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RESEARCH ARTICLE

Electrospinning of cyanoacrylate tissue adhesives for human dural repair in endonasal surgery

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Abstract

Cerebral spinal fluid (CSF) leakage is a major postoperative complication requiring surgical intervention, resulting in prolonged healing and higher costs. Biocompatible polymers, such as cyanoacrylates, are currently used as tissue adhesives for closing surgical defects and incisions. Coupling these polymers with nanofiber technology shows promising results for generating nanofibers used in wound care, tissue engineering, and drug delivery. Fiber membranes formed by electrospinning of *n*-octyl-2-cyanoacrylate (NOCA) are investigated for in situ dural closures after neurosurgery to improve the quality of the closure and prevent post-surgical CSF leaks. Electrospun NOCA fiber membranes showed significantly higher sealing capabilities of defects in human dura, with an average burst pressure of 149 mmHg, compared with that of an FDA-approved common dural sealant that had an average burst pressure of 37 mmHg. In this study, microfabrication of NOCA fibers demonstrates a promising technique for dural repairs.

KEYWORDS
Adherus®, craniotomy/durotomy, CSF, cyanoacrylate, Dermabond®, dural leakage, electrospinning, endonasal

1 | INTRODUCTION

1.1 | Overview of tissue adhesives: Cyanoacrylates

Proper closure of surgical incisions and defects is imperative for optimal healing post-surgery.[1] While synthetic sutures and staples are common methods for closing incisions, tissue adhesives, such as cyanoacrylate (CA), are now considered a standard for wound closure and sealant for surgical and hemostatic procedures. Indirect deposition, while attractive from the point of view of allowing separate pre-preparation of the sealant, unfortunately would compromise the adhesive strength between glue and substrate. An example of separate preparation of soft issue adhesives has been reported by Boda et al. electrospinning of chitosan nanofibers.[2] However, the membrane requires post-fabrication surface modification, which would not be practical for an endonasal application. These types of tissue adhesives have also been shown to provide an essential barrier function against microbial penetration to the wound and prevent cerebral spinal fluid (CSF) leakage.[3-6]

Tissue adhesives comprised of CA are made of liquid monomers that polymerize within seconds when in contact with weak bases, such as water or biological tissue surfaces, via an exothermic reaction.[7] The result is a strong and pliable film that bonds to the edges of the defect in the tissue.[4] Advantages, including rapid application, ease of use, a relative absence of pain, and antimicrobial properties, make CA tissue adhesives attractive over conventional sutures.[8] The direct cost associated with surgical CA is higher than other wound closure implements, such as sutures or staples. However, cost-effective analyses demonstrate that tissue adhesives are overall more cost effective. These cost savings are accredited to the reduced need for follow-up, physician time, and required supplementary supplies.[9,10]

Organic substrates such as fibrin glue, Adherus®, and L-3,4-dihydroxyphenylalanine (Dopa) offer an alternative class of tissue adhesives. Dural sealing capabilities of fibrin glue were assessed by van Doormaal et al., with burst pressures associated with fibrin glue being shown to be lower than normal physiological intracranial pressure.[11] Mussel-inspired, adhesive hydrogels (Dopa) represent an exciting possible avenue of future research given their promising adhesive performance in an aqueous environment.[12] This may be especially true in surgeries for internal organs that require wet tissue adhesion. In a homeostatic environment the nasal cavity is moist. However, following surgery, it is common to experience desiccation and nasal crusting. It is unclear as to whether the strength of mussel-inspired adhesives would represent an improvement over hydrogel sealants (current industry standard) in this setting. Adherus® Autospray ET Dural Sealant is a polyethylene glycol ester/polyethyleneimine solution equipped with a 170 mm long tip making it an accessible solution for closing dural defects using an endonasal endoscopic application. The polymer comes in a two-part system which must be mixed prior to administration, requiring a single-use apparatus. After application, the biodegradable polymer can swell up to 46% (by volume) from the initial size and absorbs into the body over 90 days.

