Assessment of blinding may be inappropriate after the trial

Hemilä Harri

2009-01-30T12:39:45Z


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In their paper discussing the assessment of blinding in clinical trials, Bang et al. [1] based their analysis on the premise that “all participants randomly guess their assignment … This is the most ideal scenario in reality” [ref. 1, p. 149]. However, this premise makes an implicit assumption that the drug does not differ from placebo in any physiological effects that a person could observe subjectively, which is a very strong assumption. If a drug is truly effective, such as penicillin for pneumococcal pneumonia, both the patient and the physician can infer the treatment with high certainly by subjective observations. Thus, when the drug is truly effective, we are expecting “breaking of blindness.”

Bang et al. [1] admit in their discussion, that “it is possible that unsuccessful blindness may not influence statistical analysis in the end.” Thereafter they state that “in a well-known trial of vitamin C, the perceptions affected the endpoint concerning cold symptoms,” thus providing the Karowski et al. [2] trial as the single example of a trial in which breaking of blindness may have caused the observed difference between the study arms.

The Karowski trial was planned as a double-blind placebo-controlled trial. Because of the shortage of time, no appropriate placebo (e.g. citric acid) was manufactured, and they used lactose-placebo which is sweet and differs in taste from vitamin C (ascorbic acid). At the end of the trial many participants guessed correctly their treatment, and this led Karowski to carry out a subgroup analysis by the blindness status of the participants. Vitamin C appeared effective among “unblinded” participants, but no effect was seen among “blinded” participants [2,3]. This subgroup finding was spectacular by indicating that knowledge of treatment explained the differences between the study arms. Therefore the Karowski trial has been frequently cited as an example of the importance of blinding, e.g., in the CONSORT statement pointing out the importance of trial quality [4], and as the only example by Bang et al. [1].

However, the subgroup analysis by Karowski et al. [2,3] is not valid. For example, a total of 249 common cold episodes were recorded in the trial, but the subgroup analysis contained only 144 episodes, so that 105 episodes (42% of all) were missing [5]. Karowski did not mention the exclusion of 105 episodes from their subgroup analysis, nor did they present their rationalization for the greater than average benefit (sic!) in the excluded participants who were neither “blinded” nor “unblinded” [5]. Further problems of the “placebo effect explanation” are detailed elsewhere [5]. Chalmers, the principal author, commented on the re-analysis of the Karowski trial [6], but his criticism appears to be invalid [7].

Vitamin C has consistently reduced the duration and severity of colds [8,9], and some of the largest trials explicitly reported that vitamin C and placebo tablets looked and tasted the same [10-12]. The validity of the placebo should be determined before the trial. Blindness at the end of the trial may be influenced by the true physiological effects of the drug [5].
References


