

Antibiotic-Impregnated Versus Silver-Bearing External Ventricular Drainage Catheters: Preliminary Results in a Randomized Controlled Trial

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Abstract

Background Evaluation of antibiotic-impregnated (AI) and ionized silver particle coated external ventricular drainage catheters (EVD) in patients with subarachnoid (SAH) or intracranial hemorrhage (ICH).

Methods Between February 2011 and June 2012, 40 patients with acute hydrocephalus due to SAH, ICH or intraventricular hemorrhage were enrolled in a prospective, randomized, mono-center pilot study. Primary endpoints were defined as: number of events of cerebrospinal fluid (CSF) infections. Secondary endpoints were defined as: neurosurgical complications following the placement of the EVD, number of revisions of EVD catheters, and cost effectiveness.

Results Sixty-one EVD placements in 40 patients, 32 antibiotic-coated (Bactiseal[®]), 29 silver-bearing catheters (VentriGuard[®]), have been performed. Confirmed or high suspicion of CSF infections occurred in 11 out of 61 events (confirmed infection: $p = 0.71$, probable infection: $p = 0.90$). Revisions of EVD were needed in 13 cases (22 %) due to CSF infection, dysfunction, impaired healing, or malplacement ($p = 0.37$).

Conclusion Regarding CSF infection rate and dysfunction, no statistical significant differences between the two EVD catheters Bactiseal[®] versus VentriGuard[®] were found. The silver-bearing catheter might offer a safe and cost-conscious alternative to the AI catheter.

Keywords External ventricular drainage catheter · Antibiotic-impregnated · Silver-bearing · Neurosurgery · Cerebrospinal fluid infection · Hydrocephalus

Introduction

The placement of external ventricular drainage catheters (EVD) belongs to the standard surgical procedures in managing acute hydrocephalus [1–3]. Perioperative complications, however, such as infections, intracranial hemorrhages (ICHs), or catheter malplacements are well known [3, 4]. Several previous trials have focused on catheter related cerebrospinal fluid infections (CSF) and bacterial colonization due to different types of EVDs (0–27 %), [4–7].

Zabramski et al. [6] and Abba et al. [7] reported about the efficacy of EVD polyethylene catheters impregnated with rifampicin and clindamycin versus non-coated catheters. Antibiotic-coated catheters (AI) have shown decreased colonization and CSF infection rates [6, 7]. Recently, however, Pople et al. presented an international, prospective, randomized, open label trial indicating low infection rates in both study arms, i.e., AI catheters (17.6 %) versus standard EVD (20.4 %). Furthermore, AI catheters were not associated with a lower infection rate compared to non-coated catheters [8].

In retrospective trials, Lackner and Fichtner et al. analyzed the efficacy of the silver-impregnated EVD catheters

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(SI) versus non-coated EVD. Both studies showed a significant reduction of bacterial colonization and CSF infection rate in the SI group (18.9 %) [9, 10]. Keong et al. reported in a double-blinded, prospective, randomized controlled trial a significant difference in infection rate between the two study arms (non-coated: 21.4 % vs. silver-bearing: 12.3 %, $p = 0.04$). They concluded that silver-bearing catheters reduce the risk of CSF infections [11].

At the University Hospital Zurich, Department of Neurosurgery, a prospective, randomized, mono-center pilot study was established in order to evaluate antibiotic-impregnated (AI) versus ionized silver particle coated EVDs with regard to the incidence of CSF infections and neurosurgical complications following the placement of the EVD, as well as to the number of revisions of EVD catheters and the cost effectiveness.

Patients and Methods

From February 2011 to June 2012 a mono-centric, prospective randomized controlled trial to evaluate complications with AI versus silver-ionized EVD catheters was performed at the Department of Neurosurgery of the University Hospital Zurich (approved by the ethics committee: KEK-ZH-Nr: 2010-214). Written informed consent was obtained from all participating patients. Primary endpoints were defined as: number of events of CSF infections. Secondary endpoints were defined as: neurosurgical complications following the placement of the EVD, number of revisions of EVD catheters, and cost effectiveness.

Study Population

Patients between 18 and 80 years, admitted to the emergency unit with the initial diagnosis of subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH) or intraventricular hemorrhage, and occlusive hydrocephalus were randomized and enrolled. Exclusion criteria were: prior infections (meningitis, ventriculitis, sepsis, bacteremia, chronic infection disease, or skin infection close to the implantation site), allergic reactions to rifampicin or clindamycin, pregnancy or residency outside Switzerland.

