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Use of intrathecal hyaluronidase in the management of tuberculous meningitis with hydrocephalus

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Abstract. A preliminary study to evaluate the efficacy of intrathecal hyaluronidase was carried out in nine children suffering from tuberculous meningitis with communicating hydrocephalus. This was followed by a randomized trial in which five cases were treated with intrathecal hyaluronidase, while six cases were treated by the insertion of a ventriculoperitoneal shunt. No untoward reaction of any significance was noted. The results were judged in terms of improvement in the sensorium and mentation, in specific neurological deficit (e.g., visual impairment and hemiparesis), and in overall functional performance. Although most of the patients receiving hyaluronidase showed some improvement in the sensorium, only one of the nine preliminary cases and one of the five cases in the randomized trial showed a total recovery of function. Two of the six shunted patients, however, showed complete recovery. Shunt insertion led to further improvement in two of the nine preliminary cases who had failed to respond to treatment with hyaluronidase. This preliminary study shows that intrathecal hyaluronidase does, in most cases, lead to an improvement in the sensorium but does not offer any particular advantage over shunt insertion in terms of regression of specific neurological deficit or overall functional improvement.

Key words: Hyaluronidase – Hydrocephalus – Tuberculous meningitis – Intracranial arachnoiditis – Intrathecal hyaluronidase.

A fair number of patients with tuberculous meningitis develop impairment of cerebrospinal-fluid (CSF) circulation owing to basal exudate [18]. This leads to the development of hydrocephalus and raised intracranial tension, which adversely affects the course of the disease [2, 3, 6, 9, 10, 23, 25]. It is more often seen in children than in adults [11]. The insertion of a ventriculoatrial or ventriculoperitoneal shunt has shown encouraging results in many of these patients [3, 4, 5, 6, 7, 22]. However, shunt surgery is associated with problems of sepsis, blockage, slit-ventricle syndrome, and shunt dependency.

Gourie-Devi and Satish [13, 14] used intrathecal hyaluronidase to see if it could resolve the exudate and reestablish CSF circulation. The results obtained in a small, nonrandomized series were gratifying. No significant side effects were noted, and the patients tolerated the treatment well. We, therefore, felt that we should carry out a study to see whether we could reproduce the results described by Gourie-Devi et al., using a proper randomized trial, comparing patients treated with intrathecal hyaluronidase with patients treated with shunt insertion in order to evaluate the efficacy of these two modes of therapy.

Materials and methods

The study involved 20 consecutive cases of children suffering from tuberculous meningitis with hydrocephalus who were admitted to the Department of Neurosurgery of the J. J. Group of Hospitals, Bombay. Tuberculous meningitis was diagnosed when the CSF showed a glucose level of below 400 mg/l and a mainly lymphocytic cellular response of less than a few hundred cells. Many of our patients had an elevated erythrocyte sedimentation rate (ESR) and a positive Mantoux test. After grading the patients according to their level of consciousness and neurological deficit, a preliminary trial was performed in which nine cases were treated with intrathecal hyaluronidase. Thereafter, a randomized trial was conducted with alternate patients graded first and then treated with intrathecal hyaluronidase or ventriculo-peritoneal shunt insertion. The grading of patients was as follows: grade I, alert with no neurological deficit; grade II, alert with neurological deficit; grade III, drowsy with/without neurological deficit; grade IV, semiconscious with/without neurological deficit; grade V, unconscious with/without decerebrate response. Besides the neurological and general examination, routine hematological, biochemical, and radiological investigations were performed. The size of the ventricles and the type of hydrocephalus were determined by air or Conray ventriculography, or by a computed tomography (CT) scan. Only cases with communicating hydrocephalus were included in the study. In the group receiving hyaluronidase, the enzyme was administered once a week. One-

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thousand units of intrathecal hyaluronidase (Hylase; Rallis, India) were administered in the first injection, and thereafter 1,500 units were injected weekly. The efficacy of the therapy was assessed by weekly CSF pressure measurements and cytochemistry. In the preliminary study, all nine patients were put on intrathecal hyaluronidase. If deterioration occurred in the sensorium, vision, or neurological deficit, the treatment was considered a failure, and a shunt was inserted. The randomized trial involved 11 patients, 5 of whom were treated with intrathecal hyaluronidase, while 6 received ventriculoperitoneal shunt insertion. These are referred to as trial hyaluronidase and trial shunt, respectively.

Observations

Preliminary study

Of a total of nine children, eight were under 5 years of age, and one was 6 years old. There were four females and five males. Five had impaired levels of consciousness, one being drowsy, two semicomatose, and two comatose in a decerebrate state. Thus, there were four patients in grade II, one in grade III, and two each in grades IV and V (Table 1).

