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Axillary Block–Induced Chemical Sympathectomy in the Setting of Digital Ischemia

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Background: Digital ischemia is associated with several rheumatologic disorders and is often difficult to treat. Symptoms and sequelae can include pain, disability, need for amputation, and poor quality of life.

Methods: Patients diagnosed with digital ischemia were referred for an ultrasound-guided axillary nerve block using liposomal bupivacaine (Exparel, Pacira Pharmaceuticals). The primary outcome measure was radial and ulnar artery diameter preprocedure and postprocedure. Doppler waveform analyses were performed to measure arterial diameter and blood flow velocity. The QuickDASH questionnaire was administered to evaluate upper extremity function and perceived disability.

Results: Mean radial and ulnar artery diameters increased from 0.19 cm and 0.16 cm to 0.23 cm and 0.20 cm, respectively, 1 hour postprocedure. Concomitant increases in blood flow velocities and hand temperature and lower pain scores were also noted. Although pain generally returned to baseline after 1 week, QuickDASH symptom/disability scores improved at 30 days, and 2 patients' ischemic symptoms resolved spontaneously during the study period in the absence of other interventions.

Conclusion: Data regarding chemical sympathectomy using regional anesthesia are limited at this time. Our experience suggests a potential role in the treatment and evaluation of digital ischemia. Patients with digital ischemia from rheumatologic conditions appeared to have a greater benefit from a chemical sympathectomy than patients whose conditions had an atherosclerotic or anatomic etiology. Even when the vasodilatory effects are transient, such an intervention may be useful when a more permanent option such as surgical sympathectomy is being considered. Liposomal bupivacaine is only approved for surgical infiltration at this time.

Keywords: *Anesthesia–conduction, bupivacaine, CREST syndrome, nerve block, Raynaud disease, scleroderma–systemic, sympathectomy*

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INTRODUCTION

Secondary Raynaud phenomenon (RP) may lead to digital ischemia in the setting of connective tissue disease, with progressive systemic sclerosis or scleroderma being the most common rheumatologic diagnosis.[1-4] Although other etiologies of digital ischemia exist, such as trauma, severe peripheral vascular disease, and thrombotic or vasoocclusive disorders, we limit the scope of this discussion primarily to digital ischemia secondary to RP.

Digital ischemia secondary to RP is often difficult to treat and results in poor quality of life. Conservative therapy and medical management, including vasodilating agents and calcium channel blockers, are minimally effective in the treatment of RP.[5,6] A paucity of evidence-based data is available on invasive techniques such as stellate ganglion blocks, and instances of block failure, limited duration of effect, and the need for multiple repeat procedures are not uncommon.[3] Alternatives such as botulinum toxin injection, spinal cord stimulation, and surgical sympathectomy may be undesirable first-line measures because of their associated cost or invasive nature.[3] If digital ischemia is inadequately treated, pain, digital ulcers, infection, and gangrene may develop, resulting in disability and the need for amputation.

Regional anesthesia techniques, such as brachial plexus blocks, cause a local anesthetic–induced blockade of sympathetic fibers and have been used to treat digital ischemia from a variety of etiologies.[1-4,7-9] While perineural

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blockade results in the simultaneous benefits of vasodilation and analgesia, data regarding local anesthetic–induced sympathectomy characteristics are limited at this time. Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals) is an encapsulated formulation of bupivacaine designed for slow, continuous release.[10,11] Given the potential for prolonged vasodilation and analgesia, we sought to investigate these properties in patients whose symptoms persisted despite medical management and conservative measures. Liposomal bupivacaine is only approved by the US Food and Drug Administration for wound infiltration; perineural use is considered off-label and should be reserved for investigational use.[10,11]

METHODS

This study was approved by the Ochsner Institutional Review Board and registered on clinicaltrials.gov (identifier NCT02374320) prior to patient enrollment. Risks, benefits, and alternatives were explained to patients prior to obtaining written informed consent.

