MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Cyanoacrylates Safety Profile

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Executive Summary

Key Points

1. Searches identified 1010 citations; 49 articles were selected for inclusion
2. For cyanoacrylates (CA) fixation, although the most common reported local responses were foreign object sensation, seroma formation, recurrence or reoperation, and chronic pain, moderate-quality evidence indicates that none of these responses are unique or elevated when CA was used for fixation in controlled studies. One randomized control trial (RCT) provided low-quality evidence of a systemic inflammatory response (erythrocyte sedimentation rate [ESR]) that was increased in the CA group at 3 months post-procedure.
3. For CA as a tissue adhesive, moderate-quality evidence found that the most common reported local responses (inflammation, bleeding dehiscence, discharge, drainage, erythema, and keloid formation) are not elevated for CA compared to control material/devices. Low-quality evidence from a study on cardiac device implantation reported higher rates of excoriation, incrustation, and incomplete closure for CA compared to sutures, and a study of breast surgery reported a higher rate of skin blistering for CA compared to sutures. One RCT provided low-quality evidence of a higher incidence of respiratory distress with use of CA over sutures within 2 to 4 weeks following circumcision in children less than 7 years of age (3 CA, 0 sutures).
4. For CA used in embolization, moderate-quality evidence found that local responses were not elevated for CA compared to control material devices. Some responses (gastroesophageal variceal rebleeding, ulcer occurrence and ulcer bleeding) were substantially lower for CA compared to band ligation. One non-randomized comparative study reported that a systemic response (grade 3 and 4 serum ALT and AST elevation) was less likely to occur in the NBCA group compared to absolute ethanol within 8 weeks after portal vein embolization.
5. For CA used as a sealant, moderate-quality evidence found that rates of the most common responses (drainage or leakage) were generally lower for CA compared to controls.
6. For CA used to anchor dressings for catheter placement, moderate-quality evidence found that rates of the most common adverse events (skin irritations and dislodgement or failure of catheter dressings) generally are similar between CA and control materials (although failure rates were somewhat inconsistent among studies).
7. One accident investigation concluded that liquid embolic system (sealant) used in the incident procedure was dispersed into non-targeted vessels resulting in neurological complications. The unintended release of this sealant was a result of internal catheter over pressurization due to a kink in the catheter's distal tip.
8. One Problem Reporting Network (PRN) described "small pimples" developing at an area where a single coat of Liquiband was applied to a wound. Additionally, the liquiband failed to completely seal the wound.
9. Approximately 90% of all PSO reports regarding CA involved adhesives with the top two complications being allergic reactions to adhesives (53%) and hemorrhage/hematoma (17%). Twenty reports resulted in non-harm (harm scores of B1, C and D) while 4 were categorized as harm (harm scores of E and F) and 6 were not categorized. Of the reports resulting in harm, 3 involved an allergic reaction to adhesives and 1 involved skin redness and blistering at the site of liquid bandage application.
10. Health Technology Alerts database returned 9 manufacturer issued alerts none of which involved biocompatibility responses to CA.
11. Evidence gaps:

a. Overall, there is a lack of studies investigating systemic responses to CA for all applications indicating a need for further research.
b. Only one human study investigated host responses/device events related to CA used for wound closure indicating more research is needed.
c. There is a need for further research in all host responses associated with gastroesophageal varices and NCBA transarterial embolization procedures, with the exception of varicose veins.

Overview - Cyanoacrylates

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to cyanoacrylates (CA). If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to Cyanoacrylates?

Local responses/device events varied somewhat across different CA applications; all studies involved human subjects. In comparative studies, most responses/events had similar occurrence rates in patients receiving CA and patients receiving non-CA comparators. The majority of ECRI surveillance data were related to allergic reactions to adhesives.

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. Two studies used patch testing and demonstrated allergic skin reactions to Dermabond.
ii. In studies of CA used for fixation, the most common reported local responses were foreign object sensation, seroma formation, recurrence or reoperation, and chronic pain. None of these responses were unique or elevated when CA was compared to non-CA materials/devices.
iii. When used as a tissue adhesive, the most common reported responses were inflammation, bleeding dehiscence, discharge, drainage, erythema, and keloid formation, none of which were elevated for CA compared to non-CA material/devices. A study on cardiac device implantation reported higher rates of excoriation, incrustation, and incomplete closure for CA compared to sutures, and a study of breast surgery reported a higher rate of skin blistering for CA compared to sutures.
iv. When used for embolization of varicose veins, the most common responses were phlebitis, ecchymosis, paresthesia, and pigmentation. When used for treatment of acute gastroesophageal variceal bleeding, rebleeding was the most common response/event. None of these responses were elevated for CA compared to non-CA material devices (gastroesophageal variceal rebleeding, ulcer occurrence and ulcer bleeding were substantially lower for CA compared to band ligation).
v. When used as a sealant, the most common responses were drainage or leakage which was generally lower for CA compared to controls (statistically significant difference in 2 randomized control trials (RCTs) involving mastectomy or thyroidectomy, lower but not statistically significant in 2 other RCTs that used non-CA sealant for gastrectomy surgery).
vi. Only 1 study evaluated CA for wound closure in dental surgery and reported more post-operative bleeding with CA compared to sutures, while other event rates were similar between groups.
vii. In other applications, CA was used most often to anchor dressings for catheter placement. The local responses reported most often across studies were skin irritations and dislodgement or failure of catheter dressings, which generally did not differ between CA and non-CA control materials (although failure rates were somewhat inconsistent among studies). One study reported a higher rate of skin tears with CA while another found no difference. One study of CA for attaching eye muscle to the sclera reported higher inflammation symptoms and signs in the CA group compared to fibrin glue.
viii. The quality of evidence for the more frequently described responses noted above was moderate. For events investigated by few studies, the quality of evidence was low.

b. Over what time course does this local host response appear?

i. One patch test study reported allergic reactions at 27 to 44 days after Dermabond application.

ii. For CA fixation, responses occurred from 4 hours to 7 years following procedures.
iii. For CA as a tissue adhesive, responses occurred from 2 weeks to 1 year following CA application.
iv. Responses following use of CA for embolization occurred from 1 week to 15 years post-procedure.
v. For CA as a sealant, responses occurred from 5 days to 3 years post-procedure.
vi. For CA as an anchor for catheter dressings, responses occurred from 2 to 7 days post-procedure. Response to use of CA in eye surgery occurred within 3 months post-procedure.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

For CA fixation vs non-CA fixation, one RCT reported no difference in inflammatory markers at 48 hours post-op, but erythrocyte sedimentation rate (ESR) was increased in the CA group at 3 months post-procedure. For CA as a tissue adhesive, one RCT found a higher incidence of respiratory distress with use of CA over sutures within 2 to 4 weeks following circumcision in children less than 7 years of age (3 CA, 0 sutures). For embolization, one non-randomized comparative study reported that grade 3 and 4 serum ALT and AST elevation were less likely to occur in the NBCA group compared to absolute ethanol within 8 weeks after portal vein embolization. One RCT found that spontaneous bacterial peritonitis was rare and did not differ between CA embolization and sclerotherapy at 6 weeks post-procedure. Mortality also did not differ between groups and was due to disease progression rather than reaction to CA. One RCT reported pediatric patient deaths with CVADs (only 1 case in the CA group and 3 in non-CA group) within 4 weeks post-procedure that were likely unrelated to CA use. Because most systemic events were reported in only 1 study the quality of evidence was low.

b. What are the likely systemic manifestations?

See under 2a above.

c. What is the observed timeline(s) for the systemic manifestations?

Systemic responses noted above occurred between 2 days and 8 weeks following procedures that included CA application (see 2a above for more details).

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

No studies addressed this question.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

One non-randomized controlled study reported that changes in laboratory data (grade 3 and 4 serum ALT and AST elevation) were likely caused by ischemic changes in the embolized liver, but this does not appear to be related to CA since it occurred less frequently in the CA group.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

No studies reported data concerning material-related factors that addressed this question.

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

a. Overall, there is a lack of studies investigating systemic responses to CA for all applications resulting in very low to low quality of evidence indicating a need for further research.
b. Only one human study investigated host responses/device events to CA used for wound closure indicating more researched is needed.

c. There is a need for further research in all host responses associated with gastroesophageal varice and NCBA transarterial embolization procedures, with the exception of varicose veins. [GAP 2]

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. For the first quarter of 2021, the following six topics were chosen:

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates (PET)

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to Cyanoacrylates?
    a. *Can that response vary by location or type of tissue the device is implanted in or near?*
    b. *Over what time course does this local host response appear?*
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    a. *What evidence exists to suggest or support this?*
    b. *What are the likely systemic manifestations?*
    c. *What is the observed timeline(s) for the systemic manifestations?*
    d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps exist and what research is needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2011 and 2021 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching
- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Text mining, logistic regression, and a search for "random" and "systematic" in titles and abstracts were used to prioritize only the top 35%-40% of the identified literature. This subset was screened against the inclusion criteria, first by title/abstract review, and then by full article review. An evidence prioritization scheme was used to ensure the inclusion of approximately 50 studies. Data were extracted from the resulting articles.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2020, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (No Error)

Circumstances or events that have the capacity to cause error.

Category B (Error, No Harm)

An error occurred but the error did not reach the patient (An "error of omission" does reach the patient).

Category C (Error, No Harm)

An error occurred that reached the patient but did not cause patient harm.

Category D (Error, No Harm)

An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to prelude harm.

Category E (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Category F (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, Harm)

An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, Harm)

An error occurred that required intervention necessary to sustain life.

Category I (Error, Death)

An error occurred that may have contributed to or resulted in the patient's death.

Definitions

Harm – Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom

Monitoring – To observe or record relevant physiological or psychological signs

Intervention – May include change in therapy or active medical/surgical treatment

Intervention Necessary to Sustain Life – Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - Cyanoacrylates

Full Name: Cyanoacrylates
CAS Registry Number: [7085-85-0]

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Cyanoacrylates (CA) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of CA. The devices in **Error! Reference source not found.** were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data. In the latter, only those devices listed in **Error! Reference source not found.** were included.

Table 1: Medical Devices Containing Cyanoacrylates provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Sealant, Polymerizing	NBE	3
Sealant, Microbial	NZP	2
Tissue Adhesive for the topical approximation of skin	MPN	2
Cutaneous tissue adhesive with mesh	OMD	2

Tissue adhesive for us in embolization of brain arteriovenous malformations	KGG	3
Crown and bridge, temporary, resin	EBG	2
Cement, Dental	EMA	2
Unit, Operative Dental	EIA	1
Agent, occluding, vascular, permanent	PJQ	3
Liquid Bandage	KMF	1

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of CA. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in **Error! Reference source not found.**. We then turn to a detailed discussion of research on CA as a material as well as research on the various device categories.

Table 2: Summary of Primary Findings from our Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Cyanoacrylates as a material (2 human studies)	Allergic response (contact dermatitis)	Moderate	No studies evaluated systemic responses	Very low
Fixation (13 human studies)	Severe cellulitis, dehiscence, otitis media with effusion, hypoesthesia, itching, pruritus, rash, or other skin irritations, foreign object sensation, seroma formation, recurrence or reoperation, chronic pain	Moderate for foreign object sensation, seroma formation, recurrence or reoperation, chronic pain Low for all other outcomes	Inflammatory response	Low
CA as a Tissue Adhesive (12 human studies)	Abscess, adhesions, allergic reaction, bleeding, cellulitis, dehiscence, skin closure, isolated wound separation, discharge or drainage, surgical site infection, edema, erythema, pruritus, hyperpigmentation, hematoma, seroma, inflammation or swelling,	Moderate for inflammation, bleeding dehiscence, discharge, drainage, erythema, and keloid formation	Respiratory distress	Low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	keloid formation, wound irritation, excoriation, incrustation, insufficient wound closure, skin blistering	Low for all other outcomes		
Embolization (13 human studies)	Phlebitis, hyperpigmentation, ecchymosis, induration, inflammation at injection site, paresthesia, deep vein thrombosis, glue extension, pain, vein ulceration, rebleeding, dysphagia, ulcer, ulcer bleeding, cerebral vascular accident, embolism, exacerbation of chemosis, blurred vision and decreased visual acuity, renal infarction, varicocele recurrence, subcapsular biloma, inflammatory cell infiltration, necrosis, ophthalmoparesis,	Moderate for phlebitis, ecchymosis, paresthesia, and pigmentation in the treatment of varicose veins, and for rebleeding after treatment for acute gastroesophageal variceal bleeding Low for all other outcomes	Grade 3 and 4 serum ALT and AST elevation, spontaneous bacterial peritonitis.	Low
Wound Closure (1 human study)	More post-operative bleeding with CA No effect of CA on wound dehiscence or post-operative swelling	Low	No studies evaluated systemic responses	Very low
Sealant (4 human studies)	Leakage, bleeding, stricture, mortality, seroma formation, seroma drainage/ leakage, seroma aspirated, hematoma, reoperation	Moderate for drainage/ leakage Low for all other outcomes	No studies evaluated systemic responses	Very low
Other Applications (4 human studies)	Itching, pruritus, rash, other skin irritations, blister, skin tears, bleeding, partial or complete dislodgement of catheter dressing, failure of catheter dressing, chemosis, conjunctival reaction, granuloma, inflammation	Moderate for skin irritations and dislodgement or failure of catheter dressings Low for all other outcomes	Death (likely unrelated to CA use)	Low

Cyanoacrylates as a Material

Two observational studies with human subjects[1,2] provided evidence for CA as a material. These studies both performed patch testing to investigate allergic responses to Dermabond or other CA adhesives, and the factors influencing such responses, in patients with previous known, or suspected, reactions to CA. One study[1] examined the frequency of allergic contact dermatitis

(ACD) after first and second exposures to Dermabond, while the other[2] examined the rate with which individual components of Dermabond and other CA adhesives induce allergic responses at differing concentrations and skin conditions. For further information see Table 1 in Appendix D.

Local Responses (human studies)

Both studies evaluated local responses to CA patch testing. One study[1] examined patients who underwent orthopedic surgery and were subsequently patch tested on the upper back with Dermabond. Duration of contact with CA was 48 hours. Of 577 surgical patients, 9 (1.5%) had an allergic reaction to Dermabond. These subjects also had positive patch test results: 6 after first application, 3 after second. Among 8 of these patients who were subsequently tested with 10% ethyl cyanoacrylate (in petroleum), 4 (50%) had reactions. Mean time of onset of ACD was 34.1 days (range, 27-44 days) after Dermabond application for the 6 patients who reacted after the first application. Mean time of onset was 5.6 days (range 4-8 days) for the 3 patients who developed initial ACD after the second application. The difference in onset time between groups was statistically significant.

The second study[2] examined 38 patients with a history indicative of contact dermatitis from cyanoacrylate- or methacrylate-containing products. Thirty-five of these patients were tested with both types of products. Follow-up periods were 2 days, 4-5 days, and 1 week. Patch testing with 10% ethyl cyanoacrylate in petrolatum caused reactions in 29% of the Dermabond-allergic patients, while 10% octyl cyanoacrylate (OCA) identified 8 of 16 (50%) of these patients. Seventeen of 21 patients (81%) with a likely clinical history of contact dermatitis from Dermabond had positive results when tested with octyl cyanoacrylate. Thirteen of the 35 patients (37%) were positive for skin responses to 1 or more methacrylates or acrylates, while 22 had negative results.

A small subset of patients were tested to identify factors influencing skin reactions. Concentration of CA was a factor in stimulating skin responses. Patch test positivity with OCA increased when tested undiluted. Four patients exhibited concentration-dependent patch test reactivity to OCA, showing negative results with 10% or 30% concentration, but positive results with undiluted (>99%). Skin abrasion, which was meant to simulate real-world clinical application, was also a determining factor for reactivity. Three patients with condition-dependent patch test reactivity to Dermabond and negative test results on intact skin had positive results on abraded skin. Several patch test reactions displayed 1 or 2 isolated papules at delayed readings, but exact numbers and conditions preceding this outcome were not specified.

Systemic Responses

No included studies reported on systemic responses.

Overall Quality of Evidence

The overall quality of evidence for establishing patch test reactivity to CA products or ingredients in patients with known or suspected CA-induced ACD was moderate. Data were provided from 2 small to moderate sized observational studies. Evidence from these studies regarding the timing ACD onset and subsequent CA exposures, and impacts of CA concentration and skin abrasion on reactivity is all of low quality, given that data on these relationships were each reported from single observational studies.

Fixation

13 human studies (9 RCTs,[3-11] 4 non-randomized comparative studies,[12-15]) provided evidence for this application of CA. All studies were conducted with human subjects. Nine of these studies[6-13,15] concerned procedures for surgical mesh attachment in hernia repair. For further information see Table 2 in Appendix D.

