

Intrathecal Hyaluronidase Treatment of Chronic Spinal Arachnoiditis of Noninfective Etiology

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Fifteen cases of spinal arachnoiditis of noninfective etiology were treated with intrathecal hyaluronidase. In 10 patients, no obvious cause was evident; in four patients, arachnoiditis was the result of disk prolapse; and in one it followed spinal surgery. Fifteen hundred international units of hyaluronidase was injected intrathecally at intervals of 7-14 days. Four to nine injections (mean, 5.9) were given to each patient, and the patients were observed for 3-30 months (mean, 9.7). The effect of the treatment was assessed by the change in clinical grading from the pretreatment phase to the last examination. Satisfactory improvement was observed in 11 patients (73.3%) and "mild" recovery was observed in three patients. Because of this therapeutic efficacy and lack of serious toxic effects, intrathecally administered hyaluronidase appears to be of value in the management of spinal arachnoiditis.

KEY WORDS: Arachnoiditis; Hyaluronidase; Spinal cord compression; Lumbar disk syndrome; Radiculomyelopathy; Cauda equina

Chronic spinal arachnoiditis was recognized as a specific entity nearly a century ago [4], but in recent years the clinical features have changed [2,21]. With the advent of chemotherapy and early diagnosis, the incidence of spinal arachnoiditis of infective etiology (such as tuberculosis and syphilis) has decreased in the developed countries. However, chronic spinal arachnoiditis due to other causes such as intrathecal medication, radioopaque substances, trauma, and surgery continues to be a problem [21].

Surgical and medical treatment of spinal arachnoiditis, irrespective of etiology, remains unsatisfactory [2]. We therefore used the enzyme hyaluronidase as an adjuvant in the management of tuberculous spinal arachnoiditis [7,8]. Because the results were favorable, we

also treated 15 cases of noninfective chronic spinal arachnoiditis with hyaluronidase.* Preliminary results are reported.

Materials and Methods

Fifteen cases of chronic spinal arachnoiditis were seen between January 1979 and January 1982. All these patients had progressive symptoms and signs over a mean period of 31.2 months (0.5-108). In 12 cases, surgical intervention had not resulted in significant improvement. Chronic spinal arachnoiditis complicating tuberculous meningitis and syphilis were not included. Neurological deficit and functional disability were graded on scales of 0 to 15 (Table 1), as described earlier [7], with additional scores for relief of pain and improvement of the function of bladder and bowel. Myodil myelography showed the characteristic features of spinal arachnoiditis [23]. Further, the diagnosis was confirmed at operation in 12 cases. A biopsy was performed on the arachnoidea spinalis in nine patients; histopathologic examination suggested nonspecific inflammation with no evidence of tuberculosis or syphilis. In three cases, a biopsy specimen could not be obtained because the arachnoidea spinalis was densely adherent to the spinal cord. In the other three cases, the radiologic features were characteristic of diffuse arachnoiditis and surgical treatment was withheld.

It should be noted that the symptoms of the disease, before institution of treatment with hyaluronidase, were present for sufficiently long a time (with the exception of case 8), to permit a meaningful assessment of the effect of enzyme therapy; in other words the "patient served as his own control." After obtaining informed consent, 1500 IU of hyaluronidase dissolved in 1-2 mL of distilled water was injected into the subarachnoid space, either by lumbar or cisternal puncture. Hyaluronidase is commercially available (Hyalase; Rallis); the source is ovine testis. We used freshly dissolved solution

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*Editor's Note: The U.S. Food and Drug Administration informed SURGICAL NEUROLOGY that "hyaluronidase has not been approved for intraspinal or intrathecal use."

Table 1. Method of Grading

Score	
<i>Functional Disability Scale</i>	
0	No disability.
1	Difficulty in walking and/or climbing stairs but not requiring assistance.
2	Can walk with support on one side.
3	Can stand unsupported; can walk with support on both the sides.
4	Cannot walk; can stand with assistance.
5	Bed ridden.
<i>Pain</i>	
0	No pain.
1	Mild to moderate pain.
2	Severe pain.
<i>Neurological Deficit Scale</i>	
0	Motor power normal; no sensory deficit.
1	Motor power grade 4; sensory loss less than 25%; mild spasticity or flaccidity.
2	Motor power grade 3; sensory loss 25%–50%; moderate spasticity or flaccidity.
3	Motor power grade 2; sensory loss 50%–75%; severe spasticity or flaccidity.
4	Motor power grade 1; sensory loss more than 75%; severe spasticity with extensor spasms or flaccidity.
5	Motor power grade 0; sensory loss 100%.
<i>Bladder</i>	
0	No symptoms.
1	Urgency, precipitancy, hesitancy.
2	Retention or incontinence.
<i>Bowel</i>	
0	No symptoms.
1	Constipation or incontinence.
15	Total possible score.

