Adverse reactions to intrathecal saline injection for control of pain

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The authors report the results of a questionnaire regarding the use of hypertonic saline for the control of pain. Of 2105 patients so treated, nearly 11% had an adverse temporary symptom or sign, reported as an untoward reaction; slightly over 1% suffered a significant morbidity, of which paraplegia or quadriplegia was by far the most common, and two patients died (0.1%).

KEY WORDS • pain • neural transmission • quadriplegia • paraplegia • spinal cord injuries • myelitis

PAIN, the most common presenting symptom, can be simultaneously a protector and a debilitator. As a protector, it warns of physiological imbalance or danger to homeostasis of the life system and requires diagnostic inquiry. As a debilitator, pain can become a disease in itself, requiring sedatives or narcotics. Until 1911, when Spiller and Martin 17 made an incision in the anterolateral portion of the spinal cord to divide the pain tracts, there were few alternatives to the chronic use of progressively less effective analgesics, which often became debilitating due to their addictive qualities. Anterolateral cordotomy is very effective in disrupting the ascending pain fibers, but this procedure is not without its disadvantages and limitations. Other operative procedures such as dorsal rhizotomy, percutaneous cordotomy, or dorsal column stimulator implantation seem useful in selected patients, but all physicians would welcome a simple, safe, and effective alternative.

One such alternative method is intrathecal saline injection, which is currently being used for the treatment of intractable pain although its mechanism of action is not clearly understood. This paper deals with the adverse reactions to this treatment, as well as their possible explanation and prevention.

Materials and Methods

To investigate adverse reactions to intrathecal saline injections, the National Spinal Cord Injury Registry at the Medical University of South Carolina mailed a questionnaire to its correspondence network of 2000 participating neurosurgeons and physicians. The questionnaire included four questions with a space for comments on a post card to be returned to the Registry. The questions were as follows:
1. How many patients with painful conditions have you been involved with who were treated with intrathecal hypertonic saline?

2. How many of the above patients have had an untoward reaction from the use of this medication?

3. Has any patient been left permanently paraplegic or quadriplegic from such a medication?

4. Has there been any patient who has died from this therapy?

The answers to Question 1 defined the data base or patient population to which the remainder of the questions applied. For ease of processing, Question 2 was answered as a percentage, and we then calculated the number of patients with an adverse reaction for each physician. We next totaled this number and compared this to the overall patient population in Question 1, thereby obtaining the total percentage of patients with adverse reactions. Questions 3 and 4 are self-explanatory. Those physicians who had observed adverse reactions invariably explained the nature and frequency of the problem in the comments section or with an attached letter.

Results

Of the 648 neurosurgeons and physicians returning the questionnaire, 202 or 31.17% reported the use of hypertonic saline for the treatment of painful conditions in a total of 1903 patients. In addition, two physicians used hypothermic isotonic saline in 136 patients, one physician used hypertonic hypothermic saline in 40 patients, and two physicians used hypotonic saline in 26 patients. The final total was 2105 patients.

Adverse reactions were reported in 223 or 10.59% of the 2105 patients treated with this medication. This total included five patients with an adverse reaction to hypothermic isotonic saline. Table 1 lists the adverse, temporary symptoms and signs reported as untoward reactions in the 223 patients. In 162 patients, or 71%, these reactions were described in the comments section or with an accompanying letter. Pain, numbness and dysesthesias, and weakness were by far the most common adverse symptoms reported. As seen, the most common signs reported were muscle spasm, changes in blood pressure, and seizure activity.

Of 2105 patients, 22 (1.03%) suffered a significant morbidity (Table 2). The most common cause of the morbidity was para- or quadriplegia which occurred in 16 (.76%) of the total patient population. Paresis of one leg occurred in one patient, and loss of hearing was reported in two (.09%) of the total patient population upon cisternal injection. The latter complication was associated with transient unilateral, ipsilateral facial weakness as listed in Table 1.

Of the 2105 patients treated with this procedure, two (.09%) died as a result of myocardial infarctions. One died with an acute massive myocardial infarction, and the second died in pulmonary edema secondary to the myocardial infarction.

