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REVIEW ARTICLE

Intravesical treatment of painful bladder syndrome: a systematic review and meta-analysis

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Abstract
Introduction and hypothesis The objective of the study was to assess the effectiveness of intravesical treatment for painful bladder syndrome (PBS).
Methods A systematic review was performed until December 31, 2010. The selection criteria included only randomized controlled trials of PBS patients who received intravesical treatment. The primary outcomes measures were clinical and urodynamic parameters. Relative risk and mean differences were used for binary and continuous outcomes respectively, with confidence interval of 95%.
Results The search strategy identified 770; however, only 28 eligible trials met methodological requirements for complete analysis. Altogether, the review included four treatment modalities: resiniferatoxin, Bacillus Calmette–Guérin (BCG), oxybutynin, and alkalinized lidocaine. Meta-analysis of BCG therapy showed improvement in symptoms according to the Wisconsin Interstitial Cystitis Symptom Inventory, but no difference in 24-h urinary frequency.
Conclusions Meta-analysis showed an improvement exclusively of the symptoms as measured by the Wisconsin Interstitial Cystitis Inventory, but not in 24-h urinary frequency, with BCG therapy. Further randomized clinical trials, including trials of more recent drugs, are required for evaluation of intravesical therapies for PBS.

Keywords Painful bladder syndrome · Interstitial cystitis · Intravesical administration · Treatment

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Introduction

Painful bladder syndrome (PBS), also known as interstitial cystitis, is a condition characterized by chronic bladder pain with symptoms of irritation (urgency, nocturia, or frequency) when all other bladder conditions have been ruled out [1–3]. PBS is a debilitating, chronic disease that has a negative impact on patient quality of life.

Due to its nonspecific symptoms, which may be the result of a variety of urogynecologic conditions, including endometriosis and bladder cancer, PBS is a diagnosis of exclusion [4–9]. Many high-quality studies have attempted to elucidate the pathophysiology of this syndrome. Nevertheless, its etiology remains unknown. Therefore, all treatments proposed thus far have been based on purely empirical evidence [2, 4–8].

Countless drugs and routes of administration with the potential to provide pain relief and induce disease remission are currently being researched [10]. Of these, intravesically administered therapies have stood out in the literature [2, 9, 11]. Despite the variety of drugs administered by this route, there is still no consensus on any therapeutic algorithm that might provide satisfactory results in the treatment of PBS. Within this context, the aim of the present study is to assess the effectiveness of intravesical treatments for painful bladder syndrome.

Materials and methods

Inclusion criteria

Study selection

This review included only randomized controlled trials. The blinding method was not considered for purposes of inclusion or exclusion criteria, nor was follow-up criteria or loss to follow-up. Study designs which did not meet these criteria, such as nonrandomized controlled trials, pilot studies, cohort studies, case–control studies, uncontrolled retrospective studies, narrative reviews, systematic reviews, case reports, case series, letters, brief reports, animal studies, or research protocols, were excluded, as well as studies whose results did not provide complete data (means and standard deviations for continuous, numerical variables and proportion of events for categorical, nominal variables).

Patients

The sample included studies that recruited patients with a diagnosis of PBS according to the Interstitial Cystitis Data Base Study criteria, NIH Urologic Chronic Pelvic Pain Consensus criteria (Baltimore, December 2007), or National Institute of Diabetes and Digestive and Kidney Diseases Criteria for Interstitial Cystitis [12–14]. There were no gender, age, or ethnicity restrictions. No distinction was made between patients with treatment-amenable or treatment-refractory PBS.

Interventions

We compared randomized clinical trials that assessed intravesical treatments for painful bladder syndrome. All included studies were designed to compare intravesical therapy to another treatment modality, regardless of the drug or dosage used or length or frequency of treatment. Studies comparing several treatment modalities that did not include intravesical therapy were excluded from analysis, as were crossover studies.