*Medical Research Council (U.K.) grading of motor power.

of hyaluronidase; if stored at 4°C and kept free from contamination, the activity of the enzyme is retained up to 6 weeks. After the injection, patients were made to lie prone for 15–30 minutes to prevent leakage through the puncture site. Cerebrospinal fluid cell count above 100/mL was a relative contraindication for treatment, in order to avoid the possible spread of an infection. The enzyme was administered at intervals of 7–14 days. Our earlier studies had shown that significant activity of the enzyme persists in the cerebrospinal fluid for as long as 3–4 weeks in patients with spinal arachnoiditis [17]. In patients subjected to surgical exploration, hyaluronidase was started 4 weeks later, to enable evaluation of the effects of the operation and to allow the clinical status to stabilize.

The duration of treatment and number of injections were determined by the clinical improvement, cerebrospinal fluid protein values, and quantitative spinal manometry. Clinical assessment was done periodically.

Results

Twelve patients (80%) were between ages 20 to 50 years; 13 (86.6%) were men (Table 2). In 66.6% (10 patients) the duration of symptoms was more than 6 months, with a range 15 days to 9 years (Tables 2 and 3). In 10 patients there was no obvious cause of arachnoiditis; in four, there was preceding history of disk prolapse. In one patient (case 1), symptoms of spinal arachnoiditis started 12 years after an operation for an intraspinal neurofibroma. In two of the four patients with disk prolapse (cases 12 and 15), dense arachnoidal adhesions were seen on the first exploration. In each of the other two patients, adhesions were detected during the second operation, which was performed for recurrence of symptoms 10 months (case 9) and 6 years (case 13), respectively, after the first operation for disk prolapse.

Clinical features were categorized into four groups:

1. Lumbar disk syndrome was seen in eight of 15 cases (53.3%). The main features were low back pain, radiating along root distribution, limitation of straight leg raising test, with motor weakness of muscles of foot, sensory deficit, and sluggish or absent ankle jerks. In four of these cases there was no evidence of disk prolapse either on myelography or at operation, however there was arachnoiditis. In the other four, prolapsed disk and arachnoiditis were present.
2. Cauda equina syndrome was seen in two patients. The classical features of multiple root involvement at the level of the cauda equina and sphincter disturbances were seen. Straight leg raising was possible to the full extent.
3. Myelopathy due to involvement of dorsal spinal cord was seen in three patients. Spastic paraplegia, sensory impairment below a segmental level, and bladder involvement were the essential features.
4. Radiculomyelopathy. Diffuse and extensive involvement of roots and spinal cord extending over a number of segments was observed in two cases. Motor weakness, patchy sensory loss, and asymmetrical deep tendon reflexes were the important features.

The severity of the illness as determined by the scoring system (Table 1), clinical group, and extent of involvement in individual cases is shown in Table 2. The extent of the lesion was determined by myelography in all the patients and confirmed at operation in twelve cases. In three patients (cases 3, 7, and 8), no operation was performed. Quantitative spinal manometry showed partial or complete block in all seven patients of groups 2, 3, and 4 and in three of group 1; and normal findings in five patients of group 1. Arachnoiditis localized to lumbar and sacral segments in group 1 obviously did not influence the cerebrospinal fluid pressure recordings

Table 2. Clinical Pattern of Spinal Arachnoiditis and Results of Hyaluronidase Treatment

Case no.	Age (yr)	Sex	Clinical pattern	Duration of symptoms (mo.)	Extent	Number of injections	Score		Cerebrospinal fluid protein (g/L)		Follow-up (mo.)
							PrT	PoT	PrT	PoT	
1	37	M	CES	84	T10-L2	6	14	8	21.0	2.0	24
2	39	M	LDS	16	L5-S1	6	10	1	0.70	0.46	30
3	38	M	LDS	2.5	L3-S1	9	9	5	2.45	0.90	9
4	23	M	MPY	24	T7-L4	7	13	6	0.90	0.60	6
5	46	M	CES	8	T10-L2	8	15	12	2.20	2.0	7
6	28	M	MPY	36	T1-4	6	14	6	10.0	2.90	4
7	50	M	LDS	4.5	L2-5	5	13	6	0.80	—	3
8	28	F	RMP	0.5	T6-L2	4	10	2	1.00	0.65	3
9	50	M	LDS	72	L4-S1	7	12	5	0.60	0.75	18
10	32	M	RMP	3	C4-T8	4	8	5	0.76	0.80	4
11	27	F	LDS	1.5	L4-S1	4	8	5	0.40	0.20	8
12	66	M	LDS	24	L4-S4	4	12	6	0.36	—	13
13	20	M	LDS	10	L4-S1	5	9	6	0.70	0.28	5
14	49	M	LDS	108	L4-S1	8	13	9	21.0	3.0	4
15	42	M	MPY	24	D3-6	5	3	3	0.60	1.0	7

CES = cauda equina syndrome; LDS = lumbar disk syndrome; MPY = myelopathy; PoT = posttreatment; PrT = pretreatment; RMP = radiculomyelopathy.

obtained by lumbar puncture at a higher level than the arachnoiditis in most of the cases.

