**Name of Journal:** *World Journal of* *Nephrology*

**Manuscript NO:** 38508

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**role of narrow band ultra violet radiation as an add on therapy in peritoneal dialysis patients with refractory uremic pruritus**

SapamR *et al*. Narrow band UVB in uremic pruritus

Ranjeeta Sapam, Rajesh Waikhom

**Ranjeeta Sapam,** Department of dermatology Jawaharlal Nehru Institute of Medical Sciences, Porompat 795005, India

**Rajesh Waikhom,** Department of Nephrology, Jawaharlal Nehru Institute of Medical Sciences, Porompat 795005, India

**ORCID number:** Ranjeeta Sapam (0000-0001-7810-7834); Rajesh Waikhom (0000-0002-1285-9133).

**Author contributions:** Sapam R is the main author and contributed to data recording, follow up and analysis; Waikhom R designed the study, did the literature search and contributed to the writing of the manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Jawaharlal Nehru Institute of Medical Sciences Institutional Review Board.

**Conflict-of-interest statement:** All authors have no conflicts of interest to report.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Rajesh Waikhom, MD, Associate Professor,** Department of Nephrology, Jawaharlal Nehru Institute of Medical Sciences, Imphal east, Manipur, Porompat 795005 India. rajesh.waikhom@gmail.com

**Telephone:** +91-897-4007290

**Received:** April 25, 2018

**Peer-review started:** April 25, 2018

**First decision:** May 8, 2018

**Revised:** June 26, 2018

**Accepted:** June 28, 2018

**Article in press:**

**Published online:**

**Abstract**

***Aim***

To assess the role of narrow band ultraviolet B (UVB) as a treatment option in peritoneal dialysis patients with refractory uremic pruritus.

***Methods***

In this retrospective study, 29 adult patients with end stage renal failure on peritoneal dialysis and who had refractory uremic pruritus were given narrow band UVB radiation as an add-on therapy to standard care for a duration of for 12 wk. The response to the pruritus was assessed by visual analogue score (VAS) weekly and at the end of study period.

***Results***

The average VAS score at the end of the study was 3.14 ± 1.59 which was significant compared to the baseline value of 7.75 ± 1.02 (*P* < 0.05). Improvements in symptoms were noted in 19 out of 21 (90.4%) patients. However relapse occurred in 6 out of the 19 patients who responded. Dropout rate was high during the study period (33.3%).

***Conclusion***

Narrow band UVB as an add on therapy is effective in peritoneal dialysis patients with refractory uremic pruritus. However the present regime is cumbersome and patient compliance is poor.

**Key words:** Narrow band ultraviolet radiation; Uremic pruritus; Peritoneal dialysis; visual analogue score; retrospective study

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Uremic pruritus is a very distressing condition commonly seen in patients with advanced renal failure. They respond poorly to the present available treatment regime. Narrow band ultraviolet (NUV-B) radiation is an option in patients with refractory symptoms. In this study we selected patients on peritoneal dialysis who had such refractory pruritic symptoms and used NUV-B as an add on therapy to the standard medical care for a period of 12 wk. We found that using NUV-B improved symptoms in more than 90% of the patients. However the present regime used is not patient friendly and compliance is poor.

Sapam R, Waikhom R. role of narrow band ultra violet radiation as an add on therapy in peritoneal dialysis patients with refractory uremic pruritus. *World J Nephrol* 2018; In press

**Introduction**

Uremic pruritus is a very common and troublesome complication seen in patients with advanced chronic kidney disease[1-4]. The pathophysiology is complex and many factors have been identified like dryness of skin[5,6], hyperparathyroidism[7,8], calcium phosphate deposition[9,10], imbalances between mu and kappa opioid receptors[11,12] and systemic inflammation. Anemia, inadequate dialysis elevated serum magnesium and aluminum levels, hepatitis C infection are also believed to have some contributing effects. However in many cases the cause remain unexplained. There are strong associations of uremic pruritus with depressive symptoms and poor sleep quality. Sometimes the pruritus is severe and refractory to treatment. Narrow band ultraviolet B (NB-UVB) phototherapy is one option in such difficult cases. Narrow Band UVB decreases the proinflammatory cytokine level and induces mast cell apoptosis. In this study, we aim to investigate the role of NB-UVB as an add-on therapy to standard treatment used in severe uremic pruritus in the peritoneal dialysis patients.

