

A PROSPECTIVE RANDOMISED CONTROLLED MULTICENTRE TRIAL COMPARING INTRAVESICAL DMSO AND CHONDROITIN SULPHATE 2 FOR PAINFUL BLADDER SYNDROME /INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Painful bladder syndrome is a syndrome which is poorly understood. Patients usually report suprapubic pain related to bladder filling and also report urinary urgency and frequency. In a subgroup of patients, typical cystoscopic findings can be noted and this defines this subgroup as interstitial cystitis. The treatment of PBS/IC is empirical. Bladder hydrodistension under anesthesia, tricyclic antidepressants, antihistaminics and intravesical DMSO instillations are the only treatments for which some evidence exists. Intravesical treatment with DMSO has stood the test of time and is the only FDA approved intravesical treatment of PBS/IC. DMSO however is also used as a solvent in the chemical industry and is in fact used 'off label' in this indication. One of the theories on which intravesical treatment is based, claims that the glycosaminoglycan layer, which protects the urothelial cells is damaged. DMSO, Chondroitin sulphate, hyaluronic acid and heparin have been used to repair the GAG layer with variable clinical success. Chondroitin sulphate seems to be promising, but comparative data are lacking. Assessing the outcome of such treatments is difficult. Objective parameters such as daytime and nighttime frequency may not always reflect the impact of the condition on the life of the patient. Patient reported outcome parameters are more frequently used to assess treatments in overactive bladder disease and in painful bladder research. Several validated questionnaires can be used to assess patients with PBS/IC. One of the most frequently used is the O'Leary-Sant questionnaire. Next to this questionnaire the Global Response Assessment will be used. This is a validated 7 point Likert scale comparing the current status of the patient to the pre-intervention status. This scale has been used in several other studies on PBS/IC.(1) Our aim was to compare the clinical effectiveness of intravesical chondroitin sulphate 2% (Uracyst™) and DMSO 50% in the treatment of patients with painful bladder syndrome.

Study design, materials and methods

An investigator driven prospective randomized multicentre study was designed. Four centres participated. Patients were randomly allocated to a treatment arm. Central randomisation was done. The control arm consisted of 6 weekly instillations with 50% DMSO in saline, while the active arm consisted of 6 weekly instillations with chondroitin sulphate 2%. The primary endpoint was the difference in the proportion of patients achieving score 6 (moderately improved) or 7 (markedly improved) in both groups in the global response assessment scale (GAS). This is a validated 7 point Likert scale. Secondary parameters were the mean 24h frequency and nocturia on a 3 day micturition diary, the change in the O'Leary-Sant questionnaire and the assessment of the suprapubic pain by a VAS scale. The O'Leary-Sant questionnaire consists of 4 questions on 5 points and two VAS scales on 10 points. The maximum score is 60, which is the most severe form of PBS possible. A power calculation ($p=0.05$ with 80% power) showed that 45 patients per arm were needed.

Patients of both genders between 18 and 75 years were included with a history of symptoms of bladder pain/discomfort described as suprapubic pain related to bladder filling, accompanied by other symptoms such as daytime and/or nighttime frequency in the absence of infection or other pathology, with or without the typical cystoscopic findings of interstitial cystitis. An intention to treat analysis is performed. Drop-outs and lost to follow-up are imputed as failures. Appropriate ethical approval was obtained according to national and international guidelines. This abstract shows a planned interim analysis for safety. A clinical evaluation committee evaluated the interim findings.

Results

In total 36 women consented and were included with a mean age of 57 (range 27-75y). 22 were allocated to the chondroitin group, 14 to the DMSO group. In the DMSO group 57% withdrew consent during the trial and only 6 patients concluded the trial. Major reasons for withdrawal were pain during and after instillation, intolerable garlic odour and lack of efficacy. In the chondroitin group 27% withdrew consent because of insufficient effect or side effects such as pain at instillations. The primary endpoint analysis of the GSA showed that only 14% achieved score 6 or 7 in the DMSO group, compared to 72.7% of the chondroitin group ($p=0.002$, 95%CI 0.05-0.72).

In table below secondary parameters are listed.

	DMSO group	Chondroitin group
VAS scale: reduction in %	8,3%	20% *
O'Leary total reduction	- 9.8 points	-7.2 points
O'Leary nocturia subscale	4.7 to 4 (-0.7)	4.5 to 2.9 (-2.4)*
O'Leary pain subscale	4.3 to 3.7 (-0.6)	5.05 to 3.8 (-1.2)*

*statistically significant

Interpretation of results

The major finding of our study was the high drop-out in the DMSO group. DMSO is considered to be the gold standard in intravesical therapy for PBS/IC. This is based on one crossover study where the DMSO arm showed improvement in 53% and the placebo arm in 18% of 33 patients.(2) Other studies are non-randomised and often only show a responder analysis and not an ITT analysis. The chondroitin group performed significantly better in pain reduction and nocturia and in subjective outcome. Chondroitin was also better tolerated than DMSO. Based on this interim analysis the clinical evaluation committee proposed to stop the trial due to the high number of drop-outs in the DMSO arm.

Concluding message

Intravesical chondroitin sulphate 2% (Uracyst™) is a viable treatment for BPS/IC with minimal side effects. DMSO, while being considered the gold standard should be used with caution and with active monitoring of side effects. More randomised controlled studies are needed on intravesical treatments for BPS/IC.

References

1. Nickel, JC et al. "A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of interstitial cystitis." *Bju International* 103.1 (2009): 56-60
2. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol* 1988 Jul;140(1):36-9.

Disclosures

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