

# Clinical Evaluation for Reduction of Adhesions by a Viscoelastic Gel in Gynecological Laparoscopic Surgery

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## Abstract

In laparoscopy, the usual adhesion prevention techniques cannot be applied or are difficult to use. As a result, a viscoelastic gel was developed.

*Methods:* In third party-blinded, randomized, four center studies, patients from 18-46 years underwent surgical laparoscopy in which adnexa and adjacent tissues were coated with viscoelastic gel. They underwent for a second look 6-10 weeks later. Adhesion scores of American fertility society were quantified with the blinded reviews of videotapes.

*Result:* For 25 patients, surgery was done on 45 adnexa. Surgical sites with risk of adhesion was covered with approximately 15 ml of viscoelastic gel in approximately 90 seconds. For 24 control patients, surgery alone was done on 41 adnexa. Decrease in AFS score (11.9-9.1) was seen in treated adnexa. In control adnexa increase in AFS score (8.8-15.8) seen. The difference (42% reduction) seen in second look AFS score is significant ( $p < 0.01$ ).

*Conclusion:* Laparoscopic administration of viscoelastic gel was easy and had significant reduction in adnexal adhesions. The patients undergoing gynecological surgeries were benefited.

**Keywords:** Laparoscopy, viscoelastic gel, adnexal adhesions, adhesion prevention, Oxiplex/AP Gel.

## AIMS AND OBJECTIVES

The aim of this study was to compare the effectiveness and safety of viscoelastic gel as an adhesion preventive device. The following parameters such as safety, complications, adverse events and time for administration were evaluated.

## MATERIAL AND METHODS

A literature search was performed using medline and the search engine Google, Springer link and Highwire press. The following search terms were used: *Laparoscopy, Adhesion, Viscoelastic gel* and *Oxiplex*. Selected papers were screened for further references. Criteria for selection of literature were the number of cases (excluded if less than 20), methods of analysis (statistical or nonstatistical) and operative procedure (only universally accepted procedures were selected).

The study was conducted in 4 centers in Europe. It was randomized, third party blinded and parallel group design. At each study center, a relevant committee approved the study plan for human evaluation. Patients included were of 18-46 years old and willing to undergo a second look of laparoscopy after 6-10 weeks as part of the treatment plan after their initial surgery. The patients included received either Oxiplex/AP Gel to prevent the adhesion, or no additional therapy after surgery (control).

Patients excluded were (a) With either history of diabetes, hepatic or renal disorders.(b) With pelvic or abdominal infection.(c) Those who received systemic corticosteroids within 30 days of the initial surgery or postoperative hydrotubation.(d) If any adhesion preventive adjuvant such as seprafilm, intergel, interceed or spray gel, or peritoneal instillates containing non steroidal anti-inflammatory agents, corticosteroids, Hyskon, or any absorbable hemostat.(e) If pregnant, ectopic pregnancy or reversal of surgical sterilizations.(f) No evidence of endometriosis or any adnexal diseases.(g) Bowel perforation or conversion to laparotomy.

## INTRODUCTION

In conservative gynecological surgeries, the use of adhesion preventive adjuvant has become significant.<sup>1</sup> Increased rates of reoperation,<sup>2</sup> chronic pelvic pain,<sup>3</sup> postoperative bowel obstruction and infertility<sup>4</sup> are the clinical consequences of adhesions after peritoneal cavity surgery. This markedly increases health care costs. This makes adhesion prevention, a major contributor in the outcome of a successful surgery.

As early as 1990, adhesion preventive adjuvant was available for gynecologists. Gynecare, USA produced interceed absorbable adhesion barrier. This was followed by site specific barriers like Preclude (Gore-Tex, USA) and Seprafilm bioabsorbable membrane (Genzyme, USA). It was challenging to use these first generation adhesion preventive devices commonly used in laparotomy to be used in laparoscopy. In 2001 food and drugs agency (FDA) approved Integral adhesion prevention solution to be used for laparotomy.<sup>5</sup> Many gynecologists found that integral administration was easy in

laparoscopy. Integral was withdrawn from market in 2003. In Europe the only instillate available during that time for reduction in postoperative adhesion formation was Adept.<sup>6</sup> Clinical studies showed that about 300 ml of N,O-carboxymethyl-chitosan was having clinical benefit.<sup>7</sup> Spray gel conducted several clinical studies for the development of site specific adhesion prevention devices that could be delivered easily during laparoscopy.<sup>8</sup> Oxiplex/SP is used recently by spinal surgeons for reducing pain and weakness due to adhesion formation following laminectomy.<sup>9</sup> Viscoelastic gel, a similar formulation of Oxiplex was found to be most effective in reducing adhesions to peritoneal surface following surgery.<sup>10</sup> The results of the first clinical study using viscoelastic gel, a single component adhesion preventive device that can be administered easily to the pelvic sites during operative surgery is reported in this paper.