The main limitation of CAs use in medical applications is due to its toxic biodegraded byproducts.[1] Research has shown tissue inflammation and cell necrosis after exposure, as the polymer can degrade freely, forming formaldehyde causing an acute or chronic inflammatory response.[13] One technique to reduce the toxicity of CAs is by extending their CH_2 alkyl chain[14-16] resulting in alternative tissue adhesives, such as *n*-octyl-2-cyanoacrylate (NOCA) and *n*-butyl-cyanoacrylate, being developed and marketed as Dermabond® (Johnson & Johnson/Ethicon, Somerville, New Jersey) and Histoacryl® (B. Braun, Melsungen, Germany), respectively.[14,15,17] Additionally, Dong et al. showed a reduced inflammatory response and postoperative tissue regeneration by precisely depositing minuscule amounts of NOCA via electrospinning after liver resection.[18] While cyanoacrylate adhesives are associated with a small amount of toxic degradation products, they are commonly used across the world for skin lacerations. Many ENT providers also use cyanoacrylate for mucosal repair following septoplasty; their safety in the nasal cavity for closure following this procedure has been documented.[19] The problem of CSF fistula following expanded endonasal surgery is significant. Complications often require a return trip to the operating room and are sometimes life threatening. It is likely that a markedly improved method of skull base reconstruction, even one that may be associated with low level toxic degradation products, would represent a significant upgrade in the care of patients requiring this form of surgery.

1.2 | Endoscopic endonasal transsphenoidal surgery and complications

Endoscopic endonasal transsphenoidal surgery is a minimally invasive surgical approach that uses specialized instrumentation to gain access to the sella turcica, a small depression in the skull that houses the pituitary gland. It is most commonly used to remove pituitary tumors and lesions. Figure 1 shows the endoscopic endonasal transsphenoidal approach. This approach reduces neurological morbidity by avoiding brain retraction and areas in the skull lined with cranial nerves. However, it does require opening the dura mater, which is associated with an increase incidence of post-operative CSF Leaks.

The dura mater is the outermost layer of the three-layered meninges that encompass the brain. It functions primarily as a barrier to contain cerebrospinal fluid (CSF) within the cranial cavity. Any opening or defect created in the dura during surgery must be successfully closed to mitigate CSF leaks. In general, use of sutures is the most commonly used method for dural repair. However, sutures are difficult to perform when using an endoscopic endonasal approach owing to technical limitations imposed by long-shaft instrumentation in the long and narrow endonasal corridor.[21] This has led to an unacceptably high incidence of postoperative CSF leakage following endoscopic endonasal transsphenoidal surgery.[22] Leakage of CSF is a major concern as it poses life-threatening complications, such as pneumocephalus and meningitis. Additionally, there is a higher cost linked with treating post-surgical CSF leaks. Grotenhuis estimated a savings of €550 per patient when there is no need to repair a postoperative CSF leak. He also estimated a dural repair cost for a single CSF leak ranges from $10,000 to $15,000 in the United States.[23]

Even with advanced technology, neurosurgeons agree there is a lack of consensus for standard practice of dural closures followed by few clinical assessments of closure outcomes.[24,25] Although robust and stable seals of the dura mater are critical for post-neurological surgery, according to systematic reviews and in vitro studies, the currently available dural sealants still lack efficacy.[26,27] Van Doormaal et al. reported a comparison analysis of nine common dural sealants using an in vitro model. With a modified ASTM F2392-04 (Standard Test Method for Burst Strength of Surgical Sealants) test methodology, their study quantified the acute burst pressure and a 3-day sustained pressure (16 mmHg) test of a dural repair using an animal model. Of the nine dural sealants evaluated, only three had burst pressures above normal physiological levels, and only two sealants could withstand the 3-day sustained pressure test. Of the nine evaluated sealants, Adherus® (Stryker) showed the highest burst pressure (87 ± 47 mmHg) and held an acceptable sustained pressure during the 3-day test.[11]

1.3 | Nanofiber fabrication technique: Electrospinning

Electrospinning produces fibers from solutions of a multitude of polymers. The resulting mesh of randomly oriented fibers with diameters ranging from tens of nanometers to microns has many attractive qualities, such as a large surface area to volume ratio, tunable porosity, and flexibility to cover various shapes and sizes. Variations in the polymer concentration in solution, applied voltage, flow rate, and distance from the collector can influence the size and shape of the nanofibers, allowing the fibers to be engineered for specific applications.[28] Development of nanofiber technology includes portable devices for