Patients with digital ischemia unresponsive to medical management were invited to participate in the study. The exclusion criteria were refusal, local anesthetic allergy, and preexisting neurologic deficits of the upper extremity. Our primary outcome measure was radial and ulnar artery diameters before and after the block procedure. Numerical rating scale (NRS) pain scores—ranging from 0 (absence of pain) to 10 (worst pain imaginable)—along with hand temperature, blood flow velocity, presence of a radial pulse, and block onset characteristics were secondary outcomes. The QuickDASH questionnaire (used with permission from the Institute for Work & Health), an abbreviated version of the Disability of the Arm, Shoulder, and Hand (DASH) outcome measure, was administered to every patient at baseline and weekly for 4 weeks. The QuickDASH is a valid and reliable instrument for measuring physical function and symptoms in patients with disorders of the upper limbs in a wide variety of patient populations.[12,13] The QuickDASH yields a disability/symptom score that ranges from 0-100, with 0 indicating no perceived disability and 100 indicating poor function. Patients with bilateral ischemic digits were eligible to enroll in the study a second time to treat the contralateral hand 30 days after the initial block procedure.

Radial and ulnar artery diameter and blood flow velocities were measured at baseline and 60 min after the nerve block with a Doppler ultrasound system and a 9-3 MHz linear transducer (Philips iE33 L9-3 transducer). Velocities were measured using pulse-wave Doppler, and a marker was used to indicate the site of initial transducer placement to ensure that subsequent scans were performed at the same location. An adhesive temperature probe was placed on the ischemic hand prior to the nerve block. NRS pain scores, hand temperature, capillary refill time, and the presence of a radial pulse before and after the block were recorded.

All blocks were performed by a single staff anesthesiologist (J.R.S.) with expertise in ultrasound-guided regional anesthesia. The axillary block site was selected (instead of other potential sites such as the stellate ganglion) because of the ease of ultrasonographic visualization and absence of pulmonary or respiratory complications. The superficial and compressible nature of the site poses minimal bleeding risks, even in anticoagulated patients. Furthermore, because of the complexity of the sympathetic outflow in the cervicothoracic region, an axillary block is more likely to result in a more complete sympathetic block than a stellate ganglion block.[1,2] After administration of intravenous sedation and skin preparation with chlorhexidine gluconate/alcohol (Chloraprep), an S-Nerve Ultrasound System L25× 13-6 MHz probe (SonoSite) was placed in the axillary crease, and the median, radial, ulnar, and musculocutaneous nerves were identified. A 22-gauge, 5-cm Stimuplex needle (B. Braun Medical, Inc.) was inserted using an in-plane technique, and 5 mL of 1.3% liposomal bupivacaine was injected around each nerve for a total of 20 mL.

After the block procedure, a research assistant assessed block onset characteristics in the various nerve distributions of the arm via pinprick at 10-, 20-, 30-, and 60-min intervals. The onset of motor block was assessed using thumb opposition (median nerve), thumb adduction (ulnar nerve), thumb abduction (radial nerve), and flexion of the elbow (musculocutaneous nerve). A score of 2 was recorded if the patient had baseline strength or sensation to pinprick, while scores of 1 and 0 indicated decreased and absent strength or sensation, respectively.

Statistical Analysis

Categorical variables are presented as counts and percentages, with differences between the groups assessed using the chi-square test or Fisher exact test. The Shapiro-Wilk and Kolmogorov-Smirnov tests were performed to determine normality of data. Continuous variables with nonnormal distributions were assessed by the Wilcoxon rank-sum test. We considered P values <0.05 statistically significant.

RESULTS

Thirteen patients were enrolled in the study, and 1 returned for a second block on the contralateral hand. One patient was in the intensive care unit with severe vasopressor-induced ischemic injury in all 4 extremities and was withdrawn from the study because of prolonged mechanical ventilation and amputations of all 4 extremities. Only the block characteristics for this patient were included in the analysis.

