WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Hydrogel-Based Neurosurgical Sealants: Narrative Review of Chemistry, Performance, Degradation, and Safety

Muhammad Kamil[1], Maryam Nadeem[1], Muhammad Haider[2]

[1]University of Agriculture Faisalabad, Faisalabad, Pakistan
[2]University of Lahore, Lahore, Pakistan
Corresponding author: Maryam Nadeem - maryamnadeem345@gmail.com

ABSTRACT :

Hydrogel sealants are widely used to prevent cerebrospinal fluid leakage after cranial and spinal surgery, but case reports describe neural compression and gel migration. This narrative review asks how hydrogel chemistry influences swelling, sealing strength and degradation, and how convincingly laboratory results establish safety for neurosurgical use. PubMed and Scopus were searched on 30 September 2026 for English language articles and supplemented with standards and regulatory documents, and two reviewers selected the studies. Chemistry sets all three properties together, because crosslink density, linker chemistry and hydrophilicity determine water uptake, strength and breakdown. Reported burst pressures for sealants range from about 21 to 325 mmHg and burst testing measures failure of the whole repair system and does not isolate interfacial adhesion. Swelling is labelled and measured freely in buffer, but no standard test for confined swelling force was identified. The main degradation standard excludes resorbable polymers, and routine cytotoxicity tests do not address neural cells. A multidomain research framework is proposed for discussion.

Keywords: hydrogel; dural sealant; cerebrospinal fluid leak; swelling; degradation; biocompatibility; neurosurgery

Introduction

Cerebrospinal fluid (CSF) leakage after cranial or spinal surgery is common, costly and sometimes dangerous. In a systematic review of 20 reports, leakage occurred in 8.2% of procedures with a sealant and 8.4% without one [1]; rates were 13.5% after elective craniotomy in one randomized trial, mostly self-limiting subgalea collections [2], and 4.4% in children [3]. In the spine, incidental durotomy occurred in 3.8% of 1326 consecutive patients [4] and up to 17% of lumbar operations in one bench study [5]. Leaks delay wound healing and are linked to infection, meningitis and pseudo meningocele [6].

Surgeons may add a sealant to sutures, grafts, sponges and glues [6]. Polyethylene glycol (PEG) hydrogels are the best-known synthetic sealants, and they differ by product. The original Dura Seal system is approved by the United States Food and Drug Administration (FDA) as an adjunct to sutured cranial dural closure [6,7]; related formulations include Dura Seal Spine and the low swell Dura Seal Exact [8,9], and Adheres combines PEG with polyethyleneimine [10]. The original formulation stopped intraoperative leaks in all 111 patients of a prospective multicenter study [11], and a randomized trial of 237 patients found complication, infection and leak rates like standard techniques [6].

The pooled evidence is mixed: one review found no fall in the leak rate with sealants but fewer surgical site infections [1], two newer meta-analyses reported fewer leaks [12,13], and 27 nonrandomized endoscopic skull base studies showed no reduction [14].

Alongside these efficacy signals sits a safety problem that early series did not show. After approval, a 13-year-old girl deteriorated after Chiari decompression because a hydrogel sealant had expanded and compressed the corticomedullary junction [15]. Reports naming Dura Seal describe cauda equina compression after laminotomy and discectomy, with swelling and migration into the canal [16], and after a transforaminal lumbar interbody fusion [17]. After lumbar laminectomy with Adheres, MRI showed an intradural collection remote from the operated level, attributed by the authors to migration of the sealant [18]. These reports involve different products and are not polluted here. A focused review also noted two instances of paralysis associated with Dura Seal, and that Bio Glue, an albumin glutaraldehyde adhesive, is classed as neurotoxic by its manufacturer [19]; as a different chemistry it is treated as indirect evidence.

These events are rare, but they expose a gap. A hydrogel works as a sealant through how it takes up water, grips wet dura and breaks down, and the same three properties decide whether it is safe beside brain and spinal cord. This review asks how hydrogel chemistry controls swelling, sealing strength and degradation, and how convincingly laboratory results establish safety for neurosurgical use.

Review approach

This is a narrative review of hydrogel sealants and adhesives used or tested for dural repair, developed with reference to the six SANRA domains [20].

Sources. PubMed and Scopus were searched on 30 September 2026, and semantic searching with Scholar Gateway was used to find related work.

Standards and regulatory documents were taken from the websites of ASTM International, the International Organization for Standardization (ISO) and the FDA. Only English language articles were included. Any study design was considered, with priority to systematic reviews, trials, quantitative laboratory studies and reports of harm. Two reviewers selected the studies, and the full text of each article was read.

Evidence labels and appraisal. Each safety concern is tagged as direct neurosurgical hydrogel evidence, indirect biomaterials evidence (other tissues or materials), clinical safety signal (harm reported in patients) or theoretical chemistry-based concern. Quality was not appraised formally; evidence was judged by how directly and consistently it answers each safety question.

Chemistry of hydrogel sealants

A hydrogel sealant is a crosslinked network of hydrophilic polymer that holds a large share of water [21]. It has to adhere to tissue, stay intact and occlude the wound [22], and in surgery it must form in place, within seconds to minutes, on a wet and moving surface. Three chemical choices decide how it behaves: the polymer backbone, the reaction that joins the chains, and the way the gel binds to tissue (reviewed in [22,23]).

Sealants and adhesives approved by the FDA and sold in the United States in 2008 fell into four chemical families: fibrin, PEG hydrogels, cyanoacrylates and albumin crosslinked with glutaraldehyde [24]. Only the first two are hydrogels in the strict sense, but all four have been used or tested for dural repair [5,19]. Table 1 sets out the main classes.

PEG ester gels. The best-known neurosurgical hydrogels are built from multi armed PEG with reactive ester end groups. The Dura Seal family (Dura Seal, Dura Seal Spine, Dura Seal Exact, CraniSeal and Spine Seal) combines the PEG ester with a Tri lysine amine solution, whereas Adheres uses polyethyleneimine as the amine component [7,25,26]. The esters react with amines to form amide bonds, which tie the PEG arms into a network [23]. An earlier vascular sealant of this reactive type sustained 125 ± 36 mmHg on collagen, and its performance depended on the activity of the reactive groups [27]. Table 2 separates the marketed products, because evidence on one formulation should not be carried over to another.

Fibrin. Thrombin converts fibrinogen to fibrin, which polymerases into a soft network [28]. Commercial forms come from human or bovine plasma [29]. Chemistry is gentle, but it depends on biological source material and sealed less well in a bench model [5].

Harsher crosslinkers. Albumin glutaraldehyde adheres strongly, but glutaraldehyde leaches out: saline over polymerized Bio Glue contained 100 to 200 µg/mL glute gene and was cytotoxic to two cell lines, and the glue caused inflammation and necrosis in rabbit lung and liver [30]. Extracts of two cyanoacrylate glues were toxic to L929 cells unless diluted tenfold [31]. Both argue for caution near neural tissue.

Light activated gels. Gelatin meth acryloyl (Gelman) and meth acryloyl trophoblastic (Metro) are crosslinked by radicals formed when light strikes a photo initiator [32,33]; a hydrophobic light activated adhesive sealed pig vessel and cardiac defects despite blood [34]. Initiator toxicity differs between cell types [35], and a newer water-soluble initiator gave fibroblast survival above 95% [36].

How gels bind tissue. Binding wet tissue is the hardest chemical problem, because water separates the two surfaces. Strategies include chain interpenetration [37], covalent bonds to tissue amines after removal of interfacial water [38], mussel inspired catechol chemistry [39] and topological entanglement with the tissue network [40].

Table 1. Chemical classes of sealants and adhesives are relevant to dural repair.

