Continuous Intrathecal Medication Delivery With the IRRA*flow* Catheter: Pearls and Early Experience

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BACKGROUND AND OBJECTIVES: Intrathecal (IT) medications are routinely introduced through catheterization of the intraventricular space or subarachnoid space. There has been sporadic use of IT medications delivered directly to the ventricle either by intermittent injection through an external ventricular drain (EVD) or by an Ommaya reservoir with a ventricular catheter. IT medication delivery through EVD has many drawbacks, including the necessary opening of a sterile system, delivery of medication in a bolus form, and requirements to clamp the EVD after medication delivery. Despite these setbacks, IT medications delivered through EVD have been used across a wide range of applications, including antibiotic delivery treatment of vasospasm with nicardipine and delivery of tissue plasminogen activator.

METHODS: We used a newly developed active fluid exchange device to treat various severe conditions involved in the cerebral ventricles. Here, we present our treatment protocols and advice on the techniques related to successful active fluid exchange therapy.

RESULTS: Seventy patients have been treated with our system with various conditions, including subarachnoid hemorrhage, intraventricular hemorrhage, ventriculitis, and cerebral abscess. Total complication rate was 14% with only 1 catheter occlusion and low rates of hemorrhage, infection, and spinal fluid leak.

CONCLUSION: Current continuous IT medication dosages and protocols are based on reports and consensus statements evaluating intermittent instillation of medication boluses. The pharmacokinetics of continuous dosing and the therapeutic and safety profiles of the medications need to be studied in a prospective manner to evaluate the true optimal dosing standards. Furthermore, the ability to deliver continuous, sterile medications directly through an IT route will open new avenues of pharmacotherapy that were previously closed. This report serves as a basic guide for the safe and effective use of the IRRA*flow* active fluid exchange catheter to deliver IT medications.

KEY WORDS: External ventricular drain, EVD, Intrathecal medication, Intraventricular hemorrhage, IRRA*flow*, Subarachnoid hemorrhage, Ventriculitis

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Hydrocephalus is common in neurosurgical patients.[1] The management of hydrocephalus is commonly accomplished by the placement of an external ventricular drain (EVD). EVDs have many advantages, including the treatment of obstructive hydrocephalus, technical feasibility, reliable monitoring of intracranial pressure (ICP), and access cerebral spinal fluid (CSF).

Intrathecal (IT) medications are routinely introduced by catheterization of the intraventricular or subarachnoid space.[2] There has been sporadic use of IT medications delivered directly to the ventricle by intermittent injection through an EVD. IT medication delivery through an EVD has many significant risks, including infection, bolus medication delivery, and clamping during treatment. Despite this, IT medications have been used across a range of applications.[2]

Recently, the IRRA*flow* (IRRAS) was introduced. This device allows irrigation directly into the ventricle without necessitating violation of a sterile system or prolonged clamping while monitoring ICP.[3] This has created the ability to continuously infuse medications into the ventricle over days or hours. Continuous IT drug delivery necessitates novel dosing algorithms and medication formulations.

ABBREVIATIONS: BBB, blood-brain barrier; **CNS,** central nervous system; **EVD,** external ventricular drain; **HCP,** hydrocephalus; **IT,** intrathecal; **NS,** normal saline; **VRE,** vancomycin-resistant enterococcus.

Previous studies have reported excellent results with the IRRA*flow* in a variety of conditions.[3-7] No reports have yet been published that guide the technical utilization of the IRRA*flow*, including delivering IT medications.

This report provides neurosurgeons, intensivists, and pharmacists with technical advice on the use of IRRA*flow* to treat patients.

The blood-brain barrier (BBB) hampers drug delivery into the central nervous system (CNS) by limiting the access of specific molecules to the brain. The BBB is absent at the interface of CSF and parenchyma.[8] This allows the passage of large molecules from the CSF into the extracellular fluid.[9] The pharmacokinetics of medications in the CSF also depend on the variation in normal CSF volumes among patients as well as lipophilicity, intracellular absorption, and capillary uptake. CSF is continuously made and reabsorbed, changing the volume of distribution and drug clearance rate. These factors can present a challenge to administering IT medications.

Traditionally, IT medication is delivered by a bolus through a ventricular catheter. Medications delivered through EVD enter the ventricle and disperse throughout the CSF. Concentrations then level out within the ventricles. Despite the relatively common practice of bolus IT dosing through EVD or Ommaya reservoir, CSF pharmacokinetics are not well understood nor are optimum dosing regimens and distribution times. For continuous and bolus IT dosing, pharmacokinetic studies are needed to determine CSF concentrations of delivered medications at steady state. Direct CNS dosing could lead to adverse drug effects without proper monitoring. Delivering IT doses through EVDs also requires open manipulation of the EVD, leading to increased infection risk.

With active fluid exchange through the IRRA*flow*, lesser concentrations of medications are provided continuously.[6] As medications distribute and delivery is balanced by drug elimination, a steady state concentration is achieved. The IRRA*flow* smart controller also provides a consistent volume of CSF within the brain by balancing irrigation, drainage, and ICP. Maintaining a constant concentration of drug within the ventricles can result in a lower incidence of adverse effects. The IRRA*flow* does not require manipulation of the circuit for medication delivery. Control of CSF volumes, continuous medication infusion, and a closed sterile circuit could improve IT drug delivery. As continuous delivery of IT medications into the ventricle is a new technique that has not been previously available, detailed pharmacokinetic studies need to be undertaken before a firm understanding of the delivered dose and bioavailability of different medications can be obtained.

