ADVERTORIAL

IRRA*flow*: A new innovative fluid management system to treat intracranial bleeding

A conversation with neurosurgeon, Dr Christos Panotopoulos

Globally, strokes claim a life every 10 seconds, and it is estimated that, every two seconds, someone somewhere in the world has a stroke (Global status report on noncummunicable diseases, 2011).[1] Every year, approximately 25 million strokes occur globally, making stroke the second leading cause of death for people above the age of 60 (Benjamin, 2018).[2]

These strokes can be broken down into two basic categories, ischaemic stroke and haemorrhagic stroke. Ischaemic stroke, or obstructions that disrupt blood flow to the brain, account for approximately 85% of all strokes (Benjamin, 2018). Haemorrhagic strokes, the second category of stroke, occur when a weakened vessel ruptures and bleeds into the brain. While these haemorrhagic bleeds occur less frequently and only account for 15% of all strokes, they do have higher morbidity and mortality, resulting in 40% of all stroke deaths (Mracsko & Veltkamp, 2014).[3]

Over the past decades, significant innovations have been introduced to treat ischaemic stroke. For example, clot removing devices (thrombectomy) have become the standard of care in acute brain ischemia. For the majority of haemorrhagic stroke cases, though, innovation has been more limited. Apart from coils and flow diverters used for intracranial aneurysms, non-surgical treatment, combined usually with invasive intracranial pressure (ICP) monitoring and passive cerebrospinal fluid (CSF) drainage, remains the standard of care. Despite being the typical treatment option for most intracranial bleedings, these passive techniques are associated with a list of well-documented complications, including occlusions, infections, excessive drainage, and secondary haemorrhage (Lele AV, 2017).[4]

Recently, new research and product development have started to focus on advancing the care of neurocritical patients with haemorrhagic bleeds. The MISTIE and CLEAR clinical trials have attempted to substantiate whether more rapid blood removal, after intracerebral or intraventricular haemorrhage, can improve patient outcomes (Hanley, 2016), (Hanley, 2017).[5,6] New technologies are now also bringing a proactive, therapeutic mentality to treating these patients.

IRRAS is an example of a cutting-edge company that is focused on bringing innovative technology to therapeutically treat haemorrhagic stroke. The company's first product, IRRA*flow*®, is an intracranial fluid management system that was recently FDA-cleared for use in the United States. IRRA*flow* provides an active, controlled fluid exchange system to therapeutically treat haemorrhagic events and is indicated for ICP monitoring and drainage of any intracranial fluid.

Dr Christos Panotopoulos

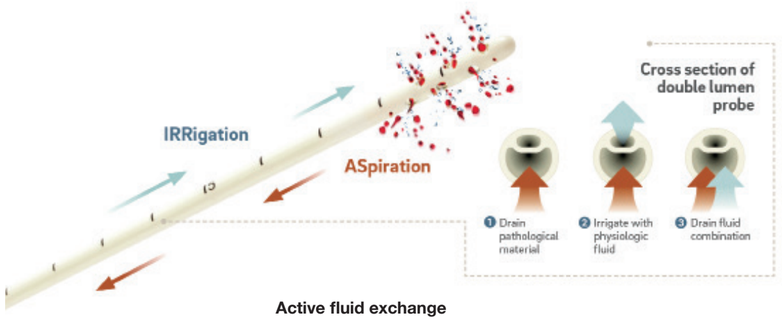
NeuroNews recently spoke with Dr Christos Panotopoulos, the inventor of IRRA*flow*, about this exciting new treatment option, the need for such advancement, and his experience to date with the system. Dr Panotopoulos currently serves as a Special Advisor to IRRAS in addition to his duties as a Senior Consultant Neurosurgeon and Head of Neurosurgical Research at Mediterraneo Hospital in Athens, Greece, BRAINS-Sparsh Hospital and BRAINS Advanced Institute of Neurosciences in Bangalore, India.

Why did you invent the IRRA*flow* system?

The IRRA*flow* system was built around the concept of active, controlled fluid exchange, based on the fact that it is faster to wash out any pathological extracellular fluid collection, as we do during open surgery, than expect it to be evacuated by gravity alone.

IRRA*flow* combines periodic, controlled irrigation and aspiration of the catheter probe in order to exchange any pathological fluid collection with neutral physiological fluids. This system's fluid exchange, by design, cleans the entire inner catheter probe's surface while the fluid movement helps to disrupt potential clot or bacteria colony formation on the catheter probe's intracranial external surface, thereby eliminating the underlying reasons for the problems associated with passive drainage: blockage and infection.

