551

Nomiya A¹, Niimi A¹, Akiyama Y¹, Tabata M², Enomoto Y², Igawa Y³, Homma Y¹

1. University of Tokyo, Department of Urology, **2.** Mitsui Memorial Hospital, Department of Urology, **3.** University of Tokyo, Department of Continence Medicine

A RANDOMIZED CONTROL TRIAL ON INTRAVESICAL INSTILLATION OF HEPARIN ALONE VERSUS A COCKTAIL OF HEPARIN PLUS ALKALIZED LIDOCAINE FOR REFRACTORY INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Interstitial cystitis (IC) is a chronic bladder disease associated with hypersensitive bladder symptoms such as bladder pain, discomfort, urgency, and urinary frequency. The etiology is largely unknown, but the deficiency in glycosaminoglycan layer is regarded as a possible cause. On this assumption intravesical therapy with heparin, which is expected to restore the glycosaminoglycan layer deficiency, has been used to relieve the symptoms [1]. To date, however, there is no study comparing the efficacy of instillation therapy of heparin versus heparin plus lidocaine. In this study, we compared therapeutic outcomes and safety of instillation of these two solutions in a randomized double-blind trial.

Study design, materials and methods

The diagnosis of IC was based on the clinical guidelines for IC and hypersensitive bladder [2]. Patients with refractory IC were enrolled to the study after submitting written informed consent. Refractory IC was defined as persisting symptom of O'Leary and Sant's Interstitial Cystitis symptom index / problem index (OSSI/OSPI) score more than six points, respectively, and numerical rating scale for pain (NRS) more than three out of ten points despite of multiple conventional therapies such as life-style modification, hydrodistension, and oral medication. The patients were randomized to 6-week weekly intravesical instillation of heparin (Group A) or heparin plus lidocaine (Group B). The solution of heparin contained 20,000unit heparin (Yoshindo, Toyama, Japan) in 30 ml physiological saline. The cocktail of heparin plus lidocaine consisted of 20,000 unit heparin and 5ml 4%lidocaine in phosphate-buffered saline adjusted at pH 7.5. At each instillation, patients were instructed to refrain from voiding for at least 30 minutes. The solution was prepared every time immediately before instillation in a sterilized condition. Symptoms were assessed via OSSI/OSPI, NRS and frequency volume chart prior to therapy and at four weeks after the last instillation. Four weeks after the therapeutic period, all the enrolled patients selected one of seven grades of global response assessment (GRA; markedly improved, improved, slightly improved, no change, slightly worsened, worsened, and markedly worsened), and patients graded better than "slightly improved" defined as responder. Adverse events were monitored by interviewing patients every time before instillation. The primary endpoint was GRA at four weeks after the last instillation. Other outcome measures were compared between the baseline and end values by signed Wilcoxon's rank sum test for paired samples and changes in clinical parameters were compared with t-test. P<0.05 was considered significant. SPSS Version18.0 (SPSS, Chicago, IL., USA) was used for statisitics.

Results

Ten patients each were enrolled for both groups (Table 1). There was no significant difference in baseline values. All the patients of Group A completed six instillations, while three patients in Group B withdrew because of symptom worsening (P=0.21). The respondse rate according to GRA was 70% in Group A and 40% in Group B, respectively (p=0.178, Table 2). Excluding three withdrawers in Group B, the changes of OSPI, NRS, and voiding frequencies showed virtually no change by instillation (Table 3), and no significant difference between the groups (Table 4). The OSSI showed significant decrease in Group B alone, and the decrease was significaltly larger in Group B than Group A (Tables 3 and 4). During the therapy, there were no adverse events except three cases of symptom worsening in Group B.

Interpretation of results

Weekly intravesical instillation with heparin alone or heparin plus lidocaine was comparably effective for refractory IC. Heparin plus lidocaine may cause symptom worsening early but improve symptoms, if completed for 6 weeks. Lack of placebo arm, a small sample size, and unknown long-term outcomes are limitation.

Concluding message

Instillation of heparin or heparin plus lidocaine is a reasonable therapeutic option for refractory IC, although heparin plus lidocaine may be associated with early symptom worsening.

Table 1. Patients' background

	Group A Group B haperin alone heparin plus lidoca		P-Value aine	
Patients (female/ male)	10 (10/0)	10 (9/1)	0.17	
Age (Years)	72.5±8.8*	66.9±17.0	0.37	
Duration of IC (Years)	8.1± 3.7	8.8±5.0	0.73	
Number of prior hydrodistension	2.2±1.4	2.3± 1.3	0.89	

^{*}mean±SD

Table 2. Global response assessment (GRA)

1 0010 2	. Ciobai ioopoi	00 00000011101	11 (0.0)					
GRA	Markedly	Worsened	Slightly	No	Slightly	Improved	Markedly	Response
	worsened		worsened	change	Improved		Improved	rate*

	_	
	_	

Group A	0	0	1	2	5	2	0	70%
Group B	3**	1	0	2	2	1	1	40%

Slightly improved or better regarded as responder

^{**:} Withdrawers were graded as "markedly worsened".

Table 3.	Change of	symptom	measures
----------	-----------	---------	----------

Variables	Group A		(n=10)	Group B		(n=7)
	Baseline	Post- Therapy	P-Value (vs. baseline)	Baseline	Post- therapy	P-Value (vs. baseline)
OSSI	12.6±4.2*	12.4±4.7	0.81	14.9±3.5	11.4±5.0	0.04
OSPI	11.0±3.6	10.2±4.3	0.28	12.0±2.4	10.3±4.5	0.33
NRS	5.4±2.7	4.8±2.3	0.37	6.9±3.2	5.6±3.10	0.41
Daily urinary frequency	15.0±4.1	15.4±4.6	0.59	17.0±5.8	15.7±5.5	0.19
Nocturnal frequency	2.9±1.3	4.0±2.7	0.11	4.0±1.5	4.3±2.4	0.67

^{*}mean±SD

Table 4. Change in symptomatic variables after the therapy.

	Group A (n=10)	Group B (n=7)	P value (A vs. B)
⊿ossi	-0.2±2.6*	-3.4±3.4	0.04
⊿OSPI	-0.8±2.2	-1.7±4.3	0.57
⊿NRS	-0.6±2.0	-1.3±3.8	0.64
∠Daily urinary frequency	0.8±2.3	-1.1±2.3	0.16
∠Nocturnal urinary frequency	1.3±1.9	0.3±1.7	0.32

^{*}mean±SD, ∠=(post-therapeutic value) – (base line value)

References

- 1. Nomiya A., et al. On- and post-treatment symptom relief by repeated instillations of heparin and alkalized lidocaine in interstitial cystitis. Int J Urol. 2013. 29; 1118-22
- 2. Homma Y., et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder updated in 2015. Int J Urol. 2016. 23; 542-9

Disclosures

Funding: lida Grant of Mitsui Memorial Hospital Clinical Trial: Yes Registration Number: University hospital Medical Information Network center, UMIN000026714 RCT: Yes Subjects: HUMAN Ethics Committee: Mitsui Memorial Hospital Ethics Committee Helsinki: Yes Informed Consent: Yes