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J Vasc Surg Venous Lymphat Disord. 2020 Mar;8(2):287-296.

https://doi.org/10.1016/j.jvsv.2019.09.010

SYSTEMATIC REVIEW AND META-ANALYSIS OF ENDOVENOUS CYANOACRYLATE ADHESIVE ABLATION FOR INCOMPETENT SAPHENOUS VEINS

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Keywords: cyanoacrylate ablation; non-tumescent endovenous ablation; varicose veins; great saphenous; meta-analysis

ABSTRACT

*Objective***:** To assess the effectiveness, safety and quality of care afforded by cyanoacrylate ablation (CA) versus existing options in treating great saphenous vein (GSV) incompetence.

*Methods***:** We conducted a systematic review, used the GRADE framework, assessed the quality of randomised clinical trials (RCTs) using the Cochrane risk-of-bias tool, and performed a meta-analysis on the available comparative measurements.

Results: Three comparative studies, two RCTs and one observational study, comprising 1,057 participants, were included for effectiveness assessment purposes. The safety assessment also included 10 case series. Available evidence allowed for comparison of CA with radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) but not with other treatments. The comparative effectiveness analysis showed that, while all three treatments reduced disease severity, none was significantly better than any other in terms of effectiveness. In terms of safety, however, CA devices gave rise to fewer adverse events and less severity at 12 months' follow-up than did EVLA or RFA. Other important advantages of CA over EVLA or RFA were linked to quality of care, with patients reporting less pain during intervention with CA than with RFA or EVLA devices, and registering shorter intervention and recovery times. Furthermore, use of tumescent anaesthesia and compression bandages were not necessary, making this technique more comfortable for the patients than endothermal techniques.

Conclusions: As compared to EVLA and RFA, CA treatments yield comparable effectiveness outcomes and lead to less frequent and less mild adverse events, without difference in mayor adverse events. Furthermore, CA devices have advantages in terms of quality-of-care indicators, such as pain during intervention, treatment and recovery times, lower use of anaesthesia, and zero use of compression bandages post-treatment.

1. INTRODUCTION

Chronic venous disease is a common condition among the adult populations of Western countries, with a prevalence ranging from 27% to 69% of the European population (1). Treatment of saphenous incompetence is currently performed by different interventionist alternatives, which include surgical, endothermal and non-thermal ablation therapies. In the last 15 years, two endothermal therapies, namely, endovenous laser ablation (EVLA) and radiofrequency ablation (RFA), were developed as new standard procedures (2). The guidelines of the European Society for Vascular Surgery (3), the American Venous Forum (4) and the UK's National Institute for Health and Care Excellence (5) recommend endovenous thermal treatment as the first-choice therapy for this condition. However, endothermal therapies present side-effects linked to thermal energy, which damage the venous wall and cause pain, skin burns, skin pigmentation, nerve damage, and even the formation of arteriovenous fistula (6, 7). Tumescent anaesthesia is mandatory to prevent thermal damage to surrounding tissues and to avoid causing pain to the patient (8-10).

In an attempt to avoid some of these unwelcome effects, non-thermal, non-tumescent endovenous ablation techniques have recently emerged, including mechanochemical endovenous ablation (MOCA), ultrasound-guided foam sclerotherapy (UGFS) and cyanoacrylate ablation (CA). This study focused on CA (11).

CA consists of delivering cyanoacrylate adhesive to the vein, which induces an inflammatory reaction of the vein wall to the foreign body (12). Currently, there are three commercial systems using CA for the treatment of great saphenous vein (GSV) incompetence, i.e., Venaseal™ (Medtronic, USA), VariClose® (Biolas, Turkey), and Venablok® (Invamed, Turkey). The main differences between devices reside in cyanoacrylate formulation and application techniques: Venaseal® and Venablock® use

n-butyl-2-cyanoacrylate, characterised by a high viscosity, slow polymerisation rate, and soft texture after polymerisation, while VariClose® uses n-butyl-5-cyanoacrylate, which presents a low viscosity, a faster polymerisation rate and hard texture after polymerisation. These treatments rely on different application techniques, with Venaseal® using segmental pullback and VariClose® and Venablock® using continuous pullback.