The majority of patients (78.6%) were female, and the mean age was 50.7 years. Block characteristics are presented in Table 1. One hour after the procedure, the mean radial and ulnar artery diameters increased from 0.19 cm and 0.16 cm to 0.23 cm and 0.20 cm, respectively. We found no difference in the ability to palpate a radial artery pulse before or after the block. Prior to the block, 57.1% of patients had impaired capillary refill (>2 seconds) compared to 23.1% postblock. A statistically significant increase in hand temperature was also noted ($P<0.01$). Percentage increases of 21%, 132%, and 79% were identified in radial artery diameter, peak systolic velocity, and mean diastolic velocity, along with concomitant

Table 1. Block Characteristics

Variable	Preblock	Postblock	*P* Value
Mean NRS pain score (0-10)	6.0	0.4	<0.01
Mean 30-day NRS pain score (0-10)		5.2	NS
Patients with radial artery pulse present, %	78.6	84.6	NS
Patients with capillary refill >2 seconds, %	57.1	23.1	0.03
Mean hand temperature, °C	26.3	29.6	<0.01
Mean radial artery diameter, cm	0.19	0.23	<0.01
Mean radial peak systolic velocity, cm/s	47.4	109.9	<0.01
Mean radial mean diastolic velocity, cm/s	12.9	23.1	NS
Mean ulnar artery diameter, cm	0.16	0.20	<0.01
Mean ulnar peak systolic velocity, cm/s	48.5	80.5	<0.01
Mean ulnar mean diastolic velocity, cm/s	9.6	21.3	<0.01

NRS, numerical rating scale; NS, not significant.

percentage increases of 25%, 66%, and 122% in ulnar artery diameter, peak systolic velocity, and mean diastolic velocity, respectively. Significant differences were identified in the mean NRS scores preblock and postblock, although the 30-day mean NRS score was similar to the mean baseline score. Figure 1 shows a Doppler study from one of our patients. These waveform findings were not uncommon and were observed in most patients. Hand color and appearance were generally improved after the block procedure compared to baseline (Figure 2). The onset and progression of sensory and motor block are illustrated in Figure 3.

The QuickDASH questionnaire was administered at baseline and weekly for 1 month. A statistically significant improvement in QuickDASH symptom/disability scores was identified at 1 month compared to baseline (P=0.03, Table 2).

Medical records for every patient were reviewed at least 6 months after enrollment, and patients were contacted via telephone (as needed) to determine the status of their digital ischemic symptoms as well as their overall health and functional status (Table 3). Interestingly, 2 patients' ischemic issues (patients 3 and 5) have resolved to date with the block alone in the absence of changes in medical management or other interventions. A third patient (patient 9) had resolution of her ischemic symptoms shortly after her block procedure; she also had changes in her medical management instituted in proximity to the study intervention, so it is unclear if the improvement resulted from the block, changes in medication, or a combination thereof. The other 10 patients had persistent ischemic symptoms at the conclusion of the study period. For 8 of these 10 patients, we recommended referral to a hand surgeon for a distal peripheral sympathectomy procedure. Three patients (patients 1, 2, and 13) were deemed surgical candidates and underwent surgery on the affected hand (1 of the 3 underwent a partial finger amputation because of the onset of gangrene prior to the surgical sympathectomy), and the remaining 5 (patients 4, 8, 10, 11, and 12) declined the referral or surgery, were deemed poor surgical candidates, or received other therapies (continued medical management, hyperbaric oxygen therapy, or referral to a pain specialist). At the time of this writing, 3 patients had died. We observed no study-related adverse events or complications.