Local Responses/Device Events (human studies)

All 14 studies evaluated local responses/device events related to surgical procedures utilizing cyanoacrylates in human subjects. We first address outcomes that most directly serve as potential indicators for adverse skin reactions to CA. We then discuss additional outcomes that may be indirectly related to adverse local reactions.

One RCT[16] found no significant difference in the incidence of severe cellulitis when using CA or staples for attaching surgical mesh for hernia repair. Only one patient out of 30 (3.3%) in the CA group experienced this outcome; no occurrences were reported for the staple group.

One RCT[3] reported no significant difference in incidence of dehiscence with CA versus staples for closing the incision following total knee arthroplasty. One RCT[5] reported on incidence of otitis media with effusion (inflammatory conditions of the inner

ear) in patients who underwent myringoplasty) for repairing tympanic membrane (ear drum) perforations. Incidence was low at 6 month follow-up whether CA (0 of 32 patients) or gelfoam (1 of 37 patients) was used to repair the perforations (no statistical analysis provided).

One RCT[11] reported on hypoesthesia (numbness or loss of sensation) in male patients who underwent mesh attachment with Lichtenstein hernia repair. There were no significant differences in incidence with use of CA versus slow-absorbing, polydiaxanone (PDS) sutures.

One RCT[9] reported on itching, pruritus, rash, or other skin irritations at locations on the skin where CA was used for attaching surgical mesh for hernia repair.[9] Only one case of pruritus (3.3%) was reported when using CA to attach surgical mesh for hernia repair, compared to no cases when using surgical staples (no significant difference).

Two RCTs investigating attachment of surgical mesh for hernia repair reported on sensation of a foreign object over 1-year[8] and 7-year follow-ups.[7] We reported on this outcome because it may relate to the degree of skin irritation. Neither study found a significant difference in this outcome with use of CA compared to use of surgical sutures[7,8] or self-gripping mesh.[8]

Three studies, 2 RCTs[6,9] and 1 non-randomized comparative study[13] reported on seroma formation in the use of CA versus surgical tacks or staples for attaching surgical mesh in hernia repair operations. Neither RCT reported a significant difference in seroma formation between groups treated with CA compared to titanium tacks[6] or staples[9]. The one RCT[9] reported a very low incidence of seroma for both groups (0 for CA and 1 for staple group; each group had 30 patients). The one cohort study[13] found incidence of seroma to be significantly higher for the CA group than for groups where mesh was anchored with tacks or with no fixation at all.

We also included studies reporting composite outcomes that included seroma. Incidence of seroma alone was not reported in these studies. Four studies, 2 RCTs[4,10] and 2 cohort studies[12,15] reported on the composite outcome of hematoma/seroma formation (we did not report on hematoma alone). Three studies reported on surgical treatment for hernia[10,12,15] while 1 study reported on attachment of skin grafts for burn victims.[4] The 3 studies concerning hernia operations found no significant difference between mesh attachment performed with CA versus tacks,[12,15] staples,[10] or no fixation.[15] One study also found no significant difference using CA versus suture or staples for attaching skin grafts on burn victims. Finally, one RCT[8] reported no significant difference in incidence of seroma or infection for inguinal hernia repair when using CA, self-gripping mesh, or sutures.

Six studies reported on recurrence or reoperations. The rationale for including these outcomes was that failure of mesh attachment, due to skin reaction at site of attachment, might compromise healing, prompting recurrence and/or need for reoperation. One retrospective cohort study[14] reported on patients who underwent rectopexy (reattachment of the rectum following prolapse) and 3 RCTs[8,9,11] reported on patients treated for hernia with attachment of surgical mesh with CA, sutures, or self-gripping mesh. The study of patients undergoing rectopexy[14] compared the incidence of recurrence and also recurrence-free survival over 18-month follow-up for CA and surgical sutures. The studies of hernia reported incidences of recurrence for CA compared to sutures[8,11] or staples[9], or self-gripping mesh.[8] None of these studies found any significant between group differences in outcomes. Reoperation was reported in 1 RCT that examined patients with hernia[7] and another RCT studied repeat skin grafts for burn patients[4] Reoperation (not due to recurrence) for hernia patients was infrequent, with only 5 total cases (3 cases [2.7%] for the CA group and 2 cases [1.7%] for the suture group; no significant group difference at 7-year follow-up). Incidence of regrafting for burn patients was lowest in the CA group (n=0) and highest for the tie-over group (n=5; 16%), while the suture group had one occurrence (3.3%). No statistical comparisons were provided for this analysis.

Three RCTs[6,7,9] reported on chronic pain following hernia repairs. They all found no significant differences in the number of patients experiencing pain when CA was compared to tacks,[6] staples,[9] or sutures[7] for attaching surgical mesh (follow-ups ranged from 3 months to 7 years). The one RCT also reported on visual analogue scores (VAS) for pain and found CA and surgical tacks to result in similar scores up to 7 months following surgery.

Systemic Responses (human studies)

One RCT with human subjects[6] reported on systemic responses/device events potentially related to utilization of cyanoacrylate for attaching surgical mesh for inguinal hernia repair. Titanium tacks were used to attach mesh in the control group. This study reported on 3 blood measures related to inflammatory response: C-reactive protein level, erythrocyte sedimentation rate (ESR), and total white blood cell (WBC) count. No significant between-group difference was found for c-reactive protein or WBC count at 48 hours post-operation (post-op). Median ESR was significantly increased in the CA group at 3 months post-op.

Factors Associated with Systemic Responses

Not reported.

Overall Quality of Evidence

The overall quality of evidence on local responses with use of CA is Moderate for foreign object sensation, seroma formation, recurrence or reoperation, and chronic pain. These outcomes were reported from multiple RCTs and non-randomized comparative studies performed on human subjects, and results were generally in agreement in indicating low incidence of such responses with use of CA. The quality of evidence for other responses/events pertaining to local reactions was of low quality because they were reported in single studies. The quality of evidence for systemic responses is low as there was only one RCT reporting on such outcomes and the findings were somewhat inconclusive with regard to blood measures indicating potential inflammatory response.

Cyanoacrylates as a Tissue Adhesive

Local Host Responses (human studies)

12 human studies (4 randomized controlled trials [RCTs],[17-20] 6 non-randomized comparative studies,[21-26] and 2 single-arm studies with within-subject controls[27,28]) provided evidence for this application of CA. All studies were conducted with human subjects. For further information see Table 3 in Appendix D.

All 12 studies evaluated local responses/device events related to surgical procedures utilizing cyanoacrylates in human subjects. We first address outcomes that most directly serve as potential indicators for adverse local reactions.

One prospective non-randomized comparative study[25] of gynecological cancer patients undergoing surgery found no adverse events with use of CA for wound closure.

One RCT[17] found a lower incidence of abscess at 8 weeks when closing a Pfannenstiel incision with CA, as opposed to sterile strips, following Cesarean delivery. However, the difference was not significant.

One RCT[18] found no statistical difference in adhesions when using CA over sutures following circumcision in children less than 7 years of age.

One retrospective non-randomized comparative study[22] found no statistical difference in allergic reaction when comparing skin closure following Achilles tendon surgery using two cyanoacrylate products and sutures.

Two RCTs[18,20] reported on post-operative bleeding and found no statistically significant differences with use of CA compared to suture. One study reported on this outcome following circumcision in young children[18] and the other on wound closure after cardiac device implantation. This latter study found no significant differences in minor or major bleeding events and incidence of events were low in both groups (≤2.2%).

One RCT[17] found no significant difference in incidence of cellulitis with use of CA compared to sterile strips after closure of Pfannestiel incisions for cesarean delivery. One comparative study[21] found a lower incidence of cellulitis after using CA as a topical skin adhesive with subcuticular sutures following pancreaticodenectomy, compared to staples and subcuticular sutures with steri-strips.

Two RCTs examined closure of surgical incisions following implantation of cardiac devices,[20] and circumcision in children under 7 years of age,[18] respectively. Neither of these studies found any significant difference in incidence of wound dehiscence with use of CA versus suture. One non-randomized comparative study examined incidence of dehiscence with use of CA as compared to sutures for C-section closure[26] and found no significant difference in incidence with the two techniques. Finally, one retrospective non-randomized comparative study[22] found no statistical difference in skin closure following Achilles tendon surgery with use of two cyanoacrylates (2-octyl cyanoacrylate [OCA] and butylcyanoacrylate [BCA]) as compared to nylon sutures. This study followed up patients for up to 12 months. The RCT on closure of Pfannestiel incisions after cesarean delivery[17] found no significant difference in isolated wound separation with use of CA compared to sterile strips.

Three studies reported on discharge or drainage from wound closures with use of CA.[17,19,22] One RCT[19] reported on discharge or drainage from wound closure following laparoscopic surgery in female patients. No statistical comparisons were reported but incidence was very low whether wounds were closed with CA or sutures (2.6% vs. 5.3% for CA and suture groups, respectively). Another RCT[17] found no difference in the incidence of wound drainage when using CA for closure of Pfannestiel incision for cesarean delivery. One retrospective comparative study[22] found no statistical difference in surgical site infection,

prolonged discharge when comparing skin closure following Achilles tendon surgery using two cyanoacrylate products and sutures.

One RCT[19] and one single-arm study[27] compared rates of edema in wounds closed with CA or sutures. The single-arm study provided within-subject comparisons, with each patient undergoing bilateral breast surgery, with CA and sutures used on opposite sides (the side of each closure method was randomized). No evidence for a significant difference in the incidence of edema with the two closure methods was found in the RCT at 2 weeks follow-up, and the rate of edema was very low for both comparison groups (0 cases for the CA group versus 1 case [2.6%] for the suture group). The single-arm study found a significantly higher rate of edema at 12 to 25 days post-treatment with use of sutures.

One RCT[19] and one single-arm study[27] reported no significant differences in erythema with the use of CA versus sutures following laparoscopic surgery or bilateral breast surgery, respectively. Erythema was very commonly observed in the RCT at 2 weeks follow-up. Precise rates of this outcome were not reported in the single-arm study, but follow-up was reported after 7 days and at 12 to 25 days. Two studies, one prospective comparative study [26] and one within-subject comparison single-arm study[28] reported on composite outcomes that included erythema. The cohort study found no significant difference in abnormal peri-wound erythema or pruritus, at up to 1-year follow-up, when using CA or sutures in female patients who underwent cesarean section. The rate was higher for suture group (6.4% vs. 2.0% for suture and CA groups, respectively). In the single-arm study, erythema and tenderness were significantly lower at 1-2 week follow-up following alveoplasty on the side of the mouth where CA was used for wound closure (but no significant difference was seen at 3-week follow-up).

One RCT[17] found CA was associated with significantly lower incidence of itchiness than sterile strips after closure of Pfannestiel incisions for cesarean delivery.

One prospective comparative study[24] reported no incidence of exudation with use of CA or sutures for wound closure in patients undergoing coronary artery bypass grafting (CABG). Follow-up ranged from 6 to 8 weeks. This study also reported on hyperpigmentation at the site of the wound, reporting a significantly higher rate with use of sutures than with CA.

One RCT[17] found no significant difference in the incidence of hematoma or seroma when using CA or sterile strips after closure of Pfannestiel incisions for cesarean delivery. The non-randomized comparison study on septal deviation surgery[23] found no incidence of septal hematoma with or without the use of CA.

Five studies[19,23,24,27,28] reported on incidence of inflammation or swelling, or on other physiological indicators of inflammation. No evidence was found to indicate that CA is associated with higher risk of inflammation following wound closure. One RCT compared use of CA to sutures following laparoscopic surgery.[19] Follow-up was 2 weeks. No significant difference was found in inflammation/swelling between the two groups. There was a very low overall incidence of inflammation (only one subject in the CA group). Results from the one prospective cohort study[24] comparing CA with sutures following CABG surgery were consistent with the above findings. Inflammation was uncommon with use of both CA and sutures (one patient per group) with no significant difference in incidence between the two closure techniques. In contrast to the above studies, one controlled study[23] found an increase in post-operative swelling following incisions for septal deviation surgery when CA was used in addition to scoring, compared to scoring alone. Two single-arm studies[27,28] provided within-subject comparisons between CA and sutures for closing wounds following alveoloplasty[28] and breast surgery,[27] respectively. In both studies, subjects were treated bilaterally and wounds on each side were closed with one of the two techniques, selected at random. Follow-up was at 1, 2, and 3 weeks post-op for the study on alveoplasty, and up to a maximum of 1 year for the study of breast surgery patients. Histological signs of inflammation (inflammatory cell infiltration and vascularity) were examined following alveoplasty and were higher with use of sutures at 7 or 14 days post-op (only vascularity at 14 days). Density of fibrocellular connective tissue were similar with both closure techniques.[28] The study of breast surgery found no significant differences in excessive inflammation with the two techniques at 6 or 12 months follow-up.

Two studies, one prospective comparative study[26] and one RCT,[20] reported on keloid formation. These studies reported, respectively, on female patients undergoing C-sections and patients undergoing implantation of cardiac rhythm devices (e.g. pacemakers or cardiac defibrillators). Neither study found a significant difference in the incidence of keloid formation with use of CA versus sutures, however, the study on patients undergoing C-section did report a higher rate for the CA group (24% vs. 14.9% for suture group). Incidence of keloid formation was very low (<1%) for both groups following cardiac device implantation.

The RCT on cardiac device implantation[20] also reported on incidences of perioperative wound irritation and insufficient wound closure. All outcomes were measured prior to patient discharge. Rates of wound irritation, excoriation, incrustation, and insufficient wound closure, were all higher when CA was utilized compared to sutures. Significant differences were measured

for excoriation, incrustation, and incomplete closure. Statistical analysis did not identify any prognostic factors for the appearance of adverse events. Specifically, adverse events were not related to patient age, the type of device implanted, or procedure duration. Finally, the single-arm study on breast surgery patients found a higher incidence of skin blistering following use of CA (utilized on one side of a bilateral procedure) as compared to sutures (used on the contralateral side). Though incidence with CA use was generally low (10.3% of patients on day 7 and only 2.5% post-op and post-op days 12 to 25), there were no incidences reported with use of suture in the same patients.

Systemic Responses

One RCT[18] found a higher incidence of respiratory distress with use of CA over sutures following circumcision in children less than 7 years of age (n=3 for CA group vs. no cases for the control group). Only 1 case of fever was reported for a patient in the control group. No statistical comparisons were provided for these individual outcomes.

Overall Quality of Evidence

The overall quality of evidence on local responses with use of CA as tissue adhesive is moderate for inflammation, bleeding dehiscence, discharge, drainage, erythema, and keloid formation, with findings derived from multiple RCTs and non-randomized comparative studies of human subjects. The quality of evidence for other local responses/events reported in single studies was low. Generally, results across studies were in agreement that use of CA as a tissue adhesive does not result in significantly different rates of adverse events than other methods such as sutures, although 2 studies did find higher rates of either wound-related outcomes or skin blistering associated with CA use compared to sutures. The quality of evidence for systemic responses is low as there was only one RCT reporting on relevant outcomes.

Embolization

13 human studies (3 systematic reviews [SR], 2 randomized controlled trials [RCT], 8 non-randomized comparative studies). For further information see Table 4 in Appendix D. In studies that used NBCA (n-butyl-2-cyanoacrylate) it was usually mixed with lipiodol in varying ratios.

