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Uremic Pruritus, Treatment and Skin Care

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Abstract

Background: Pruritus is a condition affecting about 40% of patients with end stage chronic kidney disease (CKD). Although the severity of chronic pruritus individually varies, it is in general severe in uremic pruritus (UP) and significantly affects the quality of life of patients. As the etiology of UP is not clearly understood, there are many alternatives recommended for treatment. The aim of treatment is to reduce the severity of pruritus and to increase the quality of life of patients. Emollients, gabapentin and phototherapy are recommended as first line therapy in patients who are not suitable for kidney transplantation or who are at preparation stage. In patients refractory to these treatments, μ-opioid receptor antagonists such as naltrexone or κ-opioid receptor agonist such as nalfurafine can be preferred. Certain authors recommend adjuvant medicine and alternative treatments, however evidence level of these treatments is low. In patients who are refractory to all of these treatments, kidney transplantation as a precise and last treatment option in suitable patients. In this article, uremic pruritus and current treatment approaches are reviewed.

Introduction

Chronic kidney disease (CKD) became a significant health problem world widely due to increased life expectancy in human. Uremia leads to several vascular, neurological, immunological, hematological, endocrine and dermatological problems. The most frequently seen skin signs in CKD are dryness, hair symptoms, pruritus, pigmentation disorders, and nail (half and half) and oral mucosa symptoms [**1,2**].

Complex and not fully understood pathophysiology of uremic pruritus lead to lack of an effective treatment. Before initiation of UP treatment, other dermatological/systemic conditions leading to pruritus such as atopic dermatitis, drug allergies, cholestasis, lymphoma, hypervitaminose A and iron deficiency anemia should be excluded [**3**].

A-Prevalence

Chronic pruritus rate in general population is 10-13%, while this is increased up to 20-90% in CKD patients. Pruritus affects negatively both hemodialysis and peritoneal dialysis patients. Pruritus affects 40% of end stage CKD patients [**1**].

B-Characteristics of pruritus

In patients with renal diseases, pruritus is intermittent, generalized and symmetric, and it is especially triggered at night. Many patients

say that pruritus becomes more severe during or immediately after dialysis. Pruritus affects whole body and it may be concentrated on back, face and fistula area on the arm. Typically pruritus is on the areas where the hands can reach and there is a clear area on the back to where hands can't reach. As with all kind of pruritus, this pruritus also becomes more severe by warm and sweating [**4,5**].

C-Etiopathogenesis

The mechanism of chronic uremic pruritus is not fully understood. Many etiological factors are suggested (**Table 1**) [**5,6,7**].

Skin dryness: This is the most frequent dermatological symptom seen in dialysis patients. More skin dryness is also scientifically proved in dialysis patients with pruritus than dialysis patients without pruritus. However certain authors suggest that skin dryness has no primary role, rather dryness triggers the pruritus which is already present [**8**].

Systemic inflammation: In UP, increased level of C reactive protein and certain inflammatory cytokines such as IL -2 , IL 6 , IL-31 has been demonstrated. In hemodialysis patients, abnormal production of mast cells, increased level of histamine, substance P and serotonin also have a role in etiopathogenesis. Although it is recognized that histamine is released in UP, there is no correlation between serum histamine level and pruritus severity [**5,6,8**].

Increased level of parathyroid hormone, calcium and phosphor in serum: Secondary hyperparathyroidism leads to accumulation of calcium and magnesium into the skin and release of serotonin and histamine due to mast cells degranulation. However all patients with hyperparathyroidism may not have pruritus [**5**].

Neuropathic pathway: In general uremic neuropathy is also present in patients with uremic pruritus. Neurophysiological alterations have been shown to control pain and pruritus concomitantly. Once the pruritus starts, central memory and neural sensitivity develop against to pruritus resulting from secondary changes in nerves [**4,7**].

Opioid receptors: UP is suggested to be related to u opioid receptor activation in dermal cells and lymphocytes. Endogenous opioids are secreted from kidney and serum beta-endorphin level is increased in CKD. Stimulation of opioid receptors is considered to lead pruritus by induction of skin mast cells and/or direct effect on central nervous system [**5,8**].

Glycation end products: Accumulation of advanced glycation end products resulting from hyperglycemia (AGE) in stratum corneum is suggested to have a role in UP [**5,8**].

