Enhanced Dural Sealing using a Mechanically Tough Bioadhesive

Benjamin R. Freedman[1,2,3], Siyoon Kwon[2], Daniel Kent[2,4], Matthew Torre[5], Wenya Linda Bi[6], Kyle C. Wu[6,7], David J. Mooney[1,2]
[1]John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA; [2]Wyss Institute for Biologically Inspired Engineering, Cambridge, MA; [3]Department of Orthopaedic Surgery, BIDMC, Boston, MA. [4]Department of General Surgery, BIDMC, Boston, MA. [5]Department of Neuropathology, BWH, Boston, MA. [6]Department of Neurosurgery, BWH, Boston, MA.[7]Department of Neurosurgery, Wexner Medical Center and James Cancer Hospital; OSU, Columbus, OH.

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INTRODUCTION: Cerebrospinal fluid (CSF) leakage is a common postoperative complication affecting up to one-third of patients undergoing spinal surgery and may threaten a patient's life, neurological function, and recovery. Current methods of dural reconstruction include primary closure, liquid sealants, collagen matrices, dural substitutes, and native tissue grafting. Each of these approaches faces unique challenges, which has prevented the emergence of a single definitive method of repair. For example, primary closure, dural substitutes, and tissue grafts all require the presence of viable dural tissue, which may be damaged or absent in older patients, smokers, or patients that have undergone prior surgery or radiation. Commercial sealants and tissue adhesives are limited by: (i) poor tissue adherence in aqueous environments, (ii) lack of toughness and pliability in a mobile environment (i.e. highly fracturable with manipulation), (iii) inability to reconstitute large defects (i.e. sealants may be used to augment primary closure, but not as a stand-alone closure device), and (iv) challenges with handling and deployment that limit practical use [1, 2]. Therefore, the objective of this study was to investigate a possible candidate for dural repair. Dural Tough Adhesive (DTA) is a single-step, biocompatible, hydrogel-adhesive device exhibiting the properties required for effective dural repair in this challenging environment. We hypothesized that the Dural Tough Adhesive provides unprecedented flexibility, toughness, and adhesion to definitively seal fluid leakage in this demanding environment.

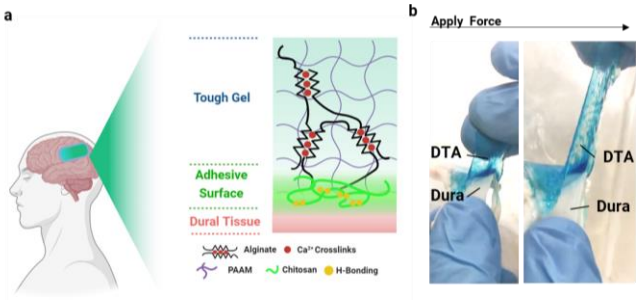

Figure 1 | Basis of the Dural Tough Adhesive (DTA). (**a**) The DTA was comprised of an alginate-polyacrylamide tough hydrogel and a chitosan-based adhesive surface. (**b**) When applied as a patch (blue), the DTA adhered rapidly to dural tissue forming a tight seal that was stretchable, yet tough, under loading.

METHODS: *DTA Synthesis*: The DTA combines a tough gel and bridging polymer (**Fig.1**). Tough gels were synthesized by combining 2.25% sodium alginate and 13.5% acrylamide in HBSS with N,N'-methylenebis (acrylamide), TEMED, ammonium persulfate, and calcium sulfate dihydrate [2]. Chitosan (2%) and coupling reagents (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and sulfated N-hydroxy-succinimide) (12 mg/ml) were used. *Adhesion Testing:* Dural tissue (D=15mm) was harvested and prepared from fresh porcine dura and placed in a burst pressure chamber. DTA's was then synthesized and applied to the dura and adhesion energy was measured through burst testing. *Porcine Efficacy Study:* A large animal trial was completed to evaluate in vivo performance of the DTA versus Duraseal®. *Analysis*: One-way (time) or two-way (time and treatment) ANOVAs were used with post hoc T-tests with Bonferroni corrections.

