Use of a cyanoacrylate skin adhesive to reduce external ventricular drain infection rates

Clinical article

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Object. Ventriculitis related to external ventricular drain (EVD) placement is a significant source of morbidity in neurological intensive care patients. Current rates of EVD-related infections range from 2% to 45% in the literature. The authors sought to determine if a 2-octyl cyanoacrylate adhesive would result in lower infection rate than standard semiocclusive dressings.

Methods. The authors tracked ventriculitis rates via CSF cultures among 259 patients whose EVD sites were dressed with sterile semiocclusive dressings and underwent routine sterile dressing exchanges every 48 hours. They analyzed data obtained in an additional 113 patients whose EVD sites were dressed one time with a surgical adhesive, 2-octyl cyanoacrylate.

Results. Ventriculitis rate in patients with standard bioocclusive dressings and wound care was 15.1%, whereas that in patients with a 2-octyl cyanoacrylate dressing was 3.54% (p = 0.002). Staphylococcus genus accounted for 79.5% of instances of ventriculitis among patients with bioocclusive dressings and routine wound care, whereas it accounted for 25.0% of the instances of ventriculitis among patients with a liquid polymer sealant dressing. A 90% reduction in Staphylococcus infection completely accounts for the observed effect (p = 0.04).

Conclusions. The one-time application of 2-octyl cyanoacrylate to EVD wounds and exit sites provided superior protection against EVD-related ventriculitis compared to conventional EVD-site wound care. Likely this protection results from a barrier to the entry of gram-positive skin flora along the EVD exit tract. The results should be validated in a randomized trial. (http://thejns.org/doi/abs/10.3171/2013.12.JNS13700)

Key Words • external ventricular drainage • iatrogenic infection • ventriculitis • cyanoacrylate skin adhesive

External ventricular drains (EVDs) are commonly used in neurosurgery. Frequent indications include severe head injury, intracranial hemorrhage, obstructive hydrocephalus, and shunt malfunction. It is often necessary to implant these drains for a protracted period of time, and they drain CSF, which is an excellent medium for bacterial growth. Consequently, EVD infection is a significant clinical problem. Such infections are defined by the Centers for Disease Control and Prevention (CDC) as meningitis or ventriculitis resulting from an EVD wherein organisms are cultured from the CSF and the patient has clinical signs/symptoms (fever, meningeal signs, and so on) along with appropriate CSF markers. These infections frequently necessitate greater therapeutic interventions, increase intensive care unit (ICU) stays, cost on average $30,000 to treat, and may lead to lifelong cognitive disabilities. The incidence of EVD infections reported in the literature varies widely, from 2% to 45%, but in most reports it ranges from 10% to 20%. Factors influencing infection include duration of drainage, presence of intraventricular or subarachnoid hemorrhage, EVD flushing, and routine catheter changes.

Given the profound impact EVD infections can have on hospital costs and patient outcomes, the minimization of EVD-related infections remains a great concern among neurointensivists and neurosurgeons. Interventions such as routine catheter exchanges, prolonged prophylactic antibiotic treatments, and rifampin/clindamycin-impregnated catheters have all been trialed in studies but have shown little impact on infection rates. To date, one of the few consistent factors proven to reduce EVD-related infections has been the repeated application of meticulous sterile post-EVD insertion wound care. At Temple University,
fluctuations in EVD-related infection rates have been noted for years, with the arrival of new staff or loosening in adherence to protocol corresponding with higher ventriculitis rates in the ICU. Therefore, we sought a simple-to-implement intervention that would maintain quality wound care while reducing the need for meticulous and repetitive human interventions, as the current standard of care for EVD wound care requires.

The material 2-octyl cyanoacrylate (Dermabond, Ethicon, Inc.) is a water-catalyzed adhesive that is especially formulated for use on skin and indicated for the primary closure of small, clean surgical wounds and trauma-induced lacerations. It is also approved as a barrier against common bacterial microbes. Given these specifications, it represented a potentially useful alternative for the standard sterile dressings used with EVD catheter sites. The authors investigated its utility for preventing EVD-related infection, and this study explores EVD-related infection rates when Dermabond is placed over the primary incision and at the tunneled EVD exit site.

