

# A systematic review of the literature on cystodistension in bladder pain syndrome

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## Abstract

**Introduction and hypothesis** There is significant variability in technique for cystodistension and an international discrepancy in the role in its treatment of bladder pain syndrome (BPS). The authors evaluate the evidence base for the use of cystodistension for BPS with particular reference to patient-related outcomes.

**Methods** In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement, a prospective search and evaluation protocol was prepared and registered with the PROSPERO database (ID CRD42017053710). A review of the literature was performed using the search terms cystodistension and hydrodistension of the bladder using the PubMed database on 6 October 2016.

**Results** A total of 59 papers were reviewed, but only 17 studies contained original data available for analysis from 1975 to 2016. Ten studies evaluated the outcome of cystodistension in a single arm design or used cystodistension as the control for evaluating adjunctive treatments. Seven studies evaluated cystodistension in combination with other agents or therapies. The best symptomatic responses reported a subjective improvement in 56% of men with moderate to severe prostatitis

and 57% in patients with “inflammatory cystitis” respectively. There were no studies that employed a validated outcome measure, neither a questionnaire nor an analogue scale, to assess the effect of cystodistension alone.

**Conclusions** Cystodistension is increasingly popular, despite a weak evidence base by current standards. The quality of available evidence falls below the level that would be expected of a new intervention. This review highlights the need for cystodistension to be further investigated with randomised control trials.

**Keywords** Bladder pain syndrome · Cystodistension · Hydrodistension · Interstitial cystitis

## Introduction

Bladder pain syndrome (BPS), as per the International Continence Society (ICS), is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency [1]. In patients with BPS other pathological conditions should be excluded. The ICS states that BPS represents a heterogeneous spectrum of disorders. Terms that include interstitial cystitis and painful bladder syndrome are no longer recommended [1].

The European Association of Urology (EAU) reports the prevalence of BPS to vary greatly, but recent reports range from 0.06% to 30%. There is a female predominance of about 10:1, but possibly no difference in race or ethnicity [2]. BPS is one condition included in the chronic pelvic pain syndromes. In the USA, \$881.5 million is spent per year on its outpatient management, and an estimated £158 million is spent annually on management in the UK [1]. The impact on quality of life is difficult to accurately

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assess given the complexity of the patient's symptoms and overlap with other conditions. An extensive European study by Breivik et al. assessing the impact of chronic pain on the quality of life has shown that 21% of patients had been diagnosed with depression because of their pain, 61% were less able to work outside their home, 19% had lost their job, and 13% had changed jobs because of their pain [3].

Management strategies for BPS are not standardised, but include both conservative and surgical treatments, including radical options. Management is based on symptom severity [4]. One of the commonest forms of treatment is cystodistension.

Cystodistension, alternatively known as bladder overdistension or hydrodistension, as a treatment for interstitial cystitis was first reported in 1930 by Bumpus [5]. Cystodistension, describes bladder filling to the maximum capacity at a fixed pressure, maintained for a set period of time. Cystodistension was also described by Helmstein in 1972 for the management of large bladder tumours that were not treatable endoscopically [6]. The rationale behind this approach lies in increased bladder wall tension, resulting in relative ischaemia and eventual bladder tumour sloughing. Subsequently, it was described as a therapeutic intervention for urgency in 1974 [7]. There are several earlier entries in the literature investigating the physiological consequences of bladder distension in spinal injury patients [8]. The beneficial effects of cystodistension in the context of urgency are thought to be mediated through degeneration of unmyelinated motor and sensory nerve fibres [9]. There is great variation in the technique used to perform cystodistension, as detailed by Turner and Stewart in 2005. The variation lies in the time of cystodistension, the number of times cystodistension was performed in one operative session, and the pressures used in the bladder.

A questionnaire study of UK-based urologists and gynaecologists, revealed that cystodistension is used as a therapeutic intervention for: bladder pain syndrome (43.4%), reduced bladder capacity (40.7%), and detrusor overactivity (35.4%) [10]. This study highlighted the significant variability in the technique for cystodistension in terms of anaesthetic, irrigation pressures, volumes, duration of distension, and number of cycles of distension and re-inspection. This is supported by another UK-based survey of consultant urologists that concluded that there is marked variability in cystodistension techniques and limited evidence to support any one technique [11].

