Topical ketamine-amitriptyline-lidocaine for chronic pruritus: A retrospective study assessing efficacy and tolerability

To the Editor: Topical analgesics have been well studied in the management of neuropathic pain,[1] however, limited data are present on their role in treating pruritus. Although noted improvement was seen with low concentrations of topical ketamine-amitriptyline in the therapy of localized itch,[2] there are no studies to our knowledge examining the combination of topical ketamine-amitriptyline-lidocaine (TKAL) on chronic itch with validated tools. Its proposed mechanism of action is aimed at reducing hypersensitivity of peripheral nerve fibers through blockade of N-methyl-D-aspartate receptor and sodium channels.[3,4] Our study was intended to retrospectively examine the clinical response and tolerability of TKAL in the setting of chronic itch.

Patients who were prescribed TKAL from September 1, 2013, to June 30, 2016, with at least 1 telephone or office follow-up visit at the Department of Dermatology at Temple University Hospital were identified. A primary review of medical charts with supplemental evaluation of pharmacy records from Temple University Hospital and a private compounding pharmacy were performed. The change in numeric rating scale before and after use of TKAL was assessed as were any adverse events. In addition, rates of prescription refills as a measure of patient adherence were documented as TKAL was not covered by most insurance. Statistical analysis was completed using software (SPSS, 16.0, IBM Corp, Armonk, NY). This study was institutional review board approved.

A total of 96 patients (68.8% female) with a mean age of 65 ± 14.4 years were identified. Patients reported a mean duration of itch of 76.7 ± 99.2 months with 38% having failed more than 3 previous treatments. TKAL was prescribed at a standardized concentration of 10% ketamine, 5% amitriptyline, and 5% lidocaine compounded in a lipoderm cream, except for 16 patients who were prescribed the combination with 5% ketamine. Patients were instructed to apply sparingly to areas that were the most severe, limiting to less than 30% of total body surface area up to 3 times daily. The most frequent indications were for neuropathic conditions (29%) and prurigo nodularis (19%). The average numeric rating scale was 8.63 ± 1.62 before and 4.19 ± 2.9 after treatment with an average reduction of 4.61 ± 2.77. Although oral systemic medications were concomitantly prescribed, most commonly gabapentin (46%) and mirtazapine (22%), 63% of patients attributed relief directly to the use of TKAL alone with reduction in numeric rating scale seen in all pruritus subtypes (Table I). Refills were granted as needed and requested on average of 2.41 times (range 0-18) with an average of 43.67 days between refills (range 7-211). Review of a pharmacy-administered telephone survey that assessed medication tolerability and efficacy of 40 patients revealed that 23 patients (58%) had relief to a great extent and 14 (35%) to a moderate extent, experiencing itch relief within 4.18 ± 3.39 minutes on average. Side effects reported by 16 subjects were primarily a mild localized burning sensation (7%) and redness (6%) at the application site (Table II).

Although limited by its retrospective nature and use of concomitantly prescribed systemic oral medications, this study further supports the use of TKAL as an effective single or adjuvant therapy when treating various pruritic conditions. Of note, a case of encephalopathy was recently reported in an elderly patient with eczema after applying TKAL over his entire body.[5] Thus, prospective investigation is necessary to further validate its safety and therapeutic potential, including the extent of body surface application.

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Table I. Change in numeric rating scale with use of topical ketamine-amitriptyline-lidocaine by diagnosis

Diagnosis	No. of patients*	Average NRS before (±SD)	Average NRS after (±SD)	Average Δ NRS (±SD)	*P* value†
Brachioradial pruritus	9	8.44 (±1.01)	3.56 (±2.65)	4.89 (±2.67)	.012
Notalgia paresthetica	3	8.67 (±1.53)	5.17 (±4.25)	3.50 (±3.04)	.180
Neuropathic pruritus NOS‡	16	9.31 (±1.35)	5.23 (±3.75)	4.03 (±3.6)	<.001
Prurigo nodularis	18	9 (±1.65)	3.78 (±1.96)	5.22 (±2.21)	<.001
Atopic dermatitis	12	9.08 (±1.24)	3.63 (±2.33)	5.63 (±2.4)	.003
Chronic pruritus NOS	14	8.57 (±1.79)	4.5 (±3.67)	4.07 (±3.54)	.005
Other§	36	8.44 (±1.76)	3.88 (±2.69)	4.81 (±2.63)	<.001
Total	96	8.63 (±1.62)	4.19 (±2.9)	4.61 (±2.77)	<.001

NOS, Not otherwise specified; *NRS*, numeric rating scale.
*Twelve patients had 2 concomitant diagnoses.
†Wilcoxon signed rank test.
‡Includes small fiber neuropathies, scrotal neuropathic itch, diabetic neuropathic itch, poststroke related pruritus.
§Includes diagnoses of xerosis, fibromyalgia-associated pruritus, advanced aging pruritus, Grover disease, psoriasis, chronic urticaria, rectal pruritus, scalp pruritus, stasis dermatitis, lichen simplex chronicus.

Table II. Reported side effects with use of topical ketamine-amitriptyline-lidocaine

Reported side effect*	No. of patients (%)
Burning	7 (7.3)
Redness	6 (6.3)
Itching	4 (4.2)
Raw/sloughing skin Sensation†	2 (2.1)
Dizziness‡	1 (2.1)
Numbness	1 (1.1)
Total (n)	16 (16.7)

*All reported side effects except for dizziness were localized to the application site only.
†One suspected case of allergic contact dermatitis was diagnosed and patient discontinued therapy.
‡Patient continued with treatment.

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Direct immunofluorescence microscopy of skin biopsy samples preserved in honey

To the Editor: Michel medium (MM) is the preferred medium for transportation of skin biopsy specimens for direct immunofluorescence (DIF). However, it has a limited shelf life and may not always be available to the dermatologist. In this study, we evaluated the utility of honey as a transport medium for skin biopsy samples meant for DIF.

Thirty-six DIF-positive skin biopsy samples were randomly allocated into 3 groups (A, B, and C; 12 biopsy specimens per group). The blocks were immersed in phosphate-buffered saline to remove the optimum cutting temperature (OCT) compound. The biopsy specimens were then placed in contact lens holding boxes and about 3 mL of honey was poured on top of the samples. They were stored at room temperature (27°-34°C) until further use. Samples in batch A were taken out after 5 days (D5), while those in batches B and C were processed after 10 (D10) and 20 days (D20), respectively. Biopsy specimens were washed in phosphate-buffered saline in a rotator at 4°C in a refrigerator for 15 hours and DIF was then carried out. Disease-wise distribution of samples and the results of DIF study are shown in Table I. Tissue-bound immune complexes were preserved for ≤20 days in all biopsy specimens stored in honey except in 1 case of dermatitis herpetiformis, which turned out to be negative at D10. Intensity of staining was comparable with the first DIF test in all except 1 case of pemphigus vulgaris, which showed reduced intensity of staining with immunoglobulin G at D20 (Fig 1).

Honey has been known for its preservative properties since medieval times; it does so by preventing autolysis and putrefaction.[1] It was used to preserve skin grafts in burns patients who required multiple skin grafting.[2,3] In the present study, we found that honey can be used as an alternate transport medium for skin biopsy specimens for DIF. We used commercially available honey (purchased from the nearby department store) in this study to ensure the easy availability of this transport medium to any physician seeking to send samples for DIF test. It is important to keep the biopsy specimen in a moist condition before DIF. In