**Methods**

We evaluated a group of patients treated between 2004 and 2012. The control group consisted of a retrospective review of data obtained in 259 patients treated from 2004 through 2009. They all underwent placement of an antibiotic-impregnated EVD catheter (Bactiseal, Codman & Shurtleff), either at bedside or in the operating room, using a sterile technique. A single dose of an appropriate prophylactic antibiotic agent, 1 g of Ancef or vancomycin, was administered immediately prior to all catheter insertion procedures. Wounds and exit sites were dressed with a nonstick dressing and a semiocclusive adhesive dressing. These dressings were steriley replaced every 48 hours per ICU protocol, in accordance with CDC central line–associated blood stream infection recommendations and reported protocols for EVD-site care described in the literature. The closed drainage portion of the EVD collection system from the proximal stopcock to the closed collection system was routinely flushed with a prophylactic gentamicin solution, as per standard hospital-approved protocol. The portion of the catheter proximal to the first stopcock—that is, the tunnelled and implanted portion—did not receive gentamicin. Patients with known cranial or intracranial infections at the time of EVD insertion were excluded from the study.

In June 2010, we implemented our practice change and began dressing the EVD wounds with 2-octyl cyanoacrylate adhesive at the time of EVD insertion. As a matter of routine care, we collected data on patients with antibiotic-impregnated EVDs of the same type used in the control arm. At that point we conducted a retrospective analysis of the data from each group. All patients had their EVDs placed in the same fashion as controls, save that their wound and EVD exit sites were dressed one time with surgical adhesive at the time of initial catheter insertion.

Collected data from each group included standard admission demographic information and admission clinical data. Laboratory values, including serum white blood cell (WBC) count, CSF WBC count, CSF red blood cell (RBC) count, and non-CSF culture data were noted and recorded. For the purposes of this study, any positive CSF culture or Gram stain was defined as an infection, in line with CDC definitions of EVD-related infection. Samples of CSF were drawn whenever the patient had a temperature exceeding 38.0°C or an elevated WBC count (> 10,000), a rising WBC count trend, or a change in mental status. The study was approved by the Temple University Institutional Review Board.

We performed a binomial regression analysis of infection rates as they related to sex, age, admission Glasgow Coma Scale (GCS) score, systemic infections, duration of EVD implantation, other cranial procedures, nature of intracranial pathology, and type of EVD-site dressing. Kaplan-Meier analysis of the time until EVD-related infections in the 2 EVD dressing groups was performed, and the log-rank (Mantel-Cox) test was used to determine p values. Culture results for all patients with EVD-related infections were reviewed, and the frequency of *Staphylococcus epidermidis* infections was compared using the Fisher exact test. We also performed a number-needed-to-treat analysis for cost purposes. A receiver operating characteristic (ROC) curve analysis was performed on scalar variables to delineate values predictive of ventriculitis in EVD-treated patients. Demographic data were compared using Pearson’s chi-square test. In all cases, a p value of < 0.05 was deemed significant. All statistical tests were performed using SPSS 17.0 (IBM).

**Results**

The demographics of each group are summarized in Table 1. Overall, the control group had a significantly older population than the study group (59.5 years vs 53.2 years, respectively; p < 0.001) and included significantly more patients with nontraumatic intracranial hemorrhages (88.5% vs 71.7%, respectively; p < 0.001). The average duration of EVD implantation among controls was 13.0 days, whereas that among patients treated with Dermabond was 10.9 days (p = 0.08). There were significantly more instances of positive cultures outside of the CSF (with or without attendant fevers, elevations in WBC count, or clinical symptoms of infection) in control patients than Dermabond-treated patients (71.0% vs 56.6%, respectively; p = 0.01), although the breakdown of positive culture sources remained similar between the groups (Fig. 1).

