ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2021, Volume 10, Number 3: 970-974
P-ISSN.2089-1180, E-ISSN: 2302-2914

Bali Medical Journal
www.BaliMedicalJournal.org
Published by Bali Medical Journal

The Comparison of intravesical hyaluronic acid and other modalities for the improvement of interstitial cystitis symptoms: a systematic reviews and meta-analysis

ST Cahyo Ariwicaksono*, Harrina Erlianti Rahardjo

Department of Urology, Cipto Mangunkusumo National Hospital, Faculty of Medicine Universitas Indonesia;

*Corresponding author:
ST Cahyo Ariwicaksono;
Department of Urology, Cipto Mangunkusumo National Hospital, Faculty of Medicine Universitas Indonesia;
Stcahyoariwicaksono.urology@gmail.com

Received: 2021-06-13
Accepted: 2021-11-26
Published: 2021-12-21

ABSTRACT

Background: Interstitial cystitis (IC) is a chronic inflammation of the bladder which causes unpleasant sensations. This condition considerably reduces patients' quality of life. Intravesical hyaluronic acid is one of the new interventions for interstitial cystitis management, in which a thorough review and meta-analysis regarding this topic are still limited. This study aimed to compare the efficacy of intravesical hyaluronic acid with other intravesical treatment modalities available to treat interstitial cystitis.

Method: Systematic literature searching with the main keywords of "interstitial cystitis" or "bladder pain syndrome" and "intravesical hyaluronic acid" was conducted. The main outcome of this study was pain assessment using a visual analogue scale (VAS) and Interstitial Cystitis Symptoms Index (ICSI), and problem index (ICPI). Meta-analysis was carried out when comparative studies were available. Eleven studies were obtained to assess intravesical hyaluronic acid's effects, including three in the meta-analysis. The intravesical treatments found as a comparison were heparin and chondroitin sulphate.

Result: There was significant heterogeneity among studies included in all parameters. The pooled analysis showed no significant difference in VAS reduction, improvement of ICSI and ICPI score ($p = 0.11$, $p = 0.35$, and $p = 0.28$, respectively) between hyaluronic acid and other intravesical treatments.

Conclusion: There was no significant difference between hyaluronic acid and other intravesical treatments. However, further research with a larger sample is needed to confirm the best modalities in interstitial cystitis.

Keywords: *hyaluronic acid; interstitial cystitis; ICPI; ICSI; pain; symptoms; VAS.*
Cite This Article: Ariwicaksono, S.T.C., Rahardjo, H.E. 2021. The Comparison of intravesical hyaluronic acid and other modalities for the improvement of interstitial cystitis symptoms: a systematic reviews and meta-analysis. *Bali Medical Journal* 10(3): 970-974. DOI: 10.15562/bmj.v10i3.2510

INTRODUCTION

Interstitial Cystitis (IC) is a chronic inflammation of the bladder that induces unpleasant sensations (pain, discomfort, pressured feeling) accompanied by lower urinary tract symptoms (LUTS) such as frequency, nocturia, and urgency.[1] Another term used for IC is bladder pain syndrome (BPS). Interstitial cystitis could be diagnosed by exclusions, which means that all examinations need to be done to rule out various common organic abnormalities lasting more than six weeks.[1] Although the prevalence of interstitial cystitis in women is only around 2.7% (US population), this condition greatly impairs the patient's quality of life.[2,3]

The etiologies of interstitial cystitis are not yet known but are speculated due to the autoimmune reactions, chronic bacterial infections, certain toxins or food substances exposure, chemical irritants, and psychosomatic aspects.[4,5] Various attempts have been made to treat interstitial cystitis, including pain management, behavioral therapy, dietary adjustments, and pelvic floor relaxation exercises. However, the results are not satisfactory. Meanwhile, standard medical therapy also provides unsatisfactory results.[4,6]

In recent times, various studies have tried using hyaluronic acid (HA) given intravesically to overcome the symptoms of interstitial cystitis. The rationale was the presumed loss of the glycosaminoglycan layer in the bladder mucosa so that there is no protection against the submucosal layer. Furthermore, that condition triggered a response from C-fibers pain in the bladder.[5,7] Although a meta-analysis has been conducted about HA therapy, the comparison was performed between HA and the combination of HA with chondroitin sulphate.[8] This meta-analysis aimed to update the recent meta-analysis and compare the overall effects of intravesical monotherapy of HA in treating interstitial cystitis with other treatments from various conducted studies.

