n=154) was a prospective study in C2-C4 patients where the diameter of GSV was <15 mm.<sup>[12]</sup> Operative time was shorter (15±2.5 vs. 33.2±5.7) and peri-procedural pain was lower (3.1±1.6 vs. 6.5±2.3) in CAA group. There were seven cases with temporary or permanent paresthesia in EVLA group compared to none in CAA. One, three, and 12-month closure rates were 87.1%, 91.7% and 92.2% for EVLA and 96.7%, 96.6% and 95.8%

for CAA, respectively. Both groups had significant improvement in VCSS and AVVQ postoperatively in 12 months. No compression stockings were used postoperatively.

Results on use of CAA alone have been published very recently in three consecutive studies from Turkey in considerable number of patients. Yasim et al.<sup>[11]</sup> documented their experience on CAA in 180 patients (169 GSV and 11 LSV). The mean follow-up was as short as 5.5 months and recanalization rate was 0%. The authors used compression stockings postoperatively without any scientific rationale, but due to surgical habits, and claimed that this high success rate was possibly due to this. Similarly, Tok et al.<sup>[29]</sup> published their results on 141 patients and 189 GSVs. The mean follow-up time was 6.7 months and occlusion rate was 98.4%. The VCSS was significantly improved. Çalık et al.<sup>[30]</sup> documented their results on 181 patients and 215 legs (206 GSV and 9 LSV); the six-month occlusion rate was 97.2%.

The cord-like solid consistency that may occur following CAA due to polymerization of cyanoacrylate has not been documented as a parameter in studies. However, it is a clinical concern especially in superficial saphenous veins. But it fades away as cyanoacrylate is metabolized.

In conclusion, with the advents in science and technology and the increasing expectations for a better, shorter and more successful method for surgical treatment of venous insufficiency, a search has been initiated. Cyanoacrylate ablation seems to be the closest technique to the ideal with documented results of the longest two years. The results are satisfactory and are comparable to the first line treatment strategies namely endovenous laser ablation. The cyanoacrylate ablation is suitable for almost all patients, since it is non-thermal and non-tumescent. The postoperative pain and discomfort as well as skin bruises, paresthesia and burns caused by thermal damage and TA are not issues. There is no need for postoperative compression stockings which also increase patient comfort. However, it should be kept in mind that early trials are always highly focused leaving important clinical issues unsolved and almost always concentrate on short-term surrogate outcome measures. Therefore, as cyanoacrylate ablation seems to displace the first line treatment endovenous thermal ablation methods and decrease their popularity, still, long-term results need to be documented.

#### **Declaration of conflicting interests**

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The author received no financial support for the research and/or authorship of this article.

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