A Modern Biomaterial for Adhesion Prevention

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Abstract: A biomaterial composed of carboxymethylcellulose, poly(ethylene oxide), and calcium can be prepared in a variety of ways to reduce fibrin deposition and adhesion formation. This biomaterial platform can be formulated into a flowable gel with tissue adherence appropriate for use in minimally invasive surgery. The device remains at the site of placement even in gravitationally dependent areas. A peridural formulation was shown in preclinical studies to be safe and effective in reducing adhesions to dura following spinal surgery. A peritoneal formulation used on pelvic organs following peritoneal cavity surgery was also shown to be safe and effective. A clinical feasibility study showed that patients with severe back pain and lower extremity weakness treated with the peridural formulation, applied over their nerve roots following laminectomy or laminotomy, experienced significantly reduced symptoms when compared with surgery-only controls. The peritoneal formulation was shown in two multicenter feasibility studies of women undergoing pelvic surgery to significantly reduce adhesion formation when compared with surgery-only controls. Confirmation of the feasibility studies awaits results from pivotal clinical trials. These formulations were safe, effective, and easy to use. This biomaterial provided a benefit to patients undergoing surgery where postsurgical adhesion formation is a concern. J Biomed Mater Res Part B: Appl Biomater 81B: 239–250, 2007

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INTRODUCTION

Postoperative adhesion formation is the single greatest complication of surgery.[1–5] Fibrous adhesions form after surgery to peritoneum, central nervous system, pericardium, pleura, and synovium. Pelvic adhesions have been found in 56–100% of patients by second-look laparoscopy after primary gynecological surgery.[6] Diamond et al.,[7] as well as DeCherney and Mezer,[8] demonstrated that gynecologic pelvic surgery typically causes adhesions to the adnexa, leading to infertility and pelvic pain. Menzies and Ellis[9] showed that adhesion formation follows general surgical procedures, especially those involving bowel. Clinical consequences of adhesions after peritoneal cavity surgery include increased rates of reoperation,[3] postoperative bowel obstruction,[10] infertility,[11] and chronic pelvic pain,[12,13] all of which markedly increase healthcare costs.[14,15]

The clinical consequences of adhesions are not limited to abdominal-pelvic operations. Fibrosis can form between spinal dura mater and interposing structures as a result of hematoma or residual necrotic tissue, including fat.[16–18] It was reported that fewer than one-third of patients who undergo a repeated operation after lumbar disc surgery show persistent improvement of their symptoms; the chance of long-term surgical success after a repeated operation may be diminished in cases in which epidural fibrosis is prevalent.[18,19] Repeat surgery for epidural fibrosis is often less successful and may require prolonged operating time and increased risks of adhesive arachnoiditis and dural tears from surgery to treat fibrosis at the surgical site.[20–22] Epidural fibrosis occurring after lumbar surgery may contribute to failed-back surgery syndrome, which is characterized by recurrent radiculopathy with symptoms including weakness and pain in the lower extremity.[23–25]

ADHESION PREVENTION ADJUVANT TECHNOLOGY

Gynecologic Surgery

Use of adhesion prevention adjuvants has become the standard of practice following conservative gynecologic sur-

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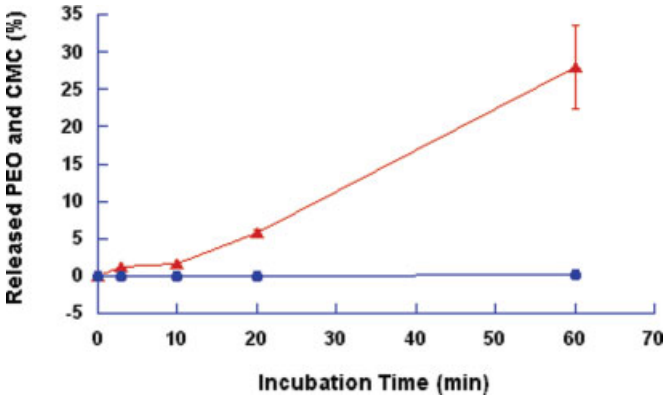

Figure 1. Release of PEO and CMC from CMC/PEO gels composed of CMC (M_W 700,000, 3.3%, w/v) and fluorescine-PEO (M_W 5000, 0.34%, w/v). Gel was coated onto porcine intestine in a petri dish and incubated with PBS at ambient temperature. The amount of CMC and PEO released was detected by UV spectrometer. Data expressed as mean ± SD ($n = 3$).[51] [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

gery.[1,26] Adhesion prevention adjuvants became available to practicing gynecologists in 1990 with the US introduction of Interceed® Absorbable Adhesion Barrier (Gynecare, Somerville, NJ).[27] Other site-specific barriers soon followed, including Preclude® (Gore-Tex, Flagstaff, AZ)[28] and Seprafilm® Bioabsorbable Membrane (Genzyme, Cambridge, MA).[29–31] These first generation adhesion prevention devices were widely used in laparotomy procedures but were found to be a challenge when used *via* laparoscopy. FDA approved Intergel® Adhesion Prevention Solution in 2001 for use *via* laparotomy.[32,33] Many gynecologists found Intergel easy to use *via* laparoscopy. When Intergel was withdrawn from the market in 2003, the only clinically available instillate indicated for the reduction of postoperative adhesion formation was Adept®[34] in Europe. Early clinical studies with *N*,*O*-carboxymethylchitosan in volumes of ~300 mL showed promising clinical benefit.[35] Development of site-specific adhesion prevention devices, which could be easily delivered during laparoscopy, was led by initial clinical studies of SprayGel™.[36,37] Although most conservative gynecological surgeries are performed by laparoscopy, there are currently no FDA approved site-specific adhesion prevention devices, which can be easily delivered *via* laparoscopy.

