EFFICACY OF HYDROCORTISONE PHONOPHORESIS ON XEROSIS CUTIS IN CHRONIC HEMODIALYSIS PATIENTS

Osama Abdellatif Mowafy1, Ahmed Abd Elkhabir Ahmed2, Nada M Yousef1, Hesham Galal Mahar1,2

1Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Giza, Egypt
2Department of Dermatology, Andrology & STDs, Faculty of Medicine, Mansoura University, Mansoura, Egypt

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Abstract

Background: Xerosis is a common dermatological complication in patients with end stage renal disease maintaining hemodialysis. Approximately 90% of them have uraemic xerosis. Purpose: The study was to clarify if phonophoresis increased the effect of hydrocortisone on xerosis in chronic hemodialysis patients. Thus the study was to clarify if phonophoresis increased the effect of hydrocortisone on xerosis in chronic hemodialysis patients.

Materials and methods: Fifty four patients from both sexes with end stage renal disease maintaining chronic hemodialysis and having moderate to severe xerosis joined the study. The ages selected were from 44 to 60 years and chosen from the Hemodialysis Unit of Dikirmis General Hospital. They underwent random assignment into three groups (18 patients per group): group (A), (B) and (C). Methods: group (A) received sufficient amount of 1% topical hydrocortisone gel under occlusive dressing for 15 minutes followed by therapeutic ultrasound, group (B) received therapeutic ultrasound followed by sufficient amount of topical 1% hydrocortisone gel under occlusive dressing for 15 minutes and group (C) received only topical 1% hydrocortisone. The sessions were day after day for one month (12 sessions). All groups were evaluated before and after 4 weeks of phonophoresis application, the intensity of xerosis cutis was assessed by employing a visual analogue scale and a Specified Symptom Score system, which involved rating the degree of scaling, roughness, redness, and cracks.

Results: The finding of current study proved a significant decrease in the Visual Analogue Scale and the scaling, redness, roughness and cracks scores in the 3 groups after-treatment compared with that pre-treatment. A significant reduction in the visual analogue scale was observed in both group A and group B compared to group C. However, the comparison of VAS scores between group A and group B did not reveal any significant difference.

Conclusion: phonophoresis increased the effect of hydrocortisone on xerosis cutis compared to topical hydrocortisone.

Keywords: Hemodialysis, Hydrocortisone, Phonophoresis, Xerosis.

Introduction:

Chronic kidney disease (CKD) is widespread and negatively impacts the quality of life. Disturbances in every system of the body are caused by impaired kidney function. The most noticeable one is the skin. Due to concerns over appearance, cutaneous signs of CKD may also result in psychological distress. Most research investigations on cutaneous signs of CKD have been carried out on people on maintenance hemodialysis (1). During end-stage renal disease (ESRD), skin symptoms are frequently observed. The involvement of the skin can be severe in those populations reducing the quality of life greatly. Clinicians can quickly diagnose and treat ESRD patients by closely observing their skin and nails, which enhances quality of life and lowers mortality (2). Previous studies have consistently identified xerosis as the most common cutaneous manifestation among patients with CKD, with prevalence rates ranging from 46% to 90%. Xerosis predominantly affects the extensor surfaces of the forearms, legs, and thighs (3).

The contributing factors of xerosis in CRF include protein-calorie malnutrition caused by dietary restrictions, sweat gland atrophy after high-dose diuretic regimens, raised plasma vitamin A, high retinol-binding protein, alkalinity of the skin, and complications of diabetes (4). According to current theories, xerosis caused by a decrease in the total water content of the stratum corneum, a disruption in sebum production due to atrophy of sebaceous glands, and a drop in the water content of the dermis layer brought on by the displacement of fluid during the procedure for dialysis (5).
According to current theories, xerosis is brought on by a drop in the dermis layer's water content caused by the fluid being displaced during the dialysis procedure, a decrease in the stratum corneum's overall water content, and a disruption in sebum secretion due to sebaceous gland atrophy (5).

Phonophoresis uses ultrasound waves to improve a drug's percutaneous absorption, typically an analgesic or anti-inflammatory medication for treating symptoms such as pain and inflammation (6).

The clinical efficacy of a topical drug depends undoubtedly on its ability to reach the deeper layers of the skin after passing through the epidermis. Over an extended period, pharmacological compounds have been applied topically, and numerous techniques utilizing energy to enhance the absorption and penetration of these substances across the skin have been studied (7).

Hydrocortisone phonophoresis is a patient treatment approach employing ultrasonic sound waves to push hydrocortisone particles inside subcutaneous tissue. The therapeutic ultrasonic frequencies used to create ultrasound waves range from 0.7 to 1.1 megacycles per second at commercially available devices (8).

