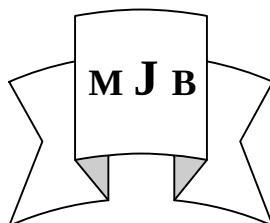


Gabapentin Therapy for Pruritus in Haemodialysis Patients

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Abstract

Background: Itch can be defined subjectively as a poorly localized, non-adapting, usually unpleasant sensation which elicits a desire to scratch. Although specialized nerve endings have been identified for a wide range of stimuli no specific receptor has been identified for itch and it is generally agreed that itch (and pain) are received by unspecialized free nerve endings located close to the dermo-epidermal junction. Generalized severe pruritus occurs in about (30-50 %) of renal failure cases, its one of the dermatological diseases that is difficult to control. Unfortunately, haemodialysis can initiate the symptom as well as improve it. Up to 85% of patients on haemodialysis suffer from itching. Many modalities of treatment are found for those patients, as topical emollients, phototherapy, antihistamine.

Aim of study: To assess the effectiveness and safety of gabapentin in treatment of pruritus induced by dialysis.

Method: This study was conducted in Merjan teaching hospital Haemodialysis unite. 23 patients were included in this study (13 male and 10 female, age more than 18 years). Haemodialysis was performed twice times per week. All patients had histories of pruritus of more than 6 weeks duration that does not respond to antihistamines and other topical treatments. Any medication with presumed antipruritic effects was discontinued one week before the study. The patients were asked to record the severity of their pruritus on a visual analogue scale twice weekly (at dialysis time). The scale consisted of a 10 cm horizontal line marked from 0 (denoting no itch) to 10 (denoting worst possible imaginable itch). Patients were assigned to receive 4 weeks of gabapentine therapy followed by 4 weeks of placebo and there was a 2 weeks of washout period between the sequential treatment phases. Gabapentine 100mg or placebo was administered orally twice weekly at the end of haemodialysis sessions.

Result: The mean pruritus score before the treatment was 8.43 ± 0.99 with a range from (7-10), after gabapentin therapy the score decreased to 1.26 ± 1 (range: 0-3; p-value < 0.0001) while after the end of the resting two weeks (interval period) the score increased to 7.56 ± 1.55 , increment continued to the end of placebo period (after one month) reached to 8.1 ± 1.01 (range: 6-10; p-value = 0.1686).

Conclusion: Gabapentin is a safe and effective drug in treatment of pruritus induced by dialysis with little side effects.

دواء الكابابنتين في علاج الحكة الناتجة من الغسل الدموي لمرضى الفشل الكلوي

الخلاصة

تعرف الحكة على انها شعور داخلي عند المريض يظهر على شكل رغبة خارجية لتخديش الجلد الى حد هذا الوقت لم توجد مستلمات عصبية نهائية متخصصة بالحكة الجلدية على افراد، لكن النهايات العصبية للحكة تشترك مع النهايات العصبية لمستلمات اخرى في الجلد وهي واقعة على الخط الفاصل بين طبقة البشرة والادمة.

٣٠-٥٠ % من مرضى العجز الكلوي المزمن يعانون من حكة جلدية منتشرة في جميع انحاء الجسم ولسوء الحظ ان الغسل الدموي لعلاج العجز الكلوي المزمن ممكن ان يؤدي الى زيادة الحكة في الجسم بالإضافة الى شفاء او تقليل الحكة. ٨٥ % من مرضى الغسل الدموي يعانون من حكة منتشرة في كل اجزاء الجسم. اجريت هذه الدراسة في مستشفى مرجان التعليمي في وحدة الغسل الدموي حيث تم اخذ ٢٣ مريض مصاب بهذا المرض وكان جميع المرضى يغسل لهم مرتين في الأسبوع بالإضافة الى معاناتهم من حكة مزمنة لمدة تزيد عن ستة أسابيع.

