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JMIG The Journal of Minimally Invasive Gynecology

Original Article

A Randomized Controlled Trial on the Efficacy and Safety of a New Crosslinked Hyaluronan Gel in Reducing Adhesions after Gynecologic Laparoscopic Surgeries

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ABSTRACT **Study Objective:** To evaluate the safety and efficacy of a new crosslinked hyaluronan (NCH) gel in reducing postoperative adhesions.

Design: Randomized controlled trial (Canadian Task Force classification I).

Settings: Seven departments of obstetrics and gynecology in China.

Patients: A total of 216 women scheduled for gynecologic laparoscopic surgery for primary removal of adhesions, myomas, ovarian cysts, or endometriotic cysts.

Interventions: Patients were randomized to receive either NCH gel or saline with 1:1 allocation.

Measurements and Main Results: All patients were evaluated using a modified American Fertility Society (mAFS) scoring system for the incidence, extent, and severity of pre-existing and postoperative adhesions at the 10 anatomic sites of ovaries/tubes and at the expanded 23 or 24 anatomic sites throughout the abdominopelvic cavity by laparoscopy. A total of 215 randomized patients were treated with either saline solution (108 of 108) or NCH gel (107 of 108), composing the full analysis set (FAS), and 196 patients (94 of 108 in the saline control group and 102 of 108 in the NCH gel group) completed the entire study, composing the per protocol set (PPS). The postoperative incidence of moderate or severe adhesions evaluated at the 10 sites (the primary endpoint for efficacy) was 27.7% in the control group and 9.8% in the NCH gel group, a difference of 14.4% (95% confidence interval [CI], 2.6%–20.6%) in the PPS, and 37.0% in the control group and 14.0% in the NCH gel group, a difference of 20.0% (95% CI, 8.9%–26.8%) in the FAS. The postoperative incidence of moderate or severe adhesions evaluated at the 24 sites was also significantly lower in the NCH gel group compared with the control group (5.9% vs 14.9%; $p = .036$) in the PPS. Also in the PPS, the NCH gel group had significantly lower postoperative adhesion scores of severity, extent, and mAFS: 60.0%, 50.8%, and 76.9%, respectively (median scores of the 10 sites; $p = .002$) and 48.5%, 50.0%, and 72.2% (median scores of the 24 sites; $p = .001$) lower than those recorded in the control group. No serious adverse events were observed, and the safety profile of NCH gel was comparable to that of saline control.

This study was supported in part by grants from BioRegen Biomedical (Changzhou) Co, Ltd. The authors have no conflicts of interest to disclose. Registered at ClinicalTrials.gov (NCT02166554).

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http://dx.doi.org/10.1016/j.jmig.2015.04.011

Submitted January 22, 2015. Accepted for publication April 12, 2015.

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Available at www.sciencedirect.com and www.jmig.org

Conclusion: This study demonstrates that NCH gel is safe and significantly reduces adnexal adhesion formation and global adhesion formation throughout the abdominopelvic cavity after gynecologic laparoscopic surgery. Journal of Minimally Invasive Gynecology (2015) 22, 853–863 © 2015 AAGL. All rights reserved.

Keywords: Adhesion prevention; Crosslinked hyaluronan gel; Laparoscopic surgery; Randomized controlled trial

Although various preventive techniques have been implemented, postoperative adhesion formation after gynecologic surgery remains inevitable [1–15]. Using physical barriers to separate healing peritoneal injuries is believed to be a promising strategy for adhesion reduction during the critical repair phase postsurgery. Ideal barriers are absorbable, safe, deliverable by either laparotomy or laparoscopic approaches, and broadly efficacious for the reduction of de novo as well as reformed adhesions throughout abdominopelvic cavity. Although some new adhesion barriers have been developed, only some of the foregoing issues have been addressed, and there remains great potential for improvement [4,5].

Hyaluronan, a nonsulfated glycosaminoglycan consisting of repeating disaccharide units (α-1,4-D-glucuronic acid and β-1,3-*N*-acetyl-D-glucosamine) and presenting in all connective tissues as a major constituent of the extracellular matrix, has unique physicochemical properties as well as distinctive biological functions in wound healing [16–18]. Although one of hyaluronan's major applications is expected to reduce postoperative adhesions, it failed to demonstrate convincing efficacy in 2 pivotal clinical studies [19,20]. Owing to its fluid nature and rapid in vivo degradation, hyaluronan could not persist long enough to keep the healing injuries separated during the critical phase of peritoneal reepithelialization (5–7 days) [20].

Crosslinking modification is an effective way to improve in vivo persistence by increasing material viscosity and retarding degradation [21–24]. Thus, crosslinked hyaluronan may yield a desired level of postoperative adhesion reduction. One such crosslinked hyaluronan is Seprafilm (Genzyme, Cambridge, MA), a film consisting of hyaluronan complexed with carboxymethylcellulose (CMC) that has proven efficacious in reducing adhesions [25–27]. Disadvantages of Seprafilm are that it is difficult to handle, site-specific only, and very challenging to apply via laparoscopy [7,9,15,20,28]. Hyalobarrier (Anika Therapeutics, Abano Terme, Italy) is another currently available crosslinked hyaluronan product for adhesion reduction. Several studies with a limited number of cases have shown that Hyalobarrier may have a site-specific antiadhesive function following laparoscopic myomectomy [29,30].

