Botulinum toxin efficacy for the treatment of pain

There have been many reports in the literature on the treatment of headache following the first published observation of successful myofascial pain and headache treatment using botulinum neurotoxin [1]. This was followed by other open label and case series of headache benefit with botulinum neurotoxin [2-4]. One widely accepted premise within evidence-based medicine, among others, supports the idea that well-designed level I studies of sufficient power are needed to best clarify issues of efficacy [5,6]. However, such large studies are very expensive. Three interesting studies have recently been reported. One open label study of 61 patients found that duration of migraine illness in years was a predictor of botulinum toxin treatment response [7]. A randomized, double-blind, placebo-controlled trial involving 355 patients given botulinum toxin type A for the treatment of chronic daily headache showed a statistically significant number of subjects experiencing a 50% or greater decrease in headache frequency [8]. Another randomized, double-blind, placebo-controlled trial looking at a subgroup of the same 355 patients studied by Mathew et al found a statistically significant difference and improvement in baseline headache frequency and severity between patients not on any prophylactic medications receiving botulinum toxin treatment and placebo treated groups [9].

But why publish another case report, such as the one in this issue of the Journal of Clinical Anesthesia entitled, "Peri-orbital Pain Associated with Spasms that Responded to Botulinum Toxin Treatment and Microvascular Decompression Surgery: A Case Report?"[10]. A thoughtful argument has been made that until more definitive studies on efficacy emerge, there should be a moratorium on publication of open-label studies and case series involving botulinum toxin for the treatment of headache pain [11].

However, while we wait for more definitive data on botulinum toxin efficacy for the treatment of headache pain to soon emerge, the case report by Iida [10] serves as a useful and timely reminder of the many controversies surrounding the off-label use and publications of botulinum toxin for pain. One of the earliest accepted observations of head and neck pain reduction was consistently observed and reported with the application of botulinum toxin in the treatment of cervical dystonia [12]. Since then, many positive, equivocal, and negative reports have been published regarding a variety of pain disorders, sometimes in conflict with one another.

The elements of controversy are complex and include conflicting and contradictory methods, techniques, and results. Perhaps there are clues that could explain the apparent disparities among the positive, neutral, and negative reports emerging. The differing results between studies could relate to variations regarding mechanisms of pain, mechanisms of treatment, methods of treatment, and the existence of subpopulations and patient selection criteria, which could influence the degree of efficacy or lack of efficacy. Comparisons of reports and the ability to make definitive conclusions on efficacy are hampered by these factors. Such factors include case reports with differing presentations, bias, and open-label use of botulinum toxin reporting benefit; blinded and double-blinded randomized controlled trials indicating either benefit or lack of benefit; the low power of studies; and differences among reports regarding preparations, methods, and injection techniques of botulinum toxin. Uncertainty as to the mechanisms for particular pain disorders, the possible direct and indirect mechanisms of action of botulinum toxin, in addition to the well-known blockade of acetylcholine release at the presynaptic neuromuscular junction, the possible contribution toward efficacy from other coexisting therapies when present, and placebo and other possible physiological effects all add to confusion and questions about prior published reports.

Many reports to date have suggested evidence for headache pain benefit from botulinum toxin when compared with other pharmaceuticals in the areas of cost, health care facility use, prolonged improvement, minimal side effect profile, prolonged pain benefit before and after clinical muscle effects, and pain refractory to other therapies [5]. Neutral and negative results also have been published [11]. A number of reviews and reports, including a randomized, double-blind, placebo-controlled study as well as a report of
efficacy [13,14], have shown minimal or no efficacy of botulinum toxin for the treatment of migraine headaches. Similar conflicting results between efficacy and lack of efficacy for the treatment of tension headaches and chronic daily headaches have been reported [15-19]. Two interesting and opposing reviews provide additional insight into the status of the current literature [5,11]. Comparing negative, neutral, and positive results among seemingly similar populations and diagnoses suggests other complexities and confounding factors. Stating the obvious, although well-designed level I studies are desired—and needed—the western scientific gold standard may not be applied so easily regarding pain and botulinum toxin efficacy.

Furthermore, there may be problems regarding selection criteria, subpopulations, techniques, and known and unknown physiological mechanisms. Basic and clinical scientific understanding of the development, perpetuation, nervous system changes and adaptations, genetic and gene associations, interaction and communication between the peripheral central nervous systems, and treatment of chronic painful states has had a focus shift from symptom control to the determination of mechanisms [20]. This recognition acknowledges the inadequacies of developing effective treatments for pain based solely on diagnosis. A diagnosis does not necessarily determine the mechanism or relative weight of mechanisms of associated pain states [21,22].

Recent research has demonstrated a relationship between botulinum toxin and regulation of calcitonin gene-related peptide secretion from cultured rat trigeminal ganglia neurons. The data demonstrated a decrease in the amount of calcitonin gene-related peptide released from the cultured rat trigeminal neurons [23]. The finding could have implications in the treatment of migraine, trigeminal neuralgia, and other pain disorders; however, the authors caution against an automatic extension to human beings from the rat model. Recent work has linked inflammation, the immune system, and activation of glial cells as factors in the development, perpetuation, and possible focus of treatment of chronic pain states [24]. Glial proinflammatory cytokines appear to mediate exaggerated pain states, one amplification point occurring at the level of the activated glia in the spinal cord [25]. Perhaps the varying interplay of peripheral and central activation of inflammatory, proinflammatory, and excitatory phenomena may explain the varying results of botulinum toxin application among subgroups of patients within clinical diagnostic categories, and patient selection criteria may be a factor in determining efficacy.

However, even with so many unknown factors implied in the chronic pain state, it is still possible to draw reasonable conclusions about specific therapeutic efficacy. An example is the recently Food and Drug Administration–approved indication for the management of diabetic peripheral neuropathic pain, duloxetine HCl. There are many possible theories to explain diabetic peripheral neuropathic pain, including central sensitization, hyperexcitability, and decreased inhibition. One accepted pain inhibition theory is the pain perception–modulating role in the brain, spinal cord, and peripheral nervous systems of endogenous serotonin and norepinephrine [26,27]. Targeting both of these endogenous neurochemical modulators may lead to central pain inhibition. The dosage and efficacy of duloxetine HCl over placebo were demonstrated in the treatment of diabetic neuropathic pain [1]. The pain inhibitory effect of duloxetine HCl is thought to be centrally mediated through potentiation of serotonin and norepinephrine activity in the descending pain pathways in the central nervous system.

Regarding the efficacy of botulinum toxin therapy for the treatment of pain and headache, we should wait for the results of randomized controlled trials with sufficient patient numbers and power to confirm the many earlier observations of therapeutic benefit reported in the literature. Given some of the positive and negative contradicting results in the literature thus far, the designing of future studies and interpretation of data may be challenging.

Efficacy differences found among subpopulations through patient selection criteria within pain disorders may also assist in understanding the mechanisms contributing to pain states as well as the possible therapeutic mechanisms and bioeffects of botulinum toxin.

Martin A. Acquadro MD, DMD, FACP, FACP M (Assistant Professor, Anesthesiology) Harvard Medical School Associate Anesthetist and Director of Cancer Pain Department of Anesthesia and Critical Care Massachusetts General Hospital 13 Parkman Street, #333 Boston, MA 02114, USA E-mail address: macquadro@partners.org

Gary E. Borodic MD (Assistant Professor, Surgeon) Harvard Medical School Boston, MA, USA Department of Ophthalmology Massachusetts Eye and Ear Infirmary Boston, MA 02114, USA

References

