Asian Journal of Surgery (2019) 42, 394–400

Available online at www.sciencedirect.com

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journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Effectiveness of hyaluronic acid/carboxymethylcellulose in preventing adhesive bowel obstruction after laparoscopic radical cystectomy

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Received 9 April 2018; received in revised form 22 June 2018; accepted 16 August 2018
Available online 26 September 2018

KEYWORDS
Urinary bladder Neoplasms;
Laparoscopy;
Cystectomy;
Adhesive;
Intestinal obstruction

Summary *Background/Objective:* Adhesive bowel obstruction is one of the most frequent complications after radical cystectomy, prolonging hospital stay and fasting period and increasing medical expenses. This study evaluated the effectiveness of hyaluronic acid/carboxymethylcellulose (HA/CMC) in preventing adhesive bowel obstruction after laparoscopic radical cystectomy.
Methods: Randomized, controlled, single-blinded study was performed. Of 76 patients who underwent laparoscopic radical cystectomy for bladder cancer, 38 received HA/CMC instillation and 38 did not. The primary endpoint was the rate of postoperative adhesive bowel obstruction. The secondary endpoint was the rate of other postoperative outcomes.
Results: None of the patients who received HA/CMC instillation experienced postoperative adhesive bowel obstructions, compared with six (15.79%) patients in the control group ($p = 0.025$). Of the six patients with ileus, two underwent adhesiolysis. There were no significant differences between the two groups in other postoperative outcomes.
Conclusion: HA/CMC instillation during laparoscopic radical cystectomy may reduce the incidence of postoperative adhesive bowel obstruction without adverse effects.

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https://doi.org/10.1016/j.asjsur.2018.08.007

1. Introduction

The prevalence of bladder cancer is relatively high, with 20% of patients diagnosed with late stage tumors and requiring radical cystectomy.[1] Although improvements in perioperative care and surgical techniques have reduced surgery-related complications and morbidity rates,[2] 25—64% of patients experience complications after radial cystectomy.[3,4] Patients undergoing cystectomy are generally older, have more comorbidities, and may be more prone to postoperative complications than patients not undergoing cystectomy.[5] Complications lengthen hospitalization periods and increase medical costs.

The most common postoperative complication after radical cystectomy is bowel obstruction. This condition causes an imbalance of electrolytes and nutritional deficiencies owing to prolonged fasting.[6,7] Postoperative bowel obstruction usually occurs within 30 days after surgery, in 9.5% of patients who have undergone abdominal surgery[8] and in 10—25% of patients who have undergone intestinal surgery.[9,10] Adhesive bowel obstruction caused by postoperative adhesions is an especially serious complication that increases patient morbidity.[11,12]

Methods used to prevent or treat postoperative bowel obstruction after radical cystectomy include bowel preparation with prophylactic antibiotics, control of nasogastric tube use, and minimally invasive surgery.[13] Most studies, however, have focused on paralytic ileus occurring during gastrointestinal recovery.[5]

This study analyzed the effects of an antiadhesive agent, hyaluronic acid/carboxymethylcellulose (HA/CMC),[14] topically applied to the abdominal cavity after radical cystectomy, on the incidence of postoperative adhesive bowel obstruction.

2. Materials and methods

2.1. Subjects and study design

This patient single-blinded, randomized controlled trial recruited 76 patients who underwent laparoscopic radical cystectomy for advanced bladder cancer from May 2007 to July 2011. Patients were included if (1) they were clinically diagnosed with stage $\geq$ T2 severe bladder cancer, (2) had high-risk or recurrent non-muscle invasive bladder cancer, (3) had T1G3 bladder cancer, (4) had extensive non-muscular invasive bladder cancer but could not be treated by transurethral resection, (5) were able to perform normal daily activities, and (6) were willing and able to participate in this study. Patients were excluded if they had (1) distant metastases, (2) contraindications to radical cystectomy due to cardiovascular dysfunction, (3) severe chronic obstructive pulmonary disease, (4) hemorrhagic disease, or (5) contraindications to laparoscopic surgery. All patients provided written informed consent, and the study protocol was approved by our Institutional Review Board.