Clinical outcomes

The primary endpoints were categorized as clinical or urodynamic. Clinical parameters included improvement of symptoms such as urinary frequency, nocturia, and urgency (as assessed by general means, such as a voiding diaries, or specific instruments such as the Global Response Assessment (GRA), O'Leary-Sant Interstitial Cystitis Symptom Index, or Interstitial Cystitis Problem Index and University of Wisconsin IC Symptom Inventory), pain (on a ten-point Likert scale or Pelvic Pain and Urgency/Frequency Symptom Scale), and impact on quality of life (measured by the Rand-36 quality of life questionnaire, SF-36). Urodynamic parameters mainly consisted of functional cystometric bladder capacity and filling volume at first urge.

These parameters were not broken down by timing of assessment in each primary study; instead, all data provided for each parameter were pooled to provide a global estimate of the intervention effect, to the detriment of methodological homogeneity across the sample. In studies where the endpoint of interest was assessed at various times during the study period, only data from the latest assessment were considered for analysis.

Literature review strategy

A systematic review was performed of all articles indexed in the PubMed/MEDLINE and LILACS databases until December 31, 2010. Identification of these articles was based on a high-sensitivity, low-specificity search strategy using subject headings and synonyms pertaining to interstitial cystitis and painful bladder syndrome, with no limitations on study design, date of publication, or country of origin. This strategy was adapted to meet the search requirements of each database (Fig. 1).

Standardization of systematic review

Study selection

All studies identified were screened by a review of titles and abstracts [15–18]. Studies, which did not provide enough information for analysis in their titles and abstracts, were read in full. Next, after all the selected studies had their methodology analyzed, according to inclusion criteria, we included or excluded them.

Furthermore, the reference lists of all chosen studies were analyzed in an attempt to increase the sensitivity of the systematic review. Articles related to each chosen study were also reviewed for this purpose.

The process was carried out by two investigators independently. At the end of the screening stage, both investigators compared their findings and any discrepancies in study selection were addressed by consensus.

Assessment of methodological quality

The methodological quality of each selected study was assessed by two investigators, using the Oxford level of evidence scale [19] and the Jadad et al. scoring system [20]. All clinical trials with a low level of evidence, that is, any other than 1a or 1b, were excluded.

Fig. 1 Search strategies used for study identification

Pubmed

((Cystitides, Interstitial OR Interstitial Cystitides OR Interstitial Cystitis OR Painful Bladder Syndrome OR Cystitis, Chronic Interstitial OR Chronic Interstitial Cystitides OR Cystitides, Chronic Interstitial OR Interstitial Cystitides, Chronic OR Interstitial Cystitis, Chronic OR Chronic Interstitial Cystitis OR "Cystitis, Interstitial"[Mesh])) AND (Therapy/Broad[filter])

Lilacs

(Cistite intersticial) OR (Cistite intersticial crônica)

Statistical analysis

Quality of life parameters, pain scores, and symptom scores were treated as qualitative, categorical variables. All urodynamic parameters were considered quantitative, numerical variables.

Quantitative and qualitative variables were expressed as weighted mean difference and relative risk respectively, both with 95% confidence intervals. The significance level was set at 5%.

Results

Our search strategy yielded 770 studies, including those obtained directly from the searched databases, those

