Original article

A prospective randomized case-control study of amitriptyline and pregabalin for bladder pain syndrome

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Objective: Pregabalin is one of the standard medications for neuropathic pain. However, few studies have been conducted to evaluate pregabalin for bladder pain syndrome (BPS). We prospectively tested pregabalin against amitriptyline for BPS. *Methods:* A total of 57 patients with BPS were enrolled to the study. Patients received amitriptyline or pregabalin, alternatively. Pregabalin dose was increased from 25mg to 150mg during 2 months; amitriptyline dose was increased from 10mg to 30mg during 2 months. *Results:* Three patients in the pregabalin group and 4 in the amitriptyline group did not return to the clinic after the first consultation. Meanwhile, 6 patients in the pregabalin group discontinued drugs due to side effects (for a continuity rate of 77%), while 8 in the amitriptyline group also did so (continuity rate 65%). The change in pain scale pre- and post-treatment by pregabalin was from 4.81±2.52 to 3.25±2.88, and by amitriptyline was from 4.87±2.45 to 2.2±2.30. The difference between them was not statistically significant p=0.52 Effects of amitriptyline were statistically better than those of pregabalin in terms of urgency, pollakisuria and pain, as measured by the O'Leary and Sant IC questionnaire. p<0.05 *Conclusion:* The efficacy of pregabalin for pain relief may be same as that of amitriptyline. On the other hand, amitriptyline may be effective more than pregabalin for lower urinary symptom of BPS.

Key words: Pregabalin; Amitriptyline; Bladder pain syndrome; Interstitial cystitis.

INTRODUCTION

Bladder pain syndrome (BPS) is a chronic condition that causes several kinds of bladder pain with urgency, frequency and nocturia.[1] Its cause is not clear, and it is still a disease diagnosed by exclusion. BPS has, however, one side of chronic pain syndrome related to neuropathic pain. Several theories regarding the mechanism of neuropathic pain have been proposed, including central and peripheral nervous system sensitization, dIfferentiation neurogenic inflammation, and the pain wind-up theory. The mainstay of treatment for neuropathic pain is pharmacological, including the use of antidepressants, antiepileptics, topical anesthetics, and opioids. Non pharmacological treatments include psychological approaches, physical therapy, interventional therapy, spinal cord stimulation, and surgical procedures. Neuropathic pain is difficult to treat, and a combination of therapies may sometimes be more effective than monotherapy.

Bladder pain syndrome (BPS) is diagnosed on the basis of chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder, and accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency. The name "Interstitial cystitis" has been deemed misleading and has been replaced by BPS.[1] It is estimated that 3.3-7.9 million (2.70%-6.53%) of women in the United States suffer from BPS.[2] Non pharmacological treatments of BPS include psychological approaches, pelvic floor rehabilitation, spinal cord stimulation, bladder hydrodistention and transurethral surgeries. Parallel non pharmacological treatments, medicines effective for internal use and readily available include Amitriptyline, Cyclosporine A, Pentosan polysulfate sodium PPS with hydroxyzine and L-arginine.[3] On the other hand, tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs) are recommended as first-choice medicines for neuropathic pain.[4] BPS has an aspect of chronic pain syndrome. Few studies, however, have considered pregabalin for BPS.

In the current study, to evaluate the efficacy of pregabalin for BPS, we conducted the randomized prospectively designed case-control study on the use of amitriptyline and pregabalin.

PATIENTS AND METHODS

This study was randomized prospectively designed case-control study and approved by the medical corporation Women's Clinic LUNA Group ethics committee. (Approved number 16) Written informed consent was obtained from all patients.

Subjects were 57 patients diagnosed with BPS in the Women's Clinic LUNA Japan. Diagnosis was based on pelvic pain and pollakisuria by questionnaire and pain scale with no abnormal findings by urine analysis, urine culture, cytology and ultrasound.[1] Patients were given pregabalin or amitriptyline randomized prospectively. The pregabalin group included 30 patients (median age 53.5±13.8; max 80, min 32. The amitriptyline group included 27 patients (median age 63±13.8; max 75, min 23). There was no statistically significant difference in age and symptoms between groups (Table 1).

In terms of dose, pregabalin was started at 25-150mg, and amitriptyline was started at 10-30mg for 2 months, because we were interested in the early effects of the medicines.

The primary outcome measure was assessment of pain by pain scale (10-grade) and second outcome measure of urinary symptoms by the O'Leary and Sant IC questionnaire (validated by the Japanese society for the study of interstitial cystitis with 5 grades for symptoms and 4 grades for problems) before and after treatment.[5]

We used a t-test from software PASW statistics 18 (S.P.S.S.Inc.Japan) to assess statistical significance at the 2-sided 5% level ($p < 0.05$).

RESULTS

Four patients in the pregabalin group and 3 in the amitriptyline group did not return to the clinic after their first consultation. Six patients in the pregabalin group and 8 in the amitriptyline group discontinued drug treatment due to side effect. Therefore, the continuity rate for pregabalin was 77% and for amitriptyline, 65%.

To evaluate pain which is primary outcome, we used the 10-grade pain scale. The change pre- and post-treatment by pregabalin was 4.81±2.52 to 3.25±2.88. For amitriptyline, change pre- and post-treatment was 4.87±2.45 to 2.2±2.30. The difference between them was not statistically significant (Fig. 1).