METHODS

Medication Preparation

Medications for the IRRA*flow* system are prepared in the pharmacy department. Preparations are compounded in a sterile IV hood, in a sterile IV room (Table 1). Concentrations are based on published daily dosing of the medications.[2,10] By using a maximum flow rate of 60mL/h, all daily drug exposure is consistent with previously published dosing. To prevent medication errors, auxiliary labels are used extensively (Figure 1).

An order set for continuous IT medication delivery was created within the electronic medical record. This order set includes instructions for the IRRA*flow* drainage and irrigation settings. Medication orders containing alteplase, vancomycin, tobramycin, daptomycin and nicardipine are listed within the order set (Figure 2).

Patients

Data were obtained retrospectively. Local IRB approval was obtained for this project. Owing to the relative rarity of pyogenic ventriculitis and cerebral abscess, the number of patients treated in these categories is small. Furthermore, for hydrocephalus not complicated by purulence or hemorrhage, we rarely use active fluid exchange. Our data and recommendations regarding these populations should be interpreted with these small numbers in mind.

Deidentified data can be made available on reasonable request to the corresponding author. Patient consent was not required for retrospective data collection. Surgical consent was obtained for all procedures.

Permission was obtained appropriately for the publication of the cadaveric images.

RESULTS

Seventy intraventricular IRRA*flow* catheters were placed for active fluid exchange. The clinical details of the patients are presented in Table 2 along with historical controls for comparison.[11,12]

In our cohort, 8/70 (11.4%) required permanent shunt placement; this compares favorably with historical reports from subarachnoid hemorrhage, where shunt rates were higher (13%-35%).[13,14] On average, our intraventricular hematoma cohort required 5 days to clear the third and fourth ventricle of hemorrhage, which is similar to the values reported in the CLEAR III trial.[15] We have found that if irrigation with alteplase is started within 24 hours of presentation, clot dissolution can be reliably

TABLE 1. Intrathecal Medication Concentrations and Dosages Across Multiple Flow Rates

		Cumulative daily dose at select rates		
Medication	**Concentration**	**20 mL/h**	**40 mL/h**	**60 mL/h**
Alteplase	2 mg/500 mL NS	1.92 mg	3.84 mg	5.76 mg
Vancomycin	4 mg/500 mL NS	3.84 mg	7.68 mg	11.52 mg
Tobramycin	4 mg/500 mL NS	3.84 mg	7.68 mg	11.52 mg
Daptomycin	2 mg/500 mL NS	1.92 mg	3.84 mg	5.76 mg
Nicardipine	3 mg/500 mL NS	2.88 mg	5.76 mg	8.64 mg

NS, normal saline.

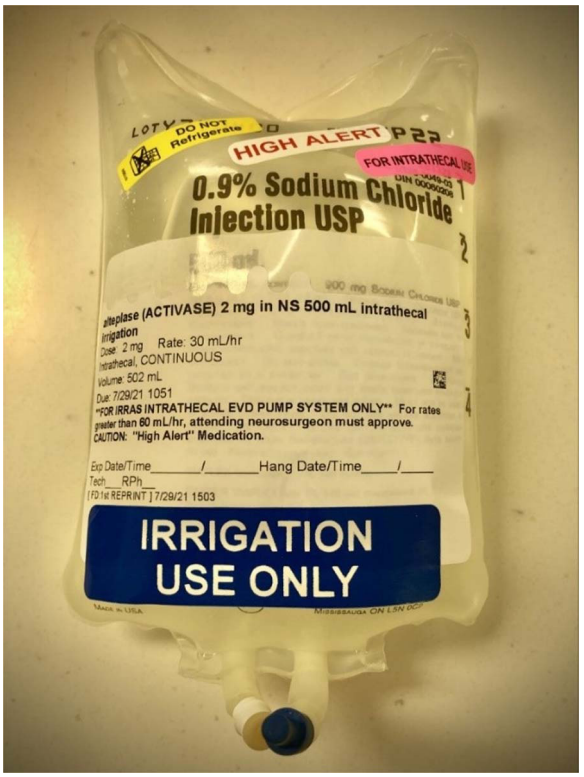

FIGURE 1. *Example of labeling for intrathecal medication preparation for infusion.*

achieved within 48 hours. This experience has led to our current recommendations above. The in-hospital mortality rate of our cohort was 17.4% with most fatalities caused by withdrawal of life-sustaining treatment. Because of the low numbers of cases other than intraventricular hematoma and subarachnoid hemorrhage, our recommendations in those patients should be considered with caution compared with the general cohort.