Spinal Surgery

There are no FDA approved products for adhesion reduction following spinal surgery. A peridural formulation of carboxymethylcellulose (CMC) and poly(ethylene oxide) (PEO) stabilized by calcium (Oxiplex™; FzioMed, San Luis Obispo, CA) was shown in preclinical studies to be effective in reducing adhesions to peridural surfaces following surgery.[38] Recently, the peridural formulation became available to European spinal surgeons for the reduction of adhesions, pain, and residual weakness in the lower extremity following lumbar surgery,[39,40] and this product is currently undergoing pivotal clinical study in the United States.

This paper reviews the formulations, preclinical pharmacology, and results of clinical trials with devices for both gynecologic and spinal applications.

FORMULATION

Devices composed of CMC or PEO or both in the form of films and gels have demonstrated adhesion reduction in a variety of animal models.[41–52] CMC is tissue adherent and functions as a barrier (Figure 1). PEO inhibits the deposition of protein onto tissue surfaces.[49–53] To control rheology, calcium chloride was added to the CMC and PEO formulation,[51] forming an intramolecular CMC-carboxylate–calcium-chloride ion complex that alters the mobility of CMC. This intramolecular complex provides the interaction between the CMC and PEO, which ultimately determines the rheology, tissue adherence, and residence time.[51] When CMC and PEO are stabilized into a composite gel, the properties of protein repulsion and tissue adherence contribute to postsurgical adhesion prevention. CMC, PEO, and calcium chloride can be formulated to yield various rheological properties at several different shear rate regimes (Figure 2). The viscosity at high shear rates is low, which allows for dispersal through a small bore cannula and manipulation during surgery. The high viscosity of the gel returns at low or zero shear rate, allowing the gel to remain at the site of tissue injury after application, promote tissue adhesion, and inhibit fibrosis.

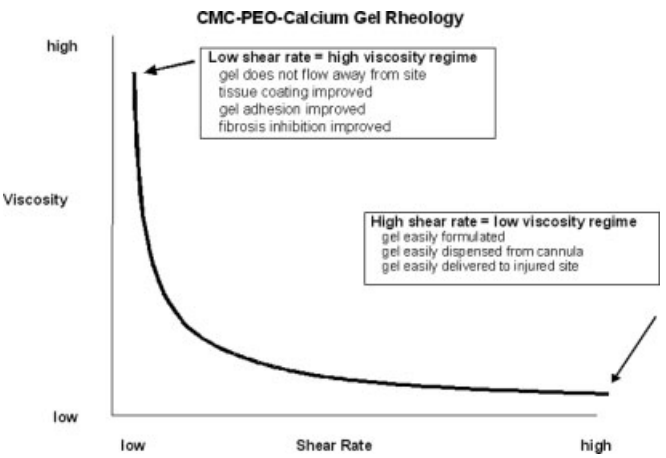

Figure 2. The blending of CMC and PEO in the presence of calcium chloride affords a gel family that enables rheological control over the formulation. By adjusting the formulation ingredients, CMC, PEO, and calcium chloride, the rheology can be varied to provide a dilute solution of a viscoelastic gel. The gel viscoelastic properties can be adjusted to formulate the elastic or solidlike properties of the gel and the viscous or liquidlike properties of the final device. The viscoelastic properties of peritoneal and peridural formulations provide optimum performance in their respective medical use.

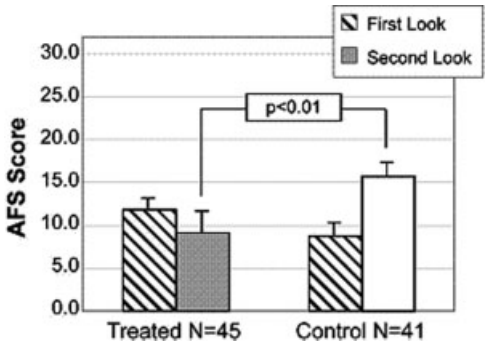

Figure 3. Patients undergoing conservative laparoscopic surgery had their adnexa covered with a peritoneal formulation of CMC–PEO–calcium (~15 mL) or served as surgery-only control. At the time of second-look laparoscopy 6–10 weeks later, the adnexa that was coated with the peritoneal formulation ($n = 45$) had a significantly ($\xi \pm$ SEM; $p < 0.01$ by Wilcoxan rank sum test) lower adnexal score, using the system of the American Fertility Society (AFS Score), compared with control adnexa ($n = 41$).[57]

