Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences

Tome 72, No 11, 2019

MEDICINE
Neurosurgery

INTRAVENTRICULAR INTRAOPERATIVE PROPHYLAXIS WITH VANCOMYCIN – A FACTOR FOR REDUCING INFECTIONS IN SHUNT OPERATIONS

Jivko Surchev, Lyudmila Todorova[*], Valentina Ignatova[**]

(*Submitted by Corresponding Member I. Mitov on November 27, 2017*)

Abstract

Shunt operations are a main method of treating internal hydrocephalus. According to literary data, 8–10% of the ventricular peritoneal shunts suffer infections. Approaches to minimize the risk of inflammatory complications are sought. For a period of 9 years (2008–2016) 295 children aged 0 to 18 years have undergone implantation of shunt for infantile hydrocephalus. For the purposes of this study, they were divided into three groups according to the type of antibiotic intraoperative prophylaxis: **Group A** – dissolving amino-glucosid antibiotic into the serum with which the valve is irrigated and injected into it. Intraventricularly, the team does not administer an antibiotic. **Group B** – non-systemic use of amino-glucoside antibiotic in the serum with which the valve is irrigated and filled, without intraventricular administration of an antibiotic **Group C** – intraoperative prophylaxis with vancomycin intraventricularly. Through the ventricular catheter, vancomycin is injected intraventricularly, and through the distal catheter – into the peritoneal cavity or the right atrium. In Group C, no case of infection was recorded for the whole period considered. In Group A 12 patients out of 202 are infected. The highest incidence of infections is in Group B – every sixth patient. There is a statistically significant difference in the comparison of infection rates among the groups, between the A and C Groups ($p < 0.001$) and between the B and C Groups ($p < 0.01$). Intraventricular intraoperative administration of vancomycin bypasses the blood-brain barrier, prevents bacterial sowing and significantly reduces infections in fluid shunt surgeries.

Key words: CSF shunt, intraventricular, vancomycin

This research was funded by the Bulgarian National Science Fund under project Ref. No. DFNI-I-02-5/2014 "InterCriteria Analysis: A New Approach to Decision Making".
DOI:10.7546/CRABS.2019.11.17

Introduction. Internal hydrocephalus is an abnormal accumulation of fluid in the ventricular system, which is associated with increased intracranial pressure. Especially often it occurs in childhood, mostly in the first year. The main method of treating internal hydrocephalus is the shunt operations in which cerebral ventricle fluid passes through a valve system unidirectional and dosed, and is usually discharged into the peritoneal cavity, right heart atrium or, more rarely, into another body cavity. This seemingly not very complicated surgical intervention is accompanied by numerous complications – mechanical, functional, infectious. Infections of ventricular peritoneal shunts, which according to literary data are at rates of 8–10% [1–4], are one of the most serious challenges for neurosurgeons. Treatment of infection requires hospitalization, surgical removal of the valve, external drainage, intravenous antibiotic therapy for varying periods of time [5,6], intraventricular treatment with antibiotic until fluid healing and implantation of a new shunt. Hospitalization usually lasts 7 to 21 days [7] and significantly increases the cost of care for children with hydrocephalus [8].

Obviously, prevention of infections is essential. Techniques and approaches to minimize risk are sought and encouraged. Many authors describe various technical innovations, drug strategies, and algorithms of implanting fluid shunt to limit inflammatory complications. These include changing gloves before working with the shunt catheter [9], using double gloves, covering the skin with adhesive foil to reduce skin contact, optimizing sterile protocols, using proper and timely antibiotic prophylaxis [10], using antibiotic-impregnated catheters. In most of the literature described protocols, parenteral antibiotic prophylaxis is used perioperatively. Regarding the choice of antibiotic prophylaxis according to Biyani et al. [17], first and second generation cephalosporin are the most commonly used perioperative antibiotics and vancomycin is fourth, and according to Gruber et al. [11] vancomycin and cephalosporin of the first generation are the most preferred.

The most common causes of shunt infectious complications are bacterial pathogens, which usually consist of skin flora – *Staphylococcus epidermidis*, *Staphylococcus aureus*, and other gram-positive and negative organisms. In case of an already emerging infection (ventriculitis, sepsis, etc.), an intraventricle injection of an antibiotic is added to the parenteral antibiotic therapy. The reason for this is the blood-fluid barrier that impedes the reach of the necessary therapeutic concentration in the fluid [9]. The efficacy of intraventricular administration of an antibiotic in the treatment of ventricular system infections is due to the "circumvention" of this barrier and is the basis for the use of an antibiotic preventively intraventricularly during implantation of the shunt. The absence of bacteria in the fluid to colonize the shunt hardware is a prerequisite for minimizing inflammatory complications. Initially intraventricular aminoglucosides were applied during the shunt implant itself [12] or the valve reservoir is filled with antibiotic solution [10]. The greater therapeutic efficacy of vancomycin against antibiotic-resistant staphylococci [11] is a reason to prefer it and to use it routinely as intraventricular intraoperative prophylaxis from 2008 onwards.