DISCUSSION

Medications

Alteplase

Intraventricular fibrinolytic therapy can accelerate hematoma breakdown and potentially improve outcome by maintaining EVD patency and accelerating blood product breakdown.[16,17]

The CLEAR III trial used a dosing strategy of 1 mg IT alteplase every 8 hours for up to 12 doses.[15] This did not improve functional outcomes at 180 days; however, there was a significant reduction in death. Previously published cumulative dosing of IT alteplase ranges between 6 and12 mg/day. We selected 2 mg/500 mL of saline with a goal rate of 60mL/h. Patients receive a cumulative 24-hour dose of ~6 mg. We selected this dosing to avoid potential neurotoxicity from tissue plasminogen activator,[18] despite neurotoxicity being controversial.[19] Other alteplase dosing strategies have been used in the IRRA*flow* with success.[20] Alteplase is rapidly denatured when given administered IT through bolus. Thus, the availability of alteplase for biological activity in bolus dosing is limited. Continuous dosing of alteplase may avoid this issue, by constantly introducing new alteplase, but this will need confirmatory pharmacokinetic studies.

Patients receiving alteplase are monitored closely in the neurocritical care unit. Imaging is at the discretion of the treating physician. Typically, daily computed tomography (CT) scans are completed until the third and fourth ventricles are open (Figure 3).

Antimicrobials

Bacterial ventriculitis carries a high mortality.[21] The BBB is an obstacle for antibiotics entering the CSF. This can prevent effective treatment, especially in cases of multi–drug-resistant organisms. With continuous irrigation, the concentration of antibiotic in the CSF stabilizes. This concentration can be effectively maintained above the mean inhibitory concentration for longer periods of time, maximizing bactericidal effects.[22] Previous reports have demonstrated the treatment CNS infections with IRRA*flow*.[6,7,23] All IT antibiotic treatments should be accompanied by systemic antibiotics based on cultures and antibiograms.

Vancomycin

Vancomycin is a glycopeptide that inhibits gram-positive cell wall growth. Gram-positive cocci are frequently involved in intraventricular infections and can be multi–drug-resistant organisms.

The concentration of 4 mg/500 mL at 60mL/h yields a dose of 11.52 mg/day, consistent with current guidelines.[10] As vancomycin equilibrates in the ventricular space, it reaches a concentration above mean inhibitory concentration of gram-positive organisms.[24] When combined with systemic vancomycin, the infection can be eradicated successfully (Figure 3). Further studies of the IT pharmacokinetics of vancomycin are warranted.

Tobramycin

The aminoglycoside, tobramycin, has activity against gram-positive and gram-negative organisms. Systemic aminoglycosides have low CNS penetration, and effective dosing is hampered by adverse effects including ototoxicity and nephrotoxicity. Tobramycin is dosed at 4 mg/500 mL, creating a daily dose within recommended ranges. We reserve tobramycin for gram-negative infections and use it in conjunction with systemic cephalosporins or carbapenems.

Daptomycin

Daptomycin has extensive gram-positive coverage that includes vancomycin-resistant enterococcus (VRE). Studied dosing of IT

