

Sympathetic Nerve Blocks, Pragmatic Trials, and Responder Analysis

SINCE the American Civil War, clinicians and neuroscientists have been mystified by patterns of persistent pain and cutaneous hypersensitivity after injuries to the limbs that are accompanied by remarkable neurovascular, sudomotor, motor, and trophic changes.¹ These syndromes traditionally were labeled as reflex sympathetic dystrophy or causalgia, according to the absence or presence of identifiable injury to major nerve trunks. The designations reflex sympathetic dystrophy and causalgia were replaced in most part with the terms complex regional pain syndrome (CRPS) types 1 and 2, respectively, by an international consensus group in 1994,² and revised³ to improve diagnostic specificity. The roles of the sympathetic nervous system in initiation or maintenance of this syndrome are matters of controversy, and the revised diagnostic criteria deemphasized the sympathetic nervous system as the primary pathophysiology and specific treatment target. Surgical interruption of sympathetic nervous system activity to treat pain was commonly used in the early and mid-twentieth century.^{4,5} Lumbar and cervicothoracic ganglia sympathetic blockade with local anesthetics have been performed for the diagnosis and management of reflex sympathetic dystrophy or CRPS since the 1940s.^{6,7} Clinicians and researchers have long noted that in some cases, local anesthetic sympathetic or somatic blocks and intravenous infusions of local anesthetics can produce prolonged interruption of pain that far exceeds the duration of known drug actions.^{8–10} Explanations are lacking for this remarkably prolonged interruption of pain by brief pharmacologic interventions.¹¹ In this issue of ANESTHESIOLOGY, van Eijs *et al.* evaluated predictors of pain alleviation in response to a single sympathetic blockade in 49 adults with CRPS in a prospective observational study during the course of stan-



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dard clinical care.¹² Among patients who had no improvement with a structured course of rehabilitative treatment and medical management, pain relief of $\geq 50\%$ occurred for 2–48 h in 5 patients and as long as 7 days in another 10. There were no identifiable predictors for favorable analgesic response, although the presence of allodynia or hypoesthesia was a *negative* predictor of a favorable response.

Despite widespread use of sympathetic blocks in pain clinics, there are very few controlled clinical trials on sympathetic interruption by a range of approaches, including paravertebral local anesthetic injection, intravenous regional administration of a range of drugs, systemic adrenergic receptor antagonists, neurolytic blocks, or surgery. Although a few trials have shown significant differences in some outcome measures between active and control interventions,¹³ systematic reviews have concluded that overall the evidence for therapeutic benefit for temporary or neuroablative sympathetic interruption for CRPS is weak.^{14–16}

In designing clinical trials, there are trade-offs between an emphasis on methodologic rigor for testing mechanistic hypotheses and an emphasis on clinical realism in assessing therapeutic benefit under conditions that reflect everyday clinical practice. Trials that emphasize mechanism have been called “explanatory,” and trials that emphasize benefit under real-world conditions have been called “pragmatic.”¹⁷ Pragmatic trials commonly are used in comparative effectiveness research, often with randomized comparison of subjects to two or more treatment regimens. Our previous study using a small dose comparison of lumbar sympathetic lidocaine to intravenous lidocaine¹⁸ and the Price *et al.*, study¹³ are examples of explanatory trials; the designs were made deliberately different from usual clinical practice to better control for confounding factors and test mechanistic hypotheses.

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The study by Van Eijs *et al.*¹² is a pragmatic single-arm, open-label trial. The method of patient selection and the technique of performing the blocks appear within accepted range of clinical practice at pain clinics in many countries. The fluoroscopic technique and the local anesthetic volumes or doses seem consistent with common practice. Although some patients did not exhibit a skin temperature increase after the injections, all injections appeared technically appropriate in the sense that the needle placements and patterns of contrast spread appeared correct. Remarkably, the presence or absence of a sufficient temperature increase did not predict immediate or longer-term analgesic response.