The aim of the present study is to analyze the efficacy of prophylactic administration of vancomycin intraventrically in patients with hydrocephalus during the implantation of the fluid shunt to reduce the number of infections.

Material and method. For a period of 9 years (2008–2016) a total of 373 children aged 0 to 18 years have undergone implantation of shunt on hydrocephalus. For the purposes of this study, those who have been treated with complications of primary implanted in other clinics shunts are excluded. In order to avoid an etiological variety of the material, the study excludes cases of tumour origin and dysraphism, and only cases of shunts in children with infantile hydrocephalus remain – 295 for the period under consideration. They were divided into three groups according to the technique and type of antibiotic intraoperative prophylaxis.

Group A – dissolution of the amino-glucoside antibiotic (gentamycin, amikacin) into the serum with which the valve is irrigated and injected into it. Intraventricularly, the team does not administer an antibiotic.

Group B – non-systemic use of amino-glucosid antibiotic in the serum with which the valve is irrigated and filled, without intraventricular administration of an antibiotic.

Group C – 1 gr vancomycin is diluted with sterile serum to 10 ml (1 ml containing 100 mg), dissolving 8 ml in the serum in which the valve is irrigated immediately before implantation and the latter is filled. After insertion of the ventricular catheter, 50 mg of vancomycin is injected intraventricularly, diluted further with the patient's fluid. After connecting the catheter with the valve, when implanting the distal catheter into the peritoneal cavity or the right atrium, the remaining amount of vancomycin (150 mg) is applied.

All three groups complied with strict aseptic conditions, including thorough disinfection of the operative field, covering the skin in the operative field with adhesive foil to limit implant's contact with the skin, and conducting perioperative parenteral antibiotic prophylaxis continuing over the next 5 days. Antibiotic prophylaxis consists of cephalosporin or vancomycin intravenously, administered before the skin incision.

The demographic data for the three groups of patient are given in Table 1.

Table 1

Epidemiological data for patients in the three groups

	Group A	Group B	Group C
Number	202	39	54
Average age (in months) at implantation (±SD)	47.04± 60.57	73.21± 71.67	95.60±68.54
Gender			
• Male	108	24	34
• Female	94	15	20

Table 2

Data for patients with infections from the three groups

	Group A $n = 202$	Group B $n = 39$	Group C $n = 54$
Number of patients with infections	12	6	0
% of patients with infections in the group	5.94%	15.38%	0
number of revisions in patients with infection	53	27	0
% of revisions in patients with infections out of the total number of revisions in the group	27.18%	71.05%	0
average number of revisions in 1 patient with infection	4.42	4.5	0

Statistical analysis was performed with SPSS Statistics 20.0. Data analysis involves comparing the results with respect to the surveyed indicators in the three groups with the help of the exact test of Fisher, Pearson's $\chi 2$ test и InterCriteria Decision Making approach [13] and < 0.05 was accepted as level of significance.

Results. By analyzing the infections in the three groups (Table 2), we found that in Group C, where vancomycin was administered intraventricularly during shunt implantation, no case of infection was recorded for the whole period considered. In Group A, where an aminoglycoside antibiotic is always dissolved in the serum filling the valve, 12 patients out of 202 are infected. The highest incidence of infections is in Group B – every sixth patient.

Patients with infections (Group A and Group B) experience an average of 4–5 times more revisions than the average for the group. As a result, they have 1/3 of all revisions in Group A revision and more than 2/3 of Group B revisions. There is a statistically significant difference in the comparison of infection rates among the groups, between the A and C Groups ($p < 0.001$) and between the B and C Groups ($p < 0.01$). I.e. patients who received vancomycin intraventricularly intraoperatively suffered statistically less frequent infections than those in whom this prophylactic measure was not applied.

It is also noteworthy that in Group C, the mean interval from shunt implantation to first revision was the highest – 16.06 months. Two times shorter (8.54 months) is this interval in Group B, which correlates with a 2 and a half times higher relative share of patients with infections in this group compared to Group A.

Kaplan–Meier curve shows the best shunt survival in Group C and the worst in Group B with sporadic use of an aminoglycoside antibiotic dissolved in serum during shunt implantation (Fig. 1).

Discussion. The purpose of antibiotic prophylaxis in shunt surgery is to prevent the colonization of bacterial pathogens in the fluid or shunt hardware. Systemic drugs, including aminoglycosides, have limited access to the CNS due to the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier.