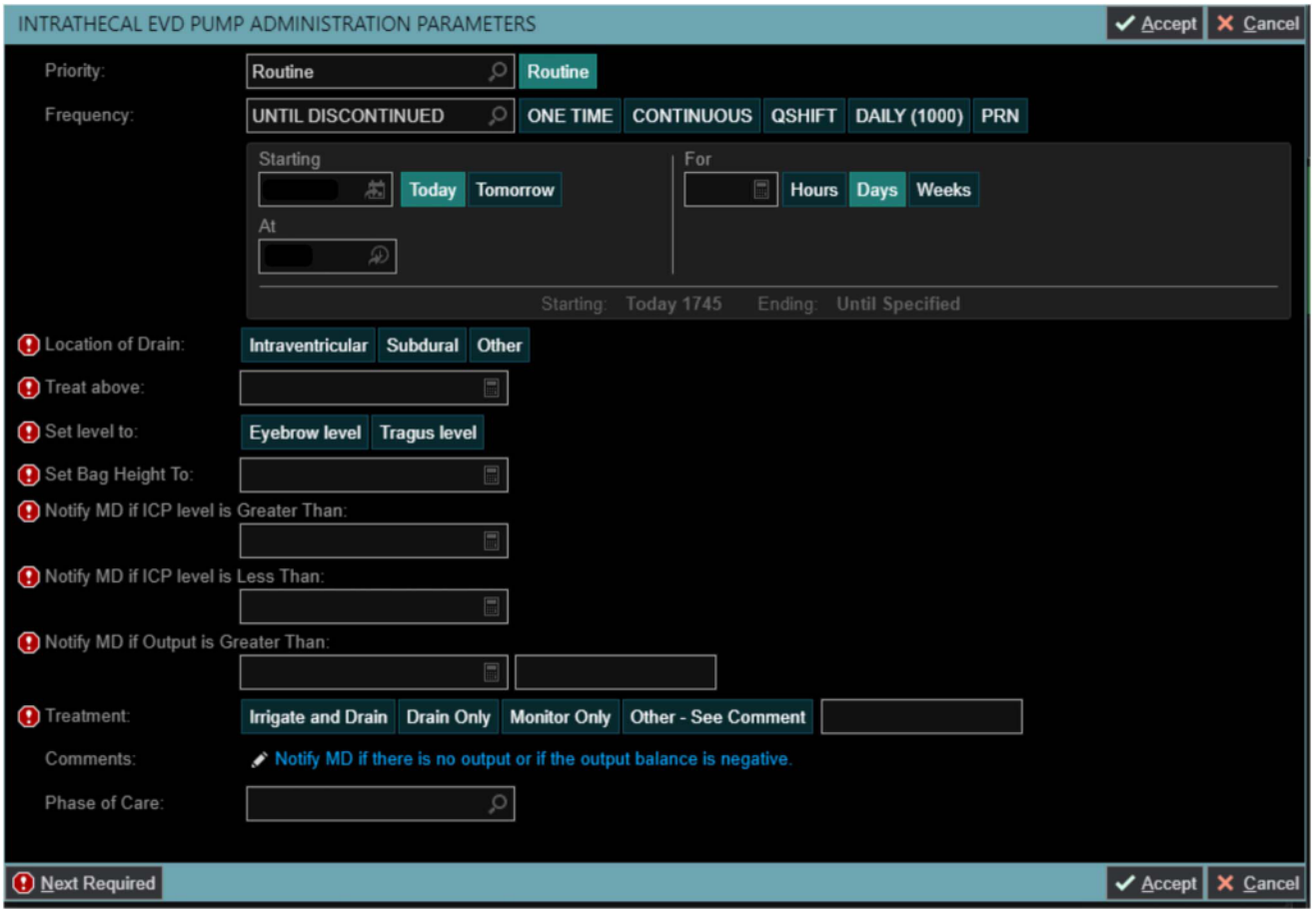

FIGURE 2. *Example of electronic medical record order set for active fluid exchange and delivery of intrathecal medication.*

daptomycin has ranged from 5 to 10 mg every 24 to 72 hours.[2] At a concentration of 2 mg/500 mL, patients receive ~6 mg/day. This irrigation is designed for resistant gram-positives, such as VRE. When compared with IT vancomycin and aminoglycosides, daptomycin is less studied. In this context, we reserve daptomycin for intraventricular VRE infection. To date, no patient at our institution has required treatment.

Nicardipine

Nicardipine is a dihydropyridine calcium channel blocker commonly used for the control of acute hypertension. Nicardipine has poor CNS penetration but has been studied using IT administration. It is hypothesized that IT nicardipine can cause vasodilation of cerebral vasculature, increasing cerebral blood flow, and brain perfusion. In a recent review, 4mg/12 hours was the most reported dose of IT nicardipine.[25] Ko et al[26] reported that intermittent dosing of nicardipine through the EVD can increase ICP in select patients, but on average, this has minimal effect on ICP while increasing cerebral blood flow. Sathialingam et al[27] established that 4-5mg of IT nicardipine as a bolus dose increased cerebral blood flow and decreased the rates of delayed cerebral ischemia (DCI) in a subset of patients with aneurysmal subarachnoid hemorrhage. Carrera et al[28] reported complete resolution of symptomatic angiographic vasospasm when continuous IT nicardipine was used as part of a multimodal salvage therapy to prevent DCI. Continuous irrigation of the ventricles allows for the treatment of vasospasm while lowering the risk for increased ICP. In total, 3 mg/500 mL of nicardipine yields a dose of ~8 mg/day. When combined with other therapies, continuous IT nicardipine can be used for treatment and prevention of DCI.

Technical Considerations

Placement of the Catheter

Catheter placement is guided by either anatomic landmarks or neuronavigation at the bedside. In brief, a CT-based plan is created on the neuronavigation machine. The ipsilateral foramen of Monro is selected as the target and Kocher point for the entry site. Registration is done in the standard way using the portable

TABLE 2. Clinical Experience With IRRA*flow* Catheter for Irrigation and Medication Delivery

	SAH	IVH	Ventriculitis	Abscess	HCP (other)	Entire cohort	Yuen 2018	Mansoor 2020
N	18	39	5	2	6	70	83	211
IT medication	8	22	4	2	3	39		
Nicardipine	6	0	0	0	1	7		
Alteplase	2	22	0	0	2	26		
Vancomycin	0	0	3	2	0	5		
Tobramycin	0	0	1	0	0	1		
Age	64 (15.1)	52.5 (25.3)	56.4 (17.9)	39.2 (14.8)	33.5 (20.5)	58.6 (18.2)	58 (17)	56.9 (14.6)
Admission GCS	9	11	8	10	14	11		
Any complication	1	6	2	0	1	10 (14.3%)		
Hemorrhage	1	1	0	0	1	3 (4.3%)	6/77 (7.8%)	5/186 (2.7%)
CSF leak	0	1	1	0	0	2 (2.9%)	NA	NA
Infection	0	3	0	0	0	3 (4.3%)	4/83 (4.8%)	15/211 (7.1%)
Early replacement	0	1	0	0	0	1 (1.4%)	12/89 (13.5%)	45/211 (21.3%)
Failure to drain	0	0	1	0	0	1 (1.4%)	NA	

CSF, cerebral spinal fluid; GCS, Glasgow Coma Scale; HCP, hydrocephalus, IT, intrathecal; IVH, intraventricular hematoma; SAH, subarachnoid hemorrhage.
Age is given as average (SD); GCS is presented as median.
Historical controls are shown with available data for comparison and context

electromagnetic localization system (mat placed under the pillow). After this, sterile preparation is done. Next, the incision and craniostomy are performed. An exit site is created at least 5 cm away from the craniostomy, and a subgaleal tunnel is placed from the exit site to the craniostomy. A Dandy needle is used with the electromagnetic stylet to create a navigated tract for placement of the IRRA*flow* catheter. The Dandy needle is then removed, and the IRRA*flow* catheter is soft-passed to the appropriate depth. The incision is then closed, and the IRRA*flow* catheter is secured in a loose circle to ensure no kinking. Special attention must be given to closing the exit site because the relatively large subgaleal tract can predispose to CSF leaks. A Dandy needle is used in our technique because the navigated stylet is incompatible with the IRRA*flow* catheter.

