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Cyanoacrylate Adhesives Used for Topical Hemostasis – A Systematic Review

Alexandru Ilie-Ene[1,2], Victor Eșanu[1,2], Vlad Făgărășan[1,2]*, Victor Petru Toșa[3], George-Călin Dindelegan[1,2]

[1]Iuliu Hațieganu University of Medicine and Pharmacy, Faculty of Medicine, 6th Department, 1st Surgery Clinic, Cluj-Napoca, Romania
[2]Cluj County Emergency Clinical Hospital, 1st General Surgery Clinic, Cluj-Napoca, Romania
[3]Technical University of Cluj-Napoca, Materials Engineering Department, Cluj-Napoca, Romania

***Corresponding author:**
Vlad Făgărășan, M.D.
Plopilor Street, No. 68, Ap. 67
Cluj-Napoca, Romania, 400383
E-mail: vlad.fagarasan@yahoo.com
ORCID no:
0000-0003-1893-1930 (Alexandru Ilie-Ene)
0000-0001-8631-0218 (Victor Eșanu)
0000-0001-8425-8399 (Vlad Făgărășan)
0000-0002-7879-4563 (Victor Toșa)
0000-0003-1485-6654 (George-Călin Dindelegan)

Abbreviations:
CA: cyanoacrylate adhesives;
PO: postoperative;
VAS: Visual Analog Scale.

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Rezumat

Adezivi pe bază de cianoacrilat folosiți pentru obținerea hemostazei topice – o sinteză sistematică

Introducere: În această sinteză sistematică au fost explorate proprietățile hemostatice topice ale adezivilor pe bază de cianoacrilat (CA).
Metodă: Patru baze de date științifice majore (Embase, Scopus, PubMed şi Web of Science) au fost interogate, regăsind sinteze sistematice cu sau fără meta-analiză, trialuri clinice, studii experimentale şi rapoarte de caz care au prezentat date privind hemostaza topică şi CA. Au fost colectate articole scrise în limba engleză, publicate în ultimii 10 ani. Ultima căutare a fost efectuată in data de 1 august 2023. Riscul de părtinire în studiile incluse a fost evaluat folosind instrumente (validate ştiințific) specifice pentru tipul studiului analizat.
Rezultate: A fost realizată o sumarizare a tuturor studiilor incluse axată pe informațiile relevante, iar rezultatele studiilor au fost sintetizate şi comparate. Un total de 42 de studii au fost incluse în sinteză (14 sinteze sistematice şi meta-analize, 11 trialuri clinice, 9 studii experimentale şi 8 rapoarte de caz). CA a prezentat calități hemostatice topice importante, comparabile cu alte materiale hemostatice performante. Deşi majoritatea studiilor incluse au concluzionat că CA sunt agenți hemostatici topici puternici, nivelul ridicat de eterogenitate dintre studii ne-a împiedicat să efectuăm o meta-analiză.
Concluzie: Rezultatele acestei sinteze sistematice demonstrează valoarea compuşilor pe bază de CA care reprezintă o direcție de cercetare importantă spre materialul hemostatic perfect.

Cuvinte cheie: hemostază locală, cianoacrilat, adeziv pentru țesut, material hemostatic

Abstract

Introduction: In this systematic review the topical hemostatic properties of Cyanoacrylate Adhesives (CA) have been studied.

Material and Method: Four major scientific databases (Embase, Scopus, PubMed, and Web of Science) were inquired, retrieving reviews and meta-analysis studies, clinical trials, experimental studies, and case reports that presented data regarding topical hemostasis and CA. English written articles, published in the last 10 years were collected. The last search was performed on the 1st of August 2023. Risk of bias in the included studies was assessed using study-design specific, evidence-based tools.

Results: A summary focused on relevant information of all included studies was drafted and the results of the studies have been synthetized and compared. A total of 42 studies have been included in the review (14 reviews and meta-analysis, 11 clinical trials, 9 experimental studies and 8 case reports). CA exhibited important topical hemostatic capabilities, comparable with other performant hemostatic materials. Although most included studies concluded that CA were potent topical hemostatic agents, the high level of heterogeneity among the studies prevented us from performing a meta-analysis.

Conclusion: The results of this review show that CA-based compounds represent an important line of research towards the perfect hemostatic material.

