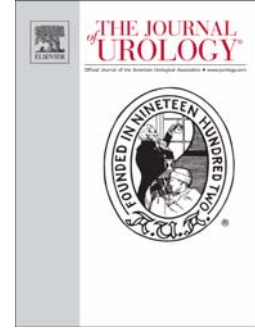


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# **Inhibition of Adhesion and Fibrosis Improves the Outcome of Epididymectomy as a Treatment for**

## **Chronic Epididymitis: a multicenter, randomized, controlled, single blind study**

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## Abstract

**Purpose:** To measure the effectiveness of inhibition of adhesion and fibrosis on patient outcomes following epididymectomy as a treatment for chronic epididymitis.

**Patients and Methods:** An initial cohort of 152 patients was treated conservatively for chronic epididymitis.

Forty-three patients did not respond to conservative treatment and, following informed consent, were enrolled in the clinical trial. The patients were randomized into two groups: 22 patients underwent epididymectomy with concurrent administration of inhibitors of adhesion and fibrosis, hyaluronic acid and carboxymethylcellulose (HA/CMC) (group A), and 21 patients underwent epididymectomy only (group B). Visual analogue pain scores and patient satisfaction scores were obtained at four weeks, 12 weeks, and 24 weeks after operation.

**Results:** There were no post-operative complications such as wound infection or hematoma in either group. one patient was lost to follow-up from group A and 2 patients were lost from group B. At 24 weeks after operation: 12 patients (57.1%) from group A and three patients (15.8%) from group B were pain free; six patients (28.6%) from group A and six patients (31.6%) from group B exhibited limited pain relief; two patients (9.5%) from Group A and seven patients (36.8%) from group B exhibited no pain relief; and one patient (4.8%) from group A and three patients (15.8%) from group B exhibited recurrence of pain after initial resolution at earlier follow-up intervals ( $p=0.028$ ).

**Conclusions:** Inhibition of adhesion and fibrosis following epididymectomy as a treatment for chronic epididymitis improves pain relief and patient satisfaction.

## Introduction

Chronic epididymitis is epididymitis that ensues for more than six weeks and is characterized by inflammation accompanied by pain, with variable epididymal pain, with or without induration, and testicular pain as the main presentations.<sup>1</sup> A prospective community based study found that approximately 1% of male subjects were diagnosed with chronic epididymitis.<sup>2</sup> The mainstay of treatment for chronic epididymitis is the administration of antibiotics together with anti-inflammatory agents and analgesics, scrotal support and nerve block as empirical treatments.<sup>2</sup> Epididymectomy may be considered following failure to respond to conservative management; however, it has therapeutic effectiveness for pain relief in only approximately 50% of patients.<sup>3,4</sup> The cause for such limited effectiveness has not been clearly identified; however, occurrences of chronic scrotal pain have also been noted following vasectomy. It has been reported that this post-vasectomy pain syndrome (PVPS) could be caused by interstitial fibrosis and extravasation of spermatozoa, induced by obstruction of the epididymal duct, and inflammation producing perineural fibrosis and adhesion.<sup>5</sup> Similarly, continuous scrotal pain following epididymectomy for chronic epididymitis may be due to perineural and interstitial fibrosis. Previous studies investigating the role of adhesion and fibrosis in causing continuous pain after epididymectomy as a treatment for chronic epididymitis have not been identified.

Recently, synthetic physical barriers, such as hyaluronic acid (HA)/carboxymethylcellulose (CMC), have been developed to supplement the damaged natural barrier. HA/CMC is a liquid-type synthetic physical sol-gel barrier with a viscosity ranging from 2500 to 3500 cP.<sup>6</sup>

To this end, the present study evaluated the effectiveness of inhibiting adhesion and fibrosis, achieved via application of HA/CMC to the operative site, on pain and satisfaction scores following epididymectomy as a treatment for chronic epididymitis.

