SPANDIDOS PUBLICATIONS

EXPERIMENTAL AND THERAPEUTIC MEDICINE 12: 445-450, 2016

Treatment effect of cyclosporine A in patients with painful bladder syndrome/interstitial cystitis: A systematic review

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Received January 25, 2015; Accepted February 4, 2016

DOI: 10.3892/etm.2016.3301

Abstract. Cyclosporine A (CyA) is emerging as a potential therapeutic strategy for painful bladder syndrome/interstitial cystitis (PBS/IC), which is currently an incurable disease. The purpose of this systematic review was to evaluate the treatment effects of CyA in PBS/IC. Electronic and manual retrieval procedures were carried out to identify eligible references for the systematic review. The entire contents of the included articles were assessed, from study design to reported results. Eight studies, comprising three randomized controlled trials (RCTs), four prospective studies and one retrospective cohort study, were included, involving a total of 298 subjects. Meta-analysis was not implemented due to heterogeneity of the manner of reporting the outcome parameters. All studies reported an improvement in symptoms following treatment with CyA. The results of the three RCTs implied that the treatment effects of CyA were better than those of pentosan polysulfate sodium. Some adverse events, for example, elevation of serum creatinine levels and an increase in blood pressure, were noted in five studies. In conclusion, the evidence from the studies implied that treatment of CyA can result in a long-term benefit in patients of PBS/IC; however, further evidence is required to verify this.

Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) occurs far more frequently in women than in men. It has been reported that among 1.3 million Americans having the symptoms of PBS/IC, >1.2 million were women in the year 2007 (1). The typical age predilection is ~40 years (2). The common symptoms of PBS/IC include urinary urgency, frequency, nocturia and suprapubic or pelvic pain without any known etiological factor. Diagnostic criteria have been established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in order to standardize the diagnosis of PBS/IC; these include objective findings of glomerulations or Hunner's ulcer at cystoscopy and subjective symptoms of bladder pain or urinary urgency, in addition to multiple exclusion criteria such as age <18 years, duration of symptoms <9 months and absence of nocturia (3). Even though numerous treatments have been reported, including intravesical botulinum toxin A injections, pentosan polysulfate sodium (PPS), dietary modification, lifestyle interventions/behavioral therapies and bladder training, no specific effective therapy has yet been identified.

As an immunosuppressive agent, cyclosporine A (CyA) suppresses the activation of T cells by inhibiting the enzymatic activity of calcineurin (4). It has been successfully used in various conditions, such as in transplant recipients, hepatitis C (5), and autoimmune diseases such as psoriasis (6), Crohn's disease (7) and rheumatoid arthritis (8). Furthermore, CyA is emerging as a potential therapeutic strategy for PBS/IC, which is an intractable condition to treat. Several studies have reported promising results for the treatment effects of CyA in PBS/IC. However, the strength of the evidence of efficacy in each independent study is limited by various factors, such as limitation of included subjects, or absence of a control group. Therefore, the present systematic review was performed in order to assess the global evidence concerning the treatment effects of CyA in PBS/IC.

Materials and methods

Search strategy. The search strategy included the following key words variably combined: 'cyclosporine A,' 'bladder pain syndrome' and 'interstitial cystitis'. Databases including China National Knowledge Infrastructure (CNKI), PubMed, Highwire, EMBASE and Science Direct were searched for relevant references. In addition, other retrieval strategies were performed to screen for relevant articles, including manual retrieval and scanning of the reference sections of eligible articles.

Inclusion/exclusion criteria. Studies were regarded as qualified for inclusion if they met all the following inclusion criteria: i) the disease type was PBS/IC with or without meeting the NIDDK criteria; ii) the study was a clinical trial, including randomized controlled trials (RCTs), and prospective or retrospective cohort studies; iii) the treatment effects of CyA in

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Key words: cyclosporine A, interstitial cystitis, painful bladder syndrome, systematic review, treatment effect

PBS/IC were measured. Studies were excluded on the basis of any of the following criteria: i) the article was a review, letter or case report; ii) the article did not relate to the treatment effects of CyA in PBS/IC.

