

Cyanoacrylates for Skin Closure

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Cyanoacrylates (CAs), first produced in 1949 [1], are liquids that polymerize in the presence of moisture to form adhesives, glues, and films. The surgical use of these compounds was first proposed by Coover et al [2] in 1959. The short-chain cyanoacrylates (methyl, ethyl) [3,4] proved to be extremely toxic to tissue, however, preventing their widespread use as tissue glues. The short-chain CAs are used in nonmedical products, such as Krazy glue (Elmer's, Columbus, Ohio), and although they are not intended for medical use, dermatologists have been quoted in the popular press as recommending these glues for the treatment of fissures on fingers and toes [5]. Butyl cyanoacrylate (BCA), an intermediate-length CA, is not toxic when applied topically. Although it is not approved by the US Food and Drug Administration (FDA) for use in the United States, it has been used in Europe and Canada for middle ear procedures, to close cerebrospinal leaks, to repair incisions and lacerations, and to affix skin grafts [6–12]. Recently, a longer chain CA, octyl-2-cyanoacrylate (2-OCA), has been approved by the FDA and is now marketed (Dermabond topical skin adhesive) for closure of lacerations and incisions in place of sutures or staples. Even more recently, a 2-OCA formulated for greater flexibility, Liquid Bandage, has been approved for use in the over-the-counter market in the United States for the treatment of minor cuts and abrasions. This article discusses the use of CAs for their original cutaneous use as glues for the repair of lacerations and incisions and for their more recent use as films for use as dressings in the treatment of abrasions and wounds.

Butyl cyanoacrylate

BCA is an intermediate-length CA that was the first CA to be widely used for cutaneous wound closure. It has been available and widely used in Europe and Canada as Histoacryl Blue and Glustitch since as early as the 1970s. Although the short-chain CAs (methyl, ethyl) were toxic to tissue, BCA is generally considered to be nontoxic when applied topically. When used in an experimental model of incisional wound healing in hamsters, BCA resulted in less inflammation than 4.0 silk sutures on histologic assessment [7]. Furthermore, a randomized clinical trial involving 94 patients who had facial lacerations suitable for tissue adhesive closure and who underwent closure using either BCA or 2-OCA failed to reveal a difference in cosmetic result at 3 months as rated from photographs by a plastic surgeon using a visual analog scale [13]. Interpreting these data to imply that BCA has no tissue toxicity should be done with caution, however; care was taken to prevent the BCA from coming in contact with exposed wound tissue because of lingering concerns that BCA when trapped in the wound itself might cause a toxic reaction [14]. Because of these concerns, BCA has never been approved for use in the United States and has never been actively advocated for use on wounds as a film-forming or bandage-like agent.

Octyl cyanoacrylate

Octyl cyanoacrylates are CAs with a longer (8-carbon) side chain. This longer side chain gives

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2-OCA several potential advantages over CAs that have short or intermediate side chains. For example, 2-OCA is stronger and more flexible than BCA, with 4 times the three-dimensional breaking strength of this shorter chain CA [15]. Because of its improved strength and flexibility properties and because of reduced fears of tissue toxicity, 2-OCA is now widely used in the United States for wound closure, and it is currently one of the largest bandage brands as ranked by dollar sales in the United States.

Octyl cyanoacrylate and cosmetic outcome

Studies of 2-OCA have revealed that it is equivalent or superior to standard suturing of wounds as judged by several criteria. When evaluated prospectively for the treatment of cutaneous lacerations [16] and elective head and neck incisions [17], no differences in cosmetic outcome at 12 weeks were noted when compared with standard suture repair. In the same studies, patients rated 2-OCA closure as less painful than standard suture closure, and wound closure took significantly less time than with suture repair. A larger study of 814 patients who had a more diverse group of wounds (383 traumatic lacerations, 235 excisions of skin lesions or scar revisions, 208 minimally invasive surgeries, and 98 general surgical procedures) also showed the equivalence of closure with 2-OCA as compared with standard suture wound closure in terms of cosmesis at 3-month follow-up. Again, wound closure with 2-OCA was faster than with standard suture wound closure (2.9 min versus 5.2 min, $P < 0.001$), and at 1 week, infection rates were similar. There were no differences in wound dehiscence rates in this study. Despite multiple studies that showed similar outcomes in 2-OCA-treated wounds and standard suture-treated wounds in both adults and pediatric patients in cosmetic appearance of the healed wound, there has been one study where 2-OCA-treated wounds had an inferior outcome [16–21]. In a study of 83 children who were seen in an emergency department with lacerations and randomized to receive either 2-OCA or non-absorbable sutures or staples, the children treated with 2-OCA ultimately had a slightly lower cosmesis score [22]. As in similar studies, however, treatment with 2-OCA resulted in a decreased repair time of 5.8 minutes with suture and staples to 2.9 minutes with 2-OCA, and a reduction was found in the parents' assessment of the pain felt by their children. Because this is the only study to show this outcome, it should be interpreted with caution, but physicians should consider whether 2-OCA is indicated for

lacerations in the pediatric population in cosmetically sensitive areas.