Local Responses/Device Events (human studies)

Varicose Veins

Three studies examined cyanoacrylate embolization for varicose veins.[29-31] Phlebitis was reported in all 3 studies.[29-31] A non-randomized comparative study (n=335) reported 4 cases of phlebitis (5%) after embolization with NBCA, which was significantly less frequent compared to radiofrequency ablation (RFA). An RCT (n=400) reported that phlebitis occurred in 3.5% of patients at one week in the NCBA ablation (VenaBlock) group, not significantly different compared to patients undergoing EVLA.[29] Similarly, an SR (n=1057) comparing CA ablation to RFA and ELA reported phlebitis rates ranging from 2.8 to 16%, not significantly different than RFA or ELA.[30] According to this study, phlebitis events in cyanoacrylate 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.[30] Applying manual pressure, using a continuous delivery method, and low-viscosity cyanoacrylates may reduce the rate of phlebitis.[30]

One study included in the SR observed hyperpigmentation in 2.6% of patients at 24 months.[30] Another study reported pigmentation in 3.5% of patients at 1 week, with all cases resolving completely by 6 months. This study noted that procedure-related skin pigmentation was developed as a result of phlebitis.[29]

One SR and one RCT reported ecchymosis rates.[29,30] The RCT reported an ecchymosis rate of 12%, significantly lower in the NCBA ablation group at 1 week compared to EVLA (26%), all cases in both groups resolved by 3 months.[29] The SR found that rates of ecchymosis ranged from 5.4 to 31.5% and they were significantly lower than for RLA but not significantly different than ELA at 12 months.[30]

Induration rate was reported by one study that found significantly less induration in the NBCA group at 1 week, but by 3 month follow-up the rate was not significantly different than EVLA.[29] Inflammation at the injection site was reported in 4 cases by one study in the SR comparing CA ablation to RFA and ELA.[30]

Two studies reported similar findings with regards to the rate of paresthesia.[29,31] In both studies, paresthesia occurred in 3% of patients at 1 week and resolved in all cases by 3 months.[29,31] In the RCT comparing NBCA to EVLA, the paresthesia rate was found to be significantly lower in the NBCA group at 1 week and 3 months.[29] Conversely, the non-randomized controlled study found no significant difference between NBCA and RFA.[31]

Deep vein thrombosis (DVT) after cyanoacrylate embolization for varicose veins was rare, with only one case of DVT reported across all 3 studies.[29-31] The non-randomized comparative study reported 1 case of DVT in the NBCA group that was clinically asymptomatic, not significantly different than RFA. The SR and RCT reported no cases of DVT or PE.[29,30] The RCT attributed the prevention of DVT and PE to compression of the saphenofemoral junction and the quick polymerization of CA, leading to rapid closure and minimal procedure time.[29] However, one study included in the SR reported two cases of minimal extension of thrombus to the deep vein and another study reported one case of posterior tibial vein extension.[30] Two studies in the SR reported a total of 3 cases of glue extension, all of which were resolved by 12 months.[30] The SR also cautioned that when using VenaSeal, initial positioning of the catheter at 3 cm of the saphenofemoral junction caused several cases of cyanoacrylate extension into the deep system.[30]

One RCT observed that pain scores were significantly lower with NBCA embolization compared to EVLA at 1 week (2.8 ± 3.1 vs. 5.4 ± 3.7, p<0.001) but not significantly different at 3 months (0.6 ± 0.4 vs. 0.7 ± 0.5, p=0.458).[29] Retained glue at the entry site was reported in 3 (3%) patients in the non-randomized comparative study and required drainage and removal. One study included in the SR reported the occurrence of vein ulceration in 3% of patients.[30] Additionally, the SR reported no cases of allergic reaction.[30]

One SR noted that for CA embolization of the great saphenous vein, the overall incidence of adverse events may be related to high scores on the preoperative CEAP classification and VCSS, large GSV diameters, and aneurysms in large vein segments.[30]

Gastroesophageal Varices

Three studies, two SRs and one RCT, reported outcomes after NBCA embolization for gastric and esophageal variceal hemorrhage.[32-34] Rebleeding was reported in all studies. One SR (n=648) reported a statistically significant 63% reduction in the hazard of GV rebleeding with CA compared to band ligation (HR 0.37; CI: 0.24 to 0.56).[33] Another SR (n=3630) reported rebleeding 13.7% of cases and noted the gastric varices may respond better to CA compared to esophageal varices.[32] This SR found that studies after 2010 reported a lower risk of rebleeding, which is hypothesized to be due in part to technological advancement in the use of CA for gastroesophageal varices.[32] The RCT (n=113) reported rebleeding in 19.3% of cases, not significantly different than sclerotherapy.[34]

The RCT also reported retrosternal pain in 6 patients (10.53%) and dysphagia in 4 patients (7.02%) after embolization for acute esophageal variceal bleeding, not significantly different than sclerotherapy (21.43% and 16.07%, respectively).[34] Additionally, no cases of distant embolization were reported in the NBCA group.[34]

One of the SRs also reported that ulcer and ulcer bleeding was significantly less likely to occur with CA compared to band ligation (OR 0.32 [CI: 0.17 to 0.67]), while vascular events including cerebral vascular accident and embolism (OR 1.76 [CI: 0.35 to 8.85]) and overall complication rates (39.02% vs. 27.1%, OR 1.02 [CI: 0.48 to 2.19]) were not significantly different.

Other Uses

Six non-randomized controlled studies reported on other uses for CA embolization.[35-40] One study (n=46) comparing NCBA transarterial embolization to transvenous coil embolization for ocular symptoms in patients with cavernous sinus dural arteriovenous fistulas (cDAVF) reported one case of partial thrombosis and one case of exacerbation of chemosis, both of which resolved within 6 weeks. Additionally, one case of blurred vision and decreased visual acuity was reported in the NBCA group that resolved within 1 week.[35] Another study (n=65) comparing NBCA embolization to TEVAR for closure of false lumen in aortic dissection reported one case of NBCA leading to renal infarction.[36] A third study (n=129) comparing NBCA to metal coils for varicocele embolization reported varicocele recurrence in 11.54% of patients, not significantly different than metal coils, and no complications in the NBCA group.[37] A fourth study (n=61) comparing NCBA to absolute ethanol for portal vein embolization reported 2 cases of subcapsular biloma and pain requiring analgesia in 35.3% of cases, neither of which were significantly different than absolute ethanol. A fifth study (n=20) comparing NBCA to trisacryl gelatin microspheres for preoperative embolization of meningiomas reported 4 cases (44%) of inflammatory cell infiltration, significantly more likely to occur in the NBCA group.[39] This study also reported 2 cases of necrosis and 1 case of ophthalmoparesis in the NBCA group that resolved with no further complications after extirpation, neither of which were significantly different than trisacryl gelatin microspheres.[39] Finally, the sixth study (n=406), comparing NBCA to polyvinyl alcohol for bronchial artery embolization for hemoptysis control, found that recanalization was significantly less frequent in the NBCA group (1.8% vs. 21.5%, p<0.001).[40] This study also reported no significant difference in overall complication rate (31% vs. 34.1%) and there were no major complications, no delayed complications, and no procedure-related mortality in the NBCA group.[40]

Systemic Responses

A non-randomized controlled study reported that grade 3 and 4 serum ALT and AST elevation were significantly less likely to occur in the NBCA group compared to absolute ethanol after portal vein embolization (2 ([5.9%] vs. 22 [81.5%] and 1 [2.9%] vs. 22 [81.5%, respectively).[38] One RCT reported spontaneous bacterial peritonitis in 2 cases (3.51%) in the NBCA group after embolization for acute esophageal variceal bleeding, not significantly different than the sclerotherapy group (3 cases, 5.36%).[34]

Mortality was reported in 2 studies and was due to disease progression in all cases.[34,41] One RCT reported 9 deaths (15.8%) with NCBA for acute esophageal variceal bleeding, not significantly different than sclerotherapy.[34] One non-randomized comparative study reported 4 deaths (26.7%) in the 30 days following NCBA embolization of iatrogenically injured arteries in paracentesis or thoracentesis for chronic liver disease, not significantly different than transarterial embolization.[41]

Overall Quality of Evidence

The evidence base was large and almost all reported studies had control groups. Overall the quality of evidence was moderate for phlebitis, ecchymosis, paresthesia, and pigmentation in the treatment of varicose veins, and for rebleeding after treatment for acute gastroesophageal variceal bleeding. For other local and systemic responses, the quality of evidence was low due to the responses being reported in few studies. Most reported adverse events were minor and reversible.

Wound Closure or Liquid Bandage

One RCT in humans[42] reported on use of cyanoacrylate (CA) for closure of wounds following extraction of 3rd mandibular molars in 120 patients. Individual patients were randomized to wound closure with either CA or 3-0 silk suture (n=60 patients per group were analyzed). The study reported on post-operative bleeding, swelling, and wound dehiscence. Subjects were followed up for 7 days after surgery. For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

This single RCT found significantly more post-operative bleeding with use of CA (70% of subjects exhibited bleeding) compared to sutures (no subjects with bleeding) for closure of wounds following molar extraction.

In contrast, no significant differences were observed in wound **dehiscence** (n=6 for CA vs. n=4 for sutures, p=0.51) or **post-operative swelling** with use of CA as compared to sutures (all p>0.30). Facial width and interincisal distance were measured before and after the procedure to quantify swelling.

Local Host Responses (animal studies)

No animal studies were included.

Systemic Responses

No outcomes of interest involving systemic responses were reported in this study.

Overall Quality of Evidence

With data for these local response outcomes based on one moderate-sized RCT, the overall quality of evidence for these outcomes was rated as low. The quality of evidence for systemic responses was very low (no evidence).

Sealant

4 human studies (2 RCTs,[43,44] and 2 non-randomized comparative studies,[45,46]) provided evidence for this application of CA. All studies were conducted with human subjects. Two of these studies[43,45] concerned procedures for reinforcing the stapler line after laparoscopic sleeve gastrectomy. For further information see Table 6 in Appendix D.

Local Responses/Device Events (human studies)

All 4 studies evaluated local responses/device events related to surgical procedures utilizing cyanoacrylates in human subjects. We address outcomes that most directly serve as potential indicators for adverse skin reactions to CA.

One RCT[43] found no significant difference in the incidence of leakage, bleeding, stricture or mortality when using CA to reinforce a staple line following laparoscopic sleeve gastrectomy. Although not statistically significant, leakage occurred in 4% patients, bleeding occurred in 14% patients and mortality occurred in 2% patients in the group where CA was used.

One RCT[44] found statistically less seroma formation, seroma drainage and seroma aspirated, as well as statistically shorter drainage time when CA adhesive was used following modified radical mastectomy or quadranectomy. Age, BMI, breast weight, tumor size and number of infiltrated lymph nodes all correlated significantly with the amount of seroma fluid produced.

One comparative study[45] found less leakage, less severe leakage, but more need for reoperation during initial stay when CA reinforced the stapler line after laparoscopic sleeve gastrectomy, however these results were not statistically significant.

One comparative study[46] found less mean total drainage and lower rate of chyle leakage when CA was used to seal thoracic duct area following total thyroidectomy with unilateral next dissection.

All four studies reported on drainage/leakage up to 36 months. Two studies[44,46] reported statistically less drainage/leakage when CA was used following modified radical mastectomy or quadranectomy or when CA was used to seal the thoracic duct area following total thyroidectomy with unilateral neck dissection. The other two studies[43,45] reported less drainage/leakage when CA was used to reinforce the stapler line in laparoscopic sleeve gastrectomy, however the difference was not statistically significant.

Two studies[44,46] reported on seroma/hematoma formation up to 24 months. One study[45] reported statistically less seroma formation when CA was used following modified radical mastectomy or quadrenectomy. Another study[46] reported seroma formation in 1.2% patients when CA was used to seal the thoracic duct area following total thyroidectomy with unilateral neck dissection.

Systemic Responses (human studies)

No outcomes of interest involving systemic responses were reported in any study.

Overall Quality of Evidence

The evidence base was small and all reported studies had control groups. Overall the quality of evidence was moderate for drainage/leakage when CA was used to reinforce the stapler line after laparoscopic sleeve gastrectomy and as an adhesive following modified radical mastectomy or quadranectomy and thoracic duct area following total thyroidectomy. For other local responses (no systemic reported), the quality of evidence was low due to the responses being reported in single studies.

Other Applications

4 human studies (all RCTs [47-50]), provided evidence for this application of CA. Three of these studies[47-49] concerned procedures for anchoring dressings for catheter placement. These studies compared use of CA to other dressings and all involved pediatric patients. One study compared the use of CA to fibrin glue for attaching eye muscle to the sclera in strabismus correction surgery.[50] For further information see Table 7 in Appendix D.

Local Host Responses (human studies)

All 4 studies evaluated local responses/device events related to surgical procedures utilizing cyanoacrylates. We first address outcomes that most directly serve as potential indicators for adverse skin reactions to CA. We then discuss additional outcomes that may be indirectly related to adverse local reactions.

Three RCTs[47-49] reported on itching, pruritus, rash, or other skin irritations at locations on the skin where CA was used to secure polyurethane dressing for a peripherally inserted central catheters (PICC) in children. One RCT[47] reported no incidences of dermatitis with use of CA, standard care, or integrated securement devices (ISDs). Two studies by Ullman and colleagues[47,48] found no evidence of increased itching associated with CA use. One study[47] found no incidences of itching in any of the treatment groups (CA, standard care, or integrated securement devices). The other study[48] found the lowest incidence for CA and sutureless securement (SSD) groups (no cases in either group), and only 1 case for the ISD group and 2 cases (18%) for standard care group.

Both studies by Ullman et al.[47,48] found no significant difference in the incidence of rash when using CA as compared to other techniques. The more recent RCT[47] reported 1 patient in each group (CA, standard care or SSD), while the other study reported no cases for the CA or ISD groups, and only 1 case each for standard care and SSD groups. The earlier RCT by Ullman et al.[48] found no significant difference in the incidence of blister (no cases in the CA or SSD groups and only 1 case each for standard care and ISD groups).

One of the above RCTs[49] reported on all-cause skin irritation (which included itch, rash, skin tear and blisters) and found no significant difference in with use of CA to anchor dressings for PICC lines compared to use of SSDs or ISDs. However, the difference did trend toward significance (p=0.10), and incidences were highest with using CA (n=10 [31%] for CA versus n=5 [16%] and n=3 [10%] for SSDs and ISDs, respectively. Bruising was included in all-cause skin irritation but there was only one incidence in the CA group). Regarding individual types of irritation, itching, rash, and blistering were not noticeably different between groups.

Two RCTs[47,49] reported on skin tears and results were conflicting. One RCT[47] found the rates of skin tear lowest for CA and standard care groups (2%) and higher for the ISD group (4%). In contrast, the other study examining dressings for PICC lines in children[49] found much more frequent incidence when using CA (n=7; 22%) than with use of standard care or ISDs (no incidence with either of these devices; statistical comparisons for individual skin irritations were not reported).

The three RCTs on catheter dressings reported on additional outcomes with potential relation to skin irritation. One RCT[47] reported on dressing changes due to bleeding and found a lower rate with use of CA group than for ISD and standard care (8% for CA, 11% for ISD, 20% for SC).

All 3 RCTs addressed the rate of partial or complete dislodgement of the catheter dressings. Two RCTs[47,49] reported on complete dislodgement and found a low incidence for all types of dressing (≤4% across both studies) with no significant group differences. One of the 2 RCTs[47] reported no cases of complete dislodgement with use of CA. Three RCTs reported on the incidence of partial dislodgement[47-49] and none found any significant differences with use of CA or other dressings.

Failure rate of catheter dressings was reported in the two studies by Ullman and colleagues.[47,48] Raw data on the rate of this outcome were somewhat conflicting but neither study found a significant difference between use of CA and the other approaches to anchoring dressings. The 2019 RCT[47] found the highest failure rate for the CA group while the 2017 RCT[48] found the most failures for the ISD group (n = 2; 17%) and no failures for CA or SC groups.

One RCT[50] compared CA to fibrin glue for attaching eye muscle to the sclera in strabismus correction surgery. This study reported on levels of chemosis and conjunctival reaction, as well as incidence of granuloma formation, and overall score for inflammatory indicators. Aside from the application and the comparator substance (fibrin glue), this study was also unique in finding use of CA to produce consistently higher levels of irritation. The level of chemosis (localized swelling of the conjunctiva) was significantly higher for the CA group at 3 weeks (p=.039) and higher with borderline significance at 3 months (p=.058), as compared to the group treated with fibrin glue. Conjunctival reaction was significantly higher in the CA group at 1 week (p=.01), 3 weeks (p=.027), and 3 months (p<0.001) follow-up. Incidence of granuloma formation was observed in 2 patients in CA group and none in the fibrin glue group. Accordingly, total inflammatory score was significantly higher in the CA group at 1 week (p=.025), 3 weeks (p=.002), and 3 months (p<0.001) follow-up.

Systemic Responses (human studies)

The 2019 RCT by Ullman et al.[47] reported on death in pediatric patients with central venous access devices (CVADs). These incidences were not likely due to CA use; only 1 out of 59 patients (1.7%) in the CA group compared to no patients in the ISD group and 3 patients (5.5%) for the standard care group. No other systemic reactions were reported.

Overall Quality of Evidence

The overall quality of evidence on local responses is moderate for various skin irritations and dislodgement or failure of catheter dressings. Outcomes were reported from a few RCTs and results were generally in agreement in indicating low incidence of such responses with use of CA. The data on skin tears, however, is an exception, with one RCT noting a higher incidence with use of CA. The quality of evidence for other local responses is low because they were reported in single studies. The quality of evidence for systemic responses (mortality only) is also low as there was only one modestly sized RCT reporting on this outcome with a low rate of occurrence, and death was unlikely to be related to CA use.

