Intrathecal Fluorescein in Endoscopic Skull Base Surgery for Identification and Repair of Cerebrospinal Fluid Leaks

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We are very pleased to offer for your attention a carefully compiled guide for a safe use of intraoperative intrathecal fluorescein to assist the endoscopic repairs of the cerebrospinal fluid (CSF) leaks.

What is remarkable about this guide is that it was spearheaded by the SHANA **forum discussion**. **Dr. Callum Gilchrist** from the Royal North Shore Hospital in Sydney, Australia initiated the discussion and subsequently took on a self-imposed task to perform a thorough literature review, write up the guide, and share it with the SHANA community. The SHANA Education Board could not be more pleased that the spirit of collegiality and the informative website discussions have proved useful to all of us at the point of clinical care.

Congratulations to **Dr. Callum Gilchrist** on the job well done!

Intrathecal Fluorescein in Endoscopic Skull Base Surgery for Identification and Repair of Cerebrospinal Fluid Leaks.

Presented by Dr. Callum Gilchrist, Royal North Shore Hospital, Sydney, Australia.

The endoscopic repair of cerebrospinal fluid (CSF) leaks is currently considered the standard of surgical care. Although preoperative high-resolution imaging studies are routinely performed for these cases, the intraoperative intrathecal (IT) fluorescein dye injection pinpoints the localization of the actual defect, facilitating surgical repair. The patient's safety will be greatly enhanced by the use of a low-dose fluorescein (e.g. 0.1% - 10 ml) and other perioperative precautions.

Technique details.

1. Obtain and document informed consent.
2. Perform a neurological exam prior to procedure and document findings.
3. Premedicate the patient with 50 mg diphenhydramine orally (previously published protocols used a 50 mg IV dose – the IV form is not available in Australia).
4. Place an IV and administer second premedication of dexamethasone 10 mg IV, plus prophylactic antibiotics cephazolin 1 g (2 g if patient's weight > 80 kg).

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5. Instruct the patient on symptoms to report during both lumbar drain insertion and during IT injection of fluorescein, such that interventions can be ceased immediately if required.
6. Perform dural puncture, place and secure the lumbar drain[1]:
    - 16G Tuohy kit best for larger catheter size, with easier CSF aspiration-drainage and less likelihood for blockage.
    - Turn Tuohy 90°after ligamentum flavum is passed to separate rather than transect the dural fibers.
    - Feed the IT catheter, then secure appropriately (can do alternatively after the CSF is collected).
7. Surgeon or anaesthetist administer the IT fluorescein[2] 30-90 min prior to surgery[3]:
    - Withdraw 10 ml of CSF.
    - Mix CSF with **0.1**-0.25 ml of additive free 10% fluorescein (sodium) solution (making a ~10 ml solution containing **10**-25 mg fluorescein) – mix with sterile saline/Hartmann's or sterile water if unable to aspirate enough CSF.[4]
    - Slow injection of fluorescein solution over a number of minutes – with patient able to communicate any symptoms.
    - 5 ml flush to follow of CSF/sterile saline over a number of minutes.
    - Can consider head-down positioning at this point.
8. Neurological observations should continue for a minimum of 12 hr after the IT injection to enable rapid detection of any problems.[5] Neurological observations should be continued for as long as the lumbar drain is in situ, and for 12 hr after its removal. Ward or ICU disposition will be institution-dependent.
9. Prophylactic antibiotics required whilst lumbar drain remains in place, in addition to regular aperients.
10. In patients with paraparesis after the IT injection, whole spine MRI should be performed.

Informed consent.

1. The IT use of fluorescein is an off-label use of the product. It has been used worldwide for this purpose since pre-2000, and is chosen by the surgeon as a technique when its possible risks are outweighed by its potential benefits. The IT fluorescein via a lumbar drain or via a single injection into the CSF serves as an important adjunct in CSF leak repair to: 1) provide accurate localization of a skull base defect; 2) assist in locating additional leak sites; and 3) confirm watertight closure of the defect.[6] Limited evidence suggests that fluorescein injection in patients with a history of seizures, hydrocephalus, spinal stenosis, acute brain injury, cerebral edema, or other neurologic conditions be avoided.[7]
2. Lumbar drains have similarly been used for many years (pre-2000) to assist in reducing the CSF-pressure, when the surgeon determines that the possible risks are outweighed by the potential benefits of the technique
3. What are the risks?