Discussion

Hitchcock described a technique of intrathecal saline injection when he reported a series of 12 cases in which hypothermic saline subarachnoid irrigation was used for the treatment of intractable pain in terminal cancer patients. Seven patients achieved worthwhile relief, while in five the results were either unsuccessful or, at best, relief was only transient. In support of this technique, he reported no demonstrable sensory changes or bladder complications. Since Hitchcock’s introduction of this procedure, there has been debate as to whether the drug’s effects are due to altered osmolality, hypothermia, or both.

The effects of hypothermia on neuronal tissue are contradictory. Von Euler demonstrated that the smaller, unmyelinated C fibers that transmit painful stimuli were more susceptible to inactivation by cooling, while the larger A fibers were not affected, and might even be stimulated. In contradiction, Lundberg found that conduction in A fibers in the cat ceased at 7°C, but conduction in C fibers continued at 0°C. Several other investigators supported the conclusion that the larger the cross-sectional diameters of the nerve fibers, the more sensitive they were to the action of hypothermia.

When isotonic, frozen saline solutions were thawed, it was observed that the supernatant fluid was often hypertonic. Since that time, other investigators have argued that hyperosmolality was responsible for the temporary effects of pain relief. For example, Collins, et al., proposed that the transient effects of hyperosmolality were secondary to
Adverse reactions to intrathecal saline injection

TABLE 1

<table>
<thead>
<tr>
<th>Temporary Symptoms and Signs</th>
<th>No. of Cases</th>
<th>% of All Patients (n = 2105)</th>
<th>% of Patients with Specified Adverse Reaction (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain</td>
<td>68</td>
<td>3.23</td>
<td>41.97</td>
</tr>
<tr>
<td>numbness and dysesthesias</td>
<td>29</td>
<td>1.37</td>
<td>17.92</td>
</tr>
<tr>
<td>muscle spasm</td>
<td>27</td>
<td>1.28</td>
<td>16.66</td>
</tr>
<tr>
<td>weakness</td>
<td>13</td>
<td>.61</td>
<td>8.02</td>
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<tr>
<td>hypertension</td>
<td>7</td>
<td>.33</td>
<td>4.32</td>
</tr>
<tr>
<td>tachycardia</td>
<td>6</td>
<td>.28</td>
<td>3.70</td>
</tr>
<tr>
<td>hypotension*</td>
<td>3</td>
<td>.14</td>
<td>1.85</td>
</tr>
<tr>
<td>syncope &amp; clonic jerks</td>
<td>3</td>
<td>.14</td>
<td>1.85</td>
</tr>
<tr>
<td>transient unilateral ipsilateral facial weakness*</td>
<td>2</td>
<td>.09</td>
<td>1.23</td>
</tr>
<tr>
<td>major motor seizure</td>
<td>2</td>
<td>.09</td>
<td>1.23</td>
</tr>
<tr>
<td>“spinal seizure”</td>
<td>1</td>
<td>.04</td>
<td>.61</td>
</tr>
<tr>
<td>transient bladder impairment</td>
<td>1</td>
<td>.04</td>
<td>.61</td>
</tr>
<tr>
<td>total</td>
<td>162</td>
<td>7.64</td>
<td>100</td>
</tr>
<tr>
<td>patients with unspecified adverse reactions</td>
<td>61</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>223</td>
<td>10.59</td>
<td></td>
</tr>
</tbody>
</table>

* Patients received cisternal injections.

“hyperdepolarization” of the neuron. Recently, King, et al., 12 demonstrated that the high chloride ion concentration and not the sodium ion concentration establishes a persistent in vitro differential C fiber block. These authors found no persistent C fiber block established by low temperature alone within the conditions that might be expected in the clinical use of cold saline infusion.

Meyer and Hunter16 found that surface cooling of cortical arteries and veins caused a diminution in the caliber of the vessels. This was most evident in arterioles. Also, they noted the capillary beds appeared pale and poorly defined at lower temperatures. Douglas and Ritchie6 found that under conditions of asphyxia, the medullated fibers were more readily blocked than the non-medullated fibers in nerve trunks of animals. Denny-Brown, et al.,5 supported by Hitchcock,7-10 proposed that the permanent effects were neurolytic. However, post-mortem examination of the spinal cord in patients treated with this medication by Mathews, et al.,14 and Savitz and Malis16 failed to reveal any demonstrable neurolysis.

