The Efficacy and Safety of 6% Gabapentin Topical Formulation in The Treatment of Pruritus in Adult Filipino Hemodialysis Patients: A Randomized, Double-Blind, Placebo-Controlled Study

TERESE MONETTE O. AQUINO, M.D., Karla Angela P. Cuenca-Luchnagco, MD, DPDS, Elizabeth V. Sanchez, MD, FPDS, Vermen M. Verallo-Rowell, MD, FPDS

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S039 Residents and Fellows Symposium

DISCLOSURES

I do not have any relevant relationships with the industry.
PRURITUS

• Unpleasant sensation of the skin

• Multidimensional phenomenon

• Primary/secondary skin condition

• Chronic Kidney Disease –Associated Pruritus (CKD-AP)
CHRONIC KIDNEY DISEASE – ASSOCIATED PRURITUS

Prevalence of CKD-AP 30-50%

Mortality
Poor quality of life
Poor sleep
Depression

BACKGROUND OF THE STUDY
MECHANISMS OF PRURITUS

**XEROSIS**
- Reduction of eccrine glands
- Atrophy of sebaceous glands
- Use of diuretics

**IMMUNE SYSTEM DERANGEMENT**
- Pro-inflammatory state
  - ↑Peptides
  - ↑Proteases
  - ↑Cytokines
  - ↑Kinins
  - ↑Prostanoids

**METABOLIC**
- Altered calcium metabolism
- Increases pruritogenic cytokines

**NEUROPATHIC**
- Neuropathy & Central sensitization to itch
  - Conveyed via nerve C-fibers (similar with pain)

**OPIOIDERVIC SYSTEM**
- Increase in opioidergic tone
- Opioid receptor antagonist alleviates pruritus
BACKGROUND OF THE STUDY
GABAPENTIN

- Neuropathic pain
- Oral form have shown to decrease intensity of CKD-AP
- Exclusive renal elimination

- Boardman et al. (2008) reported the efficacy of 6% topical gabapentin for the treatment of vulvodynia


STUDY OBJECTIVES

1. To assess the early **efficacy** of topical gabapentin in the treatment of CKD-AP

2. To assess the early **safety** of topical gabapentin in the treatment of CKD-AP
METHODS
STUDY DESIGN

1. Randomized, Double-blind, Placebo-controlled Study
2. Block randomization
3. Recruitment done in two tertiary hospitals
METHODS

INCLUSION CRITERIA

1. Adult (>18 years old) patients on hemodialysis
2. Hemodialysis (at least 2x/week) for at least 8 weeks
3. Baseline visual analog scale (VAS) pruritus score ≥ 5
4. Unrelieved by antihistamines or emollients
METHODS

EXCLUSION CRITERIA

1. Pregnant/nursing mothers
2. Patients with known allergy to gabapentin/vehicle
3. Patients with pre-existing infectious/non-infectious dermatitis at baseline
4. With prior use of anti-pruritic medications (oral or topical) within one week of recruitment
5. Attained less than a high-school degree
METHODS

6% GABAPENTIN PREPARATION

Gabapentin capsules

Dissolved in water

Compounded to a permeation cream (PG+PEG)
METHODS

PRIMARY OUTCOME MEASURE

VISUAL ANALOG SCALE
METHODS
SECONDARY OUTCOME MEASURE

1. 5-D Pruritus Scale
   - Elman et al. (2010) - good correlation with VAS pruritus scores
   - 5-component scale quantifying: duration, degree, direction, disability & distribution

2. Adverse Events Questionnaire

- Duration: During the last 2 weeks, how many hours a day have you been itching?
  - Less than 6hrs/day
  - 6-12 hrs/day
  - 12-18 hrs/day
  - 18-23 hrs/day
  - All day

- Degree: Please rate the intensity of your itching over the past 2 weeks
  - Not present
  - Mild
  - Moderate
  - Severe
  - Unbearable

- Direction: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?
  - Completely resolved
  - Much better, but still present
  - Little bit better, but still present
  - Unchanged
  - Getting worse

- Disability: Rate the impact of your itching on the following activities over the last 2 weeks
  - Sleep
    - Never affects sleep
    - Occasionally delays falling asleep
    - Frequently delays falling asleep
    - Delays falling asleep and occasionally wakes me up at night
  - Leisure/Social
    - N/A
    - Never affects this activity
    - Rarely affects this activity
    - Occasionally affects this activity
    - Frequently affects this activity
    - Always affects this activity
  - Housework/Errands
    - 1
    - 2
    - 3
    - 4
    - 5
  - Work/School
    - 1
    - 2
    - 3
    - 4
    - 5

- Distribution: Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.
  - Head/Scalp
  - Face
  - Chest
  - Abdomen
  - Back
  - Buttocks
  - Thighs
  - Lower legs
  - Tops of Feet/Toes
  - Present
  - Soles
  - Palms
  - Tops of Hands/Fingers
  - Forearms
  - Upper Arms
  - Points of Contact w Clothing
  - (e.g. waistband, undergarment)
  - Groin
METHODS
SAMPLE SIZE