Recently, a new crosslinked hyaluronan (NCH) gel has been developed to serve as an absorbable adhesion barrier by BioRegen Biomedical (Changzhou, Jiangsu, China). This NCH gel has a much higher viscosity than natural hyaluronan and is gradually absorbed within 1 to 2 weeks in vivo. Once applied, the NCH gel creates an antiadhesion barrier to keep the healing tissues separated during the critical repair phase. Animal studies have shown favorable safety and significant efficacy in adhesion reduction. Therefore, a pivotal, randomized controlled study was conducted to evaluate the safety and efficacy of this NCH gel in reducing de novo, as well as reformed, adhesion formations throughout the abdominopelvic cavity, with a specific focus on the adnexa region after gynecologic laparoscopic surgeries.

Methods

This prospective study had a randomized, reviewer-blinded, placebo-controlled, parallel-group design and was conducted at 7 departments of obstetrics and gynecology in China. The study protocol was approved by the Ethics Committee of each hospital. Investigators were qualified surgeons experienced in gynecologic laparoscopic surgery. The surgeries were video recorded according to protocol, to enable all assessments to be made through a blinded review of video recordings.

HyaRegen NCH gel is a sterile, transparent, viscoelastic, and nonpyrogenic gel composed of highly purified crosslinked hyaluronan molecules. The placebo control was saline solution purchased from commercial sources.

Participants

The inclusion criteria for this study were female, aged 18 to 45 years, and undergoing laparoscopic surgery for the primary removal of adhesion, myoma, ovarian cyst, or endometriotic cyst. All patients had a negative pregnancy test before entering the study and agreed to use adequate forms of contraception throughout the study period. Patients underwent a scheduled second-look laparoscopy (2LL) at 9 weeks after the first-look laparoscopy (1LL). All patients were required to provide written, signed informed consent before participating.

The exclusion criteria for the study included acute or severe infection; autoimmune disease; abnormal liver/renal function (alanine aminotransferase or creatine 50% above the upper normal range); abnormal cardiovascular function (grade $\geq$III from clinical evaluation); abnormal blood

coagulation; medical history of peripheral vascular disease, alcohol/drug abuse, or mental illness; known/suspected intolerance or hypersensitivity to hyaluronan or its derivatives; concurrent use of a systemic antiinflammatory drug; clinical evidence of cancer; use of anticoagulant, fibrin glue, other thrombogenic agents, or any other antiadhesion agent during the procedure; and concurrent peritoneal grafting or tubal implantation.

Participants were allowed to voluntarily withdraw from the trial for any reason at any time, and could be terminated by investigators owing to safety concerns, violations of inclusion/exclusion criteria, or pregnancy.

Study Schedule

The study duration was 12 weeks. All patients were required to make a minimum of 5 visits to the study site, including screening/baseline checking within 2 weeks before 1LL, on the day of 1LL, and at 3 (±1) days, 30 (±5) days, and 9 (±5 days) weeks after 1LL for physical examination and/or laboratory tests. The 2LL was conducted at the 9-week follow-up visit.

Treatments and Allocation

Patients were assigned at random to either the NCH gel or control group in a 1:1 ratio through a central web-based program, which the investigators in study departments contacted immediately after the completion of 1LL. The program system was administered by the Statistics Center of Medical Research at the National Center for Cardiovascular Diseases China in Beijing. A total 216 random sequences were generated by the SAS PROC PLAN procedure (stratified randomization with block size 4).

Patients in the NCH gel group had 160 mL of NCH gel instilled into the peritoneal cavity through a large-bore cannula following standard laparoscopic procedures, to coat the organ and tissue surfaces that sustained surgical trauma, as well as the adjacent and suspected adhesiogenic surfaces. Conversely, patients in the control group had 160 mL of saline instilled instead. Operators could not be blinded to treatment allocation, because NCH gel is much more viscous than saline; thus, only the patients were blinded to treatment allocation.

Surgical Technique

Standardized laparoscopic techniques were followed by the investigators in the 2 study groups. After video recording, all preexisting adhesions during 1LL and the de novo and/or reformed adhesions during 2LL were surgically removed.

Video Recording and Review

During 1LL, video recordings were made of 23 anatomic sites designated by the mAFS scoring system and the surgical sites according to protocol before any surgical intervention [31–36]. This allowed for a blinded review of the videos and scoring of the number, extent, and severity of adhesions at any of the 23 sites throughout the abdominopelvic cavity (Table S1). During 2LL, video recordings were repeated before any possible surgical interventions. A 24th site, the anterior peritoneum incision from 1LL, was observed and recorded as well.

To avoid the potential bias of operating surgeons, participant randomization was done only after the surgical procedure was completed. All videos were provided to 2 qualified reviewers for blinded assessment. To ensure minimal interobserver variability, adhesion scoring in the blinded reviewer assessments was compared, and any discrepancies were settled by the principal investigator.

Efficacy and Safety Assessment

In accordance with the mAFS scoring system, the following definitions were applied for each anatomic site: adhesion incidence was classified as presence or absence; adhesion severity was classified as mild (i.e., filmy, avascular) or severe (i.e., organized, cohesive, vascular, dense) and scored on a 3-point scale (0, none; 1, mild; 2, severe); and adhesion extent was classified according to the site covered with adhesions as localized (<1/3), moderate (1/3–2/3), or extensive (>2/3) and scored on a 4-point scale (0, none; 1, localized; 2, moderate; 3, extensive) [31–36]. Based on their severity and extent, adhesions occurring at each of the 23 or 24 sites were scored as 0 (no adhesion), 1 (severity, mild; extent, localized), 2 (severity, mild; extent, moderate), 4 (severity, mild; extent, extensive or severity, severe; extent, localized), 8 (severity, severe; extent, moderate), or 16 (severity, severe; extent, extensive) [31–36].