Class (example)	Main concern near neural tissue	Evidence label
PEG ester with amine (Dura Seal family, Adheres) [26]	Water uptake, mass effect and migration [15,16,17,18]	Clinical safety signal
Fibrin (Tassel, Evince) [19,28,29]	Plasma derived source; weaker sealing in a bench model [5]	Direct neurosurgical hydrogel evidence
Albumin glutaraldehyde (Bio Glue) [30]	Leached glutaraldehyde is cytotoxic; classed as neurotoxic by the manufacturer [19,30]	Indirect biomaterials evidence
Cyanoacrylate (Glub ran) [23,31]	Cytotoxic extracts unless diluted [31]	Indirect biomaterials evidence
Photo crosslinked protein gel (Gelman, Metro) [32,33]	Initiator toxicity and light delivery [35,36]	Indirect biomaterials evidence

Abbreviations: Gelman, gelatin meth acryloyl; Metro, meth acryloyl trophoblastic; PEG, polyethylene glycol.

Table 2. Marketed PEG sealants and a patch, by chemistry, regulatory indication, swelling and clinical evidence. Regulatory indications are from FDA documents unless stated.

Product	Chemistry and form	Regulatory indication	Swelling (label unless stated)	Key clinical evidence
Dura Seal	PEG ester, triglycine amine; cranial	Adjunct to sutured cranial repair [7]	Up to 50% in any dimension; not for confined bony structures with nerves [7]	Prospective, 111 patients [11]; randomized, 237 [6]
Dura Seal Spine	Same; spinal, 2009	Adjunct to sutured spinal repair [8]	Volume up to 200% (24 h, PBS, 37 °C); up to 50% in any dimension [8]	Randomized, 158 patients [8]
Dura Seal Exact	Same; low swell, spinal	FDA approved for spinal dural closure [9]	"Expansion rate of 19%", metric undefined (publication) [9]	Randomized, 98 [41]; post approval, 835 [9]
Adheres Auto Spray	PEG ester, polyethylene	Age 13 and over; adjunct	Up to 13% in any	Randomized against

Product	Chemistry and form	Regulatory indication	Swelling (label unless stated)	Key clinical evidence
	mine; cranial spray	to cranial closure [25]	dimension or 46% by volume (bench, 24 h, PBS, 37 °C); not for confined spaces with nerve compression risk [25]	DuraSeal, 250; success 91.2% against 90.6% [25]
Crani Seal	As Dura Seal; cranial, 2023	Adults; supplemental closure [42]	Up to 50% above original size in any direction [42]	No original trial; nonclinical comparison [42]
Spine Seal	As Dura Seal; spinal, 2025	Adjunct to sutured spinal repair [43]	No more than 12% in any direction; not for confined bony structures with nerves [43]	No trial; relies on Dura Seal Exact data [43]
Liqoseal	PEG ester layer on polyurethane; cranial patch	CE approved adjunct to cranial closure [44]	Dura plus patch on MRI: 2.14 ± 0.37 mm at 1 month from 2 mm in pigs [45]; 2.1 ± 1.2 mm at day 90 in patients [46]	First in human, 40 patients: no postoperative leak, intraoperative leak at 20 cm H_2O or wound infection [46]

Abbreviations: MRI, magnetic resonance imaging; PBS, phosphate buffered saline; PEG, polyethylene glycol.

Swelling

Swelling is set by chemistry, and it is the property most closely linked to reported neurological harm. A hydrogel takes up water until the pull of water into the network is balanced by the elastic force of the stretched chains. The main chemical lever is crosslink density: a tighter network has a smaller mesh and takes up less water, a link described quantitatively [47]. Hydrophilic and charged groups draw in more water, and swelling also responds to pH, ionic strength and temperature [48].

Newer dural sealants are designed around this problem, but each reports swelling differently. A bilayer patch with hydrophobic methyl acrylate groups and tannic acid had a mass swelling ratio of 24.2 ± 4.6% in buffer within 6 days [49], and a gelatin and four-armed PEG gel swelled by about 30% after 150 days under rat skin, whereas a comparator hydrogel compressed the rat cord [50]. A tetra PEG gel gained 200% to 540% wet weight over 7 days, yet its longest diameter on rabbit MRI rose by under 60%, peaking on day 1 and returning to baseline by day 9 [51]. A PEG ester patch with a polyurethane backing thickened from 2 mm to 2.14 ± 0.37 mm on pig MRI at one month [45].

In the spine, a low swell PEG formulation achieved watertight closure in 98.6% of 74 patients against 79.2% of 24 controls with standard methods, with no neurological deficit attributed to the sealant [41]. In a nonrandomized post approval study of Dura Seal Exact in 835 patients, neurological serious adverse events were 2.9% against 1.6% with other methods (P = 0.516), and a "very low expansion rate of 19%" was reported without a defined metric [9]. Few events occurred in each arm, so these studies are reassuring but limited.

The clinical signal has not gone away, but it is product specific. Case reports, most naming Dura Seal, place the harm within about two weeks of surgery: cauda equina syndrome on day 3 after a fusion operation [17], early cauda equina syndrome on day 6 with exploration on day 10 showing swelling and migration into the canal [16], and exploration on day 15 for the child with Chiari malformation [15]. In an analysis of the FDA Manufacturer and User Facility Device Experience (MAUDE) database, narrative review of 279 reports for Dura Seal and Adheres identified swelling or mass effect in 9.4% of the Dura Seal reports and neurological deficit in 4.3% [52]. Spontaneous reports cannot give rates, but they show that events go beyond the early case reports.

Swelling was not a surprise, because the labels in Table 2 already state expected expansion of up to 50% in any dimension (13% for Adheres) and warn against use in confined spaces with nerves [7,8,25,43]. What the bench numbers cannot show is the force the gel exerts against bone and nerve, or how it behaves as it degrades. Indirect evidence from hydrogel coated aneurysm coils shows that hydrogel effects in neural compartments can be late and of uncertain cause: unexplained hydrocephalus was commoner with hydrogel coils in a randomized trial [53], and a cohort study found it only after Hydro Coil treatment, presenting 8 to 31 months later [54].

The testing gap. Swelling is usually reported as a free swelling ratio in buffer. At the implant site the gel swells against bone, dura and neural tissue, so the force it exerts, and its time course matters as much as the ratio. Intracranially, the Monro Kellie doctrine holds that added volume must displace brain, CSF or blood [55], and in the spinal canal a swollen or migrated gel is held by rigid bone and can press directly on cord or cauda equina. Late swelling is a further concern: in model PEG hydrogels, mesh size and swelling ratio rose as ester crosslinks were cleaved [56,57], which a 24-hour test in buffer would miss. No standard test for confined swelling force or swelling pressure of a sealant was identified, and the scope statements of ASTM F2392 and the ASTM tissue adhesive test methods do not mention swelling [58,59].

Sealing strength

A sealant must stick to wet dura and hold together under pressure, and most laboratory tests measure only the second. Burst testing measures the pressure at which the sealed repair system fails and does not isolate interfacial adhesive strength, so failure mode, substrate and test configuration

need separate reporting. ASTM F2392 states that it measures burst strength of the adhesive and adherend system and not adhesive strength, that the substrate is critical, and that in vitro results should not be extrapolated uncritically to the body [58].

What the repair must withstand. Lumbar CSF opening pressure in 242 adults had a 95% reference interval of 10 to 25 cm CSF [60], and coughing adds pressure waves along the craniospinal axis [61]. Trials identify intraoperative leaks with a Valsalva man oeuvre [6,11], and in dogs hydrogel treated repairs withstood Valsalva pressures up to 20 cm H_2O [62]. A sealant must therefore hold repeated pressure peaks above the resting range, on a wet surface, while the dura heals.

