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Communication from Abroad

Treatment of Gastric Ulcer

The Randomized Clinical Trials from 1964 to 1974 and Their Impact

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Twenty-nine randomized clinical trials (RCTs) from the decade 1964-74 evaluating treatments of gastric ulcer have been analyzed. None of them fulfilled all criteria for an ideal RCT. The most frequent shortcomings were: short treatment or follow-up periods, incomplete description of the patients included, small patient samples, suboptimal experimental design, lack of double-blind testing, high number of drop-outs, less precise or less relevant types of evaluation of the treatment effect, uncontrolled ancillary treatment, or lack of statistical evaluation of the results.

The most frequently tested drug was carbenoxolone, which has been shown to be clearly effective. Judged by the effect on the recommendations in standard medical textbooks the impact of the best RCTs have been small. This situation emphasizes the need for more well-planned and performed RCTs on treatments of gastric ulcer.

Introduction

Truelove and Wright, in a review of randomized clinical trials (RCTs) in gastroenterology up to 1964,[1] concluded that strict bed-rest in hospital,[2] giving up smoking[3] and carbenoxolone (Biogastrone)[4] were of proven value in the treatment of gastric ulcer. An effect of diet,[5] intragastric milk drip containing sodium bicarbonate[6] and sedatives[2] had not been demonstrable.

The purpose of the present analysis was to evaluate RCTs on treatments of gastric ulcer during the decade 1964-1974 and their impact on current therapeutic practice. In a previous analysis RCTs on duodenal ulcer were evaluated.[7] The relevant citations were obtained from MEDLARS as previously described.[8] We accepted trials as RCTs only if: 1. patients were allocated to a treatment or a control group at random; 2. the therapeutic effect

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TABLE I

ABSOLUTE (1-7) AND RELATIVE (8-17) REQUIREMENTS OF RCTs ON THE TREATMENT OF GASTRIC ULCER

		No. of RCTs fulfilling	
		This requirement	This *and* preceding requirements
1.	a. Random allocation b. Effect evaluated by relevant variables c. GU distinguished from other ulcer	29	
2.	Ulcer diagnosed by "objective" methods	29	29
3.	Treatment schedule and dosage described	29	29
4.	Results tested (or testable) statistically	29	29
5.	Treatment or follow-up period at least 3 weeks	28	28
6.	Age, sex, or duration of history reported	25	25
7.	Group size greater than 10	24	23
8.	Adequate experimental design	24	18
9.	Double-blind testing	23	14
10.	Number of drop-outs stated	23	12
11.	Clearly defined end-points	23	10
12.	Criteria for exclusion described	22	7
13.	Statistical evaluation	20	4
14.	Ancillary treatment controlled	17	3
15.	Specification of ulcer symptoms	8	0
16.	Calculation of the type II error	0	0

was evaluated on the basis of clinically relevant variables (e.g. severity or duration of symptoms, survival, disappearance of an ulcer crater) and 3. gastric ulcer patients were distinguished from duodenal ulcer patients in RCTs evaluating both categories. Twenty-one RCTs fulfilling these criteria were obtained by the MEDLARS search. From their reference lists and from recent surveys eight additional RCTs were found. The analysis thus comprises 29 RCTs.[9-37] In 27 of these medical treatments were evaluated, one compared surgical treatments and one compared medical with surgical treatment.

METHODOLOGIC EVALUATION

The 29 RCTs on gastric ulcer have been evaluated by the absolute and relative requirements listed in Table I. If the absolute requirements are not fulfilled, we find it difficult or impossible to make use of the results of these RCTs. Failure to meet some of the relative requirements may reduce the value of the RCT to a smaller or greater extent but in most cases this will not invalidate the results completely.

Criteria:—Criterion No. 1 simply states that the trial is an RCT on gastric ulcer.

The objective methods for the diagnosis (Criterion No. 2) were radiography alone (15 RCTs), radiography plus endoscopy (13 RCTs) (in three of these biopsies were taken from the ulcer) and surgery (1 RCT). Criteria Nos. 3 and 4 are self-explanatory. Criterion No. 5 is a very moderate one, one or more years of treatment or follow-up is not unreasonable from a clinical point of view. For all the RCTs, however, the median was four weeks and the maximum 2½ years. The description of the patients included as to age, sex and duration of ulcer history (Criterion No. 6) was incomplete in many reports. All three factors were stated in only 11 RCTs but primarily we only excluded four in which *none* of them were given. Criterion No. 7 is also very moderate. Ideally the group size should be adjusted to the type I error (risk of a false positive result), the type II error (risk of a false negative result) and the minimum difference the investigators wish to detect as significant.[38] The seven absolute requirements eliminated six or more than one-fifth of the RCTs.

