Initial experience with silver-impregnated polyurethane ventricular catheter for shunting of cerebrospinal fluid in patients with infected hydrocephalus

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Objective: *Infection is a major complication and risk factor of cerebrospinal fluid (CSF) shunting procedures. Recently, antibiotic-impregnated shunt systems have been developed in an attempt to prevent or reduce the CSF infection. The aim of this study was to determine the efficacy of silver-impregnated polyurethane ventricular catheter for shunting of CSF in patients with infected hydrocephalus.*

Methods: *Seven patients who had hydrocephalus with high protein level and positive CSF culture underwent implantation of ventriculoperitoneal shunt with silver-impregnated polyurethane ventricular catheter. All of them experienced shunt failure previously due to infection. The Silverline ventricular catheter, which was connected to the Miethke gravity-assisted valve system and peritoneal catheter, was used in all patients. The mean follow-up period after operation was 14 months. Cerebrospinal fluid samples from the reservoir of the shunts were obtained at the end of the third month after operation in all patients.*

Results: *The CSF protein level of the patients was reduced significantly, and the CSF culture became negative after shunt placement with silver-impregnated polyurethane ventricular catheters. The mean CSF silver (Ag) level was 0.51 ng/ml [parts per billion (ppb)], and blood Ag level was 3.65 ng/ml (ppb) at the first month after operation. No shunt obstruction or infection was observed in the follow-up period.*

Conclusion: *Silver-impregnated polyurethane ventricular catheters appear to be safe and well tolerated in patients who sustained infected hydrocephalus. Preliminary results suggest a complete improvement of infection. Longer follow-up and large number of patients are needed to more accurately assess the efficacy of these catheters.* [Neurol Res 2008; **000**: 000–000]

Keywords: Hydrocephalus; shunt infection; silver; ventricular catheter

INTRODUCTION

Cerebrospinal fluid (CSF) shunt implantations account for a significant number of neurosurgical admissions and procedures[1]. Although they have resulted in dramatic improvements in patient's survival and neurological function, CSF shunts are associated with several complications. One of the most common is infection, which occurs in nearly 10% of patients[2–4].

Risk factors for shunt infection include surgeon's experience, duration of surgery and intraoperative handling of the device[5,6]. These risk factors can be reduced by strictly adhering to the following surgical principles: asepsis, antisepsis, antimicrobial therapy and the avoidance of hematomas[6]. The treatment of shunt infection usually requires removal or externalization of the shunt and treatment with antibiotic agents for a period of time, followed by insertion of a new shunt[7,8]. Although the use of antibiotic-impregnated shunts is a promising alternative to reduce the rate of shunt infection, it is not proven yet[9]. Furthermore, an increasing proportion of device-related infections are caused by candida[10]. Silver-impregnated ventricular catheters are recently in use in neurosurgical practice, and the broad spectrum of efficacy against hospital bacteria and yeast gives this device a very good effect[11].

We used these catheters in the treatment of previously infected hydrocephalus cases and obtained CSF, blood and urine samples to detect the level of silver. It is also essential to answer questions concerning mechanisms and clinical risk related to silver ventricular-impregnated catheters.

PATIENTS AND METHODS

Seven patients who previously underwent ventriculoperitoneal shunt operation for hydrocephalus and sustained shunt infection for a 2-year period were

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included in this study. The study design has been approved by the local medical research ethics committee. Informed consent was obtained from all patients or from their parents. Previous shunt insertions were performed by variably experienced surgeons in different hospitals. Patient's ages were between 6 months and 53 years. Four patients were women and three patients were men.

All patients had shunt infections, which were proven by CSF examinations and cultures. The CSF protein and glucose levels were measured before the removal of previous shunts. The CSF cultures were also obtained.

Operative technique

With induction of general anesthesia, a single shot of antibiotic was given to patients intravenously. Scalp hair was shaved widely before the skin was prepared. After marking skin incisions, the head, trunk and abdomen were prepared with alcoholic disinfection. The operative area was draped using sterile adhesive drapes. First, the peritoneal catheter of the previous shunt was removed; then, the valve and ventricle catheter were taken out. Initially, the distal end of the new peritoneal catheter was implanted through the previous transverse right incision paramedially to the umbilicus. The catheter was then tunneled up to the frontal area. A paramedian right pre-coronary frontal burr hole was used, followed by opening the dura and insertion of the silver-impregnated ventricular catheter. This catheter was connected to the Miethke® gravity-assisted valve (Aesculap AG & Co., Tuttlingen, Germany) and peritoneal catheter. The wounds were closed using 3.0 atraumatic sutures.