Key words: topical hemostasis, cyanoacrylate, tissue adhesive, hemostatic material

Introduction

Rationale

Achieving efficient hemostasis can be challenging in trauma setting or after resections carried out in parenchymal organs such as the spleen, liver or kidney(1-4). In that respect a plethora of hemostatic materials have been developed to accommodate this constant need (5). One group of such materials is represented by tissue adhesives which also aid in hemostasis (6). Cyanoacrylate adhesives (CA) are synthetic, absorbable chemical compounds that have been approved for intracorporeal use (7,8). The cyanoacrylate monomer is a low-viscosity liquid that polymerize spontaneously in the presence of a weak basis such as water. Setting takes place within a few seconds after exposure to atmospheric humidity. CA are mainly used for skin closure (9), hernia mesh fixation (10), endoscopic obliteration of esophageal or gastric varices (11), or as arterial embolization material (12). Experimental studies have tested the limits of CA used in vascular (13) or intestinal anastomoses (14). More importantly for this review, this material exhibited hemostatic proprieties (15). There is a considerable number of review articles that studied hemostatic and wound care materials that included CA. To our knowledge, at the time of this review, there has not been one that focuses strictly on the topical application of CA in order to achieve hemostasis. Given the fact that superficial hemostasis is still a relevant research topic, a systematic review of the latest developments of cyanoacrylate-based compounds used for achieving topical hemostasis was carried out.

Objectives: To evaluate, summarize, and compare studies that researched the topical hemostatic capabilities of CA, or of other hemostatic materials that were compared with CA. Also, we aimed to synthesize an overall conclusion in this regard.

Materials and Methods

This review followed the statement of the Preferred Reporting of Systematic Reviews and Meta-analysis checklist (PRISMA 2020) and addressed a clearly focused issue, adopting the population, intervention, comparison, and outcome (PICO) method (16).

Eligibility Criteria

Population

We included articles with human or animal subjects, that reported on the topical hemostatic proprieties of CA, either by main objective of the research or secondary result. The following study types were reviewed: reviews and meta-analyses, clinical trials, case reports and experimental.

Intervention

We considered all studies that used solely CA to achieve topical hemostasis and studies that compared other topical hemostatic materials with CA. We excluded all studies where CA were used for sclerotherapy (endoscopic injection for esophageal or gastric varices), for embolization (interventional radiology procedures) or just for their adhesive proprieties.

Comparison

Cyanoacrylate-based compounds were compared with digital pressure, cauterization, and other materials, in respect to their topical hemostatic proprieties.

Outcomes

To be included in the review, the studies had to report on the topical hemostatic proprieties of cyanoacrylate-based materials. English-written studies, from the last 10 years were considered eligible for review (July 2013 to July 2023).

Search Strategy

The following databases were used: Embase, PubMed, Scopus and Web of Science. The last inquiry was done on the 1st of August 2023.

The following keywords were included in the search strategy: ‘cyanoacrylate’, ‘topical’, ‘topic’, ‘hemostasis’, ‘haemostasis’, ‘hemostatic’, ‘haemostatic’. The results were refined by excluding studies that presented the following terms: ‘esophageal varices’, ‘gastric varices’, ‘injection’ and ‘embolisation’ or ‘embolization’. The search was aimed at the Title and Abstract, to improve the accuracy of the results yielded. Filters for language and date of publication were applied, selecting all English-written articles published from the last ten years. The following search lines were generated and used:

1. Embase: (('hemostasis'/exp OR 'hemostasis') AND 'topical' OR 'topic') AND ('cyanoacrylate'/exp OR 'cyanoacrylate') NOT ('stomach varices'/exp OR 'stomach varices') NOT ('esophageal varices'/exp OR 'esophagus varices') NOT ('injection'/exp OR 'injection') NOT ('embolization'/exp OR 'embolization') NOT ('embolisation'/exp OR 'embolisation') AND [2013-2023]/py AND [english]/lim.
2. PubMed: ((((((("hemostasis"[Title/Abstract] OR "haemostasis" [Title/ Abstract] OR "hemostatic"[Title/Abstract] OR "haemostatic"[Title/Abstract] OR "topical"[Title/Abstract] OR "topic"[Title/Abstract]) AND "cyanoacrylate"[Title/Abstract]) NOT "esophageal varices"[Title/Abstract]) NOT "gastric varices"[Title/Abstract]) NOT "injection"[Title/Abstract]) NOT "embolisation"[Title/Abstract]) NOT "embolization"[Title/Abstract]) AND ((english[Filter]) AND (2013:2023[pdat])).
3. Scopus: TITLE-ABS (hemostasis) OR TITLE-ABS (haemostasis) OR TITLE-ABS (hemostatic) OR TITLE-ABS (haemostatic) OR TITLE-ABS (topical) OR TITLE-ABS (topic) AND TITLE-ABS (cyanoacrylate) AND NOT esophageal AND varices AND NOT gastric AND varices AND NOT injection AND NOT embolisation AND NOT embolization AND (LIMIT-TO (PUBYEAR , 2013) OR

LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2018) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2022) OR LIMIT-TO (PUBYEAR, 2023)) AND (LIMIT-TO (LANGUAGE , "English")).

4. Web of Science: ((((((((((TS=(hemostasis)) OR TS=(haemostasis)) OR TS=(hemostatic)) OR TS=(haemostatic)) OR TS=(topical)) OR TS=(topic)) AND TS=(cyanoacrylate)) NOT TS=(esophageal varices)) NOT TS=(gastric varices)) NOT TS=(injection)) NOT TS=(embolisation)) NOT TS=(embolization) AND PY=2013-2023.

