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PREVENTION OF ADHESIONS AFTER LAPAROSCOPIC OVARIAN DRILLING USING AUTO CROSS LINKED SODIUM HYALURONATE (GEL BARRIER)

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Abstract

The aim of the study was to evaluate the role of Hyacorp endogel® (cross linked gel barrier) in reduction of postoperative adhesions after laparoscopic ovarian drilling (LOD) for patients with polycystic ovary syndrome (PCOS). The exploratory clinical trial study was conducted at Obstetrics and Gynecology department, Alazhar University, Cairo, Egypt between March 2012 and May 2014. Sixty patients with PCOS were treated by LOD and were randomly allocated intraoperative to receive either the Hyacorp endogel®, (study group, n = 30) or Lactated ringer solution (LRS), (control group, n = 30). A second-look laparoscopy was performed after 24 weeks to evaluate incidence, site and degree of post-surgical adhesions. 14.3 % of patients in study group and 27.78 % of patients in control group showed pelvic adhesions at second look laparoscopy, but the difference was not statistically significant (P = 0.718). Mean total adhesion score was significantly lower in the study group than the control group (4.33 ± 2.02 Vs. 11.8 ± 6.22 with P = 0.030). Patients treated with the study material appeared to have a lower risk to develop post-operative adhesions when compared to the control group [RR = 0.51 (0.14/0.27), P = 0.718], but it was statistically non-significant. The application of Hyacorp endogel ® may reduce the severity of postoperative adhesions following laparoscopic ovarian drilling.

Keywords: PCO, Ovarian Drilling, Laparoscopy, Sodium Hyaluronate, Adhesions.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the leading cause of anovulation and represents a major cause of female infertility (Mitra et al., 2015). Laparoscopic ovarian drilling (LOD) is an alternative to ovulation induction with gonadotropins for polycystic ovarian syndrome (PCOS) patients unresponsive to clomiphene citrate. It is a quick, easy to perform, cost effective procedure and had a comparable ovulation and pregnancy rates to gonadotrophins. Also it has less morbidity and mortality rates (Flyckt and Goldberg, 2011; Arda et al., 2015; Arda et al., 2016).

It has the advantage of producing unifollicular ovulation without the risk of ovarian hyperstimulation

syndrome (OHSS) or multiple pregnancies (Balen, 2006). However, concerns about post-operative adhesions and diminished ovarian reserve due to tissue damage have been raised (Mercurio et al., 2008; Fernandez et al., 2011).

Adhesions are primarily defined as a condition in which bodily tissues that are normally separate grow together or a fibrous band of scar tissue that binds together normally separate anatomical structures (Mettler, 2014).

Post-surgical adhesions affect the quality of life of millions of people leading to severe morbidities. The incidence of postoperative adhesions after general abdominal or gynecological surgery ranges from 63% to 97% (Menzies and Ellis, 1990). Although most of patients remain asymptomatic, a considerable number experience serious complications, including bowel obstruction (Hawthorn et al., 2003), female secondary

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infertility (Hershlag et al., 1991), chronic pelvic pain and difficulties in reoperation (Miller, 2000).

Thus, although the current strategy for reducing the formation of postoperative adhesions generally consists of improving surgical technique (minimizing invasiveness, surgical trauma, bleeding and ischaemia), the prevention of adhesions using additional, more effective tools would be of tremendous benefit (Mais et al., 2006).

Several alternative strategies have been proposed with the aim of reducing the incidence of postoperative adhesions. Pharmacological agents, including steroids, antihistamines and heparin, have been used without any clearly demonstrated advantage (Watson et al., 2000).

Solutions of Hyaluronic acid (HA) - a naturally occurring water soluble polysaccharide-have viscoelastic properties that have led to an interest in developing applications of Hyaluronic acid in surgical procedures for prevention of post-surgical adhesions (Renier et al., 2005; Chen and Abatangelo, 1999).

The aim of this work is to evaluate the role of auto cross linked sodium hyaluronate in reduction of development of new post-operative adhesions in PCO women undergoing laparoscopic ovarian drilling.