Before surgery, all patients underwent a physical examination and medical history taking, along with a complete blood count, blood biochemistry, urine cytology, and abdominal computed tomography.

2.2. Randomization

Of the recruited patients, 76 met our inclusion criteria and were randomized into two groups using a random number generator. The experimental group of 38 patients received HA/CMC (Guardix-sol®, Hanmi Medicare, Seoul, Korea) instillation, whereas the control group of 38 patients did not.

2.3. Surgical technique

All surgeries were performed by a single surgeon. All patients underwent laparoscopic radical cystectomy using a five port fan-shaped transperitoneal approach. The pelvic lymph nodes were initially dissected bilaterally, followed by lymph node dissection cranially to the bifurcation of the common iliac artery, laterally to the genitofemoral nerve, caudally to the circumflex iliac vein, and posteriorly to the hypogastric vessels. Lymph node dissection was extended to the area near the aortic bifurcation in patients with stage $\geq$ T3 tumors or if radiological examination revealed a positive lymph node. In females, uteruses and ovaries are also removed during the surgery. Also, female patients underwent anterior pelvectomies unless orthotopic substitution was required. Patients later underwent ureter implantation after preparing an M-shaped neobladder or ileal conduit. After surgery, 5 g HA/CMC was evenly applied on whole the lower abdominal cavity including the anastomotic site using the spray instrument (Fig. 1).

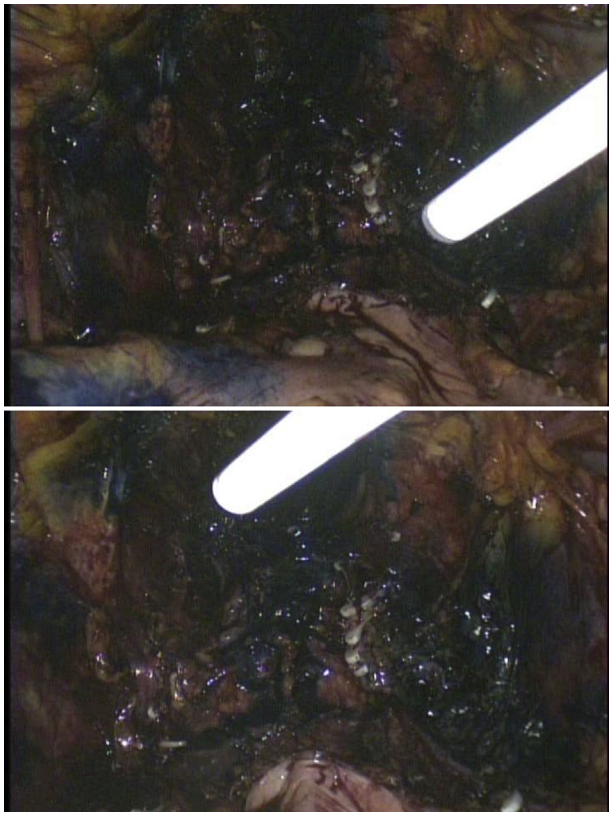

Figure 1 Instillation of HA/CMC around the ileal conduit.

2.4. Pathological analysis and adjuvant therapy

All tissue samples were evaluated according to the 2002 Union Internationale Contre le Cancer TNM classification. Patients with tumor stage $\geq$ T3 or positive lymph nodes received adjuvant chemotherapy with gemcitabine and cisplatin.

2.5. Surgical outcomes

Perioperative outcomes compared in the two groups included operation time, estimated blood loss, duration of fasting after surgery, time from surgery to ambulation, duration of drain placement, postoperative length of stay, and complication rate. Complications were classified according to the Clavien system. To diagnose an adhesive bowel obstruction, if the patient had symptoms of bowel distension, abdominal discomfort, or dyspepsia, imaging studies, including simple abdominal radiology on supine and erect positions were performed. In any cases of suspicious obstructive ileus on imaging studies, abdominal computed tomography (CT) scans were performed. Final diagnoses were made on clinical and imaging evidence of adhesive bowel obstructions. In imaging studies, visible adhesion points and associated ileus on CT scans were diagnosed as adhesive bowel obstructions.