    a. Note that the surgery itself can be responsible for some of these outcomes – it can be difficult to distinguish between side effects attributable to the surgery, to the lumbar drain and to the IT fluorescein.

    b. Rare, but severe and life-changing events, with a risk similar to that of dying in a car crash on the way home from work:

    - Permanent paraplegia of the lower limbs/legs and lower trunk/torso, i.e. total loss of motor function/strength/voluntary movement, with loss of all sensation, the potential development of neuropathic pain, plus the possible loss of all bladder and bowel control with incontinence and urinary retention. Possibly due to spinal cord damage, nerve root damage, meningitis/inflammation of the central nervous system's lining, abscess formation, or compression of neural structures by a haematoma/blood clot. Lesser damage can also occur with degrees of weakness, numbness, pain, and bowel or bladder problems. Functional capacity will be decreased should these complications occur.
    - Permanent tinnitus with impairment of enjoyment and ability to function (most likely due to the surgery itself).

- Seizures.
- Cranial nerve injury – possibly affecting the senses, the sensation and motor control of the head and neck, and the body's autonomic nervous system (e.g. the control of swallowing and breathing).
- Retention of part of the catheter, which may require procedures to remove.

c. Common – around 10% incidence:

- Ongoing post-dural puncture headache (PDPH). PDPH is caused by a persistent CSF leak from the lumbar drain site of insertion, is positional (worse when positioned upright), and can be associated with diplopia and tinnitus. Normally, PDPH lasts only a few days. PDPH treatment involves providing analgesia, rest and hydration, IV caffeine administration, and a "blood patch", which is the most effective treatment.
- Excessive CSF drainage via the lumbar drain itself.
- Transient[8] tinnitus or double vision.
- Back or neck pain, typically transient.
- Transient lower limb abnormal symptoms, e.g. weakness, numbness and radicular pain.

d. Very common:

- PDPH that is self-limiting and does not require a blood patch.
- Nausea, vomiting, malaise, dizziness.

Specific points of interest from the selected reviews published within the last 5 years.

Otolaryngology–Head and Neck Surgery 2007;137:316-20.

- Informed consent is required because of the off-label use of fluorescein. Multiple adverse events have been sporadically attributed to its use, including seizures, transient paresis, and neuropathic pain. The reported incidence of complications remains extremely low and some authors have described higher rates in patients receiving higher or more concentrated doses. The pathophysiology of these events remains incompletely defined but may be secondary to meningeal inflammation.
- In patients undergoing planned lumbar drainage, the CSF is obtained following drain placement and the drain is clamped following fluorescein injection. The IT injection stains the CSF that is already in circulation. A slow intravenous injection of 25 mg of fluorescein mixed with 3 mL of normal saline is also performed prior to surgery to stain new CSF generated by the choroid plexus during the procedure to prevent dilution. Endoscopic visualization of the fluorescein-stained CSF is performed throughout the surgery with either white light or a blue light filter (465-495 nm) with a blocking filter (515-555 nm)
- To assist resolution of post op CSF leak patients had conservative management for 5 days consisting of lumbar drainage, head-of-bed elevation, and stool softeners.

Neurosurgery 2007;61:161-6.

- Given that the typical duration of the exposure portion of the surgical procedure is 1 hr, fluorescein is given approximately 1 hr before its visualization. CSF leak repair can involve abdominal fat and fascia lata grafts from the patient.
- Etiologies for fluorescein-related symptoms include chemical meningitis, bacterial contamination, or subarachnoid hemorrhage. The authors failed to find any evidence that previously reported side effects were the result of bacterial contamination or subarachnoid blood. Instead, it seems that the more likely explanation for the previously reported complications may be chemical irritation of the meninges.
- Although the use of IT fluorescein is generally considered safe, reports have described infrequent but severe complications, including seizures, radicular symptoms, and lower extremity numbness and weakness, or paraparesis (partial paralysis of the lower limbs), hemiparesis (paralysis of one side of the body), and cranial nerve palsies. The dosages of fluorescein varied in these reports, and patients were not

always premedicated to avoid a reaction to the drug

- The authors describe some of the most common postoperative symptoms as: malaise (~57%), headache (~52%), dizziness (~31%), and nausea or vomiting (~24%). Four patients (7.4%) experienced postoperative fevers. There were no seizures. A few patients reported lower extremity weakness (13%) or numbness (3.7%).
- Of note, all patients who reported lower extremity symptoms were able to ambulate at levels comparable to their preoperative status and their neurological examinations failed to yield any objective findings (i.e. all "persistent" neurological symptoms were actually subjective). The majority of the symptoms are transient and dissipate over a period of several days. In one-third of the patients with postoperative tinnitus, the symptoms persisted on a chronic basis.

