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ORIGINAL PAPER

Keeping CSF valve function with urokinase in children with intra-ventricular haemorrhage and CSF shunts

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Abstract
Background Intra-ventricular haemorrhage (IVH) can occur spontaneously or during the surgical revision of ventricular cerebrospinal fluid (CSF) shunts.
Aim The aim of the study was to report the safety and efficacy of an original method for treatment of IVH that may occur at the time of valve revision aimed at maintaining the function of previously implanted CSF shunts.
Patients and methods We reviewed the medical records of six patients who experienced an IVH in the presence of a previously placed ventriculoperitoneal (VP) shunt. Five of the haemorrhages occurred during ventricular catheter replacement and the remaining one in a child given a VP shunt who sustained a spontaneous intra-cerebral haemorrhage. We inserted an external ventricular drainage without removing the original shunt. Urokinase was administered via the ventricular drain during several days until blood clearance in the CSF. Disappearance of the ventricular clots was checked by a cranial computerised tomography scan, while CSF shunt function was verified by the children's evolution and/or by a reservoir tap.
Results Follow-up evaluation of the six patients demonstrated that the existing VP shunts were functioning appropriately and that the treatment was safe.
Conclusions Patients with IVH complicating ventricular catheter replacement and patients with spontaneous bleeding who harbour a VP shunt can be treated by intra-ventricular urokinase to avoid the removal of the initial shunt. The technique has proven to be safe and utilises the ventricular drain placed for the acute management of the IVH. Shunt replacement will always be possible in case of failure of the technique we are reporting.

Keywords CSF shunts · Fibrinolytic therapy · Hydrocephalus · Hydrocephalus shunt complications · Intra-ventricular haemorrhage · Intra-ventricular fibrinolytic agent administration · Urokinase · Ventriculoperitoneal shunts

Introduction

One of the most frequent complications of cerebrospinal fluid (CSF) shunts consists of ventricular catheter obstruction that requires replacement [10]. During removal of the obstructed proximal catheter and even after using the most stringent techniques, an intra-ventricular haemorrhage (IVH) can take place [1, 5, 7, 9, 14, 16, 17]. In addition, one may also wish to replace the proximal catheter in cases submitted to elective valve lengthening or to shunt revision due to infection. Several methods to avoid bleeding that may complicate ventricular catheter replacement have been proposed [7, 9, 14, 16, 17]. However, none of them has proved to be fully safe. IVH may show up at the time of surgical revision or some hours later [1]. Once the haemorrhage has occurred, the patients' neurological condition often deteriorates due to

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blockage or to malfunction of the shunt. In addition, some patients given a CSF shunt may suffer a spontaneous IVH that may endanger the previously placed valve function.

Following our previous satisfactory experience in adults, we decided to assess the efficacy of endoventricular urokinase administration in children suffering IVH at the time of catheter substitution or in shunted children suffering a spontaneous intra-ventricular bleed. The procedure we report was designed to avoid further surgery by maintaining the pre-existing valve function. There is only one previous report on the treatment of shunt malfunction by thrombus by means of urokinase administration via the valve reservoir [5]. The authors' aim is to report their observations on the feasibility and efficacy of their own technique for preventing CSF shunt blockage by using urokinase injection when an IVH occurs during valve revision surgery or after IVH in the presence of a working CSF valve. To the best of our knowledge, this is the first report on this method for treatment of IVH aimed at maintaining the function of previously implanted CSF shunts.