## CONTENT

Like any surgical device for maximum patient benefit, careful attention to the details of application is important. For the application of Oxiplex/ AP Gel, the following procedures were done in the subjects. At the end of surgery, to facilitate the collection of residual fluid to the cul-de-sac, the subjects were placed in reverse Trendelenberg position. From cul-de-sac the residual fluid was aspirated until it was less than 10 ml. Through a 30.5 cm long × 5 mm canula applicator, a single layer of gel was applied in sufficient volume to coat the surgical site completely with a viscous layer of gel. The surgical sites included fallopian tube including mesosalpinx, surface of the ampulla, lateral part of uterus that could come in contact with adnexa, anterior and posterior surface of ovary, the surfaces between the fallopian tube and the ovary, and adjacent pelvic side wall including the ovarian fossa. To coat the adnexa, it did not exceed more than 30 ml of gel. Following this, the surgical instruments were removed and the pneumoperitoneum was evacuated.

A second look laparoscopic procedure was performed 6-10 weeks after the initial surgery. This time the adnexa were evaluated in a similar manner to the initial laparoscopic surgery. The image was recorded on videotape. By the method of the American fertility society (AFS, 1988), blinded reviews of the videotapes were performed to quantify the adhesion scores. AFS adnexal adhesion score is determined by the severity (severe: If the adhesion requires cutting to remove or tears peritoneal surface on blunt removal or if hemostasis is required; not severe: if filmy) and extent (area of adnexal organ covered by adhesions) of the adhesions of the ovary and fallopian tube.

Summing the scores up for the ovary and fallopian tube provided a clinical category for the adhesion score. Minimum 0-5; mild 6-10; moderate 11-20; severe 21-32. Safety evaluation was based on the patient's recovery, postoperative condition and severity of adverse events recorded throughout the study.

## STATISTICAL ANALYSIS

Using Student's t-test for continuous variables and Fischer's exact test of categorical variables, the treatment and control groups were compared. Using Student's t-test, the number and proportion of sites with adhesion were compared. Wilcoxon rank-sum test was used to compare adhesion scores. Shift tables were analyzed by the Cochran-Mantel-Haenszel test with the treatment scores which is based on the order of adhesion score categories.

## RESULTS

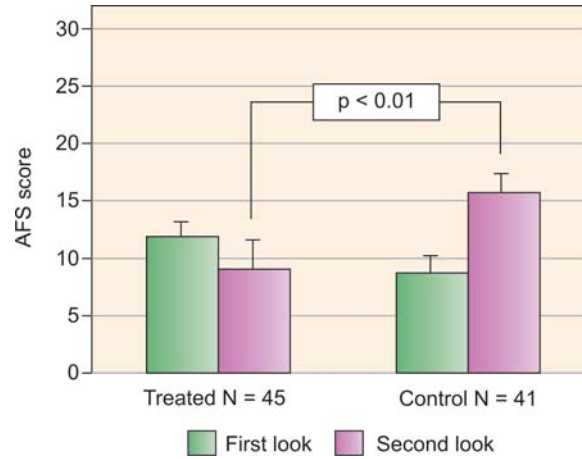
Forty-nine female patients in total between 18-46 years of age received treatment at four centers. Treatment patients were 25. In these patients surgery was performed on 45 adnexa and Oxiplex/AP Gel was applied on those adnexal sites. Control patients were 24. In these patients surgery was performed on 41 adnexa. There were no unusual postoperative complications and all the patients did well after the surgery. After 6-10 weeks, patients returned for second look laparoscopy. For all 86 adnexa, efficacy analyses are presented. For both the groups, the type and frequency of the surgical procedures were similar. Adhesiolysis was done in 12 treatment and 8 control patients. By cystectomy removal of ovarian.

Endometriosis was done in 6 treatment and 3 control patients. 33 treatment and 33 control patients had endometriosis involving parietal and visceral peritoneum. 6 treatment and 6 control patients had stage four endometriosis. No patient had prolonged hospital stay, premature readmission, prolonged constipation, fever, postoperative pain requiring evaluation on hospitalization. During this study there was no discontinuation due to any adverse event and no death occurred.

