Regular Article

Best practices for the use of intracerebroventricular drug delivery devices

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ABSTRACT

For decades, intracerebroventricular (ICV), or intraventricular, devices have been used in the treatment of a broad range of pediatric and adult central nervous system (CNS) disorders. Due to the limited permeability of the blood brain barrier, diseases with CNS involvement may require direct administration of drugs into the brain to achieve full therapeutic effect. A recent comprehensive literature review on the clinical use and complications of ICV drug delivery revealed that device-associated complication rates are variable, and may be as high as 33% for non-infectious complications and 27% for infectious complications. The variability in reported safety outcomes may be driven by a lack of consensus on best practices of device use. Numerous studies have demonstrated that employing strict aseptic techniques and following stringent protocols can dramatically reduce complications. Key practices to be considered in facilitating the safe, long-term use of these devices are presented.

1. Introduction

For patients with certain central nervous system (CNS) disorders, such as brain infections and tumors, refractory pain, and neurodegenerative conditions [1–5], effective therapy requires the direct delivery of drugs to the CNS in order to circumvent the blood-brain barrier (BBB) [6]. This physiological barrier restricts the movement of large molecules between the blood, cerebrospinal fluid (CSF), and interstitial fluid of the brain [5,7,8]. The selectivity of the BBB prevents many systemically administered drugs from reaching therapeutic levels in the CNS [4,9,10]. Intrathecal delivery methods administer soluble therapeutics directly into the CSF. Intrathecal delivery methods include intracerebroventricular (ICV), intrathecal-lumbar and intracisternal routes. The ICV route enables the administration of drugs into a lateral cerebral ventricle via an implanted device (reservoir and catheter). This delivery route, which may also be referred to as intraventricular administration, has been used worldwide for decades to treat pediatric and adult patients with a broad range of CNS disorders [1–5,11].

ICV devices allow administration of drugs either directly into the CSF or by interstitial infusion (with convection) [2,12–18]. Whereas interstitial infusion by convection reaches a perimeter from the implanted point source within the parenchyma, injection/infusion into the

CSF will distribute throughout the whole ventricular system and the external CSF spaces like the basal cisterns and over the convexity. The penetration of any given drug will be dependent on individual characteristics such as size, lipid solubility and charge. Undoubtedly there is cerebrovascular fluid transport and exchange between CSF and interstitial fluid (ISF) leading to the proposed "glymphatics" concept, but as methods including imaging are currently limited, the extent of distribution into the ISF of any given ICV-delivered substance is largely unknown, and is expected to have enormous individual variability and to be significantly impacted by disease [19,20]. This is in contrast to convection-enhanced delivery where via surrogate imaging of gadolinium into a direct interstitial infusate, the distribution can be measured and large areas can be covered with flow rates of the microcatheters limited to 1 to 2 μL per min as otherwise the fluid will not get into the tissue and collect in a cavity around the delivery catheter tip [21,22]. Many technological innovations are to be expected in the coming years. Currently, there is only short-term experience and use of implanted delivery devices for repeated access is still uncommon and beyond the scope of this review.

Through ICV devices, drugs are given by slow bolus push (with butterfly needle and syringe). These bolus deliveries may be isovolumetric, i.e. an equal volume may be removed, if volumes are 10 mL or

greater. A recently approved treatment for CLN2 disease (neuronal ceroid lipofuscinosis type 2) utilizes the ICV route via a slow infusion (2.5 mL/ h) using a Huber non-coring needle and syringe pump, with post-infusion flushing of the line to ensure complete dosing [23]. An implanted ICV device facilitates chronic therapy and affords greater convenience to healthcare professionals and patients [13,16,24]. Once the device is no longer therapeutically needed, it can remain in place indefinitely in the absence of complications [3,17,25]. In addition to their more traditional use in oncology and pain management, ICV devices are being increasingly used to administer therapies to patients with neurodegenerative diseases.