Patients and technique

Patients

The medical records of children younger than 12 years diagnosed with hydrocephalus and submitted to CSF valve-related procedures during the years 2007 and 2008 were reviewed. During this period, we performed 28 new valve insertions and 41 surgical shunt revisions. IVH was diagnosed if blood-stained CSF was documented during the operation or if haemorrhage was seen on the post-operative computerised tomography (CT) scan [1]. Patients with minimally blood-stained CSF at the time of ventricular catheter replacement who showed no clinical signs of neurological deterioration were excluded from the survey. Not infrequently, during proximal shunt revision, some blood-stained CSF could be seen coming out from the replaced catheter but it usually cleared up after thorough washing with saline. However, in five instances, the patients' neurological condition deteriorated some hours after ventricular catheter replacement, and these cases constitute our study group. A CT scan confirmed the diagnosis of IVH in all cases and ascertained its severity (Figs. 1 and 2). All five patients were given an external ventricular drainage leaving in place the recently revised shunt. The children were admitted to the Paediatric Intensive Care Unit (PICU). We also included in our study a child harbouring a ventriculoperitoneal (VP) shunt who sustained a spontaneous intra-cerebral haemorrhage with massive intra-ventricular irruption (patient 6). This girl was also given a ventricular drain after craniotomy for intra-cerebral clot removal, and she was also treated with the same regime of intra-ventricular urokinase (Fig. 3).

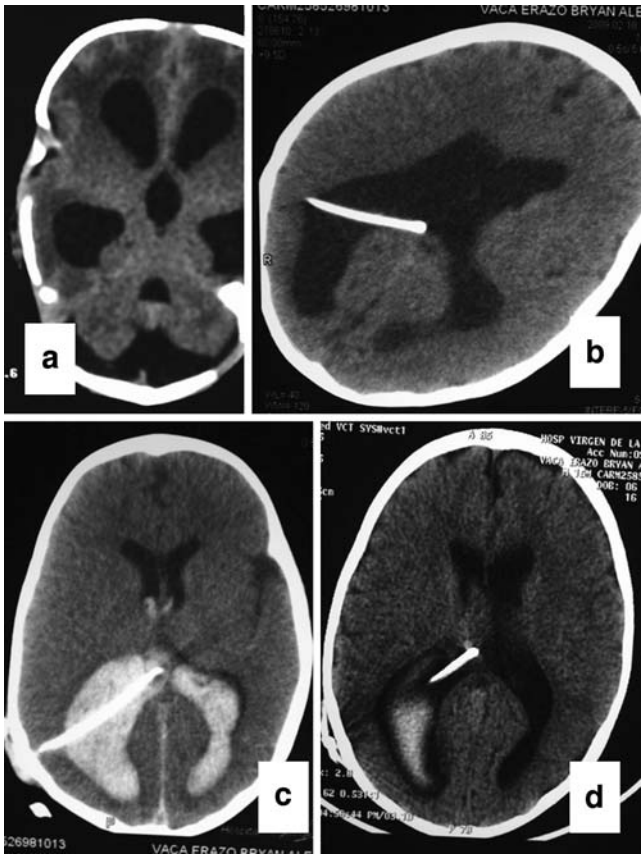

Fig. 1 Neuroimaging studies of patient 1: **a** CT depicting severe post-haemorrhagic hydrocephalus; **b** CT obtained at his second admission for shunt obstruction; **c** CT taken after neurological deterioration following ventricular catheter replacement; **d** CT performed after removal of the ventricular drainage showing a residual intra-ventricular clot

Technique of intra-ventricular urokinase administration

Urokinase (10,000 IU in a 2-ml syringe single dose) was prepared under sterile conditions at our hospital's pharmacy and kept frozen until its use [2]. The first dose of urokinase was administered either in the operating room (n=1) or shortly after the patient's return to the PICU (n=5). Urokinase (10,000 IU) was injected directly into the ventricle through a three-way stop-cock attached to the ventricular drain and then flushed with the patient's own CSF. The three-way stop-cock was then closed to drainage for 1 h but it was left open towards a sensor for continually monitoring the intra-ventricular pressure. The endoventricular injection of urokinase was repeated twice a day.

