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External Ventricular Drain Infections

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1. Introduction

The insertion of ventricular catheter is one of the most commonly performed procedures in neurosurgery. External ventricular drainage (EVD) is a reliable, accurate and cost-effective means of monitoring intracranial pressure (ICP) in acute traumatic brain injuries, subarachnoid hemorrhages, hemorrhagic and ischemic strokes. Another indication for EVD is the need for temporary cerebrospinal fluid (CSF) diversion for the treatment of acute hydrocephalus caused by intraventricular hemorrhages (IVH), infective meningitis, and space occupying lesions that obstruct CSF flow such as intracerebral hematomas and tumors. Under these circumstances, EVD serves to monitor disease progression and response to treatment until the offending pathology resolves or is dealt with definitively. As a means of CSF diversion, EVD has the advantage over permanent shunting in that CSF drainage is controlled and monitored. It can also be used as an access to the ventricles for intraventricular fibrinolysis treatment in IVH, antibiotics instillation in ventriculitis, and the performance of ventriculography (Gaberel, et al., 2011). However, EVD is only a temporizing measure for the treatment of hydrocephalus. If permanent CSF diversion is required, conversion into an internalized system using, for example, ventriculo-peritoneal shunting is necessary.

2. Surgical procedure

Depending on the available expertise and facilities, EVD may be performed by neurosurgeons, general surgeons, emergency physicians or intensivists in the operating theatre or in the ward (Ehtisham, et al., 2009). Under aseptic conditions, a scalp incision is made over the insertion site. Commonly, the Kocher's point is used which is located 2.5 cm lateral to the midline (or at the mid-pupillary line), 11 cm posterior to the nasion. To avoid the motor cortex, it should be at least one cm anterior to the coronal suture. A burr hole is then performed. After opening the dura, a ventricular catheter is passed into the ipsilateral lateral ventricle transcerebrally. This may be done free-handedly or under the guidance of ultrasound or stereotaxy. After confirming CSF drainage, the distal end of the catheter is tunneled subcutaneously and allowed to exit the skin approximately 5-cm away from the burr hole site. The catheter is connected to a closed external drainage system with an attached ICP monitoring transducer. Other authorities may elect to close the ventricular catheter with a subcutaneous reservoir without skin tunneling or externalization of the

catheter. CSF drainage is achieved post-operatively by percutaneous needle puncture of the reservoir. In general, prophylactic antibiotics would be given perioperatively. Post-operative antibiotics may be given depending on individual surgeons' preferences or protocols. The implications of these variations in practices will be discussed later.

3. External ventricular drain infection

Complications arising from EVD include hemorrhage, misplacement, dislodgement, disconnection, blockage, and, most significantly, infection. EVD-related infections may lead to further serious complications such as ventriculitis, meningitis, cerebritis, brain abscess and subdural empyema. These complications can cause profound neurological damages, significant morbidities and mortalities. Even when successfully treated, EVD-related infections may impair rehabilitation progress and negatively affect the overall prognosis of the initial conditions. An infected EVD contraindicates immediate permanent shunting and may therefore delay definitive CSF diversion. It significantly prolongs hospital stay and increases cost. Lyke et al calculated the cost of treatment and hospital stay days of a patient with ventriculitis to be as high as US$85,674.27 and 30.8 days (95% CI, 23.9–37.7, *P*=.009), respectively, compared with $55,339.21 and 22.6 days (95% CI, 19.1–26.0, *P*=.03) in those without ventriculitis. Patients in the infected group also suffered from more severe neurological damages (RR 5.33, 95% CI, 1.18–32.5) (Lyke, et al., 2001). EVD-related infections require immediate and prolonged treatment once detected. Empirical antibiotics with good CSF penetration should be given to cover the common offending organisms. The commonly used agents are cephalosporins and rifampicin. Intraventricular vancomycin may be used for resistant organisms. Revision of the EVD at a different site should be considered if CSF diversion or ICP monitoring is still required (Beer, et al., 2009).

