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Review

Hyaluronic acid and chondroitin sulphate instillation in chronic bladder diseases: a meta-analysis

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Objective

To systematically summarise and meta-analyse all uncontrolled and controlled studies evaluating the role of intravesical instillation of hyaluronic acid (HA), with or without chondroitin sulphate (ChS), in the treatment of bladder pain syndrome (BPS), recurrent urinary tract infection (rUTI) and post-radiation cystitis (pRC).

Methods

A systematic review was conducted, and a protocol was registered with PROSPERO (CRD42025640480). Studies published between 1 January 1969 and 31 August 2024 were retrieved from multiple databases. Data were analysed using random-effects and common-effects models with subgroup and sensitivity analyses.

Results

A total of 131 studies were retrieved, of which 30, 10 and three investigated the use of HA/ChS in patients with BPS and rUTI or pRC, respectively, and were included in the analyses.

Conclusion

The use of HA/ChS resulted in a significant improvement in pain as well as voiding and irritative symptoms in all the investigated conditions. In addition, the treatment reduced the risk of rUTI when compared to standard care. Although limited data were available, when randomised controlled trials were investigated, the combined use of HA/ChS resulted in better outcomes and a lower infection rate compared to either placebo or standard of care (odds ratio 0.42 [95% CI 0.25; 0.49]; $P < 0.0001$). Finally, an improvement in sexual function and quality of life was also observed.

Keywords

bladder pain syndrome, recurrent urinary tract infections, post-radiation cystitis, hyaluronic acid, chondroitin sulphate, erectile dysfunction

Introduction

Urothelial epithelial cells are coated by a thin waterproof layer formed by a combination of glycosaminoglycans (GAGs), including hyaluronic acid (HA), chondroitin sulphate (ChS), heparan sulphate, and ketaran sulphate [1]. GAGs play a role in preventing against urine solute barrier reabsorption and/or infective agent colonisation along the urothelial mucosa that, if penetrating or leaking into the lamina propria, may cause inflammation and infection. Hence, damage to the GAG layer has been associated with the early development of irritative local symptoms, such as frequent urination, urgency, urinary incontinence, and pain [1,2]. In addition, the ongoing continuation of long-term

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harm due to GAG deficiency can induce a chronic inflammatory response, which may manifest as debilitating bladder conditions, including bladder pain syndrome (BPS), recurrent UTI (rUTI), and post-radiation cystitis (pRC) [2].

Bladder pain syndrome is a chronic inflammatory condition characterised by bladder pain, urinary urgency, frequency and nocturia, in the absence of other identified causes [3]. Its prevalence varies widely depending on the diagnostic criteria used and the population studied [4,5]. The prevalence of BPS is approximately four times higher in women as compared with men [2,6,7]; however, it should be noted that the prevalence rates in men are less clear due to possible overlaps with chronic prostatitis/chronic pelvic pain syndrome [8].

Recurrent UTI is another common clinical condition, more frequently affecting women, and currently defined as the presence of two documented episodes of infection within 6 months or three documented episodes within 12 months [9]. The most effective conventional management of rUTI is intermittent or prolonged antibiotic therapy [10]. However, increasing resistance to bacterial antimicrobial agents represents a crucial limitation of this approach, therefore, alternative treatments, including the use of GAGs, have been proposed [10].

Radiation therapy is well recognised as an effective treatment for several pelvic cancers, including prostate, rectal and endometrial cancers [11]. However, early damage to the bladder with inflammation and urothelial oedema occurs in approximately 50% of treated patients. Late symptoms are present in 5%–10% of patients at an average of 35 months after therapy [11,12], and symptoms may even appear several years after radiation treatment [13].

Given the reported combination of irritative and voiding symptoms associated with the abovementioned conditions, quality of life (QoL) and sexual function can be profoundly affected in both women and men [14,15]. In addition, the intensity and frequency of the bladder symptoms can lead to high economic costs due to direct and indirect (loss of working days) consequences, which have been estimated to be approximately $750 m annually for BPS in the United States alone [6].

The use of bladder instillations of GAGs has been proposed as a management option for all the aforementioned conditions. Although several other options have been proposed, the most commonly used GAGs for intravesical treatment are HA and ChS, alone or in combination [2].

Although previous meta-analyses have assessed the role of GAGs in patients with rUTI [16,17] or BPS [18–21], no study has simultaneously investigated HA alone or in combination with ChS in all three main chronic inflammatory bladder diseases. In addition, no study has investigated the possible determinants of treatment-associated outcomes. The aim of this study, therefore, was to systematically summarise and conduct a meta-analysis of all uncontrolled and controlled studies evaluating the role and outcomes of intravesical instillation of HA, with or without ChS, in the treatment of BPS, rUTI and pRC.

Methods

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Files S1 and S2).

The following PICO criteria were used [22]: Population: male and female patients aged ≥18 years; Intervention: male and female patients treated with HA, with or without ChS, for BPS, rUTI or pRC; Comparison: prospective or retrospective changes from baseline in uncontrolled studies and changes after HA/ChS treatment compared to sham or standard care in controlled studies; Outcomes: improvement in pain and urinary symptoms and reductions in the occurrence of infections from baseline or compared to sham/standard care.

The protocol of this study (CRD42025640480) was published on the website of the University of York (Centre for Reviews and Dissemination, https://www.crd.york.ac.uk/prospero/#recordDetails).