Experience on the use of ICV devices based on institutional practices have been reported in the literature [3,24–27]. Reported ICV device access protocols and rates of device-associated complications are highly variable. A recent systematic literature review found that non-infectious complication rates per patient were as high as 33%, while infectious complication rates reached 27% [24]. The most common non-infectious complications related to ICV device access in adult and pediatric patients included intracerebral hemorrhage, catheter malposition and/or obstruction, and subcutaneous CSF leaks. The most common infections were caused by *Staphylococcus epidermidis* and *Staphylococcus aureus*. Numerous studies have demonstrated that employing strict aseptic techniques when accessing ICV devices can dramatically reduce infection rates, and following stringent standard practices for device use can help reduce complications [3,27–30]. Overall, safety and complication rates associated with ventricular access devices can demonstrate a remarkable long-term safety profile for permanent indwelling devices when following proper techniques [25]. Nevertheless, the wide variation in complication rates reported in the literature suggests the need for standardization of procedures. An international multidisciplinary group of healthcare professionals with expertise in ICV devices met to discuss current practices at their institutions. Specialties represented were neurosurgery, neuro-oncology, pediatric hematology oncology, pediatric neuro-oncology nursing and pediatric neurology. The goal was to establish a consensus on best practices for the management of ICV devices and for mitigating device-associated complications to facilitate their long-term use.

2. ICV device implantation

ICV device implantation is a procedure that is routinely performed by neurosurgeons in adults and in children including newborns [23]. The reservoir is placed under the scalp in the subgaleal space, and the catheter is commonly inserted into the lateral ventricle of the non-dominant hemisphere. Relative contraindications for ICV device implantation could include infection and coagulopathy.

ICV devices are implanted and managed in patients from all age groups (newborn to adult), and ICV devices have been implanted in patients as young as premature newborns. In a retrospective analysis that evaluated the rate of ICV shunt infections and related risk factors, the infection rate for preterm infants (33.3%) was slightly higher than that for full-term babies (25.8%) [31]. This may be due to lower immune function, lower birth weight, higher number of skin commensals, and the often prolonged hospitalization that causes more colonization with specific nosocomial microorganisms [31]. Considerations to minimize the risk of complications are listed in Table 1. All personnel involved in implanting the device must be appropriately educated, pay meticulous attention to establishing and maintaining aseptic conditions throughout the procedure, and follow all institutional policies. To aid in ensuring sterility, the implantation surgery could be scheduled as the day's first procedure. Another helpful strategy is to create a flap (half moon incision) and to place the dome of the reservoir at a safe distance from the skin incision. The use of prophylactic antibiotics perioperatively and optimal infection control measures during ICV device implantation surgery are necessary to keep infection rates low. The use of chlorhexidine skin preparation, antibiotic impregnated catheters, and

Table 1
Recommended best practices for ICV device implantation.

1. Patient's coagulation parameters and platelet counts should always be checked preoperatively.
2. Use of prophylactic intravenous antibiotics prior to skin incision. Prophylaxis for 3–5 days thereafter may be considered.
3. Within a facility that can handle complications, the procedure should be performed by an experienced neurosurgeon; the core team performing the procedure should be minimal.
4. Standard sterile procedures should be used. The operator should ensure thorough disinfection by scrubbing hands and wearing sterile gloves.
5. Ommaya reservoir should be implanted away from the burr hole and the "C-incision" site; use of a neuronavigation system may be useful in the precise placement of the catheter tip in smaller-size ventricles.
6. To confirm if the device and catheter are in the correct location, CSF flow is the hallmark test; postoperative imaging, either CT or MRI, is recommended immediately after ICV device implantation to confirm appropriate placement in ipsilateral ventricle.
7. To reduce the risk of backflow of the administered drug through the catheter tract, a wait time of ≥5 days is recommended after device implantation before first use, to allow for proper wound healing.
8. Provide postoperative instructions to patients and caregivers regarding home care of the ICV device.
9. The institution should be equipped with an on-call neurosurgeon, pediatric ED, pediatric ICU, and 24-h imaging center.

CSF = cerebrospinal fluid; ED = emergency department; ICU = intensive care unit; ICV = intracerebroventricular; MRI = magnetic resonance imaging.

prophylactic antibiotic regimen administered intravenously and/or intrathecally, may additionally be considered for minimizing incidence of infection associated with device implantation procedures [31].