Scores from all 23 or 24 sites, excluding those no longer existing, were averaged to yield a mAFS score throughout the abdominopelvic cavity for each patient. Similarly, scores from the 10 sites (ovaries and tubes) were averaged to yield an mAFS score for adnexa [32–36]. Based on mAFS scores (0–16), the adhesion degree was classified into 5 categories: none (0), minimal (>0 and ≤1), mild (>1 and ≤4), moderate (>4 and ≤8), and severe (>8 and ≤16) [32,33]. In addition, the adhesion degree of each site was classified into the same 5 categories in the same manner.

Because moderate/severe adhesions are the major concern after abdominopelvic surgery [9,32,33], in this study, the incidence of moderate/severe adhesions, evaluated at 10 sites (ovaries and tubes), was defined as the primary endpoint of efficacy. Secondary endpoints of efficacy included the incidence of moderate/severe adhesions evaluated at 24 sites, as well as the mAFS score, severity, and extent of adhesions evaluated at both 10 sites and 24 sites.

Safety evaluation was based on vital signs, physical examination, clinical signs and symptoms, electrocardiography findings, clinical laboratory tests, concomitant medications, and the type and severity of adverse events

recorded throughout the study. Laboratory tests included hematology, blood chemistries, urinalysis, C-reactive protein, and urine pregnancy test. Hematologic evaluations consisted of red blood cell (RBC), white blood cell (WBC) and blood platelet counts, neutrophil, and hemoglobin. Blood chemistry test comprised alanine aminotransferase, aspartate aminotransferase, albumin, globin, total protein, total bilirubin, glucose, urea nitrogen, creatinine, potassium, sodium, and chloride. Urinalysis consisted of protein, WBC, RBC, and glucose. The number of events and numbers of patients reporting at least 1 event were recorded. Clinically significant abnormal values from laboratory tests were also assessed as adverse events, as were any clinically significant changes from baseline.

Statistical Analysis

The primary objective of this study was to demonstrate the superiority of NCH gel over saline placebo with respect to the incidence of moderate/severe adhesions. The primary assumption was that that the estimated incidence was 60% in the control group and would be reduced to 40% by application of the NCH gel. With a 2-sided .05 significance level and 10% rate of loss to follow-up, 216 patients with a 1:1 allocation would yield 80% power to detect the superiority.

The statistical analysis was based on a predefined plan. All randomized patients who started treatment were included in the analysis according to the intent-to-treat (ITT) principle. Continuous variables were expressed as mean ± standard deviation (SD); categorical variables, as count and percentage. The Student t test and χ^2 test/Fisher's exact test were used to check the homogeneity of baseline characteristics. The Wilcoxon rank-sum nonparametric test was used for nonnormally distributed variables, and the results were expressed as median (interquartile range [IQR]). The Cochran-Mantel-Haenszel (CMH) χ^2 test with center effect adjustment was performed to estimate the difference in incidence between groups with a 95% confidence interval (CI). All analyses were performed with SAS 9.13 (SAS Institute, Cary, NC), and a p value $\leq$.05 (2-tailed; $\alpha = 0.05$) was considered significant.

Results

Figure 1 shows a flow chart of the study participants. A total of 216 patients who had undergone primary surgery of adhesiolysis, ovary cystectomy, myomectomy and/or endometriosis were enrolled and randomized. The recruitment ran from June 2011 to February 2013, with the last patient completing follow-up in April 2013. In the NCH gel group, 1 patient was mistakenly randomized and then withdrawn before receiving treatment. Therefore, during 1LL, a total of 215 randomized patients were treated with either saline (108 of 108) or NCH gel (107 of 108). According to the ITT principle, these 215 patients constituted the FAS, as well as the safety population. No patients were withdrawn because of adverse events. Nineteen patients did not undergo 2LL because they did not return within the stipulated time period. As a result, postoperative efficacy data were available for 196 patients (94 of 108 in the control group, 102 of 108 in the NCH gel group), and these patients constituted the PPS.

The 2 groups were generally comparable with respect to patient demographics and surgical history (Table S2); however, 10 more patients in the NCH gel group had undergone previous abdominopelvic surgery (36 of 108 in the control group vs 46 of 107 in the NCH gel group; p = .145).