D-Quality of Life

Moderate to severe pruritus affects significantly quality of life and social status of many patients. In UP, quality of life of patients is impaired due to factors such as insomnia, and depression. In UP, concomitant pruritus and sleep problems increase the mortality rate of hemodialysis (HD) patients. In HD patients with pruritus, mortality rate was approximately 17% higher compared to those who have no pruritus [**3,9**]. In some patients, pruritus may be unbearable and the patients may attempt suicide [**10,11**].

E-Treatment

1-General information

The precise treatment in uremic pruritus is kidney transplantation. All other treatments are still experimental and evidence-based data is insufficient. Main treatment principle in patients waiting for surgery or those who are not suitable for surgery, is to increase quality of life by reducing pruritus [**12**]. If viral hepatitis, diabetes mellitus, hyperparathyroidism, hyperphosphatemia and anemia is present, they should be managed for pruritus control [**7,13**].

It should be noted that polypharmacy (called also using multiple drugs) also is another factor triggering pruritus in patients. Thiazides and calcium channel blockers may lead to pruritus especially in aged people. Management of pruritus should address dermatolo-

gical or systemic causes of pruritus. The cornerstone of treatment is lubrication of skin and restauration of skin barrier. Side effects due to systemic treatment should be assessed according to individual patient [**14**].

Complex pathophysiology of uremic pruritus, drug side effects and already administration of multiple drugs to patients are main challenge of physician in treatment of uremic pruritus. Although dermatologists prescribe frequently antihistamines for these patients, these treatments aren't usually successful in control of pruritus [**4,7**].

Treatment efficacy has been usually shown by placebo controlled trials and with the use of visual analogue scale. Although many treatments are used in daily practice, there is no a treatment approved by Food and Drug Administration (FDA) [**13,15**].

Emollients, gabapentin and phototherapy are recommended as first line treatment. In patients refractory to these treatments, μ-opioid receptor antagonists such as naltrexone or κ-opioid receptor agonist such as nalfurafine can be preferred. In certain patients refractory to all of these treatments, a successful kidney transplantation in suitable patients, would control pruritus complaint. Neurotropic drugs such as gabapentin, naltrexone and nalfurafine were effective in uremic pruritus and well tolerated by patients. However comparative trials on the efficacy are still needed [**5,16,17**].

2. Medical treatments

2a. Usage of high-permeability dialysate:

Although the use of high quality and high permeability materials for dialysis reduced the frequency of uremic pruritus, they are not sufficient alone [**16**].

2.b Topical treatments

Emollients: Sericin 8% cream, pramoxine 1% lotion, glycerin 15% and paraffin mixture was found to be effective in uremic pruritus [**2,18**].

Gama linolenic acid: Daily administration of 2,2% cream on pruritus area has been found to be effective [**2**].

Topical capsaicin cream: capsaicin is an alkaloid obtained from red pepper. It shows its effect by reducing release of substance P from C type nerve fibers. Moreover, recently it is suggested that it shows also its effects by activating vanilloid receptors with a significant role in pruritus etiopathogenesis [**19**].

Topical corticosteroids: Topical corticosteroids can be used alone or in combination with emollients in treatment, however administration of potent corticosteroids on large areas and for long term [**20**].

Topical tacrolimus: Administration of tacrolimus 0,03% cream two times daily has been found beneficial [**2**].

Topical cromolyn: Daily administration of topical cromolyn sodium 4% cream has been found effective in UP [**21**].

2c. Systemic treatment

Gabapentin is basically used in treatment of neuropathic pain and epilepsy; however it shows its effect in chronic pruritus by targeting neural system and reducing neural hypersensitivity. Different doses of gabapentin in uremic pruritus has been recommended by different sources. In our country, a placebo-controlled, double-blind study conducted in 2004, found that gabapentin treatment administered as 300 mg 3 times weekly (following each dialysis session) was effective in UP treatment in hemodialysis patient [**22**]. Certain authors suggested and used doses at range of 100 to 400 mg [**23,24**] . Nofal an colleagues suggested gabapentin as first choice treatment in uremic pruritus at doze of 100 to 300 mg [**25**]. In chronic renal insufficiency, oral gabapentin is recommended to initiate at lower dose and then increase gradually in order to prevent gabapentin-related neurotoxicity risk [**26,27**].