A standard anatomic technique can be used. After tunneling, 10-15 cm of catheter can be aligned according to a standard anatomic trajectory and then passed into the ventricle. After CSF is observed from the catheter, it is grasped at the outer table of the skull, while the stylet is removed and then the redundant loop is reduced from the craniostomy site. A cranial bolt of sufficient diameter to accommodate the catheter can also be used.[20,23,28] Demonstrations of the surgical techniques are available in Video. Regardless of the placement technique used, placement of the catheter should be confirmed by imaging before starting treatment to ensure that all holes of the catheter lie within a ventricle.

Device Settings

The IRRA*flow* system can be set to 1 of 3 modes, "irrigation," "monitor," and "drain only." In "monitor" mode, the IRRA*flow* remains clamped and monitors ICPs, which are displayed on the control unit. 'Drain only' mode functions as a standard EVD with the exception that settings are entered using a touch screen and ICP measurements are automatic.

In "irrigation" mode, the user will have 6 settings. The first settings are the high-pressure and low-pressure alarms. During each cycle, the IRRA*flow* will record the patient's ICP. If measured ICPs exceed alarm thresholds, the irrigation portion of the cycle will not occur, and the control unit will alarm. We set the low ICP alarm at significant negative pressure to ensure that irrigation is continued in scenarios of over drainage or pneumocephalus.

The "treat above" setting is the pressure above which irrigation should continue. We recommend setting this value to a negative number (typically we choose −10 mm Hg) or disabling it. This is because we prefer irrigation to be maintained at all pressures below our high ICP alarm. The "drain above" setting of the IRRA*flow* is analogous to height settings for an EVD. This should be set according to physician preference. Finally, the irrigation rate is set in mL/h. The IRRA*flow* will always irrigate in 1 mL/1 s increments followed by the monitoring and drainage cycles. Therefore, increasing the rate of irrigation will