Burst numbers vary widely. Reported pressures for sealants range from about 21 to 325 mmHg (Table 3), and the spread reflects substrate, set up, defect size and endpoint as much as chemistry. The rank of Dura Seal and Adheres changes between and within studies: Adheres exceeded Dura Seal in one study's cranial model (87 ± 47 against 51 ± 42 mmHg) but not in its spinal model (179 ± 71 against 216 ± 95 mmHg), and Dura Seal exceeded Adheres in a second study [26,63]. The large standard deviations in the first study make its ranking uncertain. Fibrin sits at the low end [5]: Tassel held 23 ± 16 mmHg in a spinal model [63].

The dura is not a uniform test surface. Porcine dura varies by region in stiffness and composition [64], rat cranial and spinal dura differ in fiber alignment and elastin [65], and in three human cadavers the force to rupture lumbar dura longitudinally was 3.5 to 6.7 times that needed transversely [66].

Time is the next gap. Most burst tests record failure under rising pressure within minutes. In the one ex vivo study that held sealants under physiological conditions for 72 hours, Tehsil (cranial model) and Dura Seal and TachoSil (spinal model) lost attachment in all three samples, and Liqoseal, the authors' own patch, in one of three per model [63]. The other ASTM methods (lap shear, peel, tension and wound closure strength) are general soft tissue tests [59], and none is written for dura or for pulsatile CSF loading.

How chemistry raises strength. Hydrogels combining ionically and covalently crosslinked networks reached fracture energies of about 9000 J/m², against about 10 for most hydrogels, because the covalent network bridges cracks while the ionic network dissipates energy [67]. A dural tough adhesive built on a dissipative matrix exceeded five commercial agents in ex vivo porcine burst testing after 5 days in artificial CSF ($P = 0.02$), and in two pigs held a 40-mmHg Valsalva challenge while Dura Seal leaked in 40%, failing by rupture of the hydrogel and not at the interface [68].

Does strength translate into fewer leaks? Acute sealing is good: the gel stopped intraoperative leaks in 111 of 111 patients [11], yet postoperative leak rates did not differ significantly from standard closure in the cranial randomized trial (0.8% against 1.7%) [6] or the spinal post approval study (6.6% against 6.5%) [9], and pooled analyses disagree [1,12,13]. Holding at time zero is not the same as fewer leaks.

Table 3. Burst or leak pressures reported for dural sealants, with test conditions as reported.

Study and substrate	Method, endpoint and n	Result (mmHg unless stated)
Kinaci 2021 [63]: porcine dura, 3 mm gap or durotomy	2.0 mL/min artificial CSF; peak pressure before loss, mean ± SD; n = 14 to 20 per group (Liqoseal 59)	Cranial: Liqoseal 145 ± 39, Adheres 87 ± 47, TachoSil 71 ± 16, Dura Seal 51 ± 42. Spinal: Liqoseal 233 ± 81, DuraSeal 216 ± 95, Adheres 179 ± 71, TachoSil 123 ± 63, Tassel 23 ± 16
Argiti 2025 [26]: bovine dura, 20 mm incision, suture	Saline column rose slowly; first visible leak, median with 95% CI; n = 20	Suture alone 8 (11 cm H_2O); Dura Seal 33 (45.5); TachoSil 30 (41); Adheres 23 (31); Dura Gen 23 (31); Hemopathy 21 (28)
Wu 2024 [68]: porcine dura, 3 mm punch	PBS 2 mL/min, ASTM F2392; peak pressure at leak	Above five commercial agents ($P = 0.02$); pig in vivo up to 100; cadaver 80 ± 17.7
Cheng 2024 [50]: porcine casing, not dura	Pressure at 5 and 30 min, mean ± SD; n = 6	5 min: 44.3 ± 10.5 cm H_2O (fibrin 27.6 ± 7.3); 30 min: 208.0 ± 38.0 cm H_2O (153)
Zhou 2025 [49]: bovine dura	Homemade device, adhesion time 3 min, applied pressure 18 kPa; maximum tolerated pressure, mean ± SD; n = 3	Patch 325 ± 40; commercial hydrogel 76 ± 13
Preul 2007 [62]: canine dura, 8 weeks in vivo	Pressure testing at reopening, mean ± SD; n = 6 per group	Hydrogel 56.8 ± 2.5 cm H_2O (42); duality alone 9.8 ± 3.8 cm H_2O (7)

Values in cm H_2O were converted at 1 cm H_2O = 0.736 mmHg (original in parentheses). Substrate, defect and method differ, so values are not directly comparable. Electro spun cyanoacrylate fibers reached 149 mmHg against 37 for an FDA approved sealant on human dura (indirect evidence) [69]. Abbreviations: ASTM, ASTM International; CI, confidence interval; CSF, cerebrospinal fluid; PBS, phosphate buffered saline.

Degradation

Degradation is where chemistry, time and biology meet, and it is the least well tested of the three properties. A sealant must last long enough for the dura to heal and then clear without leaving harmful products, and the bonds that hold the network together decide both the speed and the products.

Chemistry sets the clock. In PEG gels the ester linkages are the weak points: PEG diacrylate gels lost properties over 12 weeks under rat skin, with a rising swelling ratio and a falling modulus, whereas a matched gel with amide links stayed stable, showing that ester hydrolysis was the main route in vivo [57]. In a degradable PEG gel, degradation time tracked crosslinker molecular weight, functionality and polymer density [56]. Protein gels add enzymatic routes: Gelman carries matrix metalloproteinase responsive motifs [32], and a trophoblastic sealant degraded in a controlled way in rodents [33].

Real clocks are slow and poorly predicted. FDA documents give absorption times of about 4 to 8 weeks for Dura Seal, Dura Seal Spine and CraniSeal, about 90 days for Adheres and 9 to 12 weeks for Spine Seal [7,8,25,42,43]. In pigs, a PEG ester sealant patch was estimated histologically to

be 90% resorbed at 6 months and fully resorbed at 12 months [45], yet several recent academic dural sealant studies report follow up of only 3 to 4 weeks [49,68,70]. The only late human imaging data found are case reports: in one, an intradural collection seen on day 4 after Adheres use had resolved by 5 months, leaving intradural inflammatory change and arachnoiditis, though the abscess that prompted surgery makes the contribution of the sealant uncertain [18]. The FDA notes that clinical studies of some absorbable devices showed absorption kinetics that bench and animal studies had not predicted accurately and asks for in vivo follow up until the material and its products are gone [71].

Standard methods help less than expected. ISO 10993 part 13 (2010), the standard for degradation of polymeric devices, considers only nonrecordable polymers, although modified procedures may be applicable to resorbable ones, and for gels that set-in situ it tests the set polymer [72]. Other frameworks cover parts of the problem: ISO 10993 part 9 applies to materials designed to degrade and to those that are not [73], part 18 can be used for chemical characterization of degradation products [74], ASTM F1635 covers in vitro degradation of hydrolytically degradable polymers but not those degrading mainly by enzymatic or oxidative routes [75], and ASTM F2900 describes methods to assess formation, degradation and agent release of hydrogels used in regenerative medicine [76]. No scope statement addresses resorbable in situ forming sealants specifically, so no standard written for their degradation was identified. Tissue also matters in rats the inflammatory response to PEG hydrogels varied with implant site, suggesting that tissue may alter degradation [77].

Products matter as much as speed. The PEG backbone is not biodegradable, and hazards reviewed for PEG in drug delivery include hypersensitivity, altered pharmacokinetics, toxic side products and possible accumulation [78]; these have not been shown for dural sealants. Polyester links release acids, and the inside of degrading particles of a lactic and glycolic acid polyester (PLGA) reached a pH as low as 1.5 in a laboratory study [79]. Cationic polymers such as polyethyleneimine can induce apoptosis in many human cell lines [80], a laboratory hazard of the polymer and not a finding about any sealant. Adheres contain polyethylene mine [10], so whether any is released as the gel breaks down is, for now, a theoretical chemistry based concern.