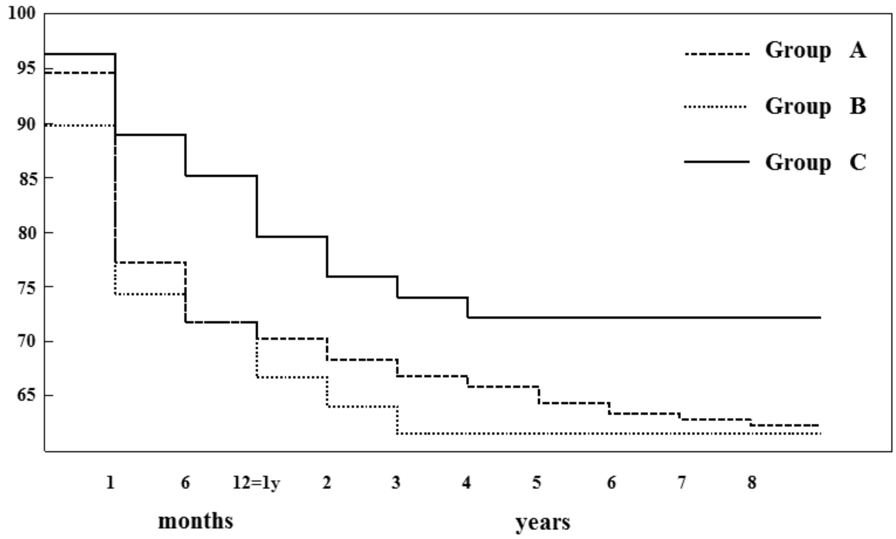

Fig. 1. Kaplan-Meier curve for shunt survival in Group A, Group B and Group C

Direct infusion of aminoglycosides into the CNS through IVT administration circumvents these physiological barriers and allows drug delivery directly to the site of action [14].

The authors have suggested that the key to reducing the incidence of infections is the reduction of bacteria in the workplace – the ventricle, the peritoneal cavity and the surgical wounds. Based on years of experience demonstrating the efficacy of intraventricularly applied vancomycin for the treatment of ventriculitis in shunt infection, the idea of its prophylactic intraventricular administration during valve implantation has arisen to reduce the incidence of inflammatory valve complications. At the beginning this hypothesis was tested prospectively and after the initial positive results (absence of infections and no side effects), the author introduced as a routine protocol the injection of vancomycin intraventricularly from 2008. The drug has an excellent effect on Gram-positive staphylococci and shows no toxic effect (no cases of allergic reaction, neurological deterioration or aseptic meningitis) with intraventricular administration [15]. It has been shown that the pH rate and osmotic pressure of CSF did not change significantly before and after administration. No statistically significant difference ($p > 0.05$) was observed before the administration of the drug and 1 week later in changes in creatine [16]. There are no detectable manifestations of ototoxicity in our study.

The level of intraventricular drugs in CSF with a working shunt decreases faster than when injected into a closed cavity. This allows the use of a relatively high dose (50 mg intraventricularly) at a relatively low potential for toxicity [15].

The present study is retrospective, non-randomized, using groups for which the surgical protocol does not include intraventricular administration of an antibiotic. Group C, which received intraventricular prophylaxis intraventricularly with vancomycin, have statistically less infections ($p < 0.001$) compared to the other 241 patients.

There are few publications in the literature on intraventricular intraoperative antibiotic prophylaxis. However, a study among members of the section on pediatric neurological surgery of the American Association of Neurological Surgeons and Congress of Neurological Surgeons on current practices to minimize the risk of infections in fluid shunts involving 100 North American neurosurgeons reported that 27% of them routinely use intraventricular intraoperative antibiotics [11]. In Bulgaria, such prophylaxis has not been used, with the exception of the routinely introduced since 2008, analyzed in this article.

Intraventricular administration of antibiotics provides higher peak concentrations and longer maintains the therapeutic concentration of the drug in the ventricular fluid. Thus, an antibiotic passes through the valve for a long time and goes through the distal catheter. The most common places where bacteria colonize are the beginning and end of the valve system. According to Ragel et al. [15] this provides better surgical prophylaxis against pathogenic organisms in the CSF and the incidence of infections drops significantly to 0.4%.

Conclusion. The strategy of intraventricular intraoperative administration of vancomycin is based on the hypothesis that a fluid that has no antibiotic levels of protection during surgery intervention is a potential reservoir for infection that allows the colonization of bacteria on the shunt during the surgery. Intraventricular intraoperative administration of vancomycin prevents bacterial sowing and thus significantly reduces the incidence of infections in fluid shunt surgeries.