Although both the American Urology Association (AUA) and EAU guidance advocate cystodistension in the work-up of suspected BPS to distinguish between inflammatory and non-inflammatory BPS, there is a discrepancy in the role of cystodistension in the treatment of BPS [12, 13]. AUA guidance suggests a role for cystodistension in the treatment for inflammatory BPS (interstitial cystitis) as a third line in the event of failed response to medical therapies and cognitive

behavioural therapies [4]. European guidance is much more guarded and highlights a lack of reliable evidence whilst recognising its widespread use. Both the EAU and AUA guidance refer to the paucity of evidence and highlight that there are no high level (I or II) studies in this field. No guidance has been published by The National Institute of Clinical Excellence on BPS.

A group of East Asian urologists developed a clinical guideline for interstitial cystitis and hypersensitive bladder syndrome in 2009, which was published in the *International Journal of Urology*. The authors state that hydrodistension of the bladder has been a common treatment for interstitial cystitis, but acknowledge that there has been no randomised control study, there is no standard technique, and there may be complications such as bladder rupture. However, cystodistension is included in their treatment algorithm [12].

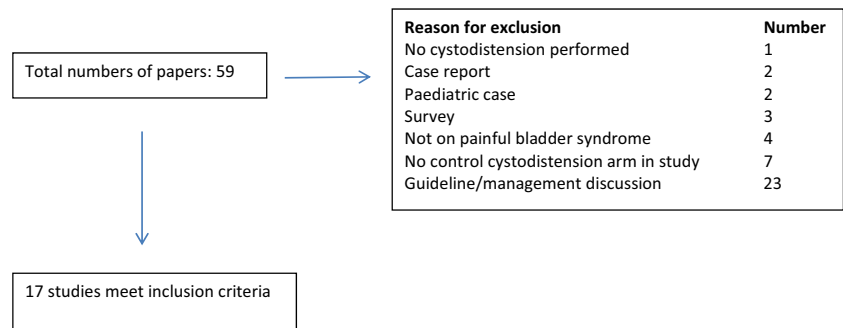
This paper evaluates the available evidence base for the use of cystodistension for BPS, with particular reference to patient-related outcome measures (PROs), and is aimed at drawing some conclusions on its use in practice.

## Materials and methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement, a prospective search and evaluation protocol was prepared and registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (ID CRD42017053710). A review of the literature was performed using search terms cystodistension and hydrodistension of the bladder using the PubMed database on 6 October 2016. The authors included both peer-reviewed and non-peer-reviewed papers in the English language and reviewed papers in full. There were two independent reviewers and the PRISMA statement was followed. In addition, studies cited in international guidelines, not present using the above search criteria, were included. Only studies including data regarding patient-related outcome measures (PROMs) were included for further analysis. In studies using cystodistension as a control arm to compare other interventions, only the cystodistension arm of patient data was recorded. Data collected from each publication included other therapies used alongside cystodistension, number of patients, follow-up, gender, age, outcome measures, the definition of success, and what the outcome was. Data extracted from the relevant papers were entered into an Excel database (Fig. 1).

## Results

The initial investigation into the therapeutic effect of cystodistension revolved around the treatment of detrusor

**Fig. 1** Flow chart of literature review

instability, with the last publication in 1995. Contemporaneous publications, however, evaluate the effect of cystodistension on conditions that are constituents of the chronic pelvic pain syndromes, including bladder pain syndrome, interstitial cystitis, and prostatitis.

Using the search terms detailed, there were 17 studies available for analysis, from 1975 to 2016. Eleven studies stated the proportion of female patients included in each study; however, six studies did not. In those 11 studies, 80.2% ( $n = 521$ ) were women. One of these studies only included male patients. If this study was excluded, the proportion would change to 88.2% ( $n = 521$ ) in 10 studies. Ten studies evaluated the outcome of cystodistension in a single arm design or used cystodistension as the control for evaluating adjunctive treatments. Seven studies evaluated cystodistension in combination with other agents or therapies (Table 1).