Search Strategy

An extensive Medline search was performed, including the following keywords: ((‘hyaluronic acid’[MeSH Terms] OR (‘hyaluronic’[All Fields]) OR ‘hyaluronic acid’[All Fields]) AND (‘cystitis’[MeSH Terms] OR ‘cystitis’[All Fields] OR ‘cystitides’[All Fields] OR ‘bladder Pain’)) AND ((humans [Filter]) AND (English[Filter])). The search, which accrued data published from 1 January 1969 up to 31 August 2024, was restricted to English-language articles reporting studies in human participants (Fig. S1). The Embase and Cochrane databases were also searched using a specific query (File S3). The use of the Embase and Cochrane databases did not modify the final results or the number of the studies derived.

The identification of relevant studies was performed independently by four of the authors (G.R., S.B., Y.R. and P.C.) according to our PICO and study selection criteria (see also below). Conflicts were resolved by consensus after discussion among all authors. We did not employ search tool software but hand-searched the bibliographies of retrieved papers for additional references. The main source of information was the published articles.

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Study Selection

All prospective and retrospective observational and controlled trials reporting data on the effect of intravesical instillation of HA with or without ChS in patients with BPS, rUTI or pRC were included. For inclusion in our study, the articles had to report at least one of the following: pain, bladder symptoms or urodynamic parameters. Sexual function and QoL outcomes were also analysed, when available. Case reports were excluded. Similarly, studies not reporting data related to the use of HA/ChS and studies on the use of HA/ChS in conditions other than those specified above were excluded from the analysis (Fig. S1). Only studies comparing HA/ChS from baseline or to standard care [10,23], including active comparators such as antibiotic prophylaxis, and/or placebo or sham when available, were analysed. Studies investigating modalities other than intravesical instillation of HA or ChS were also excluded from the analysis. Similarly, patients with chemical chronic cystitis secondary to drugs were also excluded from the analysis.

Outcome and Quality Assessment

The principal outcome measure was the assessment of patient pain in BPS, pRC and in rUTI after the use of HA/ChS. Secondary outcomes included analyses of voiding and irritative symptoms and urodynamic parameters. Sexual function and QoL improvement after HA/ChS were also investigated, whenever possible. The quality of the included trials and risk of bias were determined using the ROBINS-E tool (Table S1) [24].

Statistical Analysis

Heterogeneity was assessed using I^2 statistics. Even when low heterogeneity was detected, we used a random-effect model because the validity of heterogeneity tests can be limited when applied to a small number of component studies. We used funnel plots and the Begg adjusted rank correlation test to estimate possible publication or disclosure bias [25]. However, undetected biases may still be present because these tests have low statistical power when the number of trials is small.

In addition, since in some uncontrolled trials the significance of between-group comparisons (P value) was not reported, we evaluated the endpoint values of each parameter in different treatment groups in a non-paired fashion (a non-paired analysis). Given that some of the studies which did not describe P values nonetheless reported nonsignificant differences across groups, the mean (paired) analysis, which excludes those data, is likely to overestimate the effect of treatments. On the other hand, the non-paired analysis is a very conservative approach, which could underestimate the treatment effect. Since some parameters were evaluated through different approaches and expressed in different ways, the mean difference for each study was divided by the pooled estimate of the SD to express the effect size for each study using a common metric, namely, the standardised mean difference (SMD). According to Cohen [26], a small treatment effect size is considered to be approximately 0.2, a medium effect size to be approximately 0.5, and a large effect size to be approximately 0.8. All other data were expressed as weighted mean differences. Finally, when possible, comparisons from baseline to endpoints related to controlled trials were also used in the analysis of observational studies to improve the statistical power of the analysis.

Meta-regression analyses were performed to evaluate the effects of different parameters on pain in patients with interstitial cystitis/BPS. All data were calculated using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA). Multivariate analysis was performed with SPSS (Statistical Package for the Social Sciences; Chicago, USA) for Windows 25.1.

Results

Descriptive Statistics

Out of 131 retrieved articles, 30, 10 and three studies investigating the use of HA/ChS in patients with BPS and rUTI or pRC, respectively, were included in the analyses (Tables S2 and S3 and Fig. S1) [27–68]. The vast majority of the studies were focused only on women and the number of men included was low (Table S2). The length of treatment and frequency of HA/ChS instillation therapy differed among the studies and only a small number of controlled trials were available (Table S2).

Interstitial Cystitis/BPS

Overall, 1270 patients were included, with a mean age, body mass index (BMI) and follow-up of 47.7 years, 24.3 kg/m^2 and 34.9 weeks, respectively. The mean reported duration of the disease was 3.9 years, and the mean number of instillations was 10.5. Among the included studies, 27 prospectively evaluated the effects of HA with or without ChS, whereas three conducted a retrospective analysis. Only five of the studies included control groups (Table S2).

The I^2 value in trials assessing patient pain in uncontrolled studies was 94.18 ($P < 0.0001$). A funnel plot and the Begg adjusted rank correlation test (Kendall's τ: −0.437; $P < 0.001$) suggested publication bias (Fig. S2A).

When uncontrolled studies were considered, a significant improvement in patient pain was observed at the endpoint (Fig. 1 and Fig. S3A). Duval and Tweedie's 'trim and fill' method revealed a nonsignificant difference in effect size pain improvement (SMD −1.41 [95% CI −1.81; −1.00]; see also

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Fig. 1 Overall effects of hyaluronic acid (HA) and or chondroitin sulphate (ChS) on several symptoms and urodynamic parameters. Data are expressed as standardised mean difference unless specified (*expressed as mean) in observational uncontrolled studies. ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; LL, lower levels; PUF, pain, urgency, frequency; UP, upper levels.