The effectiveness of the treatment was checked by visual inspection of the drained CSF. Routine analysis and culture of the CSF were also performed every 48 h. Intra-venous prophylactic antibiotics (ceftriaxone and/or vancomycin) were used all along the treatment. A control CT scan was obtained when the CSF appeared clear enough or as dictated by the children's clinical evolution. If the ventricular clot had

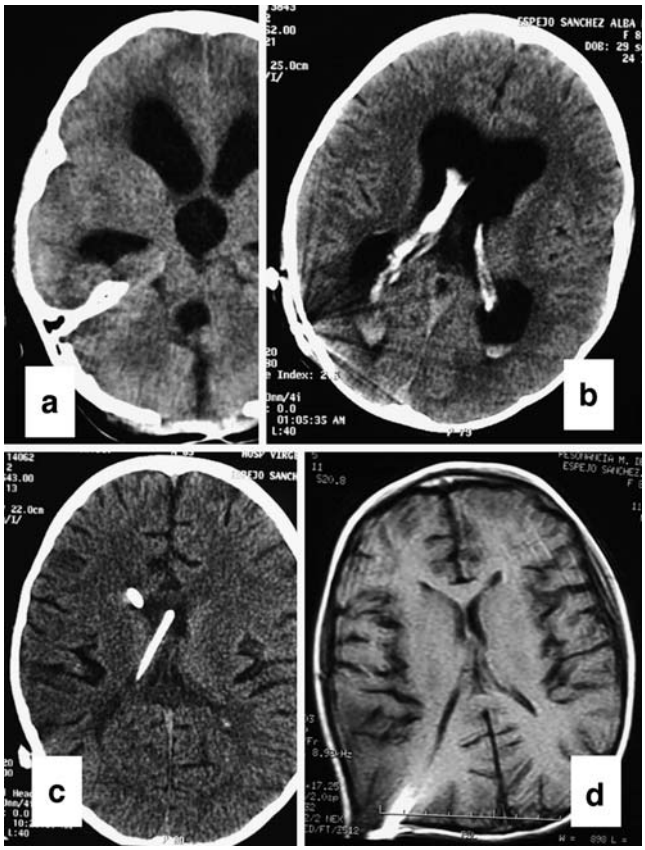

Fig. 2 Neuroimaging studies corresponding to patient 4, **a** child with delayed active tumour hydrocephalus (**a**); **b** CT taken after intra-ventricular haemorrhage following proximal catheter revision; **c** CT scan after intra-ventricular urokinase, note the position of the drainage tube at the frontal region and the position of the shunt catheter within the ventricle together with lysis of the ventricular clots; **d** magnetic resonance imaging obtained 6 months after shunt revision showing normalisation of the ventricles

already disappeared or decreased substantially, the ventricular drainage system was closed for 24 h and then it was removed. The correct functioning of the previously implanted valve was checked by examining the patient's clinical condition, by pumping the valve reservoir and, in most instances, by a reservoir tap.

Results

During the years 2007 and 2008, we performed 69 valve-related surgeries in children younger than 12 years. The surgeries included 28 new valve insertions and 41 surgical shunt revisions. A decrease in our rate of new valve insertions was noted during this period due to the increasing number of endoscopic third ventriculostomies. As stated above, patients with minor or subclinical IVH were excluded from the survey, leaving five of 41 patients who manifested IVH with clinically significant neurological deterioration. This figure represents a rate of 12.9% IVH of all CSF shunt revisions involving the surgical manipulation of the proximal catheter. An additional case, patient 6, who was previously given a VP shunt suffered a spontaneous intra-cerebral haemorrhage with massive intra-ventricular irruption. This child was admitted to hospital in deep coma.

The children's ages at the time of the IVH ranged from 9 months to 8.8 years (mean 4.1 years). There were three girls and three boys whose hydrocephalus was secondary to premature periventricular haemorrhage (n=2), posterior fossa tumours (n=2) or neonatal meningitis (n=2). There were no cases of congenital or myelomeningocele-related hydrocephalus. All children harboured a programmable (Sophy–Polaris) valve set at medium pressure. There was a mean interval from previous shunt insertion (or revision) to IVH of 6 months (range, 2 to 23 months). One of our patients (patient 2) had already undergone 12 previous shunt surgeries. Another child (patient 4) had been submitted to two previous attempts of endoscopic third ventriculostomy. During all the revision surgeries, a strict protocol for prevention of intra-operative IVH was followed [9, 16, 17]. In all instances, haemorrhagic CSF was obtained during proximal catheter replacement that prompted ventricular washing with saline until clearance of the CSF. In addition, all patients received a new catheter and sometimes a new reservoir before ending the operation. The children were awakened at the operating room and taken to the PICU.