3.1 Mechanisms of infection

The presence of an EVD essentially externalizes the intra-cranial cavity and ventricular system, and is a potential route for retrograde infection. The ventricular catheter as an indwelling foreign body is prone to bacterial colonization that may result from other unrelated sources such as systemic bacteremia. The current opinion is that EVD-related infections may arise from either (i) inoculation of skin flora during insertion, and/or (ii) contamination and colonization of the drainage system during the post-operative period, with subsequent retrograde infections (Lo, et al., 2007). The risk of inoculation is related to the sterility of the insertion procedure. It may increase with repeated revisions due to elective replacement or other clinical indications. The risk of colonization and contamination is affected by the manipulation of the drainage system, EVD maintenance protocol, and the technique of insertion (Hetem, et al., 2010). The mechanism is likely to be multifactorial and varies between individual patients.

3.2 Definition of infection

There is to date no universally accepted definition for EVD-related infection. Most authorities defined EVD-related meningitis or ventriculitis as the presence of a positive CSF microbiological culture (Lo, et al., 2007; Mayhall, et al., 1984; Schade, et al., 2005). CSF culture growing commensal organisms without other signs of infection such as altered

CSF chemistry, meningism, systemic sepsis, or the perceived need for antibiotic therapy, are considered by many to represent colonization of the EVD only rather than a genuine infection (Lozier, et al., 2008). This definition has been modified from the respective criteria set by the Centers for Disease Control and Prevention (Horan, 2004). Meanwhile some authorities adopt a more stringent definition of infection that requires the presence CSF pleiocytosis and biochemical changes (elevated CSF protein and/or decreased glucose), together with the presence of a positive CSF culture (Pfisterer, et al., 2003). Because of the varied definitions, the reported incidences of EVD-related infections ranged widely from 0 to 27% with a mean of 8.8% (Lozier, et al., 2008). This makes risk factors analysis, and the comparisons between different preventive and management protocols difficult.

3.3 Bacteriology

Coagulase-negative *Staphylococcus* is consistently reported to be the most common bacteria isolated in patients with EVD-related infections, accounting for up to 47% of infected cases (Zabramski, et al., 2003). Other common organisms include *Enterococcus, Enterobacter* and *Staphylococcus aureus.* This pattern coincides with that of the usual skin flora and hospital environment although the bacteriology may also be influenced by the presence of different nosocomial microorganisms in different institutions. Gram-positive organisms are classically associated with ventriculitis, and some centers, including the author's institution, noted that ventriculitis associated with EVD were not uncommonly caused by gram-negative bacteria such as *Klebsiella*. This is postulated to be a nosocomial colonization caused by prolonged hospital stay and the selection pressure from prophylactic antibiotics targeting gram-positive organisms (Lyke, et al., 2001).

3.4 Risk factors

Many studies have been conducted to indentify risk factors for EVD-related infections. Critical reviews of these published series have identified several important factors which will be discussed in the following sections (Dasic, et al., 2006; Hoefnagel, et al., 2008; Lozier, et al., 2008).

3.4.1 Subarachnoid hemorrhage (SAH) and Intraventricular hemorrhage (IVH)

The majority of published series reported statistically significant higher incidence of EVD-related infections in patients with SAH or IVH when compared with patients with non-hemorrhagic pathologies (Hoefnagel, et al., 2008; Stenager, et al., 1986). This has been postulated to be the result of frequent manipulations of the drainage system for flushing blocked EVD, the infusion of fibrinolytic agents, and the higher chance of EVD revision in these subgroups of patient with hemorrhages (Hoefnagel, et al., 2008). In a review by Lozier et al, the risk of infection was found to be 6 to 10% higher in patients with hemorrhages (Lozier, et al., 2008).

3.4.2 Craniotomy and other neurosurgical procedures

The conduction of craniotomies or other neurosurgical procedures were found to be a risk factor for EVD-related infections when compared with patients who had received EVD

alone. Holloway et al studied 584 patients of whom 211 had undergone neurosurgical procedures other than the insertion of EVD. The infection rate in this group of patients was 15.2%, compared with 7.8% in the EVD-only group (Holloway, et al., 1996). Mayhall et al also reported that 68% of patients with EVD-related infections had other neurosurgical procedures performed, while only 40% non-infected patients did (P =0.02) (Mayhall, et al., 1984).

