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REVIEW PAPER

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Fibrinolytic agents in the management of posthemorrhagic hydrocephalus in preterm infants: the evidence

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Abstract The objective of this study was to review current literature on the management of posthemorrhagic hydrocephalus in preterm infants with intraventricular administration of fibrinolytic agents; to this end a literature search was carried out electronically. The keywords used were "intraventricular hemorrhage" or "posthemorrhagic hydrocephalus" in combination with "fibrinolytic agent," "urokinase," "streptokinase," or "recombinant tissue plasminogen activator" and "intraventricular administration"; the search covered the years 1966–1998 and was restricted to English language papers and human subjects. It was supplemented by a search through the reference lists of the articles identified. Articles dealing with intracerebral hemorrhage or hematoma, intraventricular hemorrhage in adults, nontherapeutic issues and laboratory research were excluded. The articles included are summarized in evidence and evaluation tables. Five scientific publications evaluating the use of a fibrinolytic agent to manage posthemorrhagic hydrocephalus were retrieved. In the studies described in these reports, a total of 62 neonates received streptokinase, urokinase or r-tPA intraventricularly. No two of the regimens were identical in the drug used, method of administration and duration of therapy. The time before therapy was started ranged from 2 to 35 days after the ictus. Among the case series reported, three were small series with a total of 38 neonates. One other case series of 18 neonates compared the treatment group with an historical control group. All case series showed that endoventricular fibrinolytic therapy was practical. The proportion of cases in which shunt placement was performed ranged from 11% to 100%. Only one small prospective, randomized, controlled study was identified. That study was too small to allow useful conclusions. Overall, 3 cases of secondary intraventricular hemorrhage were reported. However, it was not possible to determine with certainty whether these episodes were related to the drug therapy itself. The reports suffer from inadequate study design, lack of descriptive information and short follow-up period. There is insufficient evidence to justify the claim that fibrinolytic agents administered intraventricularly in posthemorrhagic hydrocephalus are safe and effective. More evidence is needed to prove or disprove the effectiveness and safety of this form of therapy.

Key words Intraventricular hemorrhage · Posthemorrhagic hydrocephalus · Urokinase · Streptokinase · Recombinant tissue plasminogen activator · Fibrinolytic agent · Intraventricular administration

Introduction

We recently evaluated the use of fibrinolytic agents in adults with intraventricular hemorrhage (IVH) [2]. Because the etiology and pathophysiology of neonatal IVH differ in many important ways from those of IVH in adults, we have reviewed the evidence regarding the use of fibrinolytic agents in neonates separately.

It is well known that preterm infants are at increased risk of developing IVH. Ventricular dilatation can occur in variable proportions in these patients. Eventually, most (60%) neonates with progressive posthemorrhagic hydrocephalus (PHH) will require the placement of a ventriculoperitoneal (VP) shunt [14]. The majority of these patients need subsequent surgical revisions, and some require antibiotic therapy for shunt infection. Some of the inherent and associated neurological morbidity in these children is probably related in part to complications of medical interventions (acetazolamide, furosemide) and surgical procedures (lumbar puncture, ventricular drainage system). Recent review articles have addressed the pathology of neonatal hydrocephalus and the medical and surgical management of PHH in depth [1, 3, 10].

To understand the hypothesis that exogenously increasing ventricular fibrinolysis with fibrinolytic agents can result in better blood clearance and thereby improve outcome, the reader should consider the earlier observations made by Pang and colleagues in an animal model of IVH and by Whitelaw and colleagues in several studies evaluating local fibrinolysis in the cerebrospinal fluid (CSF) of neonates who developed IVH and PHH.

Prior to studying the effect of intraventricular administration of fibrinolytic agents in neonates with PHH and adults with IVH, Pang and colleagues had published three very interesting articles. In this series, they described a canine model of IVH, where blood was injected intraventricularly to produce a solid blood cast in the ventricular system [11]. Then, after the dose of urokinase necessary to lyse the amount of blood to be injected in the ventricles had been determined in vitro [12], a study was performed in 20 mongrel dogs. In this comparative study, half of the dogs received 20,000 U of urokinase every 12 h starting 6 h after ventricular clot injections. Treatment was continued until complete clot lysis. Dogs who received urokinase had complete clot lysis within 3–6 days, as opposed to 38–65 days for the untreated group. No cases of local or systemic hemorrhages were reported among the dogs treated with urokinase. In general, the neurological status of treated dogs improved promptly and ventricular distension post-ictus was minimized [13].