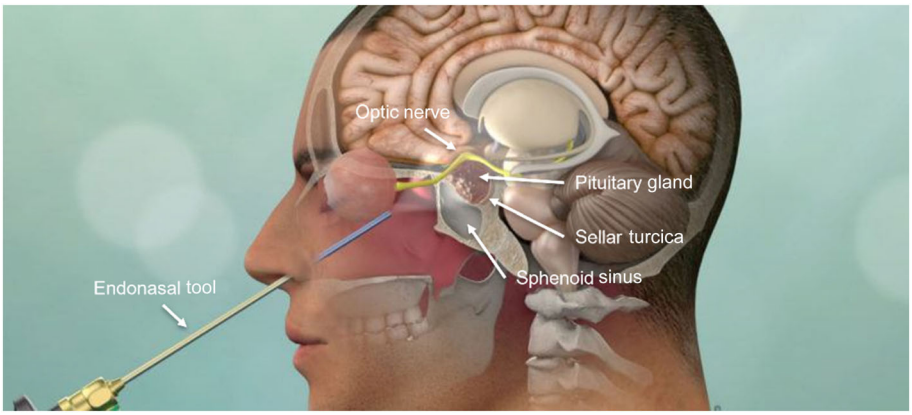

FIGURE 1 Endoscopic endonasal transsphenoidal approach.[20] Used with permission granted from Pacific Neuroscience Institute

applications in the biomedical field, such as wound closures, specifically dural repair and reconstruction after neurosurgical procedures.

The use of airflow directed in situ electrospinning was reported[29] by Jiang et al. to fabricate FDA-approved NOCA tissue adhesive nanofibers has been explored for the attachment of medical glue to achieve rapid hemostasis. By connecting an air pump to the spinneret head, airflow at 12 L/min helps focus the fiber deposition. The results demonstrate this technology can produce a nanofibrous structure that is capable of coating difficult wounds. The resulting mesh displays high strength and good flexibility. Experiments with sealing of defects in pig liver indicated the capacity of the NOCA mesh to withstand a 2-m hydraulic applied pressure (equivalent to 147 mmHg) with no blood or water seepage.

Lv et al. demonstrated[28] the use of electrospun NOCA fibers for dural repairs via a semiportable gas-assisted device. Their device demonstrates a technique that allows the cyanoacrylate fibers to be electrospun without using a solvent while maintaining a desirable apex-to-collector distance of 4–5 cm. The gas pump is connected to the auxiliary spinneret, which exerts a stretching force on the polymer solution during the electrospinning process. This technique was applied for dural closure on a sheep's brain, simulating open-brain surgery.

We utilize a microneedle in a near-field electrospinning environment to produce NOCA fibers for dural repairs in an endonasal endoscopic skull-based neurosurgery. These fibers are formed using an optimized apex-to-collector distance of 5 cm and do not require a solvent to electrospin. The configuration of the electrospinning equipment was selected to be later transferrable for actual endonasal dural repair during endonasal endoscopic neurosurgery.

2 | METHODS

2.1 | Tissue adhesive/polymer selection

Dermabond® is an FDA-approved cyanoacrylate adhesive for use in humans. However, the packaging renders extracting significant amounts of adhesives from the glass ampule extremely difficult. Surgilock® is a cyanoacrylate product approved for animal use and is much more manageable for extracting significant quantities for electrospinning. A significant physical difference between the two tissue adhesives is the viscosity. To facilitate ease of handling, Dermabond® contains thickeners that are not present in Surgi-Lock® and directly impacts the electrospinning parameters (voltage, flow rate, and apex-to-collector distance).

Based on sustained and burst pressure data reported by van Doormaal et al.[11] and the prevalence of implementing Adherus® in endonasal endoscopic dural repairs, Adherus® was selected as a baseline for comparison with the burst pressure of the dural repair using electrically spun NOCA. Adherus® was applied to our dural model according to the manufacturer's instructions.