When an open-label trial concludes that an intervention has clinically meaningful therapeutic benefit, it can be criticized because the benefit may be attributable to factors unrelated to the “specific” effect of the intervention, including placebo effects, inadvertent somatic nerve block, systemic local anesthetic effects, natural history, regression to the mean, and a range of other known or unknown factors.

With the trial by van Eijs *et al.*,¹² we have the converse problem of interpreting a pragmatic open-label trial with an overall *negative* result. Under the real-world conditions, although some subjects appeared to receive substantial and prolonged benefit, approximately as many patients felt worse initially as got better. These disappointing findings do not appear to be attributable to poor patient selection, poor technique of needle placement, inadequate local anesthetic dose or volume, or a nocebo effect attributable to bias of the clinicians or patients against sympathetic blocks.

Does this poor overall response rate mean that *nobody* should ever get sympathetic blocks as part of treatment for CRPS in the future? Probably not. Some patients clearly benefit, but currently we lack predictors of who they are, and we do not understand mechanistically why those patients benefit. The study of which patients do or do not have a response to therapies (and ideally, why) is termed responder analysis.¹⁹ Because of the mediocre effect sizes and frequent side effects of many current therapies for neuropathic pain, responder analysis has become a popular area of study for chronic pain trials.²⁰ The presence or absence of a response by an individual subject could reflect a wide variety of pharmacokinetic factors or pharmacodynamic factors, as well as variability in magnitude and durability of placebo responses.¹³ By comparison, consider the situation cited previously¹⁹ with the use of biomarkers for guiding cancer treatment. In the case of Herceptin® (Genentech, South San Francisco, CA) for the treatment of breast cancer, response rates for patients whose tumors contain the biomarker HEP-2 exceed 90%, whereas response rates for those who lack this marker are less than 10%. Because less than 20% of breast tumors contain HEP-2, without this biomarker, analysis of *average* responses in the larger population would lead to the wrong conclusion that Herceptin is an ineffective treatment for breast cancer. Currently, we lack similar mark-

ers or other predictors of responses to medications and interventions for neuropathic pain.²¹

In the current study, van Eijs *et al.*¹² attempted to perform responder analysis with sympathetic blockade using predictive models that emphasized aspects of the neurologic examination, especially sensory and neurovascular findings. The results of this well-conducted attempt were disappointing in the authors’ inability to predict a positive response based on peripheral neurologic examination. It is plausible that future mechanism-driven studies may identify subgroups of subjects who are more likely to experience response to sympathetic blockade or other injections or interventional procedures, including surgeries.^{22,23} In the interim, a middle course is recommended. The most evidence-based initial treatment of CRPS in children^{24,25} and adults²⁶ is a program of intensive rehabilitation that combines active mobilization, desensitization, psychoeducational interventions about the nonprotective character of the pain and overcoming pain-related fear of movement, and a range of cognitive-behavioral interventions. For selected patients who fail to have a response to conservative management, sympathetic blockade *sometimes* helps, but at this time we cannot predict which patients will benefit. Sympathetic blocks should not be used in isolation from rehabilitative therapies and should not be performed repeatedly in the absence of clear and prolonged benefit for the individual patient. In our pediatric chronic pain practice, we often see children with CRPS referred from outside clinics who have undergone an absurd number of sympathetic blocks, without any evidence of short-term or prolonged benefit. Our adult colleagues often report similar practices. In our view, performing repeated blocks without prolonged benefit fits Einstein’s definition of insanity; this practice should be strongly criticized.²⁷

The study by van Eijs *et al.*¹² is useful because it highlights both the mediocre average response rate and unexplained variability in responses to sympathetic blockades in a real-world setting and because it prompts us to look beyond features of the routine sensory, neurovascular, and sudomotor examination in understanding interpatient differences in underlying mechanisms and treatment responsiveness in CRPS.

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