ECRI Surveillance Data

ECRI surveillance database searches were guided by the terms listed in Appendix F. The accident investigation and PRN data on CA devices included 1 report involving a liquid bandage and 1 report involving sealant. One accident investigation concluded that liquid embolic system (sealant) used in the incident procedure was dispersed into non-targeted vessels resulting in neurological complications. The unintended release of this sealant was a result of internal catheter overpressurization due to a kink in the catheter's distal tip. One PRN described "small pimples" developing at an area where a single coat of Liquiband was applied to a wound. Additionally, the liquiband failed to completely seal the wound.

Approximately 90% of all PSO reports involved adhesives with the top two complications being 53% reporting allergic reactions to adhesives (16) and about 17% reporting hemorrhage/hematoma (5). Twenty reports resulted in non-harm (harm scores of B1, C and D) while 4 were categorized as harm (harm scores of E and F) and 6 were not categorized. Of the reports resulting in harm, 3 involved an allergic reaction to adhesives and 1 involved skin redness and blistering at the site of liquid bandage application. Health Technology Alerts database returned 9 manufacturer issued alerts none of which involved biocompatibility responses to CA.

Patient Safety Organization

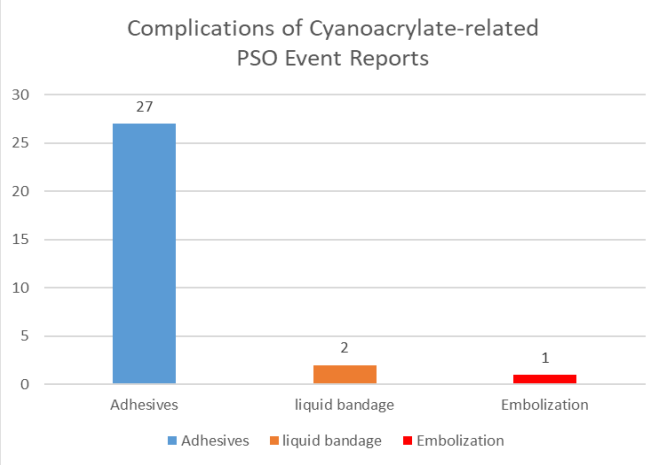
Search Results:

ECRI PSO identified 242 reports that involved Cyanoacrylate materials that occurred between April 2015 and November 2020. 30 of these involved complications. The top 5 complications included: 1) Allergic Reaction 16 (53.3%), 2) Hemorrhage/Hematoma 5 (16.7%), 3) Device malfunction 4 (13.3%), 4) Dehiscence 2 (6.7%), 5) Clinical Manifestation 1 (3.3%).

All individual PSO event reports are redacted and included in Appendix F.

Table 3: Complications in Cyanoacrylate - related PSO Event Reports

Complication	Adhesives	Embolization	Liquid bandage	Sealant	Total
Allergic reaction	16				16
Hemorrhage/Hematoma	5				5
Device malfunction	2	1	1		4
Dehiscence	2				2
Clinical manifestation	1				1
Skin redness/blisters			1		1
Cellulitis	1				1
Total	**27**	**1**	**2**	**0**	**30**



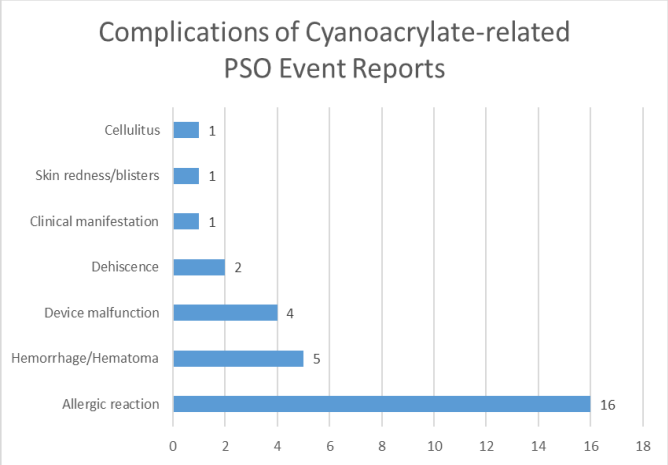


Table 4: Harm score associated with cyanoacrylate-related event reports

Harm Scores (NCC-MERP)		Adhesives	Embolization	Liquid bandage	Sealant	Total
A	No Error	1				1
B1	Error, No Harm			1		1
B2	Error, No Harm					
C	Error, No Harm	12				12
D	Error, No Harm	6				6
E	Error, Harm	2		1		3
F	Error, Harm	1				1
G	Error, Harm					
H	Error, Harm					
I	Error, Death					
NULL *		5	1			6
Total		**27**	**1**	**2**	**0**	**30**

**Harm score was not reported*

Accident Investigations

Search Results: One (1) investigation was recovered and is summarized in **Error! Reference source not found.**.

This investigation is redacted and included in Appendix F.

Table 5: Accident Investigations of Patient Incidents Involving Cyanoacrylate-related Devices

Device Type	# Investigations	Reported Problem and Findings
Codman TRUFILL n-CBA liquid embolic agent	1	Balt Magic 1.5Fr catheter burst during injection of embolization glue as a result of internal catheter overpressurization. The glue was dispersed into non-targeted vessels resulting in neurological complications. The liquid embolic system (i.e. glue) used in the incident procedure contains n-Butly Cyanoacrylate (n-BCA), ethiodized oil, and tantalum powder, which are intended to be mixed together prior to injection.

ECRI Problem Reports

Search Results: The search returned 1 report submitted by ECRI members.

Key Issues: The report detailed that the application site developed small pimples and that at follow up the incision was a large open wound.

Safety Concerns: The report specified that the the wound was still open two weeks later. Surgeon monitored the patient for re-excision of the skin and reclosure.

All problem reports are redacted and included in Appendix F

Table 6: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem (number problem reports)
Adhesive [MPN]	1	48 hours following adhesion application, small pimples developed. Follow up 12 days later, the patient had a large open wound.

Healthcare Technology Alerts

Search Criteria: See Excel sheet of search terms

Search Results: The search returned 9 manufacturer issued alerts describing problems with longer-than-expected dry times, IFU updates, premature solidification, discoloration, mislabeling, and compromised sterility, summarized in **Error! Reference source not found.**.

Table 7: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
MPN (Tissue Adhesive for the Topical Approximation of Skin)	7 Manufacturer Issued	• Premature solidification • Longer-than-expected dry time • Discoloration • Compromised sterility • Mislabeling • IFU update
KGG (Tissue Adhesive for Use in Embolization of	1 Manufacturer Issued	• IFU incorrect

Device Type	# Alerts	Reported Problem
Brain a Arteriovenous Malformations)		
PJQ (Agent, Occluding, Vascular, Permanent)	1 Manufacturer Issued	• Compromised sterility

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of CA. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

CA as a Material

There is moderate evidence (two observational studies) indicating that CA adhesives can result in allergic reactions (contact dermatitis). However, there are no studies investigating systemic responses to CA as a material indicating that more research is needed.

Fixation

Thirteen human studies (9 RCTs and 4 non-randomized comparative studies) investigated local responses/device events related to surgical procedures utilizing CA resulting in moderate evidence for foreign object sensation, seroma formation, reoperation, and chronic pain. Only one study investigated systemic responses with inconclusive results indicating that more research is needed to investigate the systemic responses to CA fixation devices.

Tissue Adhesive

Twelve human studies investigated local responses/device events related to CA tissue adhesives resulting in moderate evidence for inflammation and other complications. The quality of evidence for systemic responses is low because it only included one RCT reporting higher incidence of respiratory distress with use of CA over sutures and it did not include statistical analysis. This indicates more research is needed to investigate systemic responses for CA tissue adhesives.

Embolization

Three studies involving humans (1 SR, 1 RCT, and 1 non-randomized comparative study) reported phlebitis, ecchymosis and other complications associated with the treatment of varicose veins resulting in moderate quality of evidence. However, for all other host responses/device events including gastroesophageal varices and NCBA transarterial embolizations, there is a low quality of evidence. For systemic responses there are only 3 studies with findings of Grade 3 and 4 serum ALT and AST elevation. Overall, there is a need for further research in all host responses associated with gastroesophageal varice and NCBA transarterial embolization procedures, with the exception of varicose veins, as well as systemic responses to embolization involving CA.

Wound Closure

Overall, there is a need for further research into both local responses/device events as well as systemic responses to CA for embolization. Only one human study reported some post-operative bleeding and swelling during a procedure (low quality of evidence) and there are no studies investigating systemic responses to CA (very low quality of evidence).

Sealant

Four human studies (2 RCTs, and 2 comparative studies) investigated local responses/device events related to surgical procedures using CA as a sealant. There is moderate evidence that indicate reduced leakage when CA reinforced a staple line as well as procedures including radical mastectomy or quadranectomy and thoracic duct area following total thyroidectomy.

However, there are no studies investigating systemic responses associated with CA as a sealant indicating that more research is needed.

Other Applications

Three human studies (all RCTs) evaluated local response/device events, such as itching, rash and dressing failure, related to using CA to secure polyurethane dressing for a peripherally inserted central catheter (PICC) in children resulting in a moderate quality of evidence. The quality of evidence for complications associated with CA fibrin glue and systemic responses to CA is low because both involved a single study. For systemic responses, the lone RCT reported a death; however, it is unlikely associated with CA. Accordingly, more research is indicated for systemic responses to CA securement applications.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1	English language publication
2	Published between January 2011 and February 2021
3	Human studies
4	Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5	Studies that evaluate toxicity/biocompatibility of cyanoacrylates or priority devices that include this material

Exclusion Criteria

1.	Foreign language publication
2.	Published before January 2011
3.	Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4.	Off-topic study
5.	On-topic study that does not address a key question
6.	No device or material of interest
7.	No relevant outcomes (adverse events or biocompatibility not reported)
8.	Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1.	**Quality of comparison –** is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2.	**Quantity of data** – number of systematic reviews and individual studies providing relevant data.
3.	**Consistency of data** – are the findings consistent across studies that report relevant data?
4.	**Magnitude of effect** – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5.	**Directness of evidence** – do human studies isolate the effect of the device (i.e., can the adverse effects be attributed to the device)?
6.	Is there evidence of a **dose response or time response** (e.g., adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n=174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Literature Search for Cyanoacrylate (CA)

Set Number	Concept	Search Statement
Material		
1.	Cyanoacrylate (CA)	'cyanoacrylate'/exp OR 'cyanoacrylate'/syn OR 'cyanoacrylic acid octyl ester'/exp OR 'cyanoacrylate derivative'/exp OR 'poly(ethyl 2 cyanoacrylate)'/exp OR 'poly(hexyl 2 cyanoacrylate)'/exp OR 'poly(isobutyl 2 cyanoacrylate)'/exp OR 'ethyl cyanoacrylate'/exp OR 'butylcyanoacryl*' OR 'hexylcyanoacryl*' OR 'isobutylcyanoacryl*' OR 'ethylcyanoacryl*' OR 'methylcyanoacryl*' OR 'octylcyanoacryl*' OR 'polybutylcyanoacryl*' OR polyethylcyanoacryl* OR polyhexylcyanoacryl* OR 'polyisobutylcyanoacryl*' OR 'cyanoacryl*' OR 'cyanoacrylic*' OR ((cyano OR butylcyano OR hecxylcyano OR isobutylcyano OR ethylcyano OR methylcyano OR octylcyano) NEAR/2 acryl*)
2.	CA Trade Names	'enbucrilate'/exp OR enbucrilate* OR 'bucrilate'/exp OR bucrilate* OR bucrylate* OR mecrylate* OR mecrilat* OR ocrilate* OR ocrylate*
3.	CA Devices: General	'cyanoacrylate glue'/exp OR 'glue embolization'/exp OR 'glue embolization' OR 'cyanoacrylate closure*' OR 'cyanoacrylate adhesive*' OR ((embol* OR 'adhesive?' OR 'glue?' OR 'sealant?' OR occl* OR emboli* OR closure) AND ('nbca':ti,ab OR 'nbca': ti,ab OR 'n-hca':ti,ab OR 'nhca':ti,ab OR 'ibca':ti,ab OR ('oca':ti,ab NOT obeticholic)))
4.	CA devices: from FDA	'actabond':ti,ab,kw,dn OR 'cavilon':ti,ab,kw,dn OR 'chirurcoll':ti,ab,kw,dn OR 'cyacrin?':ti,ab,kw,dn OR 'cyanoveneer': ti,ab,kw,dn OR

	ProCodes	'dermabond*':ti,ab,kw,dn OR 'derma bond*':ti,ab,kw,dn OR 'derma flex*':ti,ab,kw,dn OR 'dermaflex*':ti,ab,kw,dn OR 'endocryl':ti,ab,kw,dn OR 'exofin':ti,ab,kw,dn OR 'fimomed':ti,ab,kw,dn OR 'flexaid': ti,ab,kw,dn OR 'flexaid':ti,ab,kw,dn OR 'glubran':ti,ab,kw,dn OR 'glubran2':ti,ab,kw,dn OR 'gluseal*':ti,ab,kw,dn OR 'glusite*':ti,ab,kw,dn OR 'glustitch*':ti,ab,kw,dn OR 'histoacryl':ti,ab,kw,dn OR 'ifabond':ti,ab,kw,dn OR 'indermil':ti,ab,kw,dn OR 'isodent':ti,ab,kw,dn OR 'isodent': ti,ab,kw,dn OR 'kanokonlit':ti,ab,kw,dn OR 'liquiband':ti,ab,kw,dn OR 'liquishield*':ti,ab,kw,dn OR 'octyldent*':ti,ab,kw,dn OR 'omnex':ti,ab,kw,dn OR 'pattex':ti,ab,kw,dn OR 'periacryl*':ti,ab,kw,dn OR 'proderma':ti,ab,kw,dn OR 'skinaffix':ti,ab,kw,dn OR 'skin affix':ti,ab,kw,dn OR 'surgi seal*':ti,ab,kw,dn OR 'surgiseal*':ti,ab,kw,dn OR 'swiftset':ti,ab,kw,dn OR 'trufill':ti,ab,kw,dn OR 'venaseal*':ti,ab,kw,dn OR 'variclose*':ti,ab,kw,dn OR 'veinoff*':ti,ab,kw,dn OR 'venablock*':ti,ab,kw,dn OR 'venoblock*':ti,ab,kw,dn OR 'venex':ti,ab,kw,dn OR 'veclose':ti,ab OR 'sapheon glue' OR cyanolit*
5.	CA devices: from literature search	'3s biokit':ti,ab,kw,dn OR 'adhflex':ti,ab,kw,dn OR 'amcrylate*':ti,ab,kw,dn OR 'compont':ti,ab,kw,dn OR 'endoacryl':ti,ab,kw,dn OR 'epidermglu':ti,ab,kw,dn OR 'epiglu':ti,ab,kw,dn OR 'evobond':ti,ab,kw,dn OR 'floraseal':ti,ab,kw,dn OR 'gluseal':ti,ab,kw,dn OR 'glueseal':ti,ab,kw,dn OR 'hystoacryl':ti,ab,kw,dn OR 'loctite*':ti,ab,kw,dn OR 'nectacryl*':ti,ab,kw,dn OR 'neucrylate*':ti,ab,kw,dn OR 'nexacryl*':ti,ab,kw,dn OR 'novocryl*':ti,ab,kw,dn OR 'octylseal':ti,ab,kw,dn OR 'safety seal':ti,ab,kw,dn OR 'safetyseal':ti,ab,kw,dn OR 'sicomet':ti,ab,kw,dn OR 'tisuacryl*':ti,ab,kw,dn OR 'topocryl*':ti,ab,kw,dn OR 'traumaseal':ti,ab,kw,dn OR 'tru fill':ti,ab,kw,dn OR 'xion':ti,ab,kw,dn OR 'zapit':ti,ab,kw,dn
6.	Combine and Limit by language and publication date	(#1 OR #2 OR #3 OR #4 OR #5) AND [english]/lim AND [2011-2021]/py
7.	Limit by publication type	#6 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

8.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
9.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
10.		Leachable* OR extractable*
11.		shrink*:ti,ab OR contract*:ti,ab OR stretch*:ti,ab OR retract*:ti,ab OR extension:ti,ab OR deform*:ti,ab OR creep:ti,ab OR plasticity:ti,ab OR disintegrat*:ti,ab OR fail*:ti,ab OR fragment*:ti,ab OR debond*:ti,ab OR migrat*:ti,ab OR leak*:ti,ab

		OR microleak*:ti,ab OR compression:ti,ab
12.		'mechanics'/exp
13.		'device material'/exp/mj
14.		'Biomedical and dental materials'/exp/mj
15.	Combine sets	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16.	**CA + Material Response**	**#7 AND #15**