Study Selection and Data Collection Process

Two researchers (AI-E and VE) independently screened the 146 scientific articles yielded by the refined search. This task was done using a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (17). Title and abstract screening was done in the first phase. Any conflicts between the two researchers were resolved by discussion and consulting the third researcher (G-CD). The resulting 135 articles were included in the second phase for full-text screening by the same two researchers. Disagreements between screeners were resolved in the same fashion. Finally, 42 articles were considered eligible and were included for analysis.

Data extraction from each study that was included in the review was done by one researcher (AI-E). The resulted information was double checked by a second researcher (VE) prior to it being included in the analysis.

The outcome for which data was sought is the achievement of hemostasis in active bleeding wounds by using CA-based compounds. This was considered a critical outcome domain. A variety of lesions in multiple tissue types (skin, mucosa, organ parenchyma) and numerous experimental models was anticipated. Given the abundancy of CA on the market, a multitude of cyanoacrylate homologs were expected to be encountered, and their chemical composition was recorded. The means of applying CA to the wound was also noted. In comparing research protocols, the standard to which CA were reported was registered. For the clinical trials and experimental studies, the number of subjects included and the statistical significance of the tests applied were considered to be relevant. Another important domain of interest was the means of measuring the hemostasis efficiency for which we had in prospect all types of quantifications.

The following data items were recorded:

- The report: authors, date of publication.
- The research design and features: article type; period from which the data was collected in the included studies.
- The materials: CA and other materials used for hemostasis.
- The intervention: technique or means of CA application.
- The results: time elapsed until hemostasis was achieved; different scales for quantifying bleeding and hemostasis.

Study Risk of Bias Assessment

Two researchers (A-IE and VE) assessed the risk of bias in the included studies using study-design specific tools. The second version of the Cochrane risk-of-bias tool was used for the randomized trials. This tool covers potential bias problems arising from the randomization process, deviations from intended interventions, missing outcome data, measurements of the outcome and the selection of the reported result (18). For the systematic reviews, the University of Bristol's ROBIS tool was used. It covers the following domains from which bias can be introduce into a systematic review: eligibility of included studies, identification and selection of studies, data collection and study appraisal, the synthesis and results (19). Any conflicts between the two researchers were resolved by discussion or consulting a third researcher (G-CD).

Effect Measures

For an objective characterization of the hemostatic proprieties of CA, the mean differences (with standard deviations) of the time needed to achieve hemostasis when comparing CA with a control or another hemostatic material was preferred. The results were defined as either 'seconds' or 'minutes', depending on the manner in which they were reported in the source paper. The duration of postoperative (PO) hospitalization (measured in days) and blood loss (in milliliters or grams) was found to be relevant and the results were presented as mean differences, alongside standard deviations or range, as reported by the authors. In several studies, various scales used to assess bleeding were encountered. To facilitate the interpretation of each included result we presented the p-value of the test that was used.

Synthesis Methods

Due to the complexity of the interventions described in the clinical trials, the included studies were categorized according to six parameters: 1. What the study design was and the period of data collection; 2. What homolog of cyanoacrylate was used; 3. On what kind of lesion the study was performed; 4. What the study groups were; 5. How many subjects were included in said groups; 6. What the results and their statistical significance were.

Based on the above dimensions, we created the following categories:

1. Article type and period of data collection.
2. Type of CA used.
3. Lesion type investigated.
4. Study vs control.
5. Number of subjects in each group.
6. Results and the p-value of the test used.

The same methodology was applied for the included experimental studies, and the following categorizing dimensions were utilized: a. What the experimental model used was; b. What homolog of cyanoacrylate was used; c. What technique was employed in applying the CA; d. What the study groups were; e. How many subjects were included in said groups; f. What the results and their statistical significance were.

The resulted categories were:

a. Experimental model used.
b. Type of CA used.
c. Application technique.
d. Study vs control.
e. Number of subjects in each group
f. Results and the p-value of the test used.

A meta-analysis of the included studies could not be undertaken due to the high level of heterogeneity of interventions, types of CA used, study designs and outcome measures.

Results

Study selection

A total of 355 records were retrieved from the 4 inquired databases. After duplicate-removal, we screened 146 records, out of which 5 were excluded due to inappropriate study design. Six of the screened articles could not be retrieved due to web-page malfunction. In the full-text review phase, 46 records were excluded because the CA were used as embolic hemostatic material (not topically), 44 studies were excluded due to the lack of information provided on the hemostatic proprieties of CA, and 3 studies had their full-text written in other languages than English (one was in Czech, and the other two in Mandarin). Finally, 42 articles that met the eligibility criteria were included in the study.

Fig. 1 displays a flow diagram of the study selection algorithm.