Sixteen studies assessed the effect on BPS, whereas one addressed both interstitial cystitis and detrusor overactivity. Subjective change was the only outcome criterion assessed in 9 out of the 16 BPS studies. The O'Leary Sant symptom score was used as an outcome measure in five of the BPS studies, whereas the University of Wisconsin Symptom Score was used in one. Other outcome measures used to assess the effect of cystodistension on BPS were any further treatment, urodynamic changes, and visual analogue pain score.

The number of patients assessed in the BPS studies varied between 14 and 191. The median follow-up in these studies was between 1 and 55 months, although three studies did not provide any median follow-up details. The response rates for painful bladder syndrome according to the defined criteria varied from 5 to 100%, with a mode of 57% [14–30].

Cole et al. reported on the second largest number of patients having cystodistension, with 185 patients undergoing cystodistension for bladder pain [17]. The authors attempted to delineate a patient cohort that would predictably improve post-distension, based on symptoms, but failed to identify any such predictive factors. The overall response, measured as any subjective improvement, was just 5% at 6 months. Accepting the heterogeneity of the outcome measures, better subjective symptomatic responses to cystodistension alone were reported by Berger et al. and by Hsieh et al., who documented

subjective improvement in 56% of men with moderate to severe prostatitis and in 57% of patients with “inflammatory cystitis” respectively [18, 19]. This beneficial effect was reported at only 1 month of follow-up in patients with prostatitis and at 6 months in patients with inflammatory cystitis. Furthermore, the results published by Hsieh et al. should be interpreted in the context of a nearly 30% drop-out rate over the 6-month period studied [19]. It is entirely conceivable that these patients were not improved following cystodistension, which would significantly alter the publication's conclusions. They did, however, report an additive benefit in terms of reduction in urgency for hydrodistension followed by structured bladder retraining.

The “best” outcome was reported by Tomoe [15]. All patients in their cohort group, those with ( $n = 7$ ) and without ( $n = 7$ ) Hunner's lesions, had an overall improvement in total O'Leary Sant scores at 6 months with hydrodistension alone. The author reports that there was no significant difference in any of the post-operative parameters between patients with and those without Hunner's lesions. The study was, however, retrospective and had only small numbers of participants ( $n = 14$ ).

The most recent report of the Helmstein method of cystodistension was reported by Glemain et al. in 2002 [20]. The Helmstein method involves 3 h of continuous bladder distension, under pressure monitoring, with patients anaesthetised by epidural or general anaesthesia. The container for the intravesical saline instillation is placed 80 cm above the bladder. This study looked at two patient cohorts, one retrospective and another prospective. There were a total of 65 consecutive patients, 33 in the retrospective and 32 in the prospective arm. The initial retrospective evaluation revealed that PROs improved in 38% at 6 months and 22% at 1 year. Treatment efficacy was best in patients with a higher initial bladder capacity (150 ml or above) and a higher distension volume. These features were validated prospectively in the second patient cohort. Adverse events were common, with 122 separate complications noted. The most common significant complication was a condom (used as a cystodistension balloon) rupture, which occurred in 22 patients (33.8%). Other complications included haematuria in 63 (97%), low back

**Table 1** Indications and outcomes of cystodistension studies

Reference	Disease	Other therapy	Study type	n	Median follow-up (months)	Gender (% female)
Niimi et al. [14]	IC	Fulguration of Hunner's lesions if present	Prospective	191	Not stated	81
Tomoe [15]	IC/BPS	Intravesical DMSO	Retrospective	14	12	Not given
Manning et al. [16]	IC/BPS	Intravesical AboBTXA	Double blind randomised	27	9	100
Cole et al. [17]	PBS/OAB	–	Randomised	185	6	99
Berger et al. [18]	Prostate pain/IC	–	Prospective	60	1	0
Hsieh et al. [19]	IC	–	Randomised	23	6	Not given
Glemain et al. [20]	IC	–	Retrospective and prospective	32	12	72
Yamada et al. [21]	IC	–	Prospective	52	36	90
	Repeat hydrodistension					
Erickson et al. [22]	IC	–	Prospective	33	1	Not given
Ottm and Teichman [23]	IC	–	Retrospective	47	2	Not given
Hanley et al. [24]	BPS/IC	Behavioural and pharmacotherapy	Prospective	14	10	100
Aihara et al. [25]	BPS/IC	4% intravesical lidocaine	Prospective	30	1	90
Lentz et al. [26]	IC/menstrual symptoms	GnRH analogue or COCP	Prospective	15	55	10
Leppilähti et al. [27]	IC	Hyaluronic acid	Prospective	11	3.5	82
McCahy and Styles [28]	IC/detrusor overactivity	–	Retrospective	45		Not given
Lloyd et al. [29]	Benign and malignant bladder disease	–	Prospective	31	24	68
Dunn et al. [30]	IC	–	Prospective	25		Not given
	Helmstein method					