Reviewing rates of infection relative to patient age, there was an increased percentage of EVD-related ventriculitis among patients younger than 60 years in our patient population, although this trend did not meet significance after confounders such as duration of EVD implantation and presenting GCS score were accounted for in binary logistic regression analysis (14.5% vs 7.9% [< 60 years of age vs ≥ 60 years of age, respectively], p = 0.28). Evaluation of patient diagnosis, whether individually reviewed (data not shown) or when categorized into “nontraumatic intracranial hemorrhage” (aneurysmal subarachnoid hemorrhage, hypertensive bleeds, lobar hemorrhage, and arteriovenous malformation) and “all others” (stroke, tumor, epidural hematoma, gunshot wound, subdural hematoma) (p = 0.57), yielded no statistically sig-
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**Table 1: Summary of information collected in control and study patients**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Controls</th>
<th>Cyanoacrylate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F ratio (%)</td>
<td>47.5/52.5</td>
<td>52.2/47.8</td>
<td>0.4</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>59.5</td>
<td>53.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>admission GCS score</td>
<td>8.7</td>
<td>9.1</td>
<td>0.38</td>
</tr>
<tr>
<td>duration of EVD (days)</td>
<td>13.0</td>
<td>10.9</td>
<td>0.08</td>
</tr>
<tr>
<td>admission WBC count</td>
<td>12,600</td>
<td>12,900</td>
<td>0.75</td>
</tr>
<tr>
<td>max WBC count w/ EVD</td>
<td>18,300</td>
<td>20,200</td>
<td>0.09</td>
</tr>
<tr>
<td>diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aneurysmal SAH</td>
<td>25.9</td>
<td>13.3</td>
<td>0.007</td>
</tr>
<tr>
<td>hypertensive ICH</td>
<td>51.0</td>
<td>34.5</td>
<td>0.003</td>
</tr>
<tr>
<td>traumatic SAH</td>
<td>2.7</td>
<td>10.6</td>
<td>0.001</td>
</tr>
<tr>
<td>stroke</td>
<td>0</td>
<td>4.4</td>
<td>0.004</td>
</tr>
<tr>
<td>tumor</td>
<td>0.4</td>
<td>8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SDH</td>
<td>5.0</td>
<td>9.7</td>
<td>0.09</td>
</tr>
<tr>
<td>lobar ICH</td>
<td>11.6</td>
<td>6.9</td>
<td>0.11</td>
</tr>
<tr>
<td>other†</td>
<td>3.5</td>
<td>12.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ICH = intracranial hemorrhage; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.
† This category includes arteriovenous malformation, gunshot wound, epidural hematoma, and congenital hydrocephalus.

A significant association with EVD-related ventriculitis rates. Admission GCS score correlated well with infection rates, with patients with an initial GCS score of less than 13 having significantly higher rates of ventriculitis than those with higher GCS scores (28.5% vs 4.6%, respectively; p = 0.002), although the predictive value of admission GCS score in ROC curve analysis was only weakly significant (p = 0.03, area under the curve [AUC] 0.391). The presence of positive cultures in tissue/fluids other than CSF did not significantly relate to higher rates of ventriculitis when compared with patients without such positive cultures (14.2% vs 6.4%, respectively; p = 0.78).

Reviewing scalar laboratory values via ROC curves, we noted a significant association between EVD-related ventriculitis and a maximum peripheral WBC count > 19,000 (p = 0.001, AUC 0.660, sensitivity 68%, and specificity 59%), a maximum CSF WBC count > 300 cells/mm³ (p < 0.001, AUC 0.769, sensitivity 73%, and specificity 70%), and a maximum CSF WBC/RBC ratio of > 0.03 (p < 0.001, AUC 0.816, sensitivity 73%, and specificity 72%). No significant correlation was noted between initial CSF cell count values or initial peripheral WBC count and ventriculitis.

The duration of EVD implantation did strongly correlate with EVD-related ventriculitis, with these rates rising quickly after 14 days of EVD implantation (Fig. 2). An EVD that remained implanted for more than 17 days strongly predicted the development of a ventriculitis (p < 0.001, AUC 0.837, sensitivity 80%, and specificity 78%).

The control group had an overall infection rate of 15.1%, and the Dermabond-treated group had an infection rate of 3.54%. Binomial regression analysis accounting for age, sex, duration of EVD implantation, presenting intracranial pathology, GCS score (< 13 or > 13), and alternate tissue/fluid-positive cultures showed a statistically significant difference between the 2 groups of EVD dressings (p = 0.002). Based on these data, an odds ratio of 6.774 was calculated (95% CI 1.967–23.323) and a number needed to treat was calculated as 8.7 patients. Examining the rate of ventriculitis over the course of EVD implantation, the average time from EVD insertion until documented ventriculitis was 11.6 days among controls and 11.5 days among the Dermabond-treated patients (p = 0.97). Control patients, however, had a significantly more robust rate of EVD-related ventriculitis early on than did Dermabond-treated patients (Fig. 3) (p = 0.001). After identifying predictive variables above in a univariate regression analysis, we performed a multivariate regression analysis and found only use of Dermabond predicted a decreased infection rate.

Examining the types of bacteria responsible for EVD-
related ventriculitis in the 2 groups revealed a marked trend toward a reduction in *S. epidermidis* infections in the Dermabond group (Fig. 4). This trend was statistically significant (*p* = 0.04).