تم إيقاف كل الأدوية الأخرى التي تستعمل في علاج الحكة الجلدية قبل أسبوع من الدخول في هذه الدراسة. طلب من كل مريض تدوين شدة الحكة لديه على مقياس معين مرتين في الأسبوع يتألف هذا المقياس من عشر درجات من صفر (أقل درجة) وتعني لا توجد حكة و ١٠ (أعلى درجة) وتعني أعلى قيمة للحكة. تم إعطاء المريض عقار الكابابنتين ١٠٠ ملغم مرتين في الأسبوع ولدة أربع أسابيع وبعد ذلك تم إيقاف العلاج لمدة أسبوعين (فترة راحة) ثم أعطي المريض بعد ذلك عقار العلاج المموه لمدة أربعة أسابيع أخرى. **النتائج:** ان معدل مقياس الحكة قبل اخذ عقار الكابابنتين كان $8,43 \pm 0,99$ لكن هذه النتيجة قلت الى $1,26 \pm 1$ بعد أربعة أسابيع، بينما في نهاية فترة الراحة صار معدل مقياس الحكة $7,56 \pm 1,55$ وهذه النتيجة اخذت بزيادة بعد استعمال علاج العلاج المموه لمدة أربعة أسابيع لتصبح $8,1 \pm 1,01$

الاستنتاج: ان عقار الكابابنتين علاج آمن وفعال في علاج الحكة الجلدية الناتجة من الغسل الدموي لمرضى العجز الكلوي

Introduction

Definition

Itch can be defined subjectively as a poorly localized, non-adapting, usually unpleasant sensation which elicits a desire to scratch.[1] Despite being the predominant symptom of skin disease and a frequent manifestation of systemic disease, pruritus (itching) has been largely neglected by investigators and consequently is poorly understood. The main difficulties have been lack of reproducible, standardized itch stimuli and absence of satisfactory methods for statistically analyzable quantification.[1]

Pathophysiology

Although specialized nerve endings have been identified for a wide range of stimuli no specific receptor has been identified for itch and it is generally agreed that itch (and pain) are received by unspecialized free nerve endings located close to the dermo-epidermal junction.[1] Itch receptors are unmyelinated, confined to the skin and cornea, and are probably members of the polymodal nociceptor class. Recent immunohistochemical research utilizing protein gene product (PGP) 9.5 or non-specific enolase antibodies has supported, but not significantly extended, earlier light-microscope studies.[2,3]

Itch-transmitting, polymodal, unmyelinated C fibres enter the dorsal horn of the grey matter of the spinal

cord, synapse there with secondary neurones which cross over to the contralateral spinothalamic tract and ascend to the thalamus. There, tertiary neurones relay itch to the level of conscious perception in the cerebral cortex.[1] This pain and itch are transmitted along the same nerve pathways was proposed by Rothman and others and has been the prevailing view until recently. According to this interpretation, low-intensity stimulation of unmyelinated polymodal C fibres results in the sensation of itch, whereas high-intensity stimulation causes pain. [4] However, a number of features of pain and itch argue against this interpretation. These include the difference in motor responses (itch induces scratching whereas pain evokes withdrawal); the differential effects of morphine which relieves pain but makes itch worse; and the ability of itch and pain to be perceived independently at the same site. [1]

Microneurographic technology has enable electrical recording to be made from individual polymodal C fibers in the peripheral cutaneous nerve fascicles. Stimulation of these neurons using histamine iontophoresis to cause itching has resulted in identification of small (less than 5% of the total) subset of slowly conducting C fibers distinct form, and with larger receptor field than mechanosensitive polymodal neurons.[5]

These pruritus specific C neurons are also temperature sensitive,

this is of clinical significant since it offers an explanation for every day observation that itching is worse in worm environment.[5]

Type of itching [6]

Pruritoceptive: where the itching sensation started at the nerve ending, due to inflammation, dryness, and other skin diseases.

Neuropathic: where the itching started due to disease localized along the course of nerve as post-zoster neuropathy.

Central (neurogenic): as in cholestasis

Psychogenic : as in parasitophobia.

Cutaneous manifestation of renal failure:

Cutaneous signs of renal failure are present only in fairly advanced cases **urea frosting**, in which crystalline urea is deposited on the skin, is rarely seen. Uraemic patients tend to have a **dry skin**, sometimes with fine scaling. A reduction in the size of eccrine sweat glands in uraemia may contribute to this effect[7], although high-dose diuretic regimen is a cofactor.[8] **Anaemia** presenting as pallor is an early and common sign in renal failure resulting from reduced erythropoiesis and increased haemolysis. A **muddy brown** hyperpigmentation develops in many cases, attributed to retention of chromogens and deposition of melanin, possibly due to impaired renal processing of MSH.[9] **Increased nail pigmentation** usually confined to the distal aspect occurs in a proportion of patients[10]. This distal brown or more normal red colour, combined with a proximal white appearance gives rise to the 'half-and-half' nails, a distinctive pattern seen in about 10% of renal failure cases .[11]

Purpura due to a mild thrombocytopenia or more marked platelet dysfunction is common and may be partly corrected by dialysis.

