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Bleeding and Infection With External Ventricular Drainage: A Systematic Review in Comparison to Adjudicated Adverse Events in the Ongoing CLEAR III Trial

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Abstract

Background—Retrospective series report varied rates of bleeding and infection with external ventricular drainage (EVD). There have been no prospective studies of these risks with systematic surveillance, threshold definitions, or independent adjudication.

Objective—We analyzed the rate of complications in the ongoing CLEAR III trial, providing a comparison with a systematic review of complications of EVD in the literature.

Methods—Cases were prospectively enrolled in the CLEAR III trial after placement of EVD for obstructive intraventricular hemorrhage (IVH) and randomized to receive recombinant tissue plasminogen activator (rt-PA) or placebo. We counted any detected new hemorrhage (catheter tract hemorrhage or any other distant hemorrhage) on CT scan within 30 days from the randomization. Meta-analysis of published series of EVD placement was compiled using STATA software.

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Results—Growing or unstable hemorrhage was reported as a cause of exclusion from the trial in 74 of 5707 cases (1.3%) screened for CLEAR III. The first 250 cases enrolled have completed adjudication of adverse events. Forty-two subjects (16.8%) experienced one or more new bleeds or expansions, and 6 of 250 subjects (2.4%) suffered symptomatic hemorrhages. Eleven cases (4.4%) had culture-proven bacterial meningitis or ventriculitis.

Conclusion—Risks of bleeding and infection in the ongoing CLEAR III trial are comparable to those previously reported in EVD case series. In the current study, rates of new bleeds and bacterial meningitis/ventriculitis are very low, despite multiple daily injections, blood in the ventricles, the use of thrombolysis in half the cases, and generalization to > 60 trial sites.

Keywords

External ventricular drain; EVD; EVD complications; intraventricular hemorrhage; hemorrhage; infection

Intraventricular hemorrhage (IVH) is a debilitating form of hemorrhagic stroke affecting nearly 1 million people worldwide each year¹. IVH has a varied etiology including head trauma, vascular malformation, aneurysm, tumor, hypertension, and clotting disorders, and affects individuals of all ages, with morbidity and mortality rates up to 90% and 78%, respectively^{2, 3}. The pathologic consequences of IVH, which lead to significant morbidity and mortality, include obstructive hydrocephalus and delayed communicating hydrocephalus. Obstructive hydrocephalus occurs when blood clots block cerebrospinal fluid (CSF) conduits, leading to an increase in intracranial pressure (ICP). This is a life-threatening condition, which requires immediate management. The current treatment for obstructive hydrocephalus is insertion of an intraventricular catheter for external ventricular drainage (EVD). This procedure allows drainage of CSF resulting in a decrease in ICP, and can allow simultaneous measurement of ICP. Other major consequences of IVH are the thrombotoxicity and inflammation in reaction to ventricular blood, negatively impacting outcome. Despite EVD, reported rates of morbidity and mortality in IVH are still up to 89% and 58%, respectively³⁻⁵. These findings indicate that EVD has a modest effect on mortality but nearly no effect on the rate of poor outcomes (death or dependence) associated with IVH, leaving us with the need for a more effective treatment³.

Intraventricular thrombolysis such as the use of recombinant tissue plasminogen activator (rt-PA) in conjunction with EVD has been optimized in the CLEAR II trial, and has shown promising prospect of accelerated clearance of blood from the ventricles and a positive impact on morbidity and mortality^{4, 6}. The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III) trial is an ongoing double blind, international, multicenter, randomized clinical trial assessing the efficacy of EVD + rt-PA for clearance of intraventricular hemorrhage⁷.

Common complications of EVD treatment include infection and catheter-related hemorrhage. Retrospective series report varied rates of bleeding and infection with external ventricular drainage (EVD). There have been no prospective studies of these risks with systematic surveillance, threshold definitions, or independent adjudication. And it is not known if these are increased in the setting of IVH or with administration of intraventricular

thrombolysis. We analyze the rate of complications in the ongoing CLEAR III trial, providing a comparison with a systematic review of complications of EVD in the literature.