3.4.3 Venue of insertion and skill level of surgeon

Many authorities advocated the operating theatre as a preferred venue for EVD insertion (Bader, et al., 1995). However, Roitberg et al, and Lo et al, demonstrated separately that inserting EVDs in the intensive care units, emergency rooms or neurosurgical wards was not inferior in terms of infection risks or other complications (Lo, et al., 2007; Roitberg, et al., 2001). The location of insertion did not appear to affect the risk of infection provided that strict aseptic technique was used. There was also no significant difference amongst EVDs that were performed by neurosurgical trainees, consultants or neurointensivists (Ehtisham, et al., 2009; Lo, et al., 2007).

3.4.4 Duration of drainage

The literature was very much divided on the issue of whether and how the duration of external CSF drainage may affect the risk of infection. A recent multivariate analysis of seven series with a total of 2199 EVDs in 2113 patients demonstrated no association between the risk of infection and the duration of drainage (Lozier, et al., 2002). The timing of EVD-related infections appeared to follow a normal distribution during the first five post-operative days, and the majority of infections occurred between day two and day 11. Lo et al postulated that these early infections may arise from initial inoculations, which developed into detectable infections after variable incubation periods of around five days (Hetem, et al., 2010). A delayed peak of infection has also been observed after day 20, but the small number of reported cases rendered confirmation difficult (Winfield, et al., 1993).

Based on the belief that the risk of infection would increase with prolonged EVD, some authorities have advocated elective revisions of EVD after a fixed interval of, say, five days. However, the review by Park et al on 595 patients with EVD insertions found that the daily infection rates would plateau after day 4 post-insertion, and remain steady beyond day 10 (Park, et al., 2004). In reported series that adopted the practice of regular elective EVD revisions, revisions were not found to decrease infection rate significantly, and may actually increase it (Lo, et al., 2007; Wong, et al., 2002). Current evidence indicates that although the duration of drainage is an independent risk factor for EVD-related infections, routine revision of EVD in the absence of other clinical indications is not recommended. It is, however, prudent and logical to minimize the duration of drainage and to remove the catheter as soon as it is safe and feasible to do so.

3.4.5 Manipulation of the EVD system

Manipulations and opening of the otherwise closed EVD system for CSF sampling or flushing may introduce microorganisms and potentially cause infection. Aucoin et al reported a 6% increase in relative risk of infection for patients whose EVD was flushed

with bacitracin solution (Aucoin, et al., 1986). A previously published report by the present authors also demonstrated intraventricular urokinase infusion as one of the risk factors for infection (Leung, et al., 2007). Historically, CSF was sampled routinely and indeed daily in some centers in an attempt to pick up early infections. This practice has been shown to increase the risk of infection; decreasing the frequency of CSF sampling to once every 3 days was associated with a lower incidence of ventriculitis (OR 0.44, 95% CI 0.22-0.88, p = 0.02) (Williams, et al., 2011). CSF sampling should be performed when there is clinical suspicion of infection but routine sampling is no longer encouraged (Korinek, et al., 2005).

In our center, we adopt a minimal-touch technique in handling EVD systems. If CSF sampling or infusion of intraventricular medication is required, we employ strict hand hygiene protocol, sterile gloving, and disinfection of the 3-way connector site with povidone-iodine before breaching the drainage system. Although it is difficult to demonstrate conclusively the benefit of these practices, many authorities in the literature support this logical awareness of strict hygiene in their EVD maintenance protocol (Korinek, et al., 2005; Leverstein-van Hall, et al., 2010). CSF leakage around the site of EVD has been identified as another major risk factor (Korinek, et al., 2005; Leverstein-van Hall, et al., 2010; Lyke, et al., 2001). Lyke et al reported that CSF leakage conferred a significant risk for ventriculitis (OR, 7.33; 95% CI, 1.05–37.47; P=.003) (Lyke, et al., 2001). Meticulous suturing of skin after EVD removal and better coupling of catheter size and dural puncture hole may effectively reduce the risk of infection (Korinek, et al., 2005). Interestingly, accidental disconnection, dislodgement or changes in the components of the system were not found to increase infection risks.