Data selection. Two researchers independently screened the initially included articles on the basis of the inclusion/exclusion criteria. Any disagreement was resolved by consensus. Baseline data and result information were extracted and assessed by the same researchers, including first author and publication year, country, inclusion/exclusion criteria of each study, subjects, gender (female/male), mean age, regimen protocol, outcome parameters, follow-up and complications. In addition, all included articles were assessed for methodological quality, according to the Newcastle-Ottawa scale (9) for nonrandomized studies and Jadad score for RCTs (10).

Results

Eligible articles. The various steps of the filtration procedure used in this review are presented in Fig. 1. Initially, 117 articles were included (26 from PubMed, 11 from CNKI, 36 from Highwire, 17 from EMBASE and 31 from ScienceDirect). No further relevant references were identified by manual search and filtration of the reference sections of included articles. Following careful screening of the titles and abstracts of each article, 95 articles were excluded, leaving 22 articles for further filtration. After screening the entire contents of these articles, 14 articles were further excluded. Eight articles (11-18) were finally included as eligible articles, which including a total of 298 subjects with a median number of 37.25 subjects per study. These 8 studies included 3 RCTs (16-18), 4 prospective cohort studies (11-13,15) and 1 retrospective cohort study (14). In the 7 studies that reported the ages of the subjects, the age predilection was 40-70 years. In one of the articles (12), the patient age could not be identified because only the abstract was available. The included subjects were mostly females; the percentage of males was relatively low. The sample sizes of the included studies were uniformly small, ranging from 10 to 64. Other characteristics of the included articles are listed in Table I.

Six studies used the NIDDK criteria for diagnosing IC (12,14,16-18); the other two studies used clinical symptoms to diagnose PBS/IC (11,13). The subjects of two studies (13,14) were patients in whom multiple first line therapies had failed. Regimen protocols were presented in all studies; the initial dosage of CyA was typically 2-3 mg/kg/day, sometimes divided into 2 daily dosages. If the symptoms were alleviated, the dosage of CyA was gradually decreased to a tolerance dose; if adverse events occurred the dose was reduced or the drug was stopped. In the three RCTs (16-18), the treatment therapy administered to the control group was 100 mg PPS 4 times daily.

Methodological quality. All studies have detailed descriptions of the ascertainment of diagnosis, assessment of outcome and the instruments used to assess outcomes. All of the articles, with the exception of one (15), reported the follow-up time; the longest duration of follow-up was 5 years (12) and, the proportion of patients lost to follow-up was <20% in all studies. On the basis of the Jadad scale, the scores for the included RCTs ranged from 1 to 3 (regard as low methodological quality).

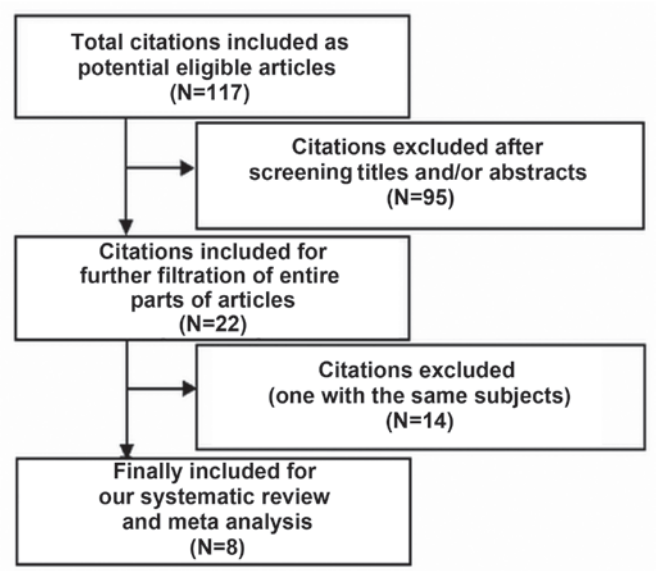

Figure 1. Reference retrieval procedure used in this systematic review of the treatment effect of cyclosporine A in patients with painful bladder syndrome/interstitial cystitis.