### ***Subjects and study design***

An initial cohort of 152 patients was diagnosed with chronic epididymitis. Patients visiting the outpatient clinics and complaining of unilateral epididymal pain persisting for more than 6 weeks were given a physical examination. A urine analysis was also performed and a urethral swab was taken. Scrotal ultrasonography was performed for patients with localized epididymal pain and tenderness but no urinary tract infection. Patients with a clinical and radiological diagnosis of unilateral chronic epididymitis were subsequently treated with a 4-week course of antibiotics (levofloxacin 500 mg once-daily) and non-steroidal anti-inflammatory drugs (ibuprofen 200 mg three times a day).<sup>2, 7</sup> Patients showing no improvement in pain stopped taking the medication and received a spermatic cord block (10 mL of 1% lidocaine without epinephrine).<sup>8</sup> Forty-three patients who failed to show resolution of their pain symptoms despite these conservative measures were enrolled in the surgical study following fully informed consent and satisfaction with the inclusion and exclusion criteria. Inclusion criteria were: clinical symptoms of continuous epididymal pain for over six weeks and diagnosis of chronic epididymitis by scrotal ultrasonography; no pain relief following six weeks of conservative treatment; and willingness to participate in the study. The exclusion criteria were: urinary tract infection, bilateral epididymal pain, prostatitis, chronic pelvic pain syndrome, previous vasectomy, previous scrotal surgery, and the presence of concurrent diseases such as an epididymal cyst or a granuloma, both of which can cause scrotal pain.

Six hospitals participated in this prospective, randomized, single blind controlled study. Full approval was obtained from the relevant institutional review boards. Patients were randomly divided into two groups by simple block method: the experimental group (group A, 22 subjects with post-epididymectomy application of HA/CMC); or the control group (group B, 21 subjects without post-epididymectomy application of HA/CMC).

The primary endpoint was the pain score (VAS Pain) at 24 weeks after operation. The secondary endpoint was patient satisfaction (Likert scale) at 24 weeks after operation. Information regarding the duration of illness and the medical history were collected at enrolment (V0). Pain and satisfaction scores were recorded four weeks (V1), 12 weeks (V2) and 24 weeks (V3) after operation.

### ***Surgical technique***

The surgery was performed under general or spinal anesthesia with the testis and tunica vaginalis exposed by vertical incision. A sharp dissection was conducted starting from the apex after epididymal head traction using the traction suture followed by isolated ligature of the efferent tubule. The epididymal tail was separated from the body with a stay suture and the specimen was clamped, divided and ligatured with Ellis forceps. After careful bleeding control, the testes were recovered to scrotum. For patients in the experimental group, 3 g of HA/CMC was applied (Guardix-sol<sup>®</sup>, Hanmi Medicare, Seoul, Korea) to the operative site including the spermatic cord. The dartos layer was sutured to the skin following confirmation that there was no bleeding. No patient required a drain.

### ***Hyaluronic acid and carboxymethylcellulose***

HA is an anionic polysaccharide and is an active ingredient of extracellular matrix and a high level polymer. HA exhibits hydropromism, non-immune properties, and viscoelasticity. HA coats and lubricates the mucosa surface, inhibiting fibrosis and adhesion post-operation.<sup>9</sup> CMC is also an anionic polysaccharide and an inducer of more hydrophilically modified celluloses from the carboxymethylated glucosidic hydroxyl base. These properties have

led to CMC being used widely as an excipient, thickening agent, lubricant, and stabilizer of pharmaceutical, cosmetic and food products.<sup>10</sup>

#### ***Assessment of efficacy and safety***

At four, 12 and 24 weeks after operation, pain scores were recorded using the VAS (0 - no pain, to 10 - extreme pain) as well as patient satisfaction scores using a Likert scale (0 - extremely satisfied, to 3 - extremely dissatisfied). The presence of adverse effects was also noted through physical examination and history taking.