The study inspected whether 1% hydrocortisone's impact on xerosis cutis in chronic hemodialysis patients was enhanced by phonophoresis.

**PATIENTS AND METHODS**

This study involved the participation of 54 patients diagnosed with chronic renal failure on chronic hemodialysis, out of which 32 were male and 22 were female. These patients exhibited moderate to severe Xerosis and experienced itching, primarily in affected areas such as the forearms, legs, and thighs. The age range of the participants was between 44 and 60 years. Patients with Xerosis that could be owed to other genetic, systemic, dermatological, or psychological causes were skipped from this study, in addition to patients with allergy to corticosteroids, skin infections or cancers, and changes in consciousness or Febrile condition.

To avoid a type II error, a preliminary power analysis was conducted considering (European group on efficacy measurement of cosmetics and other topical products (EEMCO)) as a primary outcome with the following parameters: [power \((1-\beta) = 0.90, \alpha = 0.05, \text{effect size} = 0.5\)].

The clinical scoring system used in accordance with the EEMCO guidance is the Specified Symptom Score (SRRC) system and it is considered the primary outcome of this study. It involved sorting the scaling, roughness, redness, and cracks observed in xerosis and gave a numeric value from 0 to 4 to evaluate the extent of scaling, roughness, redness, and fissuring of the skin; 0: absent, 1: slight, 2: moderate, 3: severe, and 4: extreme.

This effect size was calculated after a pilot study on 12 participants (4 in each group). The calculation determined a sample size of 18 for each group in this study. G*power software was used for sample size calculation.

Once the Ethical Committee of Cairo University had permitted the study with No:
(P.T.REC/012/003929), the recruitment of the patient started. The participant patients were randomized and equally allocated to three groups (A, B & C), 18 patients per group. Envelope cards were numbered sequentially and were placed in opaque envelopes. Then, a blind researcher opened the sealed envelope and allocated the patients according to their group. Before enrollment for treatment, each patient had their consent form. Treatment takes four consecutive weeks for each patient, including 12 sessions, three per week.

**Assessment tools**
Two measurement scales were taken for each patient, both prior to commencing the treatment and four weeks subsequent to its completion.

a) **The Visual Analogue Scale (VAS)** consists of a horizontal line of 10 cm in length. On the left side, it represents no itch, while the right side indicates the worst itching ever. Patients are asked to mark the scale at a point that reflects the current severity of their itchiness, thereby indicating the intensity of their itching sensation (9).

b) **The clinical scoring system used in accordance with the EEMCO guidance is the Specified Symptom Score (SRRC) system.** It involves sorting the scaling, roughness, redness, and cracks observed in xerosis. At the beginning of the study, participants were assessed using this scoring system, which assigned a numeric value ranging from 0 to 4 to evaluate the extent of scaling, roughness, redness, and fissuring of the skin; 0: absent, 1: slight, 2: moderate, 3: severe, and 4: extreme (10).

**TREATMENT PROCEDURES:**
Excess hair was clipped carefully from the treatment areas (the extensor surface of the forearm, legs and thighs). We used the fingertip unit (0.5 gram for each 300 cm²) to determine the amount of gel that was applied over the treatment area. The fingertip unit was doubled 4 times (2 grams) to ensure full saturation of the skin by the drug. The amount of hydrocortisone gel was determined according to the surface area we were working on and it was introduced by insulin syringe. We ensured that the patient did not use any topical medications on areas of treatment at least 3 hours before the start of the treatment procedure. The treatment takes 4 consecutive weeks for each patient, including 12 sessions, 3 per week (11).

- **Group (A) (ULTRASOUND-FOLLOWED GEL GROUP):**
  This group received the suitable dose of 1% hydrocortisone gel over the treatment areas (the extensor surface of the forearm, legs and thighs) followed by occlusive dressing for 15 minutes. An occlusive dressing was applied over the medication to improve the drug's penetration and saturation of the stratum corneum. After 15 minutes, the dressing and remaining hydrocortisone gel were removed. Then we applied aquasonic gel followed by therapeutic pulsed ultrasound using DANTELLO Computerized Ultrasound Devic (11).

  The following parameters were used:
  - Intensity: 1 W/cm².
  - Frequency: 1MHz.
  - Mode: Pulsed (1-4) (20% on -80% off)
  - Time: 1 minute for each cm².
-Group (B) (ULTRASOUND-PRECEDED GEL GROUP):

In this group, we applied aquasonic gel over the treatment area then therapeutic pulsed ultrasound using DANTELLO Computerized Ultrasound Device was applied with the same parameters as group A.