Octyl cyanoacrylate and infection

Because sutures inherently introduce foreign material into a wound, 2-OCA may have a natural comparative advantage in infection rates, especially with clean contaminated wounds. In addition, CAs have been reported to have inherent antimicrobial properties, especially against gram-positive organisms [23]. In a randomized, blinded study, incisions were made on guinea pigs and contaminated with *Staphylococcus aureus* [24]. The incisions were then randomly assigned to be closed with either 2-OCA or 5-0 polypropylene suture. At day 5, wounds were then examined histologically and determined to be infected if inflammatory cells with intracellular cocci were seen. On the same day, wounds were also examined for clinical evidence of infection and a quantitative bacteriologic analysis was performed. Of 20 wounds in the tissue adhesive group, 5 wounds were sterile on day 5, whereas all sutured wounds had positive cultures ($P < 0.05$). Fewer wounds in the tissue adhesive group were determined to be infected by histologic and clinical criteria. Generally, differences in infection rates in human trials between wounds closed with 2-OCA and standard suture wound closure techniques have not been statistically significant. Trials to date have frequently excluded patients with grossly contaminated wounds, however.

Octyl cyanoacrylate and cost

Despite the apparent evidence of equivalence or even advantage of 2-OCA for wound repair, its adoption over standard wound closure techniques has been relatively slow. This situation may be because of cost disadvantages to the treating physician or institutions. On a per-unit basis, 2-OCA (eg, Dermabond Ethicon Products, Somerville, New Jersey) is 10 times more expensive than a popular brand of black monofilament nylon sutures [25]. Despite this situation, the overall cost advantage to society and to patients probably lies with the CAs. When the three most commonly used methods for the repair of pediatric facial lacerations—nondissolving sutures, dissolving sutures, or a CA—were compared on an economic basis, which included factors such as equipment use, pharmaceutical use, health care worker time, and parental loss of income for follow-up visits, assuming an equal cosmetic outcome, there was a reduction in cost to the Canadian health care system from the use of CAs. The reduction in cost in

Canadian dollars per patient of switching from the standard nondissolving sutures to a CA was \$49.60 and for switching to dissolving sutures was \$37.90 [26]. In addition, when parents of treated patients were surveyed, they overwhelmingly (90% of parents) chose the use of the CA as their first choice for wound closure (10% chose dissolving sutures). Despite the preference of parents and reduced costs to the society, however, CAs will probably continue to be the last choice of health care providers as long as they are associated with increased direct cost to the providers.

Cyanoacrylates as wound dressings

As concerns about potential tissue toxicity abate and newer, more flexible 2-OCA formulations have become available, CAs have been used not only for the closure of wounds but also for the treatment of wounds and as a wound dressing. Many physicians remain skeptical about this use of 2-OCA out of concern of tissue toxicity in earlier CAs; however, animal studies have consistently failed to show any tissue toxicity from 2-OCA when applied directly to open tissue in wounds. In a guinea pig abrasion model of wounds, there were no differences in the mean wound-healing ratios on days 1, 7, or 14 for 2-OCA as compared with a control dressing (Bio-brane), and histopathologic analysis on day 14 failed to find any differences between the treatments [27]. In a porcine model of acute partial-thickness wounds, 2-OCA did not produce tissue toxicity (Stephen C. Davis, William H. Eaglstein, MD, Alex L. Cazzaniga, and P.M. Metz, unpublished observations, 2000). Furthermore, faster healing was seen in the 2-OCA-treated wounds as compared with the wounds treated with commercial bandages. On day 5 post wounding, 67% of 2-OCA-treated wounds were completely healed as compared with 20% of Band-Aid-treated wounds. Other studies of 2-OCA for partial-thickness wounds in pigs confirm these results and suggest that 2-OCA compares favorably with other effective dressings. For example, 115 standardized partial-thickness wounds were created in a porcine wound-healing model and treated with 2-OCA, a hydrocolloid dressing, or gauze. Biopsy specimens were taken at days 4, 5, 6, and 21 post wounding. The percentage of re-epithelialization in wounds treated with the liquid occlusive and hydrocolloid dressings was significantly greater at days 4 and 5 compared with control wounds [28]. In addition, several benefits have been attributed to the treatment of