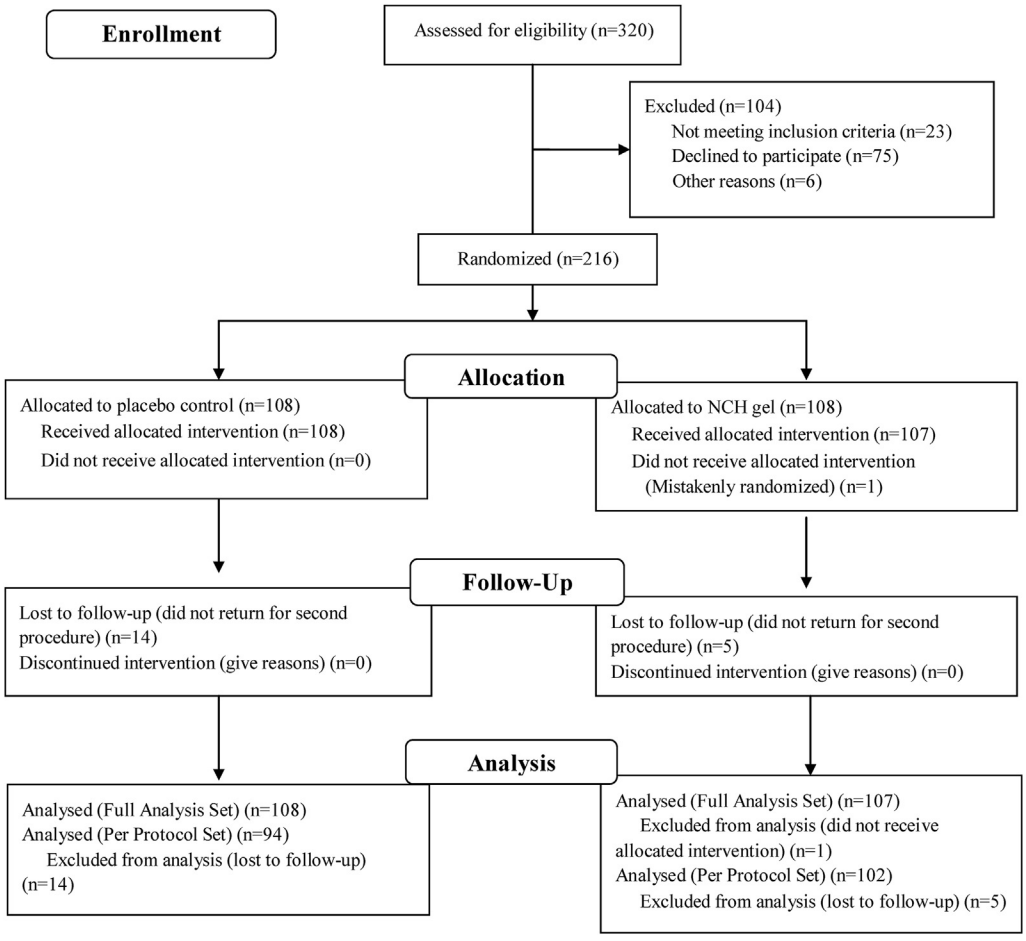
Surgical procedures and occurrence of 1LL for the patients in both groups (summarized in Table S3) were comparable for the 4 primary procedures (adhesiolysis, ovary cystectomy, myomectomy, and endometriosis), as well as the concurrent procedures. Adhesiolysis was the major procedure in both study groups (105 of 108 in the control group, 102 of 107 in the NCH gel group; p = .499), and the techniques used to lyse adhesions (blunt dissection, cautery, and sharp dissection) were comparable in the 2 groups (p = .914, .621, and .837, respectively). The etiology for most of these preexisting adhesions is previous abdominopelvic surgery and/or chronic infection, but some adhesions were not associated with a clear etiology. The duration of surgery was slightly longer in the NCH gel group compared with the control group (93.01 ± 50.13 minutes vs 82.98 ± 39.68 minutes; p = .106), and the associated blood loss was greater in the NCH group (50.67 ± 70.98 mL vs 37.69 ± 43.45 mL; p = .108).

The occurrence of surgeries and adhesiolysis alone performed at each of the 23 anatomic sites was comparable in the 2 groups for most sites. Generally, there were slightly more operative sites in the NCH gel group than in the control group (1160 sites total; 10.84 sites/patient vs 1066 sites total; 9.87 sites/patient). Similarly, slightly more sites underwent adhesiolysis in the NCH gel group (1131 sites total; 10.57 sites/patient vs 1036 sites total; 9.59 sites/patient).

Before surgery, the preexisting adhesions in both groups were first evaluated at the 10 sites (ovaries and tubes) (Table 1). The distribution of various degrees of adhesion (none, minimal, mild, moderate, or severe) did not differ significantly between the 2 groups (p = .169), and the percentage of moderate/severe adhesions was also comparable in the 2 groups (49.1% in the control group vs 57.0% in the NCH gel group; p = .244). However, compared with the control group, the severity of preexisting adhesions was significantly greater in the NCH gel group, with 12 more patients with severe adhesions (20 of 108 in the control group vs 32 of 107 in the NCH gel group), when further examining the sites with moderate/severe adhesions (p = .046) and the scores for severity, extent, and mAFS (p = .041, .031, and .025, respectively). The worse preexisting adhesions in the NCH gel group were even more evident when evaluated at 23 sites (Table 2). The between-group differences were statistically significant (p = .015–.038) in terms of distribution of degrees of adhesion, percentage

Fig. 1

CONSORT flow diagram of the study participants.



and number of sites with moderate/severe adhesions, and scores of severity, extent, and mAFS.

The postoperative adhesions evaluated at 10 sites (ovaries and tubes) are summarized in Table 3. The incidence of moderate/severe adhesions at 2LL (the primary endpoint for efficacy) was significantly lower in the NCH group compared with the control group. In FAS analysis, moderate/severe adhesions were present in 15 of 107 patients (14.0%) in the NCH gel group and in 40 of 108 patients (37.0%) in the control group, a difference of 20.0% (95% CI, 8.9%–26.8%). A similar result was obtained in PPS analysis, with moderate/severe adhesions in 10 of 102 patients (9.8%) in the NCH gel group and in 26 of 94 patients (27.7%) in the control group, a difference of 14.4% (95% CI, 2.6%–20.6%). After bias adjustment of the baseline mAFS score, this incidence difference was even more significant (FAS: 34.3%; 95% CI, 20.5%–48.2% vs PPS: 30.5%; 95% CI, 16.3%–44.7%). In the subgroup of patients with preexisting adhesions (105 of 108 in the control group and 102 of 107 in the NCH gel group), the between-group difference in incidence was significant as well (Table 3).