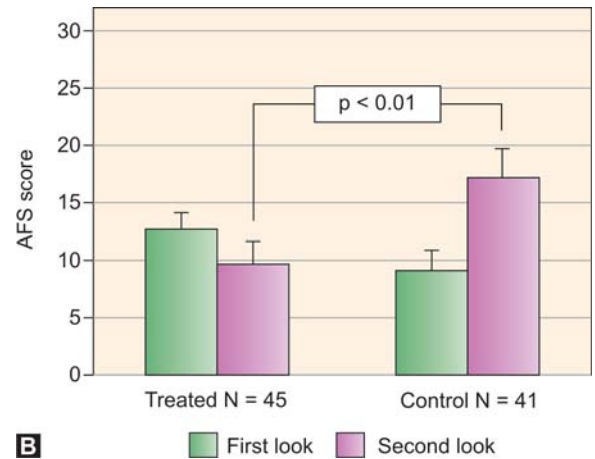
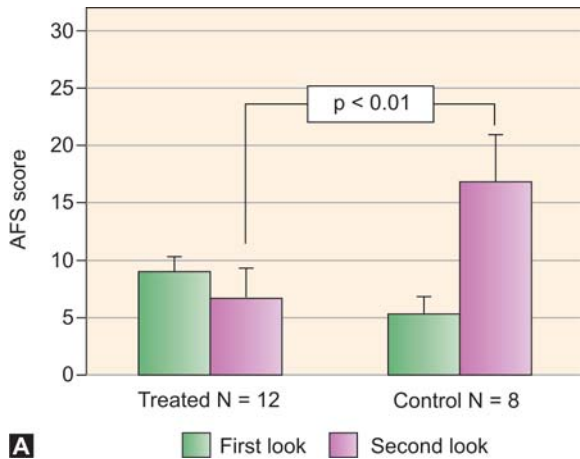
A single layer of gel was applied to the adnexa with an Oxiplex applicator consisting of 30.5 cm long × 5 mm cannula. Approximately  $94 \pm 21$  seconds was taken for gel application and approximately 15 ml of gel was applied on each adnexa.

## EFFICACY

As in Figure 1, the mean adnexal adhesion score for the control adnexa was 8.8 and for the Oxiplex/AP Gel treated adnexa was 11.9. During the second look laparoscopy, the controlled adnexa showed an increase in adnexal adhesion score from 8.8 to 15.8. In contrast, the adnexa that were covered with Oxiplex/AP Gel showed a decrease in mean adnexal adhesion score from 11.9 to 9.1. In second look AFS scores, the difference (42% reduction;  $p < 0.01$ ) was significant statistically. For the patient groups without (Fig. 2A) and with (Fig. 2B) endometriosis, the same directional difference in mean adnexal adhesion score was seen. A reduction in adnexal adhesion score in the Oxiplex/ AP Gel treated group compared to controls (Fig. 2C) was seen for patients with grade one to three endometriosis. In patients with

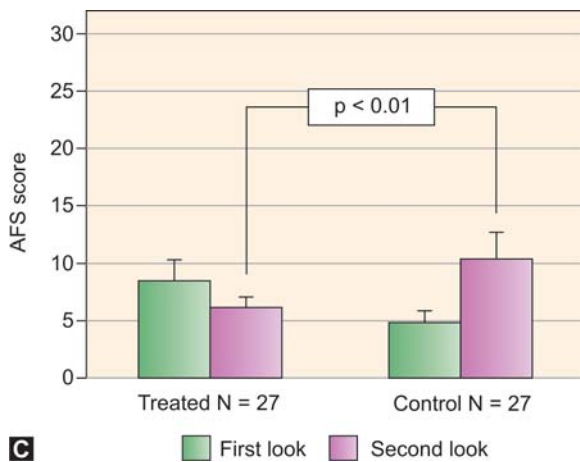


**Fig. 1:** Reduction of AFS adnexal adhesion score by using Oxiplex/AP Gel via laparoscopy. Patients undergoing conservative laparoscopic surgery had their adnexa covered with Oxiplex/AP Gel (15 ml) or served as surgery-only control. At the time of second look laparoscopy 6-10 weeks later, the adnexa coated with Oxiplex/AP Gel (n = 45) had a significantly (mean  $\pm$  SEM; P, 0.01). Lower adnexal AFS score to control adnexa (n = 41)