Initially, Elkins et al. showed that 0.9 and 1.0% CMC were effective in reducing adhesions to the rat cecum covered with CMC.[46,52] Subsequently, Fredericks showed CMC to be superior to 32% dextran 70, which was, at the time, a commonly used adhesion prevention device.[45] Diamond et al.[44] evaluated CMC in different volumes and concentrations with and without 32% dextran in a rabbit uterine horn model. CMC alone was effective in reducing adhesions while dextran, a polysaccharide commonly used in gynecologic surgery, provided no additional benefit. In these studies, an inverse correlation was noted between either the concentration of CMC (1, 2, and 3%) or the volume of 2% CMC (20, 30, 40, and 50 mL) and the extent of adhesion formation. The best results were reported with the highest viscosity (94,000 cps) CMC at the largest volume (50 mL). Diamond et al. confirmed and extended these observations in an adhesion reformation model.[54] Reduction of adhesions by CMC was also shown following bowel surgery. Wurster et al. reported that a 12 mL solution of 1% CMC reduced adhesions to the rat cecum after generalized abrasion of the small bowel serosa and, in a separate group of animals, that there was no impairment in anastomotic healing.[43] It has been hypothesized by Leach et al. that coating the tissue surfaces decreases the injured tissue apposition required for adhesion formation.[41]

Poly(ethylene oxide) is a nonionic, water-soluble polymer widely used for stabilizing colloids and for formulating pharmaceuticals. Because of the biocompatibility of PEO and its solubility in aqueous solution, PEO is used to coat a variety of materials to limit their interaction with proteins.[53] It is widely used as a dispersant because it is inert and noninflammatory. In particular, fibrin and fibrin gel matrix, precursors to the fibrin bridges that interconnect apposing surfaces leading to adhesions,[54,55] do not interact well with PEO.[53,56] Steric repulsion forces between PEO and protein in aqueous solution prevent binding of complex proteins such as fibrin to PEO (Figure 3).[51,53] Various volumes of PEO were shown to reduce adhesions in animal models.[42,58] However, the volumes required to achieve meaningful results preclude clinical use.

GYNECOLOGIC APPLICATIONS OF PERITONEAL FORMULATION

Preclinical Studies

A ''peritoneal formulation'' was developed into a site-specific antiadhesion barrier gel capable of endoscopic delivery into the peritoneal cavity. Rabbit models of abdominal surgery, including sidewall excision, double uterine horn and adhesion reformation after adhesiolysis, were used in preclinical studies.[47] In these models, effectiveness was assessed by measuring the percentage of area involved in adhesion and the tenacity of those adhesions. Several studies were performed in the sidewall excision model to identify the polymer characteristics to maximize efficacy. When the viscosity of the gel increased, the adhesion reduction efficacy of the gel also increased (Table I). Volume of gel applied also affected efficacy. Application of 3 mL resulted in 77% reduction in adhesion reformation; application of 5 mL resulted in 91% reduction in adhesion reformation. Peritoneal formulation was associated with normal repair of the surgical site and there was no indication of inflammation.

Clinical Studies

The safety and effectiveness of the peritoneal formulation was demonstrated in two prospective, controlled, randomized clinical trials: one in Europe and one in the United States.

TABLE I. Reduction of Adhesion Reformation With Peridural Formulations of CMC–PEO–Calcium in a Rabbit Adhesiolysis Model[51]

Treatment Type	No. of Animals (n)	Viscosity (cps)	Percent Adhesion Reformed (% Area)
Study 1			
Gel 1	5	272,000	22.5 ± 9.5
Gel 2	5	68,000	52 ± 20.4
Gel 3	4	1,400	80 ± 20
Control	3	NA	100 ± 0
Study 2			
Gel 1	8	210,000	8.8 + 6.5
Control	5	NA	80 + 22.4

Adhesions were induced by removing a 3 × 5-cm^2 section of parietal peritoneum from the sidewall (study site) and abrading the adjacent bowel.[48] After 10 days, the rabbits developed adhesions from the bowel to the sidewall that covered 100% of the study site area. After lysing the adhesions, three gels of different viscosity produced by adjusting polymer concentrations were applied to the study site (Study 1). Evaluation of adhesion reformation was done at necropsy eight days later. Adhesions that reformed were scored as the percent of the sidewall peritoneal study site area that was covered by adhesions. The effects of Gel 1 on reducing adhesion reformation were confirmed in Study 2.

The Peritoneal Formulation European Study. A randomized, third-party-blinded, parallel-group clinical study was conducted at four centers in Europe. Patients were 18–46 years old, required peritoneal cavity surgery by laparoscopy, and underwent a second-look laparoscopy as part of their treatment plan 6–10 weeks after the initial surgery.[57] At the conclusion of the initial laparoscopic operation, each patient received either peritoneal formulation (treatment) or no additional therapy (control). Both the initial and second-look surgeries were videotaped.

Gel Application. At the end of the surgical procedures, subjects were placed in reverse Trendelenberg position to facilitate collection of residual fluid from the *cul-de-sac*. Thereafter, residual fluid was aspirated until <10 mL of fluid remained in the *cul-de-sac*. A single layer of peritoneal formulation was applied *via* a 30.5 cm long × 5 mm cannula applicator in sufficient volume to completely coat the surgical site with a single layer of gel. The surgical sites included anterior and posterior surface of the ovary, Fallopian tube, including mesosalpinx and ampulla, adjacent pelvic sidewall, including the ovarian fossa, and the lateral aspect of the uterus. The amount of gel required to cover the adnexal surfaces with a single layer using the peritoneal formulation applicator was found to be ~15 mL per adnexa and took ~90 s to apply.