Outcome assessment. The outcome assessment of the included studies is presented in Table II. The O'Leary-Sant Symptom and Problem Indices of Interstitial Cystitis (ICSI and ICPI, respectively) were used as outcome measures in 5 studies (11-13,16,17). Other outcome parameters were reported, including mean voided volume (ml) (12,14-17), maximum awake bladder capacity (ml) (14-16), urinary frequency (24 h) (14-17), pain score (visual analog scale, VAS) (16,17), cytokine levels (11,17), daily urinary output (ml) (15), nocturia episodes (16) and improvement of quality of life (QoL) (18). All outcome parameters, with the exception of the biomarker IL-6, were reported to exhibit improvement following treatment of CyA, even though the degree of improvement varied. However, Sairanen *et al* (17) reported that IL-6 was significantly (P=0.04) decreased in patients ≥53 years old following treatment with CyA, but not following treatment with PPS (P=0.73). All reported parameters in the three RCTs implied that the treatment effects of CyA were far superior to those of PPS treatment. In addition, long-term treatment with a low dosage of CyA could provide a persistent improvement of symptoms. The symptoms were recurrence if the treatment of CyA was discontinued.

Adverse effects. Five of the 8 included studies reported complications, which mainly comprised tiredness, abdominal pain, nausea, diarrhea and gingival hyperplasia (1 patient), induced hair growth (3 patients), serum creatinine elevation (12 patients) and a rise in blood pressure (8 patients). Following symptomatic treatment, the majority of patients were able to undergo sustained CyA treatment. However, 4 patients were required to stop treatment with CyA following increases in serum creatinine levels.

Table I. Baseline characteristics of the included studies.

First author, publication year (Refs.)	Country	Study type	Inclusion/ exclusion criteria	No. of subjects	Gender (female/ male)	Mean age (years)	Regimen protocol	Outcome parameters	Follow up	Complications
Ehrén, 2013 (11)	Sweden	Cohort, prospective	Diagnosed with IC for >2 years (some for up to 10 years). Exclusion: Use of angiotensin-converting enzyme inhibitors, angiotensin II antagonists, potassium-containing drugs, any medicine that inhibits or induces CYP3A4, pregnancy, lactation, or regular intake of hypericin or grapefruit	10	6/4	58±13	CyA dosage: 3 mg/kg/day for 12 weeks; followed by 4 weeks of deescalation in two steps (1.5 mg/kg/day for 2 weeks and 0.75 mg/kg/day for 2 weeks, respectively) and no medication for the last 2 weeks	NO formation; ICSI and ICPI scores	18 weeks	Mild adverse events; no serum creatinine elevation or increase in blood pressure
Chade, 2014 (12)	Brazil	Cohort, prospective	Fulfilled the NIDDKD criteria	45	43/2	N/A	CyA dosage: 1.5 mg/kg twice a day, for 5 years	ICSI and ICPI scores; mean voided vol. (ml)	5 years	None
Forrest, 2012 (13)	USA	Cohort, prospective	Patients with no contraindications to CyA and in whom the usual IC/PBS treatments had failed	44	30/14	55.5	CyA dosage: 2-3 mg/kg divided into 2 daily dosages with a maximum of 300 mg daily; if adverse events occurred the dose was reduced or the drug was stopped	Symptom response (based on ICSI or GRA); response with vs. without HL; CyA levels	mean, 20.8 months (range, 3-81)	Serum creatinine was increased in 9 patients, causing 4 patients to stop CyA treatment; Hypertension in 3 patients
Sairanen, 2004 (14)	Finland	Cohort, retrospective	Fulfilled the NIDDKD criteria, and multiple first-line therapies had been tried without clinical success	23	20/3	65.7±7.6	CyA dosage: 3 mg/kg divided into 2 daily dosages. When symptoms were alleviated the dose was gradually decreased to as low as 1 mg/kg as a single daily dose	Mean voided vol. (ml); maximum awake bladder capacity (ml); 24-h voiding frequency	60.8±35.7 months	Hypertension and gingival hyperplasia occurred in 3 patients, respectively; induced hair growth occurred in 2 patients
Forsell, 1996 (15)	Finland	Cohort, prospective	Fulfilled the criteria for IC according to an international accrual form	11	10/1	27-75	CyA dosage: 3-6 months at an initial dose of 2.5-5 mg/kg daily and a maintenance dose of 1.5-3 mg/kg daily	No. of voids/24 h; daily urinary output; mean voided vol.; maximum voided vol.	N/A	Noted in 6 patients, including mild hypertension (n=2), mild hyperplasia (n=2), transient tremor (n=1) and growth of facial hair (n=1)