Moreover, when this fluid irrigation is combined with efficient drainage and continuous, reliable ICP monitoring that includes safety alarms, a process of active controlled fluid exchange occurs. This fluid exchange offers several advantages over historic treatments for evacuation of extravasated intracranial blood. Extravasated blood follows the intracranial path of least resistance and adheres firmly to the brain parenchyma and meninges, away from the neurosurgeon's optical field, thus resisting surgical efforts to remove it efficiently without further damaging brain tissue during an operation. Passive drainage, such as today's standard of care, the external ventricular drain (EVD), is inherently inefficient because of its inability to overcome this clot adhesion. Active irrigation of the catheter helps to enhance the ability to dilute and remove this collected blood for a much longer period than can be performed during an open craniotomy.



Active fluid exchange

When collected blood is not removed sufficiently, it can have other debilitating effects as well. In patients with subarachnoid haemorrhage due to a ruptured intracranial aneurysm, vasospasm is a major contributor to morbidity and mortality and has been reported to occur up to 30% of the time (Ota, *et al*, 2017).[7] The cause of this vasospasm is irritating by-products of the extravasated intracranial blood, which, as discussed, resists all surgical evacuation efforts. The fluid exchange principle has been shown in early clinical experience to have excellent efficiency in the most severe of these cases, which can result in optimal clinical outcomes (Venkataramana, *et al*., 2012).[8]

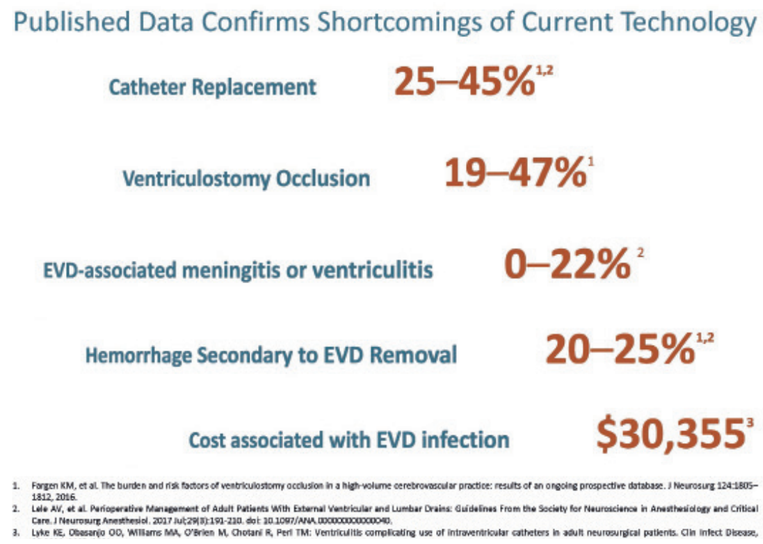
What are some of the issues that you referenced earlier with historic treatment approaches?

Drainage efficiency, blockage, infection and safety. As previously mentioned, during an open craniotomy and associated clot removal, the neurosurgeon cannot access all of the places that extravasated blood migrates intracranially. When he or she does have direct vision, there is an obvious need not to further damage the brain structures during the blood removal, which compromises the effort. EVDs, on the other hand, rely only on gravity and intracranial pressure. As a result, EVD's generally need a lot of treatment time for the evacuation of a clinically significant blood volume and often leave enough volume of residual blood to create secondary adverse effects, like hydrocephalus. It is also well established in bibliography that the treatment duration of haemorrhagic stroke patients is inversely related to their clinical outcome (Sam, Lim, Sharda, & Wahab, 2018).[9]

Extravasated blood is highly viscous and sticky even when diluted with cerebrospinal fluid, resulting in occlusive material forming at the EVD catheter's tip. These occlusions have been shown to occur up to 40% of the time (Fargen KM, 2015).[10] When these catheter occlusions do occur, needed drainage is compromised, preventing fluid and debris from being removed. If an EVD cannot provide an adequate relief of pressure, rising ICP can lead to further severe neurological damage or death.

Therefore, in any neuro ICU, we inject either saline or a thrombolytic medication to unblock the catheter. This manual flushing increases the risk of infection by opening the closed, sterile system and potentially introducing external bacteria. EVD-associated infections are a well-documented risk and have been shown to impact up to 20% of all placed EVDs (Lele AV, 2017). If this flushing process does not work, then the catheter must be removed, and a new one must be introduced. Studies have demonstrated that, when an EVD is replaced, the risk of secondary haemorrhage increases by 66% (Fargen KM, 2015). Hence, with existing technology, we are subjecting the patient to multiple interventions, increased risk of infection, and unsuitably poor outcomes.