Study Characteristics

The 42 articles included in the review were of the following type: 14 reviews (with or without meta-analysis), 11 clinical trials, 9 experimental, and 8 case reports. An overall low risk of bias in the included studies was observed. In the following paragraphs a summarization of the included papers will be presented, emphasizing the topical hemostatic aspect of CA.

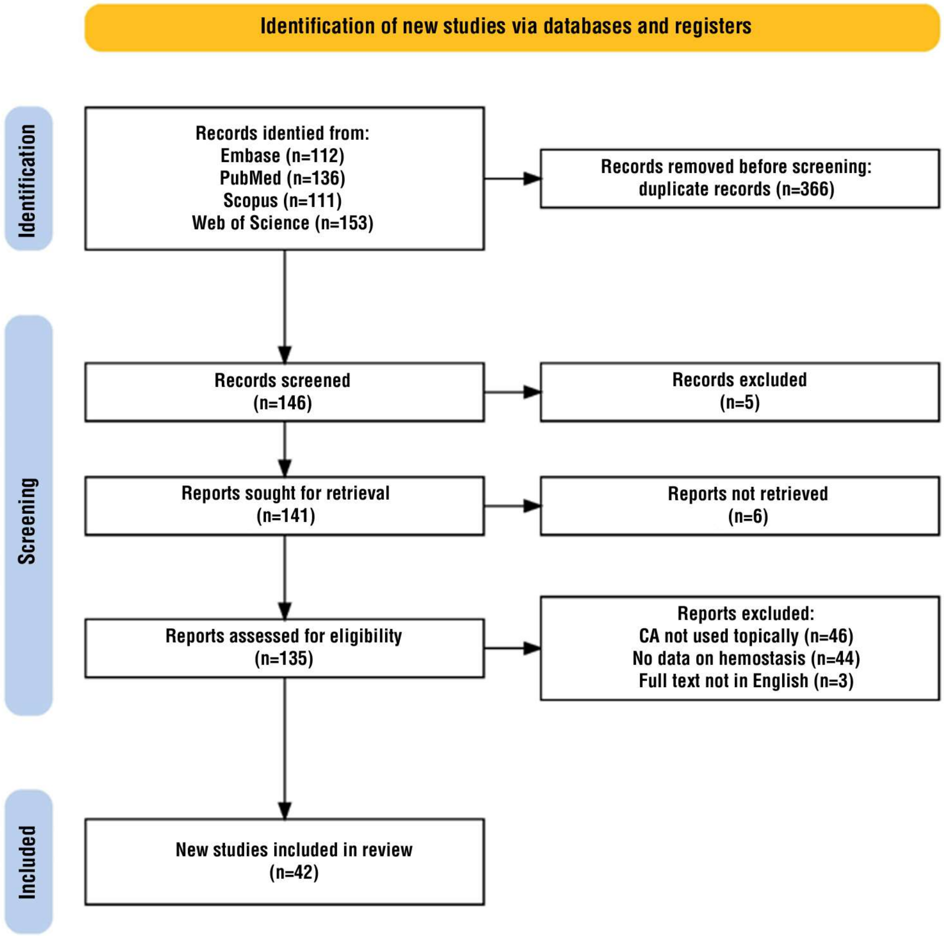

Figure 1. PRISMA 2020 flow diagram exhibiting the study selection process.

Article type – reviews ± meta-analysis (n=14)

In his review of hemostatic polymers, di Lena argues that CA polymerize rapidly in the presence of blood resulting in a compound that halts bleeding due to the electron-deficit nature of the carbon bonds in their composition (20).

Scognamiglio et al. underlines the importance of CA in preventing bleeding complications of high risk anastomotic connections(21). Another review reported an immediate control of bleeding using topical CA in more than half (54.5%) of vascular surgery patients as opposed to the control group (10%, $p < 0.001$) alongside a mean time of 23.2 seconds until hemostasis was achieved after the removal of vascular clamps (22). The use of CA as adjunctive hemostasis material for reconstructive vascular surgery was addressed in a paper focused on the clinical applications of bioadhesives (23).

Marin et al. performed a systematic review and meta-analysis regarding the use of CA for circumcision among pediatric patients. They concluded that operative time, hematoma formation and postoperative bleeding were all reduced when CA were used alone or in conjunction with sutures (24).

In a review of hemostatic materials used for trauma in emergency setting, CA was among the materials best suited for irregular, deep and bleeding wounds, notably noncompressible wounds (such as internal organs or bones)(25). The use of CA for halting superficial bleeding of ruptured hepatic carcinoma, peptic ulcer surgery and nonvariceal upper gastrointestinal hemorrhage was noted in one of the reviews (26).