2.6. Statistical analysis

Analyses were performed on an intent to treat basis. Groups were compared using Student's t-tests and Chi-square tests. All statistical analyses were performed using SPSS software v.18.0, with a p-value <0.05 considered statistically significant.

3. Results

3.1. Patients

Of the 76 patients with bladder cancer, 38 were randomized to receive postoperative topical HA/CMC (experimental group) and 38 were not treated (control group). The mean ages of patients in the experimental and control groups were 64.55 $\pm$ 9.72 years and 68.61 $\pm$ 8.03 years, respectively ($p = 0.051$). Mean follow-up times in these two groups were 470.34 $\pm$ 446.27 days and 463.24 $\pm$ 423.52 days, respectively ($p = 0.943$) (Table 1). During the course of this study, 8 and 6 patients, respectively, were lost to follow-up.

3.2. Perioperative, surgical outcomes

There were no significant differences between these two groups in surgical method, duration of surgery, amount of expected blood loss, or number of resected lymph nodes. Postoperative oral feeding was started in the experimental and control groups at an average 4.16 $\pm$ 1.60 days and 4.13 $\pm$ 1.60 days, respectively, and postoperative ambulation was started at an average 1.16 $\pm$ 0.44 days and 1.37 $\pm$ 0.68 days, respectively (Table 2).

Drainage was removed when the volume of drainage was 50 cc or less for 3 consecutive days, with no significant difference between the two groups (0.766). Patients in the experimental and control groups were discharged at 19.29 $\pm$ 8.41 days and 22.39 $\pm$ 18.75 days, respectively, after surgery ($p = 0.355$).

Histological examination showed no significant difference between the two groups (Table 3). Of the 12 patients in the experimental group lost to follow-up, four died, two

Table 1 Baseline characteristics.

	Experimental group (n = 38)	Control group (n = 38)	p-value
Age, yrs	64.55 $\pm$ 9.72	68.61 $\pm$ 8.03	0.051
Sex, n			1.000[a]
Male	32	32	
Female	6	6	
BMI, kg/m^2	25.80 $\pm$ 2.78	25.25 $\pm$ 2.26	0.344
Hypetension, n	14	18	0.353[a]
Diabetes mellitus, n	8	9	0.783[a]
Previous abdominal surgery, n	10	12	0.613[a]
Clinical stage, n			0.269[a]
cTis	2	2	
cT1	7	7	
cT2	11	16	
cT3	17	9	
cT4	1	4	
Concomitant CIS, n	8	8	1.000[a]
Neoadjuvant chemotheraphy, n	4	4	1.000[a]
No. of previous TURBT, n	1.37 $\pm$ 1.42	1.26 $\pm$ 1.57	0.760
Follow up, days	470.34 $\pm$ 446.27	463.24 $\pm$ 423.52	0.943
Lost to follow up, n	8	6	0.384[a]

BMI: body mass index, ASA: American Society of Anesthesiology, CIS: carcinoma in situ, TURBT: transurethral resection of the bladder tumor Student-t test.

[a] Chi-square test.

Table 2 Perioperative outcomes.