METHODS

This meta-analysis was composed according to the Preferred Reporting

Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guidelines. This study included clinical trials, with or without other therapy in comparison. The validity and risk of bias assessment of the articles was analyzed using Jadad scale for randomized controlled trials (RCTs), modified Jadad scale for clinical trials, where we considered a score of more than three as good quality or modified Newcastle-Ottawa Scale for descriptive studies where we considered a good quality article is a score of seven or more.

The main populations that fulfill the requirements for this study were patients who experienced interstitial cystitis or bladder pain syndrome, both those who did not respond to standard first-line non-invasive therapy thus were treated with intravesical HA, chondroitin sulphate, or pentosan polysulfate sodium (PPS).

The main intervention assessed in this meta-analysis was the administration of intravesical HA. The dose of HA administration was not limited in this study. The minimum duration of evaluation was three months from the first intravesical HA administration. All types of comparison groups between therapies would be included in the meta-analysis, whereas the articles without treatments (including placebo) would be presented as a comparison table. Articles where the subject of interest was not human, or the HA was combined with other therapy were excluded.

Outcome

The outcome of this study was the reduction in the intensity of urinary pain by evaluating the visual analog scale (VAS) after the treatment-free period compared to the initial condition or before treatment. The other variables assessed were changes in urinary symptoms leading to improvement after several months of treatment using the interstitial cystitis symptom index (ICSI) or interstitial cystitis problem index (ICPI) score.

Source of information

A literature search in this study used databases in PubMed, Medline, EMBASE, Scopus, ProQuest, and Cochrane. Then, we searched manually from the available studies. The search strategy included several critical keywords, namely "interstitial cystitis" or "bladder pain syndrome", "intravesical hyaluronic acid", "chondroitin sulphate", "PPS" or "pentosan polysulfate sodium", and "pain" or "symptoms". Two independent researchers conducted the article searching process. The search was focused on the title and abstract of the study that fit the criteria (described above). If studies could not be accessed, the researcher contacted the authors to request the full text. After recording the findings of the search results, a search result was merged between the two researchers. Duplicated results were deleted. If there were any different opinions, the final decision would be determined by the principal investigator. This study selection process followed the guidelines in the PRISMA diagram. Extracted data was processed using Review Manager version 5.3.

Statistical analysis

Initial data analysis used a fixed-effect model. Heterogeneity was assessed by I^2 statistics and would be interpreted as heterogeneous if values >40% were obtained. A random-effect model was used for this meta-analysis.

RESULTS

Literature Searching and Validity Assessment

The last date of literature searching was performed on 9th June 2020, a total of 138 studies that matched the criteria were obtained. After an in-depth review of each article, three studies matched the inclusion and exclusion criteria. The flow of the study search could be seen in Figure