REFERENCES

[1] Kestle J. R., J. Riva-Cambrin, J. C. Wellons III, A. V. Kulkarni, W. E. Whitehead et al. (2011) A standardized protocol to reduce cerebrospinal fluid shunt infection: The Hydrocephalus Clinical Research Network Quality Improvement Initiative, J. Neurosurg., **8**(1), 22–29.

[2] Riva-Cambrin J., J. Kestle, R. Holubkov, J. Butler, A. Kulkarni et al. (2016) Risk factors for shunt malfunction in pediatric hydrocephalus: a multicenter prospective cohort study, J. Neurosurg.-Pediatr., **17**(4), 382–390.

[3] Rossi N., N. Khan, T. Jones, J. Lepard, J. McAbee, P. Klimo (2016) Predicting shunt failure in children: should the global shunt revision rate be a quality measure?, J. Neurosurg.-Pediatr., **17**(3), 249–259.

[4] Souweidane M. (2014) Editorial: Combined choroid plexus coagulation and endoscopic third ventriculostomy: is North America ready?, J. Neurosurg.-Pediatr., **14**(3), 221–223.

[5] Wellons III J., C. Shannon, R. Holubkov, J. Riva-Cambrin, A. Kulkarni et al. (2017) Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study, J. Neurosurg.-Pediatr., **20**(1), 19–29.

[6] Piatt J., C. Freibott (2014) Quality measurement in the shunt treatment of hydrocephalus: analysis and risk adjustment of the Revision Quotient, J. Neurosurg.-Pediatr., **14**(1), 48–54.

[7] McAllister J., M. Williams, M. Walker, J. Kestle, N. Relkin et al. (2015) An update on research priorities in hydrocephalus: overview of the third National Institutes of Health-sponsored symposium "opportunities for hydrocephalus research: pathways to better outcomes", J. Neurosurg., **123**(6), 1427–1438.

[8] Sherrod B. A., B. G. Rocque (2017) Morbidity associated with 30-day surgical site infection following nonshunt pediatric neurosurgery, J. Neurosurg.-Pediatr., **19**(4), 421–427.

[9] Rehman A., T. Rehman, H. Bashir, V. Gupta (2010) A simple method to reduce infection of ventriculoperitoneal shunts, J. Neurosurg.-Pediatr., **5**(6), 569–572.

[10] Dawod J., A. Tager, R. O. Darouiche, M. al Mohajer (2016) Prevention and management of internal cerebrospinal fluid shunt infections, J. Hosp. Infect., **93**(4), 323–328.

[11] Gruber T. J., S. Riemer, C. J. Rozzelle (2009) Pediatric Neurosurgical Practice Patterns. Designed to Prevent Cerebrospinal Fluid Shunt Infection, Pediatr. Neurosurg., **45**(6), 456–460.

[12] Ng K., V. H. Mabasa, I. Chow, M. H. H. Ensom (2014) Systematic review of efficacy, pharmacokinetics, and administration of intraventricular vancomycin in adults, Neurocrit. Care, **20**(1), 158–171.

[13] Atanassov K., D. Mavrov, V. Atanassova (2014) Intercriteria Decision Making: A New Approach for Multicriteria Decision Making, Based on Index Matrices and Intuitionistic Fuzzy Sets, Issues in IFSs and GNs, **11**, 1–8.

[14] LeBras M., I. Chow, V. H. Mabasa, M. H. H. Ensom (2016) Systematic review of efficacy, pharmacokinetics, and administration of intraventricular aminoglycosides in adults, Neurocritical Care., **25**(3), 492–507.

[15] Ragel B. T., S. R. Browd, R. H. Schmidt (2006) Surgical shunt infection: significant reduction when using intraventricular and systemic antibiotic agents, J. Neurosurg., **105**(2), 242–247.

[16] Cook A. M., K. D. Mieure, R. D. Owen, A. B. Pesaturo, J. Hatton (2009) Intracerebroventricular administration of drugs, Pharmacotherapy, **29**(7), 832–845.

[17] Biyani N., G. Grisaru-Soen, P. Steinbok, S. Sgouros, S. Constantini (2006) Prophylactic antibiotics in pediatric shunt surgery, Childs Nerv. Syst., **22**, 1465–1471.

Medical University of Sofia
Department of Neurosurgery
St Ivan Rilski University Hospital
Clinic of Neurosurgery
15, Akad. Ivan Geshov St
1431 Sofia, Bulgaria
e-mail: `j_surchev@abv.bg`

**Institute of Biophysics and*
Biomedical Engineering
Bulgarian Academy of Sciences
Acad. G. Bonchev St, Bl. 105
1113 Sofia, Bulgaria
e-mail: `lpt@biomed.bas.bg`

***Clinic of Neurology*
Multiprofile Hospital for Active Treatment – National Heart Hospital
65, Konyovitsa St
1309 Sofia, Bulgaria
e-mail: `valyaig@abv.bg`