The topical use of CA in free gingival graft surgical wounds (donor and recipient areas) was investigated in several reviews and the results revealed a shorter bleeding time in the first week after surgery. The mechanism of hemostasis was presumed to be the forming of a macrofilm by the cyanoacrylate ester that blocks and slows the flow of blood thus providing a surface area for the coagulation cascade to take place (27–29). In a couple of meta-analyses, the effectiveness of local hemostatic materials used in anticoagulated dental patients was assessed. The authors conclude that CA was better than placebo at reducing the number of bleeding events (30,31). These results were confirmed by another review that found the use of CA beneficial in anticoagulated patients that underwent dental surgery; the CA was proven to form a mechanical barrier at the surgical site, thus providing instant hemostasis without other complications(32).

Electrospinning of CA was noted in another review, this technique makes use of a hand-held device that sprays a nonwoven mesh of adhesive in-situ that achieves rapid hemostasis (33).

Article type – clinical trials (n=11)

In a prospective randomized study, Zhang et al. showed that CA are effective in preventing delayed bleeding after endoscopic submucosal dissection of precancerous lesions or early-stage gastro-intestinal cancer. The incidence of postoperative bleeding was significantly lower in the group where CA was used on top of the usual hemostatic procedures (34). When used for hemostasis after endoscopic mucosal resection of large colorectal polyps, diathermy and CA showed no early or delayed bleeding compared with diathermy alone (35).

Kim et al. assessed the application of CA to the dissection bed after total thyroidectomy with lateral neck dissection, to achieve hemostasis and prevent chyle leakage. Median volume of peak 24-hour drainage, median volume of total drainage and total duration of postoperative hospital stay were all significantly smaller in patients treated with CA (36).

A randomized controlled study investigated the use of CA for surgical wounds closure after mandibular third molar excision for mesio-angularly impacted mandibular third molar. Immediate PO bleeding was statistically significantly lower on PO day 1 and with no difference in the following days (37). Tavelli and al. used CA by itself or in combination with other hemostatic materials in dressing the donor site of the gingival graft, achieving complete hemostasis regardless of the method (38). In some prospective randomized controlled studies on alevoloplasty wounds Suthar et al. and Narsingyani et al. independently concluded that using CA for hemostasis was faster compared with sutures: mean difference of 2.26 minutes, $p<0.001$ (39) and mean difference of 132.92±4.97 seconds, $p<0.001$ respectively (40). In one prospective randomized controlled study the authors did not find any significant difference in PO bleeding of free epithelialized mucosal grafts (FEGs) harvesting wounds between the control (collagen plug with sutures) and study groups (one of which was collagen plug with cyanoacrylate) using a Visual Analog Scale (VAS)(41). In another study of wound closure following surgical removal of an impacted mandibular third molar, CA were compared with sutures; homeostasis was assessed using a modified VAS of perceived bleeding, with no statistically significant differences on PO days 1 and 3 (42).

A Turkish scientific team described the use of CA on the resection area after open partial nephrectomy for localized tumors (43). In another study done on clampless and sutureless laparoscopic partial nephrectomy for localized tumors, CA was applied to the resection area in order to complete hemostasis when repeated monopolar coagulation was proven inefficient (44).

Article type – experimental studies (n=9)

In an innovative technique described as airflow-directed in situ electrospinning Jiang et al. managed to form a nonwoven web of CA that is deposited onto the wound site. The ultrathin polymeric fibers act as a strong barrier that stop superficial bleeding in seconds (45). A refined version of in situ electrospinning was described, using an electric field-modifier for more precise and controlled deposition of CA fibers. The resulted hemostasis was noted to be superior to the airflow-assisted control group (46). As a follow-up study, the same research team published an experimental paper on the same portable handheld auxiliary electrode used for precise, in situ application of CA using a partial nephrectomy rat experimental model. They showed a faster hemostasis than conventional spraying of CA and more precise than airflow assisted (47). In a cardiac (left ventricle wall) perforation experimental model in minipigs, rabbits and rats Gao et al. demonstrated the hemostatic capability of a novel hemostatic plug (polylactic acid + gelatin + absorbable hemostatic particles) that was secured in place by a film of in situ electrospun CA. This technique proved to be superior to medical gauze in achieving and maintaining hemostasis under a high level of pressure (48).

When compared with other adhesives (i.e., bio-based polyurethane) for their topical hemostatic properties in a vascular injury experimental model, CA exhibited similar hemostatic capabilities and a shorter drying time (49). Used in another vascular injury model for completing hemostasis after suture or partial suture of an 10mm aortic arteriotomy CA showed hemostatic capabilities. The combination of adhesive and suture performed better than suture alone regarding time needed to achieve hemostasis and survival rate of the subjects (50).

An elastic variation of CA was designed in Spain that proved superior in stopping bleeding significantly faster than other potent hemostatic material (i.e., human fibrinogen + human thrombin sponge or oxidized cellulose sponge). The experimental study was performed on a renal punch-injury model in rats. The wound healing pattern was similar across all groups (15). In a partial nephrectomy experimental model in rats, CA performed better than bovine-derived gelatin matrix + thrombin, chitosan granular dressing and suture respectively. It achieved faster hemostasis and a shorter warm ischemia time of the kidney (51).