How swelling, strength and degradation trade off

The three properties cannot be tuned one at a time, because the same chemical choices move all three. First, degradation raises swelling: in model PEG gels, mesh size and swelling ratio rose and modulus fell as ester links broke [56,57], so a gel that looks safe at 24 hours may be at its most swollen and weakest later, while the dura is still healing. Second, swelling weakens strength: conventional hydrogels all swell under physiological conditions, which drastically degrades their mechanical properties [81], and designs that suppress swelling report keeping wet adhesion [49]. Third, strong crosslinkers buy strength with toxicity: glutaraldehyde gives strong adherence [30], but its leachates and cyanoacrylate extracts were cytotoxic [30,31], while fibrin avoids those problems but sealed less well in bench models [5,63]. Fourth, the fix is often architecture and not a single bond: dissipative double networks reach high fracture energy [67], opposing swelling and shrinking components suppress swelling [81], and a backed PEG ester patch did not swell significantly in pigs [45].

Laboratory safety testing

The standard biocompatibility battery shows whether a gel is toxic to common cells and tissues. It does not show whether the gel is safe beside neural tissue. Part 1 of ISO 10993, the risk management process, was revised in 2025 as a sixth edition and partly recognized by the FDA in May 2026 [82]. The FDA's 2023 guidance on its use lists endpoints from in vitro cytotoxicity and sensitization through implantation and genotoxicity to carcinogenicity and reproductive effects and says that neurotoxicity and immunotoxicity should be considered [71]. Table 4 sets out what the routine tests can and cannot show.

Cytotoxicity is the workhorse, and its result depends on how the test is set up. ISO 10993 part 5 describes extract, direct contact and indirect contact formats, and the test is simple, fast and sensitive [83]. Glub ran extracts were toxic when undiluted and acceptable at a tenfold dilution [31], and the FDA describes dilution series for inherently cytotoxic materials, read against the clinical dose [71]. A pass on a fibroblast or myoblast line (L929, MRC5 and C2C12 in these studies [30,31]) says little about neurons, astrocytes, microglia or oligodendrocytes.

Implantation site matters. The FDA says animal implant studies should use a clinically relevant site [71]. Brain tissue has its own reaction with a defined acute and chronic time course [84], and the foreign body reaction is shaped by surface properties in the first two to four weeks yet persists for the life of the implant [85], so a four-week study captures the early phase only.

Neurotoxicity is recognized but not standardized. The FDA guidance says neurotoxicity should be considered where a traditional study would not assess end organ toxicity. Its example is a neurological device in contact with brain tissue and CSF, which may need an animal implant test of pathology, neurobehavioral effects, neurological deficits, and choroid plexus and arachnoid villi function, but this is a case-by-case judgement and not a fixed test [71].

Immunity responses to PEG are an open question. PEG is often described as inert, yet a review described 37 reported cases of immediate type hypersensitivity since 1977 and concluded that its allergenic potential is probably underestimated [86], and antibodies against PEG have been found even in healthy people not treated with PEGylated drugs [87]. Neither source addresses neurosurgical sealants, nor data on PEG sensitization after sealant placement on dura were found.

The wrong paradigm. Williams argued that biocompatibility for long term implants has mostly meant chemical and biological inertness [88]. A sealant is reactive when applied and designed to degrade, so tests built on inertness fit it poorly.

Table 4. What routine laboratory tests show for a neurosurgical hydrogel sealant, and what they miss.

Test or endpoint	What it can show	What it can miss
Extract and direct contact cytotoxicity on fibroblast lines [30,31,71,83]	Acute cell damage from leachable	Neurotoxicity, which the FDA says considers for neurological devices [71]; products that appear only during degradation [71,72]
Subcutaneous or muscle implantation [71]	Local tissue response	Response of brain, dura and CSF pathways [71]
Dural implantation in animals [62,71,84]	Tissue response at the intended site	Follow up in the studies reviewed ranged from 2 weeks to 12 months [45,49,50,51,62,68,70]
Sensitization tests [71,86,87]	Allergy potential of leachable	PEG specific immune responses [86,87]
Degradation product analysis, ISO 10993 parts 9, 13 and 18 [72,73,74]	Chemical products of degrading or set polymers	Part 13 considers only nonrecordable polymers [72]; no scope names resorbable in situ forming sealants
Burst test, ASTM F2392 [58]	Failure pressure of the sealed repair system at one time point	Interfacial adhesive strength alone [58]; repeated cough or pulsatile loading [61]
Free swelling ratio in buffer [47,48]	Water uptake without constraint	Confined swelling force [55] and late swelling [56]

Abbreviations: ASTM, ASTM International; CSF, cerebrospinal fluid; ISO, International Organization for Standardization; PEG, polyethylene glycol.

How convincing is the laboratory evidence?

The tests answer narrower questions than the one being asked. The burst test measures failure of the repair system, and its own standard cautions on extrapolating to the body [58]. A free swelling ratio in buffer does not measure force in a confined space. A pass on fibroblast cytotoxicity does not address neurons or glia [71], and no standard written for the degradation of resorbable in situ forming sealants was identified. None of these tests show what the gel does over weeks beside neural tissue.

The tests do show useful things: overtly toxic chemistry [30,31], sealing at zero under controlled conditions [26,63], and swelling early enough for labels to bound it and warning against confined spaces with nerves [7,8,25,43]. Table 5 sets out how well each safety question is addressed.

Table 5. How well does the current evidence base addresses key safety and performance questions for neurosurgical hydrogel sealants.

Safety question	What current evidence addresses	Main unresolved limitation
Is the set gel overtly cytotoxic?	Extract tests detect cytotoxic leachable, as with glutaraldehyde and cyanoacrylate (indirect) [30,31]	Fibroblast lines say little about neurons or glia [71]
Is it neurotoxic or immunogenic?	Guidance asks that neurotoxicity be considered [71]; PEG allergy is documented outside sealants [86,87]	No standardized neural test and no data on PEG sensitization after sealant placement on dura
Does it seal at time zero?	Ex vivo burst tests [26,63]	About 21 to 325 mmHg; methods differ; interface not isolated [58]
Does it keep sealing for days to weeks?	72-hour hold [63]; 8-week leak pressure in dogs [62]	Three samples per product in the 72-hour study; no cough loading [61]
How much does it swell in the body?	Labelled limits and bench ratios [7,8,25,43]; MRI thickness in pigs and rabbits [45,51]	No confined swelling test [55]
Does swelling or migration compress neural tissue?	Swelling flagged by bench data and labels [7,8,25,43]; compression in case reports [15,16,17,18] and MAUDE reports [52]	Confined swelling force and late swelling in the body were not tested; late swelling is extrapolated from model PEG gels [56,57]
How fast does it degrade, and into what?	Labelled absorption times [7,8,25,42,43]; pig histology to 12 months [45]	Tissue may alter degradation [77]; products rarely identified [72]

Abbreviations: MAUDE, Manufacturer and User Facility Device Experience; MRI, magnetic resonance imaging; PEG, polyethylene glycol.