	Experimental group (n = 38)	Control group (n = 38)	p-value
Urinary diversion			0.265[a]
Ileal conduit	26	28	
Ureterocutaneostomy	4	5	
Studer's pouch	7	2	
PCN catheter	1	3	
Operative time, min	410.26 ± 105.41	376.45 ± 137.27	0.232
Estimated blood loss, mL	763.16 ± 490.13	578.95 ± 414.05	0.081
No. of resected LN	12.45 ± 8.29	9.00 ± 8.09	0.071
Resumption of oral intake, days	4.16 ± 1.60	4.13 ± 1.60	0.943
Ambulation, days	1.16 ± 0.44	1.37 ± 0.68	0.111
Postoperative LOS, days	19.29 ± 8.44	22.39 ± 18.75	0.355
Removal of drain, days	14.89 ± 7.32	15.42 ± 8.03	0.766

PCN: percutaneous nephrostomy, LN: lymph node, LOS: length of stay Student-t test.
[a] Chi-square test.

of distant metastasis of bladder cancer, one of acute pyelonephritis, and one of pneumonia. Of the 13 patients in the control group lost to follow-up, nine died, six of distant metastasis of bladder cancer, two of pneumonia, and one of unknown causes. Mean durations of follow-up of the deceased patients in the experimental and control groups were 354.75 ± 314.86 days and 356.11 ± 237.35 days, respectively (p = 0.994).

Table 3 Oncological outcomes.

	Experimental group (n = 38)	Control group (n = 38)	p-value
Pathologic stage, n			0.959[a]
pTis	1	1	
pT1	9	11	
pT2	7	5	
pT3	13	12	
pT4	8	9	
Grade, n			0.453[a]
Grade 1	9	5	
Grade 2	26	30	
Grade 3	0	1	
Unclassified	3	2	
Histology			0.736[a]
TCC	34	34	
TCC with squamous differentiation	0	1	
Adenocarcinoma	2	2	
Squamous cell carcinoma	1	1	
Carinosarcoma	0	1	
No. of positive lymph nodes, n	0.82 ± 1.90	0.55 ± 1.72	0.529
Margin positive, n	2	7	0.153[a]
Perineural invasion, n	9	11	0.602[a]
Adjuvant chemotheraphy, n	12	12	1.000[a]
Recurrence	6	10	0.260[a]
Recurrence site			0.170[a]
Liver	2	0	
Lung	1	2	
Bone	1	1	
Duodenum	1	0	
Peritoneum	1	0	
Lymph node	0	2	
Ureter	0	2	
Multiple organs	0	3	
Death, n	4	9	0.128[a]

TCC: transitional cell carcinoma Student-t test.
[a] Chi-square test.

3.3. Complications

One patient in the experimental group experienced a perioperative injury to the rectum, which was corrected by primary repair. No other complications were observed during the follow-up period. Ten patients in the experimental group and 13 in the control group received blood transfusions ($p = 0.454$), and 8 and 20 patients, respectively, had postoperative complications other than blood transfusion. Complication rates did not differ significantly in the experimental and control groups, except for adhesive bowel obstruction, which occurred in zero and six patients, respectively ($p = 0.025$) (Table 4) (Fig. 2). Of these six patients, two were treated with surgical correction (Table 5).

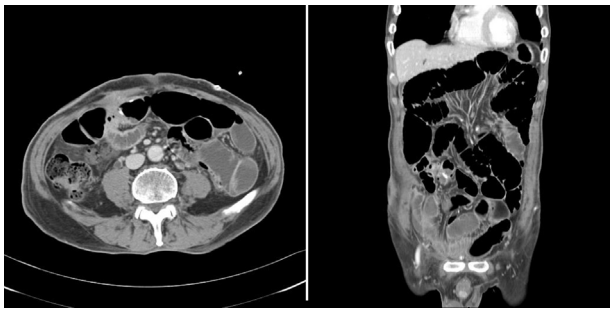

Figure 2 Adhesive bowel obstruction after radical cystectomy.

4. Discussion

This study showed that topical application of HA/CMC to the abdominal cavity after laparoscopic radical cystectomy for bladder cancer reduced adhesive bowel obstructions. Although open radical cystectomy was regarded as a standard treatment modality for invasive bladder cancer and for high-risk patients with recurrent superficial bladder cancer,[4] laparoscopic radical cystectomy is both safe and efficient and has been used more often recently, as it yields similar oncological outcomes and a lower complication rate than open radical cystectomy.[15] Minimally invasive techniques reduce complications and increase the success rate of surgery. Despite technical advances in radical cystectomy for bladder cancer, numerous surgery-related complications have been reported, and the postoperative mortality rate remains high.