3.4.6 Prophylactic antibiotics

Antibiotic prophylaxis is a widely used strategy to prevent EVD-related infections. There is, however, no consensus as to what and for how long it should be given. As demonstrated by a recent survey by McCarthy et al, responders in Europe favored a single dose of antibiotics given immediately before the operation, while those from Asia and North America tend to cover also the whole period of post-operative drainage (McCarthy, et al., 2010). In a meta-analysis by Sonabend et al, the use of prophylactic antibiotics was found to significantly reduce the risk of EVD- related infections, but the authors also noted that the available data were of suboptimal quality, and that there were wide variations in the types of antibiotics used and the definitions of infection (Sonabend, et al., 2011).

Several randomized controlled trials (RCT) have been conducted to investigate the prolonged use of prophylactic antibiotics. In one study, co-trimoxazole given for the whole lifespan of an EVD did not result in a lower infection rate (Blomstedt, 1985). Another study found that the prolonged use of ampicillin/sulbactam and aztreonam resulted in a lower infection rate compared with a single dose of perioperative ampicillin/sulbactam. However the former was associated with infections caused by resistant organisms such as methicillin-resistant *Staphylococcus aureus,* and gram-negative organisms such as *Pseudomonas* or *Klebsiella* (Poon, et al., 1998). The role of prolonged systemic antibiotics and the best regimens are yet to be defined.

Apart from systemic antibiotics, some investigators have described the possible beneficial effect of prophylactic intraventricular antibiotics. Ragel et al demonstrated that using

prophylactic intraventricular vancomycin and gentamicin together with systemic antibiotics significantly decreased the risk of infection in shunted patients (Ragel, et al., 2006). Whether this beneficial effect can be translated to EVD remains to be confirmed.

3.4.7 Coated ventricular catheter

The potential roles of coated EVD catheter have received a lot of attention and research effort in recent years. The underlying rationale is that coating the surface of the catheter with special materials or antibiotics may decrease bacterial colonization and thus prevent infection. The findings were controversial depending on the coating material used. One RCT did not show any benefit with the use of hydrogel-coated catheters presoaked in bacitracin solution (Kaufmann, et al., 2004). Silver-coated catheters were first used in central venous line with equivocal results (Bach, et al., 1999; Kalfon, et al., 2007). Thereafter, two retrospective analyses have been conducted using silver nanoparticle-impregnated catheters for EVD. Both studies showed significant reduction in infection rates and a trend of reduced bacterial colonization despite the studies' small sample sizes (Fichtner, et al., 2010; Lackner, et al., 2008).

Antibiotics-impregnated catheter is an important development. To date, two RCTs and 3 observational studies have been conducted to investigate the efficacy of antibiotics-impregnated catheters. Zabramski et al studied minocycline/rifampicin-coated catheters (M/R catheters) in a RCT involving 149 cases of M/R catheters and 139 controls with standard silastic catheters. Both groups received systemic antibiotics throughout the lifespan of the EVD. The infection rate in the M/R catheter group was 1.3% compared with 9.6% in the standard EVD group ($P<0.0012$) (Zabramski, et al., 2003). Sonabend et al pooled the data of the above RCT with other studies for a meta-analysis, and demonstrated a risk ratio of 0.19 (95%CI 0.07-0.52) for EVD-related infections in patients with antibiotics-impregnated catheters (Sonabend, et al., 2011). A more recent RCT by Abla et al compared the efficacy of M/R catheters and clindamycin/rifampicin-impregnated catheters (C/R catheters). A total of 129 patients were randomized into receiving either M/R or C/R catheters in a 3-monthly rotation. The mean duration of EVD was 12.7 and 11.8 days in the M/R and C/R groups, respectively. A single dose of perioperative cefuroxime was given to 45% of M/R group and 55% of C/R group patients. The study demonstrated a remarkable 0% infection rate in both groups of patients (Abla, et al., 2011). Only one patient showed a minimal growth of *Staphylococcus epidermidis* in one culture broth, with the culture in another broth, blood agar, gram stain being negative for the same CSF specimen. The potential side-effects of these catheters include allergy to the impregnated antibiotics and the selection of resistant organisms. To date, there have been no reports of antibiotics-impregnated catheters increasing the risk of selection of resistant organisms. A drawback of these catheters is the relaively high cost which may prevent its adoption world-wide.