Reference	Age	Range	Outcome measure	Definition of success	Outcome
Niimi et al. [14]			Freq-volume chart OLS Visual analogue pain score	Time to therapeutic failure	No difference in the long term (100 months)
Tomoe [15]	57	28–78	Freq-volume chart OLS Visual analogue pain score	Total OLS score improvement	100%
Manning et al. [16]	53		OLS	Total OLS score improvement	No significant benefit
Cole et al. [17]	–	16–84	Subjective change	Any improvement	5% (pooled over groups)
Berger et al. [18]		31–47	Subjective change	Any improvement	56% improvement with moderate/severe symptoms 29% improvement normal/mild symptoms
Hsieh et al. [19]	46.1		Subjective change	Any improvement	Pain/urgency 57%
Glemain et al. [20]	56	23–78	Subjective change	Pain reduction to tolerable levels	22–57%
Yamada et al. [21]	56		Any subsequent treatment	3 years treatment free 1 year treatment free	10% 58%
Erickson et al. [22]			University of Wisconsin symptom score	>30% score improvement	36%
Ottm and Teichman [23]	40		Subjective change	Any improvement	56%
Hanley et al. [24]	36	21–52	OLS	Change in mean score	Symptoms 8.5–7.0 Problem 8.9 to 6.7
Aihara et al. [25]	54	25–76	OLS Urodynamic changes	Any improvement N/A	Symptoms 71%, problem 71% 60 ml increase in average voided volume
Lentz et al. [26]	36	23–48	Subjective change	Any improvement	87%

**Table 1** (continued)

Reference	Age	Range	Outcome measure	Definition of success	Outcome
Leppilahti et al. [27]	65	51–76	Visual analogue pain score	At least 50% improvement in pain	Short term 45% Long term 27% <sup>a</sup>
McCahy and Styles [28]			Subjective changes	Any improvement	27%
Lloyd et al. [29]	52	18–76	Subjective change	Marked improvement Some improvement	19% 26%
Dunn et al. [30]	–	–	Subjective change	Symptom free	64%

IC interstitial cystitis, BPS bladder pain syndrome, PBS painful bladder syndrome, OAB overactive bladder, DMSO dimethyl sulphoxide, AboBTXA abobotulinum toxin A, GnRH gonadotropin-releasing hormone, COCP combined oral contraceptive pill, OLS O’Leary Sant

<sup>a</sup> Long and short term defined as before and after 18 weeks

pain in 19 (29%), epigastric pain in 12 (19%), transient deterioration of symptoms in 3 (5%), sepsis in 1 (1.5%), urine retention in 1 (1.5%), and bladder rupture in 1 (1.5%) [20].

The cohort with one of the longest follow-up periods was reported by Yamada et al. in 2003, who treated patients with interstitial cystitis with an initial cystodistension followed by a repeat procedure the following day [21]. This approach resulted in 58% and 10% of patients requiring no further treatment for 1 and 3 years respectively.

Niimi et al. compared the long-term outcome of 191 patients undergoing hydrodistension with and without electrical fulguration of Hunner’s lesions if present over a 6-year period [14]. The authors’ outcome measure was time to therapeutic failure, defined as the need for repeat hydrodistension or to initiate intravesical therapies or oral analgesia. Their results show that the mean time to therapeutic failure in patients without Hunner’s lesions was 25.5 months, compared with 28.5 months in patients who had Hunner’s lesions. The long-term outcomes were no different between the two groups after 17.3 months. Their patients were followed up to 100 months. This publication has a large number of patients ( $n = 191$ ) with a long follow-up; however, the high efficacy of hydrodistension that they report may be clouded by their loose definition of treatment failure.