Three patients had generalized tonic and clonic convulsions, and two had decerebrate spasms. Impaired vision was present in four patients. The fundi of eight patients showed disc pallor, and one early papilledema. One patient had bilateral abducens paresis, one bilateral upward gaze palsy and one supranuclear facial paresis. One child had right-sided weakness and seven had bilateral spasticity with extensor plantar responses. Increased head circumference was found in two patients and a positive Macewan's sign was present in eight. The fontanelle was bulging in two patients and was flat in four. All nine patients had an elevated ESR, and the Mantoux test was positive in four. Suture widening was seen on the skull radiographs of eight patients.

Trial hyaluronidase

All five patients in this group were under the age of 5 years. There were three males and two females. Three patients had an impaired level of consciousness. Two were semiconscious, and one was unconscious. One patient had decerebrate spasms. Thus, there were two patients each in grades II and IV, and one patient in grade V (Table 1). Visual impairment was present in one. Four patients had bilateral disc pallor, and one had bilateral papilledema. Two patients had bilateral abducens paresis, and one had supranuclear facial paresis. Three patients had left-sided hemiparesis, and two had bilateral spasticity with extensor plantar response. None of the patients had an abnormal increase in the head circumference, but Macewan's sign was positive in all. The anterior fontanelle was bulging in one patient and flat in three others. The Mantoux test was positive in four. Sutural widening was present in all five. The ESR was between 20 and 30 mm/h in one patient, 30 and 40 mm/h in one, 40 and 50 mm/h in one, and above 50 mm/h in two. Four patients had air ventriculograms, and one had a Conray ventriculogram. Two had large and three had moderately dilated ventricles.

Trial shunt

Five patients were below 5 years and one was 8 years of age. There were four males and two females. Five patients had an impaired level of consciousness. Four were drowsy and one was semiconscious. Thus, there were four patients in grade III and one patient each in grades II and IV (Table 1). Five patients had bilateral primary optic atrophy and one had early papilledema. There were three patients with impaired vision. One of these was conscious and had a visual acuity of finger counting at 3 feet. The other two patients were drowsy and had dilated and fixed pupils. Two patients had bilateral abducens paresis and two had facial asymmetry. Three patients had right-sided weakness and two had bilateral spasticity with extensor plantar responses. Macewan's sign was positive in five cases and the anterior fontanelle was open and flat in one. Suture widening was seen in five. The ESR was raised in four cases, being between 20 and 30 mm/h in two cases and between 40 and 50 mm/h in two. Air ventriculogram was done in three patients, one had a pneumoencephalogram and two had CT scans. A large communicating hydrocephalus was noted in two patients and a moderate hydrocephalus in four.

Table 1. Grading of patients

Grade of patient	Preliminary study	Trial	
		Hyaluronidase	Shunt
I	–	–	–
II	4	2	1
III	1	–	4
IV	2	2	1
V	2	1	–

Treatment

Preliminary study

All of the patients were put on an antitubercular drug regime of streptomycin, isoniazide, and rifampin with either ethambutol or pyrizinamide. They also received dexamethasone, phenobarbitone, vitamin B_6 and multivitamins.

Intrathecal hyaluronidase was injected, via the lumbar route, after sedating the patient (in order to avoid errors in the pressure recording). One thousand units of hyaluronidase were injected the first time and 1,500 units per week thereafter. One patient received less than 4 injections. Four received 4–8 injections, and four received 9–12 injections.

The time from the appearance of the first symptom to the initiation of hyaluronidase therapy varied between 7 and 270 days. Similarly, the time from the onset of symptoms referrable to intracranial hypertension to the initiation of the same treatment ranged between 3 and 105 days, except in one patient in whom the deterioration was very rapid so that treatment was initiated within a day.

Trial hyaluronidase

All of the patients were treated as in the preliminary study. Two patients received less than 8 injections. Of the remaining three patients, two received 9 injections and one received 8 injections.

The time from the appearance of first symptom to the initiation of hyaluronidase therapy varied between 7 and 160 days; the time from the appearance of symptoms referable to intracranial hypertension and the commencement of the same treatment ranged between 7 and 90 days.

Trial shunt

All six patients were treated with the same antitubercular drugs as those in the hyaluronidase group, and they also received dexamethasone, phenobarbitone, and multivitamins.

A ventriculoperitoneal shunt of the Upadhyaya type with a medium discharge rate was inserted into all of these patients.

The time from the appearance of the first symptom to the commencement of hyaluronidase therapy ranged from 90 to 365 days; the time between the appearance of symptoms referable to intracranial hypertension and treatment ranged from 5 to 180 days.