#### ***Statistical analysis***

An intent to treat analysis was conducted and each patient's baseline pain scale and degree of satisfaction were recorded. The Student's t-test was employed to compare differences between the experimental and control groups. SPSS software v.18.0 was used for the statistical analysis and a p value < 0.05 was considered to be statistically significant.



## Results

From 152 patients in the initial cohort, 73 patients were satisfied with the pain relief achieved through conservative management. From the remaining 79 patients, eight patients had pain relief after nerve block and did not undergo epididymectomy and 21 patients were lost to follow-up. From the remaining 50 patients, 43 patients met the inclusion and exclusion criteria and consented to the trial (Figure 1).

No significant inter-group differences were observed for the baseline characteristics including age and the degree of pain (Table 1). At 24 weeks after surgery, 12 patients (57.1%) from group A and three patients (15.8%) from group B were pain free; six patients (28.6%) from group A and six patients (31.6%) from group B experienced limited pain relief; two patients (9.5%) from group A and seven patients (36.8%) from group B experienced no pain relief; and one patient (4.8%) from group A and three patients (15.8%) from group B experienced recurrence of pain after initial resolution ( $p=0.028$ ) (Table 2).

From four patients exhibiting recurrence of pain after initial resolution: one patient from group A had mitigation of pain at four weeks after operation but noted a return to pre-operative pain levels at eight weeks after operation; one patient from group B had mitigation of pain at four weeks after operation but noted a return to pre-operative pain levels at 12 weeks after operation; and two patients from group B showed improvement in pain at 4 weeks after operation but experienced recurrence of pain at eight weeks after operation.

Seventeen patients (80.9%) from group A and nine patients (47.4%) from group B were satisfied with the surgery at 24 weeks after operation. Significant differences in pain and satisfaction were observed at four, twelve and 24 weeks after operation between the two groups (Table 2).

There were no peri- and post-operative complications such as wound infection, wound de-adhesion, hematoma, cord injury, or testicular injury. HA/CMC caused no adverse effects. All patients were diagnosed with chronic epididymitis upon histopathological examination of surgical samples.

## Discussion

This study has demonstrated that inhibition of adhesion and fibrosis following epididymectomy was effective in improving patient outcomes for patients with chronic epididymitis. Furthermore, no complications were associated with the use of HA/CMC as inhibiting agents. There are few studies on treatment for chronic epididymitis and no study could be identified addressing the causes of the limited efficacy of epididymectomy as a surgical treatment option following failure of conservative management. Patient satisfaction with epididymectomy has been poor, and the lack of understanding related to the cause of the limited efficacy has made treatment protocols difficult to identify (Table 3).

Studies have addressed the cause and treatment of PVPS, which presents similar clinical symptoms to chronic epididymitis.<sup>11, 12</sup> There are several hypotheses for the cause of PVPS. The leading theory argues that pain is caused by interstitial and perineural fibrosis induced by obstruction of the epididymal duct, as well as adhesion caused by extravasation and inflammation of spermatozoa. Fibrosis causes distortion and angulation of nerves by encasing the nerves in surrounding tissues and also causes lymphatic infiltration.<sup>11</sup> West et al. have shown that the degree of fibrosis occurring after post-vasectomy inflammatory response affected the duration of continuous pain.<sup>12</sup>

Patients with chronic epididymitis that do not show improvement following epididymectomy have also shown fibrosis around the spermatic cord and nerve with a post-operative inflammatory response, as well as extravasations of spermatozoa. We proposed that residual scrotal pain following epididymectomy may be caused by the same mechanism that causes PVPS. We further hypothesized that the inhibition of fibrosis and adhesion

following epididymectomy would improve pain and satisfaction scores.