3.4.8 Subcutaneous catheter tunnel

Historically, one major development was the tunneling technique which created a subcutaneous tract between the burr hole and catheter exit site. Freidman et al first proposed subcutaneous tunneling of the EVD catheter, and reported an infection rate of 0% in a series of 100 patients (Friedman & Vries, 1980). Similar principle of preventing

ascending infection has been applied to the design of indwelling intravenous catheters and, indeed, intravenous Broviac catheter has been described for cerebrospinal fluid (CSF) drainage. Although infection continued to be reported with the tunneling technique, the latter has become standard neurosurgical practice. Since then this practice has been widely adopted in the majority of neurosurgical centers. The idea was further elaborated by Khanna et al who advocated the construction of a long subcutaneous tunnel which exits over the anterior chest or abdominal wall. His group demonstrated an inverse relationship between tunnel length and infection rate (Khanna, et al., 1995). The rationale of this extended-tunnel technique was that bacterial contamination of the ventricular catheter at the site of skin penetration would act an important source of ascending infection, and that removing this site from the central nervous system would reduce the risk of infection. The disadvantages of this long-tunnel EVD include the presence of a large dead space that is theoretically prone to blockage, and the requirement of general anesthesia for the removal of the system. In our center we have previously used long-tunnel EVD which will be disucssed in the next section.

4. Extended-tunnel EVD

The procedure is performed with prophylactic antibiotics cover using intravenous cefazoline (2 grams) or co-trimoxazole (960 mg). A standard burr hole is made at the Kocher's point or posterior parietal region. An extended subcutaneous tunnel measuring 40 to 50 cm was developed from the burr hole site down to the anterior chest wall using a metallic trocar. Ventricular puncture is performed and the ventricular catheter is connected to a distal silastic catheter through an interposing Rickham CSF reservoir (Codman, Medos, Switzerland). The distal catheter is then passed down the subcutaneous tunnel and exits through the chest wall. The distal catheter is then connected to a closed external drainage system. No antibiotic is given post-operatively unless indicated for CSF or systemic infections. When CSF drainage is no longer required, removal of the catheter system is performed at the cranial end under general anesthesia. Alternatively, the distal catheter can be divided and plugged off over the chest wall under local anesthesia.

4.1 Patient outcome

We have reviewed 114 patients who have previously received the extended-tunnel EVD at our institution. There were 61 men and 53 women, ranging in age from 4 months to 90 years old (mean age = 52.6 years). The mean duration of CSF drainage was 20 days (median = 13 days). Fourteen patients received more than one EVD which yielded a total of 133 procedures. Thirty (22.6%) cases started with prior infections and 103 (77.4%) were infection-free at the time of insertion. Within the latter group, new infections developed in seven cases, yielding an overall infection rate of 6.8%. The mean time to infection was 9.7 days (median = 5.0 days). A trend of increasing daily infection risk could be observed during the first five days. It remained relatively low and constant in the second week and then increased again after the 14th day. Only intraventricular injection of urokinase was identified as a weakly significant risk factor (relative risk = 4.78, 95% confidence interval = 0.96 – 23.89, p = 0.039). Gender, age, primary neurosurgical diagnosis, immunodeficiency, diabetes mellitus, use of steroids, recent craniotomy, systemic sepsis at the time of and after 'long EVD' insertion were not found to be statistically significant risk factors of infection.

Prior to the above study period, both conventional and the extended-tunnel EVDs may be used according to individual surgeons' preferences. During this early phase, there was a total of 158 EVDs performed, including 33 (20.9%) long-EVDs. There were a total of 9 infections, yielding an overall infection rate of 5.8%. The infection rates for long- and conventional EVDs were similar at 6.25% and 5.65%, respectively (p=0.896). Operation time, emergency versus elective operations, operating surgeons, age of patient, nature of disease, and duration of drainage were not found to be significant risk factors for infections. Diabetes mellitus and immunosuppression were found to be significantly associated with infections, with odd ratios of 5.39 (95% C.I.=1.33-21.86) and 6.71 (95% C.I.=1.14-39.46), respectively. Overall, our findings indicated that the extended-tunnel techqniue was associated with a similar risk of infection as the conventional EVD. Although some authorities may continue to advocate the extended-tunnel technique, there is no evidence to show that it adds any distinct advantage, and we have since stopped using the technique.