In a clinical human study, Whitelaw and colleagues demonstrated that neonates with IVH and PHH have increased natural fibrinolytic activity [19]. Fibrinolytic activity measured by the concentration of fibrin degradation product (FDP) in the CSF obtained by lumbar (or ventricular in PHH) taps was significantly more elevated when PHH was present. The median concentration was approximately 3 and 10 times as high in the IVH and PHH infants, respectively, than in the normal preterm infant group. In addition, they suggested that the peak concentration of FDP was observed at 2 weeks after the hemorrhage in one patient. Another study demonstrated an increased but delayed endogenous fibrinolysis in a similar population of neonates by using a fibrin plate method [18]. Similarly, a subsequent report demonstrated that CSF tissue plasminogen activator was elevated in infants with IVH with ventricular dilatation. In addition, the observed fibrinolytic state could persist up to 8 weeks after the hemorrhage [23]. Finally, they reported that the level of FDP (D-dimer) was higher in neonates with PHH during intraventricular streptokinase therapy. D-dimer in the CSF increased up to 10-fold. It is of note that D-dimer levels in the plasma of study subjects were undetectable, which suggests that the fibrinolytic activity measured was local without any significant systemic effect [21]. Acute restoration of CSF flow with prevention of communicating hydrocephalus is the desired outcome in treatment of neonatal IVH. It is hoped that this will have a positive effect on cognitive outcome, but the avoidance of shunt treatment itself would have an important benefit for these patients. The safety of the treatment is also of concern, as repeated intraventricular injections and continuous CSF drainage carry a real risk of infection and an unknown risk of promoting further hemorrhage.

Method

We performed a literature search in Medline and Current Contents, using the keywords “intraventricular hemorrhage” or “posthemorrhagic hydrocephalus” in association with “fibrinolytic agent,” “urokinase,” “streptokinase,” or “recombinant tissue plasminogen activator” and “intraventricular administration”; the search covered the years 1966–1998 and was restricted to English language papers and to human subjects. It was supplemented by a search through the reference lists of the articles identified. Articles dealing with intracerebral hemorrhage or hematoma, IVH in adults, nontherapeutic issues and laboratory research were excluded. The articles that were included are summarized in Tables 1 and 2 (evidence and evaluation tables). The criteria for evaluation of these articles are those of Sackett et al. [15].

Results

Five published articles attempt to evaluate the therapeutic efficacy of thrombolysis for neonatal IVH (Tables 1, 2).

Table 1 Evidence table – intraventricular urokinase for the treatment of intraventricular hemorrhage (*IVH*); (*CFP* cerebrospinal fluid pressure, *DNA* authors did not assess, *ICP* intracranial pressure, *LP* lumbar puncture, *N/A* not applicable, *SD* standard deviation, *VAD* ventricular access device)