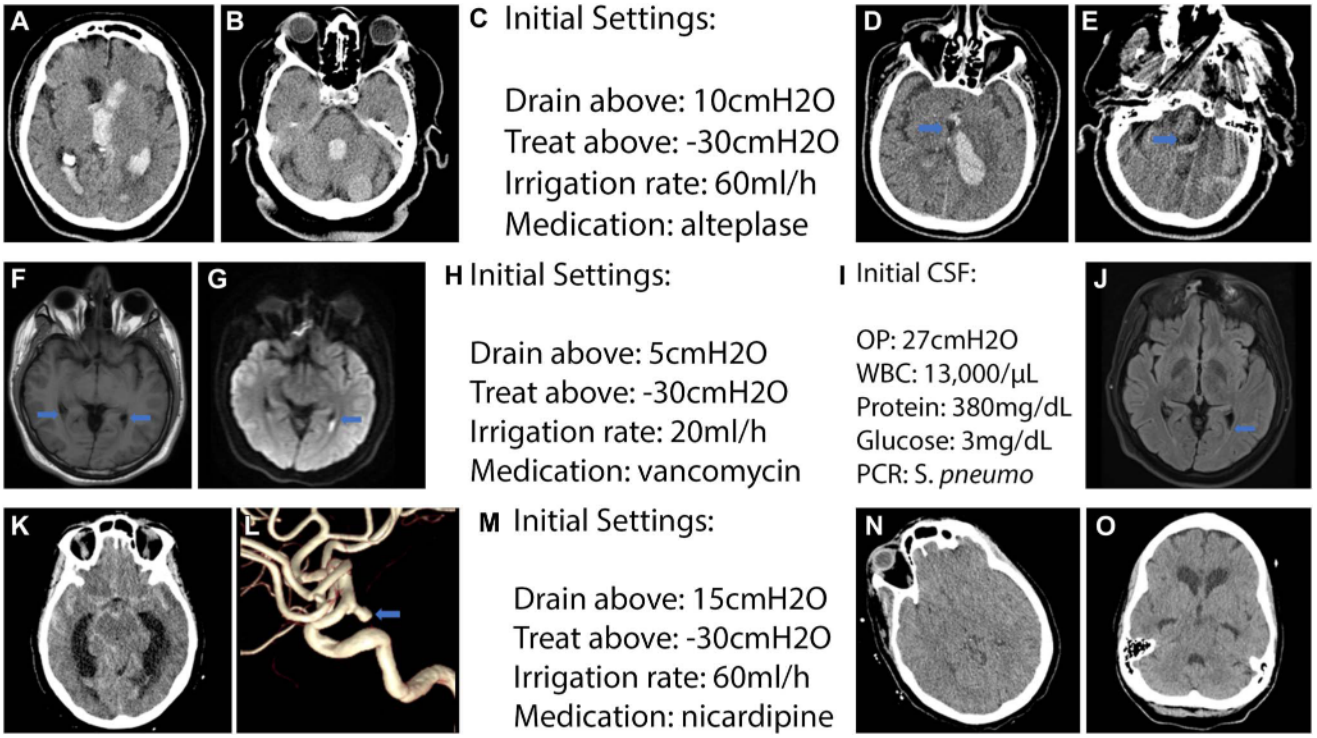

FIGURE 3. *Representative cases using the IRRAflow active fluid exchange catheter for intrathecal medication delivery.* **A**-**E**, *Case 1: An 84-year-old man presented with hypertensive thalamic hemorrhage and occlusion of the third and fourth ventricle with obstructive hydrocephalus. IRRAflow was placed at bedside hospital day 0, and alteplase infusion started after postprocedural scan showed no hemorrhage or progression of disease. The patient improved neurologically, but family elected for withdrawal of life-sustaining care rather than tracheostomy placement.* **A** *and* **B**, *Axial CT scans demonstrating IVH with the occlusion of third and fourth ventricle.* **C**, *Initial settings of the IRRAflow catheter.* **D** *and* **E**, *Axial scans from postbleed day 2 showing patency of third and fourth ventricle and decreased blood clot burden. Blue arrows represent patients' third and fourth ventricles with decreased blood clot burden.* **F**-**J**, *Case 2: A 21-year-old man with spontaneous bacterial ventriculitis related to sinus infection, treated at community hospital with antibiotics with no improvement for 3 days and transferred to university hospital after becoming comatose. After a 9-day treatment course in the neuro-intensive care unit, the patient improved substantially, was extubated, and transferred to the general floor. The patient recovered completely and now living independently.* **F**, *T1 noncontrasted axial MRI of the brain showing purulent ventriculitis. Blue arrows represent fluid-fluid level in occipital horns.* **G**, *Diffusion-weighted axial MRI of the brain showing restricted diffusion in fluid of occipital horn. Blue arrows represent restricted diffusion in dependent fluid.* **H**, *Initial settings of the IRRAflow catheter.* **I**, *Initial cerebral spinal fluid laboratory analysis.* **J**, *T2 fluid-attenuated inversion-recovery axial MRI taken on hospital day 13 showing resolution of intraventricular purulence and no cerebral edema. Blue arrows represent lack of fluid-fluid level in occipital horn.* **K**-**O**, *Case 3: A 48-year-old woman presented to community hospital with worst headache of life. Deteriorated to stupor. Hunt-Hess grade 5, Fisher grade 4 subarachnoid hemorrhage diagnosed. The patient transferred emergently to university hospital. IRRAflow was used to deliver nicardipine prophylactically from posthemorrhage days 3 to 10. After a prolonged hospital stay including 2 intra-arterial treatments for vasospasm as well as a tracheostomy, the patient made an excellent recovery and was discharged home. At 4 months posthemorrhage, she was neurologically intact and living independently.* **K**, *Noncontrast axial CT of the brain showing diffuse subarachnoid hemorrhage and hydrocephalus.* **L**, *3-dimensional reconstruction from digital subtraction angiography showing the cerebral aneurysm.* **M**, *Initial settings of the IRRAflow catheter.* **N**, *Noncontrast axial CT of the brain from postbleed day 5 showing cerebral edema but resolved hydrocephalus and resolved subarachnoid hemorrhage.* **O**, *Noncontrast axial CT of the brain 4 months after hemorrhage showing ventriculomegaly without sulcal effacement and resolved cerebral edema. CT, computed tomography; CSF, cerebral spinal fluid.*

increase the number of cycles/hour to achieve the desired irrigation rate. Device settings and reference values are presented in Table 3.

Troubleshooting

Adverse events related to the catheter in our patients are presented in Table 2. The following discussion focuses on bedside problems that we encountered as we gained experience with the technology at our center. These issues occurred with relative frequency until the following techniques and knowledge were developed based on our experience. By following these techniques/practices, we rarely encounter the issues described below.

As mentioned earlier, the stylet, which is intended to be used to insert the ventricular catheter using anatomic landmarks, is not as stiff as that included with most EVDs. This can create catheter deflections if the catheter is not grasped distally enough to prevent flexing.

TABLE 3. Settings and Parameters for the IRRA*flow* With Suggested Starting Values

Setting	Parameter	Suggested value
Treat above	The pressure above which infusion is continued	-10 mm Hg
Drain above	The pressure above which drainage occurs	5-15 mm Hg
Irrigation rate	The amount of irrigation delivered	60 mL/h
High ICP	The ICP above which an alarm will sound, and irrigation will stop	23 mm Hg
Low ICP	The ICP below which an alarm will sound, and irrigation will stop	-10 mm Hg

ICP, intracranial pressure.
These values may not be appropriate depending on the clinical scenario and specific patient and institutional factors.

The stylet can also generate significant friction when being withdrawn after placement. To prevent this, the catheter must be flushed with saline before stylet insertion. After insertion, the stylet must be withdrawn, while the catheter is maintained in a loose loop with no kinking or sharp bends to ensure withdrawal. This can be challenging as the surgeon must also maintain the proper depth of the catheter tip at the same time by securing the IRRA*flow* at the skull entrance. The soft pass technique above avoids this by removing this stylet before placement.

