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Diabetes Mellitus and Subclinical Neuropathy

A Call for New Paths in Peripheral Nerve Block Research

PERIPHERAL nerve blocks have become a popular anesthetic option in the perioperative management of patients with diabetes mellitus (types 1 and 2) because blocks provide better postoperative analgesia than does general anesthesia, while avoiding the cardiopulmonary and insulin-resistance effects of general anesthesia. Despite widespread clinical application of peripheral nerve blocks, important limits persist in our knowledge regarding their use in these patients. First, whether local anesthetics themselves are more toxic to peripheral nerves in diabetic and other preneuropathic patients is unknown, although this has been suggested by a recent report of sensorimotor nerve damage for patients with previously undiagnosed polyneuropathy.[1] Second, we do not know whether the dose of local anesthetic for effective peripheral nerve block differs in the presence of diabetes mellitus. Third, a recent report suggests that standard (nerve stimulator) approaches to localizing nerves for injection exhibit reduced effectiveness in diabetic patients.[2]

In this issue of ANESTHESIOLOGY, Rigaud *et al.*[3] take an essential step toward better understanding of the suggested problem related to needle localization using nerve stimulators in the presence of diabetes mellitus. Rigaud *et al.* first show that in normal dogs, nerve stimulation with electrical current levels in the range of 0.33–1.0 mA results in needle placement sufficiently close to the sciatic nerve in 23 of 24 insertions, with unwanted epineural penetration occurring in 1 of these nerve trials. Of note, the lower threshold for electrical perineural stimulation (*i.e.*, 0.50 mA) did not result in distinguishably better needle positioning. The authors then demonstrate that—in the presence of hyperglycemia induced by streptozotocin and alloxan—low-threshold (0.5 mA) stimulation in the hyperglycemic animals uniformly resulted in intraneural injections. The hyperglycemic animals were unfortunately not tested with high-threshold (*i.e.*, 1.0 mA or higher) electrical current. The application of the study findings directly to diabetic patients, however, is problematic because of the uncertainty of relevance of acute changes in streptozotocin hyperglycemia in animals to long-standing diabetes mellitus in people. Nonetheless, these preliminary observations provide the impetus for future research into the safety of nerve stimulation to guide needle placement for peripheral nerve blocks in patients with diabetes mellitus.

Follow-up studies will need to address a number of important questions regarding the implications of hyperglycemia and diabetes mellitus for the utility, conduct, and safety of local anesthetics in peripheral nerve blocks. Well-designed studies in this area would likely be considered highly significant for funding by the Foundation for Anesthesia Education and Research and the American Society for Regional Anesthesia and Pain Medicine. A central problem is the use of animal models to emulate the clinical conditions of human diabetes mellitus. There is currently no perfect research model for diabetes mellitus, let alone diabetic neuropathy. Perhaps the closest diabetes mellitus model to the human condition is the naturally occurring diabetes mellitus that develops in rhesus monkeys fed an *ad libitum* diet.[4] These primates develop type 2 diabetes mellitus after several years of overfeeding; however, the expenses associated with this model system make it impractical for most research questions. One interesting recently reported type 2 diabetic rat strain is the Zucker Diabetic Fatty rat,[5] and an example of a useful type 1 diabetic mouse model involves autoimmunity of the nonobese diabetic, severe combined immunodeficient mouse to a glutamic acid decarboxylase peptide.[6] Generally, these small animal models have been derived by selective breeding. Although these strains are valuable for study, they also have particular characteristics that may or may not pertain to desired abnormalities in glucose metabolism. Recently, mouse models for obesity and type 2 diabetes mellitus have been reviewed[7]; these models involve genetic manipulation to create transgenic mice with selective disruption of various genes related to insulin signal transduction. For example, mice with complete loss of insulin receptors die shortly after birth, and selective knockout approaches have been used for understanding the role of the insulin receptor in various organs. However, whether any such mouse models develop peripheral neuropathy is unknown.

Streptozotocin-induced hyperglycemia is rapid and has the advantage that studies can be performed with treated and untreated animals examined in parallel. This approach has been used in a wide range of species (*e.g.*, rat, pig, dog). At higher doses, streptozotocin is associ-

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ated with damage to liver and kidneys,[8] yet streptozotocin-induced diabetes models[9] are still in widespread use, despite limitations when using behavioral study methods (*e.g.*, nociceptive testing) due to end organ damage. Most pertinently, however, streptozotocin models are known to develop peripheral neuropathy. The study of the potential for nerve damage in hyperglycemic dogs reported by Rigaud *et al.*[3] in this issue is one example of the usefulness of the streptozotocin model.

The next questions to be addressed have immediate clinical relevance. First is whether the use of ultrasound for needle localization is equally (or more) effective when compared with electrical stimulation at higher thresholds, as one may suspect based on the case report by Sites *et al.*[2] One can now assume thousands of similar cases per day that are not reported in the literature, given the extent of the obesity–diabetes mellitus (*i.e.*, type 2) epidemic and the increasing popularity of ultrasound-guided neurolocation. Second, is the use of local anesthetics inherently safe in hyperglycemia and diabetes mellitus whether or not the epineurium is penetrated? Concerns regarding perineural local anesthetic toxicity are not new. In 1992, an important bench science report by Kalichmann and Calcutt[10] landed on the pages of ANESTHESIOLOGY. This report concluded that in rats, the traditional local anesthetics procaine and lidocaine were highly toxic (based on light microscopy) to the sciatic nerve in animals that were hyperglycemic after exposure to streptozotocin.[10] Given the prevalence and increasing incidence of diabetes mellitus, it is surprising that no one to date has followed up on the 1992 toxicity study[10] with an appropriate dose–response evaluation of any local anesthetics for neuropathic conditions such as sustained hyperglycemia or diabetes mellitus. Such studies should have been considered a research priority based on this 1992 report and are therefore long overdue.

If local anesthetics are indeed toxic in the setting of diabetes mellitus at doses that are considered safe in healthy patients, another potential avenue for basic research would involve the coadministration of perineural adjuvants, which may include one or more of the following: clonidine, dexmedetomidine, buprenorphine, midazolam, tramadol, ketamine, ziconotide, and etanercept, but probably not dexamethasone. If such multimodal perineural adjuvants reduce local anesthetic toxicity and/or reduce the required local anesthetic dose in neuropathic (and preneuropathic) patients, a potentially important public health advance would be possible. In the meantime, given the increasing incidence, prevalence, and associated neuropathic risks of diabetes mellitus, studies are urgently needed to determine whether high-threshold electrical current will help to avoid intraneural injection in the diabetic nerve. Once this is known, we will have a better perspective as to whether perineural imaging technologies[2] with or without electrical stimulation would be a logical way to partially protect patients with diabetes mellitus from unintentional nerve injury.

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