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Retrospective Evaluation

Topical Amitriptyline-Ketamine for Treatment of Rectal, Genital, and Perineal Pain and Discomfort

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Background: Pain in the rectal, genital, and perineal area is a common condition treated by pain physicians. These chronic pain syndromes are therapeutically challenging because both interventional and drug therapies often are ineffective.

Objectives: To determine if pelvic pain can be treated effectively with compounded topical amitriptyline-ketamine.

Study Design: A retrospective review of medical records.

Setting: A single academic medical center in the United States.

Methods: We identified all patients treated with topical amitriptyline-ketamine from January 1, 2004, through November 28, 2011. Medical records were evaluated to determine the diagnosis for which the medication was prescribed. Treatment efficacy and any adverse effects were recorded.

Results: Of the 1,068 patients who received amitriptyline-ketamine, 13 had the medication prescribed for genital, rectal, or perineal pain and had medication efficacy recorded. These patients were treated with a topical combination of amitriptyline 1-2% and ketamine 0.5%. Of these 13 patients, one (8%) had complete relief, 6 (46%) had substantial relief, 4 (31%) had some relief, and 2 (15%) had no response. One patient reported occasional irritation while using topical amitriptyline-ketamine with lidocaine; no other patients reported local or systemic adverse effects.

Limitations: Retrospective review; lack of uniform system for pain grading; concurrent use of other medications.

Conclusions: Topical amitriptyline-ketamine provided a high rate of pain relief with a low adverse-effect burden in patients with pelvic pain. This topical medication could offer an effective, noninvasive, nonopioid therapy for pain in the rectum, perineum, and genitals.

Key words: Amitriptyline, rectal, compounded medication, genital, ketamine, pain, pelvic, perineal.

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Pain in the perineal, genital, and rectal areas is underrecognized and can evolve into potentially life-altering chronic pain conditions (1). Because the skin and organs in the pelvic area are innervated by overlapping somatic and autonomic nerve distributions, pain in these regions often resists easy classification (2,3). Although diagnostic evaluations should always be performed in these patients, a specific cause of pain is not always identifiable. Furthermore, treatment guidelines for these pain syndromes generally are not based on robust clinical trials. Therefore, providers often choose therapies that lack sufficient evidence of

benefit, which may lead to inconsistent treatment of these patients and suboptimal outcomes (4,5).

One therapy that has been used at our institution for treatment of perineal, genital, and rectal pain is topical amitriptyline-ketamine. This compounded medication is used for neuropathic pain in various disorders, including peripheral neuropathies, neurovascular disorders, and postinfectious and postoperative neuralgias (6,7). The 2 medications in this compounded gel are hypothesized to act synergistically through different pathways to dull transmission of unpleasant stimuli (8). Amitriptyline, a tricyclic antidepressant commonly taken systemically for its mood- and pain-altering effects, most likely acts primarily as a sodium-channel blocker when administered topically (7,9). Ketamine acts to block a number of receptors, including N-methyl-D-aspartate receptors in peripheral nerve synapses and the spine (when transported orthodromically), and it also blocks 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptors (8,10). To our knowledge, little has been reported about this compounded topical medication in pelvic pain; only one published case report describes topical amitriptyline-ketamine as an effective treatment for refractory proctalgia (11).

To evaluate the use of topical amitriptyline-ketamine in the treatment of perineal, genital, and rectal pain, we retrospectively evaluated the medical records of patients with these conditions who were treated at our institution since 2004.

Methods

Identification of Patients

This study was approved by our institutional review board. Using institutional pharmacy records, we identified 1,068 patients who were prescribed amitriptyline-ketamine from January 1, 2004, through November 28, 2011. The medical records of these patients were reviewed to determine the diagnosis for which the medication was prescribed. The presenting symptoms (e.g., pain, itching, paresthesias), body area affected, pain relief, adverse effects, other concurrent treatments, and demographic information were abstracted from the record. The current study evaluated only those patients treated for perineal, genital, and rectal pain. Separate analyses (manuscripts in preparation) will examine other patients from this cohort who had different conditions treated with topical amitriptyline-ketamine.

Treatment Efficacy

Pain relief was graded using the following scale: complete (100% relief), substantial (> 50% relief or wording that denoted substantial relief [e.g., "large" or "significant"]), some (< 50% relief or wording that denoted relief without specifying substantial relief), no change, and worsening of symptoms. To count as providing relief (i.e., to be included as a positive result) in the study, any symptom relief had to be attributed specifically to the topical medication in the medical record. Any local or systemic adverse effects from the medication were recorded. Patient follow-up was assessed from communications documented in the electronic medical record.

