

SUSTAINED RELIEF OF INTERSTITIAL CYSTITIS SYMPTOMS BY COMBINED INTRAVESICAL INSTILLATION OF HEPARIN AND LIDOCAINE BICARBONATE

Hypothesis / aims of study

Interstitial cystitis (IC) is characterized by urinary frequency and bladder hypersensitivity including bladder pain or pressure with no identifiable causes. Few treatments have a significant impact on symptoms over time, and as a result, patients are subject to many different treatment modalities. Recently, several reports have focused on the effects of combined instillation of heparin and alkalized lidocaine on IC symptoms. However, these studies tested a single or at the most 7 times of instillation with short term follow up of up to 3 weeks [1,2]. We examined the efficacy of multiple intravesical instillations of heparin and alkalized lidocaine with observation extended to 6 months after the last therapy.

Study design, materials and methods

Patients diagnosed as IC at our institution were enrolled in the study. The diagnosis was based on the guideline for IC and hypersensitive bladder syndrome [3], which comprises 1) lower urinary tract symptoms such as bladder hypersensitivity, urinary frequency, bladder discomfort and bladder pain; 2) bladder pathology such as Hunner's ulcer and mucosal bleeding after over-distension; 3) exclusions of confusable diseases such as infection, malignancy and calculi of the urinary tract. The patients were also compatible with National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) consensus inclusion and exclusion criteria for clinical trials. Symptom severity was assessed by O'Leary and Sant's Interstitial Cystitis symptom index / problem index (OSSI/OSPI). Those with OSSI/OSPI more than 6 points despite of various therapies (ex. hydrodistension, medical treatment, etc.) received intravesical instillation of 20,000U heparin, 5 ml of 4% lidocaine, and 25 ml of 7% sodium bicarbonate every 1 or 2 weeks for consecutive 12 times. The solution was prepared every time immediately before instillation in a sterilized condition. The patients were instructed to retain the solution for at least 30 minutes.

All patients completed OSSI/OSPI, visual analogue scale for pain (VAS) and a frequency volume chart before the therapy at the baseline. Therapeutic effect was evaluated after the first, fourth and twelfth instillation and 1, 2, 6 months after the last instillation. In addition, the overall improvement was graded at 1, 2, 6 months after the last instillation by Global Response Assessment by patients' subjective impressions (GRA) as one of either of markedly improved, moderately improved, slightly improved, unchanged, slightly worsened, moderately worsened, and markedly worsened [score: 0 to 6]. The patients were assigned to clinical progression by any of 1) invasive therapy such as transurethral resection and intravesical instillation, 2) increased analgesic ladder or 3) GRA of slightly worsened or worse. Adverse events of the therapy were monitored by interviewing patients every time before the instillation. Paired t-test was used for analysing treatment-related change. P value less than 0.05 was considered to be significant.

Results

From June 2005 to January 2010, 28 patients (25 women and 3 men) with the average age of 64.4 years (range 35 to 79) were treated with the instillation therapy. All patients had received hydrodistension at least once prior to instillation with 1.57 times on average. They had taken tricyclic antidepressant, NSAIDs or anti-allergic agents. All the patients completed the treatment protocol (Table 1) and 11 patients finished 6 month follow up (Table 2). During the therapy all the measures showed continuous improvement, and all the patients reported improvement compared with the pre-therapy conditions at the last instillation. Following the last therapy, clinical measures showed slight deterioration yet significantly better a level compared with pre-therapeutic conditions. At 6 months, 5 of 11 patients (45%) needed no further therapy for IC (Figure). No significant adverse events requiring hospitalization or additional therapy were encountered. Four patients developed gross hematuria, which subsided spontaneously.

Interpretation of results

Twelve times of combined instillation of heparin and alkalized lidocaine gradually reduced IC-related symptoms. Unlike the former studies with short-term instillation, we demonstrated sustained effects by repeated instillations up to 6 months in a half of patients, although the effect progressively deteriorated with time.

Concluding message

Multiple sessions of combined instillation of heparin and alkalized lidocaine lead to IC symptom relief in most cases and sustained relief in about a half of patients. Further clinical trials are required to ensure the efficacy and safety of the therapy.

Table1. Symptoms during consecutive instillations of heparin and alkalized lidocaine. n=28

	OSSI	OSPI	VAS	Average voided volume(ml)	Daytime urinary frequency	Nocturnal urinary frequency
baseline	13.5±4.2	11.1±4.5	5.9±2.7	89.2±31.9	19.6±8.8	4.7±2.2
after first instillation	12.3±3.5	9.8±4.1	5.2±2.5	95.7±37.1	18.5±7.6	4.4±3.1
after fourth instillation	10.5±3.8	7.7±4.8	3.5±2.5*	138.6±46.9*	14.3±3.5	2.5±1.1*
after twelfth instillation	7.0±3.9*	5.6±3.2*	3.3±1.9*	127.6±44.5*	14.5±3.3*	2.4±1.2*

* p<0.05 versus baseline

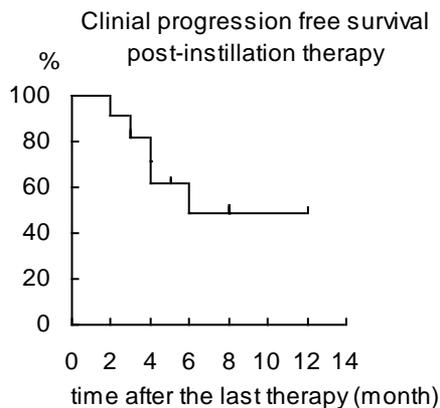
Table 2. Symptoms during post-therapy follow up

n=11

	OSSI	OSPI	VAS	Average voided volume(ml)	Daytime urinary frequency	Nocturnal urinary frequency
baseline	13.0±4.8	9.4±4.8	5.7±2.3	90.4±39.0	19.7±6.8	5.0±3.0
after twelfth instillation	7.4±3.5*	5.7±3.4*	3.2±1.7*	129.1±41.6*	13.5±2.0*	2.4±1.1*
one month post-therapy	7.3±2.6*	5.2±3.7*	2.7±1.3*	117.5±33.4*	13.6±3.0*	2.1±1.3*
two months post-therapy	8.5±3.4*	6.0±3.8*	3.3±1.9	115.0±34.6	14.2±2.7*	2.3±1.1*
six months post-therapy	9.9±4.0	7.7±4.9	4.1±2.6	120.8±54.9	15.0±4.5	2.8±1.2

*p<0.05 versus baseline

Figure



References

1. Urology 65:45-8,2005
2. Urology 71:67-70, 2008
3. Int J Urol. 16: 4-16, 2009

Specify source of funding or grant	None
Is this a clinical trial?	No
What were the subjects in the study?	HUMAN
Was this study approved by an ethics committee?	Yes
Specify Name of Ethics Committee	Ethics Committee of the Graduate School of Medicine, the University of Tokyo
Was the Declaration of Helsinki followed?	Yes
Was informed consent obtained from the patients?	Yes