METHODS

CLEAR III Patient Population, Clinical protocol and Study Characteristics

CLEAR III is enrolling patients age 18–80 with spontaneous ICH ≥ 30 ml and IVH obstructing the 3rd and/or 4th ventricles, verified by CT scan performed within 24 hours of symptom onset, requiring EVD placement, in the study. We analyzed data from the first 250 patients enrolled in the CLEAR III trial. Exclusion criteria for the trial include patients with ruptured aneurysm, tumors, and other brain lesions, which may contribute to ICH, and patients with clotting disorders. Eligible patients undergo a stability scan performed at least 6 hours after EVD placement. If there is no new or expanded (difference ≥ 5 ml) hemorrhage on the stability scan, patients are enrolled in the study; otherwise another CT scan is acquired at subsequent 6 hour intervals until the bleed stabilizes (ICH ≤ 35 ml and difference between two scans ≤ 5 ml) or 72 hours passed since the diagnostic CT scan, closing the window for enrollment. Once enrolled, patients are randomized to either rt-PA or placebo group, and are administered the test article once every 8 hours for up to 12 doses, until the obstructive ventricular blood has cleared⁷. CT scans are acquired daily or no less than once every 3rd administration of the test article. A CT scan is also acquired 24 and 72 hours post last dose and at 30 and 365 days post enrollment for follow-up. Daily white blood cell (WBC) count, hematocrit, platelet count, activated partial thromboplastin time (PTT), International Normalized Ratio (INR), CSF cultures, cell counts, protein, and glucose are documented.

The ICH hemorrhage volume was calculated by well established formula $ABC/2$ ⁸. For the CLEAR III study, hemorrhage was prospectively defined as a new or expansion of prior ICH or catheter track hemorrhage on CT scan by ≥ 5 ml in volume or ≥ 5 mm in any diameter, after placement of the EVD until 30 days after its removal. Expansion of IVH is defined as any measurable enlargement in diameter of IVH on axial CT scan slices by ≥ 2 mm, or actual volumetric enlargement of IVH by ≥ 5 ml as assessed by the trial's Reading Center. Hemorrhage as defined by these criteria was required to be reported as an adverse event by the study site, and as verified by independent reviews and volumetric assessment of each CT scan and adjudication by the trial's central Reading Center. A symptomatic bleed was defined as a hemorrhage associated with a drop by two or more points on concurrently documented Glasgow Coma Scale. We included new or expanded hemorrhage seen on head CT following EVD placement, occurring within 30 days of randomization, in line with the time window in most surgical series. Based on these articulated criteria, the trial's Reading Center adjudicated every reported bleed, and an Adverse Events Committee independently adjudicated all symptomatic bleeds.

Bacterial ventriculitis, meningitis and non-bacterial ventriculitis were prospectively surveyed and adjudicated, and we included in this study all cases with positive bacterial culture of CSF obtained through the EVD, or of EVD catheter tip. Since there is wide variability in the literature regarding definition of infection related to EVD⁹, this threshold criterion facilitated comparison with published literature and minimized the risk of bias.

Complication rates were calculated per subject, even though 83 of the 250 subjects (33.2 %) harbored more than one EVD catheter.