After removing the remaining aquasonic gel, each subject received the suitable amount of 1% hydrocortisone gel for the affected area followed by occlusive dressing for 15 minutes (11).

-Group (C) (CONTROL GROUP):

This group received only the appropriate dose of 1% hydrocortisone gel topically followed by occlusive dressing for 15 minutes to enhance the saturation of the drug by the skin.

DATA ANALYSIS

The comparison of age between groups was performed using an ANOVA test. The distribution of sex was compared using a Chi-squared test. The normal distribution of data for all variables was assessed using the Shapiro-Wilk test. To test the homogeneity between groups, Levene's test for homogeneity of variances was conducted. The effects of different groups on the Visual Analogue Scale (VAS) were compared using a one-way ANOVA test. Subsequent multiple comparisons were carried out using post-hoc tests, specifically the Tukey test. A paired t-test was used to compare pre- and post-treatment data within each group. The level of significance for all statistical tests was set at p < 0.05. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25 for Windows.

RESULTS

This study directed to investigate the efficiency of phonophoresis to boost the impact of hydrocortisone on xerosis in individuals undergoing chronic hemodialysis. The study counted in 54 patients. The characteristics of subject distribution between the three group was tested and showed that there was no significant difference between groups regards sex and age distribution (p > 0.05) (table 1).

Table (1): Basic characteristics of participants:

<table>
<thead>
<tr>
<th>Group</th>
<th>Group</th>
<th>Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 5.06</td>
<td>54.83</td>
<td>0.98</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>7 (39%)</td>
<td>9 (50%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Females</td>
<td>11 (61%)</td>
<td>9 (50%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Skin examinations conducted on patients with end-stage renal disease (ESRD) revealed that a significant percentage, ranging from 50% to 100%, exhibited at least one dermatological disorder. They frequently have pruritus and xerosis, two dermatological symptoms of uremia (12).

For unidentified factors, significant xerosis affects 50–92% of those on dialysis. Some authors have hypothesized that xerosis linked with ESRD may be caused by a drop in the percentage of water in the epidermis, a general decrease in sweat volume in patients with uremia or sebaceous gland atrophy. The stratum corneum may become dry as a consequence of these modifications (13).

Xerosis can potentially compromise the psychological and emotional well-being of patients, along with their overall health-related aspects of life. Factors such as youth and the severity of uremic itching may further contribute to a detrimental effect on the adoption of healthy lifestyle practices, exacerbating the severity of xerosis(14).

A variety of mechanisms explain the biological effects of phonophoresis in dermatological conditions. One of these explanations, according to some ideas, is microstreaming flow near the skin, which causes shear forces to stretch the stratum corneum and create channels for transdermal distribution. In addition to dilating the entrance site (hair follicles, sweat glands, etc.), boosting circulation, increasing capillary permeability, and reorganizing the lipids structured in the stratum corneum. The properties

Table (2): Mean valued of VAS pre and post treatment.

**SD:** Standard deviation, **MD:** Mean difference, **p-value:** Level of significance
of ultrasound also enhance the kinetic energy of both the local cells and the drug (15).

This study used the ultrasound to direct hydrocortisone to skin aiming to enhance its absorption and efficiency to manage xerosis. The findings demonstrated a statistically significant reduction in the mean results of both the visual analogue scale and the scores for scaling, redness, roughness, and cracks in all three groups following the treatment, as compared to the measurements taken before the treatment was administered.

A significant decrease in VAS was observed in both groups that received the ultrasound waves beside the medication (A&B) compared to group C which received the hydrocortisone alone (p < 0.05). The difference in improvement between group A and group B was not significant (p > 0.05). However, the results of group A showed better outcomes compared to group B.

The observed within-group results in this study can be attributed to the impact of the medication used, specifically hydrocortisone. These findings align with the outcomes mentioned in earlier research (16,17,18,19,20,21).

Frithz, 1983(16) and Kurian & Barankin, 2010(17) studied the peeling and lack of moisturizing in the skin in psoriasis patients concerning hydrocortisone use. It turned out that hydrocortisone worked well for xerotic skin, which had inflammation and minor eczema. It also successfully eradicated the broke down rough skin that comes with eczema while maintaining moisture in the stratum corneum. For dermatological applications, low-potency glucocorticoid 1% cream has been researched and proven relatively safe, which boosts the result of the current study.