TABLE 3. Symptoms and their duration in 54 patients receiving intraoperative fluorescein

Symptom	No. of patients	No. of symptomatic patients with transient symptoms	No. of symptomatic patients with persistent symptoms	Duration of transient symptoms (d, mean ± standard error)
Malaise	31 (57.4%)	26 (83.9%)	5 (16.1%)	12.3 ± 2.1
Headache	28 (51.9%)	23 (82.1%)	5 (17.9%)	16.8 ± 3.9
Dizziness	17 (31.5%)	15 (88.2%)	2 (11.8%)	8.5 ± 1.9
Nausea/vomiting	13 (24.1%)	12 (92.3%)	1 (7.7%)	2.0 ± 0.4
Back pain	10 (18.5%)	6 (60.0%)	4 (40.0%)	13.0 ± 5.1
Lower extremity weakness	7 (13.0%)	5 (71.4%)	2 (28.6%)	8.8 ± 3.2
Tinnitus	6 (11.1%)	4 (66.7%)	2 (33.3%)	17.3 ± 5.5
Neck pain	6 (11.1%)	6 (100.0%)	0	7.3 ± 2.3
Fever	4 (7.4%)	4 (100.0%)	0	1.3 ± 0.3
Lower extremity numbness	2 (3.7%)	0	2 (100%)	
Seizures	0 (0%)	0	0	

- It is difficult to distinguish between side effects attributable to the surgery and those attributable to fluorescein. The authors believe that the majority of nonspecific adverse events, including malaise, headache, fever, nausea, and vomiting, can be attributed to the nature of the procedure performed rather than the fluorescein. For example, transient back and neck pain are more likely a result of positioning in the operating room, and back pain may be caused by the presence of the lumbar drain as well. Moreover, because the fluorescein-related side effects disappear within a few days it is unlikely that the chronic cases of tinnitus and back pain are related to fluorescein. Instead, they are more likely the result of side effects from the endonasal portion of the procedure and lumbar puncture, respectively.

Acta Otorhinolaryngol Ital 2008;28:159-63.

- Great literature review on history of technique.
- Severe complications are always related to the direct irritant action of fluorescein by way of chemical meningeal trauma due to overdose of the stain.
- There were 7 cases of major complications reported out of 420 cases total, including one death. All these complications appeared to be related to errors in dosage. The higher the dose, the higher rate of complications is.
- Most of the serious and other complications occur with large (≥ 500 mg) or relatively large doses (e.g. 100 mg). It can, therefore, be assumed that a dose of fluorescein less than or equal to 50 mg should be safe. The safety is further enhanced by the dilution of the fluorescein in CSF, and slow fluorescein administration. It may be worthwhile pointing out that exceptional cases have been reported such as that described by Moseley et al. in 1978, where lower extremity weakness and numbness, cleared within 48 hours, was observed after intrathecal administration of only 25 mg of fluorescein.

Table I. Major publications on intrathecal administration of fluorescein with doses less than or equal to 50 mg.

	Intrathecal fluorescein ≤ 50 mg total dose	
Authors Year of publication	No. cases treated	Specific serious complications
Moseley et al. 1978	1	1 transient
Lanza et al. 1996	25	0
Wolf et al. 1997	250	0
Guimaraes and Becker 2001	23	0
Lund 2002	6	0
White et al. 2003	13	0
Keerl et al. 2004	420	2 transient ***
Meco and Oberascher 2004	900	0
Lindstrom et al. 2004	10	0
Silva et al. 2006	24	0
Locatelli et al. 2007	135	1 transient (cause unclear)
Demarco et al. 2007	18	0
Placantonakis et al. 2007	54	0
Tabaee et al. 2007	61	0
	1940	

*** 100 mg fluorescein and simultaneous intrathecal administration of radiographic contrast medium

- As far as IV administration of fluorescein is concerned, many adverse reactions have been reported, with 13 deaths, but only one major complication leading to death after a simple local lacrimal application. Obviously, these data are related to a very large number of treated cases and are not comparable to those obtained from the IT administration of the stain.