We used HA/CMC for inhibition of fibrosis and adhesion in this study. Several natural barriers such as peritoneum, omentum and amnion act to prevent adhesion between tissues.<sup>13</sup> Synthetic physical barriers such as HA/CMC have been developed to supplement damage to natural barriers. HA/CMC are also used for prevention of post-operative adhesion and fibrosis. Hong et al. observed small fibrotic changes made by the post-operative application of HA/CMC using a histological assay in an animal study.<sup>6</sup> Ahn et al. observed superior improvement in hearing status without complications following the application of HA/CMC in tympanomastoid surgery. This was proposed to be due to the anti-adhesive and anti-inflammatory effects of HA/CMC.<sup>14</sup> Further studies have demonstrated post-operative fibrosis and adhesion disturbance following application of HA/CMC.<sup>15-17</sup> The results from the present study validate the hypothesis that fibrosis and adhesion following epididymectomy may cause continual scrotal pain. Given that some patients in the experimental group failed to show improvement in pain despite the use of HA/CMC, other causes of continual scrotal pain should also be considered.

A limitation of this study is the relatively small sample size. This was due to the low incidence of chronic epididymitis, with a further reduction in numbers due to successful conservative management or failure to meet the inclusion and exclusion criteria. We did not culture the ejaculate. It is noteworthy that despite the small sample size, statistical significance was achieved, highlighting the positive role inhibition of adhesion and fibrosis may play in reducing pain following epididymectomy.

### Conclusion

The inhibition of adhesion and fibrosis following epididymectomy as a treatment for chronic epididymitis was effective in reducing post-operative pain and increasing satisfaction in patients that had failed to respond to conservative management.

### Acknowledgements

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**Figure legend**

Figure 1. Study flow diagram

ACCEPTED MANUSCRIPT

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Table 1. Baseline characteristics

	HA/CMC instillation, 22	Control group, 21	p-value
Age (year)	57.59±9.45	58.48±11.63	0.761
BMI (kg/m <sup>2</sup> )	26.27±2.96	26.04±2.58	0.836
Pain duration (months)	13.00±6.17	12.81±4.56	0.680
Pain score	7.50±1.41	7.52±1.50	0.941
Mann-Whitney test			

Table 2. Surgical outcomes

	HA/CMC instillation, 21	Control group, 19	p-value
Outcome (%)			0.028 <sup>†</sup>
Pain cured	12 (57.14)	3 (15.79)	
Improved	6 (28.57)	6 (31.58)	
No change	2 (9.52)	7 (36.84)	
Recurrence	1 (4.76)	3 (15.79)	
pain scale			
V0	7.43±1.40	7.53±1.35	0.792
V1	1.90±2.90	4.05±3.29	0.012
V2	2.10±3.22	4.58±3.31	0.012
V3	2.10±3.24	4.74±3.48	0.023
Satisfaction			
V1	0.95±1.02	1.79±1.27	0.040
V2	0.71±1.06	1.79±1.27	0.008
V3	0.67±1.11	1.74±1.33	0.008

<sup>†</sup>Chi-square test, Mann-Whitney test

Table 3. Comparison of epididymectomy outcome for chronic epididymitis from previous study

		Subjects, n	Pain cured, n (%)	Improved, n (%)	No change or recurrence, n (%)	Satisfaction, n (%)
Calleary et al. <sup>18</sup>		15	3 (20.00)	5 (33.33)	7 (46.67)	8 (53.33)
Padmore et al. <sup>3</sup>		21	5 (23.81)	9 (42.86)	7 (33.33)	Unkown
Sweeney et al. <sup>19</sup>		10	0	7 (70.00)	3 (30.00)	7 (70.00)
Chen et al. <sup>20</sup>		7	6 (85.71)	0	1 (14.29)	6 (85.71)
Lee et al. <sup>21</sup>		21	3 (14.29)	6 (28.57)	12 (57.14)	9 (42.86)
Present study	HA/CMC apply group	21	12 (57.14)	6 (28.57)	3 (14.29)	17 (80.95)
	Control group	19	3 (15.79)	6 (31.58)	10 (52.63)	9 (47.37)
Total		114	32 (28.07)	39 (34.21)	43 (37.72)	56 (60.22)