Host Response

17.		Host NEAR/2 (reaction* OR response*)
18.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
19.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj OR 'pruritus'/exp OR 'pruritus' OR 'skin irritation'/exp OR itch*:ti,ab
20.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
21.		'inflammation'/exp OR inflamm*:ti,ab OR vasculitis:ti,ab OR swell*:ti,ab
22.		'foreign body' OR granuloma* OR 'foreign body'/exp
23.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis'/exp OR necrosis OR ((skin OR wound*) NEAR/3 ulcer*)
24.		protrude* OR protrus* OR perforat*
25.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'seroma*' OR 'hematoma*' OR 'thrombosis'/exp OR 'thrombosis'/syn OR 'phlebitis'/exp OR 'phlebitis'/syn OR phlebitis OR thrombophlebitis
26.	Combine sets	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27.	Combine sets CA + Material Response+ Host Response	#16 AND #26
28.	**CA devices + Host response**	#7 AND (#3 OR #4 OR #5) AND #26
29.	**Final set**	**#27 OR #28**

Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight
                            - Extremely low birth weight
            - Body weight change
                - Body weight fluctuation
                - Body weight gain
                    - Gestational weight gain
                - Body weight loss
                    - Emaciation
                - Body weight control
                - Fetus weight
                - Ideal body weight
                - Lean body weight
                - Live weight gain
            - Dry weight
            - Fresh weight
            - Molecular weight
            - Organ weight
                - Brain weight
                - Ear weight
                - Heart weight
                - Liver weight
                - Lung weight
                - Placenta weight
                - Spleen weight
                - Testis weight

        - Thyroid weight
        - Uterus weight
      - Seed weight
      - Tablet weight
      - Thrombus weight
    - Weightlessness
  - Hydrodynamics
    - Hypertonic solution
    - Hypotonic solution
    - Isotonic solution
    - Osmolality
      - Hyperosmolality
      - Hypoosmolality
      - Plasma osmolality
      - Serum osmolality
      - Urine osmolality
    - Osmolarity
      - Blood osmolarity
      - Hyperosmolarity
      - Hypoosmolarity
      - Plasma osmolarity
      - Serum osmolarity
      - Tear osmolarity
      - Urine osmolarity
    - Osmosis
      - Electroosmotic
      - Osmotic stress
        - Hyperosmotic stress
        - Hypoosmotic stress
  - Photodynamics
    - Photoactivation
      - Photoreactivation
    - Photodegradation
    - Photoreactivity
      - Photocytotoxicity
      - Photosensitivity
      - Photosensitization
      - Phototaxis
      - Phototoxicity
    - Photostimulation
  - Proton motive force
  - Shock wave
    - High-energy shock wave
  - Stress strain relationship
  - Thermodynamics
    - Adiabaticity
    - Enthalpy
    - Entropy
- Elasticity
  - Viscoelasticity
  - Young modulus
- Force
- Friction
  - Orthodontic friction

- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics

- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity
- Viscoelasticity

Appendix C. Study Flow Diagram

I. 1010 citations identified by searches
    a. **634 citations not screened manually due to likely irrelevance** (based on text mining, logistic regression, etc.)
    b. 376 articles selected for title/abstract screening
        i. 303 selected by text mining in Distiller (30%)
        ii. 51 by logistic regression (5%), 22 for including "random" or "systematic" in the title or abstract.
            1. **111 citations excluded at the title/abstract level -** Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest
            2. 265 full-length citations reviewed
                a. **76 citations excluded at the full article level -** Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest
                b. 186 citations reviewed for evidence prioritization
                    i. **137 citations excluded at the prioritization level -** Citations excluded at this level were animal studies (50), single-arm studies (69), or other (12).
                    ii. 49 citations included

Appendix D. Evidence Tables

Table 8: Cyanoacrylates as a Material - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Asai et al. 2020[1]

Study Design: Retrospective observational study

Device or Material: Dermabond Advanced (Ethicon, Tokyo, Japan); Applied with patch test kit (Finn Chambers (SmartPractice, Phoenix, AZ) and patch test panel (Sato, Tokyo, Japan) on Medipore tape (3M, St Paul, MN); methacrylate series, methyl cyanoacrylate 10.0% pet. (Chemotechnique Diagnostics); ethyl cyanoacrylate (Aron Alpha (Toagosei, Tokyo).

Contact Duration: 48 hours

Dose: Range 0.1 to 10% concentration

Frequency/Duration: 1-2 applications

Response: Allergic contact dermatitis (ACD)

Patient characteristics (gender, mean age): Patients who underwent orthopedic surgery and subsequent patch testing on upper back with Dermabond; 26.3% male; mean 50 years of age for patients testing positive (age for overall cohort NR)

Number per group: 577 total patients

Observed adverse effects: 9 patients (1.5%) had allergic reaction to Dermabond from surgery and also had positive patch test results: 6 after first application, 3 after second; of 8 of these patients tested with ethyl cyanoacrylate (10% in petroleum); 4 (50%) had reactions

Timing of adverse effects: Mean time of onset of ACD was 34.1 days (range, 27-44 days) after Dermabond application. Mean duration of onset was 5.6 days (range 4-8 days) for 3 patients who developed initial ACD after second application.

Factors that predict response: NR

Source Citation: Cook et al. 2019[2]

Study Design: Observational

Device or Material: OCA and/or BCA (GluStitch Inc.; Delta, British Columbia, Canada), or Ethyl CA (Chemotechnique, Vellinge, Sweden, and Smart Practice, Alberta, Canada)

Contact Duration: 48 hours

Dose: Varying concentrations (range 10-99% in petroleum)

Frequency/Duration: Single application; f/u 2 days, 4-5 days, 1 week

Response: Skin patch test reactions

Patient characteristics (gender, mean age): Patients with a history of contact dermatitis from cyanoacrylate- or methacrylate-containing products; gender/age NR

Number per group: 38 patient's total

Observed adverse effects: 13 of the 35 patients (37%) tested with both methacrylates and acrylates were positive for **skin response** to 1 or more methacrylates or acrylates; 22 (63%) had negative results to the tested methacrylates and acrylates. 17 of 21 patients (81%) with likely clinical history of contact dermatitis from Dermabond had positive results when tested with OCA.

Timing of adverse effects: Results were read at 48 hours; exact time NR

Factors that predict response: **Concentration of CA**: Patch testing of Dermabond-allergic patients least sensitive with 10% ECA (6 of 21 [29%] positive) and 10% OCA (8 of 16 [50%]). Patch test positivity with OCA increased when tested undiluted. 4 patients exhibited concentration-dependent patch test reactivity to OCA: negative result with 10% or 30% concentration but positive with undiluted (>99%). **Abraded skin**: 3 patients with condition-dependent patch test reactivity to Dermabond and negative test results on intact skin had positive results on abraded skin. Not all subjects were tested with differing concentrations or abraded skin.

ACD = allergic contact dermatitis; BCA = butyl cyanoacrylate; CA = cyanoacrylate; Dose = mg/kg/day; NA = not applicable; NR = not reported; Obs = observational; OCA = octyl-2-cyanoacrylate; R = reliable; Retro = retrospective.

Table 9: Fixation - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Yu et al. 2020[12]

Study Design: Retro controlled cohort

Device or Material: CA (Histoacryl; B. Braun, Germany) vs. tacks (Protack; Covidien, USA) for securing mesh (various mfrs)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Overall post-operative complications, Seroma or hematoma Recurrence

Patient characteristics (gender, mean age): Patients undergoing laparoscopic hernia repair; 91.5% male; mean age 58.8 and 54.3 years for CA and tack groups, resp.

Number per group: CA group (n=70); tack group (n=583)

Observed adverse effects: Rate of **overall post-operative complications** not significantly different between groups. **Seroma or hematoma:** no significant difference between groups (12.9% for CA group vs. 13.9% for tack group; p=0.81). **Recurrence rates** comparable in the CA and tack groups (2.9% and 3.1%, p = 0.916).

Timing of adverse effects: NR; f/u 6 months (6 to 11) and 10 months (6 to 34) for CA and tack groups, resp.

Factors that predict response: NR; significant differences noted in mesh materials used, procedure time, intraoperative complications, and follow-up time

Source Citation: Köckerling et al. 2018[13]

Study Design: Retro controlled cohort

Device or Material: CA or tacks (for mesh fixation) vs. no mesh fixation; All materials obtained from multiple mfrs

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Seroma

Patient characteristics (gender, mean age): Patients who underwent transabdominal preperitoneal patch plasty (TAPP) for hernia repair, from database of 577 hospitals; 100% men; minimum 16 years of age

Number per group: CA fixation (n=4818; 24.1%); tack fixation (n=6387; 31.9%); no mesh fixation (n=8799; 44.0%); 20,004 total patients

Observed adverse effects: **Seroma** formation more common in CA group (3.9%) vs. tacks (2.1%) or non-fixation (0.7%); p<0.001.

Timing of adverse effects: NR; 1-year f/u

Factors that predict response: Risk of seroma development increases significantly with fixation technique and hernia defect size (p<0.001). Seroma more common with CA compared to tacks (OR 2.077[1.650 to 2.613]; p < 0.001) and with CA vs non-fixation (OR 5.448[4.056; 7.317]; p < 0.001).

Source Citation: Liew et al. 2017[6]

Study Design: RCT

Device or Material: Histoacryl glue (B. Braun) vs titanium tacks (Protack-5, Covidien); to attach polypropylene mesh (Optilene, B. Braun)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Seroma, Chronic groin pain (VAS score at extended f/u)

Patient characteristics (gender, mean age): Patients with unilateral uncomplicated inguinal hernia; 100% male; 55 years (mean of 2 group means)

Number per group: 32 CA group and 34 in tack group

Observed adverse effects: No significant difference in incidence of **seroma** between groups (7/32 [21.9%] for glue and 8/34 [23.5%] for tack groups; p=0.873). No significant difference in **post-op chronic groin pain** between groups (2/32 [6.3%] for glue and 0/34 [0%] for tack groups; p=0.231). No difference in **VAS scores** 3 months post-surgery; both groups had same median VAS scores over 5 time points following surgery.

Timing of adverse effects: Post-operative (exact time NR); VAS scores measured at 4 hours; 1, 2, and 7 days; and 3, 7 months.

Factors that predict response: Pain (VAS score) at 48 hours correlated with WBC level (r=0.035; p=0.035)

Source Citation: Matikainen et al. 2017[7]

Study Design: RCT

Device or Material: Histoacryl glue (B. Braun) vs titanium tacks (Protack-5, Covidien); to attach polypropylene mesh (Optilene, B. Braun)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Seroma, Chronic groin pain (VAS score at extended f/u)

Patient characteristics (gender, mean age): Patients with unilateral uncomplicated inguinal hernia; 100% male; 55 years (mean of 2 group means)

Number per group: 32 CA group and 34 in tack group

Observed adverse effects: No significant difference in incidence of **seroma** between groups (7/32 [21.9%] for glue and 8/34 [23.5%] for tack groups; p=0.873). No significant difference in **post-op chronic groin pain** between groups (2/32 [6.3%] for glue and 0/34 [0%] for tack groups; p=0.231). No difference in **VAS scores** 3 months post-surgery; both groups had same median VAS scores over 5 time points following surgery.

Timing of adverse effects: Post-operative (exact time NR); VAS scores measured at 4 hours; 1, 2, and 7 days; and 3, 7 months.

Factors that predict response: Pain (VAS score) at 48 hours correlated with WBC level (r=0.035; p=0.035)

Source Citation: Ronka et al. 2015[8]

Study Design: RCT

Device or Material: CA (Histoacryl; B. Braun, Germany) vs. self-gripping mesh (Parietex ProGrip; Covidien, USA) or non-absorbable sutures; mesh fixation (Optilene, B. Braun, Germany or Ultra-pro, Ethicon, USA)

Contact Duration: NR

Dose: 0.5 ml

Frequency/Duration: Single application

Response: Recurrence, Seroma or infection, Feeling of foreign object

Patient characteristics (gender, mean age): Patients undergoing inguinal hernioplasty; 94% male; mean age 57 years

Number per group: CA (n=208); self-grip mesh (n=193), or non-absorbable sutures (n=198); 599 total patients analyzed

Observed adverse effects: **Recurrence** not significantly different between groups (0.9%, 0%, and 0.9% for CA, self-grip, and suture groups, resp.; p=0.38). Incidence of **seroma** not significantly different between groups (5.0%, 6.9%, and 3.9% for CA, self-grip, and suture groups, resp.; p=0.38). **Feeling of foreign object** not significantly different (17%, 18%, and 13% for CA, self-grip, and suture groups, resp.; p=0.37).

Timing of adverse effects: 1-year f/u

Factors that predict response: NR

Source Citation: Subwongcharoen and Ruksakul 2013[9]

Study Design: RCT

Device or Material: Histoacryl vs. staples (ProTack, Covidien Surgical); to attach Ethicon UltraPro mesh (J&J)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Pruritus, Seroma, Chronic pain, Recurrence

Patient characteristics (gender, mean age): Patients with inguinal hernia; 97% men; 50 years (mean of two group means)

Number per group: CA (n=30); staple (n=30); 60 total patients

Observed adverse effects: **Pruritus:** 1 case glue group vs. 0 in staple group; **Seroma:** 1 case in staple group vs. 0 in glue group; No significant group difference in **chronic pain** at 1 year f/u (n=5 [17%] for CA group vs. n=10 [33%] for staples; p=0.36); No significant difference in **recurrence** (1 incidence in the staple group only; p=1.0).

Timing of adverse effects: Up to 1 year; 1 incidence of recurrence at 8 months follow-up

Factors that predict response: NR

Source Citation: Wang et al. 2013[15]

Study Design: Retro controlled cohort

Device or Material: **CA (Compont Medical Adhesive**, Beijing, China) vs.Titanium tacks (mfr NR); CA+ tacks; no fixation; For mesh attachment (Covidien, USA)

Contact Duration: NR

Dose: 4-5 sprays of glue over 4 quadrants of skin and mesh

Frequency/Duration: Single application

Response: Hematoma or seroma formation

Patient characteristics (gender, mean age): Patients who received laparoscopic transabdominal pre-peritoneal (LSTAPP) inguinal hernia repair; 84% male; mean 61 years old

Number per group: CA only (n=552); CA+tacks (n=47); tacks only (n=89); non-fixation (n=339)

Observed adverse effects: **Hematoma/seroma formation**: decreased incidence with CA (9.6% for CA-only and 8.5% for CA+tacks vs. 22.5% with tacks only, and 15.2% for no-fixation groups (statistical analysis NR).

Timing of adverse effects: NR; mean 19-month f/u

Factors that predict response: NR

Source Citation: Brugger et al. 2012[10]

Study Design: RCT

Device or Material: Glubran CA (G.E.M., Viareggio, Italy) vs. staples (ProTak AutoSuture; Switzerland); to attach Vypro II mesh (Ethicon Switzerland, J&J Medical)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Hematoma/seroma

Patient characteristics (gender, mean age): Patients with inguinal hernia; 98.7% men; 58 years (mean of two group means)

Number per group: CA (n=37); staples (n=40)

Observed adverse effects: **Hematoma/seroma** not significantly different (3/37 [8%] glue group vs. 1/40 [3%] staple group, p=0.34

Timing of adverse effects: Median f/u glue group 45 months (14 to 56) vs. staple group 37 months (13 to 51)

Factors that predict response: NR

Source Citation: Kim-Fuchs et al. 2012[11]

Study Design: RCT

Device or Material: CA (Histoacryl; mfr NR) vs. suture (PDS 2.0; Ethicon); For mesh attachment (VIPRO II; Ethicon, J&J, Austria)

Contact Duration: NR

Dose: Small drops CA to anchor mesh

Frequency/Duration: Single application

Response: Recurrence, Hypoesthesia

Patient characteristics (gender, mean age): Patients undergoing Lichtenstein hernia repair; 100% male; mean age 56 years

Number per group: CA group (n=131); suture group (n=134); 264 total patients

Observed adverse effects: **Recurrence** not significantly different between groups at 5-year f/u (5.8% [5 of 85] for suture group vs. and 10% [7 of 70] for CA group; p=0.379); also n.s. at 3 and 12 months. **Hypoestesia** not significantly different after 3 months (20.9% for CA vs. 23.7% for suture group; p=0.16); also n.s. at 12 months and 5 years.