Manning et al. published in 2014 a multi-centre, prospective, randomised, double-blind study that found at 3 months post-hydrodistension, with and without abobotulinum toxin A (AboBTXA), there was no difference in overall O’Leary Sant scores. The main limitation with this study is that in the control group, 19% patients developed a urinary tract infection [16].

Two publications documented cystodistension resulting in a deterioration of symptoms [22, 23]. Erickson et al. attempted to correlate the urinary markers, anti-proliferative factor, and heparin-binding epidermal growth factor-like growth factor, with symptomatic outcome [22]. Although no correlation was demonstrated, after 1 month, 36% of patients reported a significant PRO improvement whereas 30% (10 out of 33) reported deterioration. Ottem et al. reported a small number of patients (9%; 4 out of 47)

whose symptoms deteriorated following cystodistension [23]. Unfortunately, although Ottem et al. retrospectively analysed a cohort of patients with suspected IC and stratified them according to those undergoing cystoscopy with and without hydrodistension in their diagnostic work-up, they did not publish the difference in symptomatic outcome.

There were no studies that employed a validated outcome measure, neither a questionnaire nor an analogue scale, to assess the effect of cystodistension alone. Two studies employing the O’Leary Sant questionnaire evaluated the role of 4% intravesical lidocaine and behavioural therapy in parallel with cystodistension [24, 25].

In the studies included, apart from those investigating the Helmstein method of cystodistension, there was limited meaningful adverse effect reporting, except in the more recent publications [6]. Owing to the heterogeneity of the results, data, and technique, patients, PROMs, and follow up, our results are descriptive. Statistical analysis was not felt to be appropriate.

## Discussion

It is now widely recognised that BPS represents a heterogeneous group of disorders, within which inflammation, Hunner’s ulcers, and glomerulations following distension are present in a subset of patients, rather than being diagnostic of BPS. Some patients with similar historical features have normal cystoscopic features. Patients with non-inflammatory BPS tend to have other associated conditions, including fibromyalgia, chronic fatigue, irritable bowel syndrome, and depression [13]. It follows that the required treatment is likely to be multimodal rather than solely bladder-focused. The accurate distinction between inflammatory and non-inflammatory BPS has implications for future research into potentially differing therapeutic strategies.

The initial investigation into the therapeutic effect of cystodistension revolved around the treatment of detrusor overactivity, with the last publication on this topic in 1995 [28]. More contemporaneous publications have evaluated

the effect of cystodistension on conditions that are constituents of the chronic pelvic pain syndromes, including interstitial cystitis, bladder pain syndrome, and prostatitis.

Cystodistension plays a definite role in the diagnosis of bladder pain syndrome and may play a role in treatment [4]. In the available literature, there is significant heterogeneity with regard to patient selection, follow-up, and outcome measure. The variation in outcome measures employed reflects publication dates that span the uptake of evidence-based medicine in the 1990s and as such it is not appropriate to conduct a pooled analysis. Furthermore, this information is difficult to collate to improve patient counselling with regard to the potential benefit of cystodistension. The most favourable outcomes are reported at very early follow-up and this is paralleled by a poor response rate at extended follow-up.

It is debatable whether cystodistension should be performed at all. However, pragmatically, given the lack of contemporaneous evidence, cystodistension may be utilised for the initial diagnosis of BPS only. Its use for the treatment of BPS should be restricted to those enrolled in a randomised controlled trial or as part of a standardised national/international protocol with uniform technique and PROMs. The practice of using cystodistension as a control arm for other treatments appears, given the uncertainty illustrated in the outcome data, to be flawed, and should cease.

## Conclusions

Cystodistension is increasingly popular despite a weak evidence base by current standards. The quality of available evidence falls below the level that would be expected of a new intervention before widespread usage, particularly in the context of evidence-based medicine. This review highlights the need for cystodistension to be further investigated with randomised control trials in BPS or standardised national/international protocols, and only offered with careful patient counselling that can detail the lack of high-quality evidence.

## Compliance with ethical standards

**Conflicts of interest** None.

**Ethics committee/institutional review board** Ethics approval is not required for this article, as no study on humans was conducted.

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