**MaterialS and Method**

This retrospective study was conducted in department of dermatology at Jawaharlal Nehru Institute of Medical Sciences (JNIMS) Imphal, a tertiary referral center in north eastern part of India. Adult end stage renal disease patients on peritoneal dialysis with refractory uremic pruritus were included in the study. The patients were recruited from nephrology unit of 3 hospitals in Imphal during the study period from September 2011 till September 2017.The selected patients were referred to the dermatology department at JNIMS for narrow band UVB therapy.

***Inclusion criteria***

In order to be eligible for inclusion in this study, patients should be older than 18 years of age, should have end stage renal disease and be on peritoneal dialysis as treatment modality and have refractory uremic pruritus.

From September 2011 until September 2017, 29 patients satisfied the criteria. Uremic pruritus was defined as pruritus developing in patients with chronic kidney disease in the absence of other systemic, dermatological disorder or psychological factors. Refractory uremic pruritus was defined as uremic pruritus not responding to any two agents known to relieve the symptoms over 4 wk period. The agents used include topical emollients, topical capsaicin, antihistamines, pregabalin, gabapentin and tricyclic antidepressants.

***Exclusion criteria***

Those patients with a prior history of photosensitivity and other prior dermatological disease which can cause pruritus were excluded from this study.

**Protocol**: The patients were administered NB-UVB therapy every alternate day, three times per week for a total of 12 wk. They were started at a dose of 270 mJ/cm2 and then increased by 15% in each visit. If after the session patient had asymptomatic erythema then it was continued at the same dose. Dose was reduced by 15% if patient developed erythema with minimal pain/itchiness. If patient developed painful erythema or bullous lesion then it was restarted at one-third of the dosage. Phototherapy was administered using “Derma India, Chennai Lightning cubicles PUVA” which is equipped with 24 UVA lamps emitting a radiation spectrum of 320-400 nm with a maximum at 366 nm, and 24 UVB lamps emitting radiation spectrum of 290-320 nm with a maximum of 300 nm.

The patients were allowed to continue with the previous medications/agents for uremic pruritus during the study period. Peritoneal adequacy test was performed in all patients at entry to the study. Serum calcium/phosphate/intact parathyroid hormone/serum iron profile/hemoglobin were evaluated in all the patients

Visual analogue scale (VAS) (0 = no pruritus; 10 = most severe pruritus) was used to identify the intensity of itch. It was measured at baseline and weekly till the end of 12th week. After the completion of the treatment protocol it was then measured monthly during the follow up period.

The outcomes were grouped into the following: (1) Complete responders: defined as a VAS score of zero at the end of study period; (2) Partial responders: defines as a VAS score between 1 to 5 at end of treatment and the final VAS score less than the value at baseline; (3) Non responders: VAS score more than 5 at the end of treatment period.

Relapse was defined as a VAS score more than 5 after having shown complete or partial response.

After the completion of the treatment protocol, patients were followed up on a monthly basis for another 6 mo. During the follow up period patient were assessed for relapse of the pruritus. VAS score was recorded during these visits. A feedback form was also provided to the patient. The form allows them to rate their experience with the treatment protocol and provide suggestions to improve their adherence.

***Statistical analysis***

Statistical analysis was performed using the SPSS 16 software. Continuous data was described in terms of mean ± sd and categorical data by frequency and percentage. Paired *t* test was used to compare the mean VAS score at baseline and at the end of the study. A two sided *P* score of < 0.05 was considered significant.

**Results**

A total of 29 patients took part in this study. Seven patients dropped out during the treatment period. One patient died during this period. Baseline characteristics of the patient are as in Table 1.

