Special Article

Placebo and Nocebo Effects in Randomized Controlled Trials: The Implications for Research and Practice

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Abstract

Placebo and nocebo effects are known to contribute significantly to the response to symptom control, including analgesia. Clinical trial methodologies using placebo controls are designed to identify the magnitude of these effects in the research context. An adequately powered, randomized, double-blind, placebo-controlled trial of ketamine in cancer pain has recently been reported, which demonstrated no net clinical benefit for ketamine over and above that of placebo. Rates of placebo and nocebo responses were high. The setting of a clinical trial provides an opportunity to quantify the nonpharmacologic aspects of patient responses to analgesia, raising important clinical and ethical issues for practice. The findings of the ketamine study are analyzed in the context of a methodological discussion of placebo and nocebo effects, what is known about the biological and psychological bases for each of these, and their implications for a clinical trial design in the palliative care setting. Along with reviewing the use of ketamine after this negative trial, clinicians need to remain aware of the strength and significance of both placebo and nocebo responses in their own practices and the biopsychosocial complexity of why and how patients actually respond to pain management strategies. The results of this study strongly reinforce the importance of the therapeutic relationship and the context of care. J Pain Symptom Manage 2013;46:722–730.

Key Words

Placebo, nocebo, randomized controlled trial methodology, cancer pain, ketamine

Introduction

The placebo effect describes the phenomenon in which patients' symptoms may improve while receiving an inactive substance in a clinical trial; its negative counterpart, the nocebo effect, refers to adverse effects experienced

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by those receiving an inactive placebo. Placebo and nocebo effects are significant not just in research but also in clinical medicine. For clinicians, understanding these twin phenomena is crucial to interpreting the clinical trial data and the outcomes of their own treatment of patients. The implications may sometimes challenge long-standing practices. A recent double-blind, placebo-controlled trial of ketamine for cancer pain in a palliative care population has yielded a negative result at a population level and high placebo and nocebo response rates[1] (Table 1). These results—from the first large, randomized, placebo-controlled trial of ketamine as an adjuvant in cancer pain—may be both surprising and disappointing for some clinicians.

Previous underpowered studies of ketamine in comparable populations had yielded contradictory findings. The basis for ketamine use in chronic cancer pain is derived largely from studies in other chronic pain conditions, although the evidence of response in those pain syndromes is itself inconclusive. The authors of one systematic review of the use of ketamine for a range of chronic pain conditions commented that the response to ketamine was "often little more than what could be expected by a placebo effect" and noted the lack of consistent dose response across the studies, a surprisingly large therapeutic window, and generally small sample sizes, with many of the positive studies providing only Level IV evidence.[2]

The cancer pain literature is replete with case studies suggesting significant and often dramatic responses to ketamine. The most recent Cochrane review on this topic identified 32 reports of non-randomized controlled trials (RCTs) not eligible to be included in the review, involving a total of 246 patients treated with ketamine[3] of which 16 studies reported positive results that were described variously as "complete," "dramatic," or "excellent."[4–7] Only two studies reported toxicity significant enough to lead to patient withdrawal.

On this background, it is unsurprising that many palliative care clinicians have used ketamine in managing complex cancer pain. However, the Cochrane review noted a lack of prospective placebo-controlled studies of adequate size to answer the questions regarding benefits and harms of this medication for cancer pain.[3] Only two RCTs could be included in the recently updated review, involving a total of just 30 patients between them.

Using the example of ketamine, this article addresses issues facing clinicians confronted with a gap between their perception of benefit from an unproven drug (which previously held an important place in their treatment strategies) and the negative findings from a rigorous clinical trial. The high rate of placebo and nocebo (adverse) effects documented in this study illuminates the complexity of interactions among patients, clinicians, and the setting of care, as much as the pharmacologic effects of ketamine. Much can be learned from an adequately powered negative trial, and RCT methodology provides a new insight into present practice.

Placebo and Nocebo Effects in Clinical Trials

The existence and frequency of placebo and nocebo effects are the major reason for incorporating an inert control arm and for double-blinding of clinical trials where no evidence-based standard of care exists. Doing so allows us to quantify the extent to which the responses and adverse effects may be attributed to the pharmacologic action of the

Table 1
Methodology and Results of the Ketamine Randomized Controlled Trial

- Phase III, double-blind, dose escalation study
- Ketamine given by subcutaneous infusion over five days
- Study population: Advanced cancer patients with chronic uncontrolled pain despite optimized pain management with opioids and adjuvant analgesics as defined by the predefined treatment criteria
- Primary outcome: Reduction in average pain scores by ≥2 points from baseline (measured on an 11-point scale [0–10]), with ≤4 rescue analgesia doses and acceptable toxicity
- Response rates: 27% (25/92) in the placebo arm and 31% (29/93) in the intervention arm, with no significant difference ($P = 0.55$) between the proportion of positive outcomes (risk difference = 0.04, 95% CI: −0.10, 0.18)
- Adverse effects: Those in the treatment arm experienced nearly double the rate of adverse events (incidence rate ratio: 1.95, 95% CI: 1.46, 2.61, $P < 0.001$)