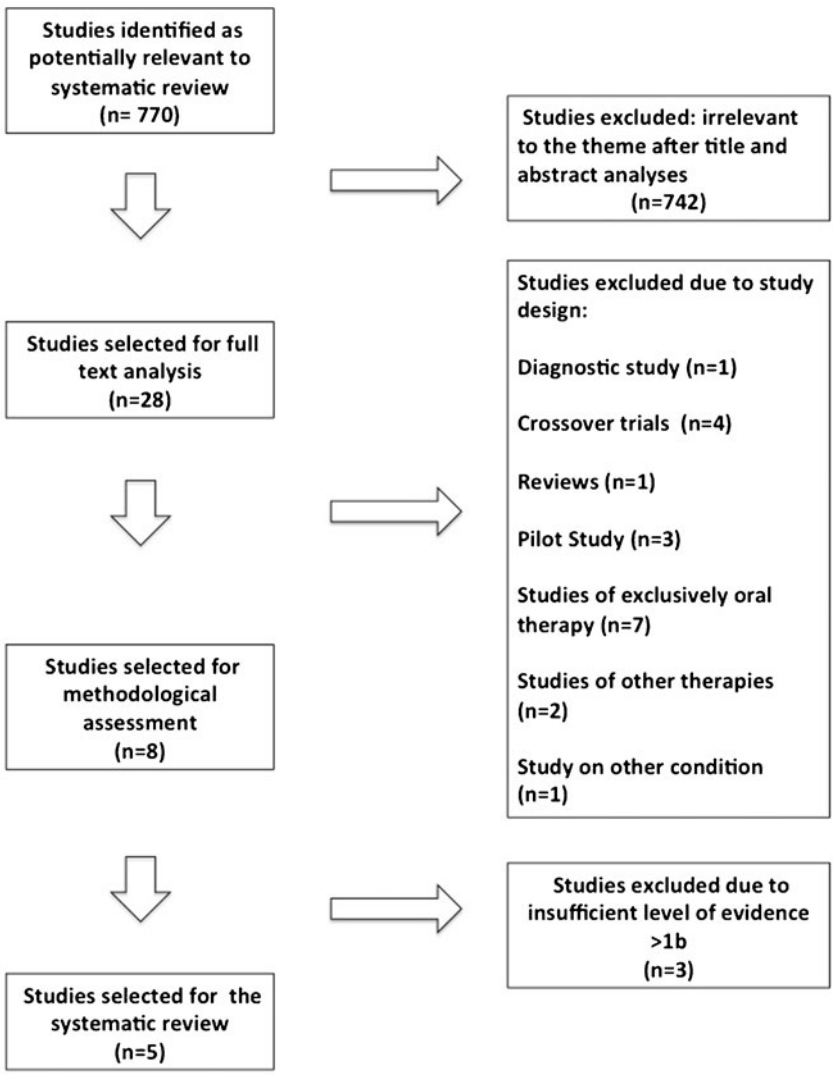

Fig. 2 Flowchart of study identification, selection, and inclusion

Table 1 Summary of studies included and analysis of methodological quality

#	Author	Year	Oxford scale	Jadad scale	Refractory to previous PBS treatments	Intervention (*n*)	Control (*n*)
1	Nickel et al. [21]	2009	1b	2	Not described	Alkalinized lidocaine (50)	Placebo (52)
2	Mayer et al. [11]	2005	1b	3	Refractory	BCG (131)	Placebo (134)
3	Payne et al. [22]	2005	1b	4	Refractory	Resiniferatoxin 0.01 μM (35), 0.05 μM (43), or 0.1 μM (41)	Placebo (40)
4	Irani et al. [23]	2004	1b	3	Not described	BCG (15)	Placebo (15)
5	Barbalias et al. [3]	2000	1b	3	Not described	Oxybutynin (17)	Placebo (14)

BCG bacillus Calmette–Guérin, *PBS* plainful bladder syndrome

recommended as "related articles," and those extracted from the references of other selected studies. Of these, 750 were located in PubMed and 20 in LILACS.

After the initial screening procedure, 28 studies were selected for full-text review, only eight of which met our level of evidence requirements. Figure 2 shows a flowchart of the article selection process. After in-depth assessment of methodological quality, 2b-level studies were excluded, yielding a final sample of five studies for systematic review.

The included studies assessed a wide variety of proposed treatment modalities (Table 1). Nickel et al. evaluated PSD597, a patented combination of 200 mg alkalinized lidocaine followed by instillation of sodium bicarbonate 8.4%, and found sustained improvement in GRA scores up to 29 days after treatment but no improvement in pain, urinary frequency, or urgency as compared to placebo [21]. Payne et al. found improved GRA scores in the placebo group as compared to patients who received resiniferatoxin (RTX). Patients who received the study drug had no significant improvement in any of the assessed parameters; furthermore, during the course of the study, the authors had to increase the dose of instilled lidocaine to relieve the pain caused by resiniferatoxin itself [22].

Barbalias et al. reported improvement both in the control and oxybutynin group for all assessed parameters (symptoms, cystometric capacity, capacity at first urge, urinary frequency), favoring the oxybutynin group [3]. Table 2 summarizes the main conclusions of the included studies and the most common adverse events reported.

