A CO-OPERATIVE DOUBLE-BLIND EVALUATION OF GASTRIC “FREEZING” IN THE TREATMENT OF DUODENAL ULCER*

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Abstract A double-blind evaluation of gastric “freezing” in the treatment of duodenal ulcer was initiated in 1963 and conducted simultaneously in five institutions. One group of patients had the true “freeze” with the temperature of the coolant at −10°C and another group had a sham procedure with the temperature of the coolant at 37°C.

The results of this study demonstrate conclusively that the “freezing” procedure is no better than the sham in the treatment of duodenal ulcer, confirming the work of others. There was no significant difference in relief of pain, secretory suppression, the number and severity of recurrences, or the development of end points in the two groups. It is reasonable to assume that the relief of pain and subjective improvement reported by early investigators were probably due to the psychologic effect of the procedure.

GASTRIC “freezing” for the treatment of duodenal ulcer was introduced by Wangensteen and his associates in 1962, and its usefulness was promptly supported by further investigation. Subsequently, this method of treatment was used in many small clinical groups throughout the country. However, the enthusiasm of early publications was soon followed by a wave of skepticism. In a panel discussion on the subject at a meeting of the American Gastroenterological Association in San Francisco in 1963, it was concluded that widespread clinical use of the procedure could not be justified until its efficacy and safety were firmly established by carefully controlled studies.

In recognition of this need, a double-blind study was initiated in 1963 and conducted simultaneously in five institutions: the University of Chicago School of Medicine, Duke University Medical Center, Louisiana State University School of Medicine, the Scott and White Clinic and Vanderbilt University School of Medicine. The same criteria were used by all five institutions in selection of patients, and identical methods employed in the “freezing” procedure, collection of data and evaluation of results. Members of the Department of Biostatistics at the University of North Carolina served as consultants in the design of the study and also analyzed the data.

OBJECTIVES

The specific objectives of the study were threefold: to evaluate the effects of gastric “freezing” on the natural history of duodenal ulcer as evidenced by recurrences, complications, morbidity and mortality; to determine its effect on gastric secretion; and to ascertain the hazards and complications of the procedure itself, as well as the subsequent morbidity and mortality.

DESIGN OF STUDY

Selection of Patients

To be eligible for entrance into the study, the patient must have had symptoms typical of an ulcer for one year or longer, with an established pattern of recurrences and at least one recurrence during the preceding 12 months. Only patients 18 years of age or older, with x-ray evidence of ulcer and a gastric secretory pattern consistent with ulcer, were included. All patients were considered to have an active ulcer at the time of the freezing procedure.

Patients with a hiatus hernia, gastric ulcer, pyloric obstruction, hemorrhage within the preceding 30 days or previous gastric surgery, or who were suspected of having an ulcer related to endocrinopathy, were excluded. Any patients having associated diseases that would render them a poor risk or make evaluation difficult were likewise excluded. All patients were informed of the nature of the study.

Procedure for Gastric “Freezing”

The procedure was performed in all institutions in a uniform manner. The team consisted of the following members: a physician who was in constant attendance and was responsible for the intubation of the patient and the general supervision of all aspects of the procedure; a technician responsible for the operation of the hypothermia machine; and a nurse or technician responsible for monitoring and recording all data.

The procedure adopted for this study was that proposed by Wangensteen et al. A Swenko hypothermia machine was used in all institutions. The volume of coolant (95 per cent ethyl alcohol) in the gastric balloon ranged from 550 to 700 ml in all the

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†Swenko Research and Development Incorporated, Minneapolis, Minn.
patients except Case 11. The temperature of the coolant returning to the hypothermia machine from the gastric balloon was maintained at $-10^{\circ}$C, and the flow rate of the coolant was maintained between 1200 and 1400 ml per minute. The duration of the procedure (time of circulation of coolant within the balloon) was 50 minutes in all cases.

Whenever possible the procedure was done in the morning after an overnight fast. Premedication consisted of 2.0 mg per kilogram of phenobarbital intramuscularly and 0.007 mg per kilogram of atropine subcutaneously 30 minutes before intubation. Ten minutes before the balloon was passed the patient was given 15 ml of lidocaine hydrochloride with sodium carboxymethyl cellulose (Xylocaine Viscous) and instructed to gargle it for five minutes and then to swallow it slowly. This was repeated, and immediately after swallowing the second dose the patient was intubated.