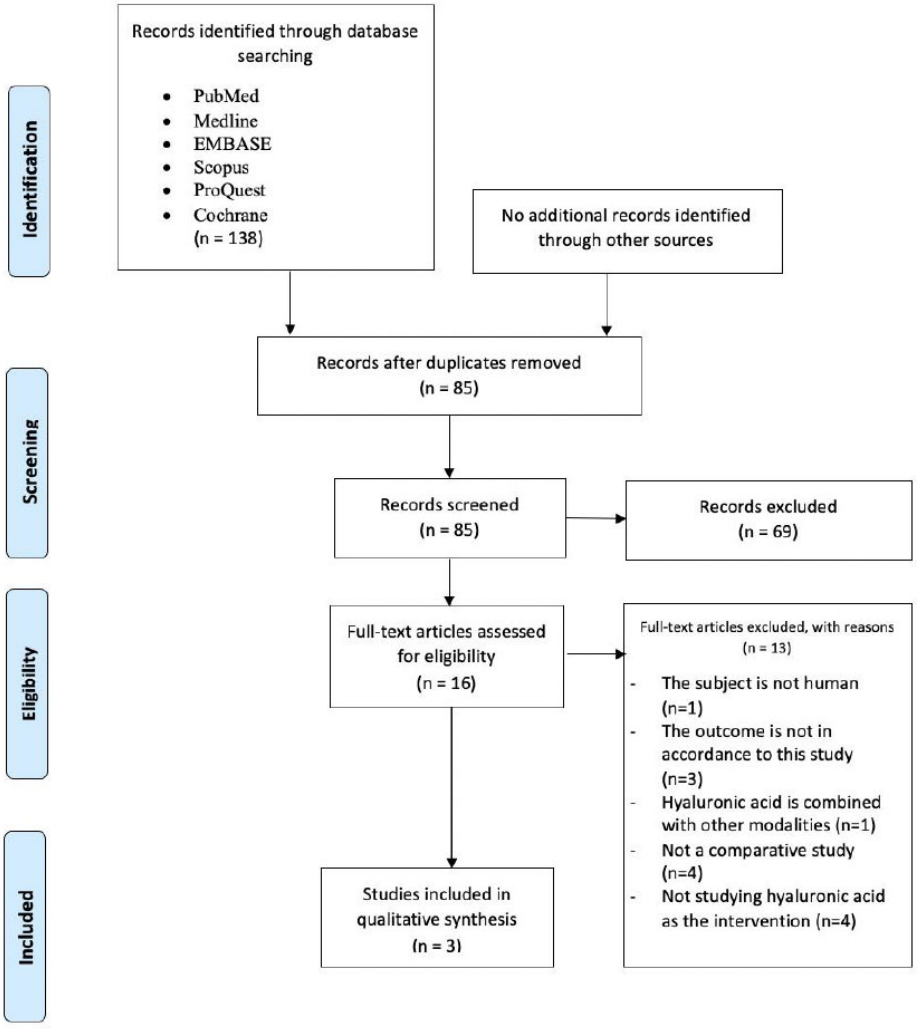

Figure 1. Study flow diagram.

Table 1. **Validity Assessment of Articles Included (source: original).**

Articles	Study Design	Quality Assessment	
		Jadad Scale	Modified Newcastle-Ottawa Scale
Shao Y, et al. (2010)[7]	Clinical Trial	4*	-
Gulpinar O, et al. (2017)[8]	RCT	5	-
Ozkidik M (2019)[9]	RCT	5	-

RCT: randomized controlled trial
*modified Jadad scale

Table 2. **Study Characteristics (source: original).**

Therapy	Articles	Dose	Patients (n)	Outcome (Mean Difference)		
				VAS	ICSI	ICPI
Comparative Study	Shao Y, et al. (2010)[7]	40 mg intravesical HA weekly in the first month then monthly in the following 2 months vs. intravesical heparin 12.500 U with 100 mg lidocaine weekly in the first month then monthly in the following 2 months	20 vs. 16	-2.2 vs. -1	-	-
	Gulpinar O, et al. (2017)[8]	Intravesical 50 mL/120 mg sterile sodium HA vs. 40 mL/80 mg sodium CS weekly in the first month, once in 15 days in second month, and monthly in third and fourth months	21 vs. 21	-3.6 vs. -3.2	-3.1 vs. -6.2	-3.4 vs. -5.9
	Ozkidik M. (2019)[9]	Intravesical 50 mL/120 mg HA vs. 40 mL/80 mg CS once a week for 6 weeks then twice a month for 6 months, then once a month until 24th month	24 vs. 24	-1.2 vs. -1.2	-2.6 vs. -2.5	-2.1 vs. -2.2

CS: Chondroitin sulphate; HA: Hyaluronic acid; ICPI: Interstitial cystitis problem index; ICSI: Interstitial cystitis symptoms index; VAS: Visual analog scale