Table I. Continued.

First author, publication year (Refs.)	Country	Study type	Inclusion/ exclusion criteria	No. of subjects	Gender (female/ male)	Mean age (years)	Regimen protocol	Outcome parameters	Follow up	Complications
Sairanen, 2005 (16)	Finland	RCT	Fulfilled the NIDDK criteria for IC. Exclusion criteria: History of cancer in the last 10 years, untreated hypertension or renal insufficiency [serum creatinine higher than normal limits (>90 mg/dl in females or >100 mg/dl in males)]	64	53/11,	Case, 56.2±14.7; control, 59.7±13.0	Case group: 1.5 mg/kg CyA twice daily (27 women, 5 men); control group: 100 mg PPS 3 times daily (26 women, 6 men)	Frequency in 24 h; max awake bladder capacity; mean voided vol.; VAS; nocturia episodes; ICSI and ICPI symptom scores, GRA; PST	6 months	Mild adverse events
Sairanen, 2008 (17)	Finland	RCT	Fulfilled the NIDDKD criteria	37	32/5,	Case, 55.7±14.8; control, 56.4±13.2	Case group: 1.5 mg/kg CyA twice daily; control group: 100 mg PPS 3 times daily	GRA; EGF, IL-6; pain score (VAS); urinary frequency 24 h; mean voided volume; ICSI score	6 months	N/A
Sairanen, 2009 (18)	Finland	RCT	Fulfilled the NIDDKD criteria	64	51/13	Case, 53.2±11.9; control, 57.3±10.0	Case group: 1.5 mg/kg CyA twice daily; control group: 100 mg PPS 4 times daily	General health perceptions; pain; emotional wellbeing; vitality; social functioning; physical capacity; sexual interest; sexual functioning	6 months	N/A

CyA, cyclosporine A; CYP3A4, cytochrome P450 3A4; EGF, epidermal growth factor; GRA, global response assessment; HL Hunner's lesion; IC, interstitial cystitis; ICPI, O'Leary-Sant Interstitial Cystitis Problem Index; ICSI, O'Leary-Sant Interstitial Cystitis Symptom Index; IL-6, interleukin 6; N/A, not available; NIDDKD, National Institute of Diabetes and Digestive and Kidney Diseases; NO, nitric oxide; PBS, painful bladder syndrome; PPS, pentosan polysulfate sodium; PST, potassium sensitivity test; RCT, randomized control trials; VAS, visual analog scale.

Table II. Outcome assessment of included studies.