It is argued that the use of cyanoacrylate is safe and effective for ablation of GSV with additional advantages, such as avoiding the use of tumescent anaesthesia and compression stockings, and reducing the risk of sensory nerve damage (13). To our knowledge, however, as yet no systematic review has established the advantages of CA over the other available options.

A systematic review of CA efficacy was published in 2017 but did not provide a comparative efficacy analysis (14). In addition, additional randomised controlled trials (RCTs) have been published since then (8, 15, 16), suggesting that it is pertinent to perform a systematic review that could ascertain the value of CA.

Accordingly, this study aimed to assess the effectiveness, safety and quality of care provided by CA as compared to existing GSV-incompetence treatment options.

2. METHODOLOGY

We performed a systematic review in accordance with PRISMA guidelines (17), with the methods of the analyses and inclusion criteria being specified in advance and documented in a protocol.

Literature search and eligibility criteria. A search of the PubMed, Embase, Web of Science, Scopus, Cochrane Library and Centre of Reviews and Dissemination databases was made in January 2018 and updated in September 2018. For the identification of

studies, we designed different search strategies tailored to each database, using a combination of MeSH terms and free text. In addition, we conducted a search of grey literature and clinical studies, as well as a manual search to identify additional literature from the references cited in the studies selected.

The selection of relevant studies was based on the Population–Intervention–Comparator–Outcome-Study Design (PICOS) criteria (Table I).

Studies that failed to meet the PICOS criteria or furnish assessable data related to the selected outcome measures were excluded. Similarly, we excluded studies that were duplicated or outdated by subsequent studies by the same institution.

Study selection: Two authors (MC and EG) first screened the titles and abstracts of the identified studies for relevance, and then read the full text to make a final selection of studies that met the inclusion criteria.

Assessment and synthesis of evidence. Methodological quality was assessed using the Cochrane risk-of-bias tool for RCTs (18) and the Canadian Institute of Health Economics (IHE) Quality Appraisal Checklist for case series (19). We used the GRADE methodology to assess the quality of the evidence (20). Data-extraction and assessment of the evidence was carried out by two independent researchers (MC and EG), with any discrepancies being resolved by consensus, and a third reviewer (II) being consulted in case of disagreement.

A meta-analysis of closure, phlebitis and ecchymosis rates of CA versus RFA or EVLA was carried out using a random-effects model with the Mantel-Haenszel method. Since the remaining outcomes were not yielded by homogeneous measurements, this did not allow for a pooled analysis. The χ^2 test and I^2 index were used for the heterogeneity

analysis and the Review Manager 5 (21) computer software programme was used for the meta-analysis.

3. RESULTS

The systematic search of the literature yielded a total of 165 references, 134 of which remained after adjustment for duplicates. Following a review of the titles and abstracts, a further 107 references were discarded for not meeting the inclusion criteria. The full text of the remaining 28 references was examined in detail. Of these, 16 studies were excluded for the following reasons: 4 studies had a follow-up of less than 6 months (22-25); 1 reference was written in Korean (26); 3 were retrospective studies (27-29); and 7 were reviews (11, 14, 25, 30-34).

Finally, 12 references were included in the systematic review (figure 1): 3 of these were comparative and compared CA to RFA or EVLA. No studies were found which compared cyanoacrylate devices to ligation and stripping or other non-endothermal techniques.

The main characteristics of the comparative studies are described below.

VeClose (NCT01807585) was a multicentre, prospective RCT (15, 16, 35, 36). A total of 222 participants were randomised into two arms, one treated with a cyanoacrylate device Venaseal® (108 patients) and the other with a radiofrequency device Covidien Closurefast® (114 patients). This trial included patients at 10 centres in the USA across the period March to September 2013.

The other RCT, which compared CA to RFA and EVLA treatments, was conducted in Turkey by Eroglu and Yasim (8). Endovenous ablation was applied to 525 patients with

GSV or small saphenous vein incompetence between November 2014 and June 2015. The patients were randomised into three arms: 175 received CA treatment with the VariClose Vein Sealing System, 175 received EVLA treatment with the EVLAs Circular-2 (FG Grup, Turkey), and 175 received RFA treatment with the Closurefast catheter (VNUS Medical Technologies, USA).

Bozkurt and Yilmaz's study (37) was an observational cohort study which enrolled 310 participants in two groups, one treated with VariClose and the other with EVLA using an Evlas® circular Fiber Kit.

