

Using Fluorescein Sodium for Real-time Identification of Cerebrospinal Fluid Leaks in Saline. (Under NDA)

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Background

Saline irrigation is used to flush debris from the surgical site as well as cool surgical tools and free them from bioburden, keeping them sharp. This allows for longer and more aggressive use of the tools, like in Figure 1, while also minimizing burning and bleeding from the patient. Cerebrospinal fluid (CSF) and saline look similar. This means if a CSF leak in saline occurs a surgeon may not be able to identify it causing post-op issues. Unrecognized CSF leaks occur in 6.8% of spinal surgeries. Current CSF leak identification methods include Computed Tomography, Magnetic Resonance Imaging, and Beta-2-Transferrin assay, which are all typically done outside of the operating room and take a while for results.



Figure 1: Stryker irrigation sleeve.

Problem Statement

Stryker has received feedback that surgeons will opt out of using irrigation, which is needed for longevity of their tools, to prevent missing a CSF leak. To address this issue Stryker has asked us to find a detection method to differentiate CSF leaks from saline irrigation during spinal neurosurgery.

Objectives

To ensure this design is successful, the following objectives will be considered:

- CSF leaks must be detected in 5 sec
- Design must function with an existing Stryker device
- Accuracy of CSF detection >90%
- Design must introduce less risk to the patient than an undetected CSF leak

Constraints

They key constraints of this project are:

- Final design completed by April 2026
- Design cost <\$100 for single use product
- Design cost <\$10,000 for add on device
- Drug benefits must outweigh the risks per FDA section 21 CFR part 320.21
- Testing must use CSF and blood substitutes

Design Alternatives

AI Detection

This alternative would train an AI algorithm on images of WBC's present in CSF. The AI would then be used to search for the WBC's in a sample from the surgical site under a microscope.

Intrinsic Factor Based B12 Biosensor

A biosensor using B12 as the analyte and Intrinsic Factor as the bioreceptor can differentiate CSF and saline. B12 is found in high concentrations in CSF but can also be found in blood. The time for detection and accuracy are the design's biggest flaws given current technology.

Biosensor with Beta-2-Transferrin Analyte

Like the previous design, this alternative would utilize a biosensor, however it would utilize beta-2-transferrin as the target analyte. Beta-2 is specific to CSF which ensures high true positive testing rates. This biosensor would be implemented into an onsite waste management device and would require expensive research with anti-transferrin.

SWIR Fluorescence

Short Wavelength infrared (SWIR) fluorescence is a method used in fluorescence guided surgery as well as other biomedical applications. This allows some differentiation between CSF and saline, however the contrast between the two is low, making accuracy a weakness.

Fluorescein Sodium Intrathecal Injection

Fluorescein sodium is an orange compound that fluoresces a neon green when mixed with clear liquids. It has been used in the spine during experimentation and has relatively low toxicity. Because this design is an injection, it brings a high to patients in comparison to the other alternatives.

Selected Design

The final selected design is the fluorescein sodium intrathecal injection. This design showed instant detection time, high contrast with the environment, and a smaller risk compared to an undetected CSF leak. Testing has also shown strong promise in this design's differentiation ability.

Testing

Test 1: Baseline Concentration Test Procedure:

1. Mix water and fluorescein sodium salt to create a 10% concentration solution

2. Observe color under ambient light with and without the blue light on, then with just the blue light on
3. Rate the intensity of fluorescence on a scale of 1-5 (1 being the worst)
4. Continued this process with lower concentrations until fluorescence scores began to drop in intensity.

Results:

Table 1: 0.001% concentration under various lighting scenarios

Concentration	Lighting Conditions		
	No Ambient / Blue ON	Ambient / Blue ON	Ambient / Blue OFF
0.001% (499.995g H2O / 0.005g NaFluo)			

Test 2: Saline-Only Leak Simulation

Procedures:

1. Used data collected from the concentration testing to test 0.001% and 0.003%.
2. Pour 150 mL of the fluorescein solution into a latex glove, tie it up, and placed it in a clean white bin.
3. Cut into the glove so the fluorescein solution is flowing out at a steady rate, observe how visible it is both in a saline bath and with saline irrigation.

Results:

Table 2: 0.001% concentration results for leak simulation

Time	Saline Irrigated	Saline Bath
1s		
5s		
10s		

Test 3: Blood Inclusion Simulation

Procedure:

1. 0.001% and 0.003% concentrations are used as they were most visible in saline.
2. Pour 150 mL of fluorescein solution into a latex glove, tie it up, and place in the testing bin.
3. Mix 40% glycerin and 60% water with red food coloring to simulate blood.

4. Cut into the glove and observe how the visible the solution is when in a saline/blood bath, with blood and saline irrigation, and with just blood.

Results:

Table 3: 0.001% concentration results for blood inclusion simulation

Time	Blood and Saline Irrigated	Blood/Saline Bath
1s		
5s		
10s		

Final Design

After testing the chosen recommended concentration was 0.001%. To use fluorescein sodium injection, the following administration procedure should be followed.

Immediately before surgery:

- Administration of fluorescein sodium via lumbar puncture.
- Withdraw 10 mL of CSF from patient
- Mix 1.5 mg of fluorescein sodium with withdrawn CSF.
- Slowly reinject the solution back into the intrathecal space over 1 min.
- Have patient lie in 10% Trendelenburg position for 30 min.

Surgical preparations can then continue as normal. During surgery when operation begins near the spinal cord the surgeon can turn on the blue excitation light device and search for CSF leaks. If a CSF leak is present, it will fluoresce neon green under the blue light allowing for detection and location of the leak.

Safety Evaluation

Although intrathecal fluorescein sodium injection is considered an off-label use, it can still be used if specific consent is granted from the patient after disclosing all known risks.

There is potential in FDA approval per section 21 CFR 320.21, as all drug benefits outweigh the risks.

Studies have shown that use of intrathecal fluorescein sodium injection is:

- Safe in doses <50mg.
- Causes transient complications in 1.6% of patients.

Unrecognized CSF leaks can:

- Cause headaches, nausea, blurry vision, muscle weakness, and spinal pain.
- Increase risk of fatal complications like injury, meningitis, and subdural hematomas.

As complications from unrecognized CSF leaks are proven to have fatal complications, while there is no evidence that intrathecal fluorescein sodium injection does <50mg, we can say that this method would theoretically reduce risk to the patient.

Economics

Table 4: Costs per surgery

Component	Cost
Fluorescein Sodium	\$0.0008
Adult Lumbar Puncture Tray	\$51.49

Table 5: Costs for device redesign

Component	Cost
Redesign	\$1,000
470 nm LED Blue Light	\$0.68

Select References

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