After a few hours (mean 3 h) and in view of the children's deteriorating condition, all patients underwent a repeat CT scan, and then they were taken back to the operating room for insertion of an external ventricular drainage, which was placed on the ventricle opposite to the one harbouring the original shunt ventricular catheter (Figs. 1, 2 and 3). The initial valve was always left in place, and the treatment protocol of intra-ventricular urokinase administration was started shortly after. In five cases, urokinase administration was initiated 6 h after bleeding, while in one patient, the enzyme injection was given at the operating room, during the insertion of the ventricular drainage. Fibrinolytic treatment required ten to 15 injections and lasted from 5 to 8 days. The patients received prophylactic antibiotics until removal of the ventricular drain. During the treatment period, continuous monitoring of the intra-ventricular pressure through the CSF drainage device was performed, trying to keep a slightly higher pressure than that of the performance characteristics of the implanted valve.

Clearance of the CSF was assessed by visual inspection of the draining CSF, by analysis of the fluid and by CT scans (Figs. 1, 2 and 3). The valve function was estimated by the children's clinical evolution and by pumping the valve reservoir. We also performed a reservoir tap in three children at the end of the treatment to verify the correct function of the valve.

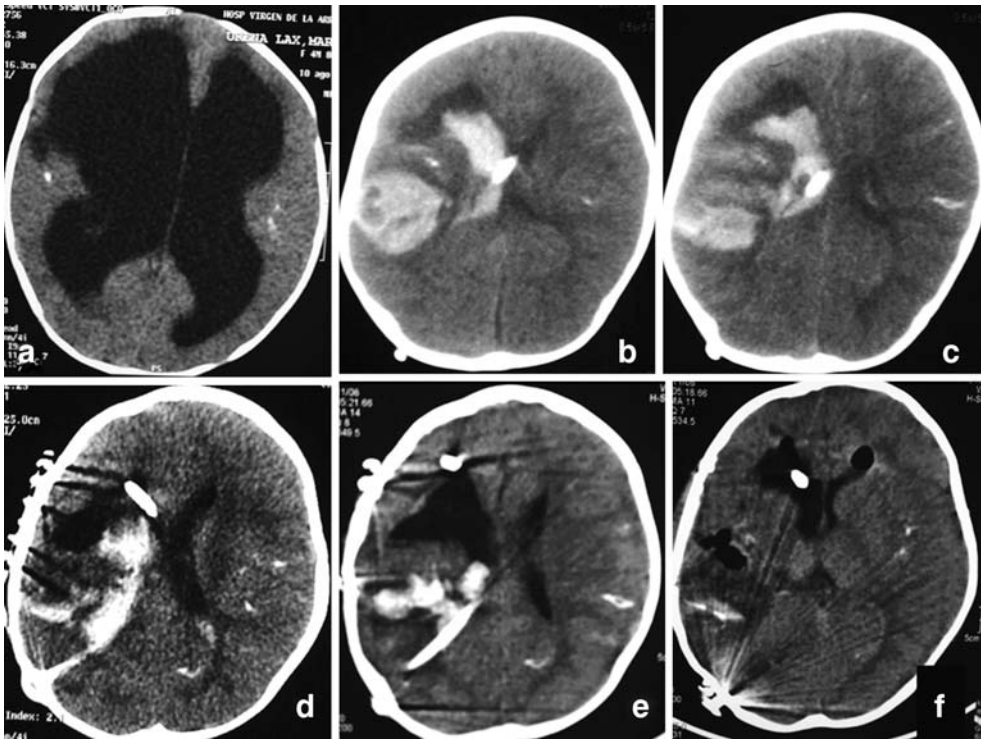

Fig. 3 Sequential CT scans corresponding to patient 6, who presented *Listeria monocytogenes* post-meningitis hydrocephalus: **a** CT scan before insertion of the original ventriculoperitoneal shunt; **b**–**c** CT taken shortly after proximal catheter replacement at the child's second admission for shunt block; **d**–**f** CT studies showing progressive resolution of the intra-ventricular clots following endoventricular treatment with urokinase (some air bubbles were involuntarily introduced in one of the injections)

