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Evaluation of the Role of Gabapentin and/or Omega-3 in Uremic Pruritus for Patients Undergoing Hemodialysis

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Abstract:

Uremic pruritus, is chronic itching that occurs in patients with advanced or end-stage renal disease. It is one of common symptoms in patients with end-stage renal disease with approximately 60–90% of patients on hemodialysis(HD) suffering from this problem. This study was designed to evaluate the efficacy and safety of prescribing Gabapentin and Omega-3 in combination or alone for relieving uremic pruritus in Iraqi patients undergoing hemodialysis. The results showed that all the three involved regimens (gabapentin, omega-3, and the combination of both drugs) had significantly reduced the pruritus score. Furthermore, theocombination0was significantly superior to other regimens in reducing pruritus score, while no significant effect was observed by all the regimens on interleukin-6 or on parathyroid hormone serum levels.In Conclusion Gabapentin 100mg plus 1000mg omega-3 based fish oil capsules containing 120mg DHA and 180mg EPA is superior to each drug alone in reducing pruritus score in a sample of Iraqi patients.

Keywords: Gabapentin, Omega-3, Uremic Pruritus, Hemodialysis

تقييم دور تأثير عقار كابابنتين مع/ أو أوميغا-٣ كعلاج مساعد في معالجة أو تخفيف أعراض الحكة المصاحبة للفشل الكلوي لمرضى وحدة الديلزة الدموية

الخلاصة:

تعتبر الحكة المصاحبة للفشل الكلوي من الانواع المزمنة ومن الاعراض الشائعة لدى المرضى الذين يعانون من القصور الكلوي المزمن حيث يعاني ما بين ٦٠ الى ٩٠ في المئة من المرضى الداخلين وحدة الديلزة الدموية منها، صممت هذه الدراسة لتقييم تأثير عقار كابابنتين والعلاج المساعد أوميغا-٣ سواء كان كل دواء لوحده او مجتمعين في تخفيف اثر الحكة المصاحبة للفشل الكلوي للمرضى العراقيين الداخلين وحدة الديلزة الدموية. اظهرت الدراسة ان جميع العقارات المستخدمة كان لها تأثير ايجابي واضح احصائيا على المرضى (قللت من درجة الحكة لدى المرضى) وكان استخدامهما مجتمعا ذا فعالية اكبر مما لو تم استعمال كل دواء على حدة فيما لم يلاحظ فرق احصائي على نسبة interleukin-6 و parathyroid hormone بين مجموعات الدراسة.وعليه يمكن الاستنتاج بأنفعالية عقار كابابنتين بجرعة ١٠٠ ملغم والعلاج المساعد أوميغا- ٣ مجتمعا ذو تأثير أفضل إحصائيا من استخدامهما منفردا في التقليل من معامل أعراض الحكة لدى المرضى العراقيين المشمولين بهذه الدراسة.

الكلمات المفتاحية:كابابنتين، اوميكا-٣، الحكة المصاحبة للفشل الكلوي، الديلزة الدموية.

Introduction:

Uremic pruritus, or more appropriately called"Chronic Kidney Disease-associated Pruritus" (CKDaP), is chronic itching that occurs in patients suffering from advanced orend-stagerenal disease [1].The title "uremic pruritus" has been previously used to describe symptoms o f itching because it is a common skin manifestation in patients with advanced renal failure. However, nowadays, the usage of the term "uremic" may be confusing due to the fact that pruritus is notfound in patients with acute kidney injury [2]. Chronic pruritus is defined as itch persisting for more than six weeks [3]. In this regard, "chronic kidney

disease (CKD)-associated pruritus" is a term that was recently proposed by Paitel*et al* to replace the older one "uremic pruritus" as a more precise nomenclature [2].

Several theories exist regarding the etiology of CKD-aP, including systemic inflammation, elevated levels of histamine, over activation of mu-opioid receptors, and possibly increased levels of C-reactive protein [1,4,5]. Data are conflicting regarding variables that associate with CKD-aP. There are, however, several groups of risk factors that show more consistent associations. These risk factors include gender, markers of bone and mineral metabolism, inadequate dialysis, and comorbid conditions [6].