The "freeze" was done with the patient sitting up (at 60°) in a hospital bed. After intubation, the balloon was filled in 50-ml increments until a sensation of fullness developed. The pulse, blood pressure and respirations were recorded at least at five-minute intervals, and rectal temperature was monitored continuously by means of a thermistor. An electrocardiogram was recorded at least every 10 minutes. To maintain body temperature, the patient was placed between electric blankets.

After the coolant had circulated in the balloon for 50 minutes, the circulating pump and refrigerating unit were turned off, and the filled balloon was allowed to remain in the stomach for 10 minutes. The balloon was then emptied at a rate of 100 ml per minute, and when empty, it was withdrawn.

Procedure for Sham Gastric "Freezing"

An attempt was made to have every aspect of the sham gastric "freeze" identical to the true "freeze" with the one exception of the temperature of the coolant circulating in the balloon. Thus, the exact procedure as described for gastric "freezing" — preparation of patient, volume of coolant in gastric balloon, duration of procedure and monitoring — was followed.

To accomplish the sham "freeze," a tube assembly was constructed to look exactly like the one used in the true "freeze." However, the assembly used in the sham procedure had a shunt proximal to the gastric balloon at 30 cm from the incisors, so that the coolant from the refrigerating unit was circulated only in the proximal part of the tube. Thus, in both procedures, the tube became frosted, and the patient felt a cold tube in the mouth, pharynx and upper esophagus. In the sham procedure, two small auxiliary tubes permitted the balloon to be filled and circulated with tap water at 37°C by an auxiliary pump and filling apparatus mounted permanently on the Swenko hypothermia machine.

Postprocedure Care

The patient was allowed nothing by mouth for two hours and then given liquids throughout the day. Bed rest was maintained for four hours, and the patient was observed in the hospital for the next three days. After discharge there were no dietary restrictions, but alcohol, caffeine-containing beverages and tobacco were forbidden.

Double-Blind Study

The number of cases treated with the coolant at $-10$ or $37^{\circ}$C was balanced within groups of eight within each institution to ensure that approximately the same number of patients would be in the true and sham "freeze" groups when the study was ended. Within the groups of eight the arrangement was determined by chance. Each institution participating in the study was supplied with envelopes numbered serially. When the patient had been prepared for the procedure the envelope with the smallest number was opened. This contained a card indicating that the temperature of the coolant was to be $-10$ or $37^{\circ}$C. The follow-up study was conducted by a physician who was unaware of which procedure had been employed. Provision was made to break the code for the protection of the patient's welfare if the need arose.

Clinical Material

One hundred and sixty-one patients were entered into the study, but one was dropped later after the demonstration of an islet-cell adenoma. There were 82 patients in Group F (true "freeze") and 78 patients in Group S (sham "freeze"). Forty-two clinical characteristics for each patient were recorded before the procedure. The more important of these are shown in Table 1. Statistical analysis of these data indicates that the two groups were comparable.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF PATIENTS</th>
<th>AVERAGE AGE (YR)</th>
<th>AVERAGE DURATION OF ULCER (YR)</th>
<th>PATIENTS WITH HISTORY OF HEMORRHAGE</th>
<th>CLINICAL SEVERITY</th>
<th>X-RAY FINDINGS</th>
</tr>
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<tbody>
<tr>
<td>F</td>
<td>82</td>
<td>39</td>
<td>9.3</td>
<td>29</td>
<td>51</td>
<td>31</td>
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<tr>
<td>S</td>
<td>78</td>
<td>41</td>
<td>9.3</td>
<td>26</td>
<td>47</td>
<td>31</td>
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Follow-up Observations

All patients were admitted to the hospital and evaluated on the basis of history, physical examination, laboratory data, including gastric analysis, and upper gastrointestinal x-ray study at six weeks and three, six, 12, 18 and 24 months after the procedure. When a patient had symptoms that required medication, appropriate therapy was instituted, but the patient was continued in the study until a well defined end point was reached or two years had passed.

Definition of End Point

An end point was considered to have been reached when any of the following occurred: perforation; ulcer pain requiring hospitalization for relief; obstruction, partial or complete, two or more weeks after hypothermia; hemorrhage; surgery for ulcer; repeat hypothermia; or x-ray therapy to the stomach.