2.2 | Dural model

A fixed human cadaver head is pinned using a Mayfield head clamp to provide stability. Next, a linear incision in the scalp is made. Self-retaining retractors are placed, and a cranial flap is turned in the usual standard fashion using the Medtronic Midas Rex drill (Medtronic; Dublin, Ireland). Underlying dura is then harvested using an 11 blade and Gerald pick-ups. This dura is used to fit the pressure model cup; excess dura is removed. The composition of dura is soft tissue; comprised of collagen, elastic fibers, and fibroblasts.[30] The fixation agent causes dehydration of soft tissues rendering them approximately 50% thinner than live tissue. Dura thickness varies from person to person but is approximately 0.36 ± 0.16 mm on average.[31] Harvested dura was stored in saline prior to electrospinning. To simulate the dural defect and subsequential dural closing in endonasal neurosurgery, a 1 cm linear opening was created in the dural component of the pressure cup model. This defect was, in turn, covered with a 1.5 cm^2 piece of temporal fascia.

2.3 | Electrospinning operation

The electrospinning operation utilized a NE-1000 syringe pump (New Era Pump System) to control the flow of the NOCA solution. A 34-gauge needle (0.25 mm OD, 0.06 mm ID) and an apex-to-collector

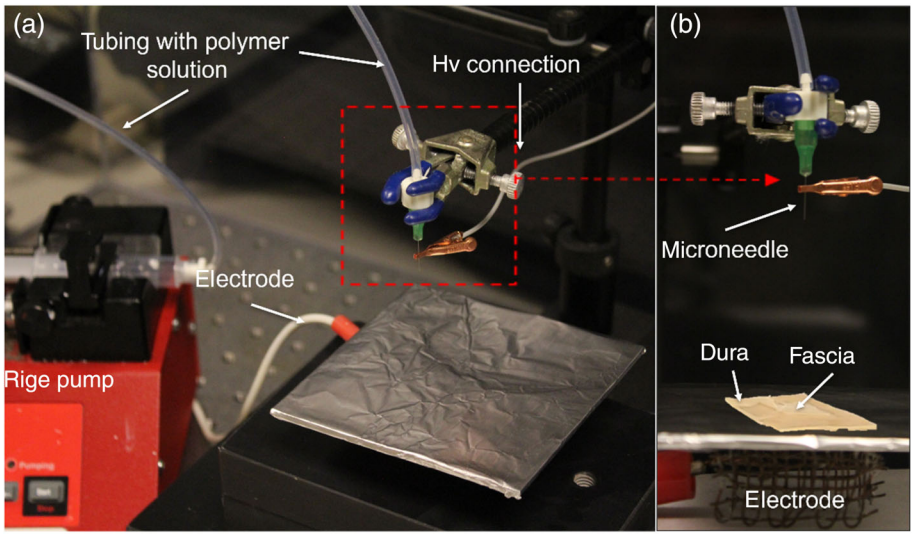

FIGURE 2 Electrospinning operation: (a) photo of instrumentation; (b) near-field electrospinning set-up with dura sample

distance of 5 cm were used in a near-field electrospinning configuration. This condition was used to accommodate eventual endonasal application where the typical distance from tool to defect is approximately 2–5 cm. Taylor cone formation and liquid jet extraction were achieved using an applied DC voltage (Glassman Series EL) of 5 kV at a solution flow rate of 0.55 ml/hr. To keep the amount of adhesive applied consistent across all samples, 300 µl of NOCA polymer was applied to the defect site over 30 min. Figure 2 illustrates the electrospinning operation, with temporal fascia covering a 1 cm linear defect in the dura mater (Figure 2b). SEM images show the presence of NOCA fibers, average fiber diameter of 436 nm, (Figure 3) among blended polymerized fibers. Bead-in-fiber morphology is formed due to the very low viscosity of NOCA solution. Uniform NOCA fiber deposition over the targeted defect area was obtained.

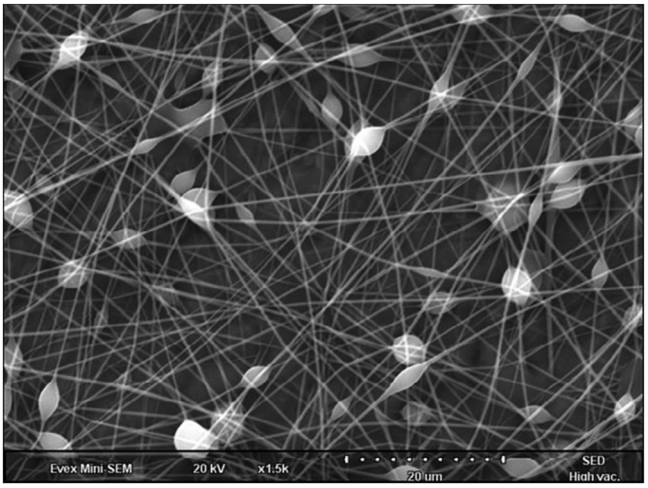

FIGURE 3 SEM image of NOCA fiber membrane at 1.5 k × magnification, average fiber diameter 436 ± 49 nm