wounds with 2-OCA, including increased resistance to bacterial challenge of the wound and increased wound hemostasis [29]. In vitro testing of 2-OCA has confirmed that it forms an excellent barrier against several bacterial and fungal pathogens [30]. Similar results from the use of 2-OCA in burns have been observed. One author evaluated the use of 2-OCA second-degree burns as compared with treatment with a polyurethane film dressing (Tegaderm). Forty-four partial-thickness burns were created on the backs of pigs, and wounds were randomly treated with 2-OCA or the film dressing. Full-thickness biopsy specimens were taken on days 7, 10, and 14 and evaluated for infection and re-epithelialization. No statistically significant difference was seen in the rates of re-epithelialization and no wounds in either treatment group became infected [31]. Singer et al [32] compared the effects of treatment of partial-thickness burns in pigs with 2-OCA, silver sulfadiazine (SSD), polyurethane film (PU), and gauze on scarring after 3 months. Forty partial-thickness burns were randomly assigned to be treated with 2-OCA, SSD, PU, or gauze. Digital images and biopsy specimens of the burns were obtained at 3 months. There were no statistical differences in the proportion of wounds with scarring among the groups (OCA = 10%, SSD = 22%, PU = 2%, gauze = 30%; $P = 0.89$) or in cosmetic scores among the groups ($P = 0.96$) as judged by blinded observers. The same authors also evaluated infection rates of contaminated second-degree burns in pigs treated similarly [33]. Eighty partial-thickness burns were created and contaminated with 0.1 mL of *S aureus* 10(5) CFU/mL and then randomly treated with 2-OCA, SSD, PU, or gauze. The treatment of contaminated partial-thickness burns with 2-OCA resulted in fewer infections at 1 week compared with the other three treatments.

Results of the use of 2-OCA for the treatment of open wounds have been similar to those in animal models. The current authors recently compared a new, flexible formulation of 2-OCA (Liquid Bandage) to a commercially available over-the-counter bandage for the treatment of cuts and scrapes [34]. Because short-chain CAs are irritating and toxic to tissues and because Dermabond, which contains the same 2-OCA as Liquid Bandage, is approved only for application to the surfaces of wounds with approximated wound edges, the authors were particularly interested in evaluating the possibility that direct application of 2-OCA to open cuts and scrapes would be toxic or irritating to wounds. Eighty-two subjects in the study applied 2-OCA directly to their cuts or scrapes and none experienced pain, redness, warmth, or edema. In addition, neither infection nor

delayed wound healing was seen in the 2-OCA-treated wounds.

Cyanoacrylates and wound hemostasis

The hemostatic activity of CAs has been reported in many studies [35–37]. In a porcine model of epistaxis, one group of authors created 24 full-thickness wounds on the nasal septae of pigs with a 4-mm punch biopsy tool [38]. Wounds were randomized to either no treatment or to topical 2-OCA before and after heparinization of the animals. The authors reported that the time to complete hemostasis was significantly shorter in the wounds treated with 2-OCA versus control (mean difference, 150 s; $P < 0.001$). In porcine studies of partial-thickness wounds, 2-OCA has been an effective hemostatic agent [28,39]. In a human trial of 2-OCA for partial-thickness wounds, it was reported to stop bleeding or oozing immediately in 93% of wounds as compared with 46% of wounds treated with standard bandages. The ability to achieve rapid hemostasis is an attractive feature of the CAs.

Cyanoacrylates as drug delivery devices

CAs offer potential as a drug delivery device in which therapeutic agents can be directly incorporated into the CA itself and as a dressing, which can keep a therapeutic agent in place in a difficult anatomic location. For the former application, CAs have been used to create nanoparticles. These nanoparticles have then been incorporated in vehicles for topical application. BCA nanoparticles have been reported as drug carriers of 5-fluorouracil, paclitaxel, and indomethacin intended for use in topical treatment [40–42]. To the authors' knowledge, however, currently no therapeutic agents have been directly incorporated into a CA itself for cutaneous application. With regard to using 2-OCA as a device for maintaining an active agent in a difficult location, in one recent trial, 31 patients with recurrent aphthous lesions were treated with either an active agent or a placebo. Both the active agent and the placebo were maintained in place by coverage with a BCA [43]. Clearly, further research is needed in both possible uses.

Miscellaneous uses of cyanoacrylates

Another use for 2-OCA is for the treatment of wounds in the oral mucosa. Orabase (Colgate,

Conton, Massachusetts), a flexible form of 2-OCA, is specifically formulated for use in the oral mucosa [44]. It is a unique product in the over-the-counter market because, unlike other products, it is an occlusive dressing, not simply a topical anesthetic. To the current authors' knowledge, Orabase is the only over-the-counter product consumers can purchase that creates a mechanical barrier providing pain relief for oral ulcerations and abrasions. In two separate studies [45] of 200 patients with an aphthous ulcer, 2-OCA when used in the oral mucosa provided significant short- and long-term pain reduction as compared with placebo treatment.

Summary

Even though the first CAs were produced in 1949, they were not widely adopted for medical use until recently because of lingering concerns about the initial tissue toxicities of the short-chain CAs. Medium-chain CAs, primarily BCA, have been widely used in Europe and Canada for several decades and have gone a long way in dispelling any lingering concerns about tissue toxicity. The newer, longer chain CA, 2-OCA, now has been approved for multiple uses in the United States and has achieved widespread acceptance by the medical and lay communities. The current authors believe this development is probably only the beginning of the use of 2-OCA and other CAs in cutaneous medicine.

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