Literature Review

We performed an OVID Medline search most recently on June 1, 2013 to identify all published articles in English between the years of 1970 to June 2013 reporting infections and hemorrhages associated with EVD using the following search terms: “external ventricular drain,” “ventricular drain,” “ventriculostomy,” and “external ventricular catheter.” Our initial search yielded 2,097 articles for the external ventricular drain or ventricular drain or ventriculostomy or external ventricular catheter and infection search criteria, and 2955 articles for the external ventricular drain or ventricular drain or ventriculostomy or external ventricular catheter and hemorrhage search criteria. We reviewed the abstracts of each of these articles for relevance. Studies of interest for inclusion in our analysis were those reporting or permitting calculation of rates of infection or hemorrhagic complications. Only studies with ≥ 30 subjects that included one or more post procedural CT scan for reporting of hemorrhagic complications and those defining infection as a positive CSF culture acquired through the catheter or by culture of the catheter tip were included in the analysis. For the studies included in the systematic review, we defined hemorrhage as any evidence of new or expanded bleeding on a CT scan, and symptomatic hemorrhage as hemorrhage associated with new neurological symptoms or other clinical sequelae. Criteria for exclusion and inclusion of studies from our systematic review are summarized in Table 1. For the meta-analysis we strictly followed AMSTAR and PRISMA criteria¹⁰.

Statistical Analysis

Meta-analyses of published rate of infection, hemorrhage and symptomatic hemorrhage after ventriculostomy were carried out using STATA12 (StataCorp LP, College Station, Texas). When the count of symptomatic hemorrhage was zero, a correction of 0.5 was added to the number of symptomatic hemorrhage and total cases, prior to calculation¹¹. Before pooling the results, heterogeneity between studies was assessed using χ^2 and I^2 test. Due to differences in the design of the trials evaluated, an inverse-variance weighted random-effects model, described by Dersimonian and Laird, was used to calculate pooled estimate of complication rates as well as 95% confidence intervals¹². Publication bias was assessed graphically using funnel plot (Figure 1A, 1B, 1C) and statistically using both Begg rank correlation test and Egger linear regression test. Specific calculations in STATA were performed using the analysis package sbe24_3 (<http://www.stata-journal.com/software/sj9-2>). Inputs of complications rates and study weights were calculated as

$$\hat{\theta}_i = \frac{\# \text{ of complications}}{\# \text{ of subjects}} \text{ and } \omega_i = \frac{1}{\sqrt{\frac{\hat{\theta}_i(1-\hat{\theta}_i)}{\# \text{ of subjects}}}} \text{ respectively for each study.}$$

RESULTS

Adverse Events in CLEAR III

Data from the first 250 patients enrolled in the CLEAR III trial were analyzed. The demographics of the enrolled patients are described in Table 2. All had an external ventricular drain placed before randomization and received regular CT scans and CSF cultures. Of the 250 cases, forty-two subjects (16.8%) experienced one or more new bleeds or expansions and 6 of them suffered symptomatic hemorrhages (2.4%) within 30 days after randomization in the study. Three of the 6 symptomatic bleeds occurred during the dosing phase, and the other 3 post-dosing (Table 3). Three of 6 symptomatic bleeds (50%) were catheter tract hemorrhage and the other 3 were new distant hemorrhage. An additional 3 cases (1.2%) had suffered a new bleed or expansion after EVD insertion and prior to enrollment in the trial none of these were symptomatic.

There were eleven cases (4.4%) of culture-proven bacterial meningitis or ventriculitis, although many manifested varying sterile CSF pleocytosis in reaction to IVH. Of the eleven cases of infection, ten were meningitis and one case was due to brain abscess. The pathogens consisted of gram positive cocci in 6 cases, gram negative cocci in 2 cases, and gram negative bacilli in 3 cases. There was also one case of gram stain positive CSF; however, it remained culture negative and thus was not included in the infection calculation. All patients in the trial were receiving prophylactic intravenous antibiotics per trial protocol. The infections occurred despite being on intravenous prophylaxis against gram positive organisms, during the entire duration of the EVD.