In an experimental study that assessed the use of CA for intravenous catheter securement, the adhesive exhibited superior hemostatic proprieties in both in vitro (on citrated whole blood, platelet-poor plasma, non-anticoagulated whole blood) and in vivo experiments. The authors concluded that CA provide a potent mechanical hemostatic effect and had an activated clotting time 12 times quicker than thromboplastin when used on anticoagulated whole blood (52).

Article type – case reports (n=8)

CA have been shown to aid in achieving hemostasis in difficult to control bleeding fingertip pad dermal avulsion injuries. Using a technique that involves placing a tourniquet proximal to the injured fingertip in order to obtain a dry enough surface for the cyanoacrylate to adhere to, optimal hemostasis and wound healing was reported (53,54). Also, in emergency setting CA were used with success in providing better hemostasis than usual wound dressing for class I and II skin tears (55). In one case report of a forehead pedicle flap used to cover a post-excision cutaneous defect of the cheek, the authors used CA near the pedicle of the flap (the exposed areas that constitute the bridge) and thus achieved less bleeding and exudation postoperatively (56). The hemostatic proprieties of CA were observed also in a variety of intraoral wounds (57,58). CA proved effective as a hemostatic agent in the treatment of a large venous malformation of the mandible (59). In a case series of persistent gastro-intestinal bleeding lesions, CA was used with success after conventional endoscopic therapies had failed (60).

Table 1. This table displays for each included clinical trial: the citation, study design, type of CA used, type of bleeding lesion studied, hemostasis material used to compare the CA, number of subjects, hemostasis-related results, statistical significance of the tests used.

Article	Article Type and period	Type of CA used	Lesion type	Study vs control	No. of subjects	Results	P-value
Zhang et al. (2013)	prospective randomized 01.2009 to 06.2012	n-butyl-2-cyanoacrylate (Compont®, Beijing, China)	Area after endoscopic submucosal dissection	Diathermy + CA vs coagulation/clips alone	89 vs. 82	1. Incidence of delayed bleeding: 0.00% vs 4.88% 2. PO hospitalization (days): 8.89 ± 2.33 vs 9.90 ± 3.30	1. $p < .035$ 2. $p < .021$
Kim et al. (2016)	retrospective randomized 03.2011 to 10.2012	n-butyl-2-cyanoacrylate (Histoacryl®; Boston Scientific, Natick, MA, USA)	Dissection area after total thyroidectomy with unilateral neck dissection	CA vs no CA applied	84 vs. 79	1. PO hospitalization (days): 4.3 ± 1.8 vs 5.7 ± 3.0 2. median volume of peak 24-hour drainage: 108(50-195) mL, vs 119(53-1110) mL; 3. median volume of total drainage: 270(97-931) mL, vs 328(113-2636) mL	1. $p < .001$ 2. $p < .023$ 3. $p < .001$
Oladega et al. (2018)	prospective randomized controlled	IsoAmyl 2-Cyanoacrylate (Amcrylate®; Concord Drugs Ltd., Hayathnagar, India)	surgical wound after mandibular third molar excision	CA vs Silk suture	60 vs 60	1. patients with PO day I bleeding: 30% vs 56.6% 2. patients with PO day II bleeding: 16.6% vs 25% 3. patients with PO day III bleeding: 5% vs 10%	1. $p < .02$ 2. $p = .38$ 3. $p = .49$
Tavelli et al. (2018)	retrospective randomized controlled 01.2016 to 12.2019	n-butyl cyanoacrylate + 2-octyl cyanoacrylate (PeriAcryl®90HV, GluStitch Inc.,Delta, Canada)	the donor site of the gingival graft	suture vs CA vs hemostatic sponge vs periodontal dressing vs CA + hemostatic sponge	10 vs 10 vs 10 vs 10 vs 10	hemostasis was achieved regardless of hemostatic method	n/a
Kayigil et al. (2019)	retrospective controlled 05.2005 to 03.2012	n-butyl-2-cyanoacrylate + methacryloxysulfolane (Glubran 2®, GEMsrl Via dei Campi 2, Viareggio, Italy)	resection area after open partial nephrectomy for localized tumor	Classical hemostasis + CA in low-risk group vs high-risk group	30 vs 20	1. Average blood loss (mL): 200±133.9 vs 315±87.5) 2. Average operation time (minutes): 178.5±22.3 vs. 212±20.15 3. PO hospitalization (days): 3.86±1.25 vs 4.7±1.65	1. $p < .001$ 2. $p < .001$ 3. $p < .034$
Zhang et al. (2019)	retrospective 02.2015 to 10. 2018	n-butyl-2-cyanoacrylate (Compont®, Beijing, China)	resection area after laparoscopic partial nephrectomy for localized tumor	Diathermy + CA vs Diathermy	98 vs 44	1. Operative time (min): 120 (50–200) vs 100 (40–180) 2. Mean estimated blood loss (ml): 100 (10–500) vs 50 (10–300)	1. $p < .016$ 2. $p < .101$
Suthar et al. (2020)	prospective randomized controlled 01.2016 to 06.2017	n-butyl-2-cyanoacrylate (Endocryl®, Samarth Life Sciences Pvt Ltd, Mumbai, India)	alveoloplasty wounds	CA vs 3-0 Silk sutures	20 vs 20	Time until hemostasis (min): 0.442±0.233 vs 2.707±1.117	1. $p < .001$
Martines et al. (2020)	prospective randomized 04.2017 to 03.2018	n-butyl-2-cyanoacrylate + methacryloxysulfolane (Glubran 2®, GEMsrl Via dei Campi 2, Viareggio, Italy)	Area after endoscopic mucosal resection	Diathermy + CA vs Diathermy	15 vs 15	Delayed bleeding: 0% vs 13.3%	1. $p = .48$
Narsingyani et al. (2023)	prospective randomized controlled 09.2019 to 06.2022	n butyl 2 cyanoacrylate	alveoloplasty wounds	CA vs 3-0 Silk sutures	25 vs 25	Time until hemostasis (seconds): 130.76±12.23 vs 263.68±21.65	$p < .001$

