

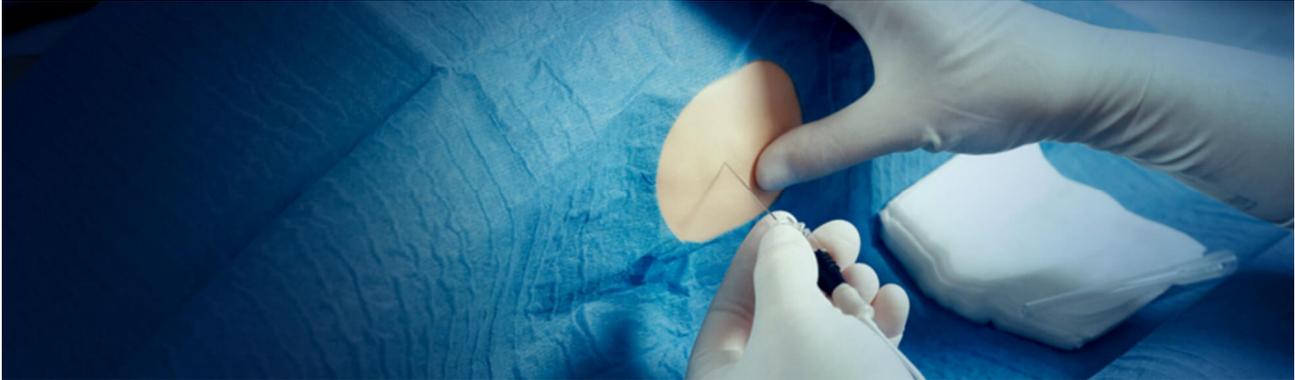
Clinical applications for the IQ-Tip® system and their potential benefits

Injeq Oy

Injeq IQ-Tip® system, comprising the analyzer, spinal needle and cable, is a smart solution for lumbar punctures. Based on bioimpedance detection it gives an alarm when the needle tip detected cerebrospinal fluid.

This whitepaper takes a closer look at the lumbar puncture, the IQ-Tip® system's first indication, and presents the results that Injeq has obtained with the system. We discuss the various advantages that the system provides compared to a conventional spinal needle.

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Background

Lumbar puncture (LP) permits a unique window to examine the state and physiology of the central nervous system (brains and spinal cord) through proper laboratory analyses of cerebrospinal fluid (CSF) drawn from the spinal canal – and be it noted, not only a window but also a door to administer the medication directly to the central nervous system. With multiple indications for diagnostics, intrathecal therapy, or spinal anesthesia, LP is a standard clinical procedure from preterm neonates to the oldest old – tens of million procedures performed annually throughout the world. Despite the enormous progress and development in the field of medical technology and imaging modalities, it is yet unforeseeable that any other technology will soon replace this more than 100 years old¹, proven method as the clinical method of choice.

LP is basically quite a straightforward procedure to perform, it requires only a simple spinal needle, provider, and aseptic technique. The challenge of LP resides in the target – CSF in the spinal canal, which is surrounded by the lumbar vertebral structures and is only accessible through narrow spaces between the spinous processes. The provider cannot see where the tip of the advancing needle is but has just to blindly rely on anatomic knowledge, haptic feeling from the needle tip, and previous experience in performing LPs.

Injeq IQ-Tip® system

The IQ-Tip® system, based on real-time bioimpedance spectroscopy, is a step forward in performing LPs. The system tells the provider with high reliability when the needle tip has reached CSF and the needle tip is in the correct place for drawing the CSF sample or injecting the medicine into the patient's spinal canal.

The quality of the CSF sample is crucial both for diagnostic accuracy and for reducing health risks that may arise either from diagnostic uncertainty or tissue trauma causing blood leakage into the spinal canal. High quality means there are no red blood cells

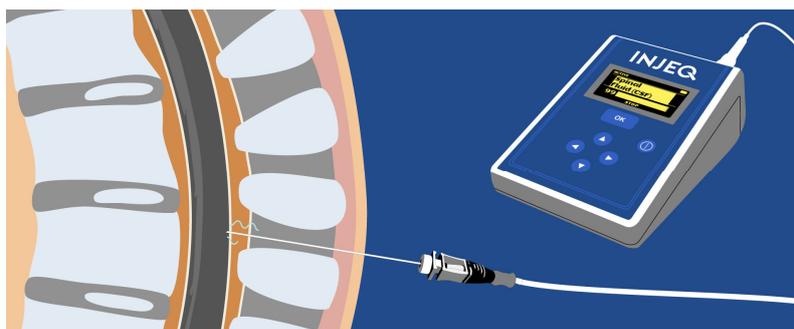
(RBC) in the CSF sample except for the true subarachnoid hemorrhage in the central nervous system, which is a life-threatening situation. However, traumatic lumbar punctures (TLP), meaning that there is a certain RBC concentration in CSF (e.g., 400 – 500 RBCs/μL), are frequent in clinical practice compromising about 40 % of LPs in neonates², 24% of LPs in children³, and approximately 15% LPs in adults⁴. Although not indicating immediate emergency, TLP may compromise or delay the patients' diagnosis and possibly weaken their prognosis, or in the case of acute lymphoblastic leukemia (ALL), blast cells along with blood leakage may enter the spinal canal and later turn into cancer of the central nervous system⁵. Using a much stricter criterion (10 RBC/μL), the incidence of TLP varies between 12% – 38% in children with ALL^{6,7}.