Several validated scales are used in studies that define the prevalence, outcomes, and treatment of CKD-aP. These scales can be divided into unidimensional (those that measure only CKD-aP severity), multidimensional (those that measure severity and other characteristics of pruritus), and scales that focus predominantly on quality of life (QOL)[7]. Commonly used unidimensional scales include the visual analog scale (VAS), the numeric rating scale (NRS), and the verbal rating scale (VRS) [6].The VAS, NRS,and VRSseem to hav e similar reliability and validity [7].

There have been many proposed treatments for CKD-aP. However, studies examining these treatments have been limited by non controlled designs at single centers, small samples sizes, and non-uniform definitions of CKD-aP treatment modalities can be categorized into immunomodulatory treatment, xerosis treatment,treatment with antihista mines, removal of uremic toxins, treatment of opioid imbalance, management of peripheral neuropathy, and treatment of hyperparathyroidism[6].

Therefore, this study was designed to evaluate the efficacy and safety of prescribing Gabapentin and Omega-3 in combination or aloneforrelieving uremic pruritus in sample of Iraqi patients undergoing hemodialysis.

Patients and Methods:

Seventy nine patients with end stage renal disease attending artificial kidney unit at the Marjan teaching hospital, Babylon governorate for hemodialysis since the fifteenth of September 2016 till the fifteenth of February 2017 suffering from mild, moderate or severe uremic pruritus were randomly allocated into either of the following three groups; **Group A**; 25 patients have been prescribed gabapentin 100 mg capsule post dialysis. **Group B**; 28 patients have been prescribed Omega 3 capsules post dialysis. **Group C**; 26 patients have been prescribed omega 3 plus Gabapentin 100 mg capsules post dialysis. Patients were followed for eight weeks and approved by the Research Ethics Committee, College of Pharmacy, University of AL-Mustansiriyah. The inclusion criteria for patients in this study include patients suffering from mild to severe uremic pruritus undergoing hemodialysis and patients aged above 18 years while the exclusion criteria included Patients on any other type of dialysis than hemodialysis or on alternate type of dialysis hemo- plus peritoneal dialysis, patients who show hypersensitivity for any of the included drugs, patients who are consuming or have been treated by the included drugs for any reason at least for two months before the start of this research and patients suffering from life threatening conditions beside end stage renal disease for whom drug therapy could end with unpredicted results such as disseminated cancers.

Biochemical Assay Methods:

Serum Interleukin 6 measurement: Serum Interleukin 6 level was determined using a ready-made kit for this purpose, the Human IL-6ELISA Kit is a solid phase enzyme-

linked immunosorbent assay (ELISA) based on the sandwich principle. [8]

Determination of Serum Parathyroid Hormone Level: An automated analysis process using Cobas e 400 auto analyser and parathyroid (PTH) kit specific for the test was utilized. The Elecsys assay for determining intact PTH employs a sandwich test principle in which a biotinylated monoclonal antibody reacts with the N‑terminal fragment and a monoclonal antibody labeled with aruthenium complex reacts with the C‑terminal fragment.Theanti bodies used in this assay are reactive with epitopes in the amino acid regions 26‑32 and37‑42.a)Tris(2,2'bipyridyl)ruthenium(II)-complex (Ru(bpy)).[9]

Gradingoof0pruritus and scale used: The severity of pruritus was assessed subjectively and scored as follows: mild: Episodic and localized pruritus without disturbance in usual work and sleep , moderate: Generalized and continuous pruritus without sleep disturbance and Severe: generalized and continuous pruritus with sleep disturbance. The major emphasis was on the sleep disturbance.[10] and a four digit verbal rating scale was used to score the severity of itch of patients starting with grade zero (0) for no itch and ending with grade three(3) for severe itch.

Statistical analysis:

Prior to the start of any statistical analysis observations were tested for normality of distribution using Shappiro-Wilk test and a visual inspection of their histograms, normal QQ plots and box plots, normally or approximately normally distributed data were statistically evaluated using *t*-test (paired t-test for dependent variables and independent two sample t-test for independent variables), and ANOVA while data showing no normal distribution were analyzed using the Wilcoxon test (Wilcoxon rank sum test for independent variables and Wilcoxon signed rank test or matched test for dependent variables), Chi square test was used to analyze categorical data, SPSS 2016 program was utilized in the calculations whenever it was possible while excel program and its equations was utilized in the others.