Seven silver-impregnated ventricle catheters (Silverline® antimicrobial ventricle catheter 8 French, polyurethane material; external diameter, 2.7 mm; internal diameter, 1.6 mm; length, 270 mm; Spiegelberg, Hamburg, Germany) were connected to the ventriculoperitoneal shunt systems (Miethke gravity-assisted valve system) and inserted to the patients through the Kocher's point. The Silverline catheter contained 1% nanoparticles of silver and 1% nanoparticles of a insoluble silver salt.

The CSF samples were obtained from the reservoir at the end of the first month after shunt placement. The blood and urine samples were also taken in the same time. In the collected samples, ion concentrations of silver (Ag^{+}) were determined *via* trace analysis through atomic absorption spectroscopy. Atomic absorption spectroscopy is an extremely sensitive method and can detect every low concentration in the parts per billion (ppb) range (1 ppb=1 ng/ml).

The culture of the CSF samples was also done to evaluate bacterial growth in the pre-insertion and post-operative period of the shunt.

RESULTS

Mean pre-operative CSF protein level was 278.44 mg/dl (range, 118–450). Coagulase (−) staphylococcus was cultured in CSF samples of six patients, and *Proteus mirabilis* was cultured in one patient. The mean CSF glucose level was 47.15 mg/dl (range, 46.3–48). For silver analysis, CSF samples were obtained from the reservoir of each shunt at the end of the first month. The mean Ag level in the CSF 1 month after the shunt placement was 0.51 ng/ml (range, 0.35–0.55). Bacterial growth was not observed in any of the samples, and mean CSF protein level was 53 mg/dl (range, 36–72).

Blood and urine samples were also obtained in the mean time with CSF samples. Mean Ag level in the blood 1 month after the shunt insertion was 3.65 ng/ml (range, 2.7–4.6), and the mean Ag level in the urine at the end of the first month after surgery was 0.025 ng/ml (range, 0.01–0.04).

The neurological status of the patients was well in the follow-up period, and no sign of silver intoxication, including skin discoloration, joint pain, mental or intellectual disturbances, was observed in this period.

DISCUSSION

Our study demonstrates that silver segregation from the catheters into the CSF was effective for antibacterial effect. Furthermore, the Ag levels are below the acceptable levels for toxic effect.

Ventriculoperitoneal shunt infection is a cause of significant morbidity, causing shunt malfunction and chronic ill health. Bacterial adhesion to the polymer surface of the catheter, be it luminal or external, is an important step in the pathogenesis of catheter-associated infections[12]. Shunt-associated infections are most frequently caused by coagulase (−) staphylococcus, followed by Gram-negative bacteria. Shunt infection was defined when CSF or the shunt tip was contaminated with bacteria and the patient showed clinical signs of acute bacterial meningitis and symptoms of shunt malfunction or obstruction. In addition, one of the following parameters of bacterial inflammation of the CSF had to be positive: (1) leukocyte count of $>0.25 \times 10^{9}$/l with predominantly polymorphonuclear cells, (2) a CSF lactate concentration of >3.5 mmol/l, (3) a glucose ratio (CSF glucose/serum glucose) of <0.4 and (4) a CSF glucose value of <2.5 mmol/l when no simultaneous value was noted in the blood glucose[13,14]. In our study, we analyzed the CSF of our patients and measured protein and glucose levels. We confirmed the bacterial inflammation by CSF examination and culture.

Colonized shunts do not function well mechanically, and eradication of infection with colonized shunts has always been a great challenge to the treating surgeon[15]. Antimicrobial therapy alone usually cannot improve the infection, and the removal of the shunt often remains the only option for treatment. The prophylactic and long-term use of antibacterial agents along with prompt removal of the shunt and replacement of the drainage system has provided best results in shunt colonization[16,17]. However, this treatment is not suitable especially for children and infants because of long-term hospitalization and bed rest.

Antibiotic-impregnated shunt catheters have emerged as a promising tool against the continuing challenge of

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shunt infection[18]. These catheters have been designed to prevent the colonization of shunt components by skin flora that occurs at surgery. Although such catheters may decrease the incidence of early shunt infections (those occurring within 6 months of shunt placement), they do not significantly increase incidence of late CSF shunt infection[19]. However, these catheters carry the risk of infection with antibiotic-resistant organisms including opportunistic infection due to organisms such as candida[20]. The antimicrobial effect of silver-impregnated catheters has already been shown have no toxic effect and, because of its broadband effect, with no danger of resistance[21], the ventriculoperitoneal shunts with such catheters might be a new approach for preventing and treating the shunt infections. In addition, it was previously shown that the antimicrobial activity of silver-impregnated catheters is tenfold higher for coagulase (−) staphylococci compared with catheters without silver[12].