Details of the postoperative adhesions evaluated at 10 sites in the PPS are presented in Table 4. There were more patients with mild, moderate, or severe adhesions in the control group than in the NCH gel group (51 of 94; 54.3% vs 27 of 104; 26.0%). There were 64.6% fewer patients with moderate/severe adhesions in the NCH gel group compared with the control group (10 of 102; 9.8% vs 26 of 94; 27.7%; $p < .001$). The mean number of sites with moderate/severe adhesions per patient was 57.5% lower in the NCH gel group (0.82 ± 1.91 vs 1.93 ± 2.67; $p = .001$). The median adhesion scores of severity, extent and mAFS were 60.0%, 50.8%, and 76.9% lower, respectively, in the NCH gel group compared with the control group ($p = .002$).

Similar results were obtained when the postoperative adhesions were evaluated at the expanded 24 sites (Table 5; PPS). There were more patients with mild, moderate, or severe adhesions in the control group than in the NCH gel group (43 of 94; 45.7% vs 19 of 102; 18.6%). The percentage of patients with moderate/severe adhesions was 66.4% lower in the NCH gel group (6 of 102; 5.0% vs 14 of 94; 14.9%; $p = .036$). The mean number of sites with moderate/severe

Table 1

Preexisting adhesions at baseline: 10 anatomic sites of ovaries and tubes, FAS analysis

Variable	Control (n = 108)	NCH gel (n = 107)	p value
Adhesion degree, n (%)			.169
None	10 (9.3)	8 (7.5)	
Minimal	22 (20.4)	12 (11.2)	
Mild	23 (21.3)	26 (24.3)	
Moderate	33 (30.6)	29 (27.1)	
Severe	20 (18.5)	32 (29.9)	
Moderate/severe adhesions, n (%)	53 (49.1)	61 (57.0)	.244
Sites with moderate/severe adhesions, mean ± SD	2.81 ± 2.90	3.66 ± 3.27	.046
Adhesion score, median (IQR)			
Severity	0.80 (0.40–1.40)	1.10 (0.60–1.50)	.041
Extent	1.10 (0.50–1.95)	1.60 (0.70–2.30)	.031
mAFS	3.80 (0.78–6.55)	4.90 (1.70–8.90)	.025

adhesions per patient was 52.5% lower in the NCH gel group (1.26 ± 3.02 vs 2.65 ± 3.69; p = .004). The median adhesion scores of severity, extent, and mAFS were 48.5%, 50.0%, and 72.2% lower, respectively, in the NCH gel group (p = .001).

In both study groups, the incidences of moderate/severe adhesions at 2LL were reduced when compared with the baseline, as shown in Figure 2 (PPS). The absolute incidence reduction (baseline - 2LL) was greater in the NCH gel group compared with the control group at the 10 sites (106% greater; 48.20% vs 23.40%) and at the 23 of 24 sites (528% greater; 33.30% vs 5.30%) (Fig. 2A). Moreover, the relative incidence reduction compared with baseline was greater in the NCH gel group compared with the control group at the 10 sites (81% greater; 83.10% vs 45.79%) and at the 23 of 24 sites (224% greater; 84.95% vs 26.24%) (Fig. 2B).

Table 2

Preexisting adhesions at baseline: expanded 23 anatomic sites throughout the abdominopelvic cavity, FAS analysis

Variable	Control (n = 108)	NCH gel (n = 107)	p value
Adhesion degree, n (%)			.035
None	3 (2.8)	5 (4.7)	
Minimal	31 (28.7)	15 (14.0)	
Mild	50 (46.3)	47 (43.9)	
Moderate	19 (17.6)	31 (29.0)	
Severe	5 (4.6)	9 (8.4)	
Moderate/severe adhesions, n (%)	24 (22.2)	40 (37.4)	.015
Sites with moderate/severe adhesions, mean ± SD	3.96 ± 3.91	5.36 ± 4.95	.023
Adhesion score, median (IQR)			
Severity	0.57 (0.37–0.85)	0.74 (0.43–1.00)	.038
Extent	0.72 (0.43–1.22)	1.00 (0.48–1.39)	.026
mAFS	2.33 (0.80–3.80)	2.83 (1.39–5.43)	.028

During the study period, no adverse events were attributed to the NCH gel treatment. No serious adverse events were observed. The adverse events were mostly mild, spontaneously resolved, and comparable in the 2 groups. Two adverse events from laboratory tests, defined as clinically significant changes from baseline (WBC count and blood glucose level), were reported at 9 weeks after surgery in the control group, whereas there were no clinical significantly changes from baseline in the NCH gel group. There were no prolonged hospitalizations or surgeries related to the adverse events.