Outcome	First author, year (Refs.)	Results
ICSI and ICPI	Ehren, 2013 (11)	ICSI: reduced from16±1 to 8±1; ICPI: reduced from 14±1 to 6±1, after 12 weeks; ICSI and ICPI remained at a low level when treatment was continued; without treatment ICSI and ICPI increased again, to 12±2 and 9±2, respectively
	Chade, 2014 (12)	ICSI: reduced from 36 initially to 21.6 at 6 months, and 8.4 at 5 years (P<0.001); ratio of patients with ICPI scores >8 reduced from 100 to 22%
	Forrest, 2012 (13)	26/44 (59%) patients with symptom response, 10/44 (23%) patients without symptom response; patients with HL had a higher response (23/34, 68%) than patients without HL; low dosage of treatment for symptom maintance
	Sairanen, 2005 (16)	Sum of ICSI + ICPI: -15.0±9.4 in CyA group vs. -3.1±4.3 in PPS group (P<0.001); ICSI: -7.9±4.5 in CyA group vs. -2.0±2.6 in PPS group (P<0.001); ICPI: -7.1±4.4 in CyA group vs. -1.5±1.8 in PPS group (P<0.001)
	Sairanen, 2008 (17)	Sum of ICSI + ICPI: Reduced from 28.8 to 15.1 in CyA group vs. 30.5 to 28.5 in PPS group; responder (GRA, 5 or 6): 13/18 (72%) in CyA group vs. 3/19 (16%) in PPS group
Mean voided volume (ml)	Chade, 2014 (12)	Upregulated from 103 pretreatment to 170 after CyA treatment
	Sairanen, 2004 (14)	Upregulated from 101.47 (SD, 42.7) pretreatment to 246.4 (SD, 97.9) after CyA treatment (P<0.001)
	Forsell, 1996 (15)	Upregulated from 100.4 (SD, 58.4) pretreatment to 173.7 (SD, 84.0) after CyA treatment
	Sairanen, 2005 (16)	Improvement: 59±57 in CyA group vs. 1±31 in PPS group (P<0.001)
	Sairanen, 2008 (17)	Improvement: From 28.8 (SD, 4.8) to 15.1 (SD, 8.6) in CyA group vs. 30.5 (SD, 3.8) to 28.5 (SD, 5.6) in PPS group (P=0.003)
Maximum awake bladder capacity (ml)	Sairanen, 2004 (14)	Upregulated from 168.8 (SD, 74.6) pretreatment to 360.7 (SD, 99.3) after CyA treatment (P<0.001)
	Forsell, 1996 (15)	Upregulated from 179.1 (SD, 96.3) pretreatment to 361.4 (SD, 137.6) after CyA treatment
	Sairanen, 2005 (16)	Improvement: 81±94 in CyA group vs. 2.8±60 in PPS group (P=0.003)
Urinary frequency (24 h)	Sairanen, 2004 (14)	Reduced from 20.8 (SD, 6.3) pretreatment to 10.2 (SD, 3.8) after CyA treatment (P<0.001)
	Forsell, 1996 (15)	Reduced from 20.55 (SD, 6.2) pretreatment to 11.9 (SD, 4.0) after CyA treatment
	Sairanen, 2005 (16)	Improvement: -6.7±4.7 in CyA group vs. -2.0±5.1 in PPS group (P<0.001)
	Sairanen, 2008 (17)	Reduced from 16.4 (SD, 3.5) to 11.0 (SD, 4.2) in CyA group vs. 19.5 (SD, 5.9) to 18.4 (SD, 6.3) in PPS group (P=0.005)
Pain score (VAS)	Sairanen, 2005 (16)	Improvement: -4.7±3.5 in CyA group vs. -1.6±3.3 in PPS group (P<0.001).
	Sairanen, 2008 (17)	Reduced from 7.0 (SD, 2.2) to 2.2 (SD, 2.5) in CyA group vs. 7.5 (SD, 2.1) to 5.8 (SD, 3.1) in PPS group (P=0.005).
Cytokine levels	Ehren, 2013 (11)	NO (ppm): Reduced after treatment with CyA, from 489±141 initially to 16±6 (2 weeks), 10±7 (4 weeks), 7±3 (6 weeks) and 3±1 (8 weeks); increased to 144±70 when the dosage of CyA was reduced to 0.75 mg/kg/day; without treatment in last 2 weeks, the level rose to 478±187.
	Sairanen, 2008 (17)	EGF (mean, ng/mg creatinine): reduced from 35 to 28 in CyA group (P=0.034) vs. 33 to 32 in PPS group (P=0.81); ≥ 53 years old, reduced from 34 to 23 in CyA group (P=0.001) vs. 31 to 30 in PPS group (P=1.00); IL-6 (mean, pg/ml): reduced from 7.1 to 3.6 in CyA group (P=0.18) vs. 11 to 11 in 0.PPS group (P=38); ≥53 years old, reduced from 10.3 to 4.1 in CyA group (P=0.04) vs. 13.7 to 10.3 in PPS group (P=0.73)
Daily urinary output (ml)	Forsell, 1996 (15)	Upregulated from 1,832.7 (SD, 754) pretreatment to 1,954 (SD, 691.6) after CyA treatment
Nocturia episodes	Sairanen, 2005 (16)	Improvement: -2.2±1.6 in CyA group vs. -0.2±2.1 in PPS group (P<0.001)
Improvement of QoL	Sairanen, 2009 (18)	Improvement greater in the CyA group than in the PPS group, including general health perceptions, pain, emotional wellbeing, social functioning, physical capacity, limitation days, % of patients undertaking sexual activity (masturbation or intercourse)