In agreement to our result, a pilot double-blinded randomly assigned, placebo-controlled, crossover experiment has been carried out. 10 individuals involved participated in the experiment and finished it. Persons suffering pruritus ani (PA) were treated with either 1% hydrocortisone cream or a white soft paraffin (placebo group) for 2 weeks, then reverse therapy for an additional two weeks. Additionally, there was a two-week cleanse interval between each therapy. Visual analogue scale (VAS) was used as the primary assessment to track itching alleviation. As a consequence of this research, the VAS test score decreased by sixty-eight percent in comparison to placebo (P = 0.019). Jirabundansuk et al., 2014(19) investigated the use of hydrocortisone in diseases such as atopic dermatitis. It was found that hydrocortisone was of benefit in the improvement of discomfort, itching, and cracked dry skin of atopic dermatitis. ZHOU, 2016 (20) examined how senile xerosis patients' skin barrier function was affected by topical hydrocortisone. 32 patients were treated with 0.1% topical hydrocortisone cream once daily for 8 weeks on one side of their forearms (the topical hydrocortisone group), while the other forearm served as the control (the control group). Using the Corneometer and Tewameter instruments, skin barrier function was assessed at 0, 2, 4, and 8 weeks following the experiment. The transepidermal water loss (TEWL) value was lowest, and the stratum corneum water content was
highest with the topical application of hydrocortisone at 2 weeks. External glucocorticoid substantially raised the hydration capacity of the strata corneum and lowered the TEWL level of the experimental stratified corneum when relative to the comparison category.

Charoenpipatsin et al., 2020\textsuperscript{(21)} used 1\% hydrocortisone ointment with xerotic circumstances for four weeks before stopping in the last week. At weeks 0, 2, 4, and 5 from the application, the same doctor evaluated the chosen locations using the severity of the symptoms, a doctor's overall evaluation, and bioengineering evaluations using the Tewameter and Corneometer instruments to measure transepidermal water loss and skin hydration, respectively. Patients also evaluated the severity of their symptoms. The doctor and patients both saw a considerable reduction in the amount of dryness, scale, and overall evaluation. This improvement persisted even for one week once treatment stopped. As assessed by the Corneometer, the hydration in skin increased significantly during the application of the ointment.

In turns, the comparison between-groups results at this research are coherent with the findings reported in prior studies \textsuperscript{(22,23,24)}.

Pottenger & Karalfa, 1989\textsuperscript{(22)} proved that ultrasonic therapy alone is not as efficient therapy method as hydrocortisone phonophoresis (HCP). The medicinal properties of hydrocortisone phonophoresis are achieved in the deeper layers of tissue with no drawbacks of anxiety, discomfort, or contamination associated with the skin administration of corticosteroids.

Shpitalnik & Dontsova, 2016\textsuperscript{(23)} tested 45 patients with psoriasis vulgaris, among them 27 (60\%) men and 18 (40\%) women aged 18 to 65 years. The clinical picture was represented by psoriatic plaques, congestive hyperemia, and infiltration with small dry white scales on the surface. All patients underwent clinical examination methods, including an examination with an assessment of the dermatological status using the Psoriasis Area and Severity Index. The study of quality of life used the Dermatological Quality Life Index. All people received phonophoresis with hydrocortisone. The findings revealed a notable decline in the severity of these symptoms.

Tedla & Ahmad, 2018\textsuperscript{(24)} assessed a patient with lateral and anterior lesions on their skin, both of which were dry and eczematous, and who was 37 years old. Outcome assessments included pain, swelling, itching, redness and irritation. The patient was assessed using the SRRC and VAS scales. For the anterior lesion on his ankle, the doctor prescribed corticosteroid ointment. He also underwent phonophoresis, which uses 1 MHZ ultrasonic waves with 0.8 w/cm\textsuperscript{2} intensity on continuous mode. A plain ultrasound was used to treat the other lesion on the outside of the foot for the same duration as the anterior lesion, with an output frequency of 1MHz and a power level of 0.8 w/cm\textsuperscript{2}. Over a two-week period, ten treatment sessions are arranged. Both lesions showed post-improvements, however, the more
anterior lesion treated with phonophoresis was better than the latter treated with simple ultrasound. We found that the results in groups A and B where ultrasound was applied were better than group C where ultrasound was absent. This could be a result of the phonophoretic impact of ultrasonic and the physical properties of ultrasound itself according to Byl, (1995) and Machet & Boucaud, (2002).

Byl, 1995 (25) found that the distribution of topically administered medicines can be facilitated by both the thermal and non-thermal properties of sound waves. Heating with ultrasound expands ports of entry such as hair follicles and sweat glands, enhances circulation in the region sonicated, and boosts the molecular kinetic energy in the medicine, as well as the cell membrane. These physiological modifications increase the likelihood that medication molecules will pass past the stratum corneum and be gathered by the dermal capillary network. Cell permeability is raised by the US's thermal and nonthermal actions. Additionally, the microstreaming of ultrasound that travels close to the skin causes shear forces that strain the stratum corneum, opening channels for transdermal delivery.