While the RCTs showed a low risk of bias in terms of selection and blinding of outcome assessment, they nevertheless entailed a high risk of performance bias because the characteristics of the treatment rendered the blinding of participants and personnel impossible (figure 2). Only the VeClose Trial specified that the analysis was performed on an intention-to-treat basis with a Bayesian predictive model, yet it suffered from a conflict of interest in that it was financed by Sapheon Inc. Bozkurt and Yilmaz's study showed a high risk of bias because it was not a randomised controlled trial.

Furthermore, this systematic review included 9 case series, which differed with respect to the type of device analysed, with VariClose® being used in 5 studies (38-42), Venaseal in 3 (2, 13, 43) and Endocryl in one (44). Bellam Premnath et al (44) applied a commonly available CA named Endocryl used off-label application (normally, is used as a topical skin adhesive or for endovascular embolisation of arteriovenous malformations) to the treatment of venous incompetence by means of a modified technique using CA adhesive embolisation.

The mean overall follow-up of patients was 15 months (range 6 to 36 months): three studies had a follow-up of less than 1 year (39, 41, 42), four had a follow-up of 12

months (13, 38, 43, 44), and two studies had a follow-up of 30 and 36 months respectively (2, 40).

The case-series studies displayed a moderate quality, with an average Institute of Health Economics (IHE) score of 12.6 (range 5-16) out of a maximum of 20, and in general provided a proper description of the participants' characteristics, procedure used, and follow-up.

3.1 Effectiveness

Three comparative studies, two RCTs and one observational study, covering 1,057 participants, were included for effectiveness assessment purposes. Their main characteristics are listed in Table II.

3.1.1 Effectiveness of CA vs RFA

The effectiveness of CA vs. RFA was analysed by two RCTs (Table III) (8, 16). Closure rates at 12 months' follow-up for CA devices were 97% (16) and 94.7% (8) vs. 97% (16) and 92.5% (8) for RFA devices. Pooled analysis indicated that there were no significant differences between CA and RFA (Figure 3a). In both studies, there were no significant differences between groups in closure rates at 24 months' follow-up. In the CA group, however, Eroglu and Yasim reported a significant difference between closure rates at 6 and 24 months' follow-up.

The recanalisation-free survival rates reported in the VeClose trial (16) at 12 months were 97% for the CA group and 90.7% for the RFA group, without significant differences. Eroglu and Yasim (8) did not report recanalisation data. At 24 months, the VeClose trial (30) reported non-inferiority for recanalisation-free survival rates in the CA group with respect to the RFA group.

The VeClose study (35) showed an improvement in disease severity in both groups, with a 4-point reduction in venous clinical severity scores (VCSS) for the Venaseal and RFA groups after 6 months' follow-up. A similar outcome was observed by Eroglu and Yasim, with decreases of 4.8 points for CA and 3.9 points for RFA. In both studies (30, 34), improvements in VCSS were maintained at 24 months' follow-up. The same trend was reported in the VeClose study (16) in respect of the impact on quality of life, with an improvement of 8.7 points on the Aberdeen Varicose Vein Questionnaire (AVVQ) for the CA group and 10.3 points for the RFA group at 6 months' follow-up. However, no statistically significant differences were observed between the groups.

3.1.2 Effectiveness of CA vs EVLA

The studies that compared CA and EVLA (table IV) reported closure rates of 95.8% (37) and 94.7% (8) for CA and 92.2% (37) and 94.2% (8) for EVLA. The pooled analysis showed no differences between CA and EVLA (Figure 3b). Bozkurt and Yilmaz (37) reported no statistically significant differences between groups in recanalisation-free survival rates.

Improvement in VCSS was observed in both studies (8, 37), with a reduction of 5.1 and 4.8 points in CA groups and 5 and 4.1 points in EVLA groups. Bozkurt and Yilmaz (37) reported an improvement on the AVVQ scale, with a reduction of 13.5 points in CA groups and 13.9 points in EVLA groups. However, the differences did not prove statistically significant.

3.2 Safety

The results of the RCTs and cohort study showed differences in safety outcomes between CA on the one hand and RFA and EVLA on the other (tables III-IV).