CyA, cyclosporine A; EGF, epidermal growth factor; GRA, global response assessment; HL Hunner's lesion; ICPI, O'Leary-Sant Interstitial Cystitis Problem Index; ICSI, O'Leary-Sant Interstitial Cystitis Symptom Index; IL-6, interleukin 6; NO, nitric oxide; PPS, pentosan polysulfate sodium; QoL, quality of life; SD, standard deviation; VAS, visual analog scale.

Discussion

The evidence from the included studies demonstrates that oral treatment with CyA may be an appropriate therapeutic strategy for patients with PBS/IC, and there is a trend towards benefit with a long-term low-dosage regimen. To the best of our knowledge, he present review summarizes all the prospective or retrospective non-randomized cohort trials and RCTs that exist on this topic.

CyA may be more advantageous in severe PBS/IC, because two studies (11,13) included patients in whom the usual IC/BPS treatments had failed, and the symptoms and parameters in those patients improved following treatment with CyA (2-3 mg/kg divided into 2 daily dosages with a maximum of 300 mg daily). In addition CyA exhibited a higher curative effect than PPS. Long-term low-dosage CyA treatment can provide and maintain good symptom relief (19). However, symptoms may recur if the therapy with CyA is stopped. Hence, it is suggested that the use of CyA may be primarily as a drug for symptom improvement rather than a fundamental solution or cure. In addition, a series of adverse effects (in particular, upregulation of serum creatinine levels and hypertension) are of concern when oral CyA therapy is carried out.

There are several advantages of this systematic review. Firstly, a critical issue has been addressed. The search strategy was full-scale and without language restrictions. Secondly, two reviewers independently screened the eligible articles and extracted data with minimum errors. Thirdly, attempts were made to contact authors of published and unpublished studies to obtain relevant details for this systematic review.

However, the included studies contained small numbers of patients with short-term or long-term follow-up. For one included study (12), only the abstract was available for analysis in this systematic review, and it was not possible to obtain further details. The heterogeneity of the diagnosis criteria of PBS/IC, differences in methods, varied number of outcome measures employed and small number of participants, create challenges in the analysis of the treatment effect of CyA in PBS/IC. Therefore, further higher quality clinical trials are required to further explore the effectiveness of oral CyA in the treatment of PBS/IC.