There was neither a case of re-haemorrhage nor of CSF infection. The only recorded death in the study group was unrelated to the shunt or to shunt complications and was due to dissemination of a posterior fossa ependymoma with infiltration of the fourth ventricle floor. Histopathological study of the removed ventricular catheters showed that their tips were occluded by choroid plexus (n=4) or by choroid plexus and old clotted blood (n=2). After a mean follow-up time of 8 months (range 3 to 13 months), the results in the five surviving patients were considered as satisfactory, in regard to valve rescue and to patients' neurological evolution. A summary of the epidemiological and clinical data of the patients is shown in Table 1.

Discussion

Endogenous CSF fibrinolysis and urokinase

Urokinase is an enzyme formed in the kidney that can be found in the urine. This enzyme activates the endogenous thrombolytic system by converting plasminogen in plasmin, which in turn lyses the fibrin clot [4, 19]. Little is known about the mechanisms by which blood clots are cleared from the CSF pathways [19]. The two main factors involved in intra-ventricular blood lysis are macrophage-mediated phagocytosis and plasminogen activation leading to fibrin lysis [19]. Fibrinolytic activity in cerebral tissue

Table 1 Summary of clinical data of six children with CSF shunts receiving local urokinase for treatment of intra-ventricular haemorrhage

No	Age/sex	Aetiology of hydrocephalus	No. previous surgeries	Interval from previous shunt insertion/ revision (months)	Number of urokinase doses	Follow-up time (months)	Result
1	14 mos/M	Post-haemorrhagic	–	14	10	3	Good (Fig. 1)
2	8.8 yrs/F	Post-haemorrhagic	12	23	10	9	Good
3	3.5 yrs/M	Tumour (4th ventricle ependymoma)	1	4	12	3	Dead, disease progression
4	8.5 yrs/F	Tumour (cerebellar astrocytoma)	2 ETV	2	15	13	Good (Fig. 2)
5	9 mos/M	Post-meningitis (*Listeria*)	–	6	10	13	Good
6	19 mos/F	Post-meningitis (S*treptococcus*)	–	11	10	7	Good (Fig. 3)

ETV endoscopic third ventriculostomy, *F* female, *M* male, *mos* months, *yrs* years

from autopsy cases was localised especially to the vascular endothelium [19].

Whitelaw reported no fibrinolytic activity in the normal CSF [19]. He also found that there was no spontaneous fibrinolysis in the CSF of 17 infants with IVH in samples obtained less than 17 days after the diagnosis of the bleeding episode [19]. However, fibrinolytic activity was detected in all but one of these infants in CSF samples taken from 17 to 52 days of IVH [19]. Delayed endogenous fibrinolysis in the CSF is common after IVH but, in certain cases, it seems to be insufficient to prevent hydrocephalus [19]. Only 22% of adults with subarachnoid haemorrhage demonstrated CSF fibrinolytic activity during the first week and only 30% during the second week. By the third week, most of CSF samples showed fibrinolytic activity [19]. This feature probably represents a protective mechanism as fibrinolysis inhibition may represent a defensive mechanism that acts by reducing the probability of re-haemorrhage [19].

Several fibrinolytic agents (streptokinase, urokinase and recombinant tissue plasminogen activator) have been used both in experimental [11–14] and in clinical settings [3, 4, 6, 8, 18] with disparate results. Pang et al. developed an experimental canine model for studying the lysis of ventricular clots [11–13]. Freshly obtained blood injected into the animals' ventricles was rapidly cleared from the CSF. For this reason, they utilised "preformed" clots that were subsequently injected into the ventricles [11]. These researchers also investigated the safety of intra-ventricular urokinase. There was neither reactive inflammatory reaction in the ventricles' walls after fibrinolytic treatment nor there were episodes of re-bleeding at the wound, brain or other systems [12]. The minimal estimated dose for producing lysis of a 10 ml intra-ventricular clot was 10,000 IU of urokinase. In their experiment, they used 20,000 IU of urokinase every 12 h for 4 days [12]. In the canine model, clot lysis occurred between 3 and 6 days of intra-ventricular urokinase administration, and only two of ten dogs developed hydrocephalus.