Results

The results were assessed in terms of improvement in (1) level of consciousness, (2) specific neurological deficit, (3) overall functional performance of the patient after therapy. Failures and complications (4) were noted.

Preliminary study

1. Improvement in the level of the sensorium. Although a mild improvement in the sensorium was seen in all patients after the first injection, overall assessment at the end of the treatment showed that the sensorium had improved significantly in only three of the five patients who had impaired levels of consciousness. Two who had been semiconscious became conscious with neurological deficit, one patient who had been unconscious with decerebrate spasms became conscious with irritability and neurological deficit. One patient who had been drowsy had an initial improvement in the level of consciousness, but after 6 injections developed intermittent abdominal distension with paralytic ileus and then died. One patient who had been unconscious and decerebrate died within 24 h of treatment, not having shown any improvement at all.

In general, the maximum improvement was found to occur up to the 5th injection. There was not further improvement with subsequent injections.

2. Specific neurological deficit. Vision improved in one patient, remained static in two, and deteriorated in one. The patient whose vision improved was a 1-year-old boy who became able to follow light after therapy and who then began to play.

One patient with hemiparesis before treatment died, and one with bilateral spasticity and decerebration was left with residual hemiparesis (Table 2).

3. Overall functional usefulness after therapy. In a total of nine patients, there were four failures (two died and two had to have shunt insertions).

Of the remaining five patients, one child showed good recovery. Before treatment, he was conscious but could not follow light and had bilateral spasticity with extensor plantar responses. After treatment, he did not have any residual neurological deficit. Three patients showed a fair recovery. One 10-month-old boy was unconscious and had decerebrate spasms before therapy. After therapy, he was conscious and had less spasticity, but could not sit up. Two patients who had been semiconscious became conscious with neurological deficit. A 1-year-old boy could not hold his head up or recognize his mother, and a 14-month-old with double spastic hemiparesis could not follow light or sit up. One child remained unchanged.

Table 2. Results in terms of specific neurological deficit

		Preliminary study	Trial	
			Hyaluronidase	Shunt
Vision	improved	1/4	–	3/3
	static	2/4	1/1	–
	deteriorated	1/4	–	–
Hemiparesis	improved	–	2/3	1/3
	static	1/1	1/3	2/3

Table 3. Overall results

	Preliminary study (9 patients)	Trial	
		Hyaluronidase (5 patients)	Shunt (6 patients)
Good	1	1	2
Fair	3	3	1
Unchanged	1	1	2
Failure	2[a]	–	–
Died	2	–	1

[a] Both subsequently improved after shunt insertion

4. Failures and complications. One of the children who died was a 1-year-old girl who had been drowsy with sluggishly reacting pupils, bilateral abducens paresis, bilateral spasticity, and right-sided weakness. The anterior fontanelle was bulging and tense, the ventricular pressure 300 mm H_2O, the lumbar pressure 170 mm H_2O (with 140 cells/mm^3, 2 g/l protein, and 180 mg/l glucose). An air ventriculogram revealed moderate communicating hydrocephalus. After six injections of hyaluronidase, the child's level of consciousness improved and the anterior fontanelle became lax. Her CSF pressure decreased to 80 mm H_2O with no cells (0.70 g/l proteins, and 220 mg/l glucose). She developed paralytic ileus, respiratory distress, and died. Four days before death, the child showed intermittent abdominal distension, which was temporarily relieved by a flatus tube, Ryle's tube aspirations, and intravenous fluids.

The other child who died had a clinical history of only 7 days' duration. He was decerebrating, had a ventricular pressure of 300 mm H_2O and a lumbar pressure of 360 mm H_2O (with 60 cells/mm^3, 0.40 g/l proteins, and 520 mg/l glucose). The ventriculogram showed mild communicating hydrocephalus.

The first of 2 patients who required shunt insertion was a 2-year-old girl who was conscious with a vacant look, had sluggishly reacting pupils and bilateral optic-disc pallor with bilateral spasticity and extensor plantar re-

sponses. Her ventricular pressure was 70 mm H_2O (6.50 g/l proteins, 150 mg/l glucose, and 1,020 cells/mm^3). After 5 hyaluronidase injections, the child did not show improvement and developed persistent vomiting. A ventriculoperitoneal shunt was inserted. After the shunt, the lumbar CSF showed a decrease in cells to 20/mm^3, but the protein level increased to 35 g/l. Vision improved, and the child could follow light. The sensorium also improved.