2.4 | Pressure model

This research aimed to develop an application method for NOCA tissue adhesive for closing dural defects that is useful for endonasal endoscopic surgery. A simple pressure test model was used for testing the effectiveness of electrospun CA as a tissue adhesive. A specimen container cup (150 ml) affixed with dural tissue was used for initial testing following the model reported by van Doormaal et al.[11] The procedure for sample assembly can be found under Appendix S1.

2.5 | Burst and sustained pressure test

Pressure was applied using a 60 ml syringe filled with dyed saline and a syringe pump (Harvard Apparatus PHD Ultra). Under nominal conditions, CSF forms at a rate of 0.3–0.6 ml/min while flowing through the ventricles.[22] For this reason, we chose to apply pressure to the defect site using a flow rate of 0.5 ml/min. A transducer (Harvard Apparatus APT 300) linked the syringe to the sample via two arterial catheter tubes connected to a 3-way stop cock in the sample container (Figure 4). Pressure was measured (mmHg) using a transducer amplifier module (TAM-D, Harvard Apparatus). The pressure test comprised of two segments: (a) initially, the sample was brought to a pressure of approximately 30 mmHg slightly elevated from nominal psychological conditions and held there for 30 min; (b) then the pressure was increased, at a flow rate of 0.5 ml/min, to establish the maximum burst pressure threshold of the defect repair.

3 | RESULTS AND DISCUSSION

Ten samples of dura were each provided with a defect that was subsequently sealed with electrospun NOCA. A representative as-sealed sample is shown in Figure 5a. The samples exhibited a "sweating" effect of saline through the dura (see example in Figure 5b), as fixed

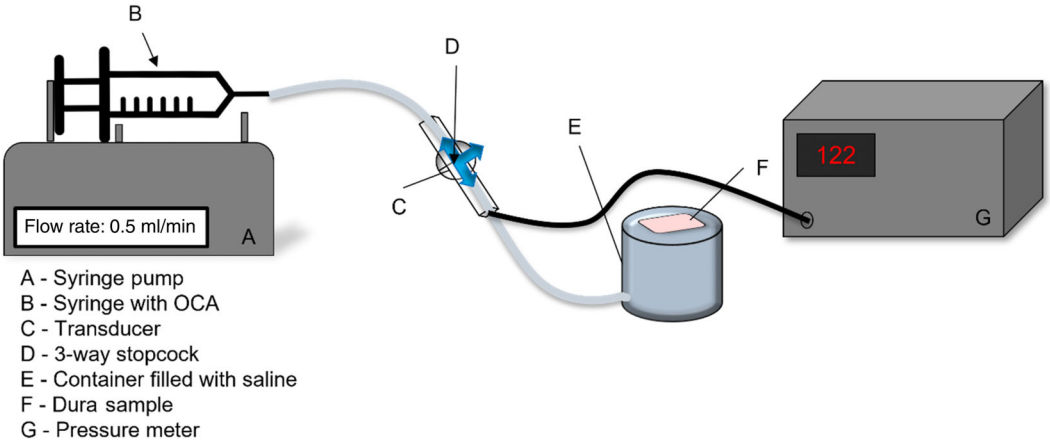

FIGURE 4 Schematic of pressure testing setup. Syringe is filled with saline to simulate CSF