PATIENTS AND METHOD

This clinical trial was carried out at Alazhar University Hospitals between March 2012 and May 2014, sixty PCO women with primary infertility were recruited with the following criteria; age < 35 years, BMI < 30 kg/m², had normal basal hormonal profile, had ultrasound picture of PCO, had no history of pelvic or abdominal surgery and had no other pelvic lesions. All women were underwent laparoscopic ovarian drilling and were randomly allocated intra-operatively (randomization was done based on computer randomization programs) into 2 groups; group 1 (study group, n = 30) who received the auto cross linked sodium hyaluronate (Hyacorp endogel, Bioscience GmbH, Germany) which is an absorbable anti-adhesive barrier gel helps to prevent post-operative adhesions formation distilled on the ovaries after drilling. It is a biodegradable barrier that appears to have efficacious anti-adhesive action. For each patient, 5 ml of the endogel was applied on the surface of each ovary after drilling. In group 2 (control group, n = 30), Lactated ringer solution (LRS) was instilled. The study was conducted after informed consent from all patients enrolled in the study. Both groups were underwent a second look laparoscopy 6 months after the initial procedure for assessment of adhesions. Pregnant women were excluded from the second look laparoscopy in both groups.

Adhesions were assessed according to: site, extent and severity using modified American Fertility Society (mAFS) scoring system, which assess the incidence and severity of adhesion in 24 anatomical sites (Di Zerega et

al., 2002) (table 1).

Statistical analysis

This study was an exploratory trial. So, the sample size was not derived from statistical considerations. Descriptive statistics and inferential methods were used to analyze data using the test of hypothesis with the significance level set at 5%.

The primary outcome will be a total adhesion score using the modified American Fertility Society (m AFS) Scoring System applied to 24 anatomical sites. Scores from all potential adhesion sites will be averaged (divided into 24) to yield a total adhesion score, ranging from 0 to 16. The secondary outcome will be proportion of sites with adhesions, a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. Additional secondary variables will include the extent and severity of all categories of adhesions.

Comparison of quantitative data was done using the independent t test $\{t = (mA - mB) / \sqrt{(s^2/nA + s^2/nB)}\}$, where **mA** and **mB** represent the means of groups A and B, respectively and **nA** and **nB** represent the sizes of group A and B, respectively. **s²** is an estimator of the common variance of the two samples or using the Mann Whitney test (U) when appropriate.

$$U = n_1 n_2 + \frac{n_2 (n_2 + 1)}{2} - \sum_{i=r_1+1}^{n_2} R_i$$

Where:

N1 = sample size one

N2 = Sample size two

Ri = Rank of the sample size

Qualitative data were compared using the Chi-square test (χ^2). The formula for chi-square is: $\chi^2 = \sum (E-O)^2 / E$, where E is the expected values and O is the observed values. The sigma sign means that everything that follows is summed. So '(expected - observed) ² / expected' is calculated for each cell in the contingency table (Table 2).

P-value was significant if ≤ 0.05 . Randomization was done using computerized randomization programs.

RESULTS

Table 2 shows that cases in both groups are comparable as regard; age, BMI, duration of infertility and basal hormonal profile.

Table 3 showed that incidence of post-operative adhesions was non-significantly higher in the control group when compared to the study group, Figure 1.

Table 4 showed the sites affected by adhesions in all patients (3 in the study group and 5 in the control group divided by the total number of patients in each group after excluding the dropped out and pregnant cases) at

Table 1. Modified American Fertility Society (mAFS) scoring system

Anatomical sites evaluated:		
Anterior peritoneum (Caudal, right cephalad, left cephalad, incision), Uterus (Anterior, posterior), Omentum, Bowel (Small, large right, large left, rectosigmoid large), Cul-de-sac, Pelvic side wall (Right, left), Right ovary (Lateral, medial, fossa), Left ovary (Lateral, medial, fossa), Fallopian tube (Right, left), Ampulla (Right, left).		
Extent of adhesions		
Localized (< 1/3 site covered)	Moderate (1/3- 2/3 site covered)	Severe (> 2/3 site covered)
Severity of adhesions		
Mild (Filmy and avascular)		Severe (Organized, dense and vascular)
MAFS score system		Score
No adhesions		0
Severity	Extent	
Mild	Localized	1
Mild	Moderate	2
Mild	Extensive	4
Severe	Localized	4
Severe	Moderate	8
Severe	Extensive	16

Table 2. Demographic characteristic and hormonal profile for both groups

Variables (mean)	Study group (n = 30)	Control group (n = 30)	P Value
Age (years)	28.27 ± 3.61	29.97 ± 3.76	0.079
BMI (kg/m ²)	27.63 ± 4.35	26.93 ± 5.90	0.603
Infertility duration (years)	5.97 ± 3.04	6.28 ± 3.92	0.153
Day 3 FSH (IU/L)	6.23 ± 1.58	6.59 ± 2.54	0.509
Day 3 LH (IU/L)	7.26 ± 1.93	6.85 ± 2.22	0.317
Day 3 E2 (pg/ml)	47.00 ± 16.55	42.94 ± 14.25	0.796

Table 3. Comparison between both groups as regard adhesions

Adhesions	Study group		Control group		Chi- square test	
	No.	%	No.	%	χ²*	P- value
Patients with adhesions	3	14.29	5	27.78	0.691	0.718
Patients free of adhesions	18	85.71	13	72.22		
Total	21	100	18	100		

*Chi-square test was used for comparison.

