EDITOR'S CHOICE

A Double-Blind Placebo Randomized Controlled Trial of Minocycline to Reduce Pain After Carpal Tunnel and Trigger Finger Release

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Purpose Minocycline is a microglial cell inhibitor and decreases pain behaviors in animal models. Minocycline might represent an intervention for reducing postoperative pain. This trial tested whether perioperative administration of minocycline reduced time to pain resolution (TPR) after standardized hand surgeries with known prolonged pain profiles: carpal tunnel release (CTR) and trigger finger release (TFR).

Methods This double-blinded randomized controlled trial included patients undergoing CTR or TFR under local anesthesia. Before surgery, participants recorded psychological and pain measures. Participants received oral minocycline, 200 mg, or placebo 2 hours prior to procedure, and then 100 mg of minocycline or placebo 2 times a day for 5 days. After surgery, participants were called daily assessing their pain. The primary end point of TPR was when participants had 3 consecutive days of 0 postsurgical pain. Futility analysis and Kaplan-Meier analyses were performed.

Results A total of 131 participants were randomized and 56 placebo and 58 controls were analyzed. Median TPR for CTR was 3 weeks, with 15% having pain more than 6 weeks. Median TPR for TFR was 2 weeks with 18% having pain more than 6 weeks. The overall median TPR for the placebo group was 2 weeks (10% pain $>$ 6 weeks) versus 2.5 weeks (17% pain $>$ 6 weeks) for the minocycline group. Futility analysis found that the likelihood of a true underlying clinically meaningful reduction in TPR owing to minocycline was only 3.5%. Survival analysis found minocycline did not reduce TPR. However, subgroup analysis of those with elevated posttraumatic distress scores found the minocycline group had longer TPR.

Conclusions Oral administration of minocycline did not reduce TPR after minor hand surgery. There was evidence that minocycline might increase length of pain in those with increased posttraumatic stress disorder symptoms. *(J Hand Surg Am. 2017;42(3):166–174.*

Type of study/level of evidence Therapeutic I.

Key words Minocycline, carpal tunnel release, postoperative pain, glial cell inhibitor.

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CHRONIC POSTSURGICAL PAIN (CPSP) is a major problem occurring in up to 10% to 50% of patients following any surgery including that performed in the hand.[1–3] There is a need for effective treatments that improve the rate of pain resolution and prevent the development of CPSP. Over 10 years ago, studies showed that spinal microglial cells release pronociceptive chemokines following peripheral nerve injury and this activation is a necessary step for the development of chronic neuropathic pain.[4–9] Others have suggested that dysregulated spinal microglial mitogen-activated protein kinase phosphorylation in response to surgical injury drives the transition from acute incisional pain to persistent pain.[10] These findings led to an interest in blocking the microglial cells as a potential intervention to reduce CPSP.

Minocycline is a strong microglial cell inhibitor and also has long been used as an antibiotic with a strong safety profile.[11] In rat nerve injury models, inhibition of microglial cells with minocycline decreased the transition to chronic pain.[12–14] In 2013, Martinez et al[15] reported the first human test of minocycline to prevent persistent pain following lumbar discectomy. They reported that perioperative minocycline failed to reduce pain intensity at the single time point of 3 months following lumbar discectomy in 100 patients randomized to either placebo or 8 days of perioperative minocycline (100 mg twice daily).

Carpal tunnel release (CTR) and trigger finger release (TFR) present an excellent model for studying chronic surgical pain. Both surgeries are very standardized with little technical variation and, as done in this study, can be performed using local anesthesia alone. Carpal tunnel release and TFR also have a well-described persistent pain rate of at least 20% of patients.[16–18] This persistent pain rate is similar to that of other surgical procedures such as inguinal hernia repair, mastectomy, and thoracotomy.[3]

This study tested whether perioperative minocycline administration reduced the time to pain resolution (TPR) following open CTR and TFR. Our primary hypothesis was that administering minocycline around the time of surgery would decrease the TPR compared with placebo. We secondarily hypothesized that perioperative minocycline would reduce the proportion of patients who have persistent pain and improve scores on the Quick Disabilities of the Arm, Shoulder, and Hand measure (*Quick*DASH) 3 months after CTR and TFR. Third, we hypothesized that patients with posttraumatic distress syndrome (PTSD) symptoms (often reported to be at greatest risk of chronic pain) would receive the most benefit from minocycline. Animal studies have found that prestressed animals had decreased pain duration after painful interventions.[19]

METHODS

This pilot study was a randomized placebo-controlled double-blinded trial. Our institutional review board approved the trial and written informed consent was obtained from all subjects.

Participants were adult veterans undergoing surgery at the VA Palo Alto Health Care System hospital. Intake data were collected in person and by telephone for the follow-up measures. Inclusion criteria were subjects diagnosed with carpal tunnel syndrome or trigger finger and undergoing release in the minor procedure suite.

Exclusion criteria were primarily based upon minocycline's side effect profile. Because dizziness is a common side effect of treatment with minocycline, frail patients deemed to be a fall risk were excluded. Although liver dysfunction and nephritis are rare side effects of minocycline use, there is no known test to see who will develop these hypersensitivities. To minimize risk of further kidney or liver damage, patients with elevated liver function (3 times normal) and creatinine (2 times normal) values were excluded. Patients with a history of prior complex regional pain syndrome are at increased risk of developing recurrent complex regional pain syndrome in another extremity following surgery so these patients were excluded. Other exclusion criteria also related to rare potential interactions with minocycline and included platelet count less than 75 000/mL, pregnancy, history of lupus, history of amyotrophic lateral sclerosis, inability to understand the survey, or tetracycline allergy. We did not exclude preoperative analgesic use because there is a high prevalence of chronic pain and analgesia use in this population.[20]

Participants received minocycline, 200 mg, or placebo 2 hours prior to procedure, and then minocycline, 100 mg 2 times a day for 5 days or placebo given at the same intervals. This dose of minocycline is the U.S. Food and Drug Administration recommended dose for oral minocycline to treat skin infections. Minocycline was prepared by overencapsulating a 100-mg minocycline capsule. The placebo was identical in appearance and consisted of the same large capsule filled with lactose and then overencapsulated. The preoperative dose was directly observed. Subsequent doses were taken at home unobserved, and study medication compliance was assessed each day by phone.