Lower urinary tract symptoms (LUTS) on the O'Leary and Sant IC questionnaire which are second outcome are

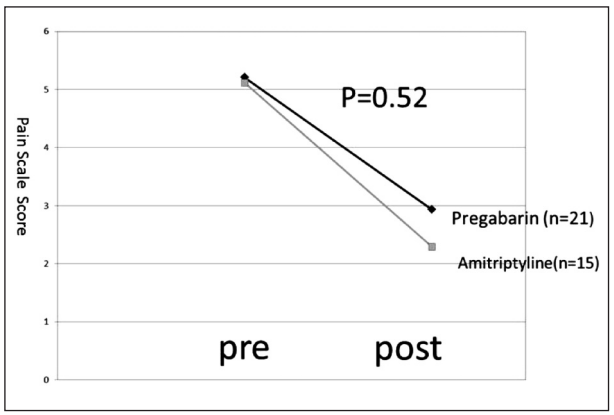

Figure 1. – This is the results of the 10-grade pain scale. The change pre- and post-treatment by pregabalin was 4.81±2.52 to 3.25±2.88. For amitriptyline, change pre- and post-treatment was 4.87±2.45 to 2.2±2.30. The difference between them was not statistically significant.

listed in Table 2. There were statistically significant differences among symptoms of urgency and pain, as well as with problems of pollakisuria and pain. In terms of side effects, patients in the pregabarin group experienced dizziness, drowsiness, nausea, loss of concentration, palpitation, and weight gain; there were also 4 cases of drowsiness 4 in the amitriptyline group, as well as continued pain, dizziness, disturbance of taste, and constipation.

DISCUSSION

Our results indicated no statistically significant difference in pain reduction between pregabarin and amitriptyline by pain scale. The main symptom which patients suffer is pain on bladder. Therefore both drugs are available to PBS for first choice of treatment

There were, however, statistically significant differences in pain reduction, urgency and pollakisuria between pregabarin and amitriptyline by the O'Leary and Sant IC questionnaire. This suggests evaluation of the pain sensation only is different from evaluation of specific symptoms including pain, urgency and pollakisuria. Amitriptyline has an anti-serotonin and adrenaline reuptake effect, as well as an anti-cholinergic effect. This may be one reason why amitriptyline was rated more effective than pregabarin on the O'Leary and Sant IC questionnaire.

The continuity rate of pregabalin within 150 mg was 77%, while that of amitriptyline within 30mg was 65%. If patients can tolerate the drug, amitriptyline may be more effective than pregabalin for BPS at first. However the usual maximum dose of pregabalin is 300mg, and that of amitriptyline is 150mg.Therefore the dropout rate of pregabalin may be estimated as lower than that of amitriptyline. And if patients cannot tolerate amitriptyline, we can take the strategy that pregabalin will be given for first choice and after reduction of pain, any cholinergic agents will be added on.

Furthermore the effective point of pregabarin is different from that of amitriptyline. Pregabarin mainly blocks the source of pain while amitriptyline mainly blocks the points of accepting pain. Therefore pregabarin which reduces the pain of peripheral injury of bladder mucosa are available first for the patients who have suffered for BPS within a few years. And amitriptyline which recovers the hypersensitivity of central neural systems are available the patients who have suffered for BPS over a few years. And serious BPS patients may need both types of medicine for combination therapies

In this study, medication doses were set at 30mg for amitriptyline and 150mg for pregabalin. These were first

Table 1. Background.

(median±st.)	pregabalin	amitriptyline	p value
age	56±13.9	62±13.9	0.9
VAS	5±2.4	5±2.3	0.3
IS-SI(total)	8±3.3	8±3.5	0.42
iS-CI(total)	8.5±4..2	8±4..8	0.46

Table 2. The results of O'Leary and Sant IC questionnaire.

	S1 Urgency	S2 Pollakisuria	S3 Nocturia	S4 Pain	P1 Pollakisuria	P2 Nocturia	P3 Urgency	P4 Pain
Pregabalin (n=21)								
Pr (average)	0.96 ±1,14	2.86 ±1.48	1.89 ±1.40	2.73 ±1.21	2.39 ±1.34	2.07 ±1.46	1.36 ±1.28	2.61 ±1.26
Post (average)	1.47 ±2.33	2.07 ±1.53	1.4 ±1.24	2.33 ±1.62	1.87 ±1,46	1.2 ±1.08	1.07 ±1.16	2.07 ±1.67
Amitriptiline (n=15)								
Pre (average)	1.1 1±1.42	2.85 ±1.70	1.81 ±1.54	3.47 ±0.99	2.29 ±1.54	1.96 ±1.63	1.7 ±1.62	3.07 ±1.11
Post (average)	0.65 ±0.76	1.18 ±0.88	1.18 ±1.34	1.4 ±1.26	1.06 ±0.90	0.71 ±0.92	0.8 2±0.88	1.12 ±1.11
P Value	0.043	0.11	0.5	0.018	0.04	0.35	0.42	0.035

treatment doses, and there was room to increase the dosage of both drugs. Therefore this paper should be considered a preliminary report, and more evaluation is needed.

In conclusion, The efficacy of pregabalin for pain relief may be same as that of amitriptyline. On the other hand, amitriptyline may be effective more than pregabalin for lower urinary symptom of BPS.

DISCLOSURE STATEMENT

We declare no conflict of interest.

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