References

1. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM and McKinlay JB; BACH Survey Investigators: Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 177: 1390-1394, 2007.
2. Held PJ, Hanno PM, Wein AJ, Pauly MV and Cahn MA: Epidemiology of interstitial cystitis. In: Interstitial Cystitis. Hanno PM, Staskin DR, Krane RJ and Wein AJ (eds) Springer, London, pp29-48, 1990.
3. Gillenwater JY and Wein AJ: Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases workshop on interstitial cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 140: 203-206, 1988.
4. Ogawa H, Kameda H, Amano K and Takeuchi T: Efficacy and safety of cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. Lupus 19: 162-169, 2010.
5. Forns X and Navasa M: Cyclosporine A or tacrolimus for hepatitis C recurrence? An old debate. Am J Transplant 11: 1559-1560, 2011.
6. Maza A, Montaudiè H, Sbidian E, Gallini A, Aractingi S, Aubin F, Bachelez H, Cribier B, Joly P, Jullien D, *et al*: Oral cyclosporin in psoriasis: A systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol 25 (Suppl 2): S19-S27, 2011.
7. Sternthal MB, Murphy SJ, George J, Kornbluth A, Lichtiger S and Present DH: Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. Am J Gastroenterol 103: 937-943, 2008.
8. Dijkmans B and Gerards A: Cyclosporin in rheumatoid arthritis: Monitoring for adverse effects and clinically significant drug interactions. BioDrugs 10: 437-445, 1998.
9. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analysis. Eur J Epidemiol 25: 603-605, 2010.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ and McQuay HJ: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 17: 1-12, 1996.
11. Ehrén I, Hallén Grufman K, Vrba M, Sundelin R and Lafolie P: Nitric oxide as a marker for evaluation of treatment effect of cyclosporine A in patients with bladder pain syndrome/interstitial cystitis type 3C. Scand J Urol 47: 503-508, 2013.
12. Chade J, Chade D, Lucon AM, Bruschini H and Srougi M: 462 5-year follow-up of patients with refractory interstitial cystitis treated with cyclosporine A: A prospective single-institution study. Eur Urol (Supp 13): e462, 2014.
13. Forrest JB, Payne CK and Erickson DR: Cyclosporine A for refractory interstitial cystitis/bladder pain syndrome: Experience of 3 tertiary centers. J Urol 188: 1186-1191, 2012.
14. Sairanen J, Forsell T and Ruutu M: Long-term outcome of patients with interstitial cystitis treated with low dose cyclosporine A. J Urol 171: 2138-2141, 2004.
15. Forsell T, Ruutu M, Isoniemi H, Ahonen J and Alfthan O: Cyclosporine in severe interstitial cystitis. J Urol 155: 1591-1593, 1996.
16. Sairanen J, Tammela TL, Leppilahti M, Multanen M, Paananen I, Lehtoranta K and Ruutu M: Cyclosporine A and pentosan polysulfate sodium for the treatment of interstitial cystitis: A randomized comparative study. J Urol 174: 2235-2238, 2005.
17. Sairanen J, Hotakainen K, Tammela TL, Stenman UH and Ruutu M: Urinary epidermal growth factor and interleukin-6 levels in patients with painful bladder syndrome/interstitial cystitis treated with cyclosporine or pentosan polysulfate sodium. Urology 71: 630-633, 2008.
18. Sairanen J, Tammela TL, Leppilahti M, Onali M, Forsell T and Ruutu M: Potassium sensitivity test (PST) as a measurement of treatment efficacy of painful bladder syndrome/interstitial cystitis: A prospective study with cyclosporine A and pentosan polysulfate sodium. Neurourol Urodyn 26: 267-270, 2007.
19. Gao X, Ma Y, Sun L, Chen D, Mei C and Xu C: Cyclosporine A for the treatment of refractory nephritic syndrome with renal dysfunction. Exp Ther Med 7: 447-450, 2014.