Assessment. Blinded reviews of videotapes from both surgeries were performed to quantitate adhesion scores by the method of the American Fertility Society (AFS).[59] The AFS score is determined by assessing the extent (area of adnexal organ covered by adhesions) and severity (severe: if the adhesion requires cutting to remove or tears peritoneal surfaces when removed bluntly or requires hemostasis; filmy if not severe) of adhesions involving the Fallopian tube and ovary. The sum of the scores for the Fallopian tube and the ovary provided a clinical category for the adhesion score: minimum, 0–5; mild, 6–10; moderate, 11–20; severe, 21–32.

Results of the Peritoneal Formulation European Study. Of the 25 treatment patients, surgery was performed on 45 adnexa, followed by coverage of those adnexal sites with peritoneal formulation. Of the 24 control patients, surgery alone was performed on 41 adnexa. All patients did well following surgery, with no unusual postoperative complications. All patients returned for second-look laparoscopy within 6–10 weeks (86 adnexa). Treatment and control patients underwent adhesiolysis only (treatment, $n = 12$; control, $n = 8$ adnexa) and removal of ovarian endometriomas by cystectomy (treatment, $n = 6$; control, $n = 3$ adnexa). Endometriosis involving parietal and visceral peritoneum was present in 33 treatment and 33 control adnexa. Severe endometriosis (stage IV) was treated in six treatment and six control adnexa.

As shown in Figure 3, the difference in second-look AFS scores (42% reduction) was statistically significant ($p < 0.01$). The same directional difference in AFS score was seen for the patient groups without [Figure 4(a)] and with

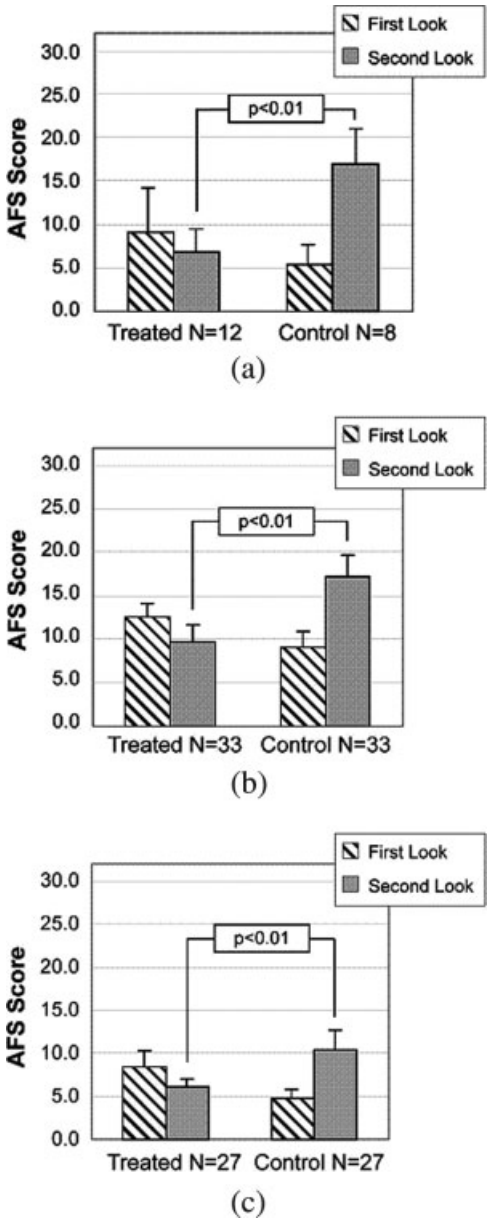

Figure 4. (a) Patients with no endometriosis; (b) Patients with endometriosis stages I–IV; (c) Patients with endometriosis stages I–III. Adnexa from patients undergoing conservative gynecological surgery were coated with a peritoneal formulation of CMC–PEO–calcium (~15 mL) or served as surgery-only controls. Adnexal adhesions were determined using the system of the American Fertility Society (AFS Score) at the time of initial surgery as well as at second-look laparoscopy 6–10 weeks later (± SEM). Adnexa from patients undergoing adhesiolysis only who had no endometriosis (a), patients with endometriosis AFS stages I–IV (b), as well as from those patients with endometriosis stages I–III (stage IV excluded, c) that were coated with the peritoneal formulation showed a significant improvement in adnexal AFS score when compared with controls ($p < 0.01$ by Wilcoxan rank sum test).[57]

[Figure 4(b)] endometriosis. Patients with grade I–III endometriosis showed a reduction in AFS score in the peritoneal formulation treated group when compared with controls [Figure 4(c)]. Although peritoneal formulation worked well to prevent an increase in adhesion score in patients with

TABLE II. Shift Analysis[63]

Treat: Surgery + Peritoneal Formulation

				Second Look			
	Category			Minimal	Mild	Moderate	Severe
	AFS		Total	0 - 5	6 - 10	11 - 20	21 - 32
Baseline	Minimal	0 - 5	23	22	1	0	0
	Mild	6 - 10	5	2	2	1	0
	Moderate	11 - 20	5	2	1	1	1
	Severe	21 - 32	12	1	1	2	8
		Total	45	27	5	4	9

Control: Surgery Only

				Second Look			
	Category			Minimal	Mild	Moderate	Severe
	AFS		Total	0 - 5	6 - 10	11 - 20	21 - 32
Baseline	Minimal	0 - 5	23	13	7	1	2
	Mild	6 - 10	4	0	0	3	1
	Moderate	11 - 20	5	0	0	1	4
	Severe	21 - 32	9	0	0	1	8
		Total	41	13	7	6	15

[Color table can be viewed in the online issue, which is available at www.interscience.wiley.com.]

endometriosis, it did not appear to provide that benefit to patients with grade IV endometriosis.