Table 2 Summary of study conclusions and most common adverse events

Drug	Follow-up until	Urodynamic	Quality of life	Conclusion	Most common adverse events
BCG (Mayer et al. [11])	34 weeks	No difference in functional capacity	NE	Statistical significance in favor in 24 h frequency, urgency score and Wisconsin IC inventory. No difference in GRA, functional capacity, ICSI and ICPI	Bladder symptoms
BCG (Irani et al. [23])	24 months	Improved bladder capacity	NE	Improves quality of life (SF-36), Wisconsin IC inventory painful intercourse, dysuria and pelvic pain	Not mentioned
Resiniferatoxin (Payne et al. [22])	12 weeks	NE	NE	Not effective in relieving symptoms	Dose-dependent increase in instillation pain and urgency
Alkalinized lidocaine (Nickel et al. [21])	15 days	NE	NE	Provides short-time amelioration of symptoms	Bladder pain
Oxybutynin (Barbalias et al. [3])	6 months	Improved mean cystometric bladder capacity, mean cystometric vol. at first sensation, mean functional bladder capacity, mena vol. at first sensation	NE	Improvement in volume at first sensation and functional bladder capacity	Not mentioned

BCG, Bacillus Calmette–Guérin, *ICSI* O'Leary-Sant IC Symptom Inde, *ICPI* O'Leary-Sant IC Symptom Index and Problem Index, *GRA* global response assessment, *NE* not evaluated

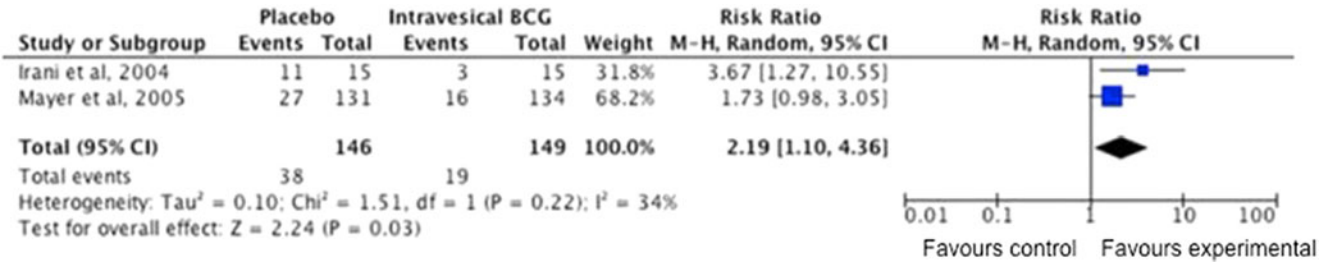

Fig. 3 Meta-analysis of symptom assessment according to the Wisconsin Interstitial Cystitis Inventory after intravesical BCG administration

Two studies in our final sample assessed intravesical administration of Bacillus Calmette–Guérin (BCG). Therefore, a meta-analysis was performed of the variables shared by these two studies, using the same scale (Figs. 3 and 4). Calculations showed that intravesical BCG administration improves the symptoms of PBS, without any effect on 24-h urinary frequency [11, 23].

Discussion

Although the etiology of PBS remains unknown, a variety of factors are believed to interact in its pathogenesis [3]. The presence of macroscopic changes in the bladder mucosa and deficiencies in the quantity and quality of its constituent compounds, identified as characteristic manifestations of the disease, have guided several studies designed to find ways of restoring bladder homeostasis in the hope of developing a definitive treatment for this disorder [2, 3]. Intravesically administered therapies are particularly relevant in this context.

The literature on these treatment modalities is vast and substantially varied. And although classified as secondary sources, systematic reviews of the literature provide the highest level of evidence for guidance of interventions in health care. It was thus imperative that a systematic review on this theme be conducted, in order to extract practical recommendations on the treatment of PBS from the literature [15–18].

The searched databases index a substantial portion of the most highly renowned publications in the field of urogynecology. Furthermore, a high-sensitivity, low-specificity search strategy was used to ensure detection of all studies on the topic [16]. In 2010, Timothy et al. published a systematic review of existing treatments for PBS [24]. Although properly conducted, this review employed a search strategy limited to studies published until 2006; a more recent review of the topic was thus required. Furthermore, the selection criteria defined by the authors allowed inclusion of low-quality trials, as shown by the presence of randomized crossover trials and pilot studies in their sample.