Pregabalin has also mechanism of action similar to gabapentin. Pregabalin is recommended as 25-75 mg/ day/oral [**28**]. Solak and colleagues suggested that neither gabapentin nor pregabalin was superior to each other in UP treatment [**27**].

μ-opioid-receptor antagonist /naltrexone: Its efficacy in uremic pruritus has been shown [**17**]. However there is still need for compara-

Table 1. Pathogenesis of uremic pruritus [2]

Electrolyte imbalance	Endocrine disease	Neuro-cutaneous alterations	Other
Hypervitaminose A	Secondary hyperparathyroidism	Abnormal stimulation of sensory neurons	Skin dryness
Hypercalcemia		Peripheral neuropathy	Increased IL -2, IL -6, IL-31
Hyperphosphatemia		Increased serum beta endorphin	Increased CRP
Hypermagnesemia		Substance P	Iron deficiency anemia
			AGE

tive study of efficacy [**5,17**].

Kappa agonists/nalfurafin treatment: Oral nalfurafin 5 micrograms was administered every night for 52 weeks and relevant improvement were seen in pruritus scores of patients. There are authors also suggesting its administration at different dosage following each hemodialysis session [**29, 30, 31**]. However there is still need for comparative study of efficacy [**5,17**].

Antidepressants/anxiolytics/sedatives

Daily administration of oral sertraline 50 mg has been shown effective in UP [**15**].

Mirtazapine: It is presynaptic alpha 2 adrenergic inhibitor; it is considered that its effect is due to its anxiolytic effect [**15**].

Other: There are few studies showing the efficacy of fentanyl, methadone, phosphate bindings, naltrexone, thalidomide [**20**] , active charcoal [**2,5**].

2d. Phototherapy

Narrow band uvb treatment controls the pruritus by reducing pro-inflammatory cytokines. However its efficacy starts on month 1 or 2 of treatment and severity of pruritus may be increased during first 2 weeks. Treatment is suggested 3 times weekly until the control of pruritus, then once or twice weekly. As phototherapy is expensive than topical treatments and requires to be administered at hospital, it requires longer time, however this is an effective and safe treatment in uremic pruritus. It can be used in patients refractory to topical treatments, in those who don't tolerate or use oral treatments. However recurrence of pruritus following treatment and increased risk of skin tumor due to phototherapy may rise questions around the continuity of treatment. In the literature, there is no data on total UVB dose [**17,32**].

However there are also authors suggesting that phototherapy is not effective in uremic pruritus [**33**].

3- Surgical treatment

Kidney transplantation: It is considered as precise and last treatment option in UP [**12**].

Parathyroidectomy: Subtotal parathyroidectomy is preferred in suitable patients [**2,8**].

4- Adjunctive medicine and alternative treatments

Physicians and patients started commonly alternative treatments methods world widely. However the efficacy and safety and side effect profile of these treatments are not clearly understood. Patients with chronic renal disease also may use these treatments without counselling their physician. Methods such as herbal medicines and nutritional supplements, aquapressure, acupuncture, homeopathy, exercise, yoga and reflexology are being tried by patients. Although these treatments are commonly used in UP, evidence-based data is less. There also publications suggesting that these treatments are not effective [**4,17,34,35,36**].

Patients should be informed in right way and it should be noted that certain wrong methods may impair the hemodynamic by in-

creasing glomerular filtration rate and that there may be drug interactions.

5-Patient education

Patients are advised to avoid itching and to stop itching by rigid and sharp objects. Frequents administration of moisturizing agent on pruritus area and application of ice for maximum 2 minutes are recommended. Patients are also advised to keep balanced room temperature, to take measures for warm weather and to wear slim and cool dress. Regular administration of moisturizing agents, avoidance from warm bath and from peeling are also significant points for patients [**4,8**]. Patients should be asked whether they use adjunctive and/or alternative medicine and patients should be informed about these treatments [**34**].

Conclusion: Pruritus, is a condition impairing quality of life regardless of subject. Physician responsibility is to pay attention to patient with pruritus and to advise them about protective measures and to initiate appropriate treatment following determination of severity of pruritus.

Appropriate approach and treatment for chronic pruritus present in approximately in half of end stage CKD patients, would be possible by multidisciplinary approach of nephrologist and dermatologists and therefore quality of life of patients would be significantly increased.

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