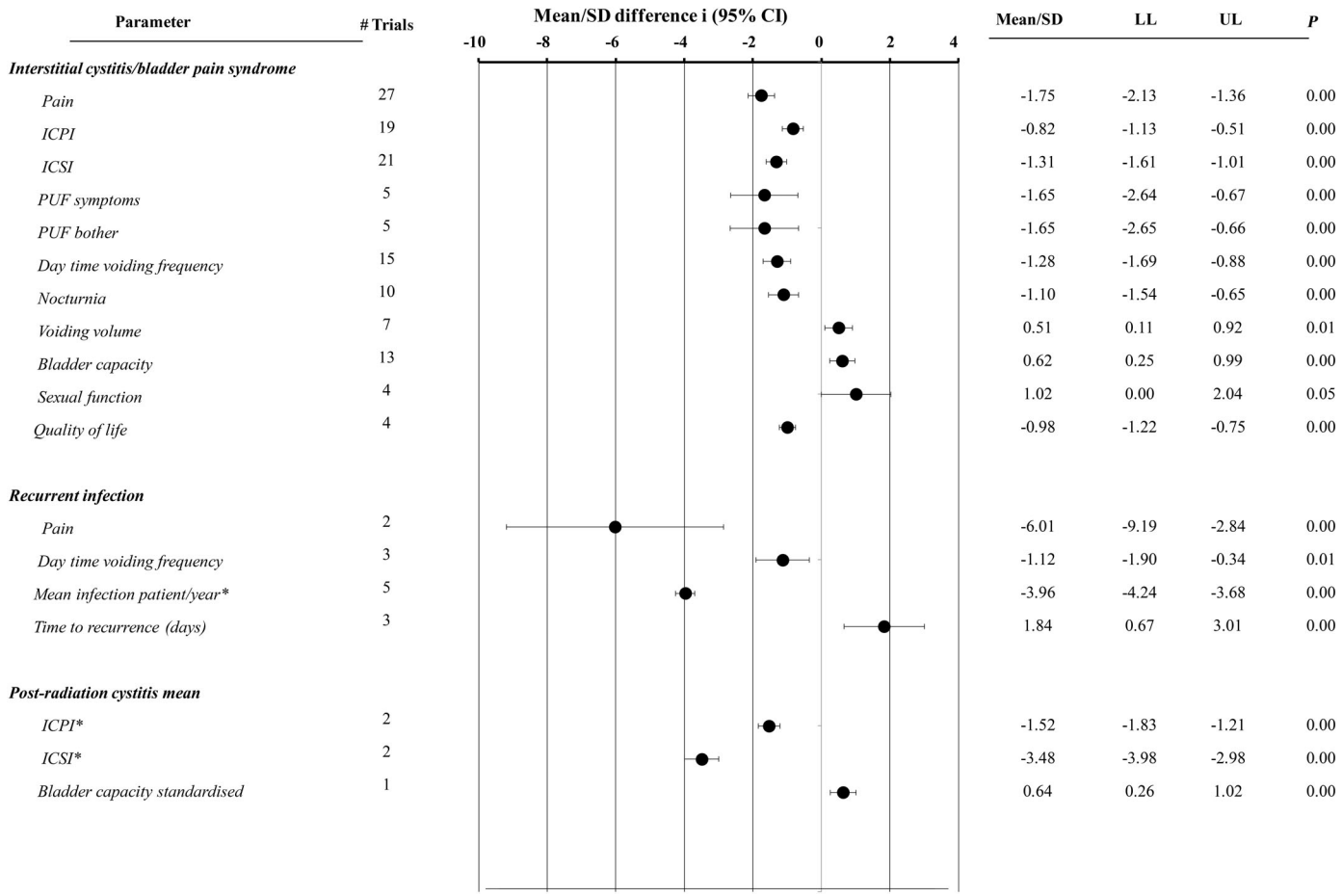

Fig. S2B). Similar results were confirmed when outliers [31,33–37,48–51,56] were excluded in order to reduce heterogeneity (I^2 = 47.9; $P < 0.01$; SMD at endpoint −0.82 [−0.97; −0.67]; $P < 0.0001$).

No difference in pain improvement was observed when prospective and retrospective studies were compared (Q = 2.28; P = 0.123).

Meta-regression analysis showed that the improvement in pain was greater, although not reaching statistical significance, in studies that provided a greater number of instillations and in those that included patients with a younger mean age and a higher mean BMI (Fig. 2A–C). In addition, studies with a longer follow-up and a longer reported duration of symptoms reported better outcomes (Fig. 2D,E). Finally, pain improvement was less evident in studies with a higher prevalence of post-menopausal women (Fig. 2F), and a trend toward a lower effect in studies with a higher prevalence of men was also observed (Fig. 2G). All these associations were confirmed in separate multivariate analyses after adjusting for age and study duration (adj. r = −0.418, −0.151, and 3.85 for BMI, symptom duration, and menopausal status, respectively; all $P < 0.001$).

When other symptoms were investigated, the use of HA/ChS resulted in a significant improvement in overall Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) scores (Fig. 1 and Fig. S3B, C). In addition, improvements in associated irritative and voiding symptoms were also noted. Accordingly, a reduction in pain, urgency, frequency symptoms and bother questionnaire scores, as well as in daily and nocturnal voiding frequency, was observed (Fig. 1 and Fig. S3D–G). In line with the latter findings, a significant increase in mean voiding volume and maximum bladder capacity was detected (Fig. 1 and Fig. S3H,I).