Literature Review

Hemorrhage—Per our literature inclusion/exclusion criteria, we identified 18 studies with a cumulative total of 2829 cases (Table 4). Of the total 2829 identified cases of EVD placement, there were 270 cases of CT-verified reported hemorrhage. The pooled hemorrhage incidence rate from these studies was 8.4% [5.7%, 11.1%] compared to 16.8% [12.5%, 21.9%] in CLEAR III (Test for heterogeneity: $\chi^2=260.16$, $df=17$, $p<0.001$; $I^2=93.5\%$ and test for publication bias: Egger' test: $p<0.001$; Begg's test: $p=0.001$) (Figure 2). Of the 18 studies, 10 studies reported clinically significant symptomatic hemorrhages with a tally of 25 cases. The pooled symptomatic hemorrhage incidence rate was 0.7% [0.4%, 1.1%] compared to 2.4% [0.5%, 4.3%] in CLEAR III (Test for heterogeneity: $\chi^2=12$, $df=12$, $p=0.45$; $I^2=0\%$ and publication bias: Egger' test: $p=0.001$; Begg's test: $p=0.012$) (Figure 3).

Infection—Thirty-three studies reported infection rates (Table 5). Of the 9667 cases identified from these 33 studies, there were 568 cases of reported infection. The pooled infection incidence rate was 7.9% [6.3%, 9.4%] compared to 4.4% [1.9%, 6.9%] in CLEAR III trial (Test of heterogeneity: $\chi^2=342.01$, $df=32$, $p<0.001$; $I^2=90.6\%$ and publication bias: Egger' test: $p<0.001$; Begg's test: $p=0.016$).

DISCUSSION

Analysis of first 250 patients enrolled in CLEAR III trial showed 16.8% hemorrhage rate, 2.4% symptomatic hemorrhages rate and 4.4% infection rate compared to the 8.4% hemorrhage rate, 0.7% symptomatic hemorrhages rate and 7.9% infection rate calculated from the literature meta-analysis (Figures 2–4).

Hemorrhage

The studies analyzed in our literature review included post-procedure head CT scans, but none with as frequent or systematic imaging surveillance as CLEAR, and most studies did not report bleeds as late as 30 days post EVD placement. In the literature there was wide variation in the stringency and frequency of CT scans after EVD placement. With the exception of the paper by Naff et al.¹⁵, the definitions of symptomatic bleed also differed among published studies, with retrospective reports lacking GCS data or other criteria defining clinical deterioration. The various studies also do not consider potential interventions, such as correction of coagulopathy, that may or may not have been deployed to prevent the conversion of asymptomatic bleeds to symptomatic ones.

Two of the studies that reported higher rate of hemorrhage after EVD placement than the other 16 studies, Gardner et al.¹³ (41%) and Manikar et al.¹⁴ (32.5%), also had very stringent post-procedural CT scan criteria comparable to the criteria used in CLEAR III trial. The study by Gardner et al.¹³ used both CT or MRI, which is known to be more sensitive in detecting blood, to detect hemorrhage. The study by Naff et al.¹⁵ (27.1%), which also reported a higher rate of hemorrhage, was a thrombolytic dose escalation study. Thus, comparing similar studies, the hemorrhage rate of the CLEAR III trial is lower.

It is likely that most published rates are an underestimate, due to variability in definition of catheter-related hemorrhage and limited information on, or lack of adjudicated assessment of, new bleeds. The study reported by Naff et al. (CLEAR Phase II trials) had one of the three highest published rates of hemorrhage. Not surprisingly, this included patients receiving thrombolysis, with prospectively articulated definitions and systematic imaging with third party adjudication of new bleeding and symptomatic bleeding (tracked as adverse events). The Naff et al. study included dose escalation, with some subjects receiving a higher dose (3 mg) of rt-PA. The protocol has been modified to 1mg rt-PA thrice daily for the CLEAR-III trial. The lower rates of hemorrhage in CLEAR III compared to those reported by Naff et al. likely reflect optimized dosing based on the Phase II trial and other lessons learned requiring demonstrated stability of hemorrhage before administration of rt-PA, and avoiding any EVD replacement or manipulation within a day of administering thrombolytic agent¹⁶. These practices have been incorporated in CLEAR III.