The mean age of the patients was 56 ± 15 years. The mean duration on peritoneal dialysis of these patients at the time of study was 10 ± 8 mo. The average baseline VAS for pruritus was 7.75 ± 1.02. At the end of the treatment period the average VAS score was 3.14 ± 1.59 which was a significant drop from the baseline score (*P* < 0.05). Twenty-one patients completed the study and 19 of them (90.4%) had improvement in the severity of pruritus. In 3 patients (14.2%) complete resolution of pruritus was noted. Two patients (9.5%) continued to have persistent pruritus with VAS score more than 5 (Table 2).

Follow up data were available on 14 patients. The mean VAS score at the end of follow up period was 4.14 ± 2.85. Six patients relapsed with pruritus VAS score more than 5. The mean time to relapse was approximately 4.2 ± 2.99 mo.

No significant adverse effects attributable to NB-UVB were identified.

**Discussion**

Uremic Pruritus is a fairly common entity in patients with advanced renal failure including patients on hemodialysis as well as peritoneal dialysis. In a recent study in Chinese patients, the prevalence of uremic pruritus in patients on peritoneal dialysis was approximately 62.5%[13].

The usual protocol followed in managing patient with uremic pruritus includes optimization of the dialysis dosage, optimizing treatment of hyperparathyroidism, hyperphosphatemia and anemia. Initially patients are usually managed with emollients and topical analgesics for symptomatic measures. Many of these patients eventually require systemic medications-anti-histamines/pregabalin/gabapentin/anti-depressants. Hemoperfusion has been used in combination with hemodialysis for hyperparathyroidism and pruritus in maintenance hemodialysis patients[14]. A small population of patient continues to have persistent symptoms in spite of all such measures. Phototherapy may be tried as a treatment modality in such cases.

In a small open pilot study, Ada et al reported a satisfactory response to narrow band UVB in patients with uremic pruritus[15].The randomized clinical study by Ko *et al*[16] showed significant improvement in the pruritus intensity however the beneficial effect was marginal when compared to control group which received long-wave UVA radiation.

In our study we noted that NB-UVB Phototherapy was helpful as an add-on therapy in relieving symptoms of uremic pruritus in patients on peritoneal dialysis. A previous randomized controlled trial by Ko *et al* failed to show any substantial benefit compared to broadband UVA phototherapy. This lack of benefit was due to improvement in pruritus intensity in the control arm which they attributed to placebo effect. However the population studied in that trial differs from our study. In our study we included only patients with end stage renal disease on peritoneal dialysis while the study by Ko *et al* had a mixed population of patients including chronic kidney disease patients on conservative treatment. Only 3 patients in that study were on peritoneal dialysis. Another important difference from that study is the duration of the treatment period. As per our protocol the total duration of therapy was 12 wk compared to the 6 weeks used in the randomized trial. The extended duration of our treatment is based on our preliminary experience with such patients where we noted a more significant improvement in symptoms when they receive a more prolonged course of treatment.

The pathophysiology involved in uremic pruritus is very complex and multifactorial. Multiple hypotheses have been proposed-anemia, xerosis, hyperparathyroidism, hyperphosphatemia, inadequate dialysis, imbalance of opioid receptors and presence of inflammatory state. Some of the factors contributing to pruritus in non-dialysis patient may not be applicable in patients already on peritoneal dialysis. The response of uremic pruritus to phototherapy may differ in peritoneal dialysis population compared to patients on hemodialysis. The beneficial effect of NB-UVB is believed to be due to induction of mast cell apoptosis and reduction in proinflammatory cytokine level[17].

In our study the mean hemoglobin levels (9.99 ± 0.9) is very near the target set by KDIGO[18].The serum phosphate levels (mean value 4.44 mg/dl) and intact parathyroid levels(mean value 132.28 pg/ml) were also reasonable for patients on dialysis. 19 out of the 21 patients who completed the study had adequate small solute clearance (weekly kt/v > 1.7) suggesting that factors other than inadequate dialysis played a significant role in the pathogenesis of uremic pruritus in our patients.