Timing of adverse effects: Specific times NR

Factors that predict response: NR

Source Citation: Sundaram et al. 2020[3]

Study Design: RCT

Device or Material: CA (Dermabond, Ethicon, J&J, USA) and polyesther mesh vs. staples (mfr. NR)

Contact Duration: Mesh removed 4 weeks post-op

Dose: NR

Frequency/Duration: Single application; 4 weeks

Response: Dehiscence, Severe cellulitis

Patient characteristics (gender, mean age): Patients undergoing total knee arthroplasty; 38.3% male; mean 62 years old

Number per group: 30 patients per group; no attrition

Observed adverse effects: **Dehiscence** not significantly different between groups (1/30 [3%] for CA/mesh group and 0/30 [0%] for staple group, p=1.0). **Severe cellulitis** not significantly different between groups (1 patient in CA group vs. 0 in staple group, p=1.0)

Timing of adverse effects: Dehiscence NR; cellulitis 4 days post-op

Factors that predict response: NR

Source Citation: Samal et al. 2019[4]

Study Design: RCT

Device or Material: CA vs. staples or suture "tie-over" method for skin graft fixation (device mfrs NR)

Contact Duration: Sutures staples removed 9-12 days; CA remained; mean duration presentation 24 months

Dose: NR

Frequency/Duration: Single application

Response: Hematoma/seroma, Need for regrafting

Patient characteristics (gender, mean age): Patients with post-burn neck contracture; 59% male; mean age 26 years (range 10 to 46)

Number per group: CA (n=27); stapler (n=30); tie-over (n=30); 87 patients total

Observed adverse effects: **Hematoma/seroma** incidence not significantly different between groups (n=5 [16.7%] for suture vs. n=9 [30%] for staples and n=4 [14.8%] for CA; p=0.106). **Need for regrafting** more

frequent in suture group (n=5; 16.7%) than suture (n=1; 3.3%) or CA (n=0) groups (no stat analysis provided)

Timing of adverse effects: NR; mean duration presentation 24 months (n.s. difference between groups)

Factors that predict response: Hematoma/seroma, Need for regrafting

Source Citation: Li et al. 2018[5]

Study Design: RCT

Device or Material: CA vs. gelfoam + saline packing For graft attachment/ stabilization (mfrs NR)

Contact Duration: 6 month f/u

Dose: NR

Frequency/Duration: Single application

Response: Otis media with effusion

Patient characteristics (gender, mean age): Patients with tympanic membrane perforations undergoing myrigoplasty; 50.7% male; median age 38 and 39 by CA and control (gelfoam) groups, respectively (range 18 to 58)

Number per group: CA (n=32); control (n=37); 69 patients total analyzed

Observed adverse effects: Incidence of **otis media with effusion** between groups (0 patients in CA group vs. 1 of 37 patients [2.7%] in control group; p=0.55)

Timing of adverse effects: NR; 6-month follow-up

Factors that predict response: NR

Source Citation: Kleidon et al. 2017[49]

Study Design: RCT

Device or Material: **CA** (Histoacryl; B. Braun, Germany) vs. **Standard care (SC)** sutureless securement device (StatLock) or **ISD** (SorbaView SHIELD SV254; Centurion Medical Products, Williamston, Michigan) For securing polyurethane (BPU) dressing (Tegaderm 1614 or 1616 (3M, St Paul, MN, USA)

Contact Duration: Median dwell time 7-8 days

Dose: NR

Frequency/Duration: Single application; 7-8 days

Response: All-cause skin complications, Itchiness, Rash, Skin tear, Blister, Complete or partial dislodgement of dressing

Patient characteristics (gender, mean age): Pediatric patients with peripherally inserted central catheters (PICC); 51% male; mean age 7.5 years

Number per group: CA (n=33); ISD (n=34); standard care (n=34); 101 pts total

Observed adverse effects: **All-cause skin complications** higher for CA group, but not significant (31%, 10%, 16% for CA, ISD, and SoC groups, respectively; p=0.11). (No significant group differences in **itchiness** (6%, 10%, 6% for CA, ISD, and SoC groups, respectively); **rash** (6%, 6%, 9%); **skin tear** (22%, 0%, 0%); or **blisters** (3%, 6%, 3%). No significant difference in **complete dislodgement** (3%, 0%, 3% for CA, ISD, and SC groups, respectively) or **partial dislodgement** (9%, 6%, 10%).

Timing of adverse effects: NR Median PICC line dwell time (days): 7-8 days for 3 groups

Factors that predict response: NR

Source Citation: Silveira et al. 2017[14]

Study Design: Retro controlled cohort

Device or Material: **CA** (Ifabond; Peters Surgical, France) **vs. suture** (3 non-absorb.; mfr NR); For attaching polyester mesh (Swing Technologies, France)

Contact Duration: NR

Dose: 0.5 ml

Frequency/Duration: Single application; 18-month f/u

Response: Recurrence, Recurrence-free survival

Patient characteristics (gender, mean age): Patients undergoing ventral mesh rectopexy for treatment of rectal prolapse; 100% female; mean age 59 years

Number per group: CA (n=66); suture (n=110); 176 total patients

Observed adverse effects: **Recurrence** occurred in 10.6% of CA group and 10.9% of suture group (n.s.). **Recurrence-free survival** not significantly different between groups (17.2 months [CI 95% 16.54–17.80] for CA and 17.3 months [CI 95% 16.89–17.77] for suture group; $p > 0.05$).

Timing of adverse effects: Recurrence increased steadily over course of 18 month f/u

Factors that predict response: External rectal prolapse, alone, or in combination with other anatomical abnormalities was significant predictor of recurrence (HR = 0.37; CI 95% 0.14 to 0.93; p=0.03).

Source Citation: Liew et al. 2017[6]

Study Design: RCT

Device or Material: Histoacryl glue (B. Braun) vs titanium tacks (Protack-5, Covidien); to attach polypropylene mesh (Optilene, B. Braun)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application. 3-month f/u

Response: C-reactive protein levels, ESR (Erythrocyte sedimentation rate), Total WBC count

Patient characteristics (gender, mean age): Patients with unilateral uncomplicated inguinal hernia; 100% male; 55 years (mean of 2 group means)

Number per group: 32 CA group and 34 in tack group

Observed adverse effects: No significant difference in median **C-reactive protein or WBC levels** between groups 48 hours post-op ($p>0.05$). Median **ESR** increased significantly at 3 months post-op for glue group, but not significantly different between groups ($p>0.05$).

Timing of adverse effects: Post-operative (exact time NR); ESR measured post-op and at 3 months.

Factors that predict response: NR

BPU = bordered polyurethane; CA = cyanoacrylate; CRP = C-reactive protein; Dose = mg/kg/day; ESR = erythrocyte sedimentation rate; f/u = follow-up; ISD = integrated securement dressing; J&J = Johnson and Johnson; mfr =

manufacturer; ml = milliliter; NA = not applicable; NR = not reported; NRS = numerical rating scale for pain; Obs = observational; post-op = post-operative; R = reliable; resp. = respectively; Retro = retrospective; SC = standard care; VAS = visual analog scale for pain; WBC: white blood cell

Table 10: Tissue Adhesive (Topical and Non-Topical) - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Flick et al. 2020[21]

Study Design: Non-randomized comparative study

Device or Material: CA as a topical skin adhesive following open pancreaticodenectomy (Dermabond™)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Surgical site complications (abscess, fat necrosis, seroma and cellulitis)

Patient characteristics (gender, mean age): 18.7% Male. 81.3% Female. Mean age = 68.6 years.

Number per group: 205 (subcuticular and TSA); 139 (staples); 74 (subcuticular and steri-strips)

Observed adverse effects: Surgical site complications were significantly less for the suture + CA group (9.8%), compared to the staples group (20.1%).

Timing of adverse effects: NR

Factors that predict response: Seroma increased with age and estimated blood loss. Abscess statistically increased with wound closure (staples compared to suture + CA). Fat necrosis statistically increased with preoperative radiation.

Source Citation: Braginsky et al. 2019[17]

Study Design: Randomized controlled study

Device or Material: CA for closure of Pfannenstiel incision for cesarean delivery (2-octyl cyanoacrylate)

Contact Duration: 8 weeks

Dose: NR

Frequency/Duration: Single application

Response: Drainage, Cellulitis, Abscess, Seroma, Hematoma Isolated wound separation

Patient characteristics (gender, mean age): 100% Female.

Number per group: 252

Observed adverse effects: Wound drainage seemed unaffected by CA (RR=0.96). Cellulitis decreased with CA (RR=0.76) Abscess decreased with CA (RR=0.63) Hematoma or seroma increased with CA (RR=2.03)I solated wound separation increased with CA (RR=1.21) None of these differences were statistically significant.

Timing of adverse effects: 8 weeks

Factors that predict response: NR

Source Citation: Omran et al. 2018[24]

Study Design: Prosp controlled cohort

Device or Material: CA (Dermabond) vs. suture (polyglactin 3-0); mfrs not specified

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Exudation from incision, Hyperpigmentation, Inflammation

Patient characteristics (gender, mean age): Patients undergoing coronary artery bypass grafting (CABG); 75% male; mean 67 and 62 years of age for CA and suture groups, respectively

Number per group: 20 patients per group; 40 patients total

Observed adverse effects: No patients in either group showed **exudation** from the incision site. **Inflammation** was uncommon and not significantly different between groups (n=1 patient per group; p=1.0). **Hyperpigmentation** more common in the suture than the CA group (n=18 vs. n=2 patients, respectively; p<0.05).

Timing of adverse effects: NR; 6-8 week f/u

Factors that predict response: NR

Source Citation: Park, et al. 2018[22]

Study Design: Retrospective comparative study

Device or Material: CA (2-octyl cyanoacrylate [Surgiseal®] and n-butyl cyanoacrylate [LiquiBand®]) for skin closure following Achilles' tendon surgery.

Contact Duration: 12 months

Dose: 2 layers, 15 seconds apart

Frequency/Duration: Single application

Response: Surgical site infection, Prolonged discharge, Wound dehiscence, Allergic reaction

Patient characteristics (gender, mean age): 87% female; 13 % male. Mean age = 38.9 years

Number per group: Nylon suture (40); 2-octyl cyanoacrylate (43); n-butyl cyanoacrylate (39)

Observed adverse effects: No statistical difference in surgical site infection, prolonged discharge, wound dehiscence or allergic reaction.

Timing of adverse effects: 12 months

Factors that predict response: NR

Source Citation: Alemayehu, et al. 2017[18]

Study Design: Randomized controlled study

Device or Material: CA over sutures following circumcision

Contact Duration: 2-4 weeks

Dose: NR

Frequency/Duration: Single application

Response: Early complications (bleeding, wound dehiscence, infection, respiratory distress, fever), Adhesion

Patient characteristics (gender, mean age): 100% male. Mean age = 16.8 months.

Number per group: CA = 125. No CA = 119.

Observed adverse effects: There was no statistical difference in early complications between the groups. There was no statistical difference in adhesions between the groups

Timing of adverse effects: 2-4 weeks

Factors that predict response: NR

Source Citation: Kobayashi et al. 2016[25]

Study Design: Prosp controlled cohort

Device or Material: CA (2-octyl cyanoacrylate monomer, mfr NR) vs. natural closure (absorbent pad with no CA)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: No adverse events reported

Patient characteristics (gender, mean age): Patients with gynecologic cancer who underwent surgery including lymphadenectomy; 100% female; mean 54 years of age

Number per group: 17 patients per group; 34 total

Observed adverse effects: None reported

Timing of adverse effects: None reported

Factors that predict response: NA

Source Citation: Blondeel et al. 2014[27]

Study Design: Prosp case series within-subject comparison

Device or Material: PRINEO Skin Closure System (Ethicon, Raleigh, NC, USA) vs. intradermal sutures (mfr NR)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Edema, Erythema, Inflammation

Patient characteristics (gender, mean age): Patients undergoing elective surgery for bilateral breast procedures; 100% female; mean age 39 years

Number per group: 79 patients; each patient received PRINEO and intradermal sutures

Observed adverse effects: Intradermal sutures demonstrated more **edema** than CA at 12 to 25 days (p=0.016) but no significant differences at post-op or 7 days. **Erythema** not significantly different at post-op, 7 days, or days 12 to 25. No significant difference in **excessive inflammation** at 6 or 12 months (p=1.0 for both f/u). **Skin blistering** observed for CA group at post-op (2 of 79 pts, 2.5%), day 7 (8 of 79, 10.3%), and day 12 to 25 (2 of 79, 2.5%) vs. no incidences for the suture group.

Timing of adverse effects: Precise time NR; f/u at post-op, 7-days, 12-25 days, and 90-days for adverse events; up to 1 year for inflammation

Factors that predict response: NR

Source Citation: Kim, et al. 2014[23]

Study Design: Controlled study.

Device or Material: CA on scoring incisions following septal deviation

Contact Duration: 6 months

Dose: NR

Frequency/Duration: Single Administration

Response: Post-operative swelling, Septal hematoma

Patient characteristics (gender, mean age): 59% male; 41% female; mean age = 27.1 years

Number per group: 27 (scoring alone); 24 (scoring + CA)

Observed adverse effects: Post operative swelling (>1 month) occurred in 3 patients in the scoring + CA group No incidence of septal hematoma in either group

Timing of adverse effects: 6 months

Factors that predict response: Complications arose when a relatively high volume of CA was used.

Source Citation: Tan et al. 2014[26]

Study Design: Retro controlled cohort

Device or Material: CA (2-octyl cyanoacrylate) vs. suture (monocryl, poliglecaprone 25)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Dehiscence, Keloid formation, Adverse peri-wound conditions (pruritus or erythema)

Patient characteristics (gender, mean age): Women who delivered via Caesarean section via Pfannenstiel incision; 100% female; mean age 31 years

Number per group: CA group (n=50); suture group (n=47)

Observed adverse effects: Wound **dehiscence** was not observed in either group. No significant difference in **keloid formation** between groups, though rate was higher for the CA group (24% vs. 14.9% for suture group; p=0.382). No significant difference in **abnormal peri-wound conditions** (erythema, pruritus) between groups, though rate was higher for suture group (6.4% vs. 2.0% for suture and CA groups, respectively).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Jan et al. 2013[19]

Study Design: RCT

Device or Material: CA (Liqui-Band Surgical S, Advanced Medical Solutions, UK) vs. sutures (Vicryl 3-0 absorbable; Ethicon, Scotland)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Edema, Erythema, Discharge/drainage, Inflammation

Patient characteristics (gender, mean age): Patients undergoing laparoscopic surgery; 100% female; mean 42 and 45 years of age for CA and suture groups, respectively

Number per group: CA group (n=59); suture group (n=55); 114 total patients

Observed adverse effects: Complications were very small in number and total complications not significantly different between groups. **Edema** (0 for CA group vs. 1 [2.6%] for suture group); **erythema** (74.3% for CA vs. 76.3% for suture group); **inflammation** (n=1 [2.6%] in CA group vs. 0 in suture group); **discharge/drainage** (n=1 [2.6%] in CA group vs. n=2 [5.3%] in suture group). (Statistical comparisons for individual outcomes NR.)

Timing of adverse effects: Precise time NR; 2 week f/u

Factors that predict response: NR

Source Citation: Vastani et al. 2013[28]

Study Design: Prospective case series, within-subject comparison study

Device or Material: CA (isoamyl 2-cyanoacrylate, Novocryl; Alkem Labs, India) vs. 3-0 silk suture (Mersilk, J & J, India)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application, Response: Erythema and tenderness, Inflammatory cell infiltration and vascularity, Density of fibro cellular connective tissue, Histological evidence of inflammation

Patient characteristics (gender, mean age): Patients undergoing alveoloplasty; 70% male; age range 40 to 70 years

Number per group: 30 patient's total; each patient had one side each closed with CA and suture; choice of side randomized.

Observed adverse effects: **Erythema and tenderness** (clinical signs of inflammation) significantly lower for CA side ($p<0.01$), except on 21st day post-op (n.s.); **inflammatory cell infiltration and vascularity** (histological signs of inflammation) higher for suture side than for CA side at 7 days post-op; only **vascularity** higher on suture side at 14 days post-op; **Density of fibrocellular connective tissue** similar for CA and suture treatments.

Timing of adverse effects: Most clinical and histological signs of inflammation different 7 days and 14 days post-op

Factors that predict response: NR

Source Citation: Spencker et al. 2011[20]

Study Design: RCT

Device or Material: CA (2-octyl-cyanoacrylate) vs. absorbable suture (intracutaneous polydioxanon); mfrs NR

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Bleeding, Dehiscence, Wound excoriation, Wound irritation, Incrustation, Keloid formation

Patient characteristics (gender, mean age): Patients with pacemaker (PM), implantable, cardioverter defibrillator (ICD), or loop recorder implantation; 68.2% male; mean of 70 and 66 years of age for CA and suture groups, respectively

Number per group: CA (n=183); suture (n=185); 368 patients total

Observed adverse effects: No significant difference in **minor or major bleeding** prior to discharge (≤2.2% in both groups; p≥0.69). No significant difference in overall **wound irritation** (6 and 3.8% for CA and suture groups, respectively, p=0.16). Significantly more wound **excoriation** with CA (4.9% vs. 0% for suture; p=0.02). Significantly more wound **incrustation** with CA (5% vs. 0% for suture; p<0.05). No significant difference in wound **dehiscence** at 3 months f/u (both groups <2%; p=0.31). No significant difference in **keloid formation** at 3 months f/u (both groups <1.0%; p=0.31).