Study [literature reference]	Whitelaw et al. [20]	Hudgins et al. [6]	Whitelaw et al. [24]	Luciano et al. [8]	Hansen et al. [4]
Type of study	Case series	Case series	Case series	Randomized, prospective	Case series
Controls	None	Retrospective	None	Ventricular drainage if high ICP or furosemide only	None
No. treated	9	18	22	6	7
No. of controls	None	39	None	6	None
Age at time of IVH					
Treatment group	25–31 weeks of gestation	23–33 weeks of gestation	26–33 weeks of gestation	Mean: 29 weeks of gestation	26–38 weeks of gestation
Control group		23–33 weeks of gestation		Mean: 29 weeks of gestation	
Birth weight					
Treatment group	724–1750 g	580–1830 g	805–2500 g	Mean (SD) 1425 (1166) g	845–1620 g
Control group		510–1800 g		Mean (SD) 1233 (666) g	
Clinical baseline					
Treatment group	IVH with ventricles enlarged to >4 mm over the 97th centile	IVH grade 3 or 4	IVH grade 3 or 4 (median 3)	IVH with ventricles enlarged to >4 mm over the 97th centile	Head circumference growth >2 cm/week with diuretics and LP
Control group		IVH grade 3 or 4			
Therapy started	8–27 days after birth	2–35 (mean 12) days after ictus	8–26 days after birth	3–24 (mean 12) days after birth	26–30 days of age
Treatment duration	12- to 72-h continuous infusion; total dose: 7,000–70,000 IU	7 days; total dose 110,000–140,000 IU in group 1 or 280,000 IU in group 2	1–5 (median 2 or 3) doses; duration 1 or 7 days	96-h continuous infusion interrupted for CSF drainage	72-h intermittent infusion with-ventricular drainage every 90 min
Dose	Streptokinase 20,000–25,000 IU/24 h	Urokinase 10,000–20,000 IU q 12 h, patients divided into low- and high-dose-treatment groups	r-tPA 0.5 mg or 1 mg bolus administration at 1- to 7-day (median 2-day) intervals	Streptokinase 20,000 IU/24 h	Urokinase 20,000 IU/24 h
Method	Through percutaneous ventricular catheter, LP performed during therapy to optimize drug distribution	VAD, intermittent ventricular drainage before urokinase administration	Ventricular puncture; or external ventricular catheter; LP performed to optimize drug distribution	Percutaneous endo-ventricular catheter, frequent CSF drainage for high ICP, CSF tap daily	VAD: ventricular catheter with attached subcutaneous reservoir
Monitoring	Twice-daily cranial ultrasound to monitor size. Ventricular fluid removed to control CFP	Cranial ultrasound performed every other day; 1–4 months' follow-up	Cranial ultrasound daily during treatment, then twice weekly; at least 9 months' follow-up	Cranial ultrasound performed every other day and VAD removal	Cranial ultrasound, daily for 3 days, then 4 days after urokinase infusion
Results					
Treatment group	No data of interest regarding size of ventricles over time reported; no evidence of systemic effect	Better LVH/HW ratio pre/post with urokinase ($P<0.001$); shunt placement lower in low-dose group (37%) than in controls ($P<0.002$)	No change in plasma fibrinogen observed; r-tPA half-life in CSF 24 h	Statistically significant enhancement of CSF lysis determined by fibrin degradation product during treatment	Quantitative measurement of D-dimer increased during treatment but ventricle and clot size decreased inconsistently
Control group	N/A	3 had VAD infection requiring replacement	N/A	No data of interest reported	N/A

Table 1 (continued)

Study [literature reference]	Whitelaw et al. [20]	Hudgins et al. [6]	Whitelaw et al. [24]	Luciano et al. [8]	Hansen et al. [4]
Outcome					
Treatment group	Duration of follow-up not stated	1 death	12 patients were discharged, no note of morbidity	1 death	1 death before full treatment completed
Control group	N/A	3 deaths prior to shunt placement; 3 shunt infections in survivors	N/A	1 death	N/A
Hydrocephalus					
Treatment group	1 case of progressive hydrocephalus with shunt placement	12/18 needed shunt	9 survivors with shunt placement	3/5 survivors with shunt	All survivors (6/6) required shunt placement
Control group	N/A	33/36 survivors required shunt	N/A	3/5 survivors with shunt	N/A
Complications in treatment group	Intraventricular bleed (1); catheter removal (3); no CSF infection	No hemorrhage; VAD infection (4)	Death (1); intraventricular bleed (1); no ventriculitis	Intraventricular bleed 48 h after infusion (1); meningitis during septicemia (1)	CSF leukocytosis (1); no hemorrhage; no infection

Table 2 Evaluation table – intraventricular urokinase for the treatment of intraventricular hemorrhage (*IVH*)[a]; (*CFP* cerebrospinal fluid pressure, *DNA* authors did not assess, *ICP* intracranial pressure, *LP* lumbar puncture, *N/A* not applicable, *SD* standard deviation)