Proposed multidomain framework for evaluating neurosurgical hydrogel sealants

Based on the gaps identified in this review, a framework of eight connected evidence domains is proposed for evaluating hydrogel sealants. It has not been validated or agreed by consensus, the domains inform one another and are not sequential pass or fail gates, and the criteria are starting points for discussion. Three domains address areas where no standard written for resorbable neurosurgical hydrogel sealants was identified: measuring swelling (2), measuring degradation (4) and testing neural cells and immunity (5). Sealing (3) is left unshaded because a general burst standard exists, although it was not written for dura or pulsatile loading. Figure 1 shows the domains.

proposed multidomain framework · 8 linked evidence domains, 3 lack a fit for purpose standard

Figure 1. Proposed multidomain framework for evaluating neurosurgical hydrogel sealants. The eight domains are connected, and a finding in one should prompt reassessment of others. The framework is a proposal and has not been validated. Shaded domains are those for which no standard written for resorbable neurosurgical hydrogel sealants was identified.

1. **Define chemistry.** List every component, reactive group, leaving group, residual, initiator and breakable linker, and expected products. Criterion: all identified and assessed for toxicity [71,72].
2. **Measure swelling.** Record free swelling in artificial CSF at 37 °C until the gel has degraded, and confined swelling in a standardized apparatus of defined compliance, with force recorded. Criterion: peak force and volume, including late swelling [56,57], stay below limits set in advance for the target compartment [55].
3. **Measure sealing.** Use species matched dura, a real suture line, cyclic pressure, blood contamination and a hold of 72 hours or longer, reporting mmHg and failure mode. Criterion: the seal holds above resting and cough pressures at the site [58,60,61,63].
4. **Measure degradation.** Follow mass, modulus and swelling in artificial CSF at 37 °C, with and without enzymes, identify products chemically using ISO 10993 parts 9 and 18 as the starting framework [73,74], and test extracts of the unset, set and degrading gel. Criterion: all products identified and none above toxicity limits [71,72].
5. **Test neural cells and immunity.** Use neurons, astrocytes and microglia in extract and contact formats, plus sensitization testing [71]; antibody testing against PEG is an exploratory question [86,87]. Criterion: no toxicity at dilutions relevant to the local dose [71].
6. **Study a large animal.** Test at the clinically intended interface under worst case exposure, including neural contact through placement, migration or expansion. Use a randomized, blinded design reported to ARRIVE 2.0 [89], measuring leak pressure, swelling on MRI, neurological function and histology, with follow up to full resorption. Criterion: no neurological harm, complete clearance and a steady state tissue response [45,62,71].
7. **Introduce the device in stages.** Start with a small series, scheduled imaging and stopping rules set in advance [90], and use it in the posterior fossa, spinal canal and children only after earlier stages are clean [15,16].
8. **Watch after approval.** Keep a registry with imaging and neurological outcomes and read adverse event reports with narrative review and not only structured codes [52].

Future directions

Four changes would make the evidence for neurosurgical sealants more convincing.

First, agree with a consensus protocol for confined swelling that fixes the medium (artificial CSF), temperature, the compliance of the constraint and the duration, which should run to full degradation, and reports force and volume together.

Second, build neural endpoints into the standard development package: neurons, glia and oligodendrocytes tested with extracts and in contact, and animal studies that measure function as well as histology. The canine study of a PEG sealant shows that neurotoxicity can be assessed at the dural site [62].

Third, make the sealant visible in patients through standardized imaging of its appearance, volume and temporal evolution. In a small skull base series, Adheres was more likely than Dura Seal to be identifiable on the immediate postoperative MRI, 50% against 20.8% [91], and reliable imaging would let teams catch early expansion.

Fourth, keep developing designs that break the couplings between swelling, strength and degradation, such as low swell, tough and layered gels [45,49,50,67,81], and test each against the same pathway.

Limitations

This was a narrative review and not a systematic review, so relevant studies may be missing, and the selection may favor papers that fit the argument. The search covered PubMed, Scopus and semantic searching only and was limited to English, so studies in other languages or databases may have been missed. Many laboratory studies are single reports with different substrates, defects and endpoints, which limit comparison (Table 3). Statements about standards refer to their published scope.

Conclusions

Hydrogel chemistry decides swelling, sealing strength and degradation together. Crosslink density, linker chemistry and hydrophilicity move all three, so none can be tuned alone, although recent designs try to break the couplings with dissipative networks, hydrophobic domains, opposing swelling and shrinking components and backing layers.

Laboratory evidence is useful for hazard screening and acute performance characterization but is insufficient, on its own, to establish comprehensive neurosurgical safety, particularly for constrained swelling, degradation associated changes, breakdown products and uncommon neurological complications. Swelling related compression has been reported in patients with PEG sealants even though swelling was bound in the labels, and standard tests are least able to detect it. These findings support caution when hydrogel sealants are used in anatomically confined spaces where even modest expansion could produce clinically important mass effects [15].

Declarations

Author.

Author contributions. Muhammad Kamil formulated the review question and prepared the manuscript. Maryam Nadeem contributed to the literature review, study selection, critical evaluation, and revision of the manuscript. Muhammad Haider contributed to the literature review, critical evaluation, and revision of the manuscript. All authors reviewed and approved the final manuscript.

Funding. No external funding was received for this work.

Conflicts of interest. The authors declare that they have no conflicts of interest.

Ethics approval. Not applicable. This study is a narrative review based exclusively on previously published literature and did not involve human participants or animals.

Data availability. No new data was generated. All sources are listed in the references.

Use of artificial intelligence: Claude was only used for grammar checking and for rewriting certain sentences during the manuscript preparation.