The second child who required a shunt was a 4-year-old female who was conscious but irritable, and was unable to follow light. Her ventricular pressure was 300 mm H_2O (0.35 g/l proteins and 380 mg/l glucose); the lumbar pressure was 210 mm H_2O (300 cells/mm^3, 1.4 g/l proteins, and 220 mg/l glucose). Her CT scan showed moderate communicating hydrocephalus and basal exudates. She was given a total of 8 injections of hyaluronidase. Her lumbar pressure decreased to 140 mm H_2O (no cells, 0.5 g/l proteins, and 480 mg/l glucose). Her vision improved, and she could see moving bodies at 6 m by the 6th injection. Therafter, however, the pressure rose again to 300 mm H_2O (140 cells/mm^3, 4 g/l proteins, and 520 mg/l glucose). The child's vision deteriorated to total blindness over the next 2 weeks. A ventriculoperitoneal shunt was inserted. Postoperatively the visual acuity improved to seeing moving bodies at 2 m with reduction of head circumference from 48.5 to 47.5 cm.

Thus, in spite of the intrathecal administration of hyaluronidase, two children died and two needed shunt insertions as further deterioration occurred.

Pyogenic meningitis, pyrexia, root pains, paraplegia, sphincter disturbances, or allergic manifestations were not seen. However, after the 1st injection, one patient showed choreiform movements which disappeared after 3 weeks. The two patients who had choreiform movements before therapy enjoyed cessation of these movements but were left with weakness of the affected limbs.

Trial hyaluronidase

1. Sensorium. All of the children showed improvement in the sensorium level after the 1st injection and, regarding the overall assessment after treatment, all three patients who had altered levels of consciousness improved. Two patients who had been semiconscious with neurological deficit became conscious but with persistent neurological deficit. One patient who had been unconscious with decerebrate spasms became conscious but drowsy with neurological deficit.

2. Neurological deficits. Vision remained static in one patient in whom definite deficit could be assessed before therapy. Hemiparesis improved in two patients and remained static in one (Table 2).

3. Functional usefulness. One patient remained unchanged after 6 injections. Three patients showed a fair response. One, who had been decerebrate, improved and became drowsy; spasticity diminished, but he could not recognize his parents and suffered a left third nerve paresis.

Two patients who had been semiconscious became conscious, but the neurological deficits persisted. One of these remained blind with left-sided weakness, whereas the other remained blind with bilateral spasticity (Table 3).

4. Failures and complications. One child in this group developed a rash 10 days after the initiation of treatment, and so hyaluronidase injections were stopped temporarily. The rash was diagnosed as atypical Steven Johnson's syndrome due to thiacetazone. After treatment with this drug had been discontinued, hyaluronidase administration was restarted.

After 2 weeks of therapy, 1 child developed left-sided choreiform movements which disappeared after the 7th injection. A carotid angiogram obtained at the onset of development of the involuntary movements showed arteritis of the internal carotid artery at the base of the skull. The child was left with residual left hemiparesis after the movements had stopped.

Trial shunt

1. Improvement in the sensorium. Of the six patients who had shunt insertion, four were drowsy and one was semiconscious. Three of these showed improvement in the sensorium and became alert. In two, the sensorium did not improve. One patient died.

2. Specific neurological deficit. Three patients with impaired vision showed definite improvement. One, who had been alert and able to count fingers at 1 m, improved and was able to count fingers at 2.4 m bilaterally. Of the other two patients who had been drowsy with dilated, fixed pupils, one showed improvement in the sensorium and began to follow light. The other patient's sensorium remained unchanged, but the pupils started reacting to light. Hemiparesis improved in one patient and remained unchanged in two (Table 2).

3. Functional usefulness after therapy. Two patients showed a good response. One of them had been drowsy with non-reacting pupils and bilateral spasticity. He became conscious and alert and started obeying commands and speaking. After shunt insertion, the other patient's vision improved from 1 m to 2.4 m finger counting, with no other focal neurological deficit. Two patients remained unchanged after shunt insertion (Table 3).

4. Failures and complications. One patient who died was a 2-year-old boy with a 1-month history of fever and vomiting, deterioration in the level of consciousness, and tonic spasms. Before treatment, he was semiconscious with bilateral primary optic atrophy, bilateral spasticity with extensor plantar responses. After shunt insertion, the

patient became more responsive, but on the 7th post-operative day, he developed paralytic ileus and died within 24 h.

Discussion

The results of shunt surgery for tuberculous meningitis with hydrocephalus have been gratifying, mainly in patients whose consciousness has not been much depressed: only 10% of those in a semicomatose and comatose condition have returned to normal [6]. However, the performance of shunt surgery by new residents has contributed significantly to the poor results that are occasionally seen even in patients with a good sensorium. The morbidity in these patients often stimulates one to seek other forms and modes of therapy that might provide better results.