Study [literature reference]	Whitelaw et al. [20]	Hudgins et al. [6]	Whitelaw et al. [24]	Luciano et al. (1997)	Hansen et al. (1997)
Assignment random?	No	No	No	Yes (method not stated)	No
RCT Quality Score	N/A	N/A	N/A	1	N/A
Group similarities?	N/A	Age, weight, IVH grade	N/A	Age, weight	N/A
Prognostic stratification?	None	Yes (by IVH grade)	By IVH grade	None	None
Report all clinically relevant outcomes?	Partially	Partially	Partially	Yes	Yes
Mortality and morbidity?	Yes (partially)	Yes	Yes	Yes	Yes
Deaths from all causes?	Yes (assumed)	Yes (assumed)	Yes (assumed)	Yes	Yes (assumed)
Quality of life assessment?	No	No	No	DNA	Partially
Study patients similar to own patients?	Possibly	Yes	Possibly	Yes	Possibly
Defined exclusion criteria?	None	None	Partially	None	Partially
Both statistical and clinical significance considered?	DNA	Yes	DNA	DNA	DNA
Therapy available and feasible in practice?	Yes	Yes	Yes	Yes	Yes
Contamination avoided?	No	Assumed, not stated	Not stated	Assumed, not stated	DNA
Compliance measured?	No	Not stated	Yes	Assumed, not stated	Briefly stated
All patients accounted for?	Yes	Yes for treatment group	Yes	Yes	Yes
Drop-outs, withdrawals handled correctly?	N/A	Yes for treatment group; not stated for controls	N/A	Yes	N/A

[a] This table is abridged. The authors would be pleased to provide the unabridged version upon application

Whitelaw and colleagues published the first results of a pilot study in which a fibrinolytic agent was administered intraventricularly to preterm infants with PHH [20]. In their study, they treated a total of nine premature neonates diagnosed with IVH and progressive ventricular dilatation with a continuous intraventricular infusion of streptokinase. In all cases, IVH was diagnosed within 96 h of birth but therapy was started 8–27 days postnatally. In their series, only one infant had a surgical shunt placed after the administration of streptokinase. Although the authors qualified their findings as encouraging, and favorable in comparison with the results of the multicenter ventriculome-

galy trial [17], several questions remain. It is not possible to determine from the report precisely how long after the ictus the fibrinolytic treatment was started. This is an important detail if one assumes that a fibrinolytic agent may have to be administered at a strategic moment during the natural fibrinolysis cycle. In addition, this study cannot be replicated, since there is no information on the IVH grade of the patients, inclusion criteria and clinical follow-up. In terms of safety, one infant developed a fresh intraventricular bleed, which was "effectively managed." No further detail relating to that case was provided. From this series, one can only hypothesize that intraventricular administration of a fibrinolytic agent may be a useful therapeutic option. The full assessment of clinical outcome is not possible because of the lack of information and the undefined follow-up period. Noteworthy is the fact that in a subsequent publication, the same authors briefly mentioned that based on that same protocol, a total of 13 patients were later enrolled. Of this number, 4 neonates underwent shunt placement and 1 died early [24]. Because these patients were not described, we have not included them in Table 1 (the evidence table).

Another group of investigators led by Whitelaw also completed a phase I trial in which 22 neonates with PHH received recombinant tissue plasminogen activator (r-tPA) [24]. In this report, the authors stated that they chose not to use streptokinase, partly on the basis of their previous clinical experience, but also because of its potential immunogenicity, decreased plasminogen activity, reduced specificity for fibrin and pharmacokinetic properties. Unlike the previous report with streptokinase, this one presents the inclusion criteria, which are reproducible (similar to those in the Ventriculomegaly Trial), and the subjects' clinical states were better described. The inclusion criteria were: (1) IVH documented by ultrasound scan; (2) progressive expansion of ventricular width; (3) smaller ventricular width exceeding 4 mm over the 97th centile; (4) no more than 28 days elapsed since the estimated date of hemorrhage. Overall, all patients had IVH grade III or IV (as previously defined by Papille [14]) and received up to five doses of r-tPA. Nine patients ultimately required shunt placement. The study suffers from the absence of standardization in terms of dosing regimens, total number of doses given, method of administration (ventricular puncture or catheter) and adjunctive therapy. In light of the results presented, it is difficult to fully evaluate the effect of the pharmacotherapy on the outcome of interest. The time delay between the ictus and the first dose given was relatively long, and the treatment duration might have been too short in some cases. Although the method was not described, no association was reported between the adverse outcome and the patients' baseline parameters and clinical condition. No cases of clinically significant systemic bleeding tendency were reported. Also, it appears that r-tPA, when administered by ventricular puncture, had an elimination half-life of approximately 24 h. However, in this phase I study, one patient re-bled intraventricularly during the treatment period, and this episode certainly deserves further evaluation in the use of these pharmacological agents.