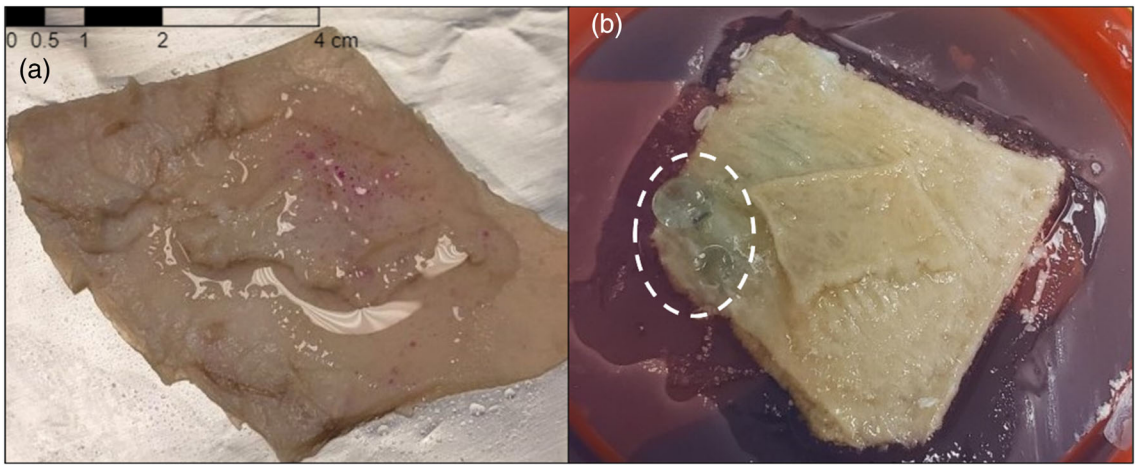

FIGURE 5 Photographs of representative samples of dura with defects covered by a piece of fascia and then sealed by an electrospun NOCA membrane (~1–1.5 mm thick): (a) immediately after NOCA application; (b) example of sweating effect (see dashed region) on the coated dura area with fascia covering

dura is approximately 50% thinner than fresh dura. This phenomenon occurred in various areas around the surface of the dura where no NOCA present and did not decrease the pressure during testing. A similar effect was reported by van Doormaal et al. in their animal dural model.[11]

Nine out of the ten samples withstood the 30-min sustained pressure test. One sample which did not survive the sustained pressure test failed just above physiological CSF pressure due to the dura separating from the specimen container while the defect closure remained intact, which was not caused by the sealing failure on the testing area between the dura and facia layers. The average burst pressure of the NOCA series was 149 ± 71 mmHg. Typical individual test results are shown in Figure 6. While the individual burst pressures varied in the series, all samples achieved a burst pressure that exceeds the nominal physiological CSF pressure range of 8–15 mmHg.

For comparison to the electrospun OCA application, nine samples of Adherus® application to dura defects were performed. A representative as-sealed sample is shown in Figure 7a. The adhesive displayed a bubbling effect directly after application (Figure 7a), and once dried, small pockets of trapped air were visible. After drying, spotty areas that lack full coverage are observed around the defect (Figure 7b).

Two out of the nine samples in the Adherus® did not survive the 30-min sustained pressure test, with leaks originating from the sealed defect itself. The average burst pressure for the Adherus® series was 38 ± 20 mmHg, which is significantly lower than the 87 ± 47 mmHg reported by van Doormaal et al.[11] Individual test results are shown in Figure 8. A Welch's *t*-test was performed to determine if there was a statistically significant difference in burst pressures between dural closures with Adherus versus dural defects closed using electrospun NOCA. The *t*-test revealed that there was a statistically significant difference in mean exam scores ($t = -4.28$, $p = .00206$) between the two groups.

One possible reason for the difference in burst pressures could be the different pressure testing setup. Van Doormaal et al.[11] used a machined metal apparatus that pressed on the dura from above to seal it to the container. This may have provided reinforcement to the