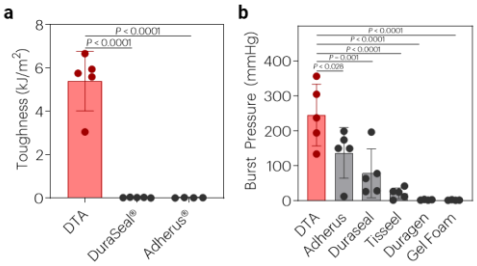

Figure 2 | The DTA exhibits superior adhesive and mechanical strength to existing closure devices. (**a**) The fracture toughness of the DTA compared to commercial dural sealants. (**b**) Burst pressure testing with the DTA compared to commercial products. Data shown as mean +/- sd (n=4-5 samples/group), as evaluated by a one-way ANOVA with post hoc T-tests with Bonferroni corrections.

RESULTS: Dural Tough Adhesives possess a remarkable blend of toughness and stretchability (**Fig.2**). These properties are readily demonstrated by their resilience to manual compression, in contrast to commercial sealants which fracture under identical forces and conditions. Peak pressures achieved by DTAs were an order of magnitude greater than that withstood by existing commercial agents. Semiquantitative blinded histochemical analysis by a board-certified neuropathologist revealed minimal irritation caused by the TAs, consistent with commercially available sealants (not shown). During Valsalva stress testing, no leakage occurred from the DTA group. The DuraSeal® group experienced leakage in 45% of cases, leading to their exclusion from peak pressure testing (**Fig.3**). Subjects who went on to peak pressure testing were subject to a steady injection of 0.9% normal saline through the infusion catheter, until leakage was observed due to adhesive or gel failure. Closure with DTAs held peak pressures approximately 3x greater than those with DuraSeal® closure.

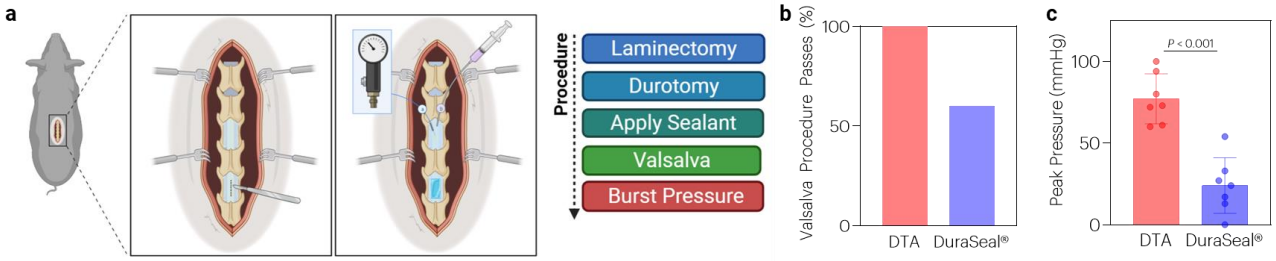

Figure 3 | Efficacy of the DTA in a large animal model. (**a**) A laminectomy and durotomy were performed prior to application of sealants and evaluation of their performance. (**b**) Valsalva procedure passes comparing the DTA and DuraSeal® (N= 7 gels/group, DuraSeal® Pass Rate 60%). (**c**) Evaluation of peak burst pressures for the DTA versus DuraSeal® in the sutureless incisional injury model. N=7 samples/group, as evaluated with a Student's T-test. Data shown as mean +/- s.d.

DISCUSSION: Iatrogenic cerebrospinal fluid leakage contributes to healthcare costs, morbidity, and mortality of patients undergoing spine surgery, with significant opportunity for improvement. In contrast to commercial technologies, the pliability, coupled with progressive time-based adhesion, enables seamless manipulation of DTAs, while permitting precise adjustments during placement. Such properties make it ideal for un-suturable regions including: deep targets, minimally invasive approaches, and endoscopic surgeries.

SIGNIFICANCE: The performance properties and ease-of-use of Dural Tough Adhesives make them an exciting tool to add to the surgeon's armamentarium to augment or even supplant sutured dural repair.

REFERENCES: [1] Li+ 2017 *Science* 357(6349):378-381. [2] Sun+2012 *Nature* 489(7414):133-6.

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