Individual patient benefit is demonstrated by the number of patients whose adhesion scores shifted to a better AFS score category after surgery.[60–66] An increase in adnexal adhesion score category indicates a worse prognosis for pregnancy. Prognostic categories for minimal (score, 0–5), mild (6–10), moderate (11–20), and severe (21–32) scores are provided for each patient group (Table II). The number of individual adnexal adhesion scores (Table IIIA) that improved or stayed the same from first- to second-look laparoscopy *versus* those that worsened reveals a significant treatment benefit from the use of peritoneal formulation (87 vs. 32% respectively; $p < 0.01$). When individual adnexal adhesion scores are grouped by prognostic category (Table IIIB), the number that improved or stayed the same, from first- to second-look laparoscopy *versus* those that shifted to a worse category, also demonstrates a significant treatment effect of peritoneal formulation. Ninety-three percent of the adnexa that received treatment with peritoneal formulation did not have a worse categorical score, while only 56% of the control adnexa did not have a worse categorical score at the time of second look.

Peritoneal Formulation Pilot US Clinical Study. In a pilot clinical study performed in the United States to support FDA approval, 28 patients underwent laparoscopic sur-

TABLE III. Shift in AFS Category Following Pelvic Surgery

A.

	Individual Scores		
	Improved or Unchanged	Worsened	Total
CMC-PEO-Ca	87% (39)	13% (6)	45
Control	32% (13)	68% (28)	41

B.

	AFS Category		
	Improved or Unchanged	Worsened	Total
CMC-PEO-Ca	93% (42)	6% (3)	45
Control	56% (23)	44% (18)	41

The significant benefit of the peritoneal formulation of CMC–PEO-calcium in reducing adhesions was shown by both a reduction in average AFS Score (A) as well as a reduction in AFS prognostic category (B) as a result of treatment ($p < 0.01$, χ^2 test for both).[60] [Color table can be viewed in the online issue, which is available at www.interscience.wiley.com.]

gical therapy of their adnexa to remove existing adhesions or endometriosis.[67] During the initial surgical procedure, 18 adnexa in the control group and 29 adnexa in the treated group were subjected to surgical therapy (47 adnexa). The peritoneal formulation was applied over the surface of their Fallopian tubes, mesosalpinx, ampulla, ovaries, ovarian fossae, and lateral portion of the uterus. AFS scores were determined at both first and second look.

Results of the Peritoneal Formulation US Clinical Study. The baseline AFS scores were the same at the time of initial surgery for both the treatment and control groups. The AFS score for the treated patients was essentially unchanged at the time of second-look laparoscopy in the treatment group. In contrast, the AFS score for the control patients increased 36%. At second look, twice the percentage of control adnexa had an increased AFS score when compared with the treated adnexa (Figure 5). This 32% reduction in adhesion formation, as shown by the change in AFS score, is a clinically significant improvement in patient outcome.[67] The AFS score was designed to predict the patient's chance of becoming pregnant based on the adnexa with the lower score.[63,68] When adnexa were stratified by AFS score at primary surgery, the benefit of peritoneal formulation treatment to the adnexa with greater disease was evident through a reduction in the increase of adhesion scores. For adnexa with AFS scores <6 at primary surgery, the change in mean score between first and second surgeries was 1.9 for the treated *versus* 2.6 for the control group. For adnexa with AFS scores >6 at primary surgery, the change in mean scores was –1.0 in the treated *versus* 4.9 in the control group. Sixty-two percent of the adnexa in the control group that had an initial AFS score of >6 increased their AFS score at second look. In contrast, only 28% of the treated adnexa had an increase in their AFS score (Figure 6).

Perspective: Peritoneal Formulation in Gynecologic Surgery

Challenges facing the gynecologic surgeon in placement of an adhesion prevention device include (1) ease of use and (2) device retention at application site. The most commonly used site-specific adhesion prevention devices either cannot be applied or are difficult to apply during minimally invasive surgery. As a consequence, many surgical procedures still do not use adhesion barriers. The peritoneal formulation of CMC, PEO, and calcium is a transparent, viscoelastic gel that is readily administered to the specific anatomical site(s) where adhesion formation is a concern. This ease of use includes packaging stored at room temperature that when opened delivers the sterile gel (in two 20-mL syringes) and applicator directly to the operating field. The rate of peritoneal formulation delivery to the surgical site is directly controlled by the surgeon; when the surgeon stops depressing the syringe, the gel stops flowing. Gel residing within the applicator tube does not harden, allowing for continued application at the convenience of the surgeon. With experience, the investigators found that a single layer of gel was sufficient to cover the adnexal surface and adjacent sites. Typical volume to cover an adnexum was ~15 mL, which was administered in ~90 seconds.