REFERENCES

1. Kinaci A, Algar A, Huets S, O'Donnell D, van der Zwaan A, van Doorman T. Effectiveness of dural sealants in prevention of cerebrospinal fluid leakage after craniotomy: a systematic review. World Neurosurgeon. 2018; 118:368 to 376.e1. PMID 29969744. https://doi.org/10.1016/j.wneu.2018.06.196
2. Hutter G, von Felten S, Sailer MH, Schulz M, Mariani L. Risk factors for postoperative CSF leakage after elective craniotomy and the efficacy of fleece bound tissue sealing against dural suturing alone: a randomized controlled trial. J Neurosurgeon. 2014;121(3):735 to 744. PMID 25036199. https://doi.org/10.3171/2014.6.JNS131917
3. Slot EMH, van Baarsen KM, Hoving EW, Zuithoff NPA, van Doormaal TPC. Cerebrospinal fluid leakage after cranial surgery in the pediatric population: a systematic review and meta analysis. Childs Nerv Syst. 2021;37(5):1439 to 1447. PMID 33538867. https://doi.org/10.1007/s00381-021-05036-8
4. Guerin P, El Fegoun AB, Obeid I, Gille O, Lelong L, Luc S, et al. Incidental durotomy during spine surgery: incidence, management and complications. A retrospective review. Injury. 2012;43(4):397 to 401. PMID 21251652. https://doi.org/10.1016/j.injury.2010.12.014
5. Dafford EE, Anderson PA. Comparison of dural repair techniques. Spine J. 2015;15(5):1099 to 1105. PMID 23973097. https://doi.org/10.1016/j.spinee.2013.06.044
6. Osbun JW, Ellenbogen RG, Chesnut RM, Chin LS, Connolly PJ, Cosgrove GR, et al. A multicenter, single blind, prospective randomized trial to evaluate the safety of a polyethylene glycol hydrogel (Duraseal Dural Sealant System) as a dural sealant in cranial surgery. World Neurosurg. 2012;78(5):498 to 504. PMID 22381303. https://doi.org/10.1016/j.wneu.2011.12.011
7. US Food and Drug Administration. DuraSeal Dural Sealant System: instructions for use, premarket approval P040034 (labeling revision dated 2005 Feb 17). Silver Spring (MD): US FDA. https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040034c.pdf
8. US Food and Drug Administration. DuraSeal Spine Sealant System: summary of safety and effectiveness data, premarket approval P080013. Silver Spring (MD): US FDA; approved 2009 Sep 4. https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080013b.pdf
9. Kim KD, Ramanathan D, Highsmith J, Lavelle W, Gerszten P, Vale F, et al. DuraSeal Exact is a safe adjunctive treatment for durotomy in spine: postapproval study. Global Spine J. 2019;9(3):272 to 278. PMID 31192094. https://doi.org/10.1177/2192568218791150
10. Lee YM, Ordaz A, Durcanova B, Viner JA, Theodosopoulos PV, Aghi MK, et al. Cerebrospinal fluid leaks and pseudomeningocele after posterior fossa surgery: effect of an autospray dural sealant. Cureus. 2020;12(5):e8379. PMID 32626623. https://doi.org/10.7759/cureus.8379
11. Cosgrove GR, Delashaw JB, Grotenhuis JA, Tew JM, Van Loveren H, Spetzler RF, et al. Safety and efficacy of a novel polyethylene glycol hydrogel sealant for watertight dural repair. J Neurosurg. 2007;106(1):52 to 58. PMID 17236487. https://doi.org/10.3171/jns.2007.106.1.52
12. Cantarini Aguiar C, Filho U, Bonatti BF, Oliveira MDJ, Ely V. Comparative effectiveness of dural sealants versus conventional dural closure methods in cranial neurosurgery: a systematic review and meta analysis. Neurosurg Rev. 2025;49(1):33. PMID 41313498. https://doi.org/10.1007/s10143-025-03965-5
13. Yu S, He J, Xiong K, Cheng Z, Zhang Y. Comparative analysis of the efficacy and safety of dural sealants in preventing complications after craniotomy: a systematic review and Bayesian network meta analysis. Acta Neurochir (Wien). 2026;168(1). PMID 42387243. https://doi.org/10.1007/s00701-026-06971-8
14. Pang JC, Bitner BF, Nottoli MM, Abiri A, Bui AT, Nguyen CH, et al. Tissue sealant impact on skull base reconstruction outcomes: a systematic review and meta analysis. Laryngoscope. 2024;134(8):3425 to 3436. PMID 38470297. https://doi.org/10.1002/lary.31390
15. Blackburn SL, Smyth MD. Hydrogel induced corticomedullary compression after posterior fossa decompression for Chiari malformation. Case report. J Neurosurgeon. 2007;106(4 Suppl):302 to 304. PMID 17465365. https://doi.org/10.3171/ped.2007.106.4.302
16. Mulder M, Crosier J, Dunn R. Cauda equina compression by hydrogel dural sealant after a laminotomy and discectomy: case report. Spine (Phila Pa 1976). 2009;34(4): E144 to E148. PMID 19214084. https://doi.org/10.1097/BRS.0b013e31818d5427
17. Neuman BJ, Radcliff K, Rihn J. Cauda equina syndrome after a TLIF resulting from postoperative expansion of a hydrogel dural sealant. Clin Ortho Relate Res. 2012;470(6):1640 to 1645. PMID 21952743. https://doi.org/10.1007/s11999-011-2071-z
18. Obeng Gyasi B, Line TA, Brown W, Chinthala AS, Kussow NJ, Mao G. The remote intradural migration of polyethylene glycol based hydrogel sealant following lumbar laminectomy: a case report. J Clin Med. 2025;14(5):1472. PMID 40094962. https://doi.org/10.3390/jcm14051472

19. Epstein NE. Dural repair with four spinal sealants: focused review of the manufacturers' inserts and the current literature. Spine J. 2010;10(12):1065 to 1068. PMID 21094467. https://doi.org/10.1016/j.spinee.2010.09.017

20. Baethge C, Goldbeck Wood S, Mertens S. SANRA, a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5. PMID 30962953. https://doi.org/10.1186/s41073-019-0064-8

21. Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev. 2002;54(1):3 to 12. PMID 11755703. https://doi.org/10.1016/s0169-409x(01)00239-3

22. Ghobril C, Grinstaff MW. The chemistry and engineering of polymeric hydrogel adhesives for wound closure: a tutorial. Chem Soc Rev. 2015;44(7):1820 to 1835. PMID 25649260. https://doi.org/10.1039/c4cs00332b

23. Nam S, Mooney D. Polymeric tissue adhesives. Chem Rev. 2021;121(18):11336 to 11384. PMID 33507740. https://doi.org/10.1021/acs.chemrev.0c00798

24. Spotnitz WD, Burks S. Hemostats, sealants, and adhesives: components of the surgical toolbox. Transfusion. 2008;48(7):1502 to 1516. PMID 18422855. https://doi.org/10.1111/j.1537-2995.2008.01703.x

25. US Food and Drug Administration. Adherus AutoSpray Dural Sealant: summary of safety and effectiveness data, premarket approval P130014. Silver Spring (MD): US FDA; approved 2015 Mar 30. https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130014b.pdf

26. Argiti K, Shah MJ, Joseph K, Ravi VM, Stathi A, Volz F, et al. Platelet rich fibrin and commercial sealants for dural closure in neurosurgery: an in vitro study. PLoS One. 2025;20(4):e0319349. PMID 40168286. https://doi.org/10.1371/journal.pone.0319349

27. Wallace DG, Cruise GM, Rhee WM, Schroeder JA, Prior JJ, Ju J, et al. A tissue sealant based on reactive multifunctional polyethylene glycol. J Biomed Mater Res. 2001;58(5):545 to 555. PMID 11505430. https://doi.org/10.1002/jbm.1053

28. Janmey PA, Winer JP, Weisel JW. Fibrin gels and their clinical and bioengineering applications. J R Soc Interface. 2009;6(30):1 to 10. PMID 18801715. https://doi.org/10.1098/rsif.2008.0327

29. Spotnitz WD. Fibrin sealant: past, present, and future: a brief review. World J Surg. 2010;34(4):632 to 634. PMID 19820991. https://doi.org/10.1007/s00268-009-0252-7

30. Fürst W, Banerjee A. Release of glutaraldehyde from an albumin glutaraldehyde tissue adhesive causes significant in vitro and in vivo toxicity. Ann Thorac Surg. 2005;79(5):1522 to 1528. PMID 15854927. https://doi.org/10.1016/j.athoracsur.2004.11.054

31. Montanaro L, Arciola CR, Cenni E, Ciapetti G, Savioli F, Filippini F, et al. Cytotoxicity, blood compatibility and antimicrobial activity of two cyanoacrylate glues for surgical use. Biomaterials. 2001;22(1):59 to 66. PMID 11085384. https://doi.org/10.1016/s0142-9612(00)00163-0

32. Yue K, Trujillo de Santiago G, Alvarez MM, Tamayol A, Annabi N, Khademhosseini A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. Biomaterials. 2015;73:254 to 271. PMID 26414409. https://doi.org/10.1016/j.biomaterials.2015.08.045

33. Annabi N, Zhang YN, Assmann A, Sani ES, Cheng G, Lassaletta AD, et al. Engineering a highly elastic human protein based sealant for surgical applications. Sci Transl Med. 2017;9(410):eaai7466. PMID 28978753. https://doi.org/10.1126/scitranslmed.aai7466

34. Lang N, Pereira MJ, Lee Y, Friehs I, Vasilyev NV, Feins EN, et al. A blood resistant surgical glue for minimally invasive repair of vessels and heart defects. Sci Transl Med. 2014;6(218):218ra6. PMID 24401941. https://doi.org/10.1126/scitranslmed.3006557

35. Williams CG, Malik AN, Kim TK, Manson PN, Elisseeff JH. Variable cytocompatibility of six cell lines with photoinitiators used for polymerizing hydrogels and cell encapsulation. Biomaterials. 2005;26(11):1211 to 1218. PMID 15475050. https://doi.org/10.1016/j.biomaterials.2004.04.024