Table 1. This table displays for each included clinical trial: the citation, study design, type of CA used, type of bleeding lesion studied, hemostasis material used to compare the CA, number of subjects, hemostasis-related results, statistical significance of the tests used (continue)

Article	Article Type and period	Type of CA used	Lesion type	Study vs control	No. of subjects	Results	P-value
Basma et al. (2022)	prospective randomized controlled 09.2020 and 08.2021	n-butyl cyanoacrylate + 2-octyl cyanoacrylate (PeriAcryl®90HV, GluStitch Inc., Delta, Canada)	ree epithelialized mucosal f grafts (FEGs) harvesting wounds	collagen plug + sutures (CPS) vs collagen plug with cyanoacrylate (CPC) vs platelet rich fibrin (PRF) + sutures vs palatal stent only (PS)	18 vs 18 vs 18 vs 18	Average daily bleeding mean scores: 1.0 (±1.9) vs 0.9 (±1.9) vs 0.6 (±1.4) vs 0.7 (±1.6)	n/a
Thoniyottupurayil et al. (2022)	prospective randomized controlled	isoamyl 2-cyanoacrylate (Mervilyte®)	wounds following surgical removal of an impacted mandibular third molar	CA vs 3–0 Silk sutures	7 vs 7	1. mean rank of perceived bleeding PO day I: 6.71 vs 8.29 2. mean rank of perceived bleeding PO day III: 7.50 vs 7.50	1. $p = .535$ 2. $p = 1$

Table 2. This table displays for each included experimental study: the citation, study design, the CA used, technique of application for the CA, hemostasis material used to compare the CA, number of subjects, hemostasis-related results, statistical significance of the tests used.

Article	Experimental model	Type of CA used	Application technique	Study vs control	No. of subjects	Results	P-value
Jiang et al. (2014)	In vivo pig liver resection	n-octyl-2-cyanoacrylate	Airfow-directed in situ electrospinning	n/a	20 pigs	no blood seeping was observed after 1 minute	n/a
Kubrusly et al. (2015)	vascular injury in guinea pigs	2-octyl-cyanoacrylate (Dermabond®)	topical application using swab stick	CA vs BPC* (mixture time = 6.5 min) vs BPC*(mixture time = 3.5 min)	8 vs 4 vs 4	1. drying time (seconds): 81.5±51.5 vs 40.5±8.6 vs 126.1±23.0 2.Blood Loss (grams): 0.17±0.42 vs 0.002±0.005 vs 0.008±0.005	1. $p < .023$ 2. $p < .069$
de Carvalho et al. (2015)	vascular injury in heparinized rabbits	2-octyl cyanoacrylate + butyl lactoyl cyanoacytate (Omnex®, Ethicon, Johnson & Johnson, S. Josı dos Campos, SP, Brazil)	topical application by dripping	CA + suture vs suture alone	8 vs 4	1. CA and suture had a better outcome then suture alone (survival-wise) 2. time until hemostasis (minutes): 4.31 vs 39.7	1. $p < .01$ 2. $p < .004$
Yucel et al. (2016)	partial nephrectomy in rats	n-butyl-2-cyanoacrylate (General Enterprise Marketing, Lucca, Italy)	topical application by dripping	CA vs bovine-derived gelatin matrix + thrombin vs chitosan granular dressing vs suture	8 vs 8 vs 8 vs 8	1. time until hemostasis (seconds): 32.9±1.2 vs 40.9±1.1 vs 55.8±1.8 vs 140.1±10.2 2. warm ischemia time (seconds): 43.3±1.7 vs 52.1±1.7 vs 66.6±2.2 vs 150.4±10.2	1. $p < .001$ 2. $p < .001$
Lloris-Carsv et al. (2016)	renal punch-injury in rats	elastic CA (Adhflex®, Bioadhesive Medtech Solutions SL, University of Alicante, Alicante, Spain)	topical application by dripping	CA vs human fibrinogen + human thrombin sponge vs oxidized cellulose sponge vs untreated	27 vs 27 vs 27 vs 6	Bleeding time (seconds): 27.67±12.91 vs 77.56±7.42 vs 82.56±14.48 vs 135.78±11.58	$p < .05$