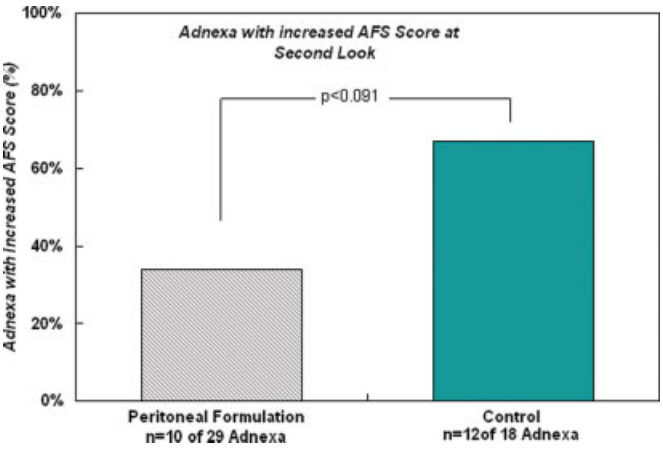

Figure 5. Percentage of adnexal adhesion scores, determined by the system of the American Fertility Society (AFS Score), that increased at the time of second look in patients undergoing conservative gynecological surgery by laparoscopy. A peritoneal formulation of CMC–PEO–calcium was used to cover the adnexa ($n = 29$) of 18 patients at the time of initial laparoscopic surgery. Ten patients (adnexa: $n = 18$) served as surgery-only controls. Although the number of adnexa in this pilot study precludes statistical significance ($p = 0.091$ by Wilcoxan rank sum test), there was a marked reduction in the number of adnexa that failed surgical therapy with peritoneal formulation.[67] [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

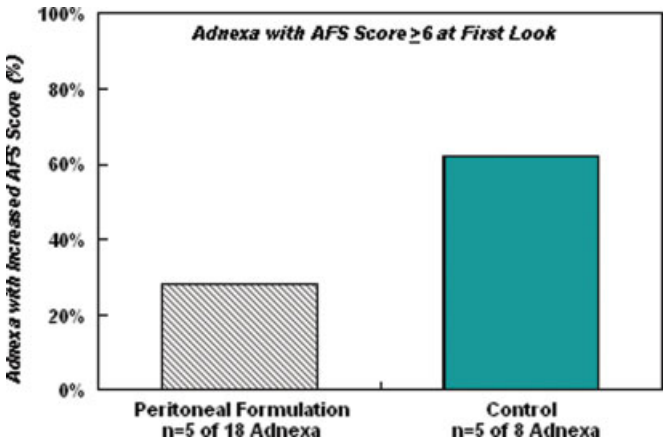

Figure 6. Percentage of adnexal adhesion scores, determined by the system of the American Fertility Society (AFS Score), that increased at the time of second look in patients undergoing conservative gynecological surgery by laparoscopy for patients in whom the initial score was ≥6. A peritoneal formulation of CMC–PEO–calcium was used to cover the adnexa ($n = 18$) of 12 patients at the time of initial laparoscopic surgery. Six patients (adnexa: $n = 8$) served as surgery-only controls. Although the number of adnexa in this pilot study precludes statistical significance ($p = 0.24$ by Student's t test), there was a marked reduction in the number of adnexa that failed surgical therapy with peritoneal formulation.[67] [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The gel was resorbed in most cases from the peritoneal cavity before the time of second-look laparoscopy, usually within 6 weeks. In four cases, small collections ($\sim 5 \times 5$ mm^2) of gelatinous material (presumably residual gel) were noted in areas where multiple layers of gel had been applied or in areas deep in the *cul-de-sac* where intraperitoneal clearance may have been affected,[69,70] particularly in cases of grade IV endometriosis where the *cul-de-sac* is obliterated.[71] In two instances, biopsies of these sites were consistent with residual gel. There did not appear to be any clinical significance of the residual gel; it was not associated with adhesions; it did not obstruct organ mobility. Although it is reassuring to see gel persisting at the site of application, avoidance of applying excess gel is recommended.

Conclusion: Peritoneal Formulation

At present, the peritoneal formulation seems well suited to address the need for general adhesion prophylaxis in peritoneal cavity surgery. However, clinical needs do remain. Patients with intraperitoneal infections as well as those with severe endometriosis represent remaining challenges to device technologies. Strategies combining pharmaceuticals with devices to provide prolonged, physiological effects at the site of potential adhesion formation appear promising.

SPINAL FORMULATION IN LUMBAR SURGERY

Although good surgical technique is effective in reducing postoperative epidural fibrosis, compression or tethering of the nerve root may cause recurrent radicular pain and physical impairment.[4,5,23,72] Repeated surgery is complicated by epidural adhesions, which prolongs operating time and increases the risks for adhesive arachnoiditis and dural tears due to difficult dissection.[19–22,25] Many types of materials have been implanted in the epidural space in an effort to reduce scar formation.[41,72–74] One formulation, Adcon®-L (Gliatech, Cleveland, OH), received FDA approval for scar reduction following lumbar surgery.[74–77] Nevertheless, widespread use of Adcon-L was limited by reports of late-onset headaches and associated leakage of cerebrospinal fluid from dural injuries; these adverse events were potentially related to delayed healing and foreign body reaction and the product was discontinued.[76,77]

Preclinical Studies

CMC, PEO, and calcium in several formulations of gels and films were evaluated in a standardized rabbit model of peridural fibrosis generated by a two level laminectomy.[38] The laminectomy sites were randomized such that one site was treated with gel or gel covered by film and the other site served as a surgical control. The ratios of the constituents (CMC and PEO) and the molecular weight of the polymers were varied. Efficacy measurements included the number of rabbits free of peridural adhesions and the severity of peridural adhesions of treated *versus* control animals. Adcon-L was chosen as a positive control because of prior studies reporting reduction of peridural fibrosis.[75] Experimental gels reduced tethering of the dura to the site of injury and increased the number of rabbits without dural adhesions when compared with controls. Similar results were observed in animals treated with both gels and films together. The optimal gel/film combination produced up to 84% laminectomy sites free of dural adhesions in one study of five treated animals. The treatment sites were examined histologically. The results indicate that 90% of the sections from the treatment sites of animals treated with gels and films were free of or had slight epidural adhesions. Normal muscle and bone healing accompanied the prevention of peridural fibrosis. The optimal gel formulation, ''peridural formulation'', was evaluated in clinical studies.

