

# The Clinical Use of Tissue Adhesives: A Review of the Literature

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## KEYWORDS:

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Sutures have traditionally been used in the emergency room and in the primary care setting for wound and laceration closure, but over the past several decades we have seen alternative methods of wound closure emerge. Tissue adhesives are starting to become the front-runner as the alternative to sutures. They possess many advantages and have shown great results when compared to sutures to include cost effectiveness, reduced infection rate, a reduced time requirement and improved cosmetic results. Over the past several years many other indications have started to emerge such as treatment for esophageal varices, application of skin grafts, and vascular embolization. The different chemical compositions and functions will also be reviewed. Disadvantages of tissue adhesives include lower tensile strength and a potential for systemic absorption or embolization. Overall, tissue adhesives provide an excellent means for wound closure in multiple settings and are the first choice method amongst clinicians across disciplines.

## INTRODUCTION

In the ever-evolving world of medicine, continual research and new advances in technology have aided our care for patients for many years. With the recent changes in healthcare policies and procedures, our search for improved patient care has been directed at finding better ways to be cost-effective and time-efficient, while still directing our treatment goals towards providing the highest quality patient care. One of the areas that have continually seen advances in cost and time efficiency is the treatment and closure of wounds and lacerations.

Sutures have conventionally been the method of approximating wound edges due to their high tensile strength and favorable cosmetic outcomes. Sutures do, however, have some downfalls in that they require increased time and a skilled individual to accomplish good cosmetic outcomes. Over the past four decades, advances have seen other forms of wound closure methods emerge that address some of the disadvantages of sutures.<sup>3,6,7,8,11</sup>

This article will focus mainly on tissue adhesives, specifically octyl-2-cyanoacrylate (OCA), also known as 'dermabond'. We will review literature and discuss some of the common clinical applications of tissue adhesives, as well as compare and contrast tissue adhesives with other wound closure techniques. The chemical composition, advantages, disadvantages, and complications will also be discussed. The goal of this literature

review is that one will have a better understanding of tissue adhesives, which will further aid in the treatment of patients.

## MATERIALS AND METHODS

### Selection criteria

Five different journal search engines were used to screen for relevant and appropriate sources to include Pubmed, Medline and Medscape. In addition to these search engines, databases within *New England Journal of Medicine*, *Annals of Surgery*, *Annals of Internal Medicine*, *JAMA*, *Mayo Clinic Proceedings*, *Circulation*, *Journal of Endourology*, *Journal of Trauma Injury*, and *Journal of Trauma and Acute Care Surgery* were searched to also screen for sources.

The initial search for dermabond yielded more than 3500 results, and from those nine were selected using identified inclusion criteria which included relevance to the Primary Care Physician, statistically significant data, a clearly identified patient-oriented, evidence-based outcome, and publication in a peer-reviewed journal. The remaining sources were found within the journal databases using the same inclusion criteria identified above. Keywords that were used in the searches were dermabond, liquid bandage, liquid adhesives, cyanoacrylate, and 2-octyl-cyanoacrylate.

## DISCUSSION

H. Coover first discovered cyanoacrylates in the mid-20<sup>th</sup> century as an all-purpose adhesive originally designed for around-the-house use; but Coover did not discover its true medical potential until the late 1950s after he further studied the chemical composition.<sup>6,7,8,11</sup> It was not until the mid-1980s that cyanoacrylates started being used in Europe and Canada as a tissue adhesive.

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In the United States, cyanoacrylates have been used for several decades in the form of n-butyl-cyanoacrylate, but only with a limited clinical application due to its lower tensile strength.<sup>3,5,7</sup> In the United States, the FDA did not approve cyanoacrylates in the use of tissue adhesive until 1998, when it approved OCA.<sup>3,6,7,11</sup> OCA is now approved and widely used in the United States for many different procedures other than wound edge approximation, due to its higher tensile strength compared to earlier forms. This makes it more applicable to areas that are under more stress and tension, and no longer limits cyanoacrylates to the treatment of topical wounds only.<sup>3,5,6,7,8,12</sup>

Cyanoacrylates are liquid monomers that become polymerized upon exposure to air, liquid, and tissue, to form a strong bond that aids in the approximation of wound edges.<sup>3,7,8,11</sup> Approximately 55 seconds is needed for the polymerization to take place, depending on the surface to which it is being applied.<sup>1</sup> Plasticizers, stabilizers, and other substances have been added that allow for many different formulations of the compound, but the change in the number of alkyl groups being added to cyanoacrylates has shown the most improvement in strength.

