Randomized versus Historical Controls for Clinical Trials

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To compare the use of randomized controls (RCTs) and historical controls (HCTs) for clinical trials, we searched the literature for therapies studied by both methods. We found six therapies for which 50 RCTs and 56 HCTs were reported. Forty-four of 56 HCTs (79 percent) found the therapy better than the control regimen, but only 10 of 50 RCTs (20 percent) agreed. For each therapy, the treated patients in RCTs and HCTs had similar outcomes. The difference between RCTs and HCTs of the same therapy was largely due to differences in outcome for the control groups, with the HCT control patients generally doing worse than the RCT control groups. Adjustment of the outcomes of the HCTs for prognostic factors, when possible, did not appreciably change the results. The data suggest that biases in patient selection may irretrievably weight the outcome of HCTs in favor of new therapies. RCTs may miss clinically important benefits because of inadequate attention to sample size. The predictive value of each might be improved by reconsidering the use of $p < 0.05$ as the significance level for all types of clinical trials, and by the use of confidence intervals around estimates of treatment effects.

Since James Lind's experiments on the treatment of scurvy in 1747, the controlled clinical trial has been increasingly recognized as the best method of establishing the value of new therapies. The number of controlled trials published has grown in recent years [1], and they have become increasingly sophisticated in terms of design, management and analysis. A comparatively new development has been the use of randomization in the assignment of patients to treatment and control groups. Randomization has a number of practical and theoretical advantages including reduction of bias in assignment of patients to treatment groups, the opportunity for blinding of patient and physician as to treatment and the provision of a setting in which the assumptions underlying statistical tests are more closely approximated. If the investigators so choose, RCTs can be stratified to ensure that known prognostic factors are equally divided between treatment and control groups. The investigators depend on the randomization process to produce a reasonable division of unknown or unstratified risk factors, and this is generally (but certainly not always) the result.

Acceptance of the RCT is growing but still far from universal, and the majority of published clinical trials do not use this method [1,2]. Recent articles have argued that RCTs are impractical in surgery [3,4] and often unnecessary in cancer medicine [5]. Double-blind RCTs have been criticized on ethical and practical grounds, and it is claimed

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TABLE I Conclusions of RCTs and HCTs on Six Therapeutic Questions

Question Studied	RCT		HCT			
			All Trials		Matched or Adjusted for Prognostic Factors	
	Effective	Ineffective	Effective	Ineffective	Effective	Ineffective
Cirrhosis with varices	6	14	12	6	2	1
Coronary artery surgery	1	7	16	5	9	1
Anticoagulants for acute myocardial infarction	1	9	5	1	3	1
5-FU adjuvant for colon cancer	0	5	2	0	2	0
BCG adjuvant for melanoma	2	2	4	0	4	0
DES for habitual abortion	0	3	5	0	1	0
Totals	10	40	44	12	21	3

that comparison with recently treated patients with the same disorder (HCTs) can evaluate new therapies more rapidly without exposing patients to possibly ineffective therapies and uncertainties [6]. Proponents of HCTs claim that adjustments can be made for differences in known prognostic factors between the two groups, leaving a valid estimate of the effect of the treatment. These issues have been debated in the literature and were a major topic at a recent international symposium [7]. The present study attempts to provide data for a rational comparison by looking at therapies studied by both methods.

MATERIALS AND METHODS

Since 1955, one of the authors (TCC) has maintained a file of RCTs published in English. Articles for this file are gathered by computer and manual literature searches of *Index Medicus* on specific topics of interest, by weekly review of *Current Contents* and by checking references of reviews and papers already in the file. At the same time, HCTs and uncontrolled trials are also filed. RCTs were defined as trials in which both treatment and control groups were gathered prospectively and randomly assigned. Trials in which prospectively collected treatment groups were compared with either previously published series or previously treated patients at the same institutions were considered HCTs if the authors drew conclusions about relative efficacy from these comparisons. HCTs were further subdivided into those that simply compared over-all outcome and those that matched or adjusted outcome rates on the basis of prognostic categories, or provided sufficient data so that some such adjustments could be made by the reader. Therapies were considered for inclusion in the present study if at least two RCTs and two HCTs were found for the same therapy. When published reports gave results by prognostic categories as well as treatment, these data were used to produce adjusted survival, or other outcome, rates. For each paper, listed prognostic factors were weighted equally to produce an equivalent average rate [8]. Studies were considered positive (i.e., they found the new therapy to be effective) if a statistically significant benefit in outcome was found for treatment over control regimen, or, when no statistical analysis was presented, if the authors concluded that the therapy was superior to the control regimen. Trials that did not meet these criteria were considered negative. When multiple outcomes were studied, the most serious (e.g., death) was used.