Dural Healing

The effect of peridural formulation and Adcon-L on preventing healing of dural nicks was compared in a rabbit model. Histological evaluation revealed a difference in the healing of dural incisions. The peridural formulation did not inhibit healing of dural incisions, whereas Adcon-L application was correlated with an absence of dural healing and, additionally, foreign body reaction was observed at the microscopic level. Histological evaluation revealed that in the majority of sections (27 of 34 sections, 79%) with a detectable defect, the dural incision was healed or partially healed (i.e. the dura mostly healed by day 14 after injury) in control animals. In animals that received peridural formulation at the laminectomy site, similar results to the con-

trols were observed (32 of 35 sections were healed, 91%). However, when Adcon-L was added to the laminectomy site at the time of surgery, healing of the dural injury did not occur in the majority of sections (12 of 28 sections were healed, 43%; Adcon-L vs. control $p = 0.007$; Adcon-L vs. peridural formulation, $p < 0.001$). Adcon-L application was correlated with an absence of dural healing and the presence of a foreign body reaction. In contrast, peridural formulation did not delay healing of dural incision and was cleared from the surgical site by 28 days.

Clinical Study: Lumbar Discectomy

A 12-month evaluation of the safety and effectiveness of peridural formulation in the reduction of pain and radiculopathy was done in patients undergoing single level lumbar discectomy.[39,40] A randomized, single-blind, multicenter, pilot clinical trial was conducted to evaluate the performance of peridural formulation in patients who underwent surgery for unilateral herniation of the lumbar disc at L4-5 or L5-S1. Patients were adults scheduled to undergo their first surgery for removal of a unilateral, herniated, lumbar, intervertebral disc associated with radiculopathy. Specific inclusion criteria included signs and symptoms of lumbar or lumbosacral radiculopathy affecting one predominant nerve root level, radiological evidence of nerve root compression, and/or confirmed existence of extruded or sequestered disc fragment at the L4-5 or L5-S1 level compatible with clinical signs and symptoms. Patients underwent at least a 2-week period of nonoperative treatment without resolution of pain as well as presurgical eligibility evaluations, including examination by a neurosurgeon or orthopedic spine surgeon, and magnetic resonance imaging (MRI) of the spine.

Eighteen patients with severe leg pain and lower extremity weakness (11 women and 7 men) were randomly assigned intraoperatively to receive the gel at the conclusion of surgery (treatment group) or to undergo surgery alone (control group). A self-assessment questionnaire (Lumbar Spine Outcomes Questionnaire, LSOQ) related to patients' pain, symptoms, and activities of daily living, was completed preoperatively and at scheduled postoperative intervals (30 days, 90 days, 6 months, 12 months).[78–81] A computer-generated paradigm randomized patients to treatment (peridural formulation) or control groups with balanced assignment across the study and per center. Randomization occurred immediately prior to wound closure.

Exclusion Criteria. Patients were excluded if they had previous spinal surgery, were treated with epidural steroids within 4 weeks of the proposed surgery or with oral steroids within 10 days prior to the proposed surgery, and/or if they received aspirin or other nonsteroidal antiinflammatory drugs within 7 days prior to the proposed surgery. Other exclusion criteria included involvement in a current or anticipated worker's compensation claim, and/or party to a current or anticipated personal injury litigation. Patients were excluded intraoperatively for dural entry, discovery of intraspinal tumor, the need to involve more than one level, exploration of the contralateral side, placement of an epidural fat pad, or retention of a hemostatic agent.

Treatment Response Assessments. Self-assessment measure of clinical outcome was performed by using the LSOQ.[78,79,82] Pain scales are a common method for assessing patient outcome following back surgery. BenDebba et al. developed a comprehensive, disease-specific questionnaire for assessing complaints of low back pain and evaluating the outcomes of treatments for these complaints.[82,83] The LSOQ was shown to have high test–retest reliability, good content and construct validity, and was responsive to change following treatment. It was reported to be acceptable to patients and easy to administer. The LSOQ was used in this study as an instrument designed specifically to measure clinical outcomes following lumbar discectomy for herniated discs in patients with pain and radiculopathy. Patients had evidence of substantial leg pain and/or lower extremity weakness at baseline. Composite scores were derived from the patients' responses to the LSOQ. Higher scores were indicative of more severe pain.

Efficacy. All patients tolerated the surgical procedures well and had uneventful postoperative recoveries. There were no device-related adverse events and no clinically significant changes in laboratory values. The analysis of MRI images, including observations of enhancing and nonenhancing abnormalities, did not reveal significantly different results between the control and treated patients. The 11 patients with severe leg pain and significant lower extremity weakness who were treated with peridural formulation had a reduction in those symptoms at 30 days, 90 days, 6 months, and 12 months after discectomy, compared with the seven control patients who underwent surgery only. When this group of patients was analyzed, clear separation in clinical outcome measures between the treated patients and control patients was evident. The treated patients who had severe leg pain (Table IV) and weakness (Table V) continued to show an improvement relative to the controls, which continued through the 12-month study interval. No device related safety issue arose during the 12-month study. A larger clinical trial to confirm these findings is underway. Confirmation of these results awaits completion of an expanded, ongoing pivotal clinical study.