Several studies have attempted to identify the causes and prevent postoperative complications.[16] For example, one study reported that 109 of 304 patients (35.9%) who underwent radical cystectomy had minor surgery-related complications, with 69 of these 304 patients (22.7%) having intestinal obstruction.[7] Another study reported intestinal obstruction in 18% of patients who underwent radical cystectomy.[17] An evaluation of risk factors for postoperative complications in 2538 patients who had undergone radical cystectomy found that 774 (30.5%) had experienced surgery-related complications, including 247 (9.7%) with intestinal obstruction. Intestinal obstruction was the most frequent complication after radical cystectomy, followed by urinary tract infection and wound infection.[18] Several previous studies reported bowel obstruction following radical cystectomy,[5] but most of these studies focused on risk factors for and prevention of paralytic ileus during gastrointestinal recovery after intestinal surgery. To our knowledge, no previous prospective study has assessed rates of bowel obstruction after radical cystectomy.

Adhesion is the main cause of postoperative bowel obstruction,[19] being observed in 70% of patients with postoperative bowel obstruction. Adhesive bowel obstruction has been reported in about 25% of patients who have undergone abdominal surgery.[20] The present study showed 6 patients (7.89%) of adhesive bowel obstruction in the control group, and this result could be considered a relatively high occurrence rate compared with previous studies.[7,17,18] In this study, we have analyzed and described several factors on patients with adhesive bowel obstruction (Table 5). This study shows that application of HA/CMC helps to reduce the incidence of adhesive bowel obstruction. However, because the total number of subjects in this study is relatively small, further research will be needed. In the two cases of adhesiolysis, as their symptoms had not improved after conservative treatments and the electrolyte imbalance was progressive, operations were considered in consultation with the general surgery team.

The mechanism of development of postoperative adhesive bowel obstruction is due to an inhibition of fibrinolysis following peritoneal injury. Peritoneal injury induces a

Table 4 Complications.

	Experimental group (n = 38)	Control group (n = 38)	p-value
Intraoperative complication			
Rectal injury	1	0	0.500[a]
Postoperative complication (Clavien units)			
Grade II	19	22	0.643
Transfusion	10	13	
APN	2	3	
Paralytic ileus	6	4	
Mood disorder	1	0	
Delirium	0	1	
Constipation	0	1	
Grade IIIa	3	7	0.309[a]
Wound disruption	1	3	
Hydronephrosis	1	0	
Anastomosis site stricture	1	1	
Anastomosis site leakage	0	1	
Perinephric urinoma	0	1	
Esophageal variceal bleeding	0	1	
Grade IIIb	1	6	0.108[a]
Urethral stricture	1	0	
Adhesive bowel obstruction	0	6	0.025[a]

APN: acute pyelonephritis Chi-square test.
[a] Fisher's exact test.

Table 5 Characteristics of the patients with adhesive bowel obstruction.

Sex/Age	Underlying dz.	Neoadjuvant CTx	Underlying disease	Urinary diversion	Op time, mins	EBL, mL	drain, days	LN dissection	ABO, POD	Treatment	Clinical stage	Pathologic stage	f/u, days	Recurrence
M/66	none	none	DM	ileal conduit	465	900	23	standard	36	conservative treatment	T2N0M0	T3aN1M0	1375	0
M/74	none	none	none	ileal conduit	580	600	12	standard	16	adhesiolysis at POD#20	T2N0M0	T1N0M0	1296	0
M/76	appen-dectomy, cholecys-tectomy	none	none	ileal conduit	475	500	17	standard	22	adhesiolysis at POD#29	T2N0M0	T3aN1M0	647	0
M/76	none	none	HTN, DM	ileal conduit	420	200	15	standard	17	conservative treatment	T2N0M0	T1N0M0	1009	0
M/67	none	none	none	ileal conduit	350	700	15	standard	33	conservative treatment	T4N1M0	T3aN1M0	433	lung, bone, death
M/72	appendectomy, herniorrhaphy	none	HTN	ileal conduit	190	200	17	standard	20	conservative treatment	T1N0M0	T1N0M0	222	0

