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Commentary: Perioperative Pregabalin and Intraoperative Lidocaine Infusion to Reduce Persistent Neuropathic Pain After Breast Cancer Surgery: A Multicenter, Factorial, Randomized, Controlled Pilot Trial

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As clinical researchers, we are ultimately interested in conducting trials that eventually succeed in positively effecting patients' lives. However, the medical problems we aim to solve are complex and affected by a number of factors involved. Since we aim to understand the isolated effects of an intervention, protocols may aim to control/restrict on many of these variables. While such studies may ultimately be successful in obtaining statistically significant results, it is important to consider the implications of such stringent protocols on limiting generalizability of study findings.

In 2009, Paul J. Karanikolas et al.[1] discussed this idea and proposed a methodological framework when developing randomized controlled trials. They stated that the purpose of a trial should determine researchers' choices regarding the trial's structure and the structure of a trial determines the extent to which a decision maker will find the results useful. The focus of our research program is persistent pain after surgery, and like many other chronic pain conditions, it develops due to multiple etiologic pathways. For instance, there are data to suggest that the development of persistent pain after surgery is influenced by physical processes (i.e., neuronal injury[2]), psychological factors (i.e., preoperative catastrophizing[3]), belief and expectations (i.e., patient coping and expectations about recovery[4]), ethnicity, and perioperative interventions[5]. While it may seem appealing to attempt to control these factors to understand the isolated effects of the intervention under investigation, restricting certain interventions or patients may result in a less generalizable study. Further, a strategy that could help investigators understand areas worth adjusting in a clinical trial is by conducting a pilot/feasibility study.

Our pilot study[6] sought to assess perioperative pregabalin and intravenous lidocaine on the prevention of persistent pain after breast surgery. It was a multicenter 2 × 2 factorial, randomized, placebo-controlled trial of 100 female patients, aged 18-75, undergoing unilateral or bilateral lumpectomy or mastectomy. The main outcome was feasibility of conducting a larger adequately powered randomized trial. Feasibility was assessed using recruitment duration, follow-up rate, and study drug compliance. Secondary outcomes of the pilot trial are the primary outcomes of the larger definitive trial and were outcomes related to efficacy of these interventions in reducing persistent pain. The study successfully demonstrated feasibility and laid the groundwork for a definitive

large, multicenter international trial currently underway (Prevention of persistent pain with LidocAine iNfusions in breast cancer surgery (PLAN) Trial [NCT04874038]).

Our pilot study illustrates the challenges mentioned. It was important to recognize the vast number of factors, both known and unknown, that contribute to the development of chronic post-surgical pain in designing our protocol. This led us to use minimal restrictions and exclusions (i.e., allow for co-interventions, not restrict postoperative pain regimen) and enroll a diverse heterogenous population (i.e., inclusive eligibility criteria). While we aimed to understand whether adjusting a specific component of a patient's care (i.e., intravenous lidocaine in our case) could lead to improved outcomes, we wanted to create a protocol that was generalizable and easily applicable to real-world practice. Conducting a pilot study allowed us to identify barriers to achieving this goal – for example, we learned that many patients stopped their pregabalin after surgery due to side effects. This finding has real-world application, in that, even if we determined pregabalin had an ability to improve persistent pain, if patients could not tolerate taking this medication, it would ultimately not be useful in the clinical setting. Based on this and other data suggesting a lack of effect (including in the pilot), we omitted pregabalin from the definitive trial.

In summary, as clinical researchers we must accept the multitude of factors involved in disease pathogenesis, while simultaneously looking to isolate whether our intervention/exposure could still result in a meaningful effect (i.e., the signal is evident within the noise). When dealing with a complex, multifactorial condition, such as persistent pain after surgery, a practical, inclusive protocol may be favored for the intervention to be generalizable, practical, and implementable in real-world conditions.

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