Given the anticipated improvements in the success rate of LPs in pediatric patients with ALL and neonates with suspected meningitis, these two patient groups were chosen as the primary target groups for the IQ-Tip® system. Clinical investigations have been conducted earlier in both patient groups with promising results^{8,9}. Below the potential benefits from the clinical use of the IQ-Tip® system are shortly speculated. In addition, intrathecal therapy of rare diseases offers a potential clinical application for the IQ-Tip® system.

Acute lymphoblastic cancer

ALL is the most common malignancy diagnosed among children showing the peak incidence around 3 – 6 years of age. The incidence of ALL is about 30 – 60 cases per million children aged no more than 15 years old, depending on the geographic region¹⁰. In Finland, there are about 50 new diagnosed pediatric cases with ALL every year¹¹. In developed countries, long-term event-free survival rate and full recovery ALL is high, about 90% or more^{12,13,14}.

However, the probability of event-free survival is lower if the CSF is contaminated by blasts. Approximately half of the TLPs contain blasts. According to the study by Shaikh et al.¹⁵, a poorer prognosis (i.e., relapse, another malignancy, or death) concerns



Injeq IQ-Tip system provides immediate CSF detection after the dura matter is penetrated

approximately two out of 10 patients, who had had blast-contaminated TLP in their intrathecal treatment LPs.

Results with IQ-Tip® system

Based on electronic health record data from two Finnish university hospitals, about 30% of LPs had been traumatic¹⁶. This means that 15% of CSF samples may contain blasts and indicate thus a poorer prognosis. Reflecting these numbers to 50 new annual cases in Finland, this would mean 1 – 2 patients every year who would have a poor long-term recovery because of blast-contamination to CSF. Speculatively, if we were able to halve the incidence of TLP in pediatric patients with ALL, as our recent clinical investigation with the IQ-Tip® system suggests⁹, one child with ALL might survive without malignant events.

Apparent reduction in the incidence of the post-dural puncture headache (PDPH) is another very promising finding from our clinical investigation⁹ (see the table below). PDPH is a common complication of lumbar punctures and it occurs in all patient groups. PDPH is typically defined as debilitating headache that greatly worsens when sitting on standing, thus confining the patient to a bed rest. The pathophysiology of PDPH is not completely understood. However, it is well known that a puncture of the dura matter allows CSF leakage and decreased CSF pressure and volume¹⁷.

It is reasonable to assume, that the immediate detection of CSF provided by the IQ-Tip® system helps in the prevention of PDPH. The CSF detection allows the physician to minimize the unnecessary needle tip movement and prevents accidental perforations of the anterior dura matter.

Common LP complications. The use of IQ-Tip® system appears to halve the incidence of two common LP side-effects.

	TLP ^A	PDPH ^B
Pediatric ALL patients	32 % ¹⁶	13 % ¹⁸
Other pediatric	48 %	
Adults	~35 % ¹⁹	24 % ¹⁷
IQ-LP-03	17 %	6 %

A) traumatic lumbar puncture, ≥ 10 RBC/ μ L

B) with comparable needle type

Since the patient's treatment protocol of ALL is nowadays based on individual risk assessment²⁰, a lower incidence of TLP may alleviate the patient's risk and thus avoid unnecessary intrathecal chemotherapy and reduce the burden on the patient. Depending on the individual risk classification, the intrathecal therapy comprises from 5 to 21 LPs at the different phases of treatment protocol. The first puncture success rate of the IQ-Tip® system was 80%, and when this happened the incidence of TLP was only 11% in our clinical study. This also speaks for the apparent clinical utility of this system.

Neonatal meningitis

Incidence of neonatal meningitis is relatively low (about three cases per 10000 live births), but it is yet one of the major causes of neonatal mortality in developed countries. LP complemented by cytometric analysis and culture of the CSF sample provide the standard diagnostic procedures not only for neonatal meningitis but also for neurological (e.g. status epilepticus²¹) and metabolic diseases of small patients.

Nontraumatic LPs are essential for reliable diagnoses and distinguishing between bacterial and viral conditions of meningitis. Precise knowledge of the disease would help physicians make timely and proper treatment decisions to manage the severe and potentially life-threatening conditions of small patients. Uncertainty and delays in proper diagnosis may turn critical and lead to prolonged intensive care and extra costs. One day in intensive care costs about 3500 euros.

Intrathecal therapy of rare diseases

During the last decade, there has been substantial progress in the development of intrathecal gene and enzyme replacement therapies for rare neurological diseases, such as spinal muscular atrophy (MSA), Huntington's disease, Hunter's syndrome, and metachromatic leukodystrophy (MLD). The incidences of these diseases are around one per 100,000 births and the conditions do not necessarily become evident not earlier than at the age of a year or two. Medicines for these diseases can be very expensive. For example, one intrathecal injection of nusinersen for MSA costs up-to 80,000 euros while several injections may be needed each year. Therefore, all possible options to perform these injections as optimally as possible should be considered. Obviously, the IQ-Tip® system is one of these options.

Investigations of neurological disorders in adults

As the populations around the world are ageing, the clinical need for diagnostic LP is likely to increase. In adults, common diagnostic indications for LP pertain to inflammation of central nervous system manifest as various forms of meningitis,^{22,23} neurological diseases and conditions,^{24,25} such as Alzheimer's disease,^{26,27,28} Parkinson's disease,²⁹ multiple sclerosis,³⁰ autoimmune encephalitis,³¹ epileptic seizures,³² memory concerns,³³ and altered mental status,³⁴ as well as to differentiation of subarachnoid hemorrhage (SAH).^{35,36}

Conclusions

Injeq IQ-Tip® system represents state-of-the-art in lumbar punctures. The system is a great resource for any physician when high first puncture success rate and low probability of blood contamination and post-dural puncture complications are desired.

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