3.2.1 Safety of CA vs RFA

The safety of CA vs. RFA was analysed by two RCTs (8, 16), with the most frequently reported adverse events being phlebitis (inflammation of superficial veins) and ecchymosis, both considered mild adverse effects. Only, one case of serious adverse events, as Deep Vein Thrombosis (DVT) (clot in a deep vein), was observed in RFA group.

Both RCTs reported more ecchymosis events in the RFA than in the CA groups. The VeClose trial (16) reported an ecchymosis rate of 31.5% for CA and 50.9% for RFA, while Eroglu and Yasim (8) reported an ecchymosis rate of 5.4% for CA versus 18.1% for RFA (Table II). The pooled analysis (Figures 3c) showed that CA groups had a lower probability of ecchymosis events than did the RFA group, with RR=0.46 (I^2=71%). However, the analysis indicated a high degree of heterogeneity, due to the fact that the studies showed differences in disease severity among the participants. The VCSS scores in Eroglu and Yasim's study for the CA, RFA and EVLA groups were 7.8, 7.7 and 7.6 respectively (34) as compared to those in the VeClose which reported VCSS scores of 5.5 (33) for CA versus 5.6 for RFA (33).

Phlebitis rates differed between RCTs. In the VeClose trial (16), phlebitis eventswere more common in CA than in RFA treatment (36), with phlebitis rates of 20% for CA versus 15% for RFA (P=0.036). In contrast, Eroglu and Yasim (8) reported more phlebitis events in RFA than in CA treatments, with 12.8% for RFA versus 6.5% for CA. Pooled analysis showed no significant difference in phlebitis events (Figure 3d).

One comparative study (8) reported one case serious adverse events, as deep vein thrombosis (DVT) solely in the RFA group. No significant difference was observed among groups. No pulmonary embolism (PE) event was reported by RCTs in CA or RFA groups.

3.2.2 Safety of CA vs EVLA

Safety of CA vs. EVLA treatments was analysed by one RCT (8) and a cohort study (37). As in the case of CA vs. RFA, the most common adverse events were ecchymosis and phlebitis.

Eroglu and Yasim (8) reported ecchymosis rates of 5.4% for CA and 4.3% for EVLA, while Bozkurt and Yilmaz (37) reported ecchymosis rates of 14.3% for CA and 46.8% for EVLA. Pooled analysis showed no significant difference (Figure 3e).

Phlebitis events were less frequent in CA than in EVLA groups. Eroglu and Yasim (8) reported 6.5% of phlebitis cases in the CA group versus 9.3% in the EVLA group. Bozkurt and Yilmaz's findings were in line with these data, with a phlebitis rate for CA of 4.5% versus 7.7% for EVLA. Pooled analysis showed no significant difference in phlebitis events (Figure 3f).

No case of DVT or PE was reported by comparative studies in the CA or EVLA groups.

Additionally, ten case series were also included for safety assessment. Four case series reported phlebitis, with rates of 4% to 16% (2, 13, 38, 40). Paraesthesia and ecchymosis rates observed in cases series ranged from 0% to 1.8% (39, 41-43). None of the case series reported serious adverse events, such as DVT or PE. In the case of Venaseal®, the catheter was initially positioned at 3 cm of the saphenofemoral junction (SFJ) but this position caused several cases of cyanoacrylate extension into the deep system (2).

Calik (39) and Proebstle (13) reported glue extension in two patients and one patient respectively, which disappeared at 6 and 12 months' follow-up. Chan (43) reported two cases of minimal extension of thrombus to deep vein.

The study undertaken by Bellam (44) detected a posterior tibial vein extension of cyanoacrylate, considered to be as serious as DVT.

Other adverse events reported in the case series were inflammation, wound infection, pigmentation and ulceration. Almeida (2) reported four cases of inflammation in the injection zone. Pigmentation and ulcerations events were only reported by Almeida (2), who observed a hyperpigmentation rate of 2.6% at 24 months, and 3.0% in the case of ulceration. Almeida (2), Chan (43) and Proebstle (13) each reported one case of local infection. No cases of allergic reaction were reported by any of the studies included.

3.3 Quality of Care

Important differences were observed between CA and endothermal devices in terms of quality-of-care outcomes, such as pain felt during the process, treatment time, and time of recovery and return to work.