The two catheters examined were the AI ventricular drainage catheter (12 Charrier, Rifampicin/Clindamycin; Bactiseal[®], Codman and Shurtleff, Johnson & Johnson, Ranyham, Massachusetts) and the silver-ionized (SI) ventricular drainage catheter (8.5 French, ionized, silver-bearing; VentriGuard[®] Neuromedex, Zollikon Zurich, Switzerland).

Treatment

After randomization EVDs were placed according to a standardized insertion protocol [3]. CSF samples were collected during insertion and every third day thereafter and analyzed for leukocytes and microorganisms. Clinical signs of infection, such as fever, change of vigilance, and local wound control were documented. Detected microorganisms in the CSF and on the catheters were identified by direct microscopy and/or cultures performed by a blinded microbiologist (Department of Microbiology, University Hospital Zurich). CSF findings were categorized as follows: CSF infection was assigned to be “confirmed” if the leukocyte count per visual field was >200 and clinical signs of CSF infection were present and microorganisms were identified in the CSF and/or the catheter tip. CSF infection was categorized as “probable” if the leukocyte count per visual field was >100 and/or one but not all of the characteristics above were present. Primary endpoints were the events of CSF and EVD infections. Secondary endpoints were surgical complications (impaired wound healing/CSF leakage, hemorrhage in trajectory, or malplacement), changes of EVD, overall costs of EVD, and identifying most common microorganisms in the CSF in cases of confirmed infection.

Statistical Analysis

We present numbers of patients and percentages of total for categorical variables, and continuous variables as mean \pm standard deviation (SD). For the univariate comparison of primary and secondary outcomes in the comparison groups AI-EVD and SI-EVD, we used χ^2 tests. Significance level α was set at 5 %. All analyses were performed with R (R Development Core Team 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

From February 2011 to June 2012 27 female (67 %) and 13 (33 %) male patients, with the mean age of 56.5 years (mean \pm SD 13.2) were enrolled. 32 patients suffered from SAH (80 %), 8 from ICH (20 %). Twenty-eight patients with ruptured aneurysms were treated with clipping (8 patients) or coiling (20 patients), in 4 patients no aneurysm was detected in the angiography. In seven patients an ICH and in one patient an arteriovenous malformations was documented. Overall, 61 EVD catheters (32 Bactiseal vs. 29 VentriGuard) were placed in 40 patients. Mean time in situ was 15 days (range 3–30 days). Duration of stay in

the ICU was 27.6 ± 14.8 (mean \pm SD). The overall mortality rate was 16 % (Tables 1, 2).

Primary Endpoint

CSF infections (including categories “confirmed” and “probable”) occurred in a total of 11 out of 61 events (18 %), 3 confirmed with AI and 3 confirmed with SI catheters (10 %, $p = 0.71$), 2 probable with AI and 3 probable with SI catheters (8 %, $p = 0.90$). Median onset of infection was day 11 (range 5–30 days). In confirmed infections the microbiological examinations revealed *Staphylococcus coagulase* negative (in total 4 events; 2 events with AI and 2 events with SI catheters) and *Escherichia coli* (in total 2 events; 1 with AI and with SI catheters) (Table 3).

Secondary Endpoint

Overall revisions of EVD were necessary in 13 cases (22 %, $p = 0.37$). In three patients (a hemorrhage in the trajectory line (2 patients with AI, 1 with SI catheters, 5 %, $p = 0.51$) and in two patients a malplacement of the EVD (with AI catheter) occurred (3 %, $p = 0.93$). No allergic reactions occurred in either of the groups. In 12 patients (30 %) ventricular peritoneal shunt placement (VP-shunt) was performed later on. Overall costs of EVD devices were 20.345 USD (5.103 USD higher in the AI group) (Table 4).

Discussion

The present pilot study in 40 patients revealed equal rates of CSF infection in patients with AI compared to patients with SI catheters. With six (10 %) confirmed and five (8 %) probable infections, the overall infection rate was comparable with previous published data [3, 4, 6, 8, 9, 11].