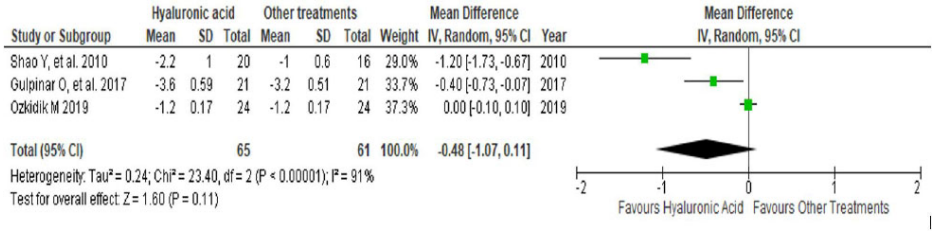

Figure 2. Forrest plot of hyaluronic acid and other treatments visual analog scale.

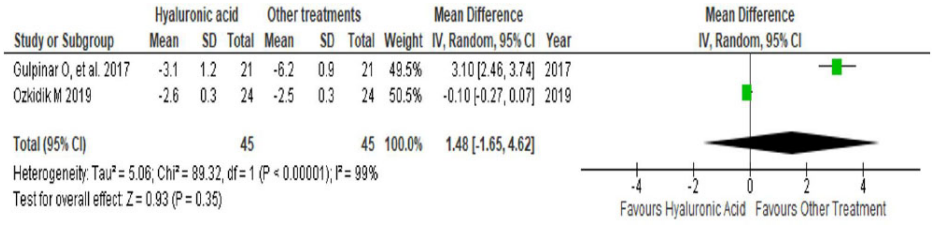

Figure 3. Forrest plot of hyaluronic acid and other treatments interstitial cystitis symptom index.

1. The validity of each article is shown in Table 1.

Outcome comparison

Table 2 shows the characteristics of the studies included. The data extracted provides for the study's intervention and the outcome parameters such as VAS, ICSI and ICPI score before and after treatment.

Heterogeneity

The result of the heterogeneity tests for all outcomes revealed heterogeneity for every parameter (pain, ICSI score and ICPI score). Therefore, the forest plot analysis used the random-effect model.

Improvement in Pain Symptom

The pain symptom was measured using the VAS. The meta-analysis compared HA with the other treatments (heparin in Shao et al. and chondroitin sulphate, in the studies by Gulpinar et al. and Ozkidik et al.).[7-9] There was no significant difference

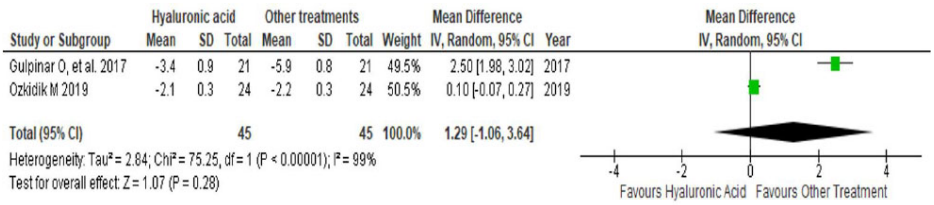

Figure 4. Forrest plot of hyaluronic acid and other treatments interstitial cystitis problem index.

in the reduction scale of VAS between HA and other treatments ($p = 0.11$). The forest plot is presented in Figure 2.

Interstitial Cystitis Symptom Index

The ICSI was compared between HA and another treatment, which was chondroitin sulphate. The study included in this analysis were the ones by Gulpinar et al. and Ozkidik M.[8,9] There was no significant difference in the reduction of ICSI score between the two groups ($p = 0.35$; Figure 3).

Interstitial Cystitis Problem Index

Following the ICSI, the ICPI score did not show statistically significant differences (p=0.28) between HA with other treatments (which in this case: chondroitin sulphate) (Figure 4).

DISCUSSION

This meta-analysis showed that administration of intravesical HA was able to improve symptoms in patients with interstitial cystitis, especially in the VAS, ICSI, and ICPI score. However, the pooled analysis on those parameters showed no statistically significant difference between HA and other intravesical treatments.