36. Fairbanks BD, Schwartz MP, Bowman CN, Anseth KS. Photoinitiated polymerization of PEG diacrylate with lithium phenyl 2,4,6 trimethylbenzoylphosphinate: polymerization rate and cytocompatibility. Biomaterials. 2009;30(35):6702 to 6707. PMID 19783300. https://doi.org/10.1016/j.biomaterials.2009.08.055

37. Li J, Celiz AD, Yang J, Yang Q, Wamala I, Whyte W, et al. Tough adhesives for diverse wet surfaces. Science. 2017;357(6349):378 to 381. PMID 28751604. https://doi.org/10.1126/science.aah6362

38. Yuk H, Varela CE, Nabzdyk CS, Mao X, Padera RF, Roche ET, et al. Dry double sided tape for adhesion of wet tissues and devices. Nature. 2019;575(7781):169 to 174. PMID 31666696. https://doi.org/10.1038/s41586-019-1710-5

39. Lee H, Dellatore SM, Miller WM, Messersmith PB. Mussel inspired surface chemistry for multifunctional coatings. Science. 2007;318(5849):426 to 430. PMID 17947576. https://doi.org/10.1126/science.1147241

40. Yang J, Bai R, Suo Z. Topological adhesion of wet materials. Adv Mater. 2018;30(25):e1800671. PMID 29726051. https://doi.org/10.1002/adma.201800671

41. Wright NM, Park J, Tew JM, Kim KD, Shaffrey ME, Cheng J, et al. Spinal sealant system provides better intraoperative watertight closure than standard of care during spinal surgery: a prospective, multicenter, randomized controlled study. Spine (Phila Pa 1976). 2015;40(8):505 to 513. PMID 25646746. https://doi.org/10.1097/BRS.0000000000000810

42. US Food and Drug Administration. CraniSeal Dural Sealant: premarket approval P220014, recently approved device summary. Silver Spring (MD): US FDA; approved 2023 Jul 6. https://www.fda.gov/medical-devices/recently-approved-devices/craniseal-dural-sealant-p220014

43. US Food and Drug Administration. SpineSeal Spine Sealant: summary of safety and effectiveness data, premarket approval P240027. Silver Spring (MD): US FDA; approved 2025 Feb 14. https://www.accessdata.fda.gov/cdrh_docs/pdf24/P240027B.pdf

44. Slot EMH, Colmer N, Serra C, Holzmann D, Regli L, van Doormaal TPC. Ex vivo and in vivo evaluation of transsphenoidal Liqoseal application to prevent cerebrospinal fluid leakage. Acta Neurochir (Wien). 2023;165(6):1511 to 1521. PMID 36624231. https://doi.org/10.1007/s00701-022-05477-3

45. Kinaci A, Bergmann W, van Thoor S, Redegeld S, van der Zwan A, van Doormaal TPC. Safety and biodegradability of a synthetic dural

sealant patch (Liqoseal) in a porcine cranial model. Animal Model Exp Med. 2021;4(4):398 to 405. PMID 34977491. https://doi.org/10.1002/ame2.12184

46. Van Doormaal T, Germans MR, Sie M, Brouwers B, Carlson A, Dankbaar JW, et al. Single arm, open label, multicentre first in human study to evaluate the safety and performance of dura sealant patch in reducing cerebrospinal fluid leakage following elective cranial surgery: the ENCASE trial. BMJ Open. 2021;11(7):e049098. PMID 34321304. https://doi.org/10.1136/bmjopen-2021-049098

47. Canal T, Peppas NA. Correlation between mesh size and equilibrium degree of swelling of polymeric networks. J Biomed Mater Res. 1989;23(10):1183 to 1193. PMID 2808463. https://doi.org/10.1002/jbm.820231007

48. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000;50(1):27 to 46. PMID 10840191. https://doi.org/10.1016/s0939-6411(00)00090-4

49. Zhou H, Fan Y, Huang J, Huang H, Li H, Liang Z, et al. A wet adhesive hydrogel patch with rapid adhesion, anti swelling, and pro healing properties for sutureless repair of dural tear. Adv Healthc Mater. 2025;14(16):e2500761. PMID 40346970. https://doi.org/10.1002/adhm.202500761

50. Cheng X, Zhang Z, Ren H, Zou Z, Zhang Y, Qu Y, et al. A low swelling hydrogel as a multirole sealant for efficient dural defect sealing and prevention of postoperative adhesion. Natl Sci Rev. 2024;11(6):nwae160. PMID 38867893. https://doi.org/10.1093/nsr/nwae160

51. Zhu T, Wang H, Jing Z, Fan D, Liu Z, Wang X, et al. High efficacy of tetra PEG hydrogel sealants for sutureless dural closure. Bioact Mater. 2021;8:12 to 19. PMID 34541383. https://doi.org/10.1016/j.bioactmat.2021.06.022

52. Porwal M, Mach A, Jaffee S, Yu A. Post market safety patterns of hydrogel dural sealants: a comparative manufacturer and user facility device experience analysis. J Neurosurg Sci. 2026;70(4):271 to 278. PMID 41823721. https://doi.org/10.23736/S0390-5616.26.06744-5

53. White PM, Lewis SC, Gholkar A, Sellar RJ, Nahser H, Cognard C, et al. Hydrogel coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. Lancet. 2011;377(9778):1655 to 1662. PMID 21571149. https://doi.org/10.1016/S0140-6736(11)60408-X

54. Fanning NF, Willinsky RA, ter Brugge KG. Wall enhancement, edema, and hydrocephalus after endovascular coil occlusion of intradural cerebral aneurysms. J Neurosurg. 2008;108(6):1074 to 1086. PMID 18518706. https://doi.org/10.3171/JNS/2008/108/6/1074

55. Mokri B. The Monro Kellie hypothesis: applications in CSF volume depletion. Neurology. 2001;56(12):1746 to 1748. PMID 11425944. https://doi.org/10.1212/wnl.56.12.1746

56. Zustiak SP, Leach JB. Hydrolytically degradable poly(ethylene glycol) hydrogel scaffolds with tunable degradation and mechanical properties. Biomacromolecules. 2010;11(5):1348 to 1357. PMID 20355705. https://doi.org/10.1021/bm100137q

57. Browning MB, Cereceres SN, Luong PT, Cosgriff Hernandez EM. Determination of the in vivo degradation mechanism of PEGDA hydrogels. J Biomed Mater Res A. 2014;102(12):4244 to 4251. PMID 24464985. https://doi.org/10.1002/jbm.a.35096

58. ASTM International. Standard test method for burst strength of surgical sealants. ASTM F2392, 2024 edition. West Conshohocken (PA): ASTM International; 2024. https://store.astm.org/f2392-24.html

59. ASTM International, Committee F04, Subcommittee F04.15 on Material Test Methods. Standard test methods for tissue adhesives: ASTM F2255 (lap shear), F2256 (T peel), F2258 (tension) and F2458 (wound closure strength), 2024 editions. West Conshohocken (PA): ASTM International; 2024. Available online: https://store.astm.org/f2255-24.html, https://store.astm.org/f2256-24.html, https://store.astm.org/f2258-24.html, https://store.astm.org/f2458-05r24.html

60. Whiteley W, Al Shahi R, Warlow CP, Zeidler M, Lueck CJ. CSF opening pressure: reference interval and the effect of body mass index. Neurology. 2006;67(9):1690 to 1691. PMID 17101909. https://doi.org/10.1212/01.wnl.0000242704.60275.e9

61. Williams B. Cerebrospinal fluid pressure changes in response to coughing. Brain. 1976;99(2):331 to 346. PMID 990900. https://doi.org/10.1093/brain/99.2.331