Lozier and colleagues [12, 13] analyzed a cumulative CSF infection rate of 8.8 % (range 2.2–21.9 %) in 23 studies. A very low proven infection rate (2.5–2.8 %) was recently reported by Pople et al. [8], though the rate was influenced by abundant use of antibiotics and based on primary EVD placements only. The silver trial of Keong et al. [11] with an infection rate of 12.3 % showed more comprehensible results. Our patient population represented a group of most severely ill patients with long ICU stays, consecutive high risks of infections and complications as well as revisionary and secondary EVD placements. Antibiotics were used only if systemic infections or proven, respectively, probable CSF infections were detected. Onset of infection or length of implantation did not influence the infection rate in our population. However, data on the comparison of AI versus SI catheters have not been published yet.

Bacterial resistance and allergic reactions, especially seen in colonization with *Staphylococcus aureus* in rifampicin and clindamycin coated catheters, are still under discussion in the literature [4]. Furthermore, observations of neurotoxicity of silver ions have been described [14]. However, no allergic reactions were reported in either of the groups and no evident neurotoxic side effects of silver particles were observed in the group with SI catheters.

The overall surgical complication rate of 7 % (Table 1) fits in the lower median as reported in literature (range 1–33 %) [3, 15, 16]. Following a retrospective evaluation of surgical complication rates at the Department of Neurosurgery of the University Hospital Zurich [3], a standardized surgical and handling protocol was established which enabled to reduce the surgical complication rate from 10 to 7 %. Therefore, standardized surgical protocols and thoroughly maintained EVD devices improve the surgical and overall complication rate and should be established in every center [3, 5, 8, 11–13, 15, 16].

Handling and maintenance of AI or SI catheters in ICU were standardized and showed no difference in either

Table 1 Patient characteristics, severity measures, and outcome scores

Variables	Category	Percentage
Gender	Male: $n = 13$	33
	Female: $n = 27$	67
Age (mean \pm SD, y)	56.5 ± 13.2	
Admission disease	SAH: $n = 32$	80
	AVM: $n = 1$	3
	ICH: $n = 7$	17
Days in ICU (mean \pm SD)	27.6 ± 14.8	
Glasgow outcome scale	1: $n = 6$	15
	2: $n = 0$	0
	3: $n = 3$	7.5
	4: $n = 9$	22.5
	5: $n = 22$	55

SD standard deviation, y years, ICU intensive care unit, SAH subarachnoid hemorrhage, AVM arterio-venous malformation, ICH intracranial hemorrhage

Table 2 Scores by reason for admission

	Reason for admission		
	SAH (<i>n</i> = 32)	AVM (<i>n</i> = 1)	ICH (<i>n</i> = 7)
WFNS			
1	4		
2	9		
3	3		
4	5		
5	11		
Hunt + Hess			
1	2		
2	15		
3	5		
4	5		
5	5		
Fisher			
1	0		
2	1		
3	14		
4	16		
GCS			
3			1
8–3		1	4
15–8			2

WFNS World Federation of Neurosurgeons, GCS Glasgow coma scale

Table 3 Primary endpoints: CSF infections

Characteristics	Overall (<i>n</i>)	AI-EVD (<i>n</i>)	SI-EVD (<i>n</i>)	<i>p</i> *
EVD	61	32	29	–
CSF infection	11	5	6	0.92
Confirmed inf.	6	3	3	0.71
Probable inf.	5	2	3	0.90
Onset of CSF inf.	11 (<i>d</i> , median)	–	–	

n number, AI-EVD antibiotic external ventricular drainage catheter, SI-EVD silver-ionized external ventricular drainage catheter, CSF cerebrospinal fluid, inf infection, *d* day

* *p* value from χ^2 test

Table 4 Secondary endpoints: revision, surgical complications, costs

Characteristics	Overall (<i>n</i>)	AI-EVD (<i>n</i>)	SI-EVD (<i>n</i>)	<i>p</i> *
Revision	13	5	8	0.37
Malplacement	2	1	1	0.51
Hemorrhage	3	2	1	0.93
Costs (USD)	20.345	–	–	
Difference in costs (USD)		+5.103		

n number, AI-EVD antibiotic external ventricular drainage catheter, SI-EVD silver-ionized external ventricular drainage catheter, USD US Dollar

* *p* value from χ^2 test

group. From an economic and diagnose related group point of view, it seems that the SI catheter is more cost-efficient than the AI catheter (Table 4).