Patients received from 4 to 9 (mean, 5.9) intrathecal injections of hyaluronidase. Eleven patients (73.3%) showed satisfactory improvement (score < 6) (Table 3). In three patients mild improvement was noticed, and in one, no change occurred. There was no clinical deterioration in any patient. Because the number of cases in each clinical group is small (Table 2), it is difficult to comment with confidence upon the correlation of recovery pattern and clinical group. Generally, the patients with lumbar disk syndrome and radiculomyelopathy showed a better response than others. Patients with symptoms for less than 2 years fared better with the enzyme treatment. Pretreatment mean score of the whole group was 10.9 (3-15), which improved to 5.7 (1-12) after treatment (Table 2). Relief of pain and recovery of bladder function were striking. Quantitative

spinal manometry showed complete clearing of the subarachnoid block in seven patients, partial relief in two patients, and persistence of the block in one.

Cerebrospinal fluid protein content decreased in most cases, especially when the initial cerebrospinal fluid protein was above 1 g/L. In three patients, cerebrospinal fluid protein increased at first, then decreased with additional injections. Except for case 3, no significant change in the cell count was observed; this patient had an episode of aseptic meningitis for 48 hours, with full recovery.

No allergic or anaphylactic reactions were observed, and there were no immediate or late toxic effects on the nervous system. During the injection few patients had mild local pain, which was reduced by slowing the rate of injection. Mean follow-up was 9.7 months (3-30 months). There was no recurrence of symptoms or any deterioration. A second course of treatment was not considered necessary in any case.

Table 3. Duration of Symptoms before Hyaluronidase Treatment and Degree of Recovery

Duration of symptoms in months	No. of cases	Excellent (0-3)*	Good (4-6)*	Fair (>7)*	No change
<6	5	1	4	—	—
6-12	2	—	1	1	—
12-24	4	1	2	—	1
24-60	1	—	1	—	—
>60	3	—	1	2	—
Total	15	2	9	3	1

*Figures indicate the posttreatment score.

Discussion

Intrathecal steroids, radiotherapy, or surgical intervention, though advocated earlier [5,19], do not have a significant therapeutic role in the management of chronic spinal arachnoiditis irrespective of etiology [1,2]. Intrathecal injection of pancreatic ribonuclease, streptokinase, and streptodornase have been abandoned because of questionable therapeutic effects and serious toxic reactions [12]. We found the enzyme hyaluronidase effective in tuberculous spinal arachnoiditis [7,8], and the present report confirms its efficacy in noninfective arachnoiditis. Treatment with this enzyme led to

satisfactory recovery in 11 of the 15 patients and "mild" but significant improvement in three cases. In seven of them, surgical decompression and release of arachnoidal adhesions done earlier had not resulted in appreciable improvement, and in five patients there had been definite deterioration immediately after the operation. Gegalian [6] reported dramatic improvement after intrathecal hyaluronidase treatment in one patient with paraparesis due to adhesive spinal arachnoiditis.

The safety of hyaluronidase administration by various routes including injection into subarachnoid space as well as after repeated and prolonged use has been emphasized by many workers [3,16,18,20]. Experimental perineural injection of hyaluronidase into the sciatic nerve of rats did not affect myelin or axons [11]. Except for mild pain during intrathecal injection of hyaluronidase, worsening of spinal cord or bladder functions and other serious toxic effects like allergic reaction or convulsions were not observed in our study. Intrathecal steroid administration, however, is known to cause convulsions [10] and sphincter disturbances [24].

Cerebrospinal fluid cell count did not generally show any significant rise after injection of the enzyme. We have given more than 600 intrathecal injections of hyaluronidase. Aseptic meningitis with pleocytosis was observed only on two occasions (one in the present series). Fortunately, spontaneous recovery occurred in both cases. Cerebrospinal fluid protein value showed a progressive decline during enzyme therapy and was a useful guideline for monitoring the treatment. Occasionally, an initial rise was observed with a subsequent decline. This feature can be attributed to the breaking down of arachnoidal adhesions by the enzyme, which would release protein-rich encysted fluid into the cerebrospinal fluid. In no instance did worsening of the spinal block lead to a "dry tap" after repeated intrathecal injections of hyaluronidase in the present series. Paradoxically, intrathecal steroid therapy may cause adhesive arachnoiditis [15]. Quantitative spinal manometry provided a rough guide to the degree of block.

Hyaluronidase has been widely used for other conditions, and with favorable results [3,6,9,13,18]. The therapeutic effect of hyaluronidase is attributed to resolution of adhesions, absorption of exudate, increased capillary permeability resulting in enhanced transport of nutrients [3,22], and reduction of barrier effect due to hydrolysis of the glucosaminidic bonds of hyaluronic acid and other mucopolysaccharides of the ground substance [14].

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