Results & Discussion:

The demographic data for patients who have completed the study are shown in table -1:

Table -1: Demographic data of the patients

	Omega-3	**Gabapentin**	**Combination**	***P* value**
Number	14	18	18	-
Age	50.57±14.95	54.06 ± 11.70	59.89 ± 14.00	0.150
Gender				
Female	7 (50.0%)	6 (33.3%)	6 (33.3%)	0.552
Male	7 (50.0%)	12 (66.7%)	12 (66.7%)	
Residence				
Rural	6 (42.9%)	9 (50.0%)	13 (72.2%)	0.205
Urban	8 (57.1%)	9 (50.0%)	5 (27.8%)	
Chi square and independent t test used				

Table-1 shows that there were no significant differences in age, gender and residence between the study groups. A result that empowers study design and the group).

Dialysis characteristics of the study groups:

The dialysis characteristics of the patients who have completed the study are shown in table-2 and figure -1:

Table -2: Dialysis characteristics of study groups

	Omega-3	**Gabapentin**	**Combination**	***P* value**
Number	14	18	18	-
Sessions length (hours)				0.465
2	0 (0.0%)	0 (0.0%)	1 (5.6%)	
3	14 (100.0%)	17 (94.4%)	17 (94.4%)	
4	0 (0.0%)	1 (5.6%)	0 (0.0%)	
Number of sessions per week				0.039[a]
1	1 (7.1%)	0 (0.0%)	0 (0.0%)	
2	8 (57.1%)	17 (94.4%)	11 (61.1%)	
3	5 (35.7%)	1 (5.6%)	6 (33.3%)	
4	0 (0.0%)	0 (0.0%)	1 (5.6%)	
Chi square and independent t test used [a]To account for the 9 cells with expected frequency less than 5% with performed Monte Carlo exact test using 10,000 resampling with 99% CI of *P* = 0.034 – 0.044)				

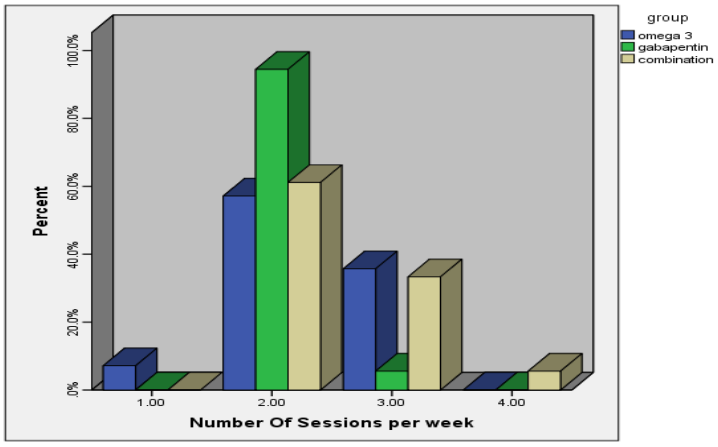

Figure (1): Number of sessions per week

There were no significant difference between dialysis sessions length and type of therapy, however gabapentin group had significantly lower number of dialysis session compared to omega 3 and combination therapy, as illustrated in table (2) and figure (1).

Of course we could not manipulate the number of sessions required for each patient per week because such a thing depends on many factors including for example the residual renal function of the patient, the Kt/v value, the patient week by week overall condition, fluid and electrolytes homeostasis, etc. a fact that have faced most of the researches conducted before, despite that the research team did not find any statistically significant result that could be linked to the significantly lower number of sessions per week seen in the gabapentin group.

Effect of Omega-3, Gabapentin alone and in combination on interleukin-6 (IL-6) and parathyroid hormone (PTH) serum levels:

Table (3) and figures (2) and (3) show the effect exerted by Omega-3 , Gabapentin alone and in combinationon the serum levels of interleukin-6 and parathyroid hormone.