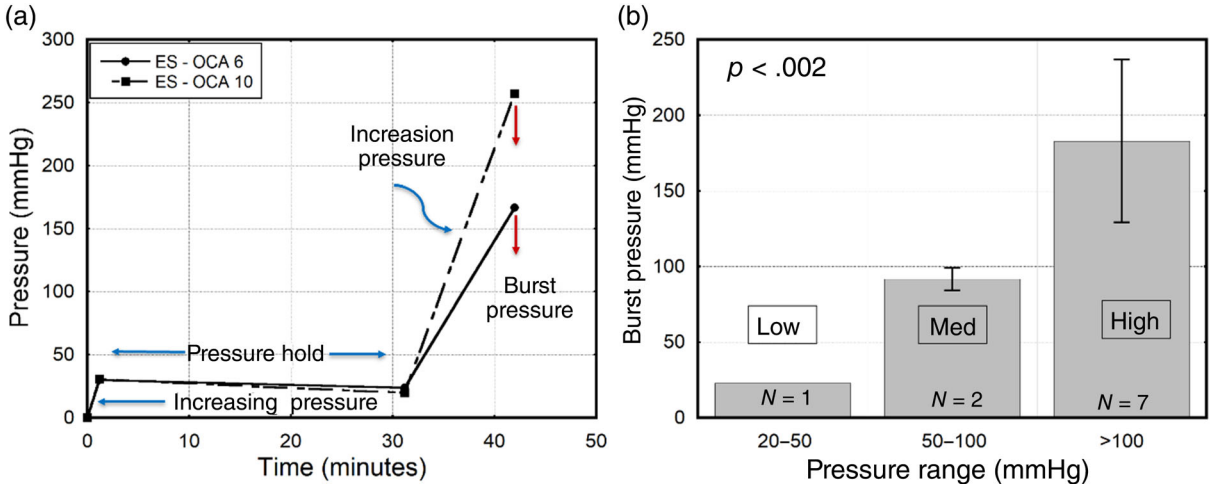

FIGURE 6 Pressure response of dura defects sealed by electrospun OCA application: (a) pressure versus time curves for two representative samples; (b) average burst pressure results of all ten samples combined into three groups—low (but sufficient), medium, and high. Error bars represent ± *SD*

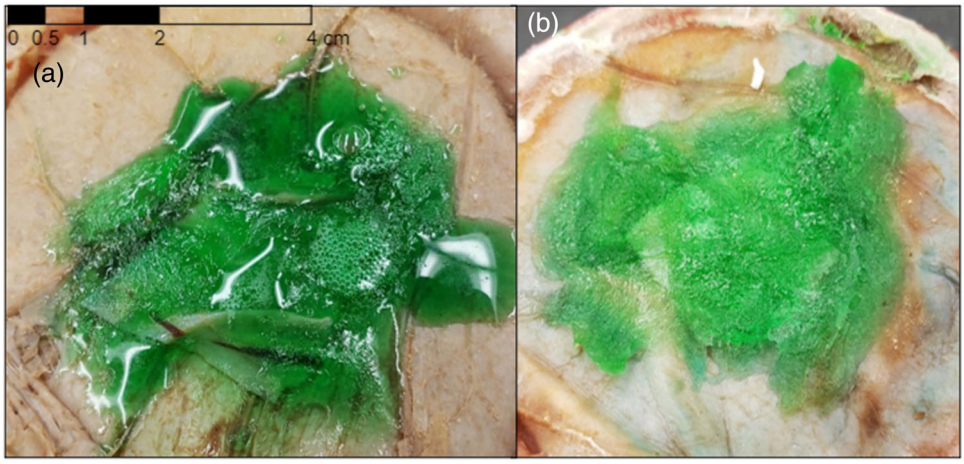

FIGURE 7 Photographs of representative samples of dura with defects covered with fascia and then sealed by Adherus® application: (a) immediately after application, bubbling from dispensation can be seen; (b) 1 hr after application, variable coverage is observed