The RCTs and cohort study included in this analysis used different methods of pain measurement: the VeClose trial (33) rated pain on a numerical scale of 0 to 10; Eroglu and Yasin's study asked patients to describe the sensation of pain felt during the intervention as 0, 1, 2 or 3, where 0 represents 'no pain' and 3 'severe pain'; and Bozkurt and Yilmaz measured pain on a numerical visual analogue scale ranging from 0 to 10 (0, no pain; 10, extreme pain).

3.3.1 Quality of care of CA vs RFA

The RCTs (8, 37) reported that pain during the intervention was significantly lower in the group treated with the CA device than in the RFA group (Table II). The VeClose trial (33) reported mean pain ratings that were similar for the CA and RFA groups during venous access (1.6 for CA versus 2.0 for RFA; P= 0.13) and intraprocedure (2.2 for CA versus 2.4 for RFA; P=0.11). On the other hand, Eroglu and Yasim reported a significant difference in pain sensation between CA and RFA patients. Whereas 61.3% of CA patients reported experiencing no pain, not a single RFA patient reported such absence of pain; in addition, mild pain was felt by 31% of CA as opposed to 50.3% of RFA patients, moderate pain was felt by only 7.7% of CA as opposed to 35.6% of RFA patients, and severe pain was felt by no CA patients as opposed to 14.1% of RFA patients.

The treatment time reported displayed significant statistically differences between CA and RFA groups. The CA group registered a procedure time of 24 minutes in the VeClose trial versus 19 minutes for the RFA group (33), and 15.3 minutes in Eroglu and Yasim's study (34) versus 27.3 minutes for the RFA group.

Time of recovery and return to work with CA devices was one day (8, 40, 43). Eroglu and Yasim (8) reported significant differences between the CA group, in which 95.8% of those treated returned to work within one day, and the RFA group in which the equivalent percentage was 50.3%.

Although the CA procedure does not require the use of compression bandages, some studies nonetheless reported such use: the VeClose trial (33) reported the use of compression bandages in the CA and RFA groups for a full 3 days and 4 additional days during waking hours (33). However these authors of these study describe that

compression stoking were used after the procedure in CA and RFA groups to reduce bias, as instructions for use for RFA require compression (36). Previous CA trials did not require the use of postprocedure compression for subjects treated with CA (13, 33)."

In contrast to other techniques, such as EVLA or RFA, treatment with CA does not require tumescent anaesthesia. However, lidocaine is applied to reduce the pain from injection. The VeClose reported a non-significant difference in the amount of lidocaine used in both groups (1.6 ml in CA and 2.7 ml in RFA) (16).

3.3.2 Quality of care of CA vs EVLA

Difference in pain measures were observed in evidence between the CA and EVLA groups. Eroglu and Yasim observed that whereas 61.3% of CA patients reported feeling no pain, not a single EVLA patient reported such absence of pain; furthermore, mild pain was felt by 31% of CA versus 47.5% of EVLA patients, moderate pain was felt by 7.7% of CA versus 43.9% of EVLA patients, and lastly, severe pain was felt by no CA versus 8.6% of EVLA patients. According to Bozkurt and Yilmaz's study, mean pain during the intervention was 3.1 ± 1.6 for the CA versus 6.5 ± 2.3 for the EVLA group (P <0.001).

CA and EVLA techniques displayed differences in terms of duration of procedure. Bozkurt and Yilmaz (35) reported a duration of 15 minutes for CA versus 35 minutes for EVLA. These findings were similar to those observed by Eroglu and Yasim (34), who reported a duration of 15.3 minutes for CA versus 33.2 minutes for EVLA.

Eroglu and Yasim (8) reported significant differences between the CA and EVLA groups in terms of time of return to work: 95.8% of patients treated with CA returned to work within one day as compared to 75.5% of patients treated with EVLA.

Differences were also observed in the use of compression bandages, i.e., in Bozkurt and Yilmaz's study, these were not prescribed for patients treated with CA but were prescribed for those treated with EVLA (37).

The case series included in this study reported pain measures and use of compression bandages. Four cases-series studies reported pain during the intervention as being rated from 6 to 9 (13, 39, 40, 43). With regard to compression bandages, their use of these stockings was indicated in four case-series studies as follows: Calik (39) for 1 day; Bellam (44) and Chan (43) for 1 month; and Proebstle (13) in some specific cases.