Wound healing is prolonged and patients may be more susceptible to pressure sores. [12] **Calcifying panniculitis** has been reported occasionally in renal failure caused by a mechanism known as calciphylaxis.[13] Metastatic skin calcification is a rare phenomenon in uraemic patients; it usually presents as papular or nodular cutaneous lesions around large joints or flexural sites. Non-cutaneous metastatic calcification is by comparison much more common[14]. **A perforating disorder** variously described as perforating collagenosis, (Kyrle's disease) or perforating folliculitis occurs in renal failure .[15]

Uraemic neuropathy affects some 60% of patients with renal failure or on long-term haemodialysis.[16] Up to 40% of patients with renal failure may develop **gynaecomastia** while receiving dialysis.[17]

Generalized severe **pruritus** occurs in about (30-50%) of renal failure cases, less troublesome involvement in many more. Unfortunately, haemodialysis can initiate the symptom as well as improve it. Up to 85% of patients on haemodialysis suffer from itching, in one study one-third before dialysis, the others after it; 12% had reduced pruritus after 6 months' dialysis.[18]

A number of different mechanisms have been proposed to explain the origin of uremic pruritus, but none are completely convincing. Xerosis, or dry skin, is the most frequent dermatological manifestation in patients undergoing dialysis therapy. Reduced hydration of the stratum corneum in dialyzed patients with pruritus has been reported , although high-dose diuretic regimen is a cofactor.[7] other causes of itching in chronic renal failure are secondary Hyperparathyroidism, increased serum histamine levels, hypervitaminosis A,

iron-deficiency anemia, and neuropathy have been implicated. Complications such as Kyrle's disease, lichen simplex chronicus, and prurigo nodularis may develop and contribute to the degree and severity of pruritus.[19]

Treatments of uremic pruritus

Because of the poorly understood pathophysiological mechanisms of uremic pruritus, the treatments of this condition have largely been empirical, and no treatment has been shown to have sufficient efficacy and safety.[20] The proposed treatment options for uremic pruritus are listed as follow: [20]

Topical treatment

Skin emollients, Capsaicin (0.025%) cream

Physical treatment

Phototherapy (Ultraviolet),

Systemic treatment

Antihistamine & ketotefin ; Low-protein diet ; Lidocaine & opioid antagonists; Active charcoal; Cholestyramine; Thalidomide; Parathyroidectomy

Dialysis-related treatment

Efficient dialysis; Erythropoietin; Kidney transplantation

Aim of study

To assess the effectiveness and safety of gabapentin in treatment of pruritus induced by dialysis.

Patients and Methods

This study was conducted in Merjan teaching hospital Haemodialysis unit. 23 patients were included in this study (13 male and 10 female, age more than 18 years) . Haemodialysis was performed twice times per week via a polysulphon dialyser (FB-170 TGA, NIPRO) on Fresenius medical care machine (Germany) using bicarbonate dialysis fluid containing 134mmol/L Na, 1.4 mmol/L Ca, 0.8 mmol/L Mg, 98

mmol/L Cl, 4 mmol/L acetate and 36mmol/L bicarbonate .Blood flow was 150-350 mL/min and dialysate flow was 500ml/min. All patients had histories of pruritus of more than 6 weeks duration that does not respond to antihistamines and other topical treatments. Patients with other dermatological , liver ,haematological and metabolic diseases associated with pruritus were excluded from the study . Any medication with presumed antipruritic effects was discontinued 1week before the study. The patients were asked to record the severity of their pruritus on a visual analogue scale twice weekly (at dialysis time). The scale consisted of a 10 cm horizontal line marked from 0 (denoting no itch) to 10 (denoting worst possible imaginable itch). Patients were assigned to receive 4 weeks of gabapentine therapy followed by 4 weeks of placebo(100 mg starch) and there was a two weeks washout period between the sequential treatment phases. The twice weekly pruritus scores of patients were collected for each period of the study (the 1 week preceding the trial, the active treatment phase, the placebo phase and the washout period). The median of the scores for each period was accepted as the score of that period. Gabapentine 100 mg or placebo was administered orally twice weekly at the end of haemodialysis sessions. A reduction in scores of $\geq 50\%$ was considered as the desired improvement in symptoms during treatment. Pre-dialysis blood samples were drawn for complete blood picture, serum Ca, serum phosphate , albumin , liver function test and renal function test. The differences in mean values were tested by a one way analysis of variance. The significance of the differences between the groups was calculated by the paired-samples t-

test. Statistical significance was assigned to p- value of ≤ 0.05 .