Discussion

Meticulous surgical technique with less trauma has been considered particularly important for adhesion prevention. Laparoscopy is believed to cause fewer peritoneal injuries and thus is expected to cause fewer adhesions, although an unequivocal consensus has not yet been reached [37]. The reduction in adhesion formation by laparoscopic surgery alone remains unsatisfactory, however. In this study, postoperative adhesions were still formed/reformed in a high proportion of patients: 77.7% total and 27.7 % with moderate/severe adhesions at 10 sites in ovaries and tubes (Table 4), and 88.3% total and 14.9% with moderate/severe adhesions at 24 sites throughout the abdominopelvic cavity (Table 5). This high incidence is consistent with those reported in the literature: 75.4% and 86.1% of patients with de novo adhesion formation after laparoscopic myomectomy and ovarian cystectomy, respectively [36] and 55% to 100% of patients (mean, 85%) with reformed adhesion formation after adhesiolysis irrespective of whether laparotomy or laparoscopy was performed [38].

This pivotal randomized controlled study demonstrates that NCH gel application during laparoscopic surgery significantly reduced postoperative adhesion formation compared with laparoscopic surgery alone (saline control group), as indicated by the lower incidence of moderate/severe adhesions, fewer sites with moderate/severe adhesions, and lower scores for adhesion severity, extent, and mAFS in the NCH gel group at the 10 sites and the expanded 24 sites (Tables 3–5 and Fig. 2). These results confirm that NCH gel is efficacious in reducing postoperative adhesion formation at the adnexa and throughout the abdominopelvic cavity.

Adhesion-reducing agents generally fall within 2 main categories: physical barriers (e.g., films, gels) and solutions (intraperitoneal instillates) [4–15]. Despite the biochemical

Table 3

Incidence of moderate or severe adhesions at 9 weeks after surgery: 10 anatomic sites of ovaries and tubes

	FAS analysis		PPS analysis	
	Control (n = 108)	NCH gel (n = 107)	Control (n = 94)	NCH gel (n = 102)
Incidence, % (n)	37.0 (40)	14.0 (15)	27.7 (26)	9.8 (10)
Difference, % (95% CI)*	20.0 (8.9–26.8)		14.4 (2.6–20.6)	
	34.3 (20.5–48.2)†		30.5 (16.3–44.7)†	
	19.0 (7.4–26.0)‡		13.8 (1.4–20.4)‡	
	35.0 (20.8–49.1)§		31.5 (17.0–46.0)§	

* Incidence difference (%) was calculated by point estimation, and 95% CI was calculated by CMH χ^2 test after the adjustment of center effect; difference = control - NCH gel.
† Sensitivity analysis after bias adjustment of the preexisting adhesion mAFS score.
‡ Sensitivity analysis, subgroup of patients with preexisting adhesions (105 of 108 in the control group and 102 of 107 in the NCH gel group).
§ Sensitivity analysis, subgroup of patients with preexisting adhesions after bias adjustment of the preexisting adhesion mAFS score.

differences, all of these agents have a common primary mode of action as a physical barrier to separate the healing tissues from other tissue surfaces during the critical period of peritoneal reepithelialization [7,9,15]. In general, physical barriers are site-specific (i.e., reducing adhesions where they are placed), but have no effect on the global reduction of adhesions throughout the entire abdominopelvic cavity. Conversely, solutions typically have the advantage of providing broad coverage throughout the cavity [4–15].

Currently, the Food and Drug Administration has approved only 2 physical barriers for adhesion reduction after laparotomy: oxidized regenerated cellulose (Interceed; Ethicon, Somerville, NJ) and Seprafilm. However, a number of other site-specific barriers have been approved for use in Europe, including polyethylene oxide/CMC gel (Intercoat; Ethicon), polyethylene glycol hydrogel (CoSeal; Baxter International, Deerfield, IL), and Hyalobarrier [7,9,12,15]. These physical barriers have demonstrated variable efficacy for reducing site-specific adhesion formation, although most of them, except Interceed and Seprafilm, have not yet been evaluated through pivotal randomized controlled trials [7,9,12,15,39].

To date, Adept (4% icodextrin solution; Baxter BioSurgery, Deerfield, IL), approved in Europe for abdominal surgery and in US for laparoscopic gynecologic adhesiolysis, is the only broad-coverage solution agent shown to be safe and to have some efficacy in global adhesion reduction throughout the abdominopelvic cavity [7,9,12,15]. This agent has not demonstrated sufficient performance, however. In a pivotal randomized controlled study in the US, Adept did not reduce the extent and severity of

Table 4

Postoperative adhesions at 9 weeks: 10 anatomic sites of ovaries and tubes, PPS analysis

Variable	Control (n = 94)	NCH gel (n = 102)	p value
Adhesion degree, n (%)			<.001
None	21 (22.3)	22 (21.6)	
Minimal	22 (23.4)	53 (52.0)	
Mild	25 (26.6)	17 (16.7)	
Moderate	15 (16.0)	4 (3.9)	
Severe	11 (11.7)	6 (5.9)	
Moderate/severe adhesions, n (%)	26 (27.7)	10 (9.8)	<.001
Sites with moderate/severe adhesions, mean ± SD	1.93 ± 2.67	0.82 ± 1.91	.001
Adhesion score, median (IQR)			
Severity	0.50 (0.10–1.10)	0.20 (0.10–0.50)	.002
Extent	0.61 (0.10–1.50)	0.30 (0.10–0.60)	.002
mAFS	1.30 (0.10–4.80)	0.30 (0.10–1.10)	.002