RESULTS

One hundred six papers on six therapeutic questions met our criteria for inclusion in the study. Over-all, 10 of 50 RCTs (20 percent) found a benefit from the therapy studied, while 44 of 56 HCTs (79 percent) on the same questions concluded that the therapies were beneficial (**Table I**). Twenty-nine of the 50 RCTs (58 percent) gave the probability that the difference found could be due to chance (α) or provided sufficient data so that the probability could be calculated; in seven (14 percent), this probability was less than 0.05. Twenty-six of the HCTs (46 percent) provided probability values or data for estimating α; in 22, it was less than 0.05 (**Table II**). Most of the papers that found a probability greater than 0.05 did not give the actual value. Thirty-one papers (three RCTs and 28 HCTs) presented neither statistics nor sufficient data to calculate them.

Cirrhosis with Esophageal Varices. Twenty RCTs [9–28] and 18 HCTs [29–46] were found on treatment of cirrhotic patients with esophageal varices. Table I shows that six of 20 RCTs (30 percent) found a benefit from the therapy studied compared with 12 of 19 HCTs (63 percent). Two of the three HCTs that attempted to adjust or match treatment and control groups for prognostic factors (including age, sex, severity, concurrent diseases, etc.) found a benefit.

Ten RCTs and seven HCTs gave survival data, either in-hospital or long-term, that could be analyzed. The

TABLE II Levels of Significance (α) Reported in 106 Clinical Trials

	$p < 0.001$	$0.001 < p < 0.01$	$0.01 < p < 0.05$	$0.05 < p < 0.10$	$p > 0.10$	$p > 0.05$ but Unstated	No Statistics	Totals
RCT	0	1	6	3	19	18	3	50
HCT	9	11	2	1	3	2	28	56

TABLE III Early Survival in the Treatment of Varices

	No. Studies	No. Patients	Mean Percent Early Survival		
			Treatment	Control	Difference
RCT	10	677	81	74	7
HCT	7	565	66	33	33

average early survival rates for the treatment groups in the two types of studies were 81 percent and 66 percent, respectively (**Table III**). However, the early survival of the control groups was 74 percent in the RCTs and 33 percent in HCTs, and the apparent effect of the treatment increased from an average of 7 percent in the RCTs to 33 percent in the HCTs. The long-term survival data were similar. Thirteen trials compared surgery (mostly portosystemic shunt procedures) with medical management (**Figure 1**). The pooled five-year survival curves for the RCTs show little difference between medical and surgical therapy. The survival of patients who underwent shunt procedures in HCTs is slightly better than both groups in the RCTs, but the survival of the control subjects in the HCTs falls rapidly and remains much lower throughout the five years.

Coronary Artery Surgery. Eight RCTs [47–54] and 21 HCTs [55–75] (12 of which adjusted for or gave data on prognostic factors) were found on the surgical treatment of coronary artery disease. Only one of the RCTs found a significant benefit in over-all survival between surgically and medically treated groups (although certain subgroups showed a benefit from operation), but nearly all of the HCTs found a benefit from surgical treatment. A comparison of long-term survival

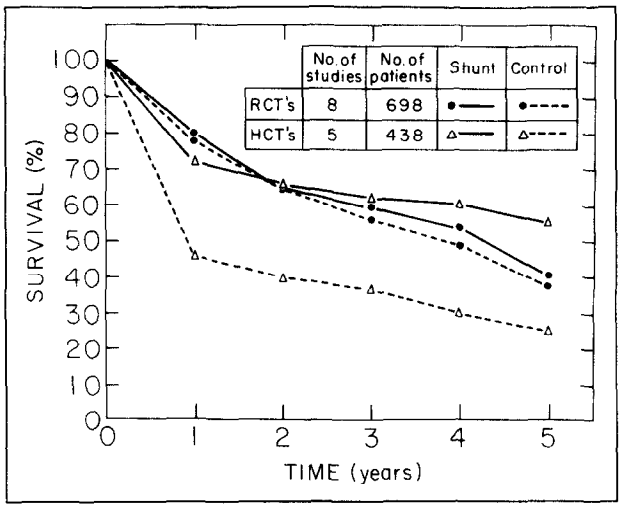

Figure 1. *Survival of treated and control groups in clinical trials of shunt surgery for cirrhosis with esophageal varices.*

in the six RCTs and nine HCTs that gave such data is shown in **Table IV.** The pooled HCTs show both a higher survival for surgical patients and lower survival for medical patients. When the HCT data are adjusted to have the same over-all proportion of patients with one-,