Although the caseload of this prospective, randomized, mono-center pilot study is limited, our preliminary data suggest that there is no difference between the AI or SI catheters in this selected patient population.

Conclusion

This is the first prospective, randomized, mono-center pilot study to evaluate the incidence of CSF infections after placement of AI versus silver-ionized ventricular drainage catheters. No significant differences between the two EVD catheters, especially regarding the CSF infection rate, were found. The silver-ionized catheter might be a safe and cost-conscious alternative to the AI catheter. To underline these observations, further multicenter randomized trials would be needed.

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References

- van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M, van Crevel H. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1985;63:355–62.
- Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke*. 1989;20:747–53.
- Woernle CM, Burkhardt JK, Bellut D, Krayenbuehl N, Bertalanffy H. Do iatrogenic factors bias the placement of external ventricular catheters?—a single institute experience and review of the literature. *Neurol Med Chir (Tokyo)*. 2011;51(3):180–6.
- Scheithauer S, Burgel U, Ryang YM, Koch S, Schiefer J, Hafner H, Haase G, Lemmen SW. Prospective surveillance of drain-associated meningitis/ventriculitis in a neurosurgery and a neurologic intensive care unit. *J Neurol Neurosurg Psychiatry*. 2009; 80(12):1381–5.
- Hoefnagel D, Dammers R, Ter Laak-Poort MP, Avezaat CJ. Risk factors for infections related to external ventricular drainage. *Acta Neurochir (Wien)*. 2008;150:209–14; discussion 214.
- Zabramski JM, Whiting D, Darouiche RO, Horner TG, Olson J, Robertson C, Hamilton AJ. Efficacy of antimicrobial-impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. *J Neurosurg*. 2003;98(4):725–30.
- Abla AA, Zabramski JM, Jahnke HK, Fusco D, Nakaji P. Comparison of two antibiotic-impregnated ventricular catheters: a prospective sequential series trial. *Neurosurgery*. 2011;68(2):437–42; discussion 442.
- Pople I, Poon W, Assaker R, Mathieu D, Iantosca M, Wang E, Zhang LW, Leung G, Chumas P, Menei P, Beydon L, Hamilton M, Kamaly I, Lewis S, Ning W, Megerian JT, McGirt MJ, Murphy JA, Michael A, Meling T. Comparison of infection rate with the use of antibiotic-impregnated vs standard extraventricular drainage devices: a prospective, randomized controlled trial. *Neurosurgery*. 2012;71(1):6–13.
- Fichtner J, Güresir E, Seifert V, Raabe A. Efficacy of silver-bearing external ventricular drainage catheters: a retrospective analysis. *J Neurosurg*. 2010;112(4):840–6.
- Lackner P, Beer R, Broessner G, Helbok R, Galiano K, Pleifer C, Pfausler B, Brenneis C, Huck C, Engelhardt K, Obwegeser AA, Schmutzhard E. Efficacy of silver nanoparticles-impregnated external ventricular drain catheters in patients with acute occlusive hydrocephalus. *Neurocrit Care*. 2008;8(3):360–5.
- Keong N, Bulters D, Richards H, Farrington M, Sparrow O, Pickard J, Hutchinson P, Kirkpatrick P. The SILVER (Silver-Impregnated Line Vs EVD Randomized) Trial: a double-blind, prospective, randomized controlled trial of an intervention to reduce the rate of external ventricular drain infection. *Neurosurgery*. 2012;71(2):394–403; discussion 403–4.
- Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES Jr. Ventriculostomy-related infections: a critical review of the literature. *Neurosurgery*. 2002;51(1):170–81; discussion 181–2.
- Le Roux AA, Wallace MC. Outcome and cost of aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am*. 2010;21(2): 235–46 (Review).
- Lansdown AB. Critical observations on the neurotoxicity of silver. *Crit Rev Toxicol*. 2007;37(3):237–50.
- Maniker AH, Vaynman AY, Karimi RJ, Sabit AO, Holland B. Hemorrhagic complications of external ventricular drainage. *Neurosurgery*. 2006;59:ONS419–24; discussion ONS24–5.
- Saladino A, White JB, Wijdicks EF, Lanzino G. Malplacement of ventricular catheters by neurosurgeons: a single institution experience. *Neurocrit Care*. 2009;10:248–52.