ICV catheters can be inserted in ventricles of all sizes. Stereotactic guidance may be especially helpful in patients with slit-like ventricles [32,33]. Confirming placement of the catheter is critical. CSF "backflow" is the hallmark indicator to confirm placement; however this may not be sufficient to confirm location of the tip of the catheter (as catheter tip may be in third ventricle and not in lateral ventricle). Intraoperative or post-operative imaging is recommended as routine practice. This may be performed any time prior to first use of the device. Catheter tip malposition has been reported to occur in up to 6% of reservoir placement procedures (total of 840 procedures in 5 studies); however, this rate has declined since the introduction of navigation-guided reservoir placement [3]. In addition, endoscopy may be useful to assist ventricular catheter placement, particularly when the ventricle is small and/or has abnormal anatomy [34].

Although theoretically the device may be used immediately, a waiting period between implantation and first use of the device is recommended to allow for wound healing and to reduce the risk of backflow through the tract created by the catheter. It is also helpful to monitor for post-operative complications before starting a new medication and distinguish the complications from the procedure versus the drug instilled into the ventricles. This is especially important for chemotherapy agents as cases of focal leukoencephalopathy have been described and may be related to such backflow. The minimum recommended waiting period is 5 days, but often 7 days is preferred to allow swelling to decrease in order to ensure reservoir margins are clearly palpable on the surface of the scalp and ensure a successful access with minimal pain. For pediatric cases where chronic therapies are needed, a successful first experience is especially important.

Once implanted, ICV devices can remain in place for life. However, the length of usage of devices is not well established and devices should be monitored for leakage/failure. Infection, device failures, catheter malpositioning or occlusion may require removal and/or surgical revision. Device replacement may be necessary.

3. ICV device access

Infections can be minimized with strict adherence to aseptic techniques by creating and following institutional protocols and by limiting
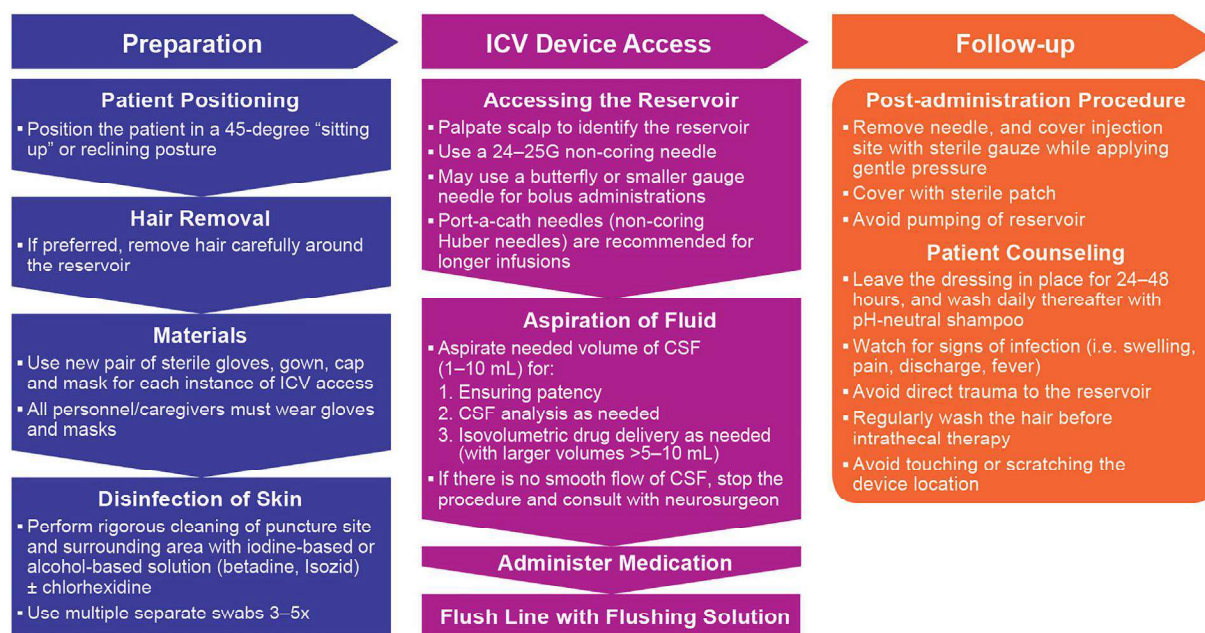
Fig. 1. Recommended best practices for the use of ICV drug delivery devices. CSF = cerebrospinal fluid; ICV = intracerebroventricular.