**Discussion**

Most cases of EVD-related ventriculitis may result from the retrograde migration of skin flora back along the drain exit tract. The offending organism is most commonly *S. epidermidis* (73%); this is followed by *S. aureus* (18%) and then by *Enterococcus faecalis* (2.5%), *Acinetobacter baumannii* (2.5%), or *Pseudomonas aeruginosa* (2.5%). Much effort has been put into limiting the viability of retrograde colonization of the CSF by these organisms. Sterile technique at the time of drain insertion, combined with periprocedural antibiotics, presumably reduces the likelihood of immediate EVD tract contamination; however, the often prolonged duration of implantation of these drains leaves them at risk for future inoculation from skin flora beyond the prepared field. Regular prophylactic antibiotics and routine drain exchanges, although once commonly employed, have now been shown in several randomized controlled trials not to provide long-term benefit in reducing skin flora colonization of the CSF. Several antibacterial EVD catheters have also been used in recent years, with mixed results, in an effort to prevent bacteria from growing along the EVD tract. A randomized controlled trial comparing silver-impregnated EVD catheters to plain EVD catheters demonstrated a significant reduction in EVD catheters demonstrated a significant reduction in EVD-related infections, from 21.4% to 12.3%. In contrast, another randomized controlled trial comparing rifampin- and clindamycin-impregnated catheters to plain EVD catheters found no statistically significant reduction in CSF infections. Moreover, it has been noted by some that the use of these antibiotic-impregnated catheters in ventriculoperitoneal shunt–treated patients has led to the selection of antibiotic-resistant strains of bacteria within the CSF spaces and that CSF results taken in the setting of antibiotic-impregnated catheters may generate false-negative results when attempting to diagnose an EVD-related ventriculitis.

Despite these many novel technologies aimed at reducing bacterial colonization of EVD catheters, one of the few consistently proven methods for reducing EVD-related infections has been the strict execution of sterile dressing care around the catheter wound and exit site. Presumably, maintenance of a meticulous sterile region of skin around the catheter exit site eliminates the possibility of skin flora violating the EVD tract and reaching the CSF. These interventions are laborious, however, and prone to repeated opportunities for human error.

In our study, we demonstrated that a simple, one-time application of a cyanoacrylate surgical adhesive may provide a superior barrier to infection in comparison with conventional sterile wound dressings, reducing EVD-related infections by 4-fold. Given the concomitant 3-fold

![Fig. 2. Overall escalation in ventriculitis over time in the Dermabond and occlusive dressing groups, with an increase in infection rate beyond 14 days of EVD implantation trending toward significance in the occlusive dressing group (*p* = 0.06).](image)

![Fig. 3. Kaplan-Meier graph demonstrating reduction in EVD-related ventriculitis rate in the Dermabond group compared with control group (*p* = 0.001, log-rank test).](image)
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reduction in all species causing ventriculitis in the 2-octyl cyanoacrylate group compared with controls, and the 9-fold reduction in Staphylococcus infection, it can be hypothesized that the cause of this reduction in EVD-related infections is from a reduction in the migration of Staphylococcus and other skin flora along the EVD exit tract. Cyanoacrylates polymerize with water vapor as a catalytic agent, forming a polymer plug around and within the EVD exit site that may result in a seal around the EVD tract with lower microbial permeability than that created by less malleable sterile bioocclusive dressings. Some studies have also suggested that 2-octyl cyanoacrylate may have weak antibacterial properties, allowing it to reduce bacterial wound infections both by physical barrier to bacterial ingrowths and by bactericidal properties.9,10

Some studies have suggested that semiocclusive dressings promote bacterial growth,11,14 which also intimates that frequent dressing changes may promote infection. Indeed, it is our hypothesis that the 2-octyl cyanoacrylate dressing is superior to conventional dressing care in that regard. That being said, there is a sizable body of evidence in the literature demonstrating that carefully administered dressing changes reduce rather than increase EVD-related infections.8,9

From an economic standpoint, Dermabond also offers significant advantages to hospitals. A single vial of Dermabond costs $25 (http://www.amazon.com, accessed 4/8/13), while an EVD-related ventriculitis results in additional charges of $30,000 per patient on average.20 We calculated a number needed to treat of 8.7 patients to prevent one infection. An expenditure of $198.00 worth of Dermabond sealant applied initially at EVD exit wounds can potentially eliminate $30,000 worth of ventriculitis care expenses for a savings of $29,802.00 per 9 patients in whom Dermabond is applied at the EVD wound/exit site, resulting in an approximate expected value of savings of $3400 per patient.