Hyaluronan, as one component of glycosaminoglycans, has various mechanisms to protect the urinary tract mucosa. Other components of glycosaminoglycans are chondroitin sulphate and dermatan sulphate.[10] The administration of intravesical HA is thought to successfully inhibit the complex immune reaction of PMN cells, inhibit migration and leukocyte aggression, improve fibroblast regulation, and enhance tissue repair.[11] Since the composition glycosaminoglycan layer is not only consisted of HA, this could be the rationale for administering HA therapy with chondroitin sulphate simultaneously.[12]

Since its first experiment trial in 1996, various studies have reported high success rates using intravesical HA, ranging from 30-85 %. Some previously used therapies before intravesical HA therapy are intravesical heparin, intravesical lidocaine, PPS, and its combination with chondroitin sulphate.[12]

In line with the results of previous studies, administration of HA is considered to improve the glycosaminoglycan layer in the bladder. Repairing this layer will undoubtedly reduce the exposure of the submucosal layer to the irritants contained in the urine.[13] The direct impact felt by the patient is a reduction in the symptom of pain. This improvement was not only seen after administration of HA but also lasted for several months following the intervention. Therefore, administration of intravesical HA should be given periodically. Although there was no universally standardized therapeutic guide, most researchers recommend HA given every week in the first 1-2 months of treatment, then proceed with administration every 2 weeks or 1 month to a period of 4-6 months. There was no significant difference between the duration of the treatment regimen, but further research is needed.[9,14]

The possible reason behind the insignificancy of our study result is the scarce source of the data available regarding the comparison of HA to other single intravesical treatments. Furthermore, the samples recruited were too few in all studies available. This fact led to heterogeneity in our analysis. It was not possible to strongly conclude that there was no difference in VAS, ICSI, and ICPI score between intravesical modalities in treating interstitial cystitis. This is the limitation of our study.

Improvement of symptoms can also be seen from the ICSI and ICPI scores with many modalities used. However, there has been no study to compare head-to-head between the current treatment modalities. The European Association of Urology (EAU) guideline, also adopted in the Indonesian Guideline on Bladder Pain Syndrome, dictates that the recommended intravesical therapy in interstitial cystitis includes PPS, HA chondroitin sulphate, lidocaine with sodium bicarbonate, and heparin before any invasive measure is considered. The study included in this meta-analysis compared intravesical HA either with intravesical heparin or intravesical chondroitin sulphate, in which the recommendation level of both the intravesical HA and intravesical chondroitin sulphate is weak according to EAU guidelines.[15,16] A possible reason for the weak recommendation was the scarcity of studies assessing the efficacy of intravesical HA compared with other intravesical modalities. In addition, The American Urological Association (AUA) also stated heparin and lidocaine intravesical therapy as the second-line therapy (strength of recommendation: low-moderate quality evidence). However, AUA did not mention any recommendation regarding intravesical HA. Instead, AUA recommended another intravesical treatment, i.e., Dimethyl Sulfoxide (DMSO). The studies regarding intravesical therapy for interstitial cystitis are important because PPS, which the EAU and Indonesian Guideline strongly recommend, is not available in some countries, including Indonesia.

Nevertheless, this meta-analysis showed that HA was able to improve the VAS, ICSI, and ICPI scores of the patients with interstitial cystitis. There was no significant difference in clinical parameters (pain, ICSI, ICPI) with other intravesical treatment modalities. While the only intravesical treatment available in Indonesia for interstitial cystitis is HA, this study impacts daily clinical practice since the difference between HA and other intravesical treatments was not significant.

CONCLUSION

Based on the pooled analysis, there is no significant difference in the improvement of pain, ICSI and ICPI between HA and other intravesical modalities. However, the research opportunity regarding this topic is still available. The authors strongly recommend conducting further research to compare various intravesical treatments with a larger sample with a head-to-head comparative study design.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was exempt in this article, since it was a meta-analysis study and not included any human subjects. No ethical approval is needed because data from previous published studies in which primary investigators obtained informed consent will be retrieved and analyzed.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available on demand

COMPETING INTEREST

The authors declare that they have no competing interests

FUNDING

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

ACKNOWLEDGMENT

None.