Timing of adverse effects: Dehiscence and keloid formation reported at 3-month f/u; all other outcomes prior to discharge

Factors that predict response: No prognostic factors for adverse events were identified. Specifically, adverse events were not related to patient age, the type of device implanted, or procedure duration.

Source Citation: Alemayehu, et al. 2017[18]

Study Design: Randomized controlled study

Device or Material: CA over sutures following circumcision

Contact Duration: 2-4 weeks

Dose: NR

Frequency/Duration: Single application

Response: Bleeding, Dehiscence, Wound excoriation, Wound irritation, Incrustation, Keloid formation

Patient characteristics (gender, mean age): Patients with pacemaker (PM), implantable, cardioverter defibrillator (ICD), or loop recorder implantation; 68.2% male; mean of 70 and 66 years of age for CA and suture groups, respectively

Number per group: CA (n=183); suture (n=185); 368 patients total

Observed adverse effects: No significant difference in **minor or major bleeding** prior to discharge (≤2.2% in both groups; p≥0.69). No significant difference in overall **wound irritation** (6 and 3.8% for CA and suture groups, respectively, p=0.16). Significantly more wound **excoriation** with CA (4.9% vs. 0% for suture; p=0.02). Significantly more wound **incrustation** with CA (5% vs. 0% for suture; p<0.05). No significant difference in wound **dehiscence** at 3 months f/u (both groups <2%; p=0.31). No significant difference in **keloid formation** at 3 months f/u (both groups <1.0%; p=0.31).

Timing of adverse effects: Dehiscence and keloid formation reported at 3-month f/u; all other outcomes prior to discharge

Factors that predict response: No prognostic factors for adverse events were identified. Specifically, adverse events were not related to patient age, the type of device implanted, or procedure duration.

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 11: Embolization - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Garcia-Carpintero et al. 2020[30]

Study Design: Systematic Review Includes VeClose trail (NCT01807585)

Device or Material: CA ablation (VenaSeal, VariClose, VenaBlock) vs. radiofrequency ablation and endogenous laser ablation for great saphenous vein incompetence

Contact Duration: Mean overall follow-up 15 months (range 6 to 36 months)

Dose: NR

Frequency/Duration: Single administration

Response: Phlebitis, Ecchymosis, Glue extension, Inflammation at injection site, Hyperpigmentation, Ulceration, Posterior tibial vein extension, Extension of thrombus to deep vein

Patient characteristics (gender, mean age): Gender NR, adults, mean age NR

Number per group: 12 studies; 1057 patients

Observed adverse effects: Reported ecchymosis rates ranged from 5.4% and 31.5% for CA. Pooled analysis showed that ecchymosis less likely to occur with CA compared to RFA (RR=0.46 [CI: 0.22 to 0.95], p=0.04), but there was no significant difference in ecchymosis rates between CA vs. EVLA (RR=0.57 [CI: 0.15 to 2.23], p=0.42). Phlebitis rates ranged from 2.8% to 6.5% in comparative studies and 4% to 16% in case series. Pooled analysis showed no significant difference between CA and RFA (RR=0.58 [CI: 0.30 to 1.11], p=0.10) or EVLA (RR=0.65 [CI: 0.36 to 1.17], p=0.15). Other reported adverse events include 3 cases of glue extension, 4 cases of inflammation in the injection zone, 2 cases of minimal extension of thrombus to deep vein, and 1 case of posterior tibial vein extension. One study reported that hyperpigmentation occurred in 2.6% of patients treated with CA at 24 months and ulceration occurred in 3.0%. No DVT or PE events were reported. No cases of allergic reaction were reported.

Timing of adverse effects: NR

Factors that predict response: For VenaSeal, positioning the catheter at 3 cm of the saphenofemoral junction caused several cases of cyanoacrylate extension into the deep system.The incidence of adverse events may be related to high scores on the preoperative CEAP classification and VCSS, large GSV diameters, and aneurysms in large vein segments. 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. Applying manual pressure, using a continuous delivery method, and low-viscosity cyanoacrylates may reduce the rate of phlebitis and thrombophlebitis events.

Source Citation: Çalik et al. 2019[29]

Study Design: RCT

Device or Material: NBCA ablation (Turkish Glue Kit/VenaBlock) vs. EVLA for great saphenous vein insufficiency

Contact Duration: Mean follow-up 14 months (range 10 to 16)

Dose: 0.03 cc of CA per cm of vein; mean length of treated GSV 30.4 ± 5.3 cm

Frequency/Duration: Single unilateral or bilateral administration

Response: Induration, Pigmentation, Ecchymosis, Paresthesia, Phlebitis, Pain

Patient characteristics (gender, mean age): 55.6% female; CA 38.6 ± 11.8, EVLA 38.4 ± 11.9

Number per group: 400 (200 NBCA, 200 EVLA)

Observed adverse effects: Complications of NBCA vs. EVLA: Pain score: 2.8 ± 3.1 vs. 5.4 ± 3.7, p<0.001 (1 week); 0.6 ± 0.4 vs. 0.7 ± 0.5, p=0.458 (3 months), Induration: 4.2 ± 2.3 vs. 9.2 ± 4.6, p<0.001 (1 week); 0.3 ± 0.2 vs. 0.4 ± 0.3, p=0.523 (3 months), Pigmentation: 7 (3.5%) vs. 11 (5.5%), p=0.554 (1 week); 1 (0.5%), vs. 3 (1.6%), p=0.087 (3 months), Ecchymosis: 24 (12%) vs. 52 (26%), p<0.001 (1 week), Paresthesia: 6 (3%) vs. 28 (11%), p<0.001 (1 week); 2 (1.1%) vs. 13 (7%), p<0.001 (3 months), Phlebitis: 7 (3.5%) vs. 14 (7%), p=0.328 (1 week), DVT: 0 vs. 2 (1%), p=0.123 (1 week); 0 vs. 2 (1.1%), p=0.633 (3 months)

Timing of adverse effects: Induration and ecchymosis rates were significantly lower in the NBCA group at 1 week, but not significantly different at 3 months. Paresthesia rate was significantly lower in the NBCA group at 1 week and 3 months. Pigmentations resolved completely by 6 months follow-up in all patients.

Factors that predict response: Procedure related skin pigmentation was developed as a result of phlebitis. Compression of the saphenofemoral junction and the quick polymerization CA lower the risk of CA fluid flowing into the deep vein. The rapid closure and minimal procedural time may prevent DVT and pulmonary embolism.

Source Citation: Yang et al. 2019[31]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization (VenaSeal) vs. radiofrequency ablation for varicose veins

Contact Duration: Mean short-term follow-up 7.2 ± 0.2 days; mid-term follow-up 58 ± 1 days

Dose: Mean 1.8 ± 0.1 mL

Frequency/Duration: Single administration in one or more veins

Response: Phlebitis, Paresthesia, DVT, Retained glue at entry site

Patient characteristics (gender, mean age): 78% female; 57 ± 1 years

Number per group: 335 (148 CA; 328 radiofrequency ablation)

Observed adverse effects: Phlebitis occurred significantly less frequently in CA compared to RFA (4 [5%] vs. 25 [16%], p<0.05). Paresthesia occurred in 3 cases (3%), all of which resolved by mid-term follow. DVT occurred in 1 case (1%) and was clinically asymptomatic. Three cases of retained glue in the subcutaneous tissue at the entry site were noted in the CA group that required drainage and removal of foreign body.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Hu et al. 2020[32]

Study Design: Systematic Review

Device or Material: CA embolization alone vs. CA in combination with other treatments for gastroesophageal varices

Contact Duration: 6 weeks to 15 years

Dose: NR

Frequency/Duration: NR

Response: Recurrent bleeding

Patient characteristics (gender, mean age): Gender NR, mean age NR

Number per group: 39 studies; 3630 patients

Observed adverse effects: Pooled overall risk of rebleeding after treatment with CA for gastric varices was 0.30 (CI: 0.30 to 0.31), p=0.00. Sensitivity analysis for pooled risk of rebleeding was 0.15 (CI: 0.11 to 0.18), p=0.4. Risk of rebleeding after treatment with CA combined with ethanolamine: 0.08 (CI: 0.02 to 0.14), endoscopic ultrasound guided coils: 0.07 (CI: 0.03 to 0.11), percutaneous transhepatic variceal embolization*: 0.10 (0.03 to 0.17), sclerotherapy*: 0.10 (CI: 0.05 to 0.18), polidocanol*: 0.10 (CI: 0.02 to 0.19), lipiodol*: 0.13 (CI: 0.03 to 0.22), balloon-occluded retrograde transvenous obliteration (gastroesophageal): 0.31 (CI: 0.13 to 0.49)

Pooled overall risk of rebleeding after CA treatment for esophageal varices was 0.29 (CI: 0.11 to 0.47), p=0.54. Risk of rebleeding after treatment with CA combined with: ethanolamine: 0.02 (CI: −0.02 to 0.05), percutaneous transhepatic variceal embolization: 0.16 (CI: 0.10 to 0.22), p=0.889, TIPS*: 0.06 (CI: −0.01 to 0.12), sclerotherapy*: 0.12 (CI: 0.04 to 0.20), band ligation*: 0.10 (CI: 0.04 to 0.24)

*One study, not pooled

Timing of adverse effects: NR

Factors that predict response: The lower risk of rebleeding in studies after 2010 is hypothesized to be due in part to technological advancement in the use of CA for gastroesophageal varices. In terms of lower risk of rebleeding, gastric varices may respond better to CA compared to esophageal varices, while esophageal varices may respond better than gastric varices to the combination of cyanoacrylate and ethanolamine and the combination of cyanoacrylate and percutaneous transhepatic variceal embolization.

Source Citation: Elsebaey et al. 2019[34]

Study Design: RCT (NCT03388125)

Device or Material: NBCA embolization (GluStitch Twist) vs. sclerotherapy for acute esophageal variceal bleeding

Contact Duration: 6 weeks

Dose: 0.5-1 mL, mean 0.66 ± 0.235

Frequency/Duration: Single administration

Response: Rebleeding, Retrosternal pain, Dysphagia

Patient characteristics (gender, mean age): 71.7% male; CA 55.26 ± 10.38, sclerotherapy 58.43 ± 9.93

Number per group: 113 (57 NBCA; 56 sclerotherapy)

Observed adverse effects: Complications of NBCA vs. sclerotherapy: Rebleeding: 11 (19.30%) vs. 15 (26.79%), p=0.344, Retrosternal pain: 6 (10.53%) vs. 12 (21.43%), p=0.113, Dysphagia: 4 (7.02%) vs. 9 (16.07%), p=0.132. Distant embolization from intravariceal cyanoacrylate injection was not observed in any patient.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Ye et al. 2014[33]

Study Design: Systematic Review

Device or Material: NBCA embolization vs. band ligation for acute gastric variceal hemorrhage

Contact Duration: NR

Dose: NR

Frequency/Duration: Single and repeat administration

Response: Rebleeding, Ulcer/ulcer bleeding, Cerebral vascular accident, Embolism

Patient characteristics (gender, mean age): Studies ranged from 56.8% to 86.9% male, age NR

Number per group: 7 studies, 648 patients

Observed adverse effects: Gastric variceal rebleeding: NBCA injection was associated with a statistically significant 63% reduction in the hazard of GV rebleeding (HR 0.37; CI: 0.24 to 0.56). Overall complications: NBCA (119, 39.02%) vs. band ligation (71, 27.1%), OR 1.02 (CI: 0.48 to 2.19), not significantly different. Ulcers/ulcer bleeding: OR 0.32 (CI: 0.17 to 0.67), favors NBCA. Vascular events (cerebral vascular accident and embolism): OR 1.76 (CI: 0.35 to 8.85), not significantly different.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kim et al. 2021[36]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization (Histoacryl) vs. TEVAR for closure of false lumen in aortic dissection

Contact Duration: NR

Dose: Mean 1.5 mL (range 0.25 to 5 mL)

Frequency/Duration: Single administration

Response: Glue migration, Renal infarction

Patient characteristics (gender, mean age): 76.9% male; 59 years

Number per group: 65 (12 NBCA; 53 TEVAR)

Observed adverse effects: Procedure-related complications were comparable between NBCA embolization (1 [8.3%]) and TEVAR (4 [7.5%]), p=0.701. In 1 patient, with acute Stanford type B aortic dissection, NBCA migration to aortic branch vessels occurred immediately after infusion and occlusion of the entry tear and false luminal flow failed. At 5 months, segmental right renal infarction caused by renal artery occlusion resulting from NBCA migration was detected.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Sugawara et al. 2019[38]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization vs. absolute ethanol for portal vein embolization

Contact Duration: 8 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Pain, Subcapsular biloma, Liver abscess

Patient characteristics (gender, mean age): 70.5% male; NBCA 68.9 years, absolute ethanol 65.7 years

Number per group: 61 (34 NBCA; 27 absolute ethanol)

Observed adverse effects: Twelve of the 34 patients in the NBCA group (35.3%) had pain after PVE that required analgesia (p=0.129). Subcapsular biloma (grade 3) occurred in 2 cases (5.9%) and liver abscess (grade 3) occurred in 1 case (2.9%). The incidence of grade 2 or worse non-hematological adverse events was 5.9% in the NBCA group, not significantly different than absolute ethanol (3.7%, p=0.696).

Timing of adverse effects: NR

Factors that predict response: An ipsilateral approach may minimize adverse events.

Source Citation: Arai et al. 2018[39]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization vs. trisacryl gelatin microspheres (Embosphere) for preoperative embolization of meningiomas

Contact Duration: 2 to 7 days

Dose: NR

Frequency/Duration: Single administration

Response: Ophthalmoparesis, Necrosis, Inflammatory cell infiltration

Patient characteristics (gender, mean age): 70% female; NBCA 62 ± 16 years, Embosphere 64 ± 13 years

Number per group: 20 (9 NBCA; 11 Embosphere)

Observed adverse effects: Double vision from ophthalmoparesis occurred in 1 patient, no further complications after extirpation. Necrosis: 2 (22%) vs. 3 (27%), p=0.79. Inflammatory cell infiltration: 4 (44%) vs. 0 (0%), p=0.006

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Bilreiro et al. 2017[37]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization (Glubran 2) vs. metal coils (Nester Platinum) for varicocele embolization

Contact Duration: 10 months to 3 years

Dose: NR

Frequency/Duration: Single administration

Response: Varicocele recurrence

Patient characteristics (gender, mean age): 100% male; NBCA 32.6 years, coils 32.3 years

Number per group: 129 procedures (26 NBCA, 103 coils)

Observed adverse effects: There were no reported complications in the NBCA group. Recurrence rate was 11.54% with NBCA and 5.83% with coils (p=0.40).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Pashopour et al. 2014[35]

Study Design: Non-randomized controlled study

Device or Material: NBCA transarterial embolization (Hystoacryl) vs. transvenous coil embolization for ocular symptoms in patients with cDAVF

Contact Duration: Mean follow-up 17.3 months

Dose: NR

Frequency/Duration: Single administration

Response: Partial thrombosis, Blurred vision, Decreased visual acuity, Chemosis exacerbation

Patient characteristics (gender, mean age): 65% male; 36.83 ± 11.63 years

Number per group: 46 (NBCA 26, 10 coil, 10 mixed)

Observed adverse effects: Complications related to transarterial NBCA embolization occurred in two patients (4%), and there were no complications related to transvenous embolization procedures. Partial thrombosis and exacerbation of chemosis occurred in 1 case in the NBCA group and resolved within 6 weeks. Blurred vision and decreased visual acuity occurred in 1 case in the NBCA group and resolved within 1 week.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Woo et al. 2013[40]

Study Design: Non-randomized controlled study

Device or Material: NBCA vs. PVA particles (Contour) for bronchial artery embolization for hemoptysis control

Contact Duration: 35.5 ± 29.3 months

Dose: 0.5 to 2 mL

Frequency/Duration: Single or repeat administration

Response: Recanalization

Patient characteristics (gender, mean age): 59.6% male; 56 ± 15 years

Number per group: 406 (NBCA 113, PVA 293)

Observed adverse effects: The overall complication rates were 31.0% for NBCA, not significantly different than PVA (34.1%, p=0.56). Specific complications were not defined. Recanalization of previously embolized vessels was less frequent in the NBCA group (1.8%) compared to the PVA group (21.5%, p<0.001). There were no major complications in the NBCA group (0% for NBCA; 0.3% for PVA, p=0.999). There were no delayed complications or procedure-related mortality.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Elsebaey et al. 2019[34]

Study Design: RCT NCT03388125

Device or Material: NBCA embolization (GluStitchTwist) vs. sclerotherapy for acute esophageal variceal bleeding

Contact Duration: 6 weeks

Dose: 0.5-1 mL, mean 0.66 ± 0.235

Frequency/Duration: Single administration

Response: Spontaneous bacterial peritonitis, Death

Patient characteristics (gender, mean age): 71.7% male; CA 55.26 ± 10.38, sclerotherapy 58.43 ± 9.93

Number per group: 113 (57 NBCA; 56 sclerotherapy)

Observed adverse effects: Spontaneous bacterial peritonitis: 2 (3.51%) vs. 3 (5.36%), p=0.633 Mortality: 9 (15.79%) vs. 11 (19.64%), p=0.592 Distant embolization from intravariceal cyanoacrylate injection was not observed in any patient.