DISCUSSION

We evaluated the vasodilatory and analgesic effects of a perineural injection in patients with digital ischemia. Based

Table 2. QuickDASH Symptom/Disability Scores[a]

Patient Number[b,c]	Baseline QuickDASH Symptom/ Disability Score	30-Day QuickDASH Symptom/ Disability Score
1	59.1	54.6
2	68.2	68.2
3	20.5	11.4
4	84.1	100
5	88.7	45.5
6	100	100
7	59.1	47.7
8	84.1	72.7
10	81.8	11.4
11	79.5	20.5
12	88.6	68.2
13	59.1	45.5
Mean QuickDASH symptom/disability score (all patients)	72.7	53.8[d]

[a]QuickDASH symptom/disability scores range from 0-100; a score of 0 indicates absence of disability and excellent function, whereas a score of 100 suggests a high degree of disability and poor function.
[b]QuickDASH results were missing for patient 9.
[c]Patient 14 was excluded from analysis because of prolonged mechanical ventilation and subsequent upper extremity amputation.
[d]Statistically significant difference (P=0.03).

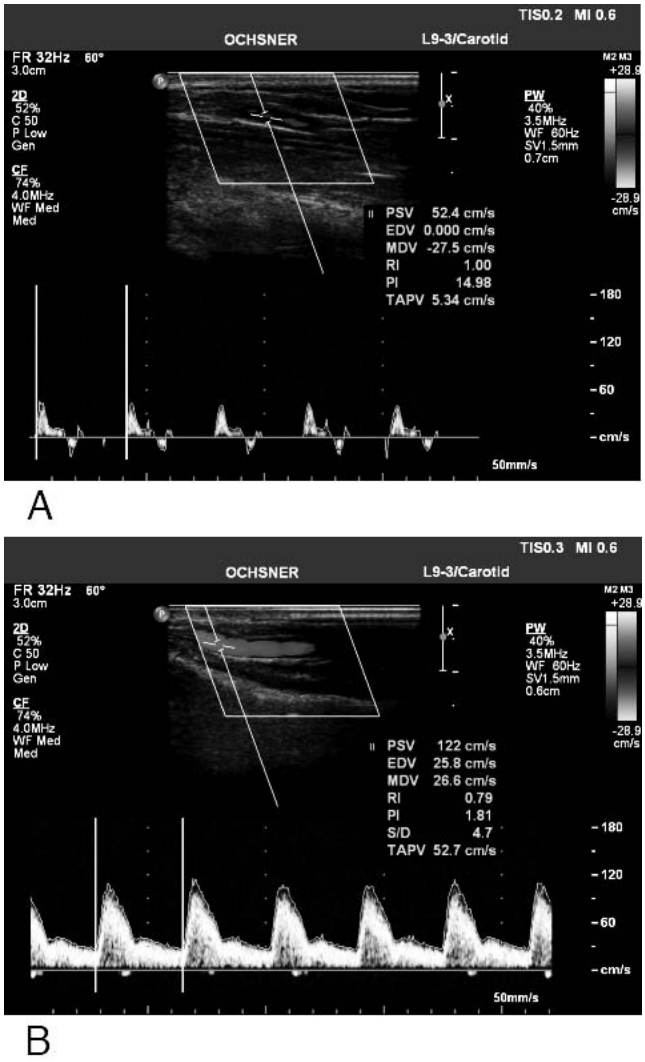

Figure 1. Doppler waveform analysis of a patient's radial artery. The skin was marked to identify the site of initial transducer placement to ensure that the subsequent measurements were recorded at the same location. A poor waveform appearance was observed at baseline (A). Increases in vessel size, peak systolic velocity, and mean diastolic velocity as well as improvement in waveform appearance were noted 1 hour after the block procedure (B).