access to a small group of well-trained, highly knowledgeable personnel [2,35,36]. Various providers including oncologists, neurologists, neurosurgeons, pediatricians, nurse practitioners, and fellows may be able to perform access procedures; the major consideration is the level of skill of the select group of providers rather than their specialty. ICV device access can be performed in various settings, commonly in outpatient settings, private rooms or low-traffic areas preferably with a closed door/curtain. Practices will vary by country and institution. Post-treatment observation of patients is usually not required, but may be preferred in certain cases (e.g. research protocols) [3]. Sedation of patients while accessing the device is not routine; however if performed, monitoring post-procedure is often preferred. The average number of punctures per device is commonly reported in the literature as 30–50; in a cohort of 98 patients, > 100 punctures were reported in 12 patients and > 200 punctures in 4 patients [3].

A summary guidance on the ICV device access procedure is shown in Fig. 1 and described in detail below.

3.1. Preparation of the access site

After allowing proper surgical wound healing, access should be performed by personnel with specialized knowledge of the ICV access procedure. Patients and caregivers should be counseled on preparation of the access site per institution's protocol, for example hair removal and use of chlorhexidine shampoo the night before or morning of the treatment may be recommended. Hair removal is optional; when hair is removed prior to access, personnel should be careful not to cause skin abrasions. Recommended methods of hair removal include depilatory cream and electric clippers. A razor may be used by experienced personnel, but may increase the possibility of minor nicks and the risk of subsequent infection. Pediatric protocols may include the use of topical anesthetic creams prior to puncturing the device. This may not always be implemented as pain perception in the scalp may be lower and the area may become numb as a result of skin incisions related to the device implantation surgery.

Rigorous cleaning of the access site and the surrounding area with an iodine- or alcohol-based solution is a crucial aspect of aseptic technique. Although 3 swabs are commonly used for cleaning, experts recommend using 5 swabs, beginning the disinfection process by wearing

2 pairs of gloves and using 3 swabs, then removing the top pair of gloves to complete disinfection with the remaining 2 swabs [3]. For any iodine-based solution, it is crucial to allow the solution to dry between each new swab. Importantly, hand disinfection and use of sterile gloves are mandatory for all personnel involved; face masks, hair covers and sterile gowns may be considered.

3.2. Device access

Depending on the patient needs, local anesthetic cream can be used at the site of the puncture [3]. Butterfly needles (25 gauge) should be used for short bolus infusions (approximately 10–15 min). Port-a-cath needles (25 gauge, non-coring Huber type needles) are recommended for longer infusions (hours) as they are stable with lower risk of needle detachment during treatment; the base of the needle should be flush against the skin (this happens when needle is inserted perpendicular to the dome center and lies in the deepest part of the reservoir). Care must be taken not to perforate the bottom of the reservoir, though this is less of an issue with steel-based Rickham reservoirs. Ensuring that device materials do not interfere with brain imaging is important. Antibiotic impregnated catheters may be considered [37].

The potential for increased intracranial pressure remains a theoretical concern during ICV drug administration, especially when large volumes are to be administered over a short period of time [16]. To address this concern, isovolumetric injection has been used, in which withdrawal of CSF prior to administration of the drug can help to avoid volume overload [38–41]. It is recommended that 1–10 mL of CSF be withdrawn immediately after puncture to: 1) check the patency of catheter; 2) permit CSF analysis as needed; and 3) (optional) allow for isovolumetric drug delivery, especially with larger volumes (> 5–10 mL). A smaller syringe should be used for aspiration to decrease the intensity of suction generated. If there is no CSF return, consultation with the neurosurgical team is recommended prior to any drug delivery. Following drug delivery, flushing the device (and infusion components) is recommended; artificial CSF or preservative-free saline may be used. CSF analysis might be considered when infection is suspected, after every drug administration, or whenever the ICV device is accessed.