Result

All patients (23) complete the study. Their characteristic parameters as follow Table 1.

Table 1 showed characteristic parameters of the patient

Parameter	Mean $\pm$ SD	Maximum	Minimum
Age (years)	40.4 $\pm$ 14.12	70	18
Dialysis duration (months)	10 $\pm$ 13	24	3
Itching duration (months)	11 $\pm$ 11	23	2
Systolic pressure (mmHg)	128 $\pm$ 24.1	170	95
Diastolic pressure (mmHg)	81 $\pm$ 15.1	110	60
Haematocrit (%)	27 $\pm$ 3.9	34	22
Serum albumin (g/dl)	29 $\pm$ 4	37	22
Calcium (mmol/l)	2.23 $\pm$ 0.32	2.8	1.6
Phosphate (mmol/l)	1.59 $\pm$.041	2.2	0.7

The mean pruritus score before the treatment was 8.43 ± 0.99 with a range from (7-10), after gabapentin therapy the score decreased to 1.26 ± 1 (range : 0-3 ; p-value < 0.0001), while after cessation of gabapentin the score return to increase reaching to $7.56 \pm$

1.55 (range 6-10) at the end of the second week of interval period, this increasing continued to the end of placebo period (after one month) reached to 8.1 ± 1.01 (range : 6-10 ; p-value = 0.1686) as shown in the following table (2)

Table 2 shown the differences in mean score of pruritus (VAS) before and after gabapentin treatment and before and after placebo treatment.

	Patients No.	Mean score of pruritus (VAS)	SD	p-value
Before treatment with gabapentin	23	8.43	0.99	< 0.0001 Highly significant
After gabapentin treatment	23	1.26	1	
Before treatment with placebo(end of interval period)	23	7.56	1.55	0.1686 Not significant
After Placebo treatment	23	8.1	1.01	

All patients showed improvement in pruritus score (reduction in score more than 50% in VAS). The response to Gabapentin not related to the age of patients nor to the

duration of the dialysis. During the course of treatment all patients showed no side effects except of slight headache and dizziness which occur mainly in the first dose of treatment.

Discussion

This is the 1st study done in our country, where those patients were referred to our department (Dermatology unit) to control their intractable itching. Because its pathophysiology is poorly understood, the treatment of uraemic pruritus remains mainly empirical. One of theories of itching in renal failure is the neuropathic theory 60-65% of patients with renal failure exhibiting a dysfunction of the peripheral nervous system.[16] Abnormal nerve conductions in both motor and sensory circuits are common concomitants of the early manifestations of uraemia, such as paraesthesias, burning feet and restless leg syndrome.[21] Pruritus may arise from a diminished threshold of perception. This augmented sensitivity to pruritic stimuli may result from nerve fibre damage. It has been demonstrated that uraemic patients on haemodialysis develop abnormal innervation. In those patients but not in control, nerve terminals and fibres have been found sprouting throughout the layers of the epidermis.[2]

In 2003, a review of over 150 original papers approved the use of gabapentin for neuropathic pain, neuritis or neuralgia of various sorts certain itchy dermatosis (prurigo nodularis, brachioradial pruritus), and suggested the assessment of its role in the management of pruritus [22]. Gabapentin is an anticonvulsant structurally related to the neurotransmitter γ -aminobutyric acid (GABA). Although its mechanism of action is not clear, gabapentin appears to have an effect on voltage-dependent calcium-ion channels. By blocking neuronal calcium influx, it may inhibit ectopic discharge activity from injured nerves thus interrupting the series of events that perhaps lead to the pruritus sensation in uremic patients . [23,24]. The differences in our study

from other studies, we are found that all patients use this treatment have dramatic response (decrease in the VAS more than 50%), the dose and frequency of treatment in our study is less (100 mg twice weekly) compared with other studies (300 mg trice weekly) [25,26], this may be due to short time of our haemodialysis (about three hours) compared with optimum haemodialysis which is longer time (four to five hours)[26].

Conclusion

Gabapentin is a safe and effective drug in treatment of pruritus induced by dialysis with little side effects.

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