• Based on prior trials which investigated similar outcomes (10-point VAS scores) in similar population but using different agents.
  • Young et al. (n=28) Topical pramoxine-based agent
  • Gunal et al (n=25) Oral gabapentin

• Central limit theorem
  • n=30 deemed large enough to yield data that will approximate the normal distribution
METHODS

Assessed for eligibility (n=30)

Randomized (n=30)

Allocation

Allocated to Experimental (Gabapentin) (n=15)
  Received allocated intervention (n=15)

Allocated to Control (Placebo) (n=15)
  Received allocated intervention (n=15)

Follow-up

Lost to follow-up at week 2 (change of schedule) (n=1)

Analysis

Analysed (n=15) *ITT analysis was done, missing data were handled using LOCF

Analysed (n=15) *ITT analysis was done, missing data were handled using LOCF
## METHODS

### STATISTICAL ANALYSIS

1. Baseline Characteristics
   - *T test for independent samples*

2. Change in Pruritus Score (within groups)
   - Baseline → wk1 & Baseline → wk2
   - **Paired T-Test**

3. Change in Pruritus Score (Experimental VS Placebo)
   - **Wilcoxon rank sum test**

4. Data analysis was done using SPSS®
   - Statistics Version 24
# RESULTS & DISCUSSION

## PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>EXPERIMENTAL (n=15)</th>
<th>CONTROL (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENDER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>14</td>
<td>0.5977*</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>1</td>
<td></td>
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<tr>
<td><strong>AGE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>46.1</td>
<td>41.2</td>
<td>0.298203</td>
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<tr>
<td>Standard Deviation</td>
<td>13.4</td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>29 - 70</td>
<td>27 - 62</td>
<td></td>
</tr>
<tr>
<td><strong>DURATION OF DIALYSIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (months)</td>
<td>23.7</td>
<td>16.5</td>
<td>0.477493</td>
</tr>
<tr>
<td>Median (months)</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>34.1</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2 - 132</td>
<td>2 - 60</td>
<td></td>
</tr>
<tr>
<td><strong>DURATION OF PRURITUS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (months)</td>
<td>18.7</td>
<td>13.8</td>
<td>0.60029</td>
</tr>
<tr>
<td>Median (months)</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>31.9</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1 - 120</td>
<td>2 - 60</td>
<td></td>
</tr>
</tbody>
</table>

*Analyzed via Chi-square statistic; Comparison of means analyzed via paired t-test for independent samples*
RESULTS & DISCUSSION

VISUAL ANALOG SCALE

Mean VAS Pruritus Scores

p value 0.58
RESULTS & DISCUSSION

VISUAL ANALOG SCALE

Mean Change in VAS Pruritus Scores

-5 -4.5 -4 -3.5 -3 -2.5 -2 -1.5 -1 -0.5 0

Baseline Week 1 Week 2

Gabapentin Placebo

p value 0.80

p value 0.01
### RESULTS & DISCUSSION

### VISUAL ANALOG SCALE

<table>
<thead>
<tr>
<th></th>
<th>EXPERIMENTAL (n=15)</th>
<th>CONTROL (n = 15)</th>
<th>p-value (Experimental vs Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pruritus score at baseline</td>
<td>5.9 ± 1.3/5 (5-8)</td>
<td>6.2 ± 1.4/6 (5-10)</td>
<td>0.58*</td>
</tr>
<tr>
<td>Mean pruritus score at week 1</td>
<td>2.7 ± 2.1/2 (0-5)</td>
<td>3.3 ± 2.2/4 (0-7)</td>
<td></td>
</tr>
<tr>
<td>Mean pruritus score at week 2</td>
<td>1.3 ± 1.5/1 (0-5)</td>
<td>3.6 ± 2.0/4 (1-7)</td>
<td></td>
</tr>
<tr>
<td>Change in pruritus score from baseline to week 1</td>
<td>-3.2 ± 2.1/3 (0-7)</td>
<td>-2.9 ± 2.0/3 (-1-6)</td>
<td>0.80*</td>
</tr>
<tr>
<td>p value^ (Baseline vs week 1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Change in pruritus score from baseline to week 2</td>
<td>-4.6 ± 2.0/5 (0-7)</td>
<td>-2.6 ± 1.9/3 (-1-5)</td>
<td>0.01*</td>
</tr>
<tr>
<td>p value^ (Baseline vs week 2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation/ median (range)

^Difference in pruritus score between baseline and week 1/ week 2 analyzed via paired t-test

*Difference in pruritus score between control and experimental groups analyzed via Wilcoxon rank sum test

p value < 0.05 considered as statistically significant
RESULTS & DISCUSSION
5D PRURITUS SCALE