The IRRA*flow* may also report negative ICPs. Usually this occurs when the system has air in the drainage line or cassette. To alleviate this issue, the system can be manually primed and inspected to make sure that there is no air in the line. If there is no trapped air, another solution is to raise the bag height, preventing over drainage and excessive siphon pressure. Siphon pressure on the transducer in the cassette can cause spurious readings. The bag height can be increased up to the "treat above" level to eliminate the siphon, but this may decrease drainage. Irrigation will be suspended by any alarm. Negative ICP readings are a common reason that irrigation is automatically halted. Setting a generous low ICP parameter is advised to preserve therapy and avoid clinically irrelevant alarms.

Spurious ICPs can also occur if the ventricles are overdrained, creating an interruption in the fluid column to the transducer. In addition, if the catheter is located directly in blood clot, ICPs can be falsely elevated until the catheter tip is in communication with the circulating CSF. Manually irrigating 1 to 2 mL of fluid into the ventricle can reinflate the ventricles and restore accurate ICP readings.

Sampling and selective clamping can be facilitated by insertion of a stopcock between the IRRA*flow* catheter lumens and the cassette. In addition, tubing should be labeled to ensure that the inflow or outflow catheters can be reliably identified.

The IRRA*flow* can irrigate into brain parenchyma if the tip is intraparenchymal rather than intraventricular. This has resulted in small intraparenchymal cysts that resolved with the removal of the drain, transient neurological deficits, and inaccurate ICP measurements. CT scans of the brain should be acquired after placement and before starting therapy on every IRRA*flow*, including when they are done with navigation.

When placing the IRRA*flow* for the delivery of medication and especially when the clinical goal is to eliminate hemorrhage or pus, it is recommended to begin irrigation and/or medication as soon as possible. Delay in initiation of active CSF exchange will limit the ability of the catheter to rapidly wash out the ventricle, especially with hemorrhage. Interpretation of CSF laboratory studies with active fluid exchange is poorly understood, and significant effort will be required to obtain objective methods of analysis. In our practice, judgment of treatment outcomes is based on visual examination of the drainage at the bedside and interpretation of neuroimaging.

Irrigation and drainage volumes are often not equal. If this occurs, then irrigation is stopped, and the physician called. The causes of this can vary, from occlusion of the drainage line to natural CSF circulation. If concern exists about trapping fluid intraventricularly, a CT should be obtained to assess ventricular volume, especially if ICPs are elevated. Irrigation has often exceeded drainage, but ventricular volumes have remained stable or decreased, indicating that the natural CSF circulation was adequate.

When sampling CSF for clinical testing, the dilution from the IRRA*flow* must be considered. Normally, the CSF obtained from an EVD is a direct ventricular sample. In the IRRA*flow*, medication and fluid have been introduced and that can affect values, including pH, sodium, and glucose. Laboratory values in this setting are difficult to interpret, and further study is necessary.

CONCLUSION

Active fluid exchange in the CSF is a new technique that is rapidly expanding in NCCUs. New technology mandates the development of new techniques and practice. The IRRA*flow* provides a new method for both active fluid exchange and delivery of IT medications that hold significant promise.

The ability to deliver continuous medications directly by an IT route opens new avenues of pharmacotherapy that were previously closed. The pharmacokinetics of continuous dosing and the therapeutic and safety profiles of continuous IT medications need to be studied in a prospective manner. As familiarity with the

technology and unique IT pharmacokinetics increases, a vast expansion of IT pharmacological treatment will likely follow.