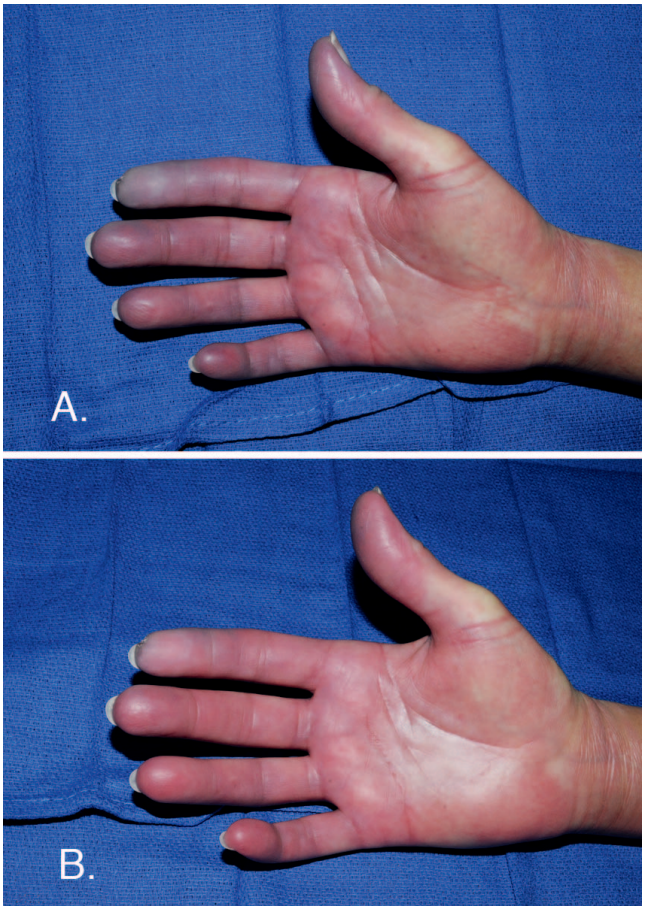

Figure 2. Photographs of a patient's hand prior to (A) and 1 hour after (B) the study intervention. Cyanosis of all digits and a small digital ulcer on the second digit are visible prior to the block. (Color photographs are available online at www.ochsnerjournal.org/toc/ochs/16/4 in the Original Research section.)

on Doppler waveform analysis and improvements in capillary refill and hand appearance, we can conclude that a perineural injection of liposomal bupivacaine results in a temporary chemical sympathectomy. The durations of sympathectomy, vasodilation, and analgesia are unknown but may be longer than the anticipated duration of liposomal bupivacaine.[7,10,11]

Multiple clinically and statistically significant changes were noted immediately after the block procedure. NRS pain scores decreased dramatically, with 12 of 13 patients reporting resolution (0/10) of pain. The increases in hand temperature as well as in nearly all hemodynamic parameters combined with the improvements in capillary refill time indicate improvements in microcirculation and macrocirculation. In summary, these changes are consistent with a local anesthetic–induced chemical sympathectomy and vasodilation.

Liposomal bupivacaine may be beneficial in the treatment and evaluation of digital ischemia. Patients who respond favorably based on Doppler waveform studies and clinical evaluation may warrant a referral to a hand surgeon for a distal peripheral sympathectomy procedure. While it is unknown if a positive response to a peripheral nerve block predicts surgical outcomes, performance of a peripheral nerve block prior to surgery is a common practice and has been advocated by multiple investigators and experts in the field.[1-4,14-16] An added potential benefit of local anesthetic–induced sympathectomy is that it may aid in healing of ulcers prior to surgery.[1,15] Furthermore, 2 patients had resolution of their ischemic symptoms during the study period despite previous failure of conservative measures and medical management.