**A**

**B**



**C**

**Figs 2A to C (A)** Reduction of American Fertility Society (AFS) adnexal adhesion score in patients without endometriosis. **(B, insert)** Patients with stage I-IV endometriosis. **(C, insert)** Patients with stage I-III endometriosis. Adnexa from patients undergoing conservative gynecological surgery were coated with Oxiplex/AP Gel (15 ml) or served as surgery-only controls. Adnexal AFS adhesion scores were determined at the time of initial surgery as well as at second-look laparoscopy 6-10 weeks later (mean  $\pm$  SEM). Adnexa from patients undergoing adhesiolysis only who had no endometriosis (A), patients with AFS stage I-IV endometriosis (B), as well as from those patients with stage I-III endometriosis (excluding stage IV, C) coated with Oxiplex/AP Gel showed a significant improvement in adnexal AFS score compared to controls (P < 0.01)

endometriosis, Oxiplex/AP Gel worked well to prevent an increase in adhesion score. Oxiplex/AP Gel did not appear to provide that benefit to patients with grade four endometriosis (Data not shown).

Seeing the number of patients whose adhesion score shift to a better category of adnexal adhesion score after surgery, the individual patient benefit can be demonstrated.<sup>11</sup> For patients, the prognosis is worse if there is increase in adnexal adhesion score.

As shown in Table 1, the prognostic categories for minimal (0-5), mild (6-10), moderate (11-20) and severe (21-32) scores are provided for each of the patient group. 23 adnexa had a minimal base line adhesion score (Row-1) in the AP Gel/Oxiplex treatment group. 22 of these remained in the minimal group. One of them shifted to mild at second look. In this one patient, review of gel application showed that adnexal surgical sites were not covered by the gel at the end of the surgery. Hence it is not known what would have been in the second look adhesion score, if the adnexum was covered with gel in a similar manner to the other 22 adnexa of this category. In control population, at the initial surgery, 23 adnexa were in the minimal category. During second look, 13 remained unchanged, 7 mild, 1 moderate and 2 severe. All together 10 had shifted to higher category. These differences in shift analysis are significant ( $p < 0.01$ ).

The significant benefit of Oxiplex/AP Gel in reducing adhesions was shown by both a reduction in average AFS score as well as reduction in AFS prognostic category as a result of treatment ( $P < 0.01$  for both).

Four adnexa in the control group and 5 adnexa in the treatment group had adhesion scores in the mild category at the initial surgery. In the Oxiplex/AP Gel treated group, 1 had a worse score (moderate) at second look and 2 had a better adhesion score (minimal). In contrast to this, in the control group, all the four had worse adhesion category at the second look. 3 were moderate and 1 was severe. In the moderate group at initial surgery, out of 5 adnexa that received Oxiplex/AP Gel, 3 had a better adhesion score at second look (2 minimal and 1 mild) and 1 had a worse score. In control group, in moderate category at first surgery, out of 5, 4 adnexa had worse adhesion scores at second look (1 moderate and 4 severe).

In the treated adnexa with severe adhesion scores at first look, 2 had stage three and 6 had stage four endometriosis. At second look all these remained in severe category. At second look, of the 4 adnexa in the severe category that did not have endometriosis, 2 were in moderate group, 1 in mild and 1 in minimal group. At initial surgery in the control patients, 9 adnexa were in the severe group. Of these, 6 had stage four endometriosis and they remained in severe category at second look. The other 3 adnexa that were severe at the initial surgery and were not in patients with stage four endometriosis, better adhesion score in the second look was seen only in 1. The other 2 adnexa stayed severe. In the shift table, these changes were statistically significant ( $p < 0.01$ ).

From the use of Oxiplex/AP Gel, the number of individual adnexal adhesion scores (Table 2) that improved or stayed the same from first to second look laparoscopy versus those that

**Table 1:** Shift analysis (Cochran-Mantel-Haenszel statistic)

Baseline American Fertility Society (AFS) category	Total	Second-look AFS scores			
		Minimal (0-5)	Mild (6-10)	Moderate (11-20)	Severe (21-32)
<b>Treatment surgery + Oxiplex/AP Gel</b>					
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
<b>Total</b>	<b>45</b>	<b>27</b>	<b>5</b>	<b>4</b>	<b>9</b>
<b>Control: surgery only</b>					
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
<b>Total</b>	<b>41</b>	<b>13</b>	<b>7</b>	<b>6</b>	<b>15</b>

**Table 2:** Outcome of clinical trials using the adnexal adhesion score of the American Fertility Society (AFS) as established in 1988

	Individual AFS scores			AFS category		
	Improved or unchanged	Worsened	Total	improved or unchanged	Worsened	Total
Oxiplex	87% (39)	13% (6)	45	93% (42)	6% (3)	45
Control	32% (13)	68% (28)	41	56% (23)	44% (18)	41

worsened reveals a significant treatment benefit. At the time of second look, 87% of Oxiplex/AP Gel applied adnexa did not have a worse adhesion score in contrast to 32% of the control adnexa. Even when the individual adnexal adhesion scores are grouped by prognostic category (Table 2), the number of adnexa that improved or stayed the same from first look to second look laparoscopy versus those that shifted to a worse category also shows a significant treatment effect of Oxiplex/AP Gel. For example—During second look, 93% of the adnexa that received Oxiplex/AP Gel did not have a worse score in contrast to 56% of the control adnexa.