We noted that using NB-UVB as an add-on therapy was effective in our patients. The mean VAS score improved from a baseline score of 7.75 ± 1.02 to 3.14 ± 1.59 at the end of completion of therapy. Complete resolution of pruritus was noted in 3 patients (14.2%).In 2 patients (9.5%) no significant improvements were noted. Out of those patients who had improvement in pruritus, relapse occurred in 6 patients (31.5%).

The beneficial effect of the phototherapy session sets in by the 3rd week and the effect becomes more pronounced after the end of 7th week. The mean VAS score at the end of 6 weeks was 5.53 ± 0.64 which means that many of these patients would have been classified as non-responders if they had received the 6 wk protocol as in previous randomized trial. The mean VAS at the end of 6 mo follow up was 4.14 ± 2.85 which was significantly lower than the baseline VAS score (*p* < 0.001)

Our study is limited by the retrospective nature. The population studied although uniform is small. We noted that it is difficult for the patients to strictly abide by the three times per week for 12 wk UVB protocol. On reviewing the feedback form we realized that our patients found the treatment regime cumbersome and many were not willing for a repeat course of such treatment sessions in future, although the duration of each session is short, usually lasting less than 2 to 3 min. Many of the patients find the frequent visits to hospital very inconvenient. Transportation is a big hindrance as many of these patients cannot drive and arranging logistic support to bring them to hospital three times a week for 12 wk becomes an issue. It would be noted that the duration of the overall treatment protocol is longer compared to previous studies. As such one might consider a slightly shorter duration of NB-UVB treatment (eg twice per week for 8 to 10 wk, 3 times per week for 8 wk).

Many questions remain unanswered at the end of this study. The treatment even if effective does not offer long term protection. Relapse occurs in nearly a third of the patient. The optimal treatment duration and frequencies of the session are not known. As such we need to come up with a large well designed randomized controlled trial which would compare different treatment regimes in order to come up with the most effective yet acceptable regime.

In conclusion, using narrow band UVB as an add-on therapy to standard agents in refractory uremic pruritus on peritoneal dialysis is effective in reducing the intensity of the itching. However there is a chance of relapse after discontinuation of the phototherapy. The 12 wk treatment regime used in this study is found to be cumbersome and patients’ acceptance is poor.

**ARTICLE HIGHLIGHTS**

***Research background***

Uremic pruritus is a common and troublesome entity in patients on peritoneal dialysis. The presence of pruritus affects both quality of sleep and lifestyle as well and at times it can lead to depressive symptoms and mood disorders. In patients with difficult to treat pruritus, narrow band ultraviolet B (UVB) can be tried as a treatment option. There is only one randomized controlled trial that have compared the role of narrow band UVB in uremic pruritus. There is very limited data regarding the use of narrow band UVB in peritoneal dialysis population. As such there is an urgent need to identify the effectiveness of such a treatment modality in the peritoneal dialysis population

***Research motivation***

With the limited data that is available there is no clear cut consensus regarding the role of narrow band UVB in peritoneal dialysis patients who have severe pruritus. The most effective and optimal duration oftreatment is also not clear. A previousrandomized trial had used three times a week for six week course. However that study had mixed population of chronic kidney disease and included patients on hemodialysis, peritoneal dialysis as well as patient who were treated conservatively and had not been initiated on dialysis. There were only three patients on peritoneal dialysis and the result of that study cannot be extrapolated to the peritoneal dialysis population. In this study we selected a very homogenous population of patients with end stage renal disease on peritoneal dialysis with severe uremic pruritus and used narrow band UVB as an add on therapy to standard treatment used in such patients.