Our meta-analysis found that intravesical BCG administration improved PBS symptoms according to Wisconsin IC Symptom Inventory without producing any change in 24-h urinary frequency [11, 23]. The analysis was limited to these two outcome measurements, only because other outcomes were not comparable, for using different outcome measurements.

In Mayer's study, they found statistical significance in favor of BCG after 34 weeks in 24 h frequency, urgency score, and Wisconsin IC inventory. However, no difference was found in Global Response Assessment, functional capacity, O'Leary-Sant IC Symptom Index, and Problem Index after intravesical BCG [11]. On the other hand, Irani et al. found that BCG improved Wisconsin IC Inventory, nocturia, dysuria, urgency, dyspareunia, pelvic pain, SF-36 score, bladder capacity, and frequency after 2 years [23].

It is very important to highlight the difference between the studies from Mayer et al. and Irani et al. mainly the number of patient in each study, 265 and 30 patients, respectively [11, 23]. However, in our meta-analysis, we took this difference into consideration and calculated the heterogeneity of the studies using I^2 [25]. We found moderate to

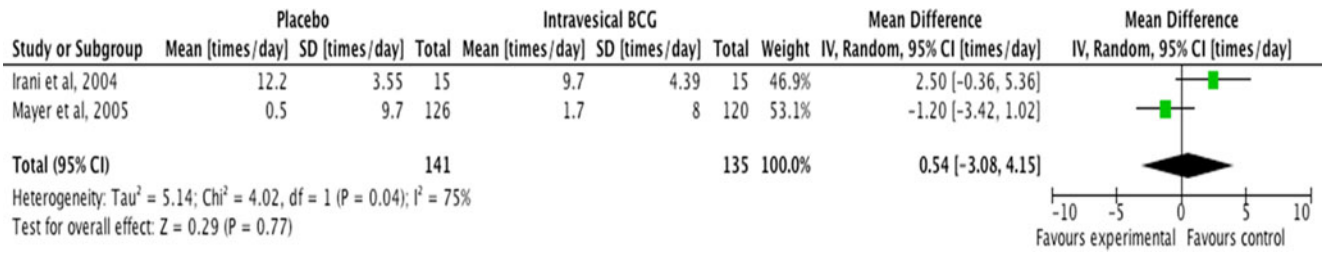

Fig. 4 Meta-analysis of 24-h urinary frequency after intravesical BCG administration

high heterogeneity; therefore, these results should be carefully analyzed and extrapolate to clinical practice.

Comparison of BCG and other evaluated drugs is questionable, as there is a lack of clinical trials for comparing the findings. Barbalias et al. proposed the use of intravesical oxybutynin in the treatment of interstitial cystitis on the basis of satisfactory patients with PBS, intravesical administration of oxybutynin led to improvement in urodynamic parameters [3].

Conversely, studies of resiniferatoxin found no significant improvement in pain or changes in voiding journal entries, despite instillation of lidocaine prior to RTX [11, 22]. This finding is significant, as Nickel et al. reported in 2008 that lidocaine instillation provides symptom improvement in PBS [21]. Therefore, one may hypothesize that resiniferatoxin administration worsens the irritative symptoms of PBS to such an extent that it nullifies the benefits of intravesical lidocaine.

Although some high-quality studies of intravesical therapy for PBS are available, the heterogeneity in methods for assessment of clinical endpoints means the results of these trials are hardly comparable; this precludes meta-analysis of the existing literature. Another issue in our analysis was the need to exclude certain clinical trials due to their pilot design, as the results of pilot studies cannot be extrapolated to clinical practice. Furthermore, no randomized clinical trials have been conducted of drugs that act not symptomatically but on the possible pathophysiology of PBS, such as hyaluronic acid.

We conclude that there are few clinical trials with high levels of evidence about intravesical treatment for painful bladder syndrome, and we could only perform meta-analysis with two studies using BCG. And according to the results of this meta-analysis, intravesical administration of Bacillus Calmette–Guérin produced improvement exclusively of the symptoms as measured by the Wisconsin Interstitial Cystitis Inventory but did not decrease 24-h frequency in patients with PBS. Further randomized clinical trials, including trials of more recent drugs, are required for evaluation of intravesical therapies for this condition.

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Conflicts of interest None.

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