Anesth Analg 2008;107:229-31.

- The authors discussed the risks such as infection, bleeding, neurologic injury, arachnoiditis, and PDPH, with the administration of 50 mg dose of fluorescein in total of 10 ml volume (0.5 ml of 10% fluorescein solution, plus 9.5 ml of CSF).
- Fluorescein-related complications are extremely rare, and should be considered a diagnosis of exclusion.
- Complications are most likely due to meningeal irritation – aseptic meningitis.
- Fortunately, most fluorescein-induced neurologic complications are reversible and typically resolve within 7–10 days.
- Limited evidence suggests that fluorescein injection in patients with a history of seizures, hydrocephalus, spinal stenosis, acute brain injury, cerebral edema, or other neurologic conditions be avoided.
- Symptoms signaling an adverse event can occur as late as 12hours post-IT injection, so patients should have at least 12hours of neurological observations and “seizure precautions”.

Acta Otorhinolaryngol Ital 2009;29:191-6.

- Fluorescent-mediated complications are dose related and transient; can include headache, nausea and vomiting, dizziness, nuchal pain, lower limb weakness, numbness, generalized seizure activity, opisthotonus and cranial nerve deficit.

Otolaryngology–Head and Neck Surgery 2010;143:626-32.

- Most advocate the placement of a lumbar drain at the onset of the surgical procedure.
- The authors of multiple large series demonstrate an acceptable safety profile of IF at low doses (< 50 mg);

however, described complications of seizures, radicular symptoms, and transient paresis and hemiparesis may still occur, warranting detailed preoperative discussion and informed consent from the patient.

Int Forum Allergy Rhinol 2011;1:173-7.

- Typically, the lumbar drains are removed at the 3 day mark (as per normal epidural catheters), but should be removed at the earliest possible juncture.
- Complications from the use of lumbar drains may occur in 5-10% of patients, but no complications could be attributed by the authors to IT fluorescein use.
- Inadvertent CSF overdrainage may lead to pneumocephalus, neurological decline, and even uncal herniation in extreme cases.

Otolaryngol Head Neck Surgery 2012; 147:196–203.

- Fifty-five studies, involving 1778 fistulae repairs, were included for analysis. Spontaneous CSF leaks were most prevalent, with the ethmoid roof and sphenoid the most common sites involved. The overall success rate of repair was high at 90% for primary and 97% for secondary repairs.
- A low, fluorescein-specific complication rate of less than 0.03% was reported.

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1. Intrathecal fluorescein via a single injection through a spinal needle in cases where a lumbar drain is not needed, but IF would be desirable, is an alternative. This minimizes risks of headache and infection, or of other catheter-related complications (Int Forum Allergy Rhinol 2011;1:173-7). The patient must be cooperative as the needle will be in situ for a few minutes, but through understanding the risks they are avoiding, the motivated patient will be keen to remain still for the duration.
2. Acta Otorhinolaryngol Ital 2008;28:159-63; Otolaryngol Head Neck Surgery 2010;143:626-32; Int Forum Allergy Rhinol 2011;1:173-7, Otolaryngol Head Neck Surgery 2012;147:196-203. Less likely to cause adverse outcomes if:
    - </=50mg fluorescein (less is best! 10mg is smallest dose I've seen claimed effective, whilst 10-25 mg is most quoted dose)
    - Further dilution of the fluorescein in CSF
    - Slow administration (e.g. over 30 min in one paper)
3. Acta Otorhinolaryngol Ital 2009;29:191-6; Otolaryngol Head Neck Surgery 2010;143:626-32.
4. Osmolality of 10% fluorescin sodium solution is 572-858 mOsm/kg (~650), such that the final 0.1-0.25% solutions for 10-25 mg/10 ml, have a osmolality of 6.5-16.25 mOsmo/kg, which is minuscule, i.e. to avoid a hypo-, or hyper-osmolality solution, it would probably be best to mix with CSF, or normal saline.
5. Anesth Analg 2008;107:229-31.
6. Otolaryngol Head Neck Surgery 2010;143:626-32.
7. Anesth Analg 2008;107:229-31.
8. Anesth Analg 2008;107:229-31; Neurosurgery 2007;61:161-6. Most fluorescein-induced neurologic complications are reversible, and typically resolve within 7–10 days.

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