***Research objectives***

The purpose of our study was to assess the effectiveness of narrow band UVB as an add-on therapy to standard treatment in peritoneal dialysis patients with refractory uremic pruritus. We included a follow up upto 6 mo post treatment completion to assess for relapse. Patients were also given a feedback form to highlight their experience with the treatment protocol and their suggestions were sought for to improve the quality of treatment

***Research methods***

This is a retrospective study in which peritoneal dialysis patients with refractory uremic pruritus were put on 12 wk course of narrow band UVB in addition to their standard treatment. We used visual analogue scale (VAS) to record the intensity of pruritus which was measured during each visits. After the completion of their treatment protocol patients were followed up on monthly basis for 6 months and during these visits their VAS score was measured as well. During this follow up visits their feedback form were also collected.

***Research results***

In this study we noted that the mean VAS score improved from a baseline of 7.75 ± 1.02 to 3.14 ± 1.59 at the end of completion of treatment. Nineteen out of the twenty-one patient who completed the study had improvement in symptoms. In 3 patients (14.2%) complete resolution of pruritus was noted. Two patients (9.5%) continued to have persistent pruritus with VAS score more than 5. Out of those patients who had improvement in pruritus, relapse occurred in 6 patients (31.5%). The mean VAS at the end of 6 mo follow up was 4.14 ± 2.85 which was significantly lower than the baseline VAS score (*p* < 0.001)

***Research conclusion***

In this study we found that narrow band UVB therapy is effective as an add on therapy in difficult to treat patients with uremic pruritus in the peritoneal dialysis population. In our study we used 12 wk treatment protocol with good effective results. We noted that the response at 6 wk was suboptimal and many of our patients would have been classified as non-responders if our treatment was confined to 6 wk period. However, patient’s compliance is poor and the frequent visits to hospital for the treatment become an issue when we use 12 wk regime. We need to come up with an effective treatment regime which will be acceptable to patients as well.

***Research perspectives***

future studies might try alternative regimes like two times a week for ten week regime or three times a week for 8 wk.

**References**

1 **Wikström B**. Itchy skin--a clinical problem for haemodialysis patients. *Nephrol Dial Transplant* 2007; **22** Suppl 5: v3-v7 [PMID: 17586843 DOI: 10.1093/ndt/gfm292]

2 **Narita I**, Alchi B, Omori K, Sato F, Ajiro J, Saga D, Kondo D, Skatsume M, Maruyama S, Kazama JJ, Akazawa K, Gejyo F. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int* 2006; **69**: 1626-1632 [PMID: 16672924 DOI: 10.1038/sj.ki.5000251]

3 **Pisoni RL**, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, Saran R, Mendelssohn DC, Young EW, Port FK. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2006; **21**: 3495-3505 [PMID: 16968725 DOI: 10.1093/ndt/gfl461]

4 **Pauli-Magnus C**, Mikus G, Alscher DM, Kirschner T, Nagel W, Gugeler N, Risler T, Berger ED, Kuhlmann U, Mettang T. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11**: 514-519 [PMID: 10703675]

5 **Rosenthal SR**. Uremic dermatitis. *Arch Dermatol* 1931; **23**: 934 [doi: 10.1001/archderm.1931.03880230110013]

6 **Cawley EP**, Hoch-ligheti C, Bond GM. The eccrine sweat glands of patients in uremia. *Arch Dermatol* 1961; **84**: 889-897 [PMID: 13877511]

7 **Massry SG**, Popovtzer MM, Coburn JW, Makoff DL, Maxwell MH, Kleeman CR. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 1968; **279**: 697-700 [PMID: 5670911]

8 **Chou FF**, Ho JC, Huang SC, Sheen-Chen SM. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg* 2000; **190**: 65-70 [PMID: 10625234]

9 **Blachley JD**, Blankenship DM, Menter A, Parker TF 3rd, Knochel JP. Uremic pruritus: skin divalent ion content and response to ultraviolet phototherapy. *Am J Kidney Dis* 1985; **5**: 237-241 [PMID: 4003393]