Finally, in female patients, an overall improvement in sexual function and QoL was also observed (Fig. 1 and Fig. S3L,M). No specific data related to men's sexual function were available.

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Fig. 2 Impact of number of total instillations **(A)**, patient age **(B)**, body mass index **(C)**, study duration **(D)**, symptom duration **(E)**, menopausal status **(F)** and male prevalence **(G)** on pain improvement in patients with interstitial cystitis/bladder pain syndrome after hyaluronic acid and or chondroitin sulphate administration.

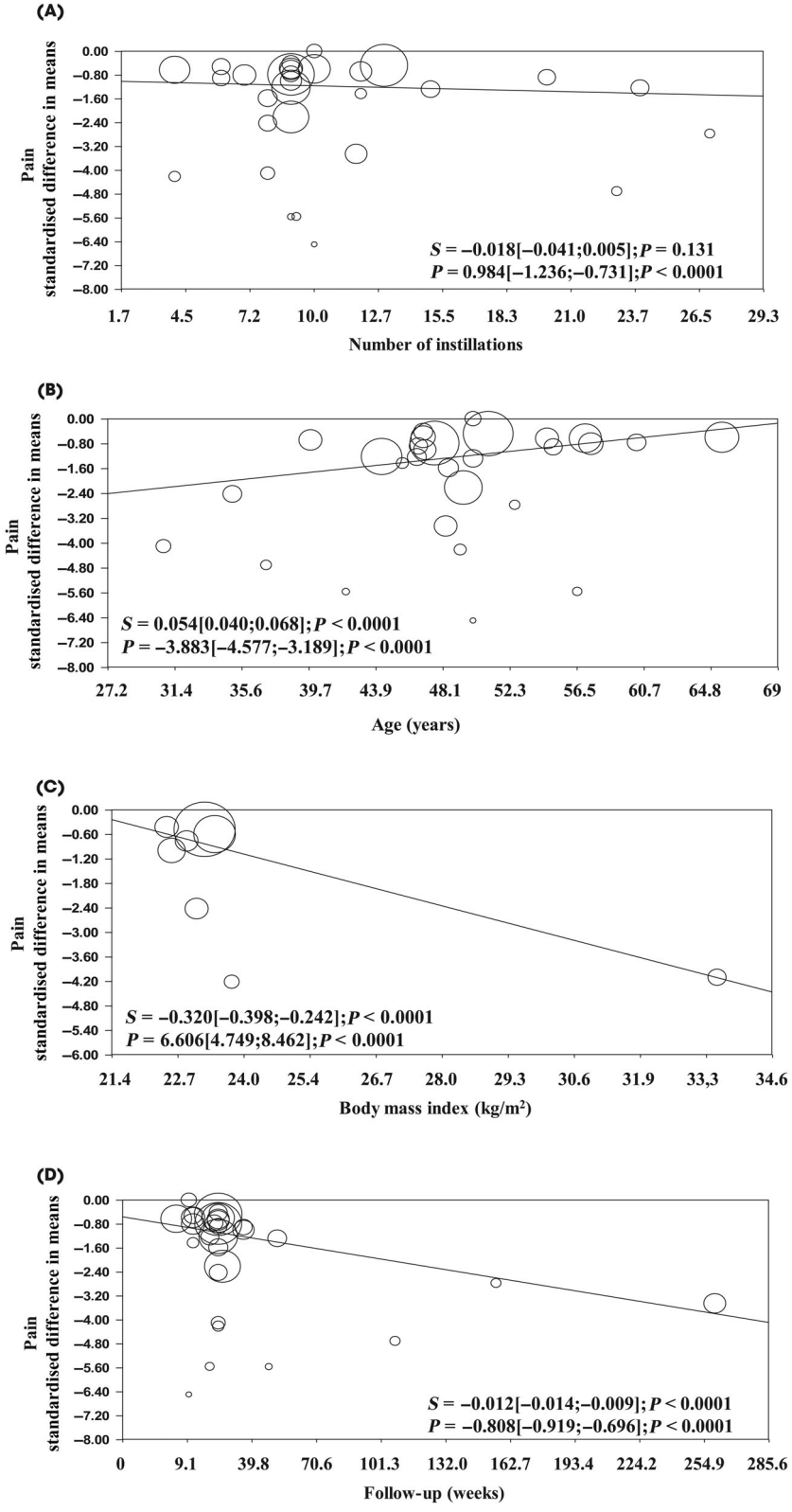

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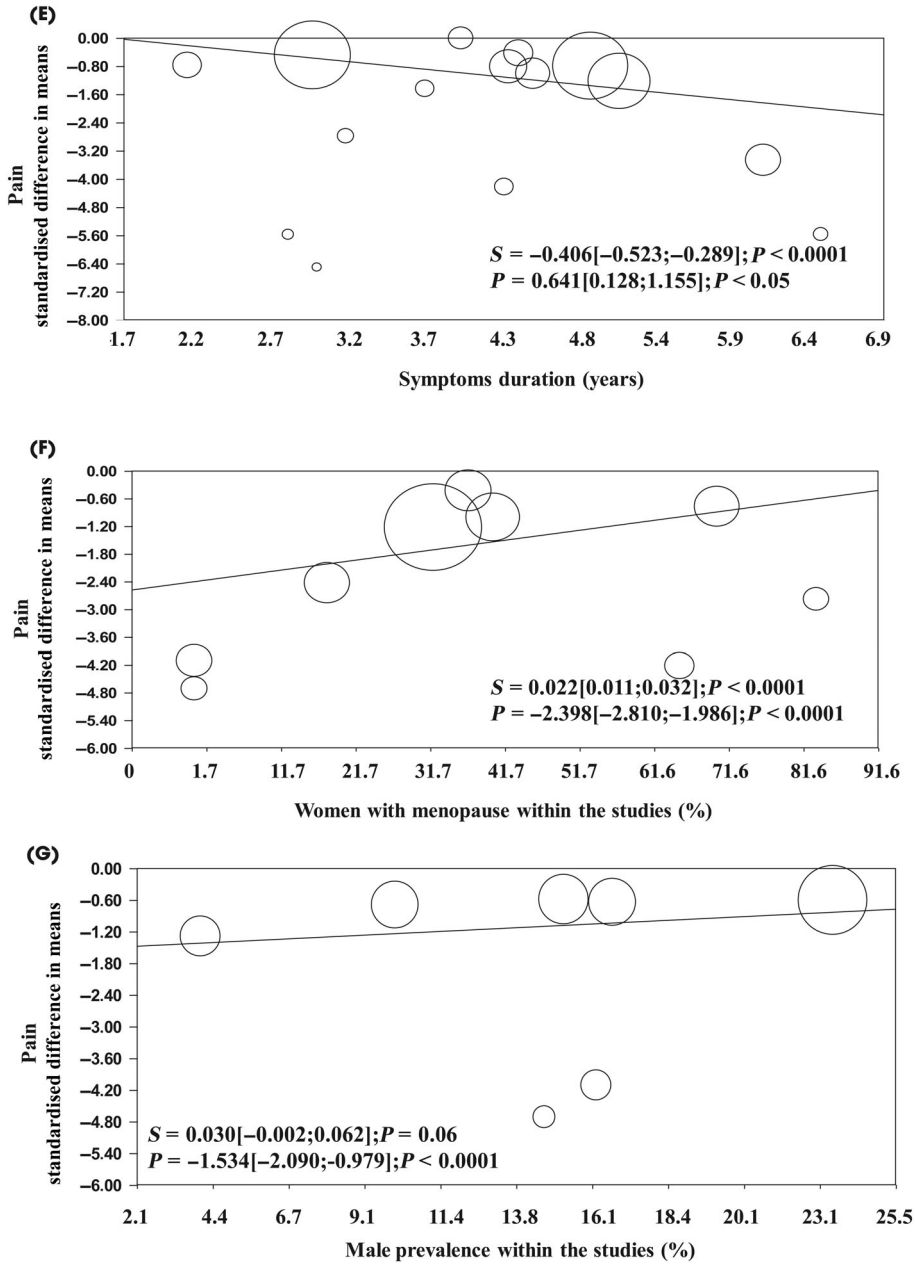
Fig. 2 Continued.



When the effect of the combination of HA/ChS was compared to that of HA alone, no differences were observed for any of the main outcomes investigated in the uncontrolled studies (not shown). However, when the same analyses were derived from controlled trials, the combined use of HA/ChS showed a better improvement in patient pain, ICPI, ICSI, and mean voiding volume, respectively, when compared to controls (Fig. 3 and Fig. S4A–D). In addition, the only study with the relevant data [49] also showed an improvement in QoL when the combination of HA/ChS was compared to HA alone (15.7 [14.2; 17.2]; $P < 0.0001$).

Recurrent Infections

We included 10 studies evaluating the effects of HA/ChS in patients with rUTI. Altogether, there were 846 patients with a mean age, BMI and follow-up of 49.3 years, 25.7 kg/m^2 and 46.7 weeks, respectively. Of the included studies, five retrospectively and five prospectively investigated the role of HA with or without ChS (Table S2). Six of the studies compared the impact of HA/ChS on infection rate when compared to standard care or placebo (Table S2).