In addition to the positive effect of 2-octyl cyanoacrylate wound dressing on EVD infection, our study also identified several other predictors of EVD-related infection, unrelated to wound care, including duration of EVD implantation and admission GCS score. Previous studies have noted the importance of limiting the time in which an EVD remains in place, as much as individual clinical scenarios allow.4,13 In our study, we saw marked rises in ventriculitis rates after EVD implantation durations of 14 days. An ROC analysis also verified that EVDs that remained in place in excess of 17 days were highly predictive of an EVD-related ventriculitis. This finding, as with past investigations into EVD-related infections, continues to underscore the need to remove EVD catheters as soon as clinically feasible as the best method for preventing a ventriculitis. In contrast to EVD catheter implantation duration, the relationship between admission GCS score and EVD-related infections has been sparsely addressed in the literature. In one article, the authors retrospectively tracked GCS scores during EVD-related infections and found no correlation with GCS score trends and the presence or absence of ventriculitis, but they did not attempt to correlate admission GCS score with subsequent EVD-related ventriculitis.15 In our study, we specifically explored this relationship and found that admission GCS score correlated strongly with ventriculitis rates, with GCS scores impaired (< 13) forming a robust correlate with higher rates of EVD-related ventriculitis. This relationship might be expected to relate to unconscious patients’ requiring longer periods of intracranial pressure monitoring, yet this correlation remained significant in regression analysis after confounding factors, such as EVD duration, were accounted for.

Despite these many positives, some limitations to our conclusions exist. One variable that could affect the nature of our results would be the use of a prophylactic EVD distal system antibiotic flush. Conceivably, the choice of antibiotic used could predispose toward particular bacterial flora. Gentamycin has been the approved standard of care for many years at our institution, but there is little in the published literature to support any one particular choice. While the efficacy of different distal drainage system prophylactic antibiotics is an important one, our study was not designed to clarify that question, and as such, that variable was static in both arms of the study.

The retrospective and nonrandomized nature of this review does prevent us from handling certain temporal variables including trends in diagnosis and patient population and variances among care providers. For example, patterns in the care of cerebrovascular patients in our region shifted during the course of this study, which accounts for most of the changes in demographics noted between the 2 groups. We attempted to account for these differences in our regression analysis and did not find any significance in these diagnoses regarding EVD-related infections. Nonetheless, even the multivariate approach that we used cannot uncover time-trend biases between the 2 groups. Quality and safety have become a hot operational topic during the time of the study, so perhaps more general attention to nosocomial infection could contribute to the difference between groups and not be accounted for in these data. While the published literature suggested a positive effect of meticulous dressing changes, our data cannot resolve whether the difference in infection rates is related to higher infection rates with semiocclusive dressings or infection suppression by Dermabond. Ultimately, a randomized clinical trial is necessary to evaluate the effect of dressing EVD wounds with a surgical adhesive.
Conclusions

External ventricular drain–related infections represent a source of serious morbidity and mortality among neurosurgical patients. Overwhelmingly, these infections derive from *S. epidermidis* and other skin flora. Current sterile dressing methods, while effective in preventing EVD catheter colonization with skin flora when rigorously implemented, are time intensive and prone to lapses in sterile technique. The surgical adhesive, 2-octyl cyanoacrylate, when applied at the time of EVD catheter insertion, appears to provide a barrier to skin flora, was shown to lead to a statistically significant reduction in EVD-related ventriculitis, and is easy to use. Additionally, a single application of Dermabond may be less expensive than multiple occlusive dressings and valuable nurse-related clinical time over the course of a typical EVD duration. The low cost, ease of use, and our preliminary results showing a reduction in EVD-related ventriculitis suggest that 2-octyl cyanoacrylate adhesive is a clinically sound and cost-effective method for EVD wound care. A randomized clinical trial is necessary to validate these results.

Disclosure

Dr. Connolly is a consultant for Covidien, Inc.

Author contributions to the study and manuscript preparation include the following: Conception and design: Connolly, Bookland. Acquisition of data: Bookland, Sukul. Analysis and interpretation of data: all authors. Drafting the article: Bookland, Sukul. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Connolly. Statistical analysis: Bookland.

Study supervision: Connolly.

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