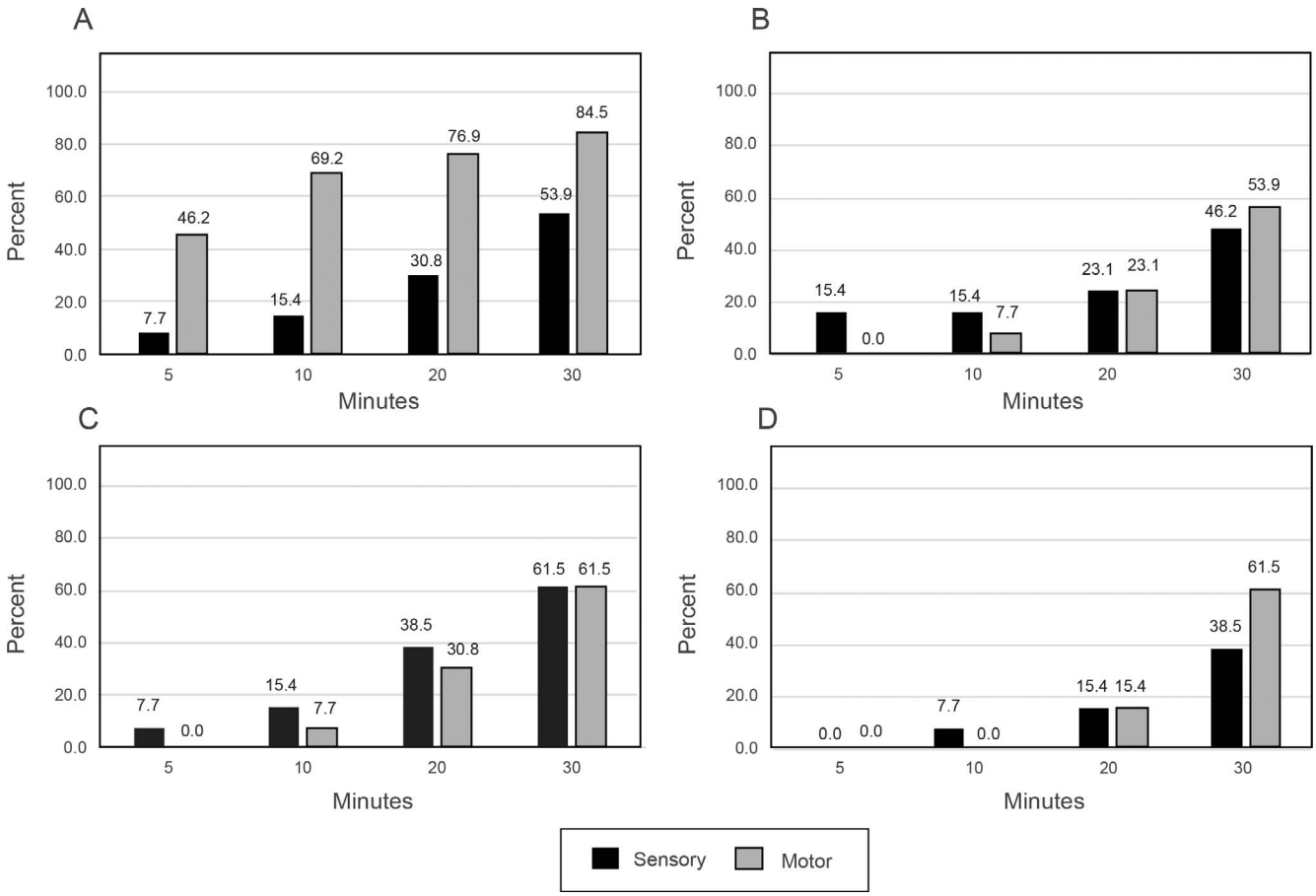

Figure 3. Progression of sensory and motor block. The graphs represent the musculocutaneous nerve (A), median nerve (B), radial nerve (C), and ulnar nerve (D). Data are presented as percentage of patients with absence of sensation or motor function in the respective nerve distribution at the specified times after the block procedure.

While a formal discussion of distal peripheral sympathectomy surgery is beyond the scope of this paper, this technique should be considered an early treatment option for patients suffering from digital ischemia. However, many providers view surgical sympathectomy as a last resort in the management of digital ischemia. As the disease progresses, patients are more likely to develop ulcers, infection, and gangrene in addition to near-constant pain and poor quality of life.[17] Momeni et al reported that patients suffered ischemic pain for an average of 9.6 years and that digital ulcers were present for an average of 10.1 months prior to referral for surgery.[17] We propose that a peripheral nerve block be part of the initial evaluation for patients with digital ischemia unresponsive to medical management or conservative measures. Patients who respond favorably in terms of Doppler studies and clinical evaluation should subsequently be referred to a hand specialist for possible surgical sympathectomy early in the course of the disease—before the onset of digital ulcers, infection, or gangrene.

