Přehledový článek | Review article

Cyanoacrylate glue in treatment of varicose veins

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SOUHRN

Ošetření vena saphena magna a parva akrylátovým lepidlem je jednou z nejnovějších technik. Používá modifikovaný cyanoakrylát. V článku jsou rozebrány současné poznatky o ošetření varixů cyanoakrylátem, mechanismus polymerizace a degradace cyanoakrylátu, jeho vlastnosti, rizika spojená s aplikací, výsledky dostupných studií, toxicita a histokompatibilita, respektive poznatky o reakci cévní stěny na cyanoakrylát.

Keywords:
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ABSTRACT

Treatment of the great and small saphenous veins with modified cyanoacrylate is one of the most recent techniques. The article discusses the current findings related to cyanoacrylate treatment of varices, the mechanism of cyanoacrylate polymerization and degradation, cyanoacrylate properties, application-related risks, results of available studies, cyanoacrylate toxicity, and its histocompatibility, or findings related to vessel wall reactions to cyanoacrylate.

Introduction

Treatment of varicose veins in lower extremities has witnessed major development during the last two decades. Despite still widely used crossectomy and conventional stripping for treatment of great saphenous vein (GSV) and small saphenous vein (SSV), mini-invasive techniques have spread enormously. The main reason is possibility of out-patient treatment, shorter and lesser burden, minimum need for anaesthesia, better cosmetic effect, shorter intervention as well as recovery period. Mini-invasive techniques can be divided to thermal (endovascular laser – EVL, radiofrequency ablation – Closer Fast, mechanochemical [ClariVein]), and chemical – sclerotherapy under ultrasound guidance and most recently treatment with cyanoacrylate (VenaSeal, VariClose).

Cyanoacrylate gluing technique is the least strenuous treatment of varicose trunks which does not necessitate tumescent anaesthesia and post procedural stocking compression.

History

Acrylates were discovered in the 1940s. Allyl acrylate was first synthesized in 1949 by American chemical scientist Ardis.[1] The "superglue" quickly found its place in aircraft and building industry, and soon also in healthcare.

It has been used as a haemostatic agent, tissue glue, or embolization material. In general surgery it has been used for sutureless bonding of wounds or venous embolization, e.g. to devitalize metastases in liver. In vascular medicine, cyanoacrylates have been used for several decades to treat AV malformations, bleeding from oesophageal varices, and traumatized arteries by endovascular application.

The very first treatment of insufficient varicose trunks in lower limbs in humans was realized by Almeida in 2010.[2]

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Properties of the glue

The alkyl side chain (R) has a decisive impact on the glue properties, namely its strength and physical properties. Short chains (R = –CH3 or –C2H5) form straighter and stronger bonds resulting in stronger, but more brittle structure. On the contrary, the longer or more complex the structure of the chain, the higher elasticity of the formed polymer.

In the body the cyanoacrylate polymer gradually degrades to formaldehyde and the respective alkyl acetate. The longer or more complex the side chain, the slower the polymer degradation. This characteristics is determined by the steric hindrance.[3] Shorter chains degrade very fast, which results in release of the degradation products. Higher concentration of formaldehyde can be toxic. At the same time the degraded products also cause inflammatory response and impair healing. The elementary cyanoacrylate structure is strictly given; however, numerous additives can significantly influence the required properties such as viscosity, speed of hardening, elasticity, colour, strength, biocompatibility, speed of degradation, or toxicity.[4]

The current medical practice uses mostly n-butyl-2-cyanoacrylate, or more recent octyl cyanoacrylate.

One of the practical options is extending the polymerization time by adding retarders. These include acetic acid[5,6] or poppy seed oil – Lipiodol Ultra-Fluid (Guerbet, France). Cyanoacrylate is used in mixture with Lipiodol at ratios of 1 : 1 through 1 : 5. The ratio between the components has been established empirically. The study by Y.J. Li[7] succeeded in demonstrating that both the components mix together well and homogeneously. The retarded polymerization is most probably due to the separation effect. Lipiodol prevents the immediate contact of the cyanoacrylate monomer with the ionized environment and tissue.

The reason for intentionally increasing the glue viscosity was a presumption first made by Gounis.[5] There is a positive correlation between an acrylate's viscosity and the adhesion of its polymer to the vessel wall. Moreover, the higher the glue viscosity, the less need to reduce the speed of blood flow.

Suga[8] investigated cyanoacrylate's ability to occlude a vessel in animals on a vein model made of vinyl tubes. With 0.7 ml of glue he was able to successfully occlude a vessel of up to 6 mm in diameter. Double quantity then sufficed for 9mm and 12mm diameters at flow speed up to 10 cm/s and 5 cm/s, respectively.