Beside the report by Naff, et al., four other studies reported asymptomatic hemorrhage rates higher than 10%^{13, 14, 17, 18}. The higher than average hemorrhage rate in these studies can be attributed to certain inherent characteristics. The study by Gardner et al. defined hemorrhage as any evidence of blood on either CT or gradient echo MRI¹³. Higher sensitivity of gradient echo MRI to detect blood most likely attributed to very high reported asymptomatic bleed in this study. Maniker et al. also defined hemorrhage as any evidence of blood on CT scan

including punctate hemorrhages¹⁴. In the study by Hoh et al. the authors were evaluating the safety of heparinization for aneurysm coiling after EVD placement¹⁷. The majority of the patients included in the retrospective study by Huyette et al. were head trauma patients, and this series also reported several multiple passes for EVD placement¹⁸.

Three of the 6 symptomatic bleeds among the first 250 subjects in CLEAR III occurred after completion of dosing of study agent, all in patients receiving thromboprophylactic or therapeutic doses of anticoagulants. With so few symptomatic hemorrhages, and many other patients without symptomatic hemorrhage receiving similar therapies, we cannot comment upon any significant contribution of these factors. Three patients suffered symptomatic bleeding during dosing, and we cannot comment at this time whether they were receiving placebo or thrombolytic agent.

Infection

The overall mean rate of EVD-related infection reported in the literature is 7.9%, which is higher than the documented infection rate of 4.4% in CLEAR III trial. The majority of the studies included in the analysis are retrospective studies. There is a large amount of variability in the reported infection rate in the literature, ranging anywhere from 1% to 28.2%, as well as variation in the definition used for defining infection. There is no CDC-provided catheter induced ventriculitis definition to provide guidance in this matter. Even though in all the studies infection is defined as positive CSF culture, the frequency of culture is highly variable. Most studies performed daily CSF sampling; however, in some studies CSF sampling was only done if there was concern for infection. There were some studies that did not specify the culture frequency. There was no obvious difference in the infection rate between retrospective vs. prospective, both the highest¹⁹ and the lowest²⁰ reporting infection rate studies were retrospective analyses. The location of EVD placement varied from intensive care unit to operating room in CLEAR III and in the various reported studies, and this did not appear to influence infection rates. Most studies in the literature did not report pleocytosis, protein or glucose concentrations in the CSF in association with infection, and many do not mention the cultured pathogens, nor associated fever or specific treatments. And the various studies do not reveal information about these CSF parameters in cases without culture proven infection, so the rates of aseptic or “partially treated” meningitis remain unknown.

Patients in CLEAR III underwent daily CSF sampling and an independent committee adjudicated the presence of infection. It has been suggested that the presence of blood may act as a culture medium, allowing bacterial growth, and thus increase the risk of infection⁹, or that frequent instrumentation of the closed CSF drainage system may increase infection rates²¹. These are not substantiated, with fewer infections in the setting of CLEAR III. It is unclear if specific protocols in CLEAR III contributed to the lower than expected infection rates, including the mandated sterile tunneling and prophylactic intravenous antibiotics from the insertion until removal of the EVD. The administration of thrombolytic or placebo required thrice daily invasion of the closed catheter drainage system for up to 72 hours, and the protocol required strict sterile conditions for each such dosing, including full sterile draping, antiseptic preparation of the tubing, closed double three-way stopcock syringe

technique (<http://braininjuryoutcomes.com/component/jdownloads/viewdownload/14/92?Itemid=0>), mask, hat and gown by a trained operator. The generalization of these practices would seem warranted in clinical practice. The EVDs were placed under full sterile technique in the operating room, emergency room or intensive care settings, and antibiotic impregnated catheters were used in some instances at the operator's discretion. The low rates of overall infections will not likely inform further refinement of these practices.

This study did not address the CSF profile in cases with or without proven infection, and cases of potential aseptic or partially treated meningitis. A detailed analysis of CSF inflammatory response in CLEAR III is currently underway, defining the range of inflammatory response with various volumes of IVH, and this will be published separately.