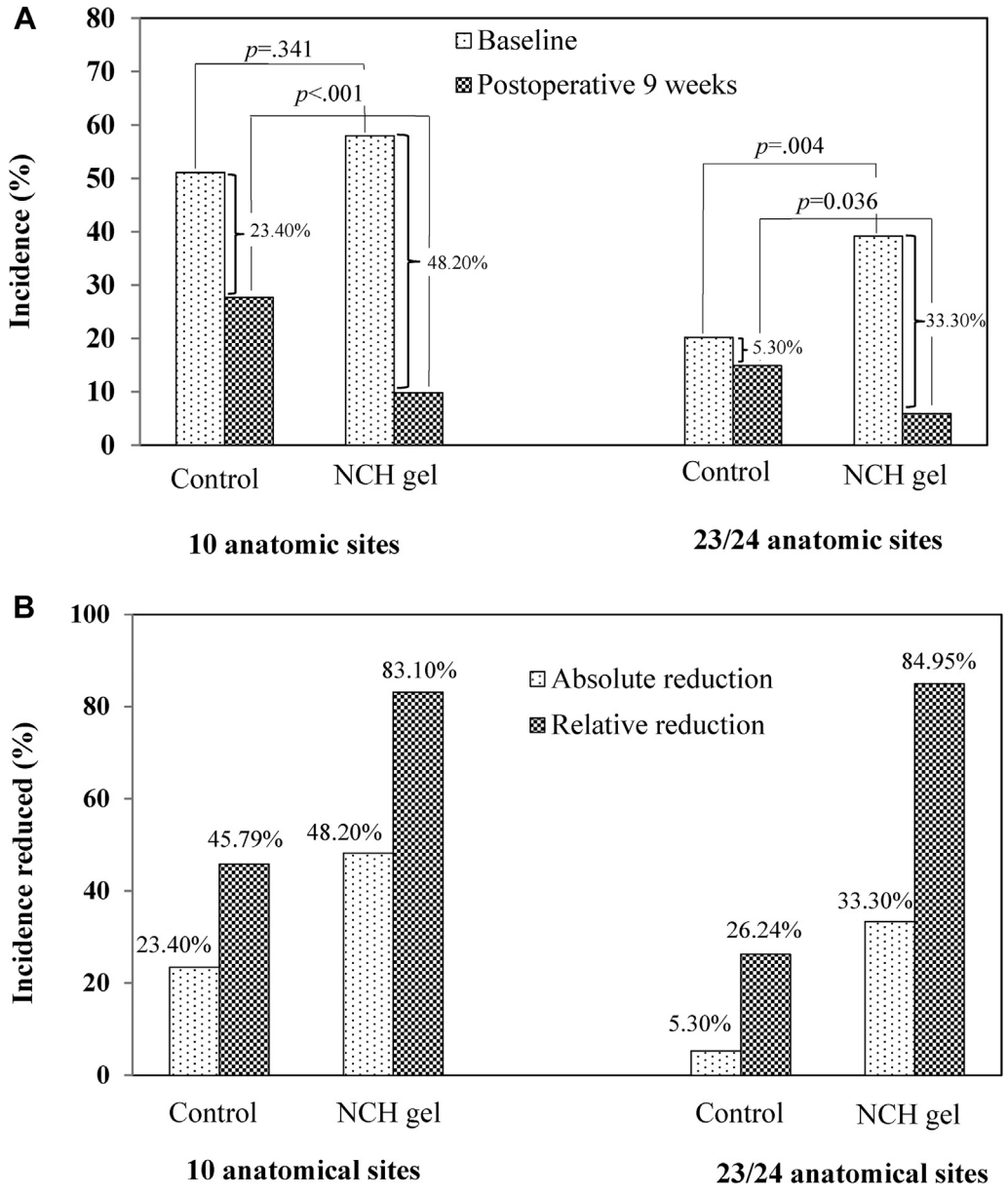
Table 5

Postoperative adhesion at 9 weeks: expanded 24 anatomic sites throughout the abdominopelvic cavity, PPS analysis

Variable	Control (n = 94)	NCH gel (n = 102)	p value
Adhesion degree, n (%)			.001
None	11 (11.7)	12 (11.8)	
Minimal	40 (42.6)	71 (69.6)	
Mild	29 (30.9)	13 (12.7)	
Moderate	13 (13.8)	5 (4.9)	
Severe	1 (1.1)	1 (1.0)	
Moderate/severe adhesions, n (%)	14 (14.9)	6 (5.9)	.036
Sites with moderate/severe adhesions, mean ± SD	2.65 ± 3.69	1.26 ± 3.02	.004
Adhesion score, median (IQR)			
Severity	0.33 (0.08–0.63)	0.17 (0.08–0.33)	.001
Extent	0.42 (0.08–0.83)	0.21 (0.08–0.42)	.001
mAFS	0.90 (0.13–2.79)	0.25 (0.08–0.71)	.001

Fig. 2

Moderate/severe adhesions at baseline and 2LL (PPS): (**A**) incidence and (**B**) incidence reduction (baseline−2LL). Absolute incidence reduction = incidence at baseline−incidence at 2LL; relative incidence reduction = (incidence at baseline−incidence at 2LL)/incidence at baseline × 100%.



adhesions, and there was only an 11% between-group difference (49% in the Adept group vs 38% in the control lactated Ringer's solution group; p = .018) in terms of clinical success, defined as a reduction in adhesions in at least 3 sites or in 30% of the sites lysed [33]. More recently, another pivotal randomized controlled study in Europe showed that Adept lacked a global effect in reducing de novo adhesions after laparoscopic gynecologic surgery [36]. The authors concluded that for the purposes of future research on this agent, focusing on site-specific (e.g., posterior uterus) changes rather than on a global effect is likely to provide more important data on clinical efficacy [36].