## DISCUSSION

During minimally invasive surgery, the most commonly used adhesion preventive devices cannot be applied or are difficult to apply. So in many surgical procedures, prophylaxis for adhesion prevention is not used. As a result Oxiplex/AP Gel was developed specifically for the needs of surgeons performing procedures that result in adhesion formation leading to failed surgical therapy.<sup>12</sup> For a gynecological surgeon, the challenges facing for an adhesion preventive device include ease of use and retention of the device at the site of application. To address these needs Oxiplex/AP Gel was specifically developed.

The polyethylene glycol and carboxymethylcellulose formulation is a transparent viscoelastic gel that is readily administered to the specific anatomical sites where there is concern for adhesion formation. The ease of use of viscoelastic gel includes single unit packaging stored at room temperature, which when opened delivers the sterile gel and applicator directly into the field of operation. The viscosity of the gel allows the surgeon to control directly the rate of Oxiplex/AP Gel delivery to the operation site. The flow of gel is automatically stopped by depressing the syringe. The gel which is residing within the applicator tube doesn't harden. This allows for the continued application of the viscoelastic gel at the convenience of the surgeon.

To maximise tissue adherence, Oxiplex/AP Gel was developed by complex of two polymers. The gel remains in its place due to its mucoadherent property.<sup>13</sup> This property allows the gel to remain in place even in gravitational dependent areas such as the anterior abdominal wall after removal of an omental adhesion, or even at the posterior surface of the uterus in case of myomectomy. In preclinical studies, a similar formulation of Oxiplex (Oxiplex/SP Gel) showed to be safe and effective in reducing adhesions to dura following spinal surgery.<sup>14</sup> Another clinical study done recently showed that patients with severe back pain and lower extremity weakness who had Oxiplex/AP Gel applied over their nerve roots following laminectomy or laminotomy had significantly reduced symptoms compared to surgery only (controls).<sup>15</sup> Oxiplex/AP Gel, which is specifically designed for use in the peritoneal cavity<sup>16</sup> was evaluated in women undergoing conservative gynecological surgery. In this case, the principle

investigators found that, with experience, a single layer of gel was sufficient enough to cover the adnexal surface and adjacent sites. In some cases, when multiple layers of gel were coated over one another, the weight of the excess gel overcame the innate tissue adherence resulting in falling of the gel from the surgical site. Typical volume of gel required to cover an adnexum was approximately 15 ml which was administered in approximately 90 seconds. It was easy to apply Oxiplex/AP Gel to adnexal surfaces including the ovarian fossa and between the ovary and mesosalpinx. The gel coverage facilitated the cessation of vascular oozing and thereby helping to prevent adhesion.

To protect the tissue during postsurgical repair, only a single layer of gel was sufficient. Within six weeks, prior to the second look laparoscopy, the gel was absorbed from the peritoneal cavity. In 4 cases, small collections (approximately 5×5 mm) of gelatinous material (presumably residual gel) were noted in areas deep in the cul-de-sac where intraperitoneal clearance have been affected particularly in cases of grade four endometriosis, or in areas where multiple layers of gel had been applied. In 2 cases, biopsies of these sites were consistent with the residual gel. There was no clinical significance of the residual gel. The residuum did not interconnect the tissue surfaces. It was not associated with any adhesions. It did not obstruct organ mobility.

## ADHESION REDUCTION

The reduction in postoperative adnexal adhesions demonstrates a clinically significant benefit of Oxiplex/AP Gel, a categorical reduction in adnexal adhesion and has been associated with better clinical outcomes.<sup>17</sup> Adhesion scoring is not only used for prognosis, but also to determine the therapy.<sup>18</sup> The US food and drug administration recently recommended that the AFS adnexal adhesion classification can be used as a clinical outcome measure in clinical studies of devices intended to reduce the postsurgical adhesion formation.

## CONCLUSION

Laparoscopic administration of viscoelastic gel was easy and had significant reduction in adnexal adhesions. The patients undergoing gynecological surgeries were benefited. Although it is reassuring to see gel persisting at the site of application, it is recommended to avoid excess gel application.

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