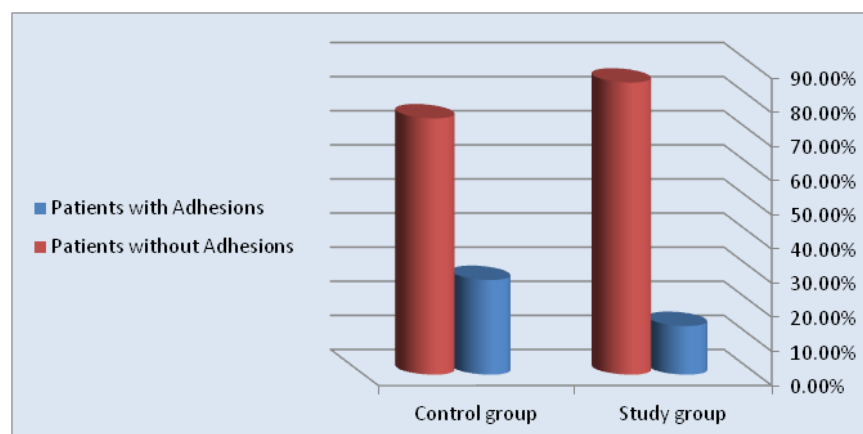


Figure 1. Bar chart shows the percentages of patients with and without adhesions after laparoscopic ovarian drilling in both groups.

Table 4. Sites of adhesions in both groups at second look laparoscopy

Site of adhesion	Study Group (n = 21)		Control Group (n= 18)	
	No.	%	No.	%
Cul-de-sac (posterior)	0	0.0	1	5.6
Lt ovary	3	14.1	5	27.5
Lt tube	0	0.0	3	16.5
Rt ovary	2	9.4	4	22
Rt tube	1	4.8	1	5.5

Table 5. Comparison between both groups as regard site and severity of adhesion

Site of adhesion	Severity	Study group		Control group		Chi-square test P- value	Significance
		No.	%	No.	%		
Rt ovary	Mild	2	9.5	1	5.6	0.04	Significant
	Severe	0	0.0	3	16.7		
Rt tube	Mild	1	4.8	0	0.0	0.16	NS ¹
	Severe	0	0.0	1	5.6		
Lt ovary	Mild	2	9.5	5	27.8	0.02	Significant
	Severe	1	4.8	0	0.0		
Lt tube	Mild	0	0.0	3	16.1	0.19	NS
Cul-de-sac	Severe	0	0.0	1	5.6	0.34	NS

NS¹, non-significant

second look laparoscopy. Posterior cul-de-sac (0% and 5.6%), Lt Ovary (14.1% and 27.5), Lt Tube (0% and 16.5%), Rt ovary (9.4% and 22%) and Rt tube (4.8% and 5.6%) in study and control groups respectively.

Table 5 showed that there was significant difference between both groups as regard severity of adhesions at ovarian sites while the difference was non-significant at tubal and cull-de-sac sites.

DISCUSSION

Post-operative peritoneal adhesions are common and significant problem of gynecological surgery that affecting the quality of life of large number of ladies leading to much undesirable morbidities. The major strategies for prevention of adhesions are optimization of surgical technique and using anti adhesive agents (pharmacological agents or barriers). In our study we tried to investigate the efficacy of Hyaluronic acid gel barrier in preventing post-operative adhesions after laparoscopic ovarian drilling for PCO ladies.

In the current study, patients in both groups were comparable as regard Age, BMI, Duration of infertility and basal hormonal profile (table 2). Of those 60 patients, five patients in the study group and seven patients in the control group were dropped out during the follow-up period after the initial laparoscopy and before scheduled time (24 weeks after laparoscopic ovarian drilling) for the second look laparoscopy due to personal reasons. Also, four patients in the study group and five patients in the control group got pregnant spontaneously

after laparoscopic drilling and excluded from second look laparoscopy. Thus, 39 patients completed the study and underwent second- look laparoscopy, 21 in the study group and 18 in the control group. No complications or adverse events were reported in both groups, after LOD or at second-look laparoscopy.

In the current study (at second look laparoscopy), although a lower number of patients whom developed adhesions was found in the study group (3 out of 21 cases, 14.2%) compared with the controls (5 out of 18 cases, 27.7%), the difference was statistically non-significant ($P = 0.718$) (table 3, figure 1).