TABLE IV Pooled Survival in Clinical Trials of Medical versus Surgical Treatment of Coronary Artery Disease

	No. Studies	No. Patients	Percent Survival			
			1 yr	2 yr	3 yr	4 yr
RCT	9	18,861				
Surgical			92.4	89.6	87.6	85.3
Medical			93.4	89.2	83.2	79.8
HCT	6	9,290				
Surgical			93.0	92.2	90.9	88.3
Medical			83.8	78.2	71.1	65.5
Surgical adjusted*			93.7	92.5	91.2	87.4
Medical adjusted*			88.2	82.2	70.9	67.7

* Adjusted to have the same proportion of patients with one-, two- and three-vessel disease as in the RCTs.

TABLE V Anticoagulants for Acute Myocardial Infarction

	No. Studies	No. Patients	Mean Case Fatality Rate		Difference
			Treated	Control	
RCT	10	4334	13.7	17.6	3.9
HCT (unadjusted)	6	2291	18.0	35.1	17.1
HCT (adjusted)	4	1312	19.1	30.1	11.0

TABLE VI DES for Habitual Abortion

	No. Studies	No. Patients	Percent Live Infants		Difference
			Treated	Control	
RCT	3	2175	87.3	87.6	−0.3
HCT (unadjusted)	4	2358	85.3	56	29.3
HCT (adjusted)	1	216	45	8	37

two- and three-vessel disease as the RCTs, the difference in survival between medical and surgical groups is decreased, but remains larger than the difference in the RCTs. (Only six of the HCTs provided data on proportions of one-, two- and three-vessel disease.)

Anticoagulants for Acute Myocardial Infarction. Six RCTs [76–81] and six HCTs [82–87] of this treatment have been previously reviewed [88] (using a different definition of HCT), and the combined data suggested a beneficial effect. Since then, four additional RCTs have been found [89–92] (**Table V**). Nine of the 10 RCTs found no significant benefit from anticoagulants, although all but one showed a trend toward better survival in the treated patients. The pooled unadjusted results from six HCTs showed poorer survival in both treated and control groups, but the difference between treated and control groups in HCTs was four times as large as the difference between treated and control groups in RCTs. Four of the six HCTs published survival data that allowed adjustment for patient's age, sex, history of previous infarction, location and severity of infarction and presence of other diseases (some studies did not give data on all these variables). When the survival rates were adjusted for these variables, the difference between treatment and control groups decreased from 17.1 percent to 11.0 percent, but this was still more than twice the difference for the RCTs.

5-Fluorouracil Adjuvant Therapy for Colon Cancer. Five RCTs [93–96] and two HCTs [97,98] of the effect of adjuvant 5-fluorouracil (5-FU) in patients with colon cancer undergoing surgery were found. Since some of the papers gave results only in terms of mortality and some gave only disease-free survival, they cannot be combined, but the pattern is similar. The RCTs found a slight trend favoring the use of 5-FU, but no significant differences in over-all survival, whereas both HCTs showed a much larger difference in favor of 5-FU. When the HCT results were adjusted for age, sex, hospital, surgeon, location of tumor, stage, histologic findings and presence of leukopenia, the differences between treatment and control groups were changed only slightly. Two studies of intraluminal 5-FU were found, with several of the same investigators participating in both studies. The first study was an HCT that found a benefit; however, when an RCT was done, there were almost identical survival curves for treatment and control groups.

BCG Adjuvant Immunotherapy. Four RCTs [99–102] and four HCTs [103–106] looked at adjuvant therapy with BCG in patients with malignant melanoma. The papers did not provide sufficient data to adjust for prognostic factors. Also, since some reported survival from the time of operation, some from time of recurrence, and some did not specify, the results could not be directly compared. All four of the HCTs reported significantly increased survival for the treated patients, while only two of the four RCTs found a benefit.