REFERENCES

1. Nordling J, Fall M, Hanno P. Global concepts of bladder pain syndrome (interstitial cystitis). World J Urol. 2012;30(4):457-64. http://dx.doi.org/10.1007/s00345-011-0785-x.
2. Lazzeri M, Montorsi F. The therapeutic challenge of "chronic cystitis": search well, work together, and gain results. Eur Urol. 2011;60(1):78-80. http://dx.doi.org/10.1016/j.eururo.2011.03.039.
3. Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, et al. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. The Journal of urology. 2011;186(2):540-4. http://dx.doi.org/10.1016/j.juro.2011.03.132.
4. Giannantoni A, Bini V, Dmochowski R, Hanno P, Nickel JC, Proietti S, et al. Contemporary management of the painful bladder: a systematic review. Eur Urol. 2012;61(1):29-53. http://dx.doi.org/10.1016/j.eururo.2011.07.069.
5. Mahmoud MS. Bladder pain syndrome/interstitial cystitis: a reappraisal for the clinician. J Reprod Med. 2011;56(9-10):405-9.
6. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2015 May;193(5):1545-53. http://dx.doi.org/10.1016/j.juro.2011.03.064.
7. Lazzeri M, Hurle R, Casale P, Buffi N, Lughezzani G, Fiorini G, et al. Managing chronic bladder diseases with the administration of exogenous glycosaminoglycans: an update on the evidence. Ther Adv Urol. 2016;8(2):91-9. http://dx.doi.org/10.1177/1756287215621234.
8. Pyo JS, Cho WJ. Systematic review and meta-analysis of intravesical hyaluronic acid and hyaluronic acid/chondroitin sulfate instillation for interstitial cystitis/painful bladder syndrome. Cell Physiol Biochem. 2016;39(4):1618-25. http://dx.doi.org/10.1159/000447863.
9. Shao Y, Shen ZJ, Rui WB, Zhou WL. Intravesical instillation of hyaluronic acid prolonged the effect of bladder hydrodistention in patients with severe interstitial cystitis. Urology. 2010;75(3):547-50. http://dx.doi.org/10.1016/j.urology.2009.09.078.
10. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol. 1991;145(4):732-5. http://dx.doi.org/10.1016/s0022-5347(17)38437-9.
11. Akbay E, Çayan S, Kılınç C, Bozlu M, Tek M, Efesoy O. The short-term efficacy of intravesical instillation of hyaluronic acid treatment for bladder pain syndrome/interstitial cystitis. Turk J Urol. 2018;45(2):129-34. http://dx.doi.org/10.5152/tud.2018.35920.
12. Gulpinar O, Kayis A, Suer E, Gokce MI, Guclu AG, Arikan N. Clinical comparision of intravesical hyaluronic acid and hyaluronic acid-chondroitin sulphate therapy for patients with bladder pain syndrome/interstitital cystitis. Can Urol Assoc J. 2014;8(9-10):E610-4. http://dx.doi.org/10.5489/cuaj.2036.
13. Ali Z and Hotasi S. Association between age, urine pH, and urinary stone incidence in Kardinah Tegal General Hospital, Indonesia. *Intisari Sains Medis* 2020;11(3): 958-962. DOI:10.15562/ism.v11i3.790
14. Riedl CR, Engelhardt PF, Daha KL, Morakis N, Pfluger H. Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(5):717-21. http://dx.doi.org/10.1007/s00192-007-0515-5.
15. Engeler D, Baranowski AP, Berghmans B, Borovicka J, Cottrell AM, Dinis-Oliveira P, et al. EAU Guidelines on Chronic Pelvic Pain. The Netherlands: EAU Guidelines Office; 2020.
16. Rahardjo HE. [Bladder pain syndrome management guidelines]. Jakarta: Ikatan Ahli Urologi Indonesia; 2019. Avaliable from: https://www.iaui.or.id/guidelines/[2019]%20Panduan%20Tatalaksana%20Sindrom%20Nyeri%20Kandung%20Kemih.pdf