This was confirmed when comparisons were made between the earlier forms of cyanoacrylates such as methyl-2, ethyl-2, and n-butyl-2-cyanoacrylate to the most recent form of OCA. OCA has been documented as having up to four times the tensile strength compared to the shorter-chained cyanoacrylates.<sup>1,3,5,6,7,8,11</sup> The stronger polymerization of OCA also aids in its delayed degradation, which causes less potential side effects of degradation products.<sup>7</sup>

## INDICATIONS

OCA has been widely documented for its use in wound closure. It has been used in orthopaedic surgeries, facial surgery, cranial surgery, spinal surgery, corneal surgery, neck surgery, laparoscopic procedures, and many others.<sup>1,2,3,14</sup> The FDA-approved indications for OCA are for the topical use in easily approximated wounds, including trocar wounds in minimally invasive surgery and for approximating skin lacerations. It is not intended to replace sutures in every situation, but can be used in conjunction with sutures.

Lins et al. noted in their review that tissue adhesives were a good alternative to conventional sutures on low-tension areas.<sup>1</sup> There are several off-label uses of OCA which have been identified, including the treatment of bleeding esophageal and gastric varices in a treatment referred to as 'cyanoacrylate sclerotherapy'.<sup>4,7</sup> OCA has also been documented to be used in the application of skin grafts, vascular embolization, and hemostasis.<sup>8,9</sup> It can also be used to hold catheters in place as an alternative to tape or a single suture.<sup>13</sup>

## ADVANTAGES

### Tensile strength and wound closure

There are many proposed advantages of tissue adhesives over sutures and staples. Tissue adhesives are considered to take less time to apply, have lower risk of infection, have comparable tensile strength, and also provide less pain and anxiety. Shivamurthy et al. concluded in their comparison of OCA and conventional sutures in facial skin closure that OCA has equal tensile strength to 5-0 sutures and is therefore better than sutures for facial skin closure.<sup>8</sup> This conclusion was most likely reached due to OCA generally being used in areas of lower tension, such as the face where the wound edges are easily approximated.<sup>3</sup>

Chen et al., in a randomized, controlled trial, compared sutures and OCA in the closing of laparoscopic port sites in 80 wounds. Half of the wounds were closed using sutures, and the other half using OCA. They found that margin separation with OCA was 1/40 compared to that seen in sutures, which was 10/40 with a p-value of 0.004.<sup>3</sup>

### Erythema and drainage

Chen et al. also found in their controlled trial that OCA was more superior than sutures in regards to erythema, tenderness, and drainage. The erythema was 1/40 versus 16/40, with a p-value of 0.0001. Tenderness was 1/40 versus 19/40, with a p-value of 0.001. Finally, the drainage was 1/40 compared to 9/40 in the conventional sutures, with a p-value of 0.007. These findings along with those mentioned earlier proved to be statistically significant; after the conclusion of their controlled trial, they found the results to be sufficient enough for their practice to change to the standard use of OCA over conventional sutures in the closure of laparoscopic port sites.<sup>3</sup>

### Risk of infection

One of the major concerns after any surgical procedure, no matter what its magnitude, is the risk of infection. There are many precautions that can be made in order to decrease this risk, and pre-treating the patient with antibiotics has shown to have the greatest effect. However, even when using all precautions there still remains a risk of the patient contracting an infection in their wound. These infections can cause a significant burden on the patient and can further prolong their hospital stay.