Timing of adverse effects: NR

Factors that predict response: The cause of death in the cyanoacrylate group was related to the severity of underlying liver disease including progressive hepatic failure in 6 patients, hepatorenal syndrome in 2 patients, and spontaneous bacterial peritonitis in one patient.

Source Citation: Sugawara et al. 2019[38]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization vs. absolute ethanol for portal vein embolization

Contact Duration: 8 weeks

Dose: NR

Frequency/Duration: Single administration

Response: Serum AST elevation, Serum ALT elevation

Patient characteristics (gender, mean age): 70.5% male; NBCA 68.9 years, absolute ethanol 65.7 years

Number per group: 61 (34 NBCA; 27 absolute ethanol)

Observed adverse effects: Increases in grades 3 and 4 in AST and ALT levels occurred 1 (2.9%) and 2 patients (5.9%) in the NBCA group, compared to 22 (81.5%) and 22 patients (81.5%), respectively, in the absolute ethanol group.

Timing of adverse effects: NR

Factors that predict response: Changes in laboratory data are likely caused by ischemic changes in the embolized liver.

Source Citation: Mukund et al. 2018[41]

Study Design: Non-randomized controlled study

Device or Material: NBCA embolization vs. transarterial embolization for iatrogenically injured arteries in paracentesis or thoracentesis for chronic liver disease

Contact Duration: 30 days

Dose: 0.5 to 3 mL

Frequency/Duration: Single or repeat administration

Response: Death

Patient characteristics (gender, mean age): NR

Number per group: 23 (15 NBCA; 8 transarterial embolization)

Observed adverse effects: 30-day mortality for NBCA (4/15, 26.7%) was not significantly different than transartierial embolization (3/8, 37.5%).

Timing of adverse effects: NR

Factors that predict response: Mortality was due to disease progression in all cases.

ALT = alanine transaminase; AST = aspartate transaminase; CA = cyanoacrylate; cDAVF = cavernous sinus dural arteriovenous fistulas; CEAP = Clinical, Etiology, Anatomy, and Pathophysiology; CI = confidence interval; DVT = deep vein thrombosis; EVLA = endovenous laser ablation; GSV = great saphenous vein; HR = hazard ratio; NBCA = n-butyl-2-cyanoacrylate; NR = not reported; PE = pulmonary embolism; PVE = portal vein embolization; RCT =randomized controlled trial; RFA = radiofrequency ablation; RR = relative risk; TEVAR = thoracic endovascular aortic repair; VCSS = Venous Clinical Severity Score; GV = gastric variceal; EVL = endoscopic variceal ligation; PVA = polyvinyl alcohol

Local Response/Toxicity

Source Citation: Oladega et al. 2019[42]

Study Design: RCT

Device or Material: CA (IsoAmyl 2-Cyanoacrylate; Concord Drugs Ltd., India) vs. suture (3-0 silk; Ethicon, J&J Medical)

Contact Duration: NR; f/u to post-op day 7

Dose: NR

Frequency/Duration: Single application

Response: Bleeding, Dehiscence, Swelling

Patient characteristics (gender, mean age): Patients undergoing extraction of mandibular 3rd molars; 37.5% male; mean 27.2 years of age

Number per group: 60 patients per group; 120 total

Observed adverse effects: Significantly more post-operative **bleeding** in CA group (42 patients [70%] vs. 0 for suture group, p=0.02). No significant difference group difference in **dehiscence** (n=6 for CA vs. 4 for sutures, p=0.51). No significant group difference in **swelling** (including facial width and interincisal distance, all p>0.30).

Timing of adverse effects: Bleeding significant difference post-op day 1

Factors that predict response: NR

CA = cyanoacrylate; Dose = mg/kg/day; J&J = Johnson and Johnson; NA = not applicable; NR = not reported; Obs = observational; post-op = post-operation; RCT = randomized controlled trial; Retro = retrospective; R = reliable

Table 13: Sealant - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Binboga, et al. 2018[43]

Study Design: Randomized Controlled Trial

Device or Material: CA as a tissue sealant to reinforce the stapler line after laparoscopic sleeve gastrectomy. (Ifabond®)

Contact Duration: 1-36 months

Dose: NR

Frequency/Duration: Single administration

Response: Leakage, Bleeding, Stricture Mortality

Patient characteristics (gender, mean age): 81% Female. 19% Male. Mean age = 40.41 years.

Number per group: 50

Observed adverse effects: Stapler line leakage in 8% (4) patients, but not statistically different than other groups. Stapler line bleeding in 14% (7) patients, but not statistically different than other groups. Stricture in 0% (0) patients, but not statistically different than other groups.

Mortality in 2% (1) patients, but not statistically different than other groups.

Timing of adverse effects: NR

Factors that predict response: Mortality was recorded due to excessive bleeding and leakage, then abdominal sepsis

Source Citation: Vasileiadou, et al. 2017[44]

Study Design: Randomized Controlled Trial

Device or Material: Cyanoacrylate adhesive following modified radical mastectomy or quadranectomy (Glubran 2)

Contact Duration: 5, 10, 15 days

Dose: NR

Frequency/Duration: Single administration

Response: Drainage duration, Seroma formation, Seroma drained, Seroma aspirated

Patient characteristics (gender, mean age): 100% Female. Mean age = 61.5 years.

Number per group: 64

Observed adverse effects: Drainage during was statistically shorter (2.51 days vs 3.63 days) in the CA group. Seroma formation was statistically less (25.46 versus 94.69) for the CA group. Seroma drained was statistically less (155.77mL versus 457.81mL) in the CA group. Seroma aspirated was statistically less (25.46mL versus 94.69mL) in the CA group.

Timing of adverse effects: NR

Factors that predict response: Age, BMI, breast weight, tumor size and number of infiltrated lymph nodes all correlated significantly with the amount of seroma fluid produced.

Source Citation: Mercier, el al. 2017[45]

Study Design: Non-randomized Comparative

Device or Material: CA as a tissue sealant to reinforce the stapler line after laparoscopic sleeve gastrectomy. (Ifabond®)

Contact Duration: 6 months

Dose: 1.5mL (1 full drop)

Frequency/Duration: Single administration

Response: Reoperation during initial stay, Gastric leak severity Hematoma

Patient characteristics (gender, mean age): 74% Female, 26 % Male. Mean age = 43.95 years.

Number per group: 99 (without CA); 94 (with CA)

Observed adverse effects: Leaks were less in the CA group (2% versus 4%), but not statistically significant. More type 1 leaks in the CA group (2 versus 1). More type II (more severe) leaks in the without CA group (0 versus 3). (Statistics NR) More reoperations during initial stay in the CA group (4% versus 3%), but not statistically different. More hematomas were reported for the CA group (5% versus 2%), but not statistically different.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kim et al. 2016[46]

Study Design: Non-randomized Comparative

Device or Material: n-Butyl-2-cyanoacrylate (NBCA) to seal thoracic duct area following total thyroidectomy with unilateral neck dissection

Contact Duration: 24 months

Dose: 0.5mL

Frequency/Duration: Single administration

Response: Drainage volume, Rate of chyle leakage Complications

Patient characteristics (gender, mean age): 25.8% Female. 74.2% Male. Mean age = 44.8 years.

Number per group: 84 (with NBCA); 79 (without NBCA)

Observed adverse effects: Mean total drainage was significantly less in the NBCA group (270mL versus 328mL). Rate of chyle leakage was significantly lower in the NBCA group (0% versus 6.3%). Abnormal ultrasonographic finding were observed in 3.6% of the NBCA group. Sermoa was found in 1.2% of the NBCA group.

Timing of adverse effects: NR

Factors that predict response: NR

NA = not applicable; NR = not reported; Obs = observational; Retro = retrospective; R = reliable; Dose = mg/kg/day

Table 14: Other Applications - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Ullman et al. 2019[47]

Study Design: RCT

Device or Material: **CA** (Histoacryl, B Braun, Melsungen, Germany) +SC; vs. **SC** (bordered polyurethane dressing, prolene sutures, chlorhexidine gluconate disc), or **ISD** (SorbaViewSHIELD [Centurion Medical Products, Franklin, MA], prolene sutures and chlorhexidine gluconate disc)

Contact Duration: Median 2.2 to 2.7 days

Dose: 2 drops

Frequency/Duration: Single application

Response: Blister, Bleeding, Complete/partial dislodgement, Failure rate, Dermatitis, Itch, Rash, Skin tears

Patient characteristics (gender, mean age): Pediatric patients with a non-tunneled, percutaneously inserted central venous access device (CVAD) (jugular, subclavian, or femoral);

Number per group: CA (n=59); ISD (n=56); standard care (n=54); 169 total patients

Observed adverse effects: Incidence of **blisters** lowest for CA group and standard care (0% for CA, 4% for ISD, 0% for SC); Dressing changes due to **bleeding** lower for CA group (8% for CA, 11% for ISD, 20% for SC). **Complete dislodgement** least frequent in CA and ISD groups (0% for CA, 0% for ISD, 4% for SC); **partial dislodgement** highest in CA group (5% for CA, 0% for ISD, 2% for SC); **failure rate** of CVAD highest for CA group but not statistically significant (p=0.174). No incidences of **dermatitis** or **itching** were reported for any groups. No significant difference in the incidence of rash (2% [n=1 patient] for all groups). Rate of **skin tear** lowest for CA and SC groups (2% for CA, 4% for ISD, 2% for SC).

Timing of adverse effects: Failure of CVAD recorded over 7 days; follow-up concluded 4 weeks after insertion, study withdrawal, removal of the CVAD, or hospital discharge

Factors that predict response: Cox regression demonstrated no clinical variables to be significantly associated with risk of CVAD failure (all p>0.05).

Source Citation: Kleidon et al. 2017[49]

Study Design: RCT

Device or Material: **CA** (Histoacryl; B. Braun, Germany) vs. **Standard care (SC)** sutureless securement device (StatLock) or **ISD** (SorbaView SHIELD SV254; Centurion Medical Products, Williamston, Michigan) For securing polyurethane (BPU) dressing (Tegaderm 1614 or 1616 (3M, St Paul, MN, USA)

Contact Duration: Median dwell time 7-8 days

Dose: NR

Frequency/Duration: Single application; 7-8 days

Response: All-cause skin complications, Itchiness, Rash, Skin tear, Blister, Complete or partial dislodgement of dressing

Patient characteristics (gender, mean age): Pediatric patients with peripherally inserted central catheters (PICC); 51% male; mean age 7.5 years

Number per group: CA (n=33); ISD (n=34); standard care (n=34); 101 pts total

Observed adverse effects: **All-cause skin complications** higher for CA group, but not significant (31%, 10%, 16% for CA, ISD, and SoC groups, respectively; p=0.11). (No significant group differences in **itchiness** (6%, 10%, 6% for CA, ISD, and SoC groups, respectively); **rash** (6%, 6%, 9%); **skin tear** (22%, 0%, 0%); or **blisters** (3%, 6%, 3%). No significant differences in **complete dislodgement** (3%, 0%, 3% for CA, ISD, and SC groups, respectively) or **partial dislodgement** (9%, 6%, 10%).

Timing of adverse effects: NR Median PICC line dwell time (days): 7-8 days for 3 groups

Factors that predict response: NR

Source Citation: Ullman et al. 2017[48]

Study Design: RCT

Device or Material: **CA** (Histoacryl, B Braun, Melsungen, Germany)+SC; vs. **SC** (BPU Dressing, Tegaderm, 3M, USA); **SSD** (staff choice from StatLock; Bard or GripLock; TIDI), or **ISD** (SorbaViewSHIELD SV254; Centurion Medical, Williamston)

Contact Duration: Overall median CVAD dwell time 12.4 days (25th and 75th pctile 5.6 to 26 days)

Dose: 1-2 drops

Frequency/Duration: Single application

Response: Blister, Itch, Rash, Partial dislodgement Failure rate

Patient characteristics (gender, mean age): Patients under 18 years of age requiring a tunneled, cuffed CVAD; 60% male; median 5 years of age

Number per group: CA (n=12; 25%); SC (n=11; 23%); ISD (n=12; 25%); SSD (n=13; 27%)

Observed adverse effects: Incidence of **blister** lowest for CA and SSD groups (0% each); only 1 case each for SC and ISD groups. **Itchiness** lowest incidence for CA and SSD groups (0% each); only 1 case for ISD group and 2 cases (18%) for SC group. Incidence of **rash** lowest for CA and ISD groups (0% each); only 1 case each for SC and SSD groups. **Partial dislodgement** of CVAD lowest for CA and SC groups; 1 each for ISD and SSD groups. CVAD **failure** was highest for ISD group (n = 2; 17%); no failures for CA or SC groups.

Timing of adverse effects: Device failure progressive over 6 days; specific times for other AEs NR.

Factors that predict response: NR

Source Citation: Topiwala et al. 2014[50]

Study Design: RCT

Device or Material: **CA** (XOIN; Reevax Pharma, Hyderabad, India) vs. **fibrin glue** (Tisseel; Baxter Healthcare Corp., India)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single application

Response: Chemosis, Conjunctival reaction, Granuloma, Total inflammatory score, Grades for all outcomes: 0 = none, 1 = mild, 2 = moderate, 3 = severe

Patient characteristics (gender, mean age): Patients requiring surgery for strabismus correction for either esotro-pia or exotropia; 50% male; mean 12 years of age

Number per group: 15 patients/group (CA and fibrin glue); 30 patient's total

Observed adverse effects: **Chemosis** significantly higher for CA group at 3 weeks (p=.039) and higher with borderline significance at 3 months (p=.058). **Conjunctival reaction** higher significantly higher in the CA group at 1 week (p=.01), 3 weeks (p=.027), and 3 months (p<0.001). **Granuloma** formed in 2 patients in CA group and 0 in the fibrin glue group. **Total inflammatory score** significantly higher in the CA group at 1 week (p=.025), 3 weeks (p=.002), and 3 months (p<0.001).

Timing of adverse effects: Chemosis significantly different at 3 weeks and borderline significant at 3 months. Conjunctival reaction and total inflammatory score significantly different 1 week, 3 weeks, and 3 months f/u

Factors that predict response: NR

Source Citation: Ullman et al. 2019[47]

Study Design: RCT

Device or Material: **CA** (Histoacryl, B Braun, Melsungen, Germany)+SC; vs. **SC** (bordered polyurethane dressing,prolene sutures, chlorhexidine gluconate disc), or **ISD** (SorbaView SHIELD [Centurion Medical Products, Franklin, MA],prolene sutures and chlorhexidine gluconate disc)

Contact Duration: Median 2.2 to 2.7 days

Dose: 2 drops

Frequency/Duration: Single application

Response: Death

Patient characteristics (gender, mean age): Pediatric patients with a non-tunneled, percutaneously inserted central venous access device (CVAD) (jugular, subclavian, or femoral);

Number per group: CA (n=59); ISD (n=56); standard care (n=54); 169 total patients

Observed adverse effects: **Death** (n=1 patient for CA, n=0 for ISD, and n=3 for SC)

Timing of adverse effects: NR; follow-up concluded 4 weeks after insertion, study withdrawal, removal of the CVAD, or hospital discharge

Factors that predict response: NR

AE = adverse event; BPU = bordered polyurethane; CA = cyanoacrylate; CRP = C-reactive protein; CVAD = central venous access device; Dose = mg/kg/day; f/u = follow-up; ISD = integrated securement and dressing; J&J = Johnson and Johnson; mfr = manufacturer; ml = milliliter; NA = not applicable; NR = not reported; n.s. = non-significant difference; NRS = numerical rating scale for pain; Obs = observational; pctile = percentile; post-op = post-operative; resp. = respectively; Retro = retrospective; R = reliable; RCT = randomized controlled trial; SC = standard care; SSD = sutureless securement device

Appendix E. References

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Specific search terms are provided here. The associated alerts are provided with this report as a separate PDF.