Intrathecal injection of hypertonic saline, which many consider effective in producing desirable results, is not without adverse symptoms, signs, and permanent complications. The more frequently reported of these, pain, transient weakness, and muscle spasm, may be explained by the theory of Collins, et al.,4 of indiscriminate depolarization and subsequent “hyperdepolarization” of neurons in the area of injection, especially the larger A fibers in the ventral and dorsal roots. King, et al.,12 demonstrated that hypertonic saline concentrations of 1250 mOsm/l applied to monkey rootlets damage A fiber conduction. A 7.5% hypertonic saline solution establishes a tonicity concentration in mOsm/l at least twice that required to damage A fibers in spinal rootlets,12.

The adverse signs reported include major motor seizures, changes in blood pressure, changes in blood pressure, and

TABLE 2

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Cases</th>
<th>%†</th>
</tr>
</thead>
<tbody>
<tr>
<td>paraplegia or quadriplegia</td>
<td>16</td>
<td>.76</td>
</tr>
<tr>
<td>partial paralysis</td>
<td>1</td>
<td>.04</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td>3</td>
<td>.14</td>
</tr>
<tr>
<td>loss of hearing*</td>
<td>2</td>
<td>.09</td>
</tr>
<tr>
<td>total</td>
<td>22</td>
<td>1.03</td>
</tr>
</tbody>
</table>

* Patients receiving cisternal injections.
† Percent of total patient population of 2105.
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changes in electrocardiogram recordings, and myocardial infarctions. The change in blood pressure, especially hypertension, is believed to be brought about by the direct stimulation of the sympathetic nerve fibers as noted by Hitchcock and McKean,\textsuperscript{11} reported segmental peripheral cyanosis, piloerection and sweating. They also noted vagal stimulation with cisternal injections, an observation supported in this series by the hypotension seen in three patients with cisternal injection.

Hitchcock and McKean\textsuperscript{11} noted electrocardiogram changes during the administration of intrathecal injections in a series of 10 patients. They reported that lumbar injections resulted in sympathetic stimulation that increased the heart rate in all 10 patients, with three patients showing ventricular, ectopic beats. They also found in cisternal injections a slowing of heart rate or sinus bradycardia and/or nodal rhythm in two of four patients. Three of these same four patients showed atrial or ventricular ectopic beats; however, no patient in this series was symptomatic.

The attending physicians in the present series considered the myocardial infarctions to be secondary to stress, occurring during or after massive muscle spasms. These physicians did not report electrocardiographic monitoring during the procedure.

The .76% incidence of paraplegia or quadriplegia in the series might be explained in the following manner. Previous meningeal inflammation and/or scarring could produce a loculated area along or on the spinal cord. Thus, the hypertonic saline, if injected into the loculated area, would not be dissipated as quickly as in the normal dural sac. This loculated sac, retaining the osmotically active solution of hypertonic saline, may then act as a mass lesion. In addition, if the wall of this sac contains the spinal cord, then a direct lytic lesion secondary to osmotic forces may be produced in the substance of the cord. A number of reporting physicians noted signs of meningeal irritation with the first injection and then paralysis on a subsequent injection performed on the same patients. One physician, in treating pain at the site of an old laminectomy performed for a fracture-dislocation in a paralyzed patient, recorded a higher level of paralysis after treatment with this procedure.

In considering the use of this technique, the preinjection workup of a patient should include a thorough cardiovascular history with emphasis on congestive heart failure, previous myocardial infarctions, and hypertensive disease. In the neurological evaluation, acute or chronic meningeal irritation, previous myelograms, lumbar punctures, trauma, and vascular or metastatic disease should receive special attention. The data presented here on the incidence of temporary adverse reactions, 10.59%, and serious complications, 1.03%, should be considered in the evaluation of individual patients for whom the procedure is being contemplated.

Conclusions

While intrathecal hypertonic saline may be effective in controlling intractable pain, the procedure is not without definite risks. Patients with a significant history of cardiovascular or hypertensive disease probably should be reviewed most carefully because of the adverse effect the stressful procedure has on the autonomic nervous system. If the patient's history indicates acute or chronic meningeal and/or arachnoid inflammation, or the presence of a meningeal malformation, the incidence of complications may be higher than usual unless cerebrospinal fluid blockage is ruled out.

References

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17. Spiller WG, Martin E: The treatment of persistent pain of organic origin in the lower part of the body by division of the anterolateral column of the spinal cord. JAMA 58:1489–1490, 1912

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