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INTENTION-TO-TREAT ANALYSIS IN THE CHRONIC SUPPURATIVE OTITIS MEDIA TRIALS
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ABSTRACT

Objective: **To determine the extent of application of the intention to treat principle in the chronic suppurative otitis media (CSOM) randomised controlled trials.**
Design: **Data were extracted from 28 CSOM randomised controlled trials.**
Main outcome measures: **Conceptual and methodological approaches of dealing with protocol deviations with respect to withdrawal, missing response and non-compliance.**
Results: **Of the 28 CSOM trials included in this study, only one (4%) trial mentioned intention-to-treat (ITT) analysis. However, 10(36%) other trials which did not mention ITT, had no protocol deviations and thus carried out an ITT analysis by default. It is highly likely that a biased treatment effect existed in the trial that mentioned ITT since the authors undertook a complete case analysis disregarding the 22% protocol deviators. There were no attempts in any of the trials to impute for missing responses and carrying out a sensitivity analysis. For trials with a big percentage of protocol deviations, the validity of their results are brought to question.**
Conclusions: **In practice, not all those entered into a randomised-controlled trial will complete the trial. Thus intention-to-treat analysis is an important aspect of randomised controlled trials of health care interventions which tries to bridge this gap. It is important for authors to explicitly state the protocol deviations, the methods used to handle them and the potential effect with reference to bias and study outcome.**

INTRODUCTION

An analysis on the intention-to-treat principle tests the strategy of offering a certain treatment to a group of randomised subjects in a trial, irrespective of whether they receive or tolerate the treatment(1,2). Basically, it requires inclusion of all randomised patients in the analysis regardless of whether they remain on protocol for the duration of study. Favoured by statisticians, intention-to-treat analysis seeks to answer the question, "Is it better to adopt a policy of treatment A if possible, with deviations if necessary, or a policy of treatment B if possible, with deviations if necessary?"(3)

However, the implementation of the ITT principle still remains a controversial issue(1,4-6) There are a lot of definitions on this principle and authors seem to have different meanings(5,7) Irrespective of all these, there is a consensus in analysing all those who were randomised into the trial. It is worth noting that an ITT analysis uniquely preserves the qualities of bias reduction of randomisation(7,8).

An ITT analysis should be as pragmatic as possible to ensure representativeness and generalisability(9). It is generally agreed that a pragmatic scenario closely resembles the clinical scenario as opposed to explanatory. Comparing a pragmatic and an explanatory analysis of the same data can reveal possible bias in the explanatory case(5,8-10). No matter how meticulously a trial is planned, it is inevitable some patients will deviate from the protocol specifications(1,11). This is bound to happen more often in the long-term trials or stringent treatment schedules. The main protocol deviations we consider in this study are non-compliance, withdrawal from the trial and missing data.

Non-compliance may be defined as non-adherence to therapeutic advice and its occurrence may radically alter the interpretation of a trial result. Compliance is known to be highly prognostic and a clinical trial where good compliers performed significantly better than poor compliers is questionable(10). The existence of patients who withdraw from intervention is a serious failing which can lead to inappropriate conclusions about treatment efficacy. Subjects maybe withdrawn from a trial because they default or do not comply with the protocol. The most important patients are those whose withdrawal is related to the trial endpoints. These must be accounted for in treatment comparisons(10).

MATERIALS AND METHODS

Inclusion criteria: In this study, we considered all the trials that mentioned ITT and/or those that had no protocol deviations.

Types of studies: Any randomised controlled trial was included that compared the different methods of management outlined in the CSOM review(12).

Types of participants: Any subject suffering from CSOM as defined by the CSOM review, including unilateral and bilateral cases.

Search strategy:

1. The Cochrane Library (Issue 3, 2001).
2. Medline search (1966-1997).
3. Searching the Hearing Network database consisting of a bibliographic collection developed by the, Hearing Impairment Research Group in Liverpool over the last ten years.
4. Hand searching two journals known to publish CSOM trials: Archives of Otolaryngology - Head and Neck surgery (1975-2000) and Clinical Otolaryngology (1976-1997).
5. Contacting members of the International Hearing Network run by the hearing impairment research group in Liverpool.

RESULTS

In all the 28 trials included in this study, only one trial (Table 1) mentioned ITT. However, despite mentioning ITT in its discussion section, it is interesting to note that the analysis done was a complete case (as per protocol). The numbers initially randomised to both treatment arms was also not provided hence making it difficult to impute for missing values.

A good number of the trials reported protocol violations although most of them did not mention ITT or use it. In the one trial where ITT was mentioned, there were protocol violations. The total drop out rate for this particular trial was 22%. It is also imperative to note that the protocol deviations were not documented. The deviations in this trial were overlooked and the analysis was done for only the cases who completed the trial. This paper indicated that the authors' intention was to carry out an ITT analysis. However, the analysis done did not comply with the ITT principle.

In Connolly's paper, it was reported that cases of non-compliance were hard to fully identify and hence all those who took at least one dose were included in the analysis. Of the 28 trials in this study, there were ten trials that had no protocol violations (Table 2).