4. Drug administration and post administration

ICV infusion through a device pump is used to deliver drugs over an extended time period and at a constant rate to mitigate gradient and loss of therapy to the periphery and to minimize risk of increased intracranial pressure [16,40]. Administration over 10–15 min is also adequate to achieve enough flow and pressure resulting in sufficient distribution throughout CSF spaces [42]. For injections given over longer periods of time, fixation of the port needle will help stabilize the infusion system over the administration. Flushing of the tubing, port needle, reservoir, and internal cannula with CSF, artificial CSF, or preservative-free saline helps ensure complete drug delivery. Following the procedure, remove the needle and cover the injection site with a sterile gauze while applying gentle pressure, followed by a sterile patch. Pumping of the reservoir should be avoided.

5. Patient counseling

Instructions should be provided to patients and caregivers regarding home care and monitoring of the ICV device. If signs of infection or increased cranial pressure are observed (i.e. swelling, pain, discharge, fever, changes in mental status), the patient should seek immediate medical care. Patients and caregivers should also be counseled about avoiding direct trauma to the reservoir and avoiding touching or scratching the skin over the device location. Patients should keep scalp/hair clean and the use of pH-neutral shampoos is recommended. Prior to ICV access, bacteriostatic shampoo can be used (chlorhexidine- or iodine-based).

6. Management of complications

Infection is the most common complication associated with ICV access devices [3]. Device-related infections are almost exclusively caused by skin bacteria, including *Staphylococcus epidermis* and *aureus*, and *Streptococcus*. Although historically reported as non-pathogenic contaminants, severe *Propionibacterium acnes* infections have been reported as complications of neurosurgical procedures and implanted devices [43]. These infections may be subclinical and may be challenging to identify both clinically and by laboratory testing (*P. acnes* is slow to grow in laboratory cultures and may take up to 10 days). Aseptic techniques and implantation away from the incision line are key practices in decreasing the risk of ICV device infections. However, upon a confirmed infection, the device is usually removed, and the waiting period for re-implantation of a new device is dependent on the length of treatment with antibiotics (typically 10–14 days) or until after at least 3 consecutive negative CSF cultures.

Non-infectious complications such as an obstruction, ventricular catheter disconnection, malposition of the catheter tip, and CSF leaks may also require device revisions or removal and replacement. It is recommended for a neurosurgeon to be present during the first ICV drug administration, or have on-call availability within 2–3 h, to address complications such as CSF leaks or infection. In the absence of complications, ICV access devices may remain in place indefinitely [25].

7. Future directions

As the use of ICV devices for chronic CNS drug delivery increases to treat a range of conditions, including neurodegenerative and genetic disorders [23,44], the need for best practice guidelines for managing these devices and preventing related complications becomes critical. Advances in ICV device technology may not only improve the precision of CNS drug delivery but also minimize complications. For example, an ICV device may be integrated with implanted pumps with drug reservoirs that could enable longer-term and more continuous dosing. These pumps could incorporate biometric feedback and CSF sampling at defined intervals to measure defined treatment-related biomarkers. As ICV device use expands to include other treatment modalities like immunotherapy [41], such biometric feedback features could allow real-time monitoring of immune response markers during treatment.

8. Conclusions

ICV drug delivery is an established route of drug administration into the CNS and can be performed safely when stringent measures are taken to minimize complications. By strictly following aseptic techniques, creating and consistently following institution protocols, and limiting device access to a select group of knowledgeable personnel, the rate of infection and complications can be kept at a minimum. Standardizing practices and developing consensus-based guidelines are expected to facilitate the safe, long-term use of ICV drug delivery devices.

Declaration of conflicting interests

Funding

Acknowledgements

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