Table (3): Effect of Omega-3, Gabapentin alone and in combination on interleukin-6 (IL-6) and parathyroid hormone (PTH) serum levels:

	Omega-3	**Gabapentin**	**Combination**	***P*-value**
Number	14	18	18	-
IL-6				
Pre	8.26 (5.27 - 39.66)	8.03 (5.55 - 17.30)	8.02 (5.96 - 16.54)	0.991 [b]
Post	7.69 (5.42 - 33.62)	7.51 (5.51 - 30.01)	8.02 (5.65 - 14.13)	0.924 [b]
Percent change	-6.9%	-6.5%	0.0%	0.974 [a]
PTH				
Pre	41.33(11.75-217.25)	49.33 (22.46 - 160.18)	22.72 (13.48 - 212.93)	0.679 [b]
Post	67.18(36.38-187.80)	164.50 (47.50 - 298.90)	46.23 (14.62 - 329.08)	0.457 [b]
Percent change	62.6%	233.5%	103.5%	0.889 [a]

[a] Box Cox transformation used to make IL-6 data normally distributed ($IL\text{-}6^{(-1)}$function used for IL-6 and Log (PTH used for PTH) , two way ANOVA used for calculation of *P* - value for interaction

[b] Kruskal Wallis test for none parametric measures used

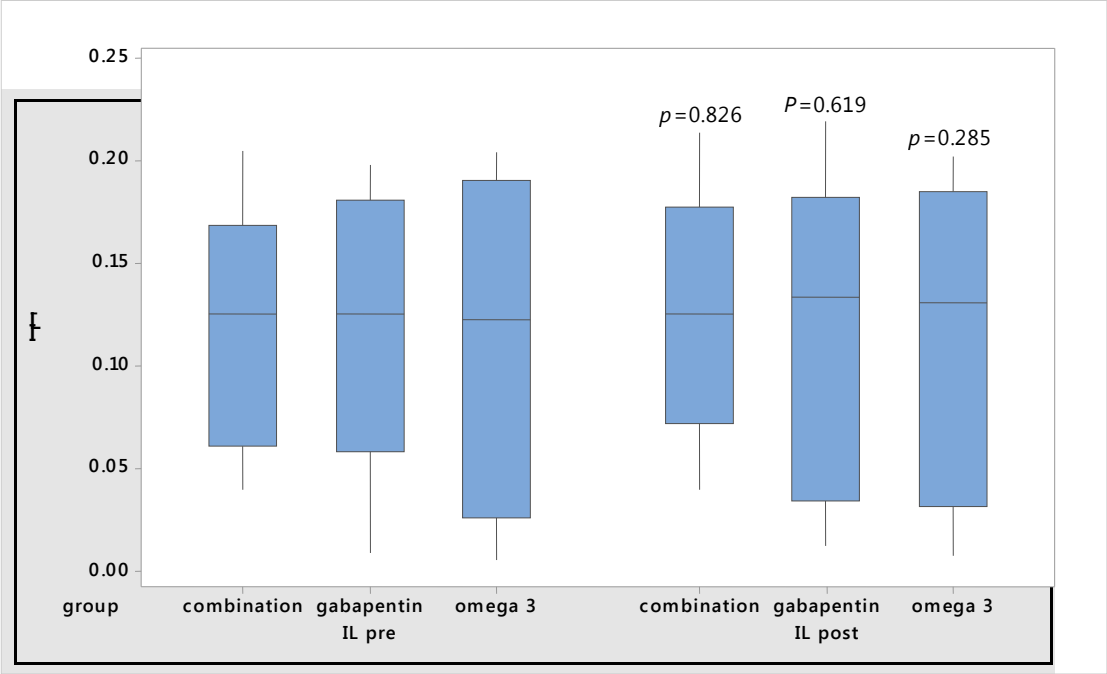

Figure -2: Box plot of IL-6 (the *P*-value shows the change for each treatment from pre to post)

No significant differences were seen in IL-6 and PTH serum levels between the study groups as illustrated in table (3) and figures (2) and (3).

The non-significant difference in interleukin-6 level which was shown in table (3) and figures (2) and (3) could be attributed to the fact that so many patients included in this study have suffered from different types of infections beside the fact that an appreciable number of them had hepatitis C viral disease making the reduction in interleukin-6 level very difficult to be statistically apparent unless the study was carried for a longer period and on a larger number of patients. Another possible explanation is that many of those studies were carried on individuals suffering from diseases other than end stage renal disease[11-15]. Furthermore most of those studies carried on hemodialized patients have used doses of omega-3 much higher than the dose used in this study making the change of interleukin serum level more obvious in a smaller period of time(14). Despite the fact that so many studies have come out with a conclusion that omega-3 supplementation reduces inflammatory response and interleukin-6[12-16] this effect was not observed in this study.