Hudgins and colleagues presented the preliminary data of their study after enrolling only four patients in the treatment group in 1994 [6]. The final report was published 3 years later [7]. In their final publication, they reported a total of 18 neonates with PHH treated with either a low- or a high-dose regimen of urokinase. They compared the results in the treatment group with those in a retrospective case series of 39 neonates with IVH who had been treated at the same institution. At baseline, the severity of the hemorrhages in the treatment and control groups appeared to be comparable, since the proportion of grade III and IV in each group (including the low- and high-dose groups) was equally distributed. In their results, neonates treated with urokinase (low dose) were significantly less likely to require a shunt (37%) than the historical control group would suggest (92%). This difference could not be statistically demonstrated for the high-dose group alone or for both treatment groups together. In addition, the treatment group as a whole had fewer shunt revisions than the retrospective control group after 2 years. Comparison of pretreatment and posttreatment ratios of the lateral ventricular width and hemispheric width as seen on ultrasound revealed differences that were statistically significant for both treatment groups. In this study, the reporting of morbidity is limited despite an apparent 24-month follow-up. From a therapeutic standpoint, it is hard to fully understand the treatment received by the control group. Specifically, the parameters for serial VAD aspiration were only briefly stated and the proportion of patients who received acetazolamide and/or underwent lumbar puncture was not mentioned for the control group. The low-dose group had their treatment started earlier after the ictus (4–21, mean 10 days, versus 8–36, mean 16 days) than the high-dose group. Moreover, the high-dose treatment group was nearly 2 weeks younger and 150 g lighter at birth than the low-dose treatment group. A multivariate analysis was not performed. It appears, however, that the combination of all these variables clearly favored the low-dose group and suggests that the differences observed between the two treatment groups may not be valid.

The study by Luciano and colleagues constitutes the first effort to report a prospective randomized clinical trial of ventricular clot lysis in neonatal IVH with a fibrinolytic agent (the study report incorrectly describes it as a "case-control" trial) [8]. The authors attempted to compare current medical/surgical management with a 96-h continuous infusion of streptokinase. The inclusion criteria were relatively reproducible, but specific definitions of "ventricles distended by clots" and the "97th centile for postmenstrual age" are not given. In addition, one cannot ascertain that groups were comparable in terms of the extent of IVH. In this study, patient enrollment was discontinued prematurely in light of the high shunt placement rate in the strep-

tokinase group (60%). Although mentioned, it is not clear whether all subjects in the control group underwent ventriculostomy. These workers concluded that the use of fibrinolytics for PHH in neonates is not more effective than conventional treatment, basing this conclusion on their outcome of interest (i.e., the proportion of patients who required shunt placement after therapy). Unfortunately, the very small sample size renders this conclusion meaningless. The authors did not comment on the statistical power of their study. Utilizing a computerized statistical power analysis program, we estimate that to have an 80% chance of demonstrating a 50% reduction in PHH requiring shunting from the 60% rate of shunting found by the authors (utilizing Chi-square) a total sample size of 98 patients would be required. A smaller, but clinically important, difference would require even more patients. In addition, the protocol used also suffers from allowing a very long period of time before the initiation of therapy following the diagnosis (possibly up to 24 days). Unfortunately, methodological flaws mean that this paper has not added to our understanding of the problem.

The last report retrieved by our search was a case series by Hansen and colleagues [4]. In this series, only infants with rapidly progressing PHH were selected to receive a 3-day continuous infusion of urokinase interrupted by sequential ventricular drainage. Originally, it was intended that 15 patients should be enrolled in that study, which was designed to evaluate the rate of VP shunt placement while measuring the CSF fibrinolytic state, ventricle and blood clot dynamics. Of seven patients enrolled, six received a complete course of therapy and one subject died from a severe pretreatment fungal infection. The clinical condition of all six surviving patients mandated VP shunt placement. The study was interrupted prematurely because no surgical intervention could be avoided by the treatment protocol. As in previous reports, fibrinolytic therapy was started several days after the ictus (not clearly stated). The baseline clinical parameters, such as IVH grade, were poorly described, and it is difficult to compare this study group with others. Despite the failure to demonstrate any positive impact on outcome, this publication reported some valuable information. No episodes of CSF bleed or infection were observed. In all patients, the CSF concentration of D-dimer was increased during treatment. Interestingly, some patients had a relatively elevated concentration of plasminogen activator inhibitor-1 (PAI-1) and a decreased level of tPA (data not reported). On the basis of these observations, it is hard to draw any conclusion on the effectiveness of the state of fibrinolysis achieved in the CSF of subjects as stated by the authors. They also could not demonstrate any correlation between the previous parameters and the clot and ventricular size. Finally, one infant developed a transient CSF leukocytosis, which could suggest that a fibrinolytic agent might cause meningeal irritation in some patients.