Limitations

Our study has limitations. The most important is that the results of the meta-analysis were based on mostly retrospective studies. Variability in defining infection and assessing hemorrhage added to the heterogeneity of the studies included from the literature review, and the studies did not typically include demographic or other patient and disease parameters that may have influenced complication rates. As with all systematic reviews, there was likely an important publication bias, and this was statistically suggested by the results in the funnel plots (Figure 1A, B, C). The impact of publication bias cannot be underestimated, hence the importance of standardizing reporting standards going forward, as we attempted to do in CLEAR III. And there were heterogeneities related to sample size of the various studies, possibly affecting the reported results.

Our reported interim rates in CLEAR III included cases receiving IVH thrombolysis or placebo, so the actual hemorrhage rates in cases receiving thrombolysis may be higher. Hemorrhage rates in the literature and in CLEAR III that were considered "asymptomatic" are not necessarily "insignificant", as the studies do not specifically assess the potential clinical impact of such bleeds. And the CLEAR III criterion for symptomatic bleed as associated with a GCS drop by 2 or more points is arbitrary, and may be insensitive to relevant clinical sequelae, particularly among patients in poor neurologic condition.

Conclusion

Our study compared the two major complication rates, hemorrhage and infection, following EVD placement from the well-designed and monitored CLEAR III trial with the meta-analysis of the rates published in the literature. Despite thrombolytic administration in half the cases, the presence on IVH, and frequent instrumentation of the CSF drainage system for injection of drug or placebo, the EVD-related complications appear low, and in the same range as the rates reported in the literature. Protocolized practices contributing to these outcomes, and the new standards for monitoring and reporting EVD complications, may be useful in clinical practice.

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Figure 1. Funnel plots of A) hemorrhage rate, B) symptomatic hemorrhage rate and C) infection rate against their respective standard errors.

Figure 2. Forest plot of random-effects meta-analysis of the incidence rate of hemorrhages. ES, hemorrhage rate; CI, confidence interval.

Figure 3. Forest plot of random-effects meta-analysis of the incidence rate of symptomatic hemorrhages. ES, symptomatic hemorrhage rate; CI, confidence interval.

Figure 4. Forest plot of random-effects meta-analysis of the infection rates. ES, infection rate; CI, confidence interval.

TABLE 1

Exclusion/Inclusion Criteria of Published Studies on EVD Hemorrhage and Infection

<i>Exclusion Criteria</i>
Procedure
-Cerebrospinal Fluid Shunting (Permanent Shunt)
-Endoscopic Third Ventriculostomy
-Lumbar Drainage
-EVD that were later converted to long tunneled catheter
Device
-Intracranial Pressure Monitors (Parenchymal)
-Rickham or Ommaya Reservoirs
Study Size
- < 30 subjects
Study Type
-Editorials
-Surveys
-In Vitro Studies
-Murine Studies
Study Population
-Pediatric (limited to < 18 years old/neonatal cases)
Other Exclusions
-Studies not in English
-Studies where incidence of complications were not reported
-Catheter revisions due to dislocation, obstruction, or otherwise not related to ventriculostomy procedure, choice of EVD catheter vs. other devices not clearly defined.
-Other: did not meet inclusion criteria
<i>Inclusion Criteria</i>
Procedure
-Primary EVD placed due to ICH
Device
-EVD
Study Size
- > 30 subjects
Study Type
-Retrospective analysis
-Prospective analysis
-Randomized controlled
Study Population
-Adult (> 18 years old)

TABLE 2

Subject Demographic and Clinical Characteristics of 250 Subjects Enrolled in CLEAR III