Table 1

Features of the connolly trial

Trial	No.	Intervention	Primary Outcome	No. (%) of exclusions
Connolly *et al.* (13)	147	Neomycin/dexamethasone Spray vs drop preparation	Resolution of discharge	32 (14)

Table 2

Trials that did not mention ITT and had no deviations

Trial	No.	Intervention
Somekh and Cordora (15)	30	Ceftazidime vs Aztreonam
Cooke and Raghuraran (16)	31	Clindamycin plus surgery vs surgery alone.
Esposfto *et al*(17)	60	Oral ciprofloxacin vs Topical ciprofloxacin vs Oral and Topical ciprofloxacin
Tutkun *et al*(18)	44	Topical ciproflox Topical gentamicin
Esposito *et al*(19)	60	Topical ciprofloxacin vs Intramuscular Gentamicin
Gyde *et al*(20)	60	Trimethoprim-polymyxin B vs Trimethoprim-sulfacetamide-polymyxin B
Gyde *et al*(21)	55	Gentamicin otic solution vs Colistin neomycin-hydrocortisone otic solution
Papastavros *et al*(14)	90	Several systemic treatments vs several topic treatments
Wilde *et al*(22)	70	TAC on ribbon gauze vs TAC with Fg lacrimal cannular
Lilholdt *et al*(23)	26	Ceftazidime in surgery vs no antibiotic in surgery

The primary outcome in all these ten trials was resolution of discharge but none of these ten trials mentioned the need to carry out an ITT analysis. However, they applied the ITT principle inadvertently during the analysis by using all the available information on each subject. In these trials, none of the authors applied the imputation method in trials that had missing data. Further to this, there was no trial that carried out a sensitivity analysis. There were five (18%) trials that had cases withdrawn after randomisation but before start of treatment.

DISCUSSION

There are many times when the event of interest, such as death, occurs after randomisation but before treatment has commenced. This event could also happen before an intervention has had an effect(24). In this study, the exclusion of patients who did not start the allocated intervention was not very common. This however breaches the ITT principle. It is desirable to design a trial so that there is a minimal delay between randomisation and the start of treatment where it is practical(7,24) At other times, it is often unclear whether the outcome of interest is related to the medical condition. Thus it is unwise to exclude such subjects from the analysis(1,7,11,24). Hence, the application of ITT seems to be the most preferred. A good example to illustrate this is the surgical versus medical therapy in bilateral carotid stenosis reported by Pocock(11). The risk reduction using the explanatory and pragmatic approaches gave different conclusions, which cast doubt on the validity of the presented results.

Any trial requires a precise definition of inclusion criterion. However in practice, one will usually find that a small proportion of ineligible patients is included by mistake. These false inclusions should generally not be excluded from the analysis(7,24). If the proportion of ineligible patients becomes unduly large, this may reflect a generally poor standard of trial organisation.

Investigators should always aim at a high degree of compliance from patients. We further note that this is an important aspect of a well administered trial. Most of the trials in this study involved drugs and these are known to contribute significantly towards non-compliance especially when administered by the patient. The greatest step in reducing non-compliance should be taken at the point of entry. At this point, it is imperative to explain carefully the treatment schedule and objectives of the trial to the subjects. Other safety measures to reduce non- compliance have been explained in the works of Pocock(11) amongst others. The issue of non-compliance is delicate and should be approached with a lot of caution(7). It is in this regard that there have been suggestions for carrying out a pilot study that will assess compliance for a major trial(11). If the rate of non-compliance is high, this may affect the validity of the trial results.

In the papers included in this study, there were no methods employed to take care of the missing responses. Indeed, there are many mechanisms, as explained below, that can be employed to handle missing responses(6,7,25). In most of the trials in this study, complete case analysis was employed.

However, this is known to violate the principle of intention-to-treat analysis and hence introducing bias(5-7,25,26). One of the most common approaches is imputing for missing responses. However, we do have a lot of alternatives under this option. The most conservative approach is using the last observation carried forward(6,7,25). But this method assumes in effect that outcome remains constant at the last observed value after drop out, which seems unlikely in many applications(6).

In other situations, an investigator might elect to rank the observed response variables and assign a rank to those participants with missing data. The highest rank could be assigned to all such participants in the intervention group, while assigning the lowest ranks to those in the control group and vice-versa. This is the extreme case analysis method that is unlikely to yield a conclusive answer in practice(7). Complex statistical methods are available for imputing missing outcomes(6,10,25,26). It is generally agreed however that imputations can never lead to an outcome that is unbiased. This is especially true due to the validity of the assumptions made on the mechanisms employed(7). How true are these assumptions? The general idea is that the ITT analysis and the per protocol analysis represent different extremes so that, if they lead to die same conclusion, then the strength of the conclusion is considerably increased. It is when they lead to different conclusions that troubles arise(5). Thus it is important to perform a sensitivity analysis on your dataset(6,7).

Thus our findings in this study are consistent with other findings on the quality of reporting of clinical trials(7,8). It is our hope that in future studies, authors shall present imputation methods used to estimate missing data and a statement on the perceived success or failure of imputation methods applied. It is also our hope that the ITT principle will be applied together with a sensitivity analysis.

CONCLUSION

A current method of adopting an ITT approach within primary research is to assume that the event of interest occurred in all patients for whom the outcome is not known. This aims to develop and implement an approach that: does not assume the same endpoint for all patients whose outcome is unknown and allows for the fact that there may be differences between the proportions of patients (for whom the outcome is unknown) who experience the event on treatment and control groups.

We strongly recommend that future trials of CSOM and others be analysed on the intention-to-treat basis.

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