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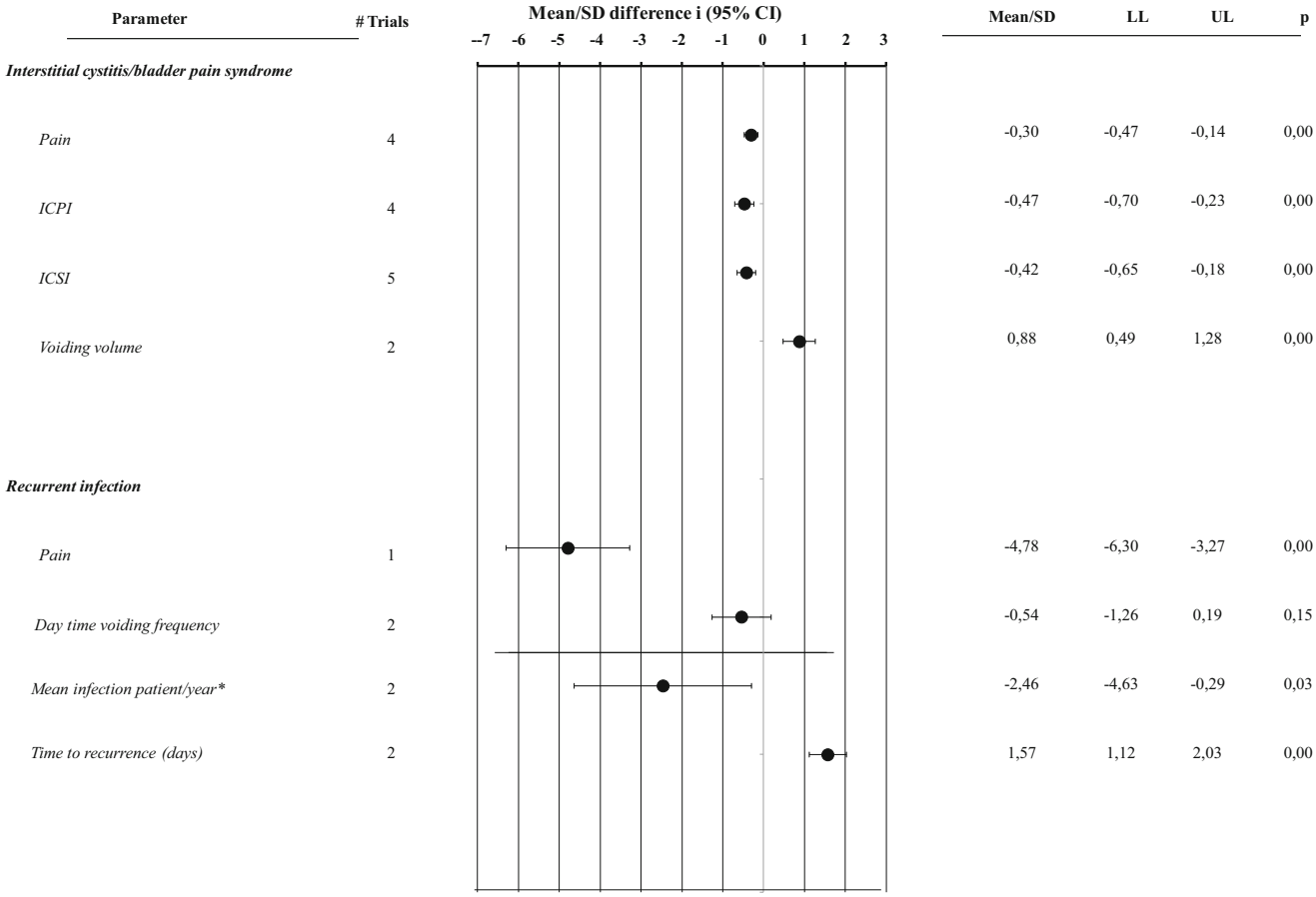
Fig. 3 Overall effects of hyaluronic acid and or chondroitin sulphate on several symptoms, urodynamic parameters and infection rates. Data are expressed as standardised mean unless specified (*expressed as mean) in randomised controlled trials. ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; LL, lower levels; UP, upper levels.



The I^2 value in studies assessing the mean number of patient infections per year in uncontrolled studies was 43.5 ($P = 0.009$). A funnel plot and the Begg adjusted rank correlation test (Kendall's τ: −0.30; $P = 0.46$) suggested no publication bias. The use of HA/ChS was associated with a significant reduction in mean number of infections per patient/year and in time to recurrence when both uncontrolled and controlled studies were considered separately (Figs 1 and 3 and Fig. S5A–D). In line with this, data derived from controlled trials showed that the combined use of HA/ChS significantly reduced the risk of infection recurrence as compared with standard care (odds ratio 0.42 [95% CI 0.25; 0.69]; $P < 0.0001$; Fig. S5, Panel E).

When specific symptoms were investigated, HA/ChS significantly improved pain when uncontrolled and controlled trials were considered separately (Figs 1 and 3 and Fig. S5F). Conversely, daytime voiding frequency improved only when uncontrolled studies were analysed, while a positive trend was observed in controlled studies (Figs 1 and 3 and Fig. S5G).

Post-Radiation Cystitis

Only three uncontrolled studies assessed the role of HA/ChS in patients with pRC. Overall, 85 patients with a mean age and follow-up of 69 years and 26.7 weeks were included. Two trials were based on patients with prostate cancer treated with radiotherapy, and one study included both men and women treated for prostate, rectal or endometrial cancers (Table S2).

In all cases, a combination of HA/ChS was used. In this population, HA/ChS was associated with a significant improvement in ICPI and ICSI as well as bladder capacity (Fig. 1 and Fig. S6A,B). Data on ICPI and ICSI were confirmed in a sensitivity analysis that excluded an older study from the same group [66] in order to avoid any possible bias due to patient overlap (SMD −1.50 [95% CI 1.82; −1.18], SMD −3.50 [95% CI −4.01; −2.99] for ICPI and ICSI, respectively; both $P < 0.0001$).

In addition, the only study with relevant data [68] also showed a significant improvement in QoL, as measured using

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the mental and physical components of the SF-36 questionnaire (5.13 [1.47; 8.79] and 9.07 [2.59; 15.55] for mental and physical components, respectively; both $P < 0.001$). No information on sexual function was provided in the studies that focused on pRC.

Discussion

This is the first study to simultaneously and systematically analyse all the data derived from controlled and uncontrolled studies investigating the role of intravesical instillation of HA alone or in combination with ChS in the three major chronic inflammatory bladder diseases: BPS, rUTI and pRC. Our data showed that this treatment could improve pain as well as voiding and irritative symptoms in all three conditions. In addition, it could reduce the risk of rUTI when compared to standard care. Furthermore, although there were limited data available, when randomised controlled trials (RCTs) were considered, the use of HA/ChS combined resulted in better outcomes and a lower infection rate compared to either placebo or standard of care. Finally, improvements in sexual function and QoL were also observed.