Fibrinolytic agents for treatment of IVH in preterm infants

Several researchers have documented a decrease in the rate of hydrocephalus, requiring shunt placement after periventricular haemorrhage in preterm infants both at low or high urokinase dosage [4, 6, 18]. Luciano et al. found no benefit in their study using streptokinase [8]. A systematic review of the current results in preventing the occurrence of hydrocephalus in preterm infants with periventricular haemorrhage has been produced by Haines et al. [3]. This review raises several questions about efficacy, dosage and timing of fibrinolytic agent application and suggests the realisation of further clinical studies [3]. Urokinase has also been utilised to prevent adhesive complications in bacterial ventriculitis with success [15].

Urokinase for treatment of blocked CSF catheters

We searched the PubMed and found only one work on the use of urokinase to treat blocked CSF shunts [5]. Hudgins et al. reported their experience in two children with IVH complicating shunt revision surgery who were treated with intra-shunt urokinase [5]. The children were symptomatic at the time of treatment, and they had ventriculomegaly demonstrated on CT scans. Following urokinase treatment, there was resolution of the children's symptoms and of ventriculomegaly on CT studies. A third patient, given a ventriculoatrial shunt, did not respond to this treatment and required two further surgeries on his proximal catheter and, finally, conversion of the CSF drainage to a VP shunt [5]. We have used this method in one occasion (patient 2) during a previous episode of shunt blockage that produced only transient improvement of symptoms.

Our instances differ from those of Hudgins et al. in that all our patients showed a rapidly evolving neurological deterioration requiring a rapid surgical solution. Accordingly, all our instances were given an external ventricular drain. External CSF drainage by itself can facilitate clearance of the bloody CSF although this process usually takes many days, which increases the risk of ventricular infection. In view of our experience with the use of intraventricular urokinase in adults with IVH, we decided to use direct injection of urokinase within the ventricles via the ventricular drainage. Another difference of our instances with those of Hudgings et al. consists of the route for delivering urokinase to the ventricles. We used direct urokinase infusion within the ventricles while those authors injected it via the valve reservoir. Regarding dosage, we empirically chose to use the smallest amount of urokinase (10,000 IU twice a day) that has proved to be effective for clot lysis in infants with IVH [6]. We also decided to start our management protocol as soon as possible to take advantage of the apparent *window of opportunity* for this treatment [19]. Endogenous fibrinolysis does not appear to occur until the third week of the haemorrhage. According to our observations, this protocol of intra-ventricular infusion of urokinase for treating IVH after shunt revision proved to be safe. We experienced no untoward effects in our patients, including two instances that were found to have minor coagulation disorders. Patient 6, the girl with the spontaneous intra-cerebral haemorrhage, was found to have a deficit of factor VII, and another child (patient 1) suffered a transient hepatic insufficiency, probably of viral origin, that also produced a coagulation deficit.

The incidence of IVH complicating shunt revision (12.9%) in our series compares favourably with that of Brownlee et al. that was of 31% [1]. This difference probably reflects the effectiveness of the measures we routinely take during shunt revision for avoiding haemorrhage that

can occur after removal of adherent ventricular catheters [9, 16, 17]. Given the short follow-up period of our patients, we could not establish the value of urokinase use in the prevention of subsequent shunt revisions as reported by Brownlee et al. [1].

Conclusions

Children submitted to CSF shunt revisions who bleed during ventricular catheter removal may show a rapid neurological deterioration due to the occurrence of IVH. Asymptomatic patients with minor IVH are best managed conservatively. However, those cases evolving with large IVH and marked neurological deterioration can be treated by placing an external ventricular drain and with intraventricular urokinase administration. This method seems to be practical and safe and can save the already implanted CSF shunt, thus avoiding further revision surgery to which children with valves are often submitted to.

Disclaimer The authors have no financial or other interests in the products and devices utilised and mentioned in this work.