5. Protocol-driven practice

Some authorities have demonstrated that adhering to a predefined protocol of EVD insertion and maintenance that incorporates evidence-based measures as discussed above would significantly reduce the risk of EVD-related infections. Infection rates have been halved by strictly following a protocol involving aseptic insertion, use of prophylactic antibiotics, subcutaneous tunneling, no routine EVD revision, and minimal manipulation such as CSF sampling; violation of the protocol was associated with increased infection rate (Dasic, et al., 2006; Korinek, et al., 2005; Leverstein-van Hall, et al., 2010). Current evidence indicates that a strict EVD protocol should be adopted in neurosurgical centers. A protocol should cover the following aspects:

Insertion of EVD

- performed in the operating theatre whenever possible, with a minimal number of attending staff
- performed in a dedicated clean treatment room if the procedure has to be done outside the operating theatre, with the surgeon and the assisting nurse dressed in sterile gown and gloves after proper hand hygiene measures
- prophylactic antibiotics to cover skin flora before incision
- shampoo the entire scalp with betadine, and disinfect with iodine alcohol
- tunneling the catheter subcutaneously for at least five cm
- covering the wound with sterile dressing

Maintenance of EVD

- respecting the close system as far as possible
- avoid CSF sampling unless infection is clinically suspected
- disinfect the connector and adopt strict aseptic technique if any breach of the system is needed
- no routine EVD revision

Removal of EVD

- aseptic condition and disinfect site with povidone-iodine/alcohol
- suture wound carefully to minimize CSF leakage

6. Conclusion

EVD is a commonly performed neurosurgical procedure for the treatment of a variety of neurosurgical conditions including hydrocephalus. It is a useful and reliable temporizing method for ICP monitoring and the controlled release of CSF. Infection is a major and serious complication of EVD that may cause significant morbidities and even mortalities. Several risk factors of EVD-related infections have been identified and preventive measures aimed at reducing these factors have been developed. These include the use of prophylactic systemic antibiotics, antibiotics-coated catheters and subcutaneous catheter tunnelling. EVD that incorporate extended subcutaneous of over 30 cm have been used without the anticipated advantage of being able to reduce infection rates. The causation of EVD-related infections is likely to be multifactorial. Adopting a clearly defined protocol which addresses various aspects of insertion and maintenance is likely to be the effective approach to minimize the occurrence of EVD-related infections.

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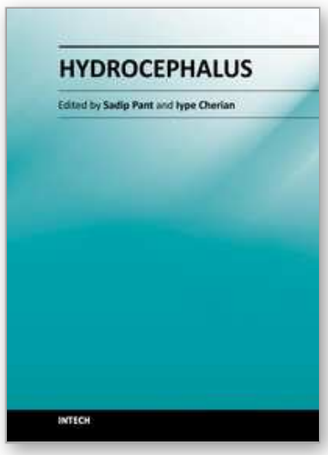

Hydrocephalus

Edited by Dr Sadip Pant

ISBN 978-953-51-0162-8

Hard cover, 214 pages

Publisher InTech

Published online 24, February, 2012

Published in print edition February, 2012

Description of hydrocephalus can be found in ancient medical literature from Egypt as old as 500 AD. Hydrocephalus is characterized by abnormal accumulation of cerebrospinal fluid (CSF) in the ventricles of the brain. This results in the rise of intracranial pressure inside the skull causing progressive increase in the size of the head, seizure, tunneling of vision, and mental disability. The clinical presentation of hydrocephalus varies with age of onset and chronicity of the underlying disease process. Acute dilatation of the ventricular system manifests with features of raised intracranial pressure while chronic dilatation has a more insidious onset presenting as Adams triad. Treatment is generally surgical by creating various types of cerebral shunts. Role of endoscopic has emerged lately in the management of hydrocephalus.

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