Results

Twenty-nine patients were identified who were prescribed topical amitriptyline-ketamine for pain in the perineal, genital, or rectal area. Of these, 13 had information available on medication efficacy; these 13 patients made up our final patient cohort. All 13 patients reported pain as the primary symptom. The mean age was 58.7 (standard deviation 15.0, median 58.5, range 31-87). Seven patients (54%) were women. The medication was applied a median of 2 times per day (range, 2-4 applications/d). The topical medication was compounded in either a moisturizing cream (Vanicream, Pharmaceutical Specialties, Inc) or pluronic lecithin organogel and contained 1-2% amitriptyline and 0.5% ketamine. Three patients (23%) received amitriptyline-ketamine that was compounded with 2% lidocaine; the rest received amitriptyline-ketamine alone. Table 1 summarizes the affected areas and response to treatment. One patient who obtained relief for external hemorrhoids had occasional irritation when using topical amitriptyline-ketamine with 2% lidocaine. No other patients reported local or systemic adverse effects.

The cause of pain for these patients varied broadly. They included radiotherapy-induced perineal mucositis, primary carcinoma of the vulva, pruritus ani, pelvic floor tension myalgia, external hemorrhoids, ulcerative colitis, lichen planus, lichen simplex chronicus, and idiopathic causes. Notably, 2 patients with radiotherapy-induced perineal pain attained relief using the combination topical. One patient had development of perineal mucositis after receiving 26 of 32 planned treatments (total dose, 4,500 of 5,760 cGy) to the pelvis and perineum for stage III/IVa, grade 4, invasive squamous cell carcinoma of the perineum. This woman required hospitalization and intensive pain management with opioids,

Table 1. *Anatomic location of pain and response to treatment (n = 29).*

		Response				
Anatomic Location	**No. of Patients**	**Complete Relief**	**Substantial Relief**	**Some Relief**	**No Response**	**Lost to Follow-up or Treatment Response Not Recorded**
Scrotum						
Scrotum only	3	. . .	1	. . .	1	1
Scrotum and penis	2	. . .	. . .	. . .	. . .	2
Scrotum and perineum	1	. . .	1	. . .	. . .	. . .
Scrotum and buttocks	1	. . .	. . .	. . .	. . .	1
Penis	2	. . .	. . .	. . .	. . .	2
Vulva						
Vulva only	4	. . .	1	. . .	1	2
Vulva and rectum	1	. . .	1	. . .	. . .	. . .
Rectum	8	1	. . .	3	. . .	4
Perineum	6	. . .	2	. . .	. . .	4
Groin	1	. . .	. . .	1	. . .	. . .

pregabalin, and topical amitriptyline-ketamine. The other patient was an elderly woman with locally advanced squamous cell carcinoma of the vulva. She had undergone 10 of 30 planned treatments (total dose, 2,000 of 6,000 cGy) when she reported a pain score of 8 (with 10 indicating the worst possible pain) for tactile and mechanical discomfort. Because of an opioid intolerance, she required alternative agents; the patient had substantial pain relief after treatment with topical amitriptyline-ketamine plus oral acetaminophen.

Discussion

Pain and discomfort in the perineal, rectal, and genital areas is an important and underrecognized cause of chronic pain worldwide. However, effective pain control strategies have not been widely published, and evidence-based guidelines derived from randomized clinical trials are lacking. Here, we present a series of 13 patients with pelvic pain who were treated with topical compounded amitriptyline-ketamine. Eleven of the 13 patients (85%) reported attaining some level of relief, with 7 (54%) reporting complete or significant relief. In addition, the medication was well tolerated, with no systemic adverse effects and only one patient reporting local irritation. Previously, only a single case report described topical amitriptyline-ketamine as a treatment for proctalgia (11); to our knowledge, its use in other pelvic pain conditions has not been reported. The current study provides evidence that this topical compound can be used for pain relief in a broader range of pelvic pain conditions.

Notably, patients in our study were treated in a multidisciplinary manner and received numerous interventions sequentially or simultaneously (data not shown). Amitriptyline-ketamine often was prescribed only after the failure of analgesics, systemic pain-modifying therapy, and invasive pain-relieving therapy. We hypothesize that topical amitriptyline-ketamine may be an effective treatment for pelvic pain that is refractory to other therapies.

This study has a number of limitations, mostly due to its retrospective design. First, the cohort was small, and 16 of 29 patients (55%) did not have information available regarding the specific efficacy of the topical medication. It is unknown in which direction these patients may have biased the results; with the large number of patients lacking outcome data, the degree of change could be quite large. Second, no uniform system was used to report levels of pain and relief. Third, patients had heterogeneous disorders underlying the chronic pain syndromes. We speculate that the combination topical is more likely to be effective for certain diagnoses, but this sample size was too small to make definitive judgments. Fourth, this medication often was administered with other systemic or topical therapy; without a placebo group, we cannot firmly determine how much relief was due to adjuvant treatments or a placebo effect.

In conclusion, we present a series of 13 patients treated with topical amitriptyline-ketamine for pain in the perineum, rectum, and genitals. In our patient

group with heterogeneous diagnoses and pain generators, many had positive responses to the medication and the medication was well tolerated. However, retrospective study of therapies for pelvic pain will continue to face considerable limitations. A renewed commitment to developing and funding clinical trials is necessary to facilitate establishment of effective, evidence-based care guidelines for these devastating pain conditions.

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