Table (3) and figures (2) and (3) also showed that a non-significant difference was observed regarding parathyroid hormone serum levels and there were no significant effect exerted by the three different regimens on its serum level, regarding that the research team unfortunately did not find any research connecting omega-3 use in uremic pruritus to parathyroid hormone serum level a fact that made us assume that unless further researches are conducted we have to accept the result observed in this study.

Furthermore, many researches have ended with a conclusion that gabapentin is useful in uremic pruritus[1,17,18-20] and also, many other researches that have ended with contradictory results regarding its effect on parathyroid hormone serum levels[21,22], the results of this study agree with those studies saying no significant effect is exerted by the drug on serum parathyroid hormone level under a condition that the drug is prescribed for not more than eight weeks to patients with end stage renal disease in a dose of 100mg post dialysis.

Effect of each intervention on pruritus score:

The effects of each therapy used in this study on the score of pruritus (after eight weeks of therapy) are shown in table (4).

Table (3-8-2): Effect of each group on pruritus score

	Pre	**Post**	**P value**
Omega 3	3 (2 – 3)	1 (0 – 1)	0.001
Gabapentin	3 (2 – 3)	1 (1 – 1.5)	0.001
Combination	3 (3 – 3)	1 (1 – 1)	<0.001
Wilcoxon signed rank test for repeated measure non-parametric used			

Table (4) shows that all therapy regimens exerted a significant effect on chronic kidney disease-associated pruritus.

According to table 4 a significant reduction in pruritus score was observed in all patients who have completed the study in all the three groups.

A significant reduction in pruritus score (*P*=0.001) was observed among patients who have completed the study and took 1 gram of omega-3 based fish oil capsules post dialysis, this result is consistent with that of Ghanei *et al*.[23] despite the fact that Ghanei *et al*. have used a much higher dose of the same drug (3 g daily), but it should be taken into consideration that in our study we had a significant failure rate also the difference in the period throw which the two studies were conducted (one month versus eight weeks)

should be thought of. So many studies were conducted using different formulas but share the common concept (increasing omega-3 consumption of dialyzed patients)[24,25], DanijelaRistic-Medic *et al* have studied the effects of dietary consumption of milled sesame/pumpkin/flax seed mixture (which is rich in omega-3 and omega-6 poly unsaturated fatty acids) and a significant reduction in inflammatory markers (TNF-alpha, IL-6, and hs-CRP, $P<0.001$) was observe after seed mixture treatment) but they did not put a score to pruritus at that study and did not give explanation to the reduction in inflammatory markers observed taking into consideration that they did not change omega-3 to omega-6 ratio[25].

A significant reduction in pruritus score ($P=0.001$) was observed among patients who have completed the study and took 100 mg of gabapentin capsules post dialysis, this result is consistent with so many studies carrying the same concept [1,2,17-20], the only difference this study carries is the dose used which was lower than that used by Eman Nofal *et al*.[26] and gave the same significance making the clame of Wisam Amin *et al*.[27], Rose MA *et al* [28] and many others[29,30] consistent with the results obtained by this study.

A significant reduction in pruritus score ($P<0.001$) was observed among patients who have completed the study and took 100 mg of gabapentin plus 1g omega-3 capsules post dialysis, unfortunately the research team did not find any other study that used the same kind of combination to compare the results observed in this study with.

Comparison between the grade of change in pruritus score exerted by each therapy regimen:

Table -5: Effect of each therapy regimen on the grade of change in pruritus score.

	Rank sum/sd	***P* -value**
Omega-3 vs gabapentin	348/+-32.619	0.0886
Omega-3 vs combination	321/+-37.416	0.6554
Combination vs gabapentin	410/+-45.345	0.0335
Wilkoxon rank sum test		

Table (5) clearly shows that gabapentin plus omega-3 regimen was significantly superior to gabapentin alone in reducing pruritus score while no significant difference was observed between other groups. Due to the fact that no comparable studies were found, further discussion of such a result will be left to the coming studies.

Conclusion:

From the results of the current investigation, it was found that no significant differences were seen in IL-6 and PTH serum levels between the study groups, All therapy regimens had significantly reduced chronic kidney disease-associated pruritus.

The combination of gabapentin 100mg plus 1 gram omega-3 based fish oil is superior to each drug alone in reducing pruritus score.

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