Perspective

Interpretation of clinical data from FDA monitored safety studies is limited beyond general safety consideration because of the relatively small number of patients. Unlike pivotal studies, which often contain more than 250 patients, safety studies, which precede pivotal studies in the United States, typically limit patient's exposure to the device. In this study,

TABLE IV. Spine Formulation Gel Pilot Study: Leg Pain

	Spine Formulation		Control		
Leg Pain	*N*	Mean ± SD	*N*	Mean ± SD	*p*
Baseline	11	64.5 ± 18.6	7	66.3 ± 9.5	0.813
30 Days					
Actual value	11	11.5 ± 18.9	7	37.6 ± 30.4	0.038
Changes from baseline	11	52.9 ± 29.0	7	28.7 ± 28.0	0.100
Relative change from baseline	11	80.3 ± 31.8	7	44.4 ± 43.9	0.060
90 Days					
Actual value	11	21.2 ± 27.0	6	31.2 ± 29.7	0.492
Changes from baseline	11	43.3 ± 30.6	6	33.3 ± 31.5	0.536
Relative change from baseline	11	67.6 ± 37.9	6	50.4 ± 49.8	0.435
6 Months					
Actual value	10	16.7 ± 16.1	6	31.2 ± 34.3	0.267
Changes from baseline	10	45.9 ± 30.0	6	33.3 ± 37.2	0.470
Relative change from baseline	10	68.5 ± 32.7	6	49.4 ± 59.8	0.419
12 Months					
Actual value	11	20.0 ± 25.6	6	27.2 ± 24.3	0.583
Changes from baseline	11	44.5 ± 19.5	6	37.3 ± 28.6	0.550
Relative change from baseline	11	73.4 ± 31.1	6	55.7 ± 42.4	0.339

the number of patients with severe leg pain and weakness of lower extremity treated with peridural formulation was 11.

Evaluation of outcomes data at 6 months seems predictive of long-term follow-up findings after lumbar discectomy. Previously, on the basis of a composite scoring system, BenDebba et al. reported that the outcomes improved over the first 6 months after surgery in patients with low-back pain undergoing discectomy.[82,83] Thereafter, pain and function scores remained relatively constant over the 2-year duration of the study. Danielsen et al. demonstrated that changes in visual analog scale scores as well as the Roland–Morris Disability Index were similar at 6 and 12 months after discectomy.[80] In a landmark study that has now extended to 5 years after decompression laminectomy for lumbar spinal stenosis, Atlas et al. showed that modified Roland scores that were reduced during the initial 6 months postoperatively remained relatively constant over the next 54 months, with data collected at 12, 24, 36, 48, and 60 months.[81] Woertgen et al. found similar results in 98 patients who were observed for 2 years after lumbar disc surgery for relief of radicular pain.[84] The Low-Back Outcome Score improved through 3 months after surgery to reach the maximal benefit, which persisted during the 12- and 24-month measures.

CONCLUSIONS

Both the peritoneal and spinal formulations consist entirely of nonanimal-, nonbacterial-derived natural or synthetic

TABLE V. Spine Formulation Gel Pilot Study: Lower Extremity Weakness

	Spine Formulation		Control		
Weakness in Lower Extremity	*N*	Mean ± SD	*N*	Mean ± SD	*p*
Baseline	11	3.55 ± 0.52	7	3.43 ± 0.53	0.653
30 Days					
Actual value	11	1.36 ± 0.67	7	2.43 ± 1.13	0.023
Changes from baseline	11	2.18 ± 1.08	7	1.00 ± 0.82	0.025
Relative change from baseline	11	59.1 ± 25.4	7	31.0 ± 24.4	0.034
90 Days					
Actual value	11	1.64 ± 0.67	6	1.83 ± 0.98	0.631
Changes from baseline	11	1.91 ± 0.94	6	1.50 ± 1.22	0.453
Relative change from baseline	11	52.3 ± 21.1	6	43.1 ± 34.3	0.500
6 Months					
Actual value	10	1.40 ± 0.70	6	2.33 ± 1.21	0.068
Changes from baseline	10	2.10 ± 0.99	6	1.00 ± 1.41	0.088
Relative change from baseline	10	58.3 ± 24.5	6	27.8 ± 40.7	0.079
12 Months					
Actual value	11	1.73 ± 0.90	6	2.00 ± 1.26	0.612
Changes from baseline	11	1.82 ± 1.08	6	1.33 ± 1.51	0.452
Relative change from baseline	11	50.0 ± 27.1	6	37.5 ± 44.0	0.476

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components (CMC, PEO, and calcium). Different combinations of CMC, PEO, and calcium allow alterations in tissue adherence and performance, which create formulations appropriate for different body cavities and surgical interventions. Gels were shown to be easy to use during surgery in the peritoneal cavity as well as the lumbar spine. Clinical studies found both the peritoneal and peridural formulations to be safe and effective. In addition to their benefits as devices, these gels may also be effective vehicles for drug delivery capable of addressing many unmet problems of surgical therapeutics.[85–88]

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