62. Preul MC, Campbell PK, Bichard WD, Spetzler RF. Application of a hydrogel sealant improves watertight closures of duraplasty onlay grafts in a canine craniotomy model. J Neurosurg. 2007;107(3):642 to 650. PMID 17886566. https://doi.org/10.3171/JNS-07/09/0642

63. Kinaci A, van Thoor S, Redegeld S, Tooren M, van Doormaal TPC. Ex vivo evaluation of a multilayered sealant patch for watertight dural closure: cranial and spinal models. J Mater Sci Mater Med. 2021;32(8):85. PMID 34297226. https://doi.org/10.1007/s10856-021-06552-4

64. Walsh DR, Ross AM, Malijauskaite S, Flanagan BD, Newport DT, McGourty KD, et al. Regional mechanical and biochemical properties of the porcine cortical meninges. Acta Biomater. 2018;80:237 to 246. PMID 30208332. https://doi.org/10.1016/j.actbio.2018.09.004

65. Maikos JT, Elias RAI, Shreiber DI. Mechanical properties of dura mater from the rat brain and spinal cord. J Neurotrauma. 2008;25(1):38 to 51. PMID 18355157. https://doi.org/10.1089/neu.2007.0348

66. Zarzur E. Mechanical properties of the human lumbar dura mater. Arq Neuropsiquiatr. 1996;54(3):455 to 460. PMID 9109991. https://doi.org/10.1590/s0004-282x1996000300015

67. Sun JY, Zhao X, Illeperuma WRK, Chaudhuri O, Oh KH, Mooney DJ, et al. Highly stretchable and tough hydrogels. Nature. 2012;489(7414):133 to 136. PMID 22955625. https://doi.org/10.1038/nature11409

68. Wu KC, Freedman BR, Kwon PS, Torre M, Kent DO, Bi WL, et al. A tough bioadhesive hydrogel supports sutureless sealing of the dural membrane in porcine and ex vivo human tissue. Sci Transl Med. 2024;16(739):eadj0616. PMID 38507468. https://doi.org/10.1126/scitranslmed.adj0616

69. Campbell B, Anderson Z, Han D, Nebor I, Forbes J, Steckl AJ. Electrospinning of cyanoacrylate tissue adhesives for human dural repair in endonasal surgery. J Biomed Mater Res B Appl Biomater. 2022;110(3):660 to 667. PMID 34596966. https://doi.org/10.1002/jbm.b.34944

70. Lee H, Lee S, Seong KY, Kang S, Seo MS, Shin SR, et al. Enhanced dural repair using biodegradable sealants based on photocurable hyaluronic acid. Macromol Biosci. 2024;24(4):e2300359. PMID 38011541. https://doi.org/10.1002/mabi.202300359

71. US Food and Drug Administration. Use of International Standard ISO 10993 1, "Biological evaluation of medical devices: Part 1: Evaluation and testing within a risk management process". Guidance for industry and FDA staff. Silver Spring (MD): US FDA; 2023 Sep 8.

https://www.fda.gov/media/142959/download

72. International Organization for Standardization. ISO 10993 part 13: biological evaluation of medical devices, identification and quantification of degradation products from polymeric medical devices. 2nd ed. Geneva: ISO; 2010. https://www.iso.org/standard/44050.html

73. International Organization for Standardization. ISO 10993 part 9: biological evaluation of medical devices, framework for identification and quantification of potential degradation products. 3rd ed. Geneva: ISO; 2019. https://www.iso.org/standard/64580.html

74. International Organization for Standardization. ISO 10993 part 18: biological evaluation of medical devices, chemical characterization of medical device materials within a risk management process. 2nd ed. Geneva: ISO; 2020. https://www.iso.org/standard/64750.html

75. ASTM International. Standard test method for in vitro degradation testing of hydrolytically degradable polymer resins and fabricated forms for surgical implants. ASTM F1635, 2024 edition. West Conshohocken (PA): ASTM International; 2024. https://store.astm.org/f1635-24.html

76. ASTM International. Standard guide for characterization of hydrogels used in regenerative medicine. ASTM F2900, 2025 edition. West Conshohocken (PA): ASTM International; 2025. https://store.astm.org/f2900-25.html

77. Reid B, Gibson M, Singh A, Taube J, Furlong C, Murcia M, et al. PEG hydrogel degradation and the role of the surrounding tissue environment. J Tissue Eng Regen Med. 2015;9(3):315 to 318. PMID 23495204. https://doi.org/10.1002/term.1688

78. Knop K, Hoogenboom R, Fischer D, Schubert US. Poly(ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. Angew Chem Int Ed Engl. 2010;49(36):6288 to 6308. PMID 20648499. https://doi.org/10.1002/anie.200902672

79. Fu K, Pack DW, Klibanov AM, Langer R. Visual evidence of acidic environment within degrading poly(lactic co glycolic acid) (PLGA) microspheres. Pharm Res. 2000;17(1):100 to 106. PMID 10714616. https://doi.org/10.1023/a:1007582911958

80. Hunter AC. Molecular hurdles in polyfectin design and mechanistic background to polycation induced cytotoxicity. Adv Drug Deliv Rev. 2006;58(14):1523 to 1531. PMID 17079050. https://doi.org/10.1016/j.addr.2006.09.008

81. Kamata H, Akagi Y, Kayasuga Kariya Y, Chung UI, Sakai T. "Nonswellable" hydrogel without mechanical hysteresis. Science. 2014;343(6173):873 to 875. PMID 24558157. https://doi.org/10.1126/science.1247811

82. International Organization for Standardization. ISO 10993 part 1, sixth edition: biological evaluation of medical devices, requirements and general principles for the evaluation of biological safety within a risk management process. Geneva: ISO; 2025. Recognised by the US FDA on 25 May 2026. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=47116

83. Li W, Zhou J, Xu Y. Study of the cytotoxicity testing of medical devices. Biomed Rep. 2015;3(5):617 to 620. PMID 26405534. https://doi.org/10.3892/br.2015.481

84. Polikov VS, Tresco PA, Reichert WM. Response of brain tissue to chronically implanted neural electrodes. J Neurosci Methods. 2005;148(1):1 to 18. PMID 16198003. https://doi.org/10.1016/j.jneumeth.2005.08.015

85. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol. 2008;20(2):86 to 100. PMID 18162407. https://doi.org/10.1016/j.smim.2007.11.004

86. Wenande E, Garvey LH. Immediate type hypersensitivity to polyethylene glycols: a review. Clin Exp Allergy. 2016;46(7):907 to 922. PMID 27196817. https://doi.org/10.1111/cea.12760

87. Yang Q, Lai SK. Anti PEG immunity: emergence, characteristics, and unaddressed questions. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2015;7(5):655 to 677. PMID 25707913. https://doi.org/10.1002/wnan.1339

88. Williams DF. On the mechanisms of biocompatibility. Biomaterials. 2008;29(20):2941 to 2953. PMID 18440630. https://doi.org/10.1016/j.biomaterials.2008.04.023

89. Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et al. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. PLoS Biol. 2020;18(7):e3000410. PMID 32663219. https://doi.org/10.1371/journal.pbio.3000410

90. Sedrakyan A, Campbell B, Merino JG, Kuntz R, Hirst A, McCulloch P. IDEAL D: a rational framework for evaluating and regulating the use of medical devices. BMJ. 2016;353:i2372. PMID 27283585. https://doi.org/10.1136/bmj.i2372

91. Soneru CP, Riley CA, Minkowitz S, Tabaee A, Anand VK, Schwartz TH. Adherus dural sealant in endoscopic skull base surgery: safety, imaging characteristics, and sinonasal quality of life. J Neurol Surg B Skull Base. 2020;81(6):659 to 663. PMID 33381370. https://doi.org/10.1055/s-0039-1694048