		Number of Patients	
		N	(%)
Gender	Male	134	53.6
	Female	116	46.4
Race	White/Caucasian	149	59.6
	Black/African American	86	34.4
	American Indian/Alaskan Native	1	0.4
	Asian	5	2.0
	Native Hawaiian/Pacific Islander	3	1.2
	Not Specified	5	2.0
	Multi-Racial	1	0.4
Ethnicity	Not Hispanic/Latino	209	83.6
	Hispanic/Latino	41	16.4
Primary Diagnosis	Primary IVH	42	16.8
	ICH with IVH	208	83.2
Tobacco Use	No	180	72.0
	Yes	70	28.0
Cocaine Use	No	237	94.8
	Yes	13	5.2
On Anti-coagulation	No	224	89.6
	Yes	26	10.4
On HRT	No	110	44.0
	Yes	6	2.4
	NA	134	53.6
Antihypertensive Med Compliant	No	65	26.0
	Yes	185	74.0
Hyperlipidemia Med Compliant	No	9	3.6
	Yes	241	96.4
On Antiplatelet	No	193	77.2
	Yes	57	22.8

Table 3

Symptomatic Hemorrhages Within 30 Days of EVD Insertion Among 250 Cases Enrolled in CLEAR III

<i>Patient #</i>	<i>Bleed</i>	<i>Timing</i>	<i>Anticoagulation</i>
1	Catheter track (during dosing)	5hrs. (after 3 doses)	No prophylactic anticoagulation
2	Catheter track (during dosing)	31hrs. (after 2 doses)	No prophylactic anticoagulation
3	Catheter track (during dosing)	48hrs	DVT prophylaxis (SQ Heparin)
4	New catheter placed for hydrocephalus after protocol; New ICH (new pontine hemorrhage)	Day 16	Full anti-coagulation (site entered reason as 'prevention of thrombosis')
5	New catheter placed for hydrocephalus after protocol; (new massive IVH in left lateral ventricle)	Day 22	On Enoxaparin (DVT prophylaxis)
6	Spontaneous new bleed; New ICH (different location than original stroke)	Day 16	On Enoxaparin (DVT prophylaxis)

Table 4

Rates of New or Expanded Hemorrhage after Ventriculostomy

	Study	Type	Cases	Hemorrhages	Hemorrhage Rate	Symptomatic Hemorrhages	Symptomatic Hemorrhage Rate
1	Gardner et al., 2009 ¹³	R	188	77	41.0%	1	0.5%
2	Guyot et al., 1998 ²²	R	274	9	3.28%	2	0.72%
3	Hoh et al., 2005 ¹⁷	R	370	37	10.0%	4	1.1%
4	Huyette et al., 2008 ¹⁸	R	98	18	18.4%	—	—
5	Kakarlia et al., 2008 ²³	R	346	17	4.9%	4	1.2%
6	Maniker et al., 2006 ¹⁴	R	160	52	32.5%	4	2.5%
7	McIver et al., 2002 ²⁴	R	45	2	4.4%	—	—
8	Naff et al., 2011 ¹⁵	RCT	48	13	27.1%	7	14.6%
9	Paramore et al., 1994 ²⁵	R	161	4	2.5%	2	1.2%
10	Wiesmann et al., 2001 ²⁶	R	92	6	6.5%	0	—
11	Woemle et al., 2011 ²⁷	R	137	5	3.6%	—	—
12	Zeng et al., 2010 ²⁸	P	136	1	0.7%	0	0.0%
13	Patil et al., 2013 ²⁹	R	111	2	1.8%	0	0.0%
14	Wang et al., 2013 ³⁰	P	45	3	6.6%	—	—
15	Park et al., 2011 ³¹	R	250	16	6.4%	—	—
16	Abdoh et al., 2012 ³²	R	66	5	7.6%	0	0.0%
17	North et al. 1986 ³³	R	199	2	1%	1	0.5%
18	Roitberg et al. 2001 ²⁰	R	103	1	0.97%	0	—
19	CLEAR III (ongoing)	P	250	43	16.8%	6	2.4%