Discussion

We identified several small trials of intraventricular administration of fibrinolytic agents. A total of 62 neonates with various degrees of PHH were treated with five different study protocols. Overall, the proportion of neonates treated with fibrinolytic agents who later required a VP shunt was 50%, but it ranged from 11% to 100%. Because of many important differences in the study designs, statistical combination of the results (meta-analysis) would be inappropriate.

Therapeutic window

As in many other medical conditions in which thrombolytic agents are used (myocardial infarction, ischemic stroke, pulmonary embolism), it is likely that there is a therapeutic window for the effective administration of intraventricular fibrinolytic therapy in IVH. That therapeutic window has not yet been identified, and the evidence published thus far does not allow us to delineate it. It is conceivable that early administration could result in faster ventricular clearance and decrease the chance of CSF outflow obstruction and communicating hydrocephalus. All studies enrolled patients up to several weeks after their ictus. Because of the limited number of subjects in each time period, it is not possible to determine what the upper time limit is. A single case report suggests that reducing the time interval between IVH and thrombolytic infusion does not prevent permanent PHH [9].

Pharmacokinetics

Thrombolytic agents display different pharmacokinetic and pharmacodynamic properties. For these reasons, it would be premature to attempt to compare them, although differences may exist in their efficacy for the treatment of IVH. Similarly, the method of administration (continuous or bolus) is likely to influence the clearance of blood clots. This is certainly true when CSF drainage through lumbar puncture or ventricular drainage is used to control elevated intracranial pressure. It is not yet possible to identify the most promising agent or how it should be administered.

Complications

The risk of recurrent hemorrhage during therapy appears to be low. Two cases were reported among the 62 patients studied. One case of late recurrent IVH was also reported (48 h after the last infusion). Four ventricular access device infections, three catheter removals and one case of CSF leukocytosis were mentioned. Case reports of secon-

dary IVH in adults should prompt clinicians to be alert to this possibility in infants [16].

Mechanism of action

Various authors have proposed different mechanisms by which patients could be refractory to the endoventricular fibrinolytic therapy. One suggested that some neonates may be deficient in plasminogen concentration and activity [22, 24]. Fibrinolytic activity in the ventricular fluid (as measured in most studies) may be different than it is near the arachnoid villi. Phagocytosis of red cells can play an important part in blood clot reabsorption [8, 18]. A report by Hansen and colleagues also demonstrated that plasminogen activator inhibitor-1 (PAI-1), which is not present in healthy neonates, was present in neonates with PHH and that the levels were significantly higher in cases of failure of fibrinolytic therapy. These observations were valid regardless of the size and severity of the initial hemorrhage and the fibrinolytic agent used. The authors suggested that it could be an important factor in explaining failure of fibrinolytic therapy seen in their small series [5, 24].

Difficulties in outcome assessment

Most reports available are case series that do not allow a thorough assessment of efficacy. At best, these case series provide some information on the safety of the fibrinolytic agent. However, a total of only 62 treated neonates has been described in the literature. The statistical power of the reported studies to answer the question of treatment efficacy was not commented upon in any of the reports. Assuming the incidence of VP shunt placement is 60% in neonates with progressive PHH and that fibrinolytic therapy could decrease the required frequency of shunt placement by 50%, in order to have an 80% chance of demonstrating that difference at least 49 patients would have to be treated and the same number followed as a control group.

An additional difficulty in assessing treatment efficacy arises from the variation in indications for shunt placement among neurosurgeons and institutions. There are important institutional differences in the timing of shunt placement in relation to rate and extent of ventricular enlargement, duration of hydrocephalus, CSF protein and cell count levels and patient weight that are considered necessary to allow shunt placement. They are not clearly specified in the reports and could make important differences in the frequency of shunt placement.