CTx: chemotherapy, OP time: operation time, EBL: estimated blood loss, LN: lymph node, ABO: adhesive bowel obstruction, POD: post-operative day; days after surgery, f/u: follow up, HTN: hypertension, DM: diabetes mellitus.

blood coagulation cascade and inflammatory changes, during which fibrinogen is converted to fibrin. Under normal conditions, the fibrin is eventually dissolved by fibrinolysis, resulting in the resolution of injury and peritoneal repair. If fibrinolysis is impaired, however, adhesions are induced by organization of fibrin and deposition of collagen.[19] Six methods to prevent postoperative adhesion have been described: minimizing peritoneal damage by using minimally invasive surgical techniques,[21] preventing fibrin formation with heparin or adenosine,[22] preventing inflammatory reactions with steroids or nonsteroidal anti-inflammatory medications,[23] promoting fibrinolysis with streptokinase or urokinase,[24] preventing fibrin organization and collagen deposition with halofuginone,[25] and separating damaged surfaces.[26]

The abdominal cavity contains several natural barriers, including the peritoneum, omentum, and amnion.[27] Adhesion can occur when these barriers are damaged after surgery. Synthetic physical barriers are required to separate injured tissue surfaces from the adjacent organs to prevent adhesion.[28] Synthetic physical barriers include film, solution, and sol—gel transition barriers.[28] Solution barriers and sol—gel transition barriers are more effective in coating an unrecognized injured surface. This study evaluated a sol—gel barrier, HA/CMC. HA is an anionic polysaccharide found in connective tissue, skin, cartilage, hyaline, and synovia, and is one of the main components of extracellular matrices. High molecular weight HA is hydrophilic, non-immunogenic, and viscoelastic, enabling it to coat the mucosal surface and have lubricating activity. HA reduces or prevents trauma in surgical patients due to its physical properties. CMC, another anionic polysaccharide, is a more hydrophilic derivative of cellulose due to the carboxymethylation of its glycosidic hydroxyl ligands. Due to its viscosity and lubricating activity, CMC is widely used as a diluting agent for pharmaceuticals, cosmetics, and foods.[29] HA/CMC has a viscosity similar to honey (2500 to 3500 cP),[30] maximizing its ability to coat injured surfaces and prevent postoperative adhesions. Moreover, HA/CMC is thought to minimize blood loss through drains.[14]

Six patients in the control group, but none in the experimental group, experienced postoperative adhesive bowel obstruction. Other than this complication, there were no significant between-group differences in surgical or oncological outcomes, or complications. Application of HA/CMC was therefore found to be safe and effective in reducing postoperative adhesive bowel obstruction after laparoscopic radical cystectomy for bladder cancer.

This study, however, had several limitations, including the small number of patients. First, there were no significant difference in preoperative conditions between the two groups, but we observed that there were relatively higher mortality and recurrence rates in the control group compared to the experimental group. Although it did not reach statistical significance, this might play a role as a potential bias to affect the occurrence of adhesive bowel obstructions. Second, we also did not control the surgical methods such as urinary diversion or lymph node dissection, and pre-/post-operative management, which includes prokinetics usage or nasogastric tube insertion. Finally, a relatively large number of the patients who lost

on their follow-up period are also a limitation of our study. Nevertheless, this study was the first randomized controlled trial to suggest a method to reduce postoperative adhesive bowel obstruction after radical cystectomy. The long-term effects of HA/CMC instillation during radical cystectomy should be confirmed by a well-designed, long-term, large scale, randomized controlled trial.

Conflicts of interest

None.

Acknowledgments

This study was sponsored by Hanmi Medicare, Seoul, Korea.

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