The experimental design (No. 8) was considered less adequate in five RCTs, in four because the employed factorial design does not prevent the tested treatments from interacting, and in one because the cross-over design was used without an intervening treatment pause. Double-blind testing (No. 9) was not done in six RCTs. In one, however, this was motivated and presumably was without marked effect on the result. The number of drop-outs (No. 10) was not stated in six reports. In five RCTs the drop-out rate was higher than 20% of the number of included patients. Clearly defined end-points (No. 11) as complete relief from ulcer pain or disappearance of an ulcer crater, were used in 23 RCTs. In seven RCTs healing was considered complete only if confirmed by endoscopy. Fifteen RCTs used both the percentage reduction of ulcer size and the proportion of completely healed ulcers for evaluation and in six only the former showed a statistically significant difference between treatments tested. Criteria for exclusion from the trial (No. 12) were given in 22 RCTs. In eight RCTs they included age limits and the presence of more than one ulcer crater. Eight RCTs reported the percentage of patients excluded. It varied from 4-146, median 65% of the number included. Statistical evaluation (No. 13) of the results was made in 20 RCTs but only 17 stated the method used. The type I error could be evaluated from the data presented in 26 RCTs with Fisher's exact probability test or Student's t-test and in five a claimed significant positive result was not confirmed at the 5% level. Ancillary treatment (No. 14) was given but not recorded in 12 RCTs. This may cause false negative results if the ancillary treatment is effective and taken in greater amounts in the control group than in the treatment group. Specification of symptoms (No. 15) was not made in three of the 11 RCTs which also evaluated the treatment effect on ulcer symptoms. In three RCTs the consumption of antacids was used as a measure of therapeutic effect. Calculation of the type II error (No. 16), i.e. the risk of a false negative result, had not been made in any of the 14 "negative" RCTs, i.e. trials with no significant difference between treatments tested. In 13 RCTs the type II error could be calculated from the data presented. In three RCTs it was less than 5% and in five it was greater than 30%, for a therapeutic improvement of 20% and a type I error risk of 5%.

The requirements listed in Table I are ranked according to the frequency with which they are fulfilled in the RCTs studied. Some requirements with a high ranking on our list may be replaced with

TABLE II

RCTs ON CARBENOXOLONE VS PLACEBO

Reference and year	Daily dosage (mg.)	Age, mean or range (years)	Female/ male ratio	Mean duration of history (years)	Duration of RCT (weeks)	Mean size of treatment and placebo group	Net mean reduction of ulcer size* (%)	Net ulcer healing rate†	
								In each RCT (%)	Cumulated (%)
10 65	300	≃ 55	0.6	≃ 2	4	23	39‡	14	
11 65	300	≃ 55	1.6	?	3	15.5	10	−5	
12 67	300-200	30-68	0.4	?	52	11	?	27	
13 69	300-150	49	0.4	7.3	5	18	?	36‡	
14** 70	300-150	24-75	0.9	?	78	20.5	?	20	
15 71	300-150	54	0	?	4	35	?	43‡	
16 72	300-150	59	0.5	?	4	22	?	54‡	
17 73	300-150	58	2.8	≃ 1	4	17	?	24	30‡

* Mean reduction of ulcer size (%) in the treatment group minus mean reduction of ulcer size (%) in the placebo group.

† Percentage of patients with completely healed ulcers in the treatment group minus percentage of patients with completely healed ulcers in the placebo group.

‡ Percentage significantly different from zero ($P = 2\alpha < 0.05$).

** RCT not double-blind

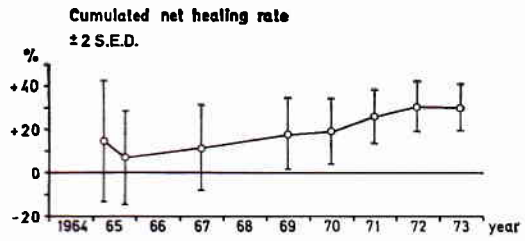

Fig. 1—Net effect of carbenoxolone on healing of gastric ulcer indicated by the cumulated net healing rate (calculated from the accumulated number of patients) ± 2 SED (standard error of the difference)[39] versus time in the period 1964-1974. Net healing rate is the percentage of completely healed ulcers in the treatment group minus the percentage of completely healed ulcers in the placebo group.[39]

others regarding RCTs dealing with other diseases.

The following analysis of different types of treatment, studied by RCTs during the decade 1964-74, only includes the 23 RCTs which meet our "absolute" requirements. In cases where the reported and the recalculated statistics differed, the later have been used.