References

1. Brownlee RD, Dold ONR, Myles ST (1995) Intraventricular hemorrhage complicating ventricular catheter revision: incidence and effect on shunt survival. Pediatr Neurosurg 22:315–320
2. Dedrick SC, Ramirez-Rico J (2004) Potency and stability of frozen urokinase solutions in syringes. Am J Health Syst Pharm 61:1586–1589
3. Haines SJ, Lapointe M (1999) Fibrinolytic agents in the management of posthemorrhagic hydrocephalus in preterm infants: the evidence. Child's Nerv Syst 15:226–234
4. Hudgins RJ, Boydston WR, Hudgings PA, Adler SR (1994) Treatment of intraventricular hemorrhage in the premature infant with urokinase. Pediatr Neurosurg 20:190–197
5. Hudgings RJ, Boydston WR, Gilreath CL (1996) Urokinase in the treatment of shunt malfunctions caused by thrombus. Pediatr Neurosurg 25:315–320
6. Hudgings RJ, Boydston WR, Hudgins PA, Adler SM, Gilreath CL (1997) Intrathecal urokinase as a treatment for intraventricular hemorrhage in the preterm infant. Pediatr Neurosurg 26:281–287
7. Hudgings RJ, Boydston WR (1998) Shunt revision by coagulation with retention of the ventricular catheter. Pediatr Neurosurg 29: 57–59
8. Luciano R, Velardi F, Romagnoli C, Papacci P, De Stefano V, Tortorolo G (1997) Failure of fibrinolytic endoventricular treatment to prevent neonatal post-haemorrhagic hydrocephalus. Child's Nerv Syst 13:73–76
9. Martínez-Lage JF, Lopez F, Poza M, Hernández M (1998) Prevention of intraventricular hemorrhage during CSF shunt revisions by means of a flexible coagulating electrode. A preliminary report. Child's Nerv Syst 14:203–206
10. Martínez-Lage JF, Almagro MJ, Sanchez del Rincón I, Pérez-Espejo MA, Piqueras C, Alfaro R, de San R, Pedro J (2007) Management of neonatal hydrocephalus: feasibility of use and safety of two programmable (Sophy and Polaris) valves. Child's Nerv Syst 24:549–556
11. Pang D, Sclabassi RJ, Horton JA (1986) Lysis of intraventricular clot with urokinase in a canine model: part 1. Canine intraventricular clot cast model. Neurosurgery 19:540–546
12. Pang D, Sclabassi RJ, Horton JA (1986) Lysis of intraventricular clot with urokinase in a canine model: part 2. In vivo safety study of intraventricular urokinase. Neurosurgery 19:547–552
13. Pang D, Sclabassi RJ, Horton JA (1986) Lysis of intraventricular clot with urokinase in a canine model: part 3. Effects of intraventricular urokinase on clot lysis and posthemorrhagic hydrocephalus. Neurosurgery 19:553–572
14. Pattisapu JV, Trumble ER, Taylor KR, Howard PD, Kovach TM (1999) Percutaneous endoscopic recanalization of the catheter: a new technique of proximal shunt revision. Neurosurgery 45:1361–1367
15. San Frutos MA, Fernández-Pavón A, Pérez-Higueras A, Roche MC, Ruza F (1986) Local urokinase for the treatment of ventriculitis complications. Acta Paediatr Scand 75:497–498
16. Steinbok P, Cochrane DD (1992) Removal of adherent ventricular catheter. Technical note. Pediatr Neurosurg 18:167–168
17. Whitfield PC, Guazzo ET, Pickard JD (1995) Safe removal of retained ventricular catheters using intraluminal choroid plexus coagulation. Technical note. J Neurosurg 83:1101–1102
18. Whitelaw A, Rivers RPA, Creighton L, Gaffney P (1992) Low dose intraventricular fibrinolytic treatment to prevent posthaemorrhagic hydrocephalus. Arch Dis Child 67:12–14
19. Whitelaw A (1993) Endogenous fibrinolysis in neonatal cerebrospinal fluid. Eur J Pediatr 152:928–930