Chronic pain is a significantly limiting and disabling symptom, regardless of its aetiology [69]. A previous study, conducted in the European Union, analysed eight prevalence databases and 10 cost databases and documented an average non-cancer chronic pain prevalence of 27% [69]. Fibromyalgia was associated with the highest unemployment rate (6%), claims for incapacity benefit (up to 29.9%), the greatest number of days of absence from work (20.9), as well as the highest patient-cost per year (approximately EUR10 000) [69]. As recently reported by the European Association of Urology (EAU) guidelines, adequate cost data have not been identified in Europe for BPS, however, it can be speculated that the burden of this disease is similar. Meta-regression analysis showed that the results with regard to pain relief were poorer in postmenopausal women and increased according to the reported duration of the symptoms. The former finding was not surprising because the lack of oestrogen and reduced testosterone levels associated with menopausal status can induce several genito-urinary changes, including the reduction of GAG expression [70]. These local changes can, in turn, favour the appearance of UTI and bladder inflammation, which represent key elements of the so-called genitourinary syndrome of menopause [71]. Similarly, emerging evidence supports the anti-inflammatory role of testosterone in several tissues, including the prostate and the genito-urinary tract [72–76]. The latter observation could, at least partially, explain the more limited effect of GAG treatment observed in male patients. Finally, the smaller improvements in pain observed in patients with a higher BMI were not surprising, since obesity is associated with a well-known chronic inflammatory process [77] as well as reduced testosterone levels in men [78,79].

The specific pathogenic mechanisms underlying bladder chronic pain (BCP) are yet to be completely elucidated. A working hypothesis supports the loss of the GAG layer, with consequent urothelial exposure to toxic urine components, which could eventually result in activation of nerve-ending neurogenic inflammation, increased frequency and amplitude of contraction of the bladder detrusor muscle, and symptom appearance [2,3]. In the early stage, patients may complain of frequent urination, nocturia and urgency. In addition, urothelial oedema and inflammatory bladder lesions can alter functional bladder capacity and reduce voiding volume. Accordingly, pre-clinical studies have documented that GAGs can impair the activation of peripheral C-fibre nociceptors and block smooth muscle contraction, as well as prevent immune cell recruitment and activation [2]. In line with this, the data in our study show that the restoration of GAG, in addition to reducing pain, can improve other bladder symptoms, including functional parameters (micturition frequency and volume and nocturia), symptom severity as derived from the ICSI questionnaire, and health problems investigated through the ICPI questionnaire. Similarly, improvements in urgency frequency and bothersome symptoms were also observed, at least in patients with BPS. Interestingly, our data also showed that HA/ChS can deliver pain relief, even in patients with a long disease duration. This supports their possible role in patients with long-standing symptoms. Pre-clinical and clinical data have shown that the effects of GAG instillation last for approximately 7 days. Hence, repeated administrations are theoretically required to maintain the clinical response [80]. Our meta-regression analysis showed a trend, without reaching statistical significance, of greater pain improvement being achieved with a greater number of GAG instillations. However, it should be recognised that the vast majority of the included studies used a protocol including approximately 10 instillations. Hence, larger and long-lasting studies using a larger number of intravesical applications are recommended to better clarify this point.

Only a few studies have investigated the role of GAG administration on sexual function outcomes in patients with BPS. The association between reduced QoL and anxiety and depressive symptoms, particularly in patients with chronic pain has been established [81,82]. Several studies have reported that women with BPS experienced impairment in all sexual function domains, including desire, arousal, lubrication, and orgasm [14]. The data in our study showed that HA/ChS can improve overall sexual function. Furthermore, the only study using the 'gold standard' method for female sexual function evaluation (the Female Sexual Function Index) [48] also showed that HA/ChS improved all

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aspects of sexual function. The GAG-induced improvements in local inflammatory processes, and in anxiety and depressive symptoms [47] and QoL, may help to explain the observed amelioration of sexual dysfunction in female patients. However, it should be noted that Arslan et al. [48] did not find any difference in female sexual function when comparing the use of HA alone with the use of HA/ChS combined. In addition, no data on male sexual function were available.

There is a large body of evidence to show that antibiotic prophylaxis is the most effective therapy for preventing rUTI [83–85]. However, this approach is associated with an increased risk of developing antibiotic resistance, which is a crucial limitation [84]. Our data showed that the use of HA/ChS can result in a lower rUTI rate and longer time to recurrence, even when compared to standard care (including antibiotic prophylaxis) or placebo. In addition to the aforementioned mechanisms, it has also been suggested that HA blocks the intercellular adhesion melecule-1 (ICAM-1) receptor, preventing leukocyte activation and reducing inflammatory processes [2]. Furthermore, GAGs prevent bacterial adherence to the bladder mucosa.

Few studies have compared the use of HA alone or in combination with ChS. In uncontrolled studies, no difference was detected for the main outcomes investigated. However, in RCTs, the combined use of HA/ChS showed superior results in terms of symptoms and urodynamic parameters as well as in reducing the risk of rUTI. In line with this finding, it has been reported that HA and ChS bound together by calcium chloride can reduce levels of inflammatory cytokines and chemokines, thus allowing stabilisation and functional amelioration of the urothelial epithelial cells [86].