Studies in animals

So far two larger studies have been published on treatment of venous trunks with cyanoacrylate in animals. They report results after 30 days[9] and 60 days[10] post application in pigs.

The vein wall reaction was studied 30 days later and examined both macroscopically and microscopically. The veins were completely occluded. The tunica intima was replaced with eosinophilic matrix, histiocytes and multinuclear giant cells. Part of the sample vein was narrowed by fibrotization, while in another the space showed signs of residues of disintegrated erythrocytes. Samples taken after 60 days continued to show signs of inflammation and the findings were similar to those described above. The tunica intima was replaced with spindle cells. Multinuclear giant cells were present.

Studies in humans

The first study in humans was published by Almeida[2] in 2013. He treated two groups of patients who were observed at 30 and 180 days. The application was performed using a new dispensing equipment. The immediate success rate (within 3 days) was 100%. After 30 days, it was 97%. The Venous Clinical Severity Score (VCSS) improved by 1.9–2.1 after 30 days (range 0–11). No complications were reported.

In Europe, Proebstle[11] published the first multicentric study, involving 69 patients, conducted in 7 centres. The technical procedure and equipment used were the same as in Almeida's US study. The immediate success rate was 100%. At one year, complete occlusion was only present in 92.9%. Side effects were nils. Phlebitic reaction occurred in 11.4%, pain in 8.6%. No serious adverse event was observed. In all 3 patients only partial recanalization occurred. Thrombus protrusion into the common femoral vein was observed in one patient.

Sixty-two GSV were treated in Tekins study with VariClose system (VVSS) (Biolas, Ankara, Turkey). Short-term results: one week and one month interval showed 100% and 93.5%, respectively. At 6 months total occlusion was 90.3% and subtotal occlusion 3.2 % of observed patients.[12]

In the largest prospective study Yasim et al. treated 169 GSV and 11 SSV with VVSS. After 5.5 month 100% of the treated veins were successfully occluded. The mid-term results published last year showed 96.6% success in 1 year and 94.1% at 30 month.[13,14]

A new prospective study was designed in USA called WAVES using VenaSeal (VSCS) (VenaSeal closer system, Medtronic, Minneapolis, USA). It concerns on quality of life, safety and effectiveness outcome for treatment of GSV, SSV, and accessory saphenous veins.[15]

The study executed by Toonder et al. deals with cyanoacrylate embolization of insufficient venous leg perforators using VSCS. The occlusion rate was 76% without serious adverse events.[16]

In a contemporary study published 2018 Prasad et al. presented 100% successful treatment of 191 insufficient symptomatic vein perforators (69 patients) in 6-month follow up. All ulcers showed complete healing within three months. Significant prolonged thrombophlebitis occurred in 38.5% of limbs. Deep venous extension of cyanoacrylate occurred in four (4.8%) patients, with no adverse clinical outcome.[17]

A comparative study between cyanoacrylate embolization using VSCS and radiofrequency ablation (RFA) ClosureFast system (Covidien, Mansfield, Mass) was published by Morrison in 2016. Two hundred twenty-two subjects with symptomatic GSV incompetence were randomly assigned to receive either VSCS (n = 108) or RFA (n = 114). Short time results after 3-month interval was 99% CEA success occlu-

sion and 96% for RFA. The long-term results were quite similar. At one-year follow-up the complete occlusion was 97.2% in VSCS and 97.2% in RFA. After two years the result was 95.3% and 94.0% for VSCS and RFA, respectively. No serious adverse events appeared. Phlebitis occurred in 20% of patients in VSCS and 14 % in RFA group.[18]

A comparative study between VVSS and endovenous laser ablation (AVLA) was published in 2017 by Koramaz et al.[19] They treated 339 patients with either the endovenous application of VVSS or EVLA. The 12-month total occlusion rates in the VVSS and EVLA groups were 98.6% and 97.3%, respectively. There were fewer adverse events after VVSS treatment compared with EVLA treatment.

Currently available techniques

Two different systems are currently available, American VenaSeal (VSCS) and Turkish VariClose (VVSS). The American set consists of a vial containing modified cyanoacrylate applied from a dispenser gun which releases 0.09 ml of modified cyanoacrylate at a single press of the trigger VSCS is modified Histoacryl with increased viscosity and retarded polymerization. An unspecified organic substance is declared as an additive. The application starts by placing the catheter about 2 cm below the junction. Amount of 0.09 ml of glue is released in one shot, follows 3-minute compression with ultrasound probe and the same process after 3 cm withdrawal of the catheter.