P, prospective; R, retrospective; RCT, randomized clinical trial

Table 5

Infection Rates After Ventriculostomy

	Study	Type	Cases	Infections	Infection Rate	Procedure Location	Culture Frequency
1	Alleyne et al., 2000 ³⁴	R	308	12	3.9%	Not specified	Twice weekly
2	Arabi et al., 2005 ³⁵	R	84	12	14.3%	Multiple locations	Daily
3	Bota et al., 2005 ³⁶	P	638	58	9.1%	Operating Room	Daily
4	Hoefnagel et al., 2008 ³⁷	R	228	53	23.2%	Operating room	3 times/week
5	Kaufmann et al., 2004 ³⁸	P	158	13	8.2%	Operating room	Daily
6	Khan et al., 1998 ³⁹	R	104	7	6.7%	Not specified	Not Specified
7	Kim et al., 1995 ⁴⁰	R	61	7	11.5%	Operating room	Daily
8	Lackner et al., 2008 ¹⁹	P/R	39	11	28.2%	Operating room	Daily in treatment group; 3 times/week in control group
9	Leung et al., 2007 ⁴¹	R	103	7	6.8%	Operating room	Not routine
10	Lyke et al., 2001 ⁴²	P	151	11	7.3%	Multiple locations	At & 2 days after EVD placement
11	Mayhall et al., 1984 ⁴³	P	172	16	9.3%	Multiple locations	Not Specified
12	Naff et al., 2011 ¹⁵	RCT	48	4	8.3%	Intensive care unit	Daily
13	Park et al., 2004 ³¹	R	595	51	8.6%	Multiple locations	Not routine
14	Pfisterer et al., 2003 ⁴⁴	P	130	21	16.2%	Intensive care unit	3 times/week
15	Roitberg et al., 2001 ²⁰	R	103	1	1.0%	Intensive care unit	Daily
16	Smith et al., 1976 ²¹	R	56	3	5.4%	Multiple locations	Not routine
17	Tse et al., 2010 ⁴⁵	R	319	15	4.7%	Operating room	Not specified
18	Zentner et al., 1995 ⁴⁶	P	226	8	3.5%	Not specified	Not specified
19	Patil et al., 2013 ²⁹	R	111	5	4.5%	Not specified	Not specified
20	Wang et al., 2013 ³⁰	P	45	6	13.3%	Not specified	Not Specified
21	Flint et al., 2013 ⁴⁷	R	262	15	5.7%	Intensive care unit	Only if concern for infection
22	Lajcak et al., 2013 ⁴⁸	R	403	29	7.1%	Operating room	Routine monitoring
23	Winkler et al., 2013 ⁴⁹	RTC	61	11	18%	Not Specified	Every third day
24	Camacho et al., 2013 ⁵⁰	P	194	12	6.2%	Operating room	Only if concern for infection
25	Kubilay et al., 2013 ⁵¹	P	2928	41	1.4%	Not specified	Only if concern for infection

Study	Type	Cases	Infections	Infection Rate	Procedure Location	Culture Frequency
26 Keong et al., 2012 ⁵²	RTC	278	47	16.9%	Not specified	Routine daily monitoring
27 Lwin et al., 2012 ⁵³	R	234	8	3.4%	Not Specified	Only if concern for infection
28 Lemcke et al., 2012 ⁵⁴	R	95	10	11%	Operating room	Only if concern for infection
29 Pople et al., 2012 ⁵⁵	RTC	434	9	2.5%	Not specified	Day of EVD placement, 3 days post EVD placement, upon EVD removal and in between if CSF infection suspected
30 Park et al., 2011 ⁵⁶	R	250	29	11.6%	Not specified	Not specified
31 Rafiq et al., 2011 ⁵⁷	P	76	9	11.8%	Operating room	Only if concern for infection
32 Guyot et al., 1998 ²²	R	274	20	7.29	Not specified	Not Specified
33 North et al., 1986 ³³	R	199	7	3.5%	Not specified	Only if concern for infection
32 CLEAR III (ongoing)	RTC	250	11	3.6%	Not specified	Daily

P, prospective; R, retrospective; RCT, randomized clinical trial