OCA can potentially lower the risk of post-operative infections due to its antimicrobial properties against gram-positive organisms. OCA also creates a more occlusive barrier than conventional sutures, which helps to prevent the optimal environment that organisms grow in.<sup>2,3,5,6,8</sup> It has been noted that sutures actually have the potential to enhance the growth

of bacteria through the adherence of bacteria to the sutures themselves.<sup>10</sup>

Wachter et al., in a prospective clinical study of 235 patients, investigated the use of OCA for wound closure in spinal surgery. They were most interested in the risk of post-operative wound infections after giving perioperative antibiotics and closing the spinal surgical wounds with OCA. The results showed that out of the 235 patients, only one contracted a post-operative wound infection, making the overall infection rate 0.43% with a p-value of <0.05. Also included in their study was a comparison of a group of 503 patients that underwent spinal surgery with wound closure using standard sutures, with and without perioperative antibiotic treatment. In this group of patients the post-operative wound infection rate was 2.2% in patients treated with perioperative antibiotics.<sup>6</sup>

### Application time

The time it takes to apply OCA is one of the major advantages it has over conventional sutures. The shorter application time makes it ideal for emergency situations, as well as for pediatric patients. Pediatric patients are usually in severe distress, in a state of anxiety, and in pain when minor surgical procedures are needed. The quicker you can stop the bleeding and approximate the edges, the quicker you can get the child into a lower state of anxiety. OCA also does not require anesthesia and the child can often remain in their parent's lap while it is applied.<sup>1,2,8,14</sup>

Shivamurthy et al. noted in their comparison of OCA and conventional sutures in facial skin closure that it took one-third of the time for wound closure using OCA versus conventional sutures.<sup>8</sup> In line with this, Sebesta et al. conducted a randomized study comparing the closure of laparoscopic trocar sites using OCA and subcuticular sutures in 59 patients with 228 trocar sites. In their results they noted that it took on average 3.7 minutes to close the wound using OCA versus 14 minutes using sutures, with a p-value of 0.00001.<sup>14</sup> However, in a blinded randomized, controlled trial of stapled versus OCA conducted by Ridgway et al., the results showed that OCA took more time to apply than staples in the closure of neck surgery incisions, with an average time of 95s compared to 28s (p<0.001).<sup>5</sup>

### Cosmesis

It has been proposed that OCA has a better cosmetic outcome over sutures. This is due in part to the suturing technique needing a more skilled individual to accomplish good cosmesis, and could also be due to the better seal that OCA accomplishes which helps account for the better wound approximation. It should be noted, however, that the application of OCA must be adequate for quality wound

approximation, although the application technique is not as demanding nor does it require as much skill.

Several studies have been conducted to evaluate the cosmetic outcomes of OCA versus conventional sutures. They have been compared using different scales devised to rate the cosmetic outcome. The Holland Wound Evaluation Scale (HWES) is one of the scales that are being used. Chen et al. used the HWES scale when they evaluated the cosmetic appearance of their 40 patients who had a total of 80 scars. They concluded that the wounds that were closed with OCA had a significantly higher total HWES score compared to wounds closed with sutures (p=0.009).<sup>3</sup>

The visual analogue scale (VAS) is rated by the patients, families, physicians, and also by independent blinded assessors for a satisfactory score. Shivamurthy et al. concluded that both the patients' and the surgeon's satisfactory score were higher in the group that received wound closure with OCA; however, these results were found to be statically insignificant. Shivamurthy et al. went on to note they had also seen these same statistically insignificant results in several other prior studies.<sup>8</sup>

### Cost

In the same study mentioned above, Sebesta et al. also noted that the average cost of using OCA per procedure was \$198 compared to \$497 using the subcuticular sutures.<sup>14</sup> Shivamurthy et al. confirmed that the use of OCA was overall cheaper. They, however, also found that the cost of OCA itself was higher than sutures, but that the cost of transportation for suture removal, lost wages, and antibiotics used with sutures was significantly higher.<sup>8</sup>

### DISADVANTAGES

The advances in tissue adhesives have come a long way, and improvements in the chemical formulation have allowed them to be used in more procedures. However, tissue adhesives come with some disadvantages. As mentioned earlier, OCA has equivocal tensile strength to 5-0 sutures, but this also limits its use.<sup>8</sup>

New formulations have increased tensile strength, but OCA is still often limited to being used on areas of lower tension such as the face or scalp. Areas such as the soles of hands and feet usually require sutures with tensile strength greater than 5-0; therefore, OCA would not be a good choice in such wounds unless combined with sutures.<sup>3,7</sup>

Chen et al. noted less margin of separation using OCA, but they also concluded in their randomized, controlled trial of 80 laparoscopic port site closures that OCA showed greater

contour irregularities compared to conventional sutures. Their study found that 6/40 wounds using OCA as the closure technique had contour irregularities compared to 1/40 wounds being closed using sutures, with a p-value of 0.047. However, these results only came about due to changes in personnel and application techniques.

