

2016 COCHRANE REVIEW: INTRAVESICAL TREATMENTS FOR BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Painful bladder syndrome (PBS) is defined by the International Continence Society (ICS) as “the complaint of suprapubic pain in relation to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary tract infection or other obvious pathology”. ICS reserves its diagnosis of interstitial cystitis (IC) to patients with “typical cystoscopic and histological features”. Bladder pain syndrome (BPS) is defined by the European Society for the Study of Interstitial Cystitis/Bladder Pain as “pelvic pain, pressure or discomfort perceived to be related to the bladder, lasting for at least 6 months, and accompanied by at least one other urinary symptom”. This is a chronic condition affecting mostly women. Treatments are varied and include dietary/lifestyle modifications, oral medication, intravesical instillations or injections and, in some cases, surgery. Rates of treatment success are generally modest and there is little consensus as to the best form of treatment for this condition. This meta-analysis of Randomised Controlled Trials (RCTs) summarises the evidence of the effects of intravesical treatment in the management of bladder pain syndrome. This is an update of the 2007 Cochrane review (1).

Study design, materials and methods

All randomised controlled trials that evaluated intravesical treatments for bladder pain syndrome, and were published or presented prior to 21st March 2016, were identified from MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL) and hand searching of journals and major conference proceedings. Included were both intravesical instillations and injection procedures. Data was extracted independently by two reviewers, a meta-analysis was performed and evidence based conclusions made.

Results

Thirty-six RCTs were included evaluating 1822 participants of which 97% were women. Risk of bias assessment showed that across all studies approximately 22% of the RCTs had adequate random sequence generation and allocation concealment, while 32% were adequately blinded to participants and personnel. Only 19% of trials had adequate blinding of outcome assessors and 37% were judged low risk for attrition bias.

Eleven RCTs with 835 participants compared intravesical treatments (including Pentosan polysulfate sodium (PPS), Capsaicin, Resiniferatoxin (RTX), Bacillus Calmette-Gurein (BCG), Lidocaine, Sodium Chondroitin Sulphate and Botulinum toxin A) with placebo. With regards to the patient reported outcome subjective cure and improvement of symptoms BCG showed greater improvement compared to placebo (RR 2.08, 95% CI 1.27 to 3.40, 28% vs. 13% respectively, 2 trials, 278 women), whereas all other agents showed no significant improvement when compared to placebo.

In the same comparison change in pain scores assessed using visual analogue scale (VAS) showed no statistically significant difference between treatment or placebo groups except for Capsaicin which showed a mean score reduction of -2.85 (95% CI -3.88 to -1.82, 2 trials, 57 women) when compared to placebo. One trial showed significant improvement using Interstitial Cystitis Problem Index (ICPI) when Lidocaine was compared with placebo with a mean score reduction of -1.63 (95% CI -0.17 to -3.09), though notably confidence intervals are wide. No other treatments reached statistical significance for this outcome. Similarly, no significant differences were found with change in the O’Leary-Sant Interstitial Cystitis Symptom Index (ICSIS) scores with any of the above intravesical treatments when compared with placebo. There were no significant differences in the change in daytime urinary frequency or nocturia between treatment and placebo groups. Pain experienced during instillation was more with Capsaicin/RTX treatments compared with placebo RR 1.51 (95% CI 1.20 to 1.89, 77% vs. 52% respectively). Only BCG showed overall higher rates of adverse events compared with placebo. No significant differences in rates of urinary tract infections and voiding dysfunction were demonstrated between treatments and placebo groups.

5 RCTs with 275 participants addressed the comparison of one intravesical treatment versus another. The trials compared chondroitin sulfate versus dimethyl sulfoxide (DMSO), BCG versus Botulinum toxin A, hyaluronic acid and chondroitin sulfate combination versus DMSO, hyaluronic acid and chondroitin sulfate combination versus hyaluronic acid, and hyaluronic acid versus chondroitin sulfate. There were no statistically significant differences in patient reported subjective cure and improvement, mean change in VAS scores for pain or adverse events between the groups above.

When comparing intravesical combination therapies with other treatments subjective cure and improvement was significantly more with a combination of Botulinum toxin A and hydrodistension compared to hydrodistension alone (RR 2.47 95% CI 1.51 to 4.01, 3 RCTs with 137 participants) as was Lidocaine and heparin combination compared to placebo (RR 4.5 95% CI 1.13 to 17.99, 1 RCT 18 participants). Change in VAS pain scores showed that Botulinum toxin A and hydrodistension in combination was better than hydrodistension alone with a mean difference in scores of -2.12 (95% CI -3.39 to -0.85, 2 RCTs, 74 participants). There was no difference between Resiniferatoxin (RTX) + hydrodistension combination versus hydrodistension alone in this outcome. There were no significant differences in daytime urinary frequency, nocturia episodes, functional bladder capacity, ICSIS index scores, voiding dysfunction and rates of urinary tract infections between RTX and hydrodistension combination versus hydrodistension alone or between Botulinum toxin A injection and hydrodistension combination versus hydrodistension alone.

Interpretation of results

This review shows the RCT evidence for intravesical treatment when compared to placebo has not been proven and there is also guarded evidence on different intravesical combination therapies. The evidence we have so far suggests marginal benefits of BCG over placebo, Botox A in combination with hydrodistension over hydrodistension alone as well as Lidocaine and heparin combination over placebo.

Concluding message

This most comprehensive and up-to-date review of RCT evidence of intravesical treatments for BPS shows that the evidence for their efficacy compared with placebo is at best guarded. There are few RCTs addressing this problem of which many have small sample sizes, moderate risk of bias, and poor outcome reporting. There are a large variety of both single agent and combination agent intravesical treatments in use and there needs to be adequate assessment through large clinical trials with high methodological quality addressing appropriate patient reported outcomes.

References

1. 1. Intravesical treatments for painful bladder syndrome/interstitial cystitis. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD006113

Disclosures

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