Turkish VVSS contains cyanoacrylate, a simple dispenser gun and a PTFE catheter. The glue has a water-like consistency and its colour is dark blue. However, the application is carried out by continuous dispensing of cyanoacrylate, while retracting the catheter at about 2 cm/s. A single press of the dispenser gun trigger releases 0.3 ml of cyanoacrylate. The catheter has several lateral openings for a more even distribution of the glue. Unlike VSCS, the VVSS glue polymerizes almost immediately. It is therefore necessary to withdraw the catheter and apply the glue without stopping, otherwise there is a risk of the catheter getting stuck.

Comparable results can also be achieved using a technique with no special instruments.[20] It uses the original procedure for the treatment of AV malformations or bleeding from oesophageal varices.

A new generation of cyanoacrylate glue that received CE mark approval was announced by Baltic international in October 2018 (https://evtoday.com/2018/10/24/ce-mark-approved-for-balts-magic-glue-cyanoacrylate--liquid-embolic-agent).

Histocompatibility and vessel wall response to cyanoacrylate

Even though cyanoacrylates are relatively widely used in human medicine, histopathological studies focus particularly on animal experiments. Examination of human tissues, whether those of living individuals or from an autopsy, is very sporadic. Evidence of vessel wall response to cyanoacrylate is provided by Canter[21], where parts of a haemangioma treated with n-butyl-2cyanoacrylate were gradually removed over 6 months. After 48 hours from cyanoacrylate application, acute inflammation of the tissue occurred. Polymorphonuclear leukocytes were predominant. Vascular structures were thrombotic due to both cyanoacrylate filling and presence of acute inflammation around the glue. The endothelium and the smooth muscle of the vessel wall were lacerated and showed signs of necrosis. After a month, the tissues showed very clear signs of chronic inflammatory reaction and reaction to a foreign body with the presence of giant and polymorphonuclear cells. Cyanoacrylate was still present in the tissues. After 6 months, signs of granulomatosis appeared in the tissues and vessels as a reaction to a foreign body. Vascular lacunas previously filled with the glue now contained chronic inflammatory cells and the vessel wall showed signs of smooth muscle cell proliferation. Neovascularization appeared in the surrounding tissue.

Signs of glue degradation in the vessel are observed as early as 2 months after application.[22] Described picture of tissue reaction is disputable if the effect on haemangioma tissue is comparable to the tissue of saphenous vein but there is few in vivo data on these reactions with human tissue.

Advantages of method

Cyanoacrylate embolization of GSV, SSV, and insufficient perforators is not inferior to other endovenous ablation methods. This technique is faster, less painful with minimum of adverse events. There is no risk of damage surrounding tissues especially peripheral nerves. It could be done without tumescent anaesthesia and also the postoperative analgesia is needed rarely. There is no need of postoperative stocking compression.

Disadvantages and risks of method

Toxicity of acrylates is determined by the length of the alkyl side chain. The longer the chain, the lower the toxicity. This is due to the slower degradation of the formaldehyde releasing molecule.[23] Potential toxicity of cyanoacrylate consists in the formation of formaldehyde during its degradation. Degradation of the used cyanoacrylate takes place in the order of months and the amount of glue applied is minimal and negligible in terms of toxicity.

Leakage of the glue during application can cause pulmonary embolism.[24] Losing a glue portion into the deep venous system is a technical failure that has to be avoided by external vein occlusion using the probe. If this is not effectively possible (obesity, compliance e.g.), another treatment should be chosen.

Literature has also described a thrombus protrusion towards the sapheno-femoral junction with a potential risk of central embolization[10] and in patients with "foramen ovale apertum" also ischemia of CNS.[25]

Another potential adverse event is the late reaction to cyanoacrylate as a foreign body, or the formation of granuloma. This reaction has not yet been described in literature in connection with the treatment of varices.

The greatest risk factor of recanalization was described by Chan.[26] Cites a diameter of the treated vein larger than 6.6 mm as a single risk factor. The results achieved with the different types of glues for different techniques are currently comparable.

When comparing cost-effectiveness of cyanoacrylate glue occlusion with high-ligation, ultrasound foam sclerotherapy, radiofrequency ablation, endovascular laser and mechanochemical ablation (MOCA), cyanoacrylate has the highest cost but is no more effective than the other therapies.[27]

Conclusion

Treatment of vein trunk insufficiency with cyanoacrylate is currently the least invasive technique. Available data show that this is a successful and promising method with minimum of adverse events. According to the available results, the success rate is currently limited by the diameter of the treated vein. Only long-term results and larger group of treated patients will give a valid answer to the question of whether this method will stand the test of time compared to other mini-invasive techniques.

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