They found in the latter half of their study that the contour irregularities had significantly improved to 1/28 irregularity versus 5/12 irregularities seen earlier, with a p-value of 0.002.<sup>3</sup> This trial is a clear example of how important application technique is with OCA. With improper technique, the tissue adhesive could incompletely approximate the wound edges, and could potentially cause scar irregularities.<sup>8</sup>

## COMPLICATIONS

Cyanoacrylates are broken down by the body into potentially toxic compounds, such as formaldehyde and cyanoacetates. The new formulations of cyanoacrylates degrade slower, due to the longer alkyl groups as mentioned earlier. This correlates with lower levels of toxic compounds being seeped into the body. However, the slower degradation allows non-degradable polymers to remain in the body. These polymers have been shown to increase the risk of infections in patients being treated with OCA.<sup>7</sup>

OCA has been increasingly used as one of the treatment options for bleeding gastric and esophageal varices in patients with liver cirrhosis. Other treatment options include transjugular intrahepatic portosystemic shunt, band ligation, and hepatic transplantation.

Singer et al. reported on a patient being treated for gastric varices using OCA in sclerotherapy. In their case study, the patient became tachycardic and febrile after completion of the cyanoacrylate sclerotherapy. With his past medical history there was concern for infection, which is a documented complication of OCA use in variceal treatment. The patient was worked up for sepsis, and subsequently obtained a chest radiograph. The radiograph had abnormal findings, which prompted further work-up with a non-contrast CT, which confirmed the suspicion of a pulmonary embolism by the radiologist.

Singer et al. further noted in previous case studies the potential complication of a pulmonary embolism when using OCA as a treatment option for bleeding esophageal and gastric varices, especially in the setting of an anatomical abnormality such as a patent foramen ovale or arteriovenous shunt.<sup>4</sup>

## APPLICATION TECHNIQUES

There are several different application techniques that are being used to approximate wounds with OCA. Wachter et al. described the application process, which started off with an initial approximation of the wound edges, either with a suture or with forceps. The inner ampule was then crushed and the OCA was pushed into the applicator head, where it was lastly applied to the wound. The liquid form polymerized upon application and became solid within 2–3 minutes, which could be left as a single layer or be applied multiple times to form several layers.<sup>6</sup>

Chen et al. showed that the correct technique was an important factor in order to achieve good cosmetic outcomes. The problem in their study, however, was that proper technique using forceps to oppose the wound edges was not followed as per the manufacturer's instructions, instead using fingertips. Contour irregularities were then noted in the patients where the manufacturer's instructions were not followed, and great improvements in contour irregularities were later seen in the patients where forceps were used to oppose the wound edges while OCA was being applied.<sup>3</sup>

## CONCLUSION

Tissue adhesives have come a long way since their conception in the 1950s. The compounds have continually been changed and combined with additives while attempting to introduce them as the new alternative to conventional sutures. Several studies have concluded that OCA has comparable tensile strength to sutures and can provide equal or better cosmetic outcomes. It has also been proven that OCA forms a much tighter seal and limits the humid environment needed for bacteria to grow, which results in less wound complication and shorter hospital stays.

It is important that our management of patients continues to be of the highest quality. Using a procedure that takes less time or is more cost-efficient is not always best practice management; however, the results of these trials show that OCA has the ability to be both time- and cost-efficient while still providing quality care.

OCA does not require a skilled person to apply, nor does it cause pain that requires anesthesia as with the suturing technique. Therefore, it can be applied in a much quicker manner and not cause any additional pain or anxiety to the patient. With these advantages and with continued improvement, tissue adhesives have become an ideal alternative to conventional sutures and could possibly become the preferred standard of care in many procedures.

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