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Disclosures

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REFERENCES

1. Chung DY, Mayer SA, Rordorf GA. External ventricular drains after subarachnoid hemorrhage: is less more? *Neurocrit Care.* 2018;28(2):157-161.
2. Erdman MJ, Marrese AR, Haller JT, Barthol CA, Small CE. Use of intraventricular medications in critically ill patients: a systematic review. *Crit Care Nurs Q.* 2020; 43(2):157-171.
3. Rajjoub K, Hess RM, O'Connor TE, Khan A, Siddiqui AH, Levy EI. Drainage, irrigation, and fibrinolytic therapy (DRIFT) for adult intraventricular hemorrhage using IRRAflow® self-irrigating catheter. *Cureus.* 2021;13(5):e15167.
4. Baig AA, Hess RM, Khan A, et al. Use of novel automated active irrigation with drainage versus passive drainage alone for chronic subdural hematoma-A propensity score-matched comparative study with volumetric analysis; *Oper Neurosurg.* 2023; 24(6):630-640.
5. Varela S, Carrera D, Elazim AA, Robinson MB, Torbey M, Carlson AP. Continuous tissue plasminogen activator infusion using a minimally invasive irrigating catheter for the treatment of intraparenchymal hemorrhage within the basal ganglia: case reports. *Oper Neurosurg.* 2022;23(6):e387-e391.
6. Hess RM, Khan A, Edwards M, Siddiqui AH, Levy EI. Continuous intraventricular vancomycin for treatment of ventriculitis using IRRAflow®: a case report. *Surg Neurol Int.* 2021;12:583.
7. Hess RM, Lazar A, Smolar D, et al. Continuous antibiotic administration using IRRAflow® catheter for treatment of intracranial abscess. *Cureus.* 2021;13(10):e19061.
8. Nau R, Blei C, Eiffert H. Intrathecal antibacterial and antifungal therapies. *Clin Microbiol Rev.* 2020;33(3):e00190.
9. Spector R, Robert Snodgrass S, Johanson CE. A balanced view of the cerebrospinal fluid composition and functions: focus on adult humans. *Exp Neurol.* 2015;273:57-68.
10. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis.* 2017;64(6):e34-e65.
11. Yuen J, Selbi W, Muquit S, Berei T. Complication rates of external ventricular drain insertion by surgeons of different experience. *Ann R Coll Surgeons Engl.* 2018; 100(3):221-225.
12. Mansoor N, Madsbu MA, Mansoor NM, et al. Accuracy and complication rates of external ventricular drain placement with twist drill and bolt system versus standard trephine and tunnelation: a retrospective population-based study. *Acta Neurochir.* 2020;162(4):755-761.
13. Rao SS, Chung DY, Wolcott Z, et al. Intermittent CSF drainage and rapid EVD weaning approach after subarachnoid hemorrhage: association with fewer VP shunts and shorter length of stay. *J Neurosurg.* 2020;132(5):1583-1588.
14. Jabbarli R, Pierscianek D, RÖlz R, et al. Gradual external ventricular drainage weaning reduces the risk of shunt dependency after aneurysmal subarachnoid hemorrhage: a pooled analysis. *Oper Neurosurg.* 2018;15(5):498-504.
15. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet.* 2017;389(10069): 603-611.
16. Vereecken KK, Van Havenbergh T, De Beuckelaar W, Parizel PM, Jorens PG. Treatment of intraventricular hemorrhage with intraventricular administration of recombinant tissue plasminogen activator. *Clin Neurol Neurosurg.* 2006;108(5): 451-455.
17. Gaberel T, Magheru C, Parienti J-J, Huttner HB, Vivien D, Emery E. Intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage. *Stroke.* 2011;42(10):2776-2781.
18. Ducruet AF, Hickman ZL, Zacharia BE, et al. Exacerbation of perihematomal edema and sterile meningitis with intraventricular administration of tissue plasminogen activator in patients with intracerebral hemorrhage. *Neurosurgery.* 2010; 66(4):648-655.
19. Ziai W, Moullaali T, Nekoovaght-Tak S, et al. No exacerbation of perihematomal edema with intraventricular tissue plasminogen activator in patients with spontaneous intraventricular hemorrhage. *Neurocrit Care.* 2013;18(3):354-361.
20. Jahromi BR, Brandmeir N, Göhre F, et al. E-214 Active removal of cerebral haemorrhage via CSF exchange. *J Neurointerv Surg.* 2022;14(suppl 1): a195-a196.
21. Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on β-lactam antibiotics: insights from the society of infectious diseases pharmacists. *Pharmacotherapy.* 2006;26(9): 1320-1332.
22. Waineo MF, Kuhn TC, Brown DL. The pharmacokinetic/pharmacodynamic rationale for administering vancomycin via continuous infusion. *J Clin Pharm Ther.* 2015;40(3):259-265.
23. Rezai Jahromi B, Tanskanen P, Koski-Pàlken A, et al. Active cerebrospinal fluid exchange system for treatment of pyogenic ventriculitis. *Neurosurg Open.* 2021; 2(4):okab030.
24. Diaz R, Afreixo V, Ramalheira E, Rodrigues C, Gago B. Evaluation of vancomycin MIC creep in methicillin-resistant Staphylococcus aureus infections-a systematic review and meta-analysis. *Clin Microbiol Infect.* 2018;24(2):97-104.
25. Hafeez S, Grandhi R. Systematic review of intrathecal nicardipine for the treatment of cerebral vasospasm in aneurysmal subarachnoid hemorrhage. *Neurocrit Care.* 2019;31(2):399-405.
26. Ko S-B, Choi HA, Helbok R, et al. Acute effects of intraventricular nicardipine on cerebral hemodynamics: a preliminary finding. *Clin Neurol Neurosurg.* 2016;144:48-52.
27. Sathialingam E, Cowdrick KR, Liew AY, et al. Microvascular cerebral blood flow response to intrathecal nicardipine is associated with delayed cerebral ischemia. *Front Neurol.* 2023;14:1052232.
28. Carrera DA, Marsh LM, Roach JJ, et al. HummingFlow: novel single twist-drill access for ventricular drainage, irrigation, monitoring, and automated local drug delivery in subarachnoid hemorrhage. *J Neurosurg.* 2023.

VIDEO. Demonstration of available insertional techniques used for placement of the IRRA*flow* active fluid exchange catheter.

COMMENTS

The authors are to be commended for providing a comprehensive overview of the IRRAflow irrigation system as applied to various intraventricular pathology. In particular, they provide helpful discussion points and protocols for intrathecal delivery of medications via continuous irrigation, as contrasted to existing literature using intermittent dosing. Table 3 summarizes outcomes and complications of most interest to readers, with promising results. However, as the authors note, it will take more data and follow-up to fully realize the promise (and/or potential pitfalls) of what is effectively a new way of ventricular washout and drug delivery to the CNS within the neurointensive care unit setting.

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