Silver is a xenobiotic element with no recognized trace metal value in the human body[22]. It is absorbed into the body through the lungs, gastrointestinal tract, mucus membranes of the urogenital tract and skin, mainly in the form of silver protein complexes. Although silver is metabolized throughout the soft tissues, it can enter tissues of the central nervous system or is a cause of neurotoxic damage[22]. The antibacterial effects of Ag salts have been noticed since antiquity[23], and Ag is currently used to control bacterial growth in a variety of applications, including dental work, catheters and burn wounds[10,24]. In fact, it is well known that Ag ions and Ag-based compounds are highly toxic to microorganisms, showing strong biocidal effects on as many as 12 species of bacteria including *Escherichia coli*[25].

The mechanism of the inhibitory effects of Ag ions on microorganisms is partially known[11]. The positive charge on the Ag ion is crucial for its antimicrobial activity through the electrostatic attraction between negatively charged cell membrane microorganism and positively charged nanoparticles[26–28]. On the other hand, the antimicrobial activity of silver nanoparticles on Gram-negative bacteria was dependent on the concentration of Ag nanoparticle and was closely associated with the formation of 'pits' in the cell wall of bacteria. Then, Ag nanoparticles accumulated in the bacterial membrane caused the permeability, resulting in cell death[29]. Metal depletion may cause the formation of irregularly shaped pits in the outer membrane and change membrane permeability, which is caused by the progressive release of lipopolysaccharide molecules and membrane proteins[30]. Danilczuk *et al.*[31] reported Ag-generated free radicals through the ESR study of Ag nanoparticles. The antimicrobial mechanism of Ag nanoparticles is related to the formation of free radicals and subsequent free radical-induced membrane damage[31]. Free radicals may be derived from the surface of Ag nanoparticles and may be responsible for the antimicrobial activity[11].

A new approach that might bypass the resistance problem is provided by catheters impregnated with silver nanoparticles[21]. It has a toxic effect of metal ions on living cells, algae, molds, spores, fungi, viruses and prokaryotic and eukaryotic microorganisms, even at low concentrations. Since 2004, silver nanoparticle-impregnated catheters are available for intraventricular placement. Although these catheters are certified within the European Union for external ventricular drainage, there are no current data on the use these catheters combined with a ventriculoperitoneal shunt system.

Silver is known to have a toxic and inflammatory effect on neural tissue[32,33]. When silver is injected into the lateral ventricles, it is absorbed into the ependymal cells of the blood–brain barrier rather than locating in the neurons or glial cells. It was previously shown that silver deposits in the rat hippocampus and in the peripheral nervous system remained stable for at least 45 days[34]. Although it is previously shown that silver-impregnated catheters are safe and effective in the prevention of infection[21,35,36], the long-term use of these catheters was not reported. The duration of silver release from catheters is not unlimited, and the release will be stopped between 10 and 30 days after implantation[37,38]. Therefore, the risk of silver intoxication is very low. To provide reliable and useful data on the silver impregnated catheter shunt system, we connected this catheter to a ventriculoperitoneal shunt system and obtained CSF, blood and urine samples.

Silver is readily absorbed into the human body with food and drink and through inhalation but in low levels commonly present in the bloodstream (<2.3 μg/l)[22]. 1
However, blood silver concentration in workers who sustained occupational exposure to silver may be more than twice that seen in unexposed individuals (11 μg/l). The concentration required for bactericidal activity should be at least 1.08 ppb[35]. In our study, the mean Ag concentration in the CSF was 0.51 ppb, which was below the bactericidal level, but the infection was improved in all patients according to clinical and laboratory parameters. In the blood, the mean Ag level was 3.65 ng/ml. This is above the normal level but not in toxic ranges. It is extremely difficult to determine the safe reference levels of silver in the CSF, as the silver deposits will be absorbed by the choroid plexus, to be eliminated eventually *via* the kidney and liver without toxic implications. It is also unclear from our study to what extent the silver released accumulated in the central nervous system or whether it evoked pathological changes.

In conclusion, silver-impregnated polyurethane ventricular catheters for the shunting of CSF in patients with infected hydrocephalus are effective alternative methods to long antibiotic therapy and external ventricular drainage by the treatment of shunt infections. Additional asseverations require more specific valid data.

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