Patients in the study group appeared to have a lower relative risk of formation of post-operative adhesions when compared with the control group [RR = 0.51 (0.14/0.27), $P = 0.718$]; i.e., adhesions were reduced by about 49 % when using the endogel. However, this observation was not statistically significant. The lack of statistical significance may be due to the smaller number of patients who completed the study.

Mean total adhesion score at second-look laparoscopy was lower in the study group when compared to the control group (mean \pm SD, 4.33 \pm 2.02 vs. 11.8 \pm 6.22 with $P = 0.030$) for both groups respectively, this finding support the idea suggesting that the application of Hyacorp endogel ® may significantly reduce the severity of postoperative adhesions following laparoscopic ovarian drilling (table 6). Adhesions were noticed more at the left and right ovarian locations in both groups (14.1 % vs. 27.5% in the left ovary) and (9.4% vs. 22% in the right ovary) for the study and control groups respectively (table 4).

As regard severity of adhesions, severe adhesions at the

Table 6. Comparison between both groups as regard total score of adhesion

Total score	Range	Mean	± SD	t-test	p-value	Significance
Study group	2- 6	4.33	2.08	4.837	0.030	Significant
Control group	6-19	11.80	6.22			

right ovary were significantly higher in the control group when compared with the study group (16.7% vs. 0%, $p = 0.04$), while mild adhesions at the left ovary were significantly higher in the control group when compared with the study group (27.8% vs. 9.5 %, $p = 0.02$). At the other sites (fallopian tubes and cal-de-sac), the difference was statistically non-significant (table 5).

Our results are in agreement with Mais et al. 2006, who conducted a randomized trial to assess the benefits of auto-crosslinked hyaluronan gel in preventing post-operative adhesions and reported that adhesion-free patients after laparoscopic myomectomy were greater in the treatment group but the difference was not statistically significant. Also, in agreement with Litta et al. 2013 who evaluated the incidence and severity of post-operative adhesions when hyaluronic acid gel was used and demonstrated that, the incidence of postoperative adhesions was the same in both groups (HA gel and control groups), but anatomically significant adhesions and site-specific modified score was significantly reduced in hyaluronic acid gel group when compared to the control group (31.8% vs 54.6% and 1.05 ± 1 vs 2.27 ± 2.5 , respectively) and with Bosteels et al. 2014 who conducted a meta-analysis to assess the benefit of the use of auto-cross-linked hyaluronic acid gel in women undergoing operative hysteroscopy; they concluded that the use of the gel was associated with a lower mean adhesion score at second-look hysteroscopy after 3 months. When de novo adhesion formation is observed at second-look hysteroscopy, there are more mild adhesions and less moderate or severe adhesions by using an anti-adhesion gel after operative hysteroscopy.

On the other hand, Mais et al. 2012 conducted a meta-analysis using five RCTs studied the use of auto cross-linked hyaluronan gel for the prevention of postoperative adhesions in gynecological surgery. They concluded that, the incidence of postoperative adhesions in patients who received auto hyaluronic acid gel was significantly lower than in patients who underwent standard surgery only. The gel had prevented both adhesions after laparoscopic myomectomy (OR 0.248, 95% CI 0.098, 0.628) and intrauterine adhesions after hysteroscopic surgery (OR 0.408, 95% CI 0.217, 0.766). Also, Zou et al. 2015 evaluated the benefits of hyaluronic acid gel versus insertion of folly's catheter in prevention of intrauterine adhesions after operative hysteroscopic adhesiolysis for moderate to severe adhesions and reported that HA gel was effective in reduction of intra uterine adhesions (76% vs. 48%, $P < 0.001$) with significant lower mean total adhesion score (2.1 ± 1.1 vs. 3.7 ± 2.5 , $P < 0.001$).

Again the non-significant difference between study and treatment groups may be due to the small number of

patients who completed the study and so another large randomized study was recommended.

After an observational study, Mettler, 2014 concluded that applying the site specific, hyaluronic acid based barrier, Hyacorp endogel' proved to be satisfying and helpful in preventing fibrous adhesions between pelvic organs and the pelvic side wall during laparoscopic gynecological surgical procedures.

Any product without side effects that diminishes postsurgical adhesions is welcome. Hyalobarrier and definitely HYAcorp endo gel are reasonably priced and effective substances that can be easily applied during endoscopic surgery. They are at present tested in many surgical facilities (Ruiz et al., 2013; Practice committee of ASRM, 2013)

CONCLUSION

Development of post-operative adhesion is a widespread consequence of surgical trauma and healing following open or laparoscopic gynecological surgery and is associated with significant complications. At present, the main strategy to avoid formation and reