INFORMATION BRIEF (RAPID REVIEW)

HYALURONIC ACID FOR TREATMENT OF INTERSTITIAL CYSTITIS

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Medical Development Division
Ministry of Health Malaysia
016/2023

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Rapid Review
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SUGGESTED CITATION: Maharita AR and Izzuna MMG. Hyaluronic Acid for Treatment of Interstitial Cystitis. Information Brief. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2023. 7p. Report No.: 017/2023

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

TITLE: HYALURONIC ACID FOR TREATMENT OF INTERSTITIAL CYSTITIS

PURPOSE

To provide brief information on the efficacy/effectiveness, safety and cost-effectiveness of hyaluronic acid (HA) for cystitis based on a request from the Director of Medical Practice Division.

BACKGROUND

Hyaluronic acid

Hyaluronic acid (HA), also called hyaluronan is the main constituent of cartilage and synovial fluid. It is a long polysaccharide (glycosaminoglycan) chain with a hydrophilicity that gives viscoelastic properties underlying the mechanical properties of cartilage (shock absorption) and synovial fluid (joint lubrication and cartilage protection).[1]

Cystitis

Interstitial cystitis or bladder pain syndrome (IC/BPS) is an unpleasant sensation of pain, pressure, or discomfort perceived to be related to the urinary bladder, associated with lower urinary tract symptoms such as urinary frequency, with or without urgency and nocturia of more than six weeks' duration, in the absence of infection or other identifiable causes.[2,3]

There is no durable treatment for this disease; however, novel treatments have been designed based on new discoveries in the pathophysiology of IC/BPS.[2] Despite decades of basic and clinical research, the aetiology of BPS/IC (BPS) remains obscure. This disease likely has a multifactorial aetiology. The current accepted theory of its cause is injury or dysfunction of the glycosaminoglycan (GAG) layer (defensive mucosal lining) that covers the urothelium. Thus, the hyaluronic acid (HA) has beenintroduced for intravesical treatment for BPS/IC patient's refractory to conventional therapy.[4]

Intravesical Hyaluronic Acid in Cystitis

Based on urothelial dysfunction studies, abnormal differentiation and defective synthesis of surface proteoglycans and barrier proteins contribute to IC/BPS. Therefore, intravesical therapy with glycosaminoglycan replacement is applied for IC/BPS treatment. The HA is a non-sulfated mucopolysaccharide component of the GAG layer. It is present on the bladder wall surface to prevent urine and solutes from crossing the cell membrane.[2] The GAG layer of the urothelium functions as an epithelial permeability barrier. When impaired, its functions can be duplicated by exogenous GAG. As a natural component of the GAG layer, hyaluronic acid (HA) was used to repair defects of the GAG layer of the urothelium. The HA may reduce the permeability of the synovial membrane and inhibit the chemotactic and phagocytic functions of

leukocytes.[11] The standard protocol of intravesical HA treatment was 4 weekly bladder instillations each with 40mg/50mL of HA solution followed by five similar monthly instillations.[4]

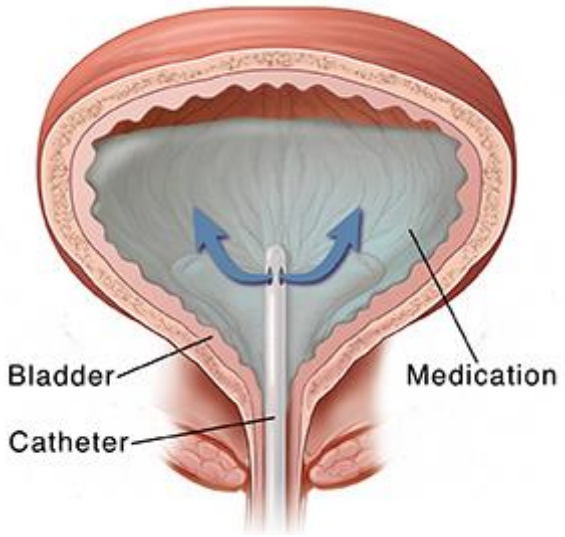

Figure 2: Intravesical medication instillation into bladder[6]

EVIDENCE SUMMARY

From the systematic search, eight studies fulfilled the inclusion and exclusion criteria. The included studies consisted of three systematic reviews (SR). The other five studies were three pre- and post-intervention studies, one case-control study and one cost analysis study. The primary outcomes evaluated were pain Visual Analog Scale (pain-VAS), Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) after intravesical HA instillation. The other outcomes were on Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ), bladder volume and voided urine volume. Most of the sample population were female who were diagnosed with IC/BPS.

Efficacy/ Effectiveness

There were two SRs on efficacy of intravesical HA instillation among IC/BPS patients. Both SRs pooled the results to compare the intravesical HA alone, chondroitin sulphate (CS) alone or combination of intravesical HA and CS (HA-CS). The SR and MA by Liu S. et. al. included 11 RCTs and only two studies evaluated the use of intravesical HA instillation; one study (n = 72) compared between HA, chondroitin sulphate (CS) and combination of HA and CS (HA-CS) and one study (n = 42) compared HA and CS. From the network MA performed, Liu S. et. al. reported that the **HA-CS combination had significant improvement in ICPI, ICSI and pain-VAS compared to single intervention**.[7] However, the SR and MA by Pyo JS. et. al. which consisted of 10 studies (n = 390; mostly women) that evaluated the efficacy of intravesical HA alone and HA-CS combination, reported that both interventions either **intravesical HA alone**

or combination significantly improved pain-VAS, ICSI, ICPI, bladder volume and voided urine volume.[8]

Meanwhile, the SR by Chen A. et. al. (2021) reviewed the current literature on sexual health outcomes in IC/BPS patients after they were being treated with various interventions including intravesical HA. Out of the 10 included studies, four studies evaluated the used of intravesical HA instillation. The results of the four studies were **conflicting** as two studies (n = 171) reported an improvement in the PISQ-9 scores up to 6 months after treatment (P < 0.0001). While the other two studies (n = 55) reported no significant changes in PISQ-12 score.[3]

Three pre- and post-intervention studies by Tsai CP et. al.[4] (n = 140 women), Hung MJ et. al.[9] (n = 103 women) and Akbay E. et. al. (n = 54 women) evaluated the response towards intravesical HA instillation among patients with IC/BPS. **All three studies reported that there was significant improvement (P < 0.001) in pain-VAS, ICSI and ICPI** after one month, three months and six months of intravesical HA instillation. Tsai CP et. al. and Hung MJ. et. al. also reported on Global Response Assessment (GRA) regarding perception of patients on the overall changes in bladder conditions. The overall results of the study showed that around 39.4% to 73.3% of the patients reported **moderate/marked (+2~+3) improvements of overall bladder conditions on GRA** after the initial of four weeks and after six months of intravesical HA instillation.[4,9] On the other hand, Akbay E. et. al. conducted **subgroup analysis and found that intravesical HA was more effective in patients aged ≥ 51.5 years old (median value), in menopausal women and in those who had no history of sexual activity.**[10]

There was one case-control by Scarneciu I. et. al. (2019) evaluated a long-term effect of intravesical installation with HA in relieving lower urinary tract irritation symptoms in patients with urinary tract infections (UTI) and IC/BPS. The study involved 30 patients with uncomplicated UTIs (UTI Group) and 24 patients with IC/BPS (IC/BPS Group). The outcomes monitored on bladder pain, daytime urinary frequency, quality of life, urgency, nocturia and bladder volume change. **In bladder pain and in quality of life, both groups showed significant improvement** after intravesical HA instillation. However, both groups did not show significant effect on bladder volume change after intravesical HA instillation. On the other hand, for daytime urinary frequency, only UTI Group reported significant improvement and, no statistically significant reduction reported in IC/BPS Group. In terms of **urgency and nocturia, only IC/BPS Group experienced significant improvement** in both conditions. Overall, 18 patients (75%) in IC/BPS Group showed completed response to intravesical HA and required no further treatment, while six patients (25%) showed no response. Meanwhile in UTI Group, 18 patients (60%) responded to the treatment and 12 patients (40%) showed no response.[11]

Safety

Intravesical HA is one of acceptable treatments for IC/BPS.[9] According to Head of Urology Services, Ministry of Health Malaysia, intravesical HA has been widely used for IC/BPS. The

most important thing is that the used must be among patients who are free from any infections and malignancies.

Scarneciu I. et. al. reported that both groups either UTIs Group or IC/BPS Group experienced **mild side effects** related to instillation of intravesical HA which was bladder irritation (six patients in UTIs group and four patients in IC/BPS group.[11]

Hung MJ. et. al. reported **no severe adverse events** related to the treatment in 103 (93.6%) patients who completed the 6-months treatment course.[9]

COST-EFFECTIVENESS (If Any)

Riedl C. et. al. (2013) conducted a cost analysis to assess the mid- and long-term costs (over 1, 5 and 10 years) of various therapies for IC/BPS in Austria. The therapies included intravesical HA, pentosanpolysulfate and amitriptyline which was listed in American Urological Association guidelines. All costs related to the responders or non-responders for each intervention were included in the calculation such as physician visit cost, hospitalisation costs, drug therapy costs and etc. In summary after the first year of therapy, the costs were €2,526 for patients in the hyaluronan group, €4,014 for those in the pentosanpolysulfate group, €2,801 for those in the amitriptyline group and €5,267 for the group receiving only symptomatic therapy. After five years, the costs of €8,407 for hyaluronan, €18,632 for pentosanpolysulfate, €13,891 for amitriptyline and €26,335 for symptomatic therapy were reported. As for 10-years cost calculations, €15,758 for hyaluronan, €36,904 for pentosanpolysulfate, €27,754 for amitriptyline and €52,670 for symptomatic therapy**. Hyaluronan was cost saving against all alternatives**. The incremental costs of hyaluronan versus the alternatives were -€10.225 versus pentosanpolysulfate, -€5.484 versus amitriptyline and -€17.928 versus symptomatic therapy.[12]

CONCLUSION

Based on the review, intravesical HA instillation has been used as one of treatments for IC/BPS. According to the included studies, HA either alone or in combination improved pain Visual Analog Scale (pain-VAS), Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) scores mostly among female patients. However, there were uncertainties that combination of HA and chondroitin sulphate had better outcome compared to single used of intravesical HA. No serious adverse events were reported due to instillation of intravesical HA. In terms of cost, there was one cost analysis conducted in Austria showed that within one year up to 10 years of IC/BPS treatment, the used of intravesical HA instillation was cost saving compared to the other interventions. Infections and malignancy must be excluded before decision to use intravesical HA.

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September 2023