The protocol in this pivotal study was similar to that for the Adept studies [33,36]. The results show that the NCH gel significantly reduced both adnexal adhesion formation and global adhesion formation throughout the abdominopelvic cavity, in terms of the incidence of moderate/severe adhesions, mAFS score, and adhesion severity and extent. To the best of our knowledge, NCH gel is the sole barrier currently able to significantly reduce

global adhesion formation throughout the abdominopelvic cavity, as supported by the data from this pivotal randomized control trial. The efficacy of the NCH gel in reducing de novo or reformed adhesions, as well as the adhesions at each site, was not determined in this study. Well-designed future studies might be necessary to demonstrate this efficacy.

When applied to the surgical site, natural hyaluronan quickly enters the systemic circulation via the lymph and is then rapidly cleared by catabolic pathways. Its reported elimination half-life ($t_{1/2}$) from the peritoneum is approximately 25.5 hours [21]. Crosslinking is believed to delay metabolic clearance and allow the material to persist for the time window of adhesiogenesis [21–23,40]. Along with Seprafilm and Hyalobarrier, another example of crosslinked hyaluronan is ionically crosslinked ferric hyaluronan (Intergel; Lifecore Biomedical, Chaska, MN). Intergel was developed with increased viscosity and prolonged in vivo persistence, and both animal and clinical studies have shown desired levels of efficacy in global adhesion reduction throughout the abdominopelvic cavity [21,32,40]. Unfortunately, this gel was withdrawn from the US market in 2003 owing to a serious possible Intergel reaction syndrome caused by the component of iron (Fe^{3+}) and ammonia [41–46].

The physical properties of the NCH gel are similar to those of Intergel; however, unlike Intergel, NCH gel was developed via a new crosslinking technology and contains no toxic agents. In a preclinical animal study, the maximum volume of NCH gel administered without any adverse effects was at least 15-fold higher than that applied in this study (unpublished data). The favorable safety profile of NCH gel is further confirmed by the present study, in which no adverse events associated with NCH gel treatment were observed.

Owing to the high safety threshold, 160 mL of NCH gel was applied to the abdominopelvic cavity to provide broad coverage on the organ and tissue surfaces that sustained surgical trauma as well as their adjacent and suspected adhesiogenic surfaces, and thus a global effect on reduced adhesion formation throughout the cavity. In the contrast, the doses for most site-specific gels are within 40 mL because of safety and/or cost concerns [29,30,34,35,47–49]. Furthermore, the widespread distribution of the gel also possibly could be achieved via intestinal peristalsis and eventually reach broader coverage, similar to that for Intergel [32]. Numerous factors may contribute to postoperative adhesions, and it is difficult to predict which locations and organs will be involved [1]; therefore, broad prophylactic coverage and comprehensive application of antiadhesive gel represent an effective approach to adhesion reduction.

Adhesion formation is inherently a defect of the peritoneal healing process; thus, any factors that theoretically aid the normal healing process may reduce adhesion formation [1,7,9,15]. Hyaluronan has been reported to have distinctive functions in scar-free wound healing by reducing inflammation and improving peritoneal reepithelialization [16–18]. In a bowel anastomotic rat model, application of NCH gel significantly improved tissue healing (unpublished data). A gel similar to NCH also has been reported to significantly improve wound healing (i.e., mucosa reepithelialization) after endoscopic sinus surgery in both animal and clinical studies [22,23,50].

Adhesions may result in infertility, pain, or bowel obstruction and may increase operating time and the risk of bowel injury during subsequent surgeries [1–15]. The present study has demonstrated the effectiveness of the NCH gel in reducing postoperative adhesion formation; however, the clinical significance of associated improved fertility, decreased pain, or reduced incidence of postoperative bowel obstruction remains to be evaluated in future studies.

Conclusion

NCH gel proved to be safe and significantly reduced postoperative adhesion formation both at the 10 anatomic sites of ovaries and tubes and at the expanded 24 anatomic sites throughout the abdominopelvic cavity. NCH gel provides a new, easy-to-use, and effective intraperitoneal barrier for adhesion reduction throughout the abdominopelvic cavity after surgery.

Acknowledgments

Other members of the HyaRegen Adhesion Study Group include Drs Yan Zhai, Ying Jiang, and Cuiqin Sang, Beijing Chao-Yang Hospital of Capital Medical University, Beijing, China; Drs Songshu Xiao, Fang Xiao, and Mingzhu Ye, Third Xiangya Hospital of Central South University, Changsha, Hunan, China; Drs Airong Zhang, Jie Jiang, Guoyun Wang, Xingsheng Yang, and Baoxia Cui, Qilu Hospital of Shandong University, Jinan, Shandong, China; Drs Qiubo Lu and Qingwei Meng, Beijing Hospital, Beijing, China; Dr Qinxia Zhang, China-Japan Friendship Hospital, Beijing, China; Dr Ye Lu, Peking University First Hospital, Beijing, China; and Dr Yang Wang, Fuwai Hospital, Beijing, China. We appreciate the language editing by Dr Gidon Ofek.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jmig.2015.04.011.

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