Clinical Evaluation

Nine RCTs evaluated carbenoxolone (Biogastrone).[9-17] One RCT showed that the effect of low doses was less than that of high doses on healing of ulcers.[9] The remaining eight RCTs compared the effect of carbenoxolone with that of placebo.[10-17] Some data of these RCTs appear in Table II. No significant differences could be found between the positive and the "negative" RCTs in regard to the various data. It appears from Figure 1 that the cumulative net effect has stabilized at 30 per cent as more RCTs have been made. In duodenal ulcer patients a similar effect has been found.[7] The rather frequent side-effects of the drug can be controlled by thiazide diuretics and potassium supplementation without interfering with the effect on ulcer healing.[9]

One RCT has demonstrated that geranylfarnecylacetate is significantly inferior to carbenoxolone in promoting healing of ulcers.[18]

Two factorial experiments testing stilbestrol (Table III) were both "negative".[10, 19] Due to the design, other simultaneously tested treatments may have obscured the results. The subgroups receiving stilbestrol alone and placebo alone were small.

Three RCTs evaluated deglycyrrhizinated licorice.[20-22] One RCT compared the agent with carbenoxolone without finding any differences between the treatments.[20] Of the remaining RCTs comparing the agent with placebo (Table III) one was positive[21] and the other which used the cross-over design was "negative".[22] By addition of the results the effect on ulcer healing was not significantly different from that of placebo (Table III).

One RCT evaluating antacids found a weak antacid (dried aluminum hydroxide gel) slightly *more* effective than a potent antacid (calcium carbonate powder) in bringing about ulcer healing, but the difference was not statistically significant.[23] In spite of the lack of a placebo group, this RCT does not support the application of antacids in gastric ulcer.

The antigastrin agent proglumid has been shown in one RCT using the matched pair design to promote healing of gastric ulcers (Table III).[24]

The bismuth-protein-complex bicitropeptide has been significantly more effective than placebo in bringing about complete healing of ulcers in one RCT (Table III).[25]

One RCT has tested Cholestyramine versus placebo (Table III).[26] The agent was found to be ineffective in promoting healing of gastric ulcers.

TABLE III

RCTs ON OTHER MEDICATIONS VS. PLACEBO

Reference and year	Agent	Daily dosage	Mean age (years)	Female/ male ratio	Mean duration of history (years)	Duration of RCT (weeks)	Mean size of treatment and placebo group	Net mean reduction of ulcer size* (%)	Net ulcer healing rate†	
									In each RCT (%)	Cumulated (%)
10 65	Stilbestrol	1 mg.	≃ 55	0.2	≃ 3	5	17	16	?	
19 68		1 mg.	≃ 50	0	?	4	16	− 9	−25	−25
21 69	Deglycyrrhizinated licorice	2.28 g	≃ 55	1.7	?	4	16.5	44‡	38‡	
22 73		2.28 g.	≃ 55	1.7	≥ 3	4	34	8	− 6	8
24 70	Proglumide	1200 mg.	47	0.3	?	8	25	?	44‡	
25 71	Bicitropeptide	640 mg.	59	0.6	4.2	6	13.5	?	52‡	
26 71	Cholestyramine	12 g	53	1.3	6.8	8	17	12	6	
27 71	Proxazole	600 mg	47	0.1	?	12	20.5	?	23	
28 72	Glycopyrrolate**	O.E.D.§	50	3.0	?	3	20	17	30	
29¶ 72	Zinc sulfate	660 mg.	≃ 55	0.4	≃ 3	4	24	17	8	
29¶ 73	Vitamin A	50,000 units	≃ 55	0.4	≃ 3	4	24	−16	− 8	

* Mean reduction of ulcer size (%) in the treatment group minus mean reduction of ulcer size (%) in the placebo group.

† Percentage of patients with completely healed ulcers in the treatment group minus percentage of patients with completely healed ulcers in the placebo group.

‡ Percentage significantly different from zero ($P = 2\alpha < 0.05$).

** This RCT is not strictly placebo controlled.

§ Optimal effective dose, i.e. highest individual dose not giving side-effects.

¶ RCT not double-blind.

The antispasmodic and antiinflammatory agent proxazole has been tested versus placebo in one RCT (Table III).[27] Proxazole was slightly more effective in bringing about complete healing evaluated by endoscopy than placebo but the difference was not significantly different (P = 0.18).

The effect of the anticholinergic glycopyrrolate on ulcer healing was compared with that of not giving the agent in one RCT (Table III).[28] Placebo was not given in this phase of the study. The mean reduction in ulcer size was 17% higher but the percentage of completely healed ulcers was not significantly higher in the treatment group (P = 0.10). In a second phase of the study the effect of glycopyrrolate on prevention of ulcer recurrence was compared with that of placebo. A marginally significant difference in favor of the anticholinergic after six and 12 months was not maintained after two years (P = 0.16).

In a multifactorial RCT the carbenoxolone analogue BX24 (lauroyl glycyrrhetinic acid) was shown not to be better than carbenoxolone in promoting ulcer healing.[29]

The same RCT also tested zinc-sulfate and Vitamin A (Table III). Neither was found significantly superior to placebo but again this could be due to the effect of other simultaneously tested treatments.