10 **Duque MI**, Thevarajah S, Chan YH, Tuttle AB, Freedman BI, Yosipovitch G. Uremic pruritus is associated with higher kt/V and serum calcium concentration. *Clin Nephrol* 2006; **66**: 184-191 [PMID: 16995341]

11 **Yosipovitch G**, Greaves MW, Schmelz M. Itch. *Lancet* 2003; **361**: 690-694 [PMID: 12606187]

12 **Umeuchi H**, Togashi Y, Honda T, Nakao K, Okano K, Tanaka T, Nagase H. Involvement of central mu-opioid system in the scratching behavior in mice, and the suppression of it by the activation of kappa-opioid system. *Eur J Pharmacol* 2003; **477**: 29-35 [PMID: 14512095]

13 **Li J**, Guo Q, Lin J, Yi C, Yang X, Yu X. Prevalence and Associated Factors of Uraemic Pruritus in Continuous Ambulatory Peritoneal Dialysis Patients. *Intern Med* 2015; **54**: 2827-2833 [PMID: 26567994 DOI: 10.2169/internalmedicine.54.4516]

14 **Morachiello P**, Landini S, Fracasso A, Righetto F, Scanferla F, Toffoletto P, Genchi R, Bazzato G. Combined hemodialysis-hemoperfusion in the treatment of secondary hyperparathyroidism of uremic patients. *Blood Purif* 1991; **9**: 148-152 [PMID: 1801857]

15 **Ada S**, Seçkin D, Budakoğlu I, Ozdemir FN. Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: an open pilot study. *J Am Acad Dermatol* 2005; **53**: 149-151 [PMID: 15965439 DOI: 10.1016/j.jaad.2004.12.052]

16 **Ko MJ**, Yang JY, Wu HY, Hu FC, Chen SI, Tsai PJ, Jee SH, Chiu HC. Narrowband ultraviolet B phototherapy for patients with refractory uraemic pruritus: a randomized controlled trial. *Br J Dermatol* 2011; **165**: 633-639 [PMID: 21668425 DOI: 10.1111/j.1365-2133.2011.10448.x]

17 **Szepietowski JC**, Schwartz RA. Uremic pruritus. *Int J Dermatol* 1998; **37**: 247-253 [PMID: 9585892]

18 IV. NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. *Am J Kidney Dis* 2001; **37**: S182-S238 [PMID: 11229970]

**P-Reviewer:** Biggar P, Cheungpasitporn W, Watanabe T **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Specialty type:** Clinical neurology

**Country of origin:** India

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**Table 1 Baseline characteristics of the patients**

|  |  |
| --- | --- |
| Age (yr) | 56.17 ± 15.65 |
| Sex (male/female) | 18/11 |
| Hemoglobin (g/l) | 9.99 ± 0.99 |
| Corrected calcium (mg/dl) | 8.92 ± 1.1025 |
| Phosphate (mg/dl) | 4.46 ± 1.35 |
| Intact parathyroid hormone (pg/ml) | 132.28 ± 176.63 |
| Mean Kt/V | 1.77 ± 0.11 |
| No. of patients with weekly Kt/V > 1.7 | 19 |
| Skin phototype | IV-20, V-9 |
| Other agents used for pruritus  Topical emollient  Topical capsaicin  Oral anti histaminics: Fexofenadine  Pregabalin  Gabapentin  Amitryptilline |  |

**Table 2 The baseline and weekly visual analogue score assessment score for pruritus**

VAS: visual analogue score.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 |
| Mean VAS score | 7.75 ±  1.02 | 7.55 ± 1.02 | 7.48 ± 0.82 | 7.03 ± 0.68 | 6.37 ± 0.49 | 5.66 ± 0.55 | 5.53 ± 0.64 | 5.20 ± 0.70 | 4.87 ± 0.74 | 4.60 ± 0.72 | 3.04 ± 1.32 | 3.42± 1.63 | 3.14 ± 1.59 |
| No. of patients | 29 | 29 | 29 | 29 | 27 | 27 | 26 | 25 | 24 | 23 | 22 | 21 | 21 |