Machet & Boucaud, 2002 (26) discovered that the mechanical properties of sound waves themselves also facilitate drug diffusion by oscillating cells rapidly, enhancing ion conductance, changing the composition of lipids, enhancing cell permeability, modulating the resting potential at the cell membrane, and possibly disrupting the membrane of some adjacent cells. As the sound wave propagates through the tissues, there may be some pushing and pulling of the cells. Our results showed that the outcomes of the group (A) were better than group (B). However, the results were not statistically significant between them. This may be attributed to the sample size the study carried out on. Therefore, in order to obtain more accurate data on the differences between utilizing ultrasound before and after drug application, we suggest performing a study with a larger sample size.

The considerable drop in VAS and SRRC scores, which is supported by the preceding analysis of these outcomes and claims from additional investigators in similar investigations indicates that hydrocortisone phonophoresis significantly contributes to the comfort of dryness and irritation. The results of the present research would provide a scientifically sound procedure to assist physical therapists, nephrologists, and dermatologists in treating skin conditions.

Limitations: Several limitations existed in this study, including the physical and psychological condition of the patients during the treatment period, the level of patient cooperation, potential human errors, and considerations related to the nutritional status of the patients.

Conclusion

Application of therapeutic ultrasound with 1% hydrocortisone gel at certain parameters for four consecutive weeks resulted in decreasing the severity of uremic xerosis in chronic kidney disease patients compared to only topical application of 1% hydrocortisone.
Conflicts of interest

There are no conflicts of interest.

REFERENCES


Table (2): Mean valued of VAS pre and post treatment.

<table>
<thead>
<tr>
<th>VAS</th>
<th>Group A mean ± SD</th>
<th>Group B mean ± SD</th>
<th>Group C mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A vs B</td>
<td>A vs C</td>
<td>B vs C</td>
<td></td>
</tr>
<tr>
<td>Pre treatment</td>
<td>6.67 ± 1.14</td>
<td>6.77 ± 1.17</td>
<td>7.22 ± 0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>Post treatment</td>
<td>0.66 ± 0.48</td>
<td>1.16 ± 0.86</td>
<td>2.83 ± 0.78</td>
<td>0.11</td>
</tr>
<tr>
<td>MD</td>
<td>6.01</td>
<td>5.61</td>
<td>4.39</td>
<td></td>
</tr>
<tr>
<td>% of change</td>
<td>90.1</td>
<td>82.87</td>
<td>60.8</td>
<td></td>
</tr>
</tbody>
</table>

SD: Standard deviation, MD: Mean difference, p-value: Level of significance

Table (3): Median values of SRRC pre and post treatment

<table>
<thead>
<tr>
<th>SRRC</th>
<th>Group A median (IQR)</th>
<th>Group B median (IQR)</th>
<th>Group C median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A vs B</td>
<td>A vs C</td>
<td>B vs C</td>
<td></td>
</tr>
<tr>
<td>Scaling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment</td>
<td>2 (3-2)</td>
<td>2 (3-2)</td>
<td>2 (3-2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Post treatment</td>
<td>0 (0-0)</td>
<td>0 (1-0)</td>
<td>1 (1-1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Z-value</td>
<td>-3.86</td>
<td>-4.24</td>
<td>-3.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment</td>
<td>2 (2-2)</td>
<td>2 (2-1.75)</td>
<td>2 (2-2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Post treatment</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.5 (1-0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Z-value</td>
<td>-4.14</td>
<td>-3.94</td>
<td>-3.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td></td>
</tr>
<tr>
<td>Roughness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment</td>
<td>2.5 (3-2)</td>
<td>2 (3-2)</td>
<td>2.5 (3-2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Post treatment</td>
<td>0 (0-0)</td>
<td>0 (1-0)</td>
<td>1 (2-1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Z-value</td>
<td>-3.87</td>
<td>-3.90</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td></td>
</tr>
<tr>
<td>Cracks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment</td>
<td>2.5 (3-2)</td>
<td>2 (2.25-2)</td>
<td>2.5 (3-2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Post treatment</td>
<td>0 (1-0)</td>
<td>0 (1-0)</td>
<td>1 (1-1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Z-value</td>
<td>-4.14</td>
<td>-3.87</td>
<td>-3.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td></td>
</tr>
</tbody>
</table>

IQR: Interquartile range. p-value: Level of significance