Only a small number of uncontrolled studies evaluated the role of HA/ChS in patients with pRC. Similar to findings in other bladder diseases, an improvement of both subjective symptoms and urodynamic parameters was seen. Two studies assessed the efficacy of GAG administration for preventing pRC. In their observational study, Hazewinkel et al. [87] evaluated the prophylactic use of intravesical ChS for preventing acute effects of radiotherapy in 20 women with uterine/endometrial cancer. In another RCT, Redorta et al. [88] tested the combination of oral administration of HA/ChS in addition to HA/ChS instillations in 49 patients with prostate cancer. Both studies concluded that the use of GAGs reduced the incidence of pain and bladder symptoms. However, at the present time, it is not clear whether the oral formulation of GAGs has any effect.

Several limitations of our meta-analysis should be recognised. First, most data were derived from observational and uncontrolled studies, and only a few RCTs were available. Statistical analysis showed a risk of bias when pain relief in interstitial cystitis/BPS was investigated. However, the data were confirmed after Duval and Tweedie's trim and fill test was applied. The potassium sensitivity test [29] has been proposed as a possible index to predict the response to GAG treatment, but limited information on this test was available among the included studies. It would also be of value to assess the effects of GAG treatment in BPS patients based on the presence or absence of Hunner's ulcers. However, such an analysis was not possible due to limited data. Previous meta-analyses have investigated the use of GAGs in patients with BPS [18–21,89] or with rUTI [16,17], but only limited information on this test was available on the use of HA/ChS was provided [18–21]. Similarly, although Pyo et al. [89] focused their analysis on HA/ChS, only 10 studies, including a total of 390 patients, were included. Furthermore, none of these studies analysed the possible determinants of pain relief. Finally, the two meta-analyses focused on rUTI combined data from controlled and uncontrolled trials, and included a lower number of patients overall when compared to our analyses [16,17]. The vast majority of the studies reported a very limited number of GAG-related side effects. Hence, the latter aspect was not investigated in the current meta-analysis. The clinical significance of the effects on female sexual function and QoL need to be confirmed. Finally, due to the limited data, the results in male patients and male sexual function need to be confirmed in larger studies.

In conclusion, our data show that intravesical HA/ChS administration represents a promising approach for patients with BPS, rUTI and pRC. However, according to the EAU guidelines [3], the limited number of RCTs included in our analysis means that the level of evidence was weak. Hence, more controlled studies are advisable to confirm the observed positive outcomes. In addition, it should be recognised that BCP is frequently associated with other chronic pain disorders, therefore, a multidisciplinary approach with the collaboration of several healthcare professionals is recommended to adequately manage this condition. Finally, the evaluation of sexual function should be regarded as a crucial target in the management of all patients with chronic bladder diseases.

Disclosure of Interests

Yacow Reisman was a Speaker for IBSA and Mikkel Fode was a speaker and consultant for Astellas. The other authors have no conflicts of interest to declare.

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Abbreviations: BMI, body mass index; BPS, bladder pain syndrome; ChS, chondroitin sulphate; EAU, European Association of Urology; GAG, glycosaminoglycan; HA, hyaluronic acid; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; pRC, post-radiation cystitis; QoL, quality of life; RCT, randomised controlled trial; rUTI, recurrent UTI; SMD, standardised mean difference.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk of bias according to the ROBINS-E tool.

Table S2. Characteristics of studies included in the meta-analysis. P, prospective trials; R, retrospective study; Quantitative variables are expressed as mean. See also Appendix 1. ChS, chondroitin sulphate; HA, hyaluronic acid. *Same study non-responder group, **same study different population, ^same study different protocol, ^^only data related to HA considered. BMI, body mass index; M, male.

Table S3. Outcomes of studies included in the meta-analysis. *Same study non responder group; **same study different population, ^same study different protocol, ^^only data related to HA considered. ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; PUF, pain, urgency, frequency.

Figure S1. Flow chart of the included studies.

Figure S2. Overall (A) and after applying Duval and Tweedie's trim and fill method (B) funnel plot of included trials examining the patient pain improvement after hyaluronic acid (HA) and or chondroitin sulphate (ChS) administration. The black circles indicate the data after applying Duval and Tweedie's trim and fill method.

Figure S3. Weighted mean or standardised mean differences (with 95% CI) of pain (A); Interstitial Cystitis Problem Index (B); Interstitial Cystitis Symptom Index (C); Pain, Urgency, Frequency symptoms (D); bother (E); day time voiding frequency (F); nocturia (G); bladder capacity (H); voiding volume (I); overall women sexual function (L) and quality of life (M) after HA, hyaluronic acid and or ChS, chondroitin sulphate therapy in uncontrolled observational studies. *same study different population.

Figure S4. Weighted mean or standardised mean differences (with 95% CI) of pain (A); Interstitial Cystitis Problem Index (B); Interstitial Cystitis Symptom Index (C); voiding volume (D); after HA, hyaluronic acid and or ChS, chondroitin sulphate therapy in controlled studies.

Figure S5. Weighted mean or standardised mean differences (with 95% CI) of patient/year infection and time to recurrence (days) in uncontrolled (A, C) or controlled (B, D) studies; odds ratio for recurrent infection in controlled studies (E); pain (F) and day time voiding frequency (G) in uncontrolled studies after HA, hyaluronic acid and or ChS,

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chondroitin sulphate therapy in controlled studies. *same study different population.

Figure S6. Weighted mean differences (with 95% CI) of Interstitial Cystitis Problem Index (A); Interstitial Cystitis Symptom Index (B) after HA, hyaluronic acid and or ChS, chondroitin sulphate therapy.

File S1. PRISMA 2009 checklist.

File S2. MOOSE (Meta-analyses of observational studies in epidemiology) checklist.

File S3. Queries used for Embase and Cochrane search.

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