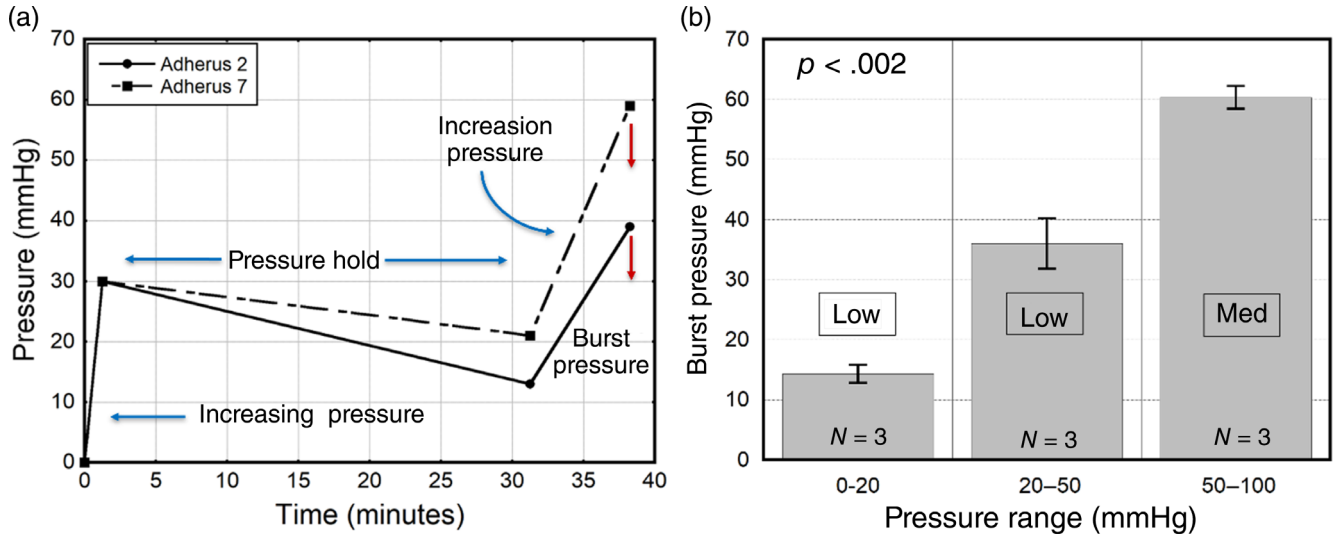

FIGURE 8 Pressure response of dura defects sealed by Adherus®: (a) pressure versus time curves for two representative samples; (b) average burst pressure results of all nine samples combined into three groups—very low (not sufficient), low, and medium. Error bars represent ±1 *SD*

adhesive covering the defect. Another possible reason could relate to the use of a stencil with a 15 mm circular opening to apply a very uniform 1 mm thick layer of Adherus® to seal the defect, which is appropriate for the side-by-side tissue adhesive comparison but not realistic for endonasal surgeries. These methods represent a slight variation from the technique used in our experimentation. As per the manufacturer, the sealant should be applied until a thin coating (~1–2 mm) is formed. We observed a thin (1–2 mm) covering after applying approximately half the syringe of Adherus®. Additionally, the dura with adhesive dynamically expanded and contracted with increasing pressure during pressure testing, which could have contributed to the lower burst pressures.

4 | CONCLUSIONS

We have demonstrated the use of electrospun NOCA for dural defect repairs that can withstand pressures significantly and consistently beyond the nominal physiological CSF range. Focused nanofibers have been created via electrospinning of octyl-2-cyanoacrylate in a near-field environment (< 5 cm) using a microneedle and an applied voltage of 5 kV. Upon contacting the dura, the NOCA fibers polymerize, creating an approximately 1–1.5 mm thick polymer layer uniformly covering the targeted defect area of approximately 2 × 2 cm^2. Our approach with optimized conditions, with some equipment modifications, could be translated into an endonasal endoscopic approach in neurosurgery. For these types of surgeries, a device should be created to mimic the thin, long-shaft design of existing instruments used in endonasal operations. Current endonasal tools could be retrofitted with tubing and wiring connected to a syringe pump and voltage source to enable electrospinning fiber extraction.

A major concern of utilizing a device requiring high voltage is safety as the nose is a moisture-rich environment, and during endonasal surgery, there is the presence of blood and CSF at the defect site. It is important to note that using high voltage within a living patient poses risks. Although low, a current is produced during the electrospinning process. One possibility to lower the risk of electrical shock would be to reduce the current (1.8–0.04 μA) using a Teflon needle coupled with a penetrating electrode.[32]

4.1 | Considerations for future work

As the NOCA membrane will be a foreign object to the human body, assessing the long-term effects on the surrounding tissues is critical. Histopathological assessment of the interface between cyanoacrylate glue and dural tissue would provide additional, useful information regarding this deposition technique. Animal studies would provide a more optimal platform for this assessment. Dural sealants currently on the market have their limitations, and further research into the development of a more efficacious and biocompatible dural sealant that could be electrospun to produce a sealing mesh fabric would be worthwhile. Any new dural sealants must be thoroughly assessed for toxicity on dura and neurological tissue before clinical application.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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