Diethylstilbestrol for Habitual Abortion. The eight studies found on this question (all published before 1955) included three RCTs [107–109], four unmatched HCTs [110–113] and one HCT that matched patients for age and previous history [114]. The results of these studies, in terms of percentage of live infants, are shown in **Table VI.** The RCTs found essentially no difference in outcome, whether or not diethylstilbestrol (DES) was given. The four unmatched HCTs had a very similar success rate in the treated patients, but the HCT control group did notably worse. In the one matched HCT, both

groups had poorer outcomes, but a large difference between treatment and control groups was again found.

COMMENTS

In each of the six areas examined, the results of clinical trials were more dependent on the method of selection of control groups than on the therapy under study. For each of the questions, HCTs were much more likely than RCTs to find a difference, despite similar outcomes for the treated patients in the two types of study. The differences were in the outcomes for the control groups, and, in general, the control groups in the HCTs had notably poorer outcomes than those in the RCTs.

In nearly always finding the treatment better than the control regimen, the HCTs we examined would rarely come to false-negative conclusions, but this may be at the expense of many false-positives. The RCTs have the opposite fault: by declaring most therapies no better than the control regimens, they would rarely come to false-positive conclusions but possibly create many false-negatives. The clinical trials examined are a small proportion of all published trials and were not chosen at random. The authors of some of the papers attached so many qualifications to their conclusions that other readers might not agree with our classification into positive and negative. Nevertheless, the papers include several specialty areas, both single-center and cooperative trials and span four decades. Thus, we think it is very probable that our findings are applicable to trials published on other therapeutic questions. It might be that negative RCT results are more likely to be published than negative HCT results. New therapies may be tried on small numbers of patients, with poorer results than standard therapy, and the results never submitted or published. Practicing physicians, however, generally have little access to unpublished data and must rely on published results to decide how to treat their patients.

Can the accuracy of HCTs be increased? We fear there is little room for improvement in this area. HCTs using literature controls have difficulty distinguishing treatment effects from differences in ancillary care, diagnostic criteria, referral patterns or trends over time. HCT control groups generally include all patients seen who meet the diagnostic criteria for the disease under study. Criteria for inclusion in the treatment group are usually more stringent. The treatment group may be consciously or unconsciously narrowed to include only those patients the investigator feels are most likely to benefit from the therapy, and the patients are enthusiastically recruited. Poor-risk patients may not be offered the treatment or offered it so unenthusiastically that they decline to participate. Even if selected for the treatment, patients may not be selected for the report of the treatment. Block et al. [115] have shown that uncontrolled trials of cancer therapy reported a higher proportion of patients listed as "nonevaluable" than controlled trials.

The data presented suggest that such biases in patient selection may irretrievably bias the outcome of the HCT. It has been claimed that retrospective adjustment for prognostic factors can be used to produce an estimate of the effect of the treatment alone, but the studies we reviewed with such adjustments (either by the original authors or by us) showed nearly the same treatment effect as unadjusted studies. These adjustments were relatively crude and do not take into account possible interactions between prognostic factors. Recently, more sophisticated step-wise multiple regression procedures have been advocated [116], but there is as yet little evidence to suggest such procedures can better recognize ineffective therapies.

The accuracy of RCTs, on the other hand, could be improved by greater attention to sample size in planning studies. A recent review of 71 "negative" RCTs [117] found that a potential 25 percent improvement could have been missed in 57, and a potential 50 percent improvement in 34. At the planning stage of a trial, consideration of the size of the benefit sought and the number of patients needed to demonstrate it can keep the possibility of this sort of type II error at acceptable levels, but with increases in the cost and duration of the study.

A possible solution is to reconsider the nearly automatic use of a p value of less than 0.05 as the critical point at which a difference is felt to be statistically significant. Perhaps well-designed and well-blinded RCTs with little chance for bias should be considered positive when α is less than 0.10 or 0.20. This would increase the proportion of positive trials and save time and money. On the other hand, our data suggest that the opportunity for bias is so large in HCTs that when α is less than 0.01 or even 0.001, the therapy still may not be effective. The decision about what significance level to accept should also take into account other factors, including the prevalence of the disease, the medical and economic costs of the disease and of the therapy and the best pretrial estimate of the likelihood that the new therapy represents an advance.

It is also important to use the results of a trial to estimate the size of the difference between treatment and control groups, and to construct confidence intervals around this estimate [118]. This replaces the often arbitrary decision of whether outcome of the new treatment is significantly different from that of the old with the best single estimate of the size of the difference and the range in which the true difference most likely falls.

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