While the ultimate outcome of interest is improvement in cognitive function, there are great difficulties in assessing cognitive function and quality of life in the infant. In future studies, the developmental, cognitive and psychological assessment of infants with and without treatment will be important. However, the difficulty of such evaluations, and the fact that several years will need to pass before sophisticated testing can be done, means that successful shunt prevention will have to be the primary outcome assessed.

Conclusion

Many questions remain to be answered:

- Does ventricular fibrinolysis reduce the need for shunt therapy in PHH?
- Does the treatment affect cognitive outcome?
- Is ventricular fibrinolysis alone sufficient or is subarachnoid fibrinolysis also required?
- When is the optimal time to begin therapy?
- What is the optimal drug administration protocol?

While there is insufficient evidence to justify any claim that fibrinolytic therapy is safe and effective, there is also insufficient evidence to justify discarding this form of treatment as ineffective or unsafe. Only a cooperative effort of many neurosurgeons and neonatalogists could produce sufficient evidence to either prove or disprove the effectiveness of ventricular fibrinolysis in the treatment of neonatal IVH.

How could one go about answering these questions? It would be necessary for a consortium of neonatal treatment centers to cooperate in a number of studies, sharing evaluation, treatment and follow-up methods. The timing and mode of administration of fibrinolysis could be examined in dose escalation trials. Short-term outcomes, such as disappearance of clot or clearing of CSF, could be used for this purpose.

The questions of optimal timing, effect on hydrocephalus and cognitive outcome would require a randomized clinical trial. The number of variables that affect these outcomes is too high for clearly interpretable results to be possible with a less rigorous evaluation strategy.

Children eligible for such a study would include those with grade III and IV IVH suffered before 34 weeks of gestation (for clear distinction from full-term choroid plexus hemorrhage). Children thought to have less than a 50% chance of 5-year survival would be excluded. Factors unrelated to IVH but known to be highly predictive of hydrocephalus requiring shunting or poor cognitive outcome should be stratified in the treatment allocation. The problem of assessing the importance of timing of treatment could be handled in three ways. An arbitrary choice for either early or delayed treatment could be made. This would minimize sample size, but not control the possibility that the wrong choice might be made regarding timing of treatment. Both early and late treatment arms could be included in the trial. This would double the required sample size but improve the chances of finding a successful

outcome. The third strategy would be to allow the treating physicians to choose the interval before treatment and then statistically control for this factor. A preliminary study would be required to determine whether there is an adequate distribution of times for starting treatment to allow this factor to be studied. Such a strategy, which has been successfully employed in the North American Symptomatic Carotid Endarterectomy Trial, would allow some parts of the trial to be terminated before others, as soon as definitive information had been obtained for a range of treatment starting times.

There would have to be agreement on the specific treatment protocol, and it would have to be consistently applied throughout the study.

The assessment of outcome would present the largest challenge. Reproducible criteria for shunt placement and revision and their consistent application at all treatment centers would be necessary. The incidence of shunting in the first year after treatment would be a primary short-term study endpoint. There would have to be carefully conceived and consistently applied neuropsychological examinations of the patients at appropriate intervals for a sufficient time period (5–10 years) to allow small but important cognitive differences to be detected.

The sample size required depends on the details of the study (how many comparison groups and the actual rate of hydrocephalus requiring shunting being most important). Assuming a simple two-group comparison of the rate of hydrocephalus in the first year after treatment, with a control group rate of shunting of 60% (approximately that shown in the studies reviewed), 186 patients would be required in each group to have an 80% chance of detecting a clinically significant 15% reduction in the rate of shunting (from 60% to 45%) utilizing a continuity-corrected Chi-square test. Assuming some loss to follow-up, if 150 patients remained in each group at 5 years, it would be possible to detect a 4-point difference in mean IQ between the groups (power 0.8, assuming a normal distribution of IQ with a mean of 100 in the treated group and a standard deviation of 10 points).

Therefore, it seems that a study of 400–600 patients followed for 5–10 years could provide very useful information about the short- and long-term effects of fibrinolytic therapy in these patients.