Lastly, a major problem with EVDs is that we do not have any safety control on pathological fluid outflow rate other than periodically having somebody manually check the patient's ICP, visually check the amount of drained fluid, and make the needed changes to the height of the drainage collection bag. As a result, underdrainage, where therapy is compromised and prolonged, overdrainage, which can cause problems such as ventricular collapse or secondary intracranial bleeding, and catheter blockage, with the above-mentioned deleterious patient effects, might be detected with a harmful or even fatal delay for the patient.



IRRA*flow* Control Unit

How does the IRRA*flow* system address these issues?

The efficiency of the fluid exchange concept for the evacuation of intracranial extravasated blood has been demonstrated with the IRRAflow system and its previous embodiments in more than 100 patients in Greece, India, Sweden, Germany, and Finland with subarachnoid, intraventricular, intraparenchymal, and subdural haemorrhages. In these cases' experience to date, treatment times were much shorter and post-treatment residual blood volumes were less than expected by the treating neurosurgeons (Venkataramana, *et al*., 2012), (Data on File at IRRAS).[11] This increased drainage efficiency can most likely be attributed to the gradual and continuous dilution of the pathological intracranial fluids by irrigating the catheter with physiological fluids as well as the continuous pressure fluctuations inside the pathological collection, which are created by the appropriate irrigation patterns. Both these factors are well known to everybody who has ever tried to wash anything.

By design, the IRRA*flow* catheter probe is irrigated regularly in a way that essentially guarantees its patency. Catheter blockages are theoretically impossible since any material build-up at the catheter's tip is washed away during the next irrigation phase, which will occur in, at most, a couple of minutes. Additionally, the volume and flow rate of each irrigation is such that the length of the IRRA*flow* catheter probe's outer surface is washed by backflow, thus potentially eliminating the chance for any bacterial colonisation (Data on File at IRRAS). On top of this, the skin's point of catheter entry is isolated from the environment by a special "dome" filled with antiseptic cream and sutured securely in place.

To date, in the early European clinical experience, probably because of these underlying design elements, there have not been any documented blockages or probe-associated infections detected in any IRRA*flow* treatment. This was also the case in the previous embodiments during the development of our fluid exchange principle (Venkataramana *et al* 2012). The growing problem of bacterial resistance in Neurosurgical Intensive Care Units and the above characteristics and clinical performance of IRRA*flow*, are the reasons for the absence of antibiotics inside the construction material of the IRRA*flow* catheters.

As for safety, IRRA*flow* also automatically, reliably, and continuously monitors ICP and alerts hospital personnel with visual and sound alarms immediately when the patient's ICP is out of the pressure range set by the treating neurosurgeon, which eliminates any delay in detecting under or over drainage and any treatment's compromise.

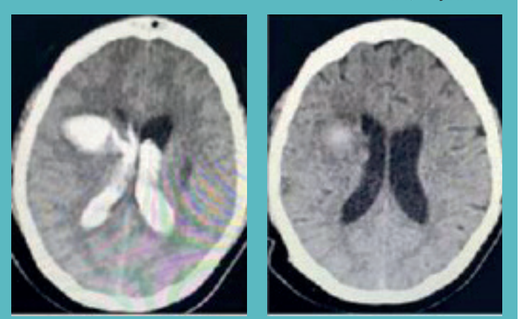
Case Review:
Intraventricular haemorrhage

Male, 18 years old

Pathology treated
- Intraparenchymal and intraventricular haemorrhage due to hypertension

Treatment description
- IRRAflow catheter probe inserted
- Active fluid exchange performed for 27 total hours

Treatment result
- Patient stabilised, returned to regular ward, discharged to rehab
- No drainage occlusions seen
- No infection seen



Pre-IRRA*flow* treatment | Post-IRRA*flow* treatment

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Dr Christos Panotopoulos, *MD, Ph.D., has been a practicing neurosurgeon and clinical researcher for the last 25 years in Greece, France, Sweden and India and has created several inventions and patents including IRRAflow. Dr Panotopoulos founded IRRAS AB in 2012, served as its Chief Medical Officer and Director until May 31, 2018 and as a Special Advisor & Member of Clinical Advisory Board since June 1, 2018. Furthermore, he is the Founder and Director of INDERES Ltd, a company which is active in brain cancer and brain trauma research since June 2018.*