Table 2. This table displays for each included experimental study: the citation, study design, the CA used, technique of application for the CA, hemostasis material used to compare the CA, number of subjects, hemostasis-related results, statistical significance of the tests used (continue)

Article	Experimental model	Type of CA used	Application technique	Study vs control	No. of subjects	Results	P-value
Luo et al. (2018)	liver resection in rats	n-octyl-2-cyanoacrylate + medical grade polymethyl methacrylate (Guangzhou Baiyun Medical Adhesive Co., Ltd.)	in situ electrospinning	electric field-modified electrospinning of CA vs airflow-assisted electrospinning of CA	20 vs 20	Hemostasis was achieved within 10 seconds	n/a
Zhang et al. (2019)	dermal incisions in heparinized swine	2-octyl cyanoacrylate + butyl cyanoacrylate (SecurePortIV® Adhezion Biomedical, LLC, Reading, USA)	topical application by dripping	CA vs Absorbable Gelatin Powder vs Calcium Sodium Alginate dressing vs no treatment	30 vs 30 vs 30 vs 30	Incision bleeding score: 1. at 3 minutes: 0.3±0.5 vs 0.1±0.5 vs 0.1±0.6 vs 0.6±1.4 2. at 6 minutes: 0.2±0.5 vs 0.2±0.6 vs 0.2±0.5 vs 0.7±1.4 3. at 9 minutes: 0.2±0.4 vs 0.2±0.5 vs 0.2±0.5 vs 0.6±1.4 4. at 12 minutes: 0.2±0.4 vs 0.2±0.5 vs 0.0±0.2 vs 0.6±1.4	$p < .05$
Luo et al. (2019)	partial nephrectomy in rats	n-octyl-2-cyanoacrylate + medical grade polymethyl methacrylate (Guangzhou Baiyun Medical Adhesive Co., Ltd.)	in situ electrospinning / spraying	in situ auxiliary electrode electrospinning vs air-flow assisted electrospinning vs spraying group vs sham group	20 vs 20 vs 20 vs 13	1. effective hemostasis in < 10 seconds; 2. faster compared to spraying group; 3. more precise than airflow assisted electrospinning	n/a

Abreviations: *BPC = bio-based polyurethane + catalyst

Results of Individual Studies

All the results of the individual clinical trials and experimental studies that were specific for the topic of this review have been synthetized and presented in *Tables 1, 2*.

Discussion

This review has shown that there is an important body of evidence in the literature supporting the clinical use of CA for topical hemostasis. Their propriety to solidify rapidly when in contact with water-based counterparts, makes them an ideal candidate for the optimal topical hemostatic (20). This fact also limits their applicability, because controlled and safe deposition of CA is unstandardized. Their hemostatic efficiency is comparable with other state-of-the art materials, and this should make them one of the favorite choices of medical professionals that are dealing with active bleeding wounds (15). Although their degradation by-products may be harmful for the human body and hinder the healing process, new homologs are being synthetized that exhibit lower toxicity at the cost of adhesive bond strength (8). Also new emerging application techniques involving modern technologies may consolidate the position of CA as prime performing topical hemostatic materials (47).

One of the limitations of this review was that the included studies presented a large degree of heterogeneity, fact that made a meta-analysis impossible. Study populations were inconstant, lesion types were of a wide variety, experimental models were diverse. In a way this attested to the versatility of CA as topical hemostatic material but made the drawing of objective conclusions process slightly harder.

Regarding the review process, limitations to the time frame of inclusion (the last 10 years) and language (English) were applied. Moreover, gray literature has not been actively inquired. Nevertheless, we are confident that these methodological limitations should not have an impact on the overall result of the analysis.

The results of this review might draw the interest of medical professionals and researchers who are looking for a better, faster, and more reliable topical hemostatic material.

Future research should try to eliminate the limitations of CA use in topical hemostasis by achieving the following: perfect the application technique for a safer and more controlled one; reduce their toxicity and combine them with other materials to obtain a new generation of hemostatic dressings.

Conclusion

Topical hemostasis is an important topic in current medical practice, and there is no perfect hemostatic material yet discovered. It has been proven that CA are proficient in achieving topical hemostasis in a variety of wounds. If the minor limitations that they present today will be overcome by future research, CA-based compounds might become a key asset for hemostasis.

Conflicts of Interests

The authors have no conflict of interests to declare.

Ethical Statement

No ethical statement is applicable to this study.

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