4. Discussion

The objective of this systematic review was to assess the effectiveness, safety and quality of care ensured by CA devices in comparison with existing GSV-incompetence treatment options. Although the authors performed an extensive literature search, only 3 comparative studies for effectiveness assessment were found. The VeClose trial compared CA and RFA, the trial conducted by Eroglu and Yasmin compared CA to EVLA and RFA, and lastly, Bozkurt and Yilmaz compared CA to EVLA. In addition, 10 cases series were included in the safety assessment.

The studies analysed were characterised by their small sample size and short-term follow-up (6 to 12 months). Only four studies, two RCTs (8, 15) and two case series (2, 40), conducted a follow-up for 24 months. The methodological quality of the studies was moderate to low.

The most frequently used CA devices were Venaseal® and VariClose®. The most important differences between the two reside in the type of cyanoacrylate and

application technique used, especially in terms of positioning the catheter tip 3-5 cm distal from the SFJ. Both systems obtained similar outcomes in terms of effectiveness and safety.

The effectiveness analysis showed that occlusion rates, recanalisation-free survival rates and VCSS scores were similar for CA and endothermal techniques. Compared to RFA and EVLA, CA occlusion and recanalisation rates were statistically non-inferior. These findings were maintained at 24 months' follow-up (8, 15).

Treatment with CA improved the symptoms, with a fall in VCSS and AVVQ scale scores post-intervention. Nonetheless, no statistically significant differences were observed with regard to RFA or EVLA treatment. The studies analysed displayed differences in mean VCSS and AVQQ scores due to differences in disease severity among the participants included.

In contrast, the safety analysis detected significant differences. The main adverse events observed in CA treatments were phlebitis and ecchymosis. Statistically significant differences in ecchymosis frequency were observed, with a lower frequency in the case of CA than in RFA. None of the studies analysed reported serious adverse events, such as DVT or PE related to CA. Phlebitis events in CA procedures may be related to an excess amount of cyanoacrylate in a vein segment, which can create a thrombus-like formation after reaction with blood (41). Calik's study (39) suggests that incidence of adverse events, such as thrombophlebitis and post-intervention pain, is related to high scores on the pre-operative CEAP (Comprehensive Classification System for Chronic Venous Disorders) and VCSS scales, as well as large GSV diameters or aneurysms in

large vein segments. Phlebitis and thrombophlebitis events could be reduced by applying manual pressure in the right place and using a continuous delivery method and low viscosity cyanoacrylates (29, 39).

Where the clearest advantages were in evidence, however, was in quality of care. In the case of pain during intervention, two studies (8, 16, 37) reported significant differences between groups, with a lower pain rate, as well as lower time of intervention and lower time of return to work in the case of patients treated with CA devices. Another advantage of cyanoacrylate systems is that, unlike endothermal techniques or surgery, they do not require the use of tumescent anaesthesia and thus avoid any risk of nerve injury. Furthermore, there is no need for compression bandages post-intervention with CA, making patient recovery more comfortable.

Our study has several limitations, in that no high-quality evidence was found, and the majority of the studies located were small-sized with short follow-up times. Due to the limited scientific evidence of the effectiveness and safety of CA systems, most clinical societies have not included recommendations about their use or they are not mentioned in clinical guidelines for the treatment of chronic venous insufficiency. It should be noted, however, that in 2017 the American Venous Forum (45) recommended the use of CA in the following cases: for veins having a diameter of less than 12 mm, with a strong grade of recommendation and a degree of evidence B; and for treatment of GSV incompetence, with a weak recommendation and a CEAP classification of C2 to C6.

5. CONCLUSIONS

The effectiveness of the CA procedure is comparable to that of endothermal techniques in terms of closure rates, recanalization-free survival rates and VCSS scores. The main differences lie in the areas of safety and quality of care, with CA devices registering lower rates of adverse events with no difference in major adverse events, lower pain rates, less use of anaesthesia and compression bandages, and shorter intervention and recovery times, thus making this technique more comfortable for the patient than endothermal techniques.

There is little scientific evidence on the effectiveness and safety of the treatment of chronic venous insufficiency with CA devices. Moreover, the evidence that does exist is of low-to-moderate quality.

RCTs targeting homogeneous groups of patients and using explicit selection criteria, a sufficient sample size and longer follow-up, would be of great interest in terms of building up the necessary body of scientific evidence on the use of cyanoacrylates.

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1