References

1. Frim DM, Scott RM, Madsen JR (1998) Surgical management of neonatal hydrocephalus. Neurosurg Clin North Am 9:105–110
2. Haines SJ, Lapointe M (1998) Fibrinolytic agents in the treatment of intraventricular hemorrhage in adults. Crit Rev Neurosurg 8:169–175
3. Hansen AR, Snyder EY (1998) Medical management of neonatal posthemorrhagic hydrocephalus. Neurosurg Clin North Am 9:95–104
4. Hansen AR, Volpe JJ, Goumnerova LC, Madsen JR (1997) Intraventricular urokinase for the treatment of post-hemorrhagic hydrocephalus. Pediatr Neurol 17:213–217
5. Hansen A, Whitelaw A, Lapp C, Brugnara C (1997) Cerebrospinal fluid plasminogen activator inhibitor-1. A prognostic factor in posthaemorrhagic hydrocephalus. Acta Paediatr 86:995–998
6. Hudgins RJ, Boydston WR, Hudgins PA, Adler SR (1994) Treatment of intraventricular hemorrhage in the premature infant with urokinase. Pediatr Neurosurg 20:190–197
7. Hudgins RJ, Boydston WR, Hudgins PA, Morris R, Adler SM, Gilreath CL (1997) Intrathecal urokinase as a treatment for intraventricular hemorrhage in the preterm infant. Pediatr Neurosurg 26:281–287
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. Luciano R, Tortorolo L, Chiaretti A, Piastra M, Velardi F, Polidori C (1998) Intraventricular streptokinase infusion in acute post-haemorrhagic hydrocephalus. Intensive Care Med 24:526–529
10. McAllister JP, Chovan P (1998) Neonatal hydrocephalus. Mechanisms and consequences. Neurosurg Clin North Am 9:73–93
11. Pang D, Sclabassi RJ, Horton JA (1986) Lysis of intraventricular blood clot with urokinase in a canine model. I. Neurosurgery 19:540–546
12. Pang D, Sclabassi RJ, Horton JA (1986) Lysis of intraventricular blood clot with urokinase in a canine model. II. Neurosurgery 19:547–552
13. Pang D, Sclabassi RJ, Horton JA (1986) Lysis of intraventricular blood clot with urokinase in a canine model. I. Neurosurgery 19:553–572
14. Papille LA, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage. A study of infants with birth weight under 1500 gm. J Pediatr 92:529–534
15. Sackett DL, Haynes RB, Guyatt GH, Tugwell P (1991) Clinical epidemiology. A basic science for clinical medicine, 2nd edn. Little, Brown, & Co, Boston Toronto London, pp 187–248
16. Schwarz S, Schwab S, Steiner HH, Hacke W (1998) Secondary hemorrhage after intraventricular fibrinolysis. A cautionary note. Neurosurgery 42:659–663
17. Ventriculomegaly Trial Group (1990) Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. Arch Dis Child 65:3–10
18. Whitelaw A (1993) Endogenous fibrinolysis in neonatal cerebrospinal fluid. Eur J Pediatr 152:928–930
19. Whitelaw A, Creighton L, Gaffney P (1991) Fibrinolysis in cerebrospinal fluid after intraventricular haemorrhage. Arch Dis Child 66:808–809

20. Whitelaw A, Rivers RP, Creighton L, Gaffney P (1992) Low dose intraventricular fibrinolytic treatment to prevent posthaemorrhagic hydrocephalus. Arch Dis Child 67: F12–F14
21. Whitelaw A, Mowinckel MC, Larsen ML, Rokas E, Abildgaard U (1994) Intraventricular streptokinase increases cerebrospinal fluid D dimer in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 83: 270–272
22. Whitelaw A, Mowinckel MC, Abildgaard U (1995) Low levels of plasminogen in cerebrospinal fluid after intraventricular haemorrhage. A limiting factor for clot lysis. Acta Paediatr 84: 933–936
23. Whitelaw A, Mowinckel MC, Fellman V, Abildgaard U (1996) Endogenous tissue plasminogen activator in neonatal cerebrospinal fluid. Eur J Pediatr 155: 117–119
24. Whitelaw A, Saliba E, Fellman V, Mowinckel MC, Acolet D, Marlow N (1996) Phase I study of intraventricular recombinant tissue plasminogen activator for treatment of posthaemorrhagic hydrocephalus. Arch Dis Child 75: F20–F26