It has been justifiably felt that if the cause of the impairment of CSF circulation could be removed by resolving the exudate or by dissolving the adhesions, hydrocephalus may be relieved and improvement occur. Antitubercular drugs may then be better concentrated on the pathological processes at the base of the brain, the manifestations due to hydrocephalus would be relieved, but those due to arteritis and infarction would persist.

Numerous intrathecal adjuvants have, therefore, been used in the last three decades in an attempt to potentiate the action of antitubercular drugs by preventing the deposition of exudate or promoting its resolution [21]. The substances used have been streptokinase [8], steroids [15], pancreatic ribonuclease [16], streptomycin [12], isoniazide, heparin [17], and purified protein derivative [1] (PPD).

Streptokinase was found to be of no value. Isoniazide was found to be toxic and to cause retrobulbar neuritis, while PPD, although somewhat effective, proved to be too difficult and dangerous for general use. Steroids have occasionally had a dramatic effect on spinal blockage, but their overall value is unproved [15].

Earlier use of intrathecal hyaluronidase produced neither a significant improvement in the condition nor any adverse reaction [19, 20, 24]. Having found the use of intrathecal hyaluronidase safe and worthwhile in cases of spinal arachnoiditis [13], Gourie-Devi and Satish extended its use to cases of tuberculous meningitis with hydrocephalus from cranial arachnoiditis [14]. The simplicity of its administration and the advantages of medical treatment are the arguments put forward for the consideration of intrathecal hyaluronidase as an important adjuvant in the treatment of hydrocephalus [14].

Gourie-Devi felt that the results of intrathecal hyaluronidase therapy compared very favorably with those of shunt insertion. She came close to advocating the abandonment of surgery. However, she did not randomize her cases and did not carry out a controlled study.

We found that the level of consciousness did improve in all but 1 of a total of 14 patients treated with hyaluronidase. The sensorium improved inasmuch as the depth of unconsciousness diminished. This improvement in the level of consciousness was observed initially, as well as at the end of therapy, in these 13 cases. After the first injection and, in general, after the completion of therapy, it was also noticed that the spasticity was reduced.

In general, the improvement in the level of consciousness and the CSF pattern was progressive until the 5th or 6th injection and, thereafter, tended to become more or less static. However, when one considers the improvement in specific neurological deficits such as vision and hemiparesis, the results are not very encouraging. In five patients with impaired vision, vision improved in one patient, deteriorated in one, and remained static in three. Hemiparesis improved in two patients and remained static in one; one patient with hemiparesis died. One patient with bilateral decerebrate responses was left with residual hemiparesis after the spasticity had diminished. Also, although the involuntary movements stopped, one patient was left with a hemiplegia.

The results for the six patients who were treated with shunt insertion were a little better, especially in terms of improvement in vision and hemiparesis. The sensorium improved in three of five; vision improved in all three; hemiparesis improved in one of three patients and remained static in two. One patient in the shunt category died after initial improvement.

We consider that overall functional improvement is most important. Even when an unconscious patient becomes fully conscious, the result must be considered poor if the child remains mentally retarded or has marked neurological deficit. We are not sure whether the results of Gourie-Devi's series are comparable to ours. A mere improvement in the level of consciousness with persistence of neurological deficit and mental impairment may have been considered by her to be a good result.

In our hyaluronidase series, we did not regard any of the cases as having on excellent response, whereas excellent results were found in 33% of patients (5 out of 15) in the study of Gourie-Devi and Satish. They also reported a good response in 5 out of 15 patients, a fair response in 4 out of 15 patients, and 1 death. Our study, however, showed good results in 2 of 14 patients, fair results in 6 of 14 patients, and no change in 2 of 14 patients. In the study of Gourie-Devi and Satish, there were no therapy failures whereas of our 14 patients 2 were distinct therapy failures who, after shunt insertion, showed a definite improvement. Also, as opposed to one death in the series of Gourie-Devi and Satish, there were two deaths in our series. In the series of Gourie-Devi and Satish, the patients who showed an excellent and good response were from the group comparable to grades IV and V in our study. However, in our study, the patients who showed a good recovery were of grade II. Our patients of grades IV and V showed only a fair response. In contrast, the improvement of overall functional usefulness in the shunt group was better: 14% showed a fair response, and 33% showed a good response.

This study shows that intrathecal hyaluronidase seems to help in improving the level of the sensorium, but has no

particular advantage over shunt insertion in terms of improvement in specific neurological deficit or overall functional usefulness. The trial is being continued to include a sufficient number of patients for the results to be statistically significant.

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