Classification of Results

Each patient was classified as being symptom free, improved, unchanged or worse at the end of each period of observation. The patient who had no ulcer distress during the period in question was considered to be symptom free. When pain was less frequent and less severe, but still present occasionally, the patient was judged improved. When the clinical course was the same as before therapy, the patient was classified as unchanged. Patients who reached an end point were arbitrarily considered worse.

RESULTS

Clinical Observations

First week. Observations were made on 104 patients one week after treatment. In Group S four showed 1+, and in Group F, one showed 1+ and procedure employed. All 160 patients were followed for 12 months, 151 patients for 18 months, and 141 patients for 24 months. Most patients were “improved” (47 per cent in Group F and 39 per cent in Group S) or “symptom free” (29 per cent in both groups) during the first six weeks. However, as time passed, most patients in both groups relapsed and became clinically “worse” (12 months, 30 per cent in Group S and 28 per cent in Group F, at 18 months, 37 per cent in Group S and 38 per cent in Group F, and at 24 months, 39 per cent in Group S and 45 per cent in Group F). At no time was there a significant difference in the two groups at any period of follow-up observation.*

Thirty-five of the patients in Group F, and 30 in Group S reached an end point (Table 2). The data on time required to reach an end point were analyzed by the life-table method. The estimated probability of reaching an end point during the two-year period was 42.5 per cent in Group S and 46 per cent in Group F. The standard error of each of these estimates was approximately 0.06. The difference did not approach statistical significance.

Laboratory Observations

Total volume, concentration and quantity of hydrochloric acid (HCl) were measured in an eight-hour nocturnal gastric secretion test. The same determinations were measured during a one-hour basal period, and during a one-hour period after the administration of betazole hydrochloride (Histalog), 50 mg. The eight-hour gastric secretion was collected before treatment, 72 hours after treatment and when possible up to three months after treatment. The basal and betazole hydrochloride tests were done at each follow-up visit.

None of the analyses revealed a statistically significant difference between the levels of gastric

![Table 2. Causes of End Point.](image)

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF PATIENTS</th>
<th>PATIENTS WITH HEMORRHAGE</th>
<th>PATIENTS WITH OPERATION</th>
<th>PATIENTS WITH HOSPITALIZATION</th>
<th>TOTAL REACHING END POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (“Freeze”)</td>
<td>69</td>
<td>9</td>
<td>17</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>S (Sham)</td>
<td>68</td>
<td>9</td>
<td>14</td>
<td>7</td>
<td>30</td>
</tr>
</tbody>
</table>

*For complete information on clinical evaluation and gastric secretory studies of patients at each clinic visit order NAPS Document No. 00450 from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th St., New York, N.Y. 10001, remitting $1 for each microfiche-copy reproduction. Checks or money orders should be made payable to American Society for Information Science-National Auxiliary Publications Service.
hours), 30 ± 31 one-hour basal, total volume (ml), 105 ± 54, and HCl (mEq per hour), 4 ± 4; one-hour beta-zeo hydrochloride, total volume (ml), 209 ± 80, and HCl (mEq per hour), 18 ± 10.

**DISCUSSION**

The evaluation of the effect of therapy in duodenal ulcer continues to be a challenge. The natural history of the disease remains variable, unpredictable and poorly understood. In a disease characterized by spontaneous remissions and recurrences, the effectiveness of any treatment is difficult to judge. Accurate assessment of the effect of a procedure or agent in the treatment of duodenal ulcer requires a carefully designed protocol with the random assignment of patients to two groups, one of controls and the other of patients receiving the therapy under consideration. Recognizing this, we designed a protocol to provide an assessment of the effect of gastric “freezing” upon the clinical course of the disease. Specific end points were defined, and the double-blind method was employed.

The results of this study demonstrate conclusively that the “freezing” procedure was no better than the sham in the treatment of duodenal ulcer, confirming the work of others.19-21 There was no significant difference in relief of pain, secretory suppression, number and severity of recurrences or development of end points in the two groups. It is reasonable to assume that the relief of pain and subjective improvement reported by early investigators was probably due to the psychologic effect of the procedure.

The importance of random assignment of patients to treatment and the double-blind method in clinical trials has been emphasized repeatedly, but these features are still too frequently ignored. Only by strict adherence to such principles and resisting the urge to publish until data have been gathered by these rigorous methods will false leads be kept to a minimum and erroneous conclusions avoided.

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**REFERENCES**