One RCT tested vagotomy and pyloroplasty versus Billroth I gastrectomy.[30] Immediate postoperative morbidity and dumping were more frequent after gastrectomy, while reoperations and diarrhea were more frequent after vagotomy and pyloroplasty. The over all functional results (Visick grading) and the recurrence rates were not significantly different in the two groups. One big multicenter RCT compared the effect of continued medical treatment (antacids, anticholinergics, sedatives, diet) with that of surgical treatment in patients with unsatisfactory healing after a treatment period in hospital.[31] Of the 111 randomized patients only 49 were followed for two years. Of these 71% (20/28) of the surgical group and 24% (5/21) of the medical group had a satisfactory outcome without recurrence or disabling postgastrectomy symptoms. The meaning of this difference which is statistically highly significant (P = 0.002) is uncertain in the light of the high drop-out rate.

Impact

The impact of the RCTs on therapeutic practice is difficult to measure directly. The recommendations for treatments in textbooks appearing around 1964 and 1974, however, give an indication of the impact of the RCTs from the intervening period.

The medical treatments recommended by standard medical and gastroenterologic textbooks are reviewed in Table IV. It appears that antacids and to a lesser degree, anticholinergics, still are being recommended in spite of practically no support from RCTs. These drugs are still considered the mainstays of the therapy of gastric ulcer. On the other hand, carbenoxolone, which has been shown to be effective in more RCTs, is only recommended in some textbooks. The side-effects of the drug can be controlled so that these should not prevent its use in most patients. The drug is not available to the practicing physician in the United States. Drugs such as proglumid and bicitropeptide, which have been shown to be effective, are not recommended for treatment. These drugs are not mentioned in any of the textbooks examined and are not available in the United States.

The recommendations for surgical treatments have been practically unchanged during the decade.[40-45, 47-51] Most prefer gastric resection including the ulcer to

TABLE IV

RECOMMENDATIONS FOR MEDICAL TREATMENT OF GASTRIC ULCER COMPARED WITH RESULTS OF RCTs

Treatment	Results of RCTs before 1964	Recommendation for treatment 1964*	Result of RCTs 1964-1974	Recommendation for treatment 1974**
Anticholinergics	no RCT	(+)	−	(+)
Antacids	−	+	−	+
Diet	−	+	no RCT	(+)
Bed-rest	+	+	no RCT	(+)
Sedatives	−	+	no RCT	(+)
Giving up smoking	+	+	no RCT	+
Carbenoxolone	+	none	+	(+)
Stilbestrol			−	−
Deglycyrrhizinated licorice			−	none
Proglumide			+	none
Bicitropeptide			+	none
Cholestyramine			−	none
Proxazole			−	none
Zinc sulfate			−	none
Vitamin A			−	none

* Based upon references 40-42.
** Based upon references 43-48.
+ Cumulated result of RCTs positive, i.e. $P = 2\alpha < 0.05$, or treatment recommended, respectively.
− Cumulated result of RCTs 'negative', i.e. $P = 2\alpha > 0.05$, or treatment not recommended, respectively.
(+) Treatment recommended in some textbooks but not in other textbooks.

pyloroplasty and vagotomy or antrectomy as some carcinomas may be missed in the latter procedures even if operative biopsy is performed.

PERSPECTIVES

The analysis has revealed that the RCTs on treatment of gastric ulcer in the decade 1964-74 are very heterogenous. They have included small and sometimes rather highly selected samples of the gastric ulcer population. The diversity as to design, blinding, selection of patients, duration of treatment or observation periods, type of evaluation and interpretation of the results indicates that many RCTs were not sufficiently well planned or performed. The contribution of the RCTs to our present knowledge on the effect of the various treatments has been rather small and the information obtained from the best RCTs has had little impact on current therapeutic practice which is predominantly based on uncontrolled observations. The explanations for these discrepancies are numerous. Results from individual RCTs are often con-

tradictory and it may be necessary to combine results of many RCTs to get a clearer picture. The RCTs are few in number[8] and some may be overlooked because they "drown" in the flood of uncontrolled therapeutic information. The results of a RCT may not be accepted if deserved criticism can be raised against it but even if it is beyond methodological criticism the results may be neglected if they clash with "clinical experience" or uncontrolled "knowledge". Doctors may be reluctant to leave treatments proved to be ineffective in RCTs if their patients think they help, even if this is a pure placebo effect.[52] To improve the situation, more well planned and well conducted RCTs must be produced and the results should be communicated more effectively to the medical profession. Future RCTs should include larger[88] and less selected samples of gastric ulcer patients, in whom the diagnosis is confirmed and the effect evaluated by gastroscopy. The duration of RCTs should be longer and the results should be evaluated statistically for both type I and type II errors.

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