This investigation has several limitations, the first being the absence of a control or placebo group. Patients were referred to participate in the study because their digital ischemia was unresponsive to medical management and conservative measures. We considered exposing patients to the risks (albeit minor) of a sham peripheral nerve block or placebo to be unethical, given the failure of previous therapies and the unremitting nature of ischemic pain. Another limitation of our study is the lack of comparison to alternative therapies such as single-injection brachial plexus blocks with nonliposomal local anesthetics, indwelling perineural catheters, stellate ganglion blockade, botulinum toxin injection, or spinal cord stimulation. Comparing these approaches, which vary in invasiveness and cost, was beyond the scope of the investigation (to evaluate the vasodilatory properties of liposomal bupivacaine) and could be the subject of future investigations. Last, our study was likely underpowered to detect rare adverse events. Further research is warranted to determine the safety and role of liposomal bupivacaine in the treatment of digital ischemia.

Table 3. Patient Outcomes

Patient Number	Etiology of Ischemia	Follow-Up
1	Progressive systemic sclerosis	Underwent distal peripheral sympathectomy surgery. No further ischemic issues.
2	Progressive systemic sclerosis	Underwent distal peripheral sympathectomy surgery. No further ischemic issues. Partial finger amputation because of gangrene.
3	Unknown etiology	Resolved with block. Rare (mild) Raynaud phenomenon with cold weather or stress.
4	Progressive systemic sclerosis	Declined referral for consideration of peripheral sympathectomy surgery. Died 1 year after the block (in-hospital cardiac arrest).
5	Unknown etiology	Resolved with block. No issues.
6	Anatomic; likely vascular stenosis after distal revascularization and interval ligation procedure	Persistent hand pain. Unclear if a neuropathic pain component was present in addition to ischemic symptoms. Died of respiratory failure 5 months after block procedure.
7	Progressive systemic sclerosis	Returned for a second block procedure on the contralateral hand (patient 9).
8	Progressive systemic sclerosis	Persistent hand pain; declined referral for consideration of peripheral sympathectomy surgery. Currently under the care of a pain management specialist.
9	Progressive systemic sclerosis	Ischemic issues under improved control with medical management (instituted during the second study intervention).
10	Systemic lupus erythematosus	Ischemic regions demarcated after the block, and symptoms improved but did not resolve completely. Recommended referral for consideration of peripheral sympathectomy surgery. Left the state and was lost to follow-up.
11	Anatomic; possible vascular steal syndrome	Persistent pain and ischemic issues. Recommended referral for consideration of peripheral sympathectomy surgery but was not deemed an appropriate candidate.
12	Dermatomyositis sine myositis	Referred for consideration of peripheral sympathectomy surgery but was considered a poor surgical candidate because of medical comorbidities. Slight improvement with hyperbaric therapy.
13	Progressive systemic sclerosis	Underwent distal peripheral sympathectomy surgery. No further ischemic issues.
14	Vasopressor-induced ischemic injury	Underwent bilateral upper and lower extremity amputations. Died 60 days later after family elected palliative care.

CONCLUSION

An axillary nerve block with liposomal bupivacaine (Exparel) produces a local anesthetic–induced chemical sympathectomy that results in analgesia and vasodilation in patients with digital ischemia. The effect, however, was generally transient. Patients who respond favorably to a peripheral nerve block should be considered for distal peripheral sympathectomy surgery, preferably early in the course of the disease. Liposomal bupivacaine is only approved for surgical wound infiltration at this time.

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