Mean 5-D Pruritus Scores

Baseline to Week 2

p value 0.07

Gabapentin
Placebo
RESULTS & DISCUSSION
5D PRURITUS SCALE

Change in 5-D Pruritus Scores

Mean Change in 5-D Pruritus Scores

Baseline

Week 2

Gabapentin
Placebo

p value 0.47
## RESULTS & DISCUSSION

### 5D PRURITUS SCALE

<table>
<thead>
<tr>
<th></th>
<th>EXPERIMENTAL (n=15)</th>
<th>CONTROL (n = 15)</th>
<th>p-value (Experimental vs Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pruritus score at baseline</td>
<td>16.8 ± 5.0/17 (11-30)</td>
<td>20.1 ± 5.9/18 (13 – 29)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Mean pruritus score at week 2</td>
<td>11.2 ± 3.6/10 (7-22)</td>
<td>13.3 ± 5.7/11 (7-25)</td>
<td></td>
</tr>
<tr>
<td>Change in pruritus score from baseline to week 2</td>
<td>-4.86 ± 5.24/4 (0 - 20)</td>
<td>-6.8 ± 7.2/6 (0-21)</td>
<td>0.47*</td>
</tr>
<tr>
<td>p value^ (Baseline vs week 2)</td>
<td>0.003</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation/ median (range)

Mean scores are the sum of all 5 components of the 5-D scale

^Difference in pruritus score between baseline and week 2 analyzed via paired t-test

*Difference in pruritus score between control and experimental groups analyzed via Wilcoxon rank sum test

p value < 0.05 considered as statistically significant
### RESULTS & DISCUSSION

#### 5D PRURITUS SCALE

<table>
<thead>
<tr>
<th>Component</th>
<th>EXPERIMENTAL</th>
<th>Control</th>
<th>*p-value (Experimental vs Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean change in scores at 2 weeks</td>
<td>p-value</td>
<td>Mean change in scores at 2 weeks</td>
</tr>
<tr>
<td>1. Duration</td>
<td>-0.087 (SD 3.6)</td>
<td>0.008</td>
<td>-1.5 (SD 1.7)</td>
</tr>
<tr>
<td>2. Degree</td>
<td>-1.13 (SD 0.74)</td>
<td>&lt;0.001</td>
<td>-0.4 (SD 0.5)</td>
</tr>
<tr>
<td>3. Direction</td>
<td>-1.1 (SD 1.4)</td>
<td>0.01</td>
<td>-0.5 (SD 1.0)</td>
</tr>
<tr>
<td>4. Disability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>-0.86 (SD 1.18)</td>
<td>0.01</td>
<td>-1.6 (SD 1.6)</td>
</tr>
<tr>
<td>Leisure/social</td>
<td>-0.46 (SD 1.5)</td>
<td>0.23</td>
<td>-1.0 (SD 1.1)</td>
</tr>
<tr>
<td>Housework/errands</td>
<td>-0.6 (SD 1.3)</td>
<td>0.09</td>
<td>-0.8 (SD 1.16)</td>
</tr>
<tr>
<td>Work/school</td>
<td>-0.33 (SD 1.4)</td>
<td>0.11</td>
<td>-0.53 (SD 1.7)</td>
</tr>
<tr>
<td>5. Distribution</td>
<td>-0.73 (0.96)</td>
<td>0.01</td>
<td>-0.6 (1.12)</td>
</tr>
</tbody>
</table>

SD standard deviation; ^Difference in pruritus score between baseline and week 2 analyzed via paired t-test; *Difference in pruritus score between control and experimental groups analyzed via Wilcoxon rank sum test; p value < 0.05 considered as statistically significant.
RESULTS & DISCUSSION

MEAN CHANGE IN SCORES
of Visual Analog Scale & Degree component of 5D (at 2 weeks)

PLACEBO < EXPERIMENTAL
(GABAPENTIN)

Effect size of 1.02 (VAS) and 1.16 (5D degree component)
RESULTS & DISCUSSION

ADVERSE EVENTS

• No adverse events noted in a 2-week span
RESULTS & DISCUSSION

1. Boardman et al. (2008) – significant clinical effect of the drug on the peripheral component of pain

2. Pain and itch share afferent similar pathway
RESULTS & DISCUSSION

Exogenous or endogenous factors

Binding to a specific-itch or pain receptor

Generates action potential
RESULTS & DISCUSSION

3. Significantly decreased VAS pruritus scores after 2 weeks of use compared to placebo.

4. Topical formulation of gabapentin in our study minimized any systemic effect.

5. Important in CKD-AP because gabapentin toxicity may be higher in patients with CKD patients.
CONCLUSIONS

1. Short-term, topical 6% gabapentin use was able to decrease VAS pruritus scores at 1 and 2 weeks versus baseline.

2. No reports of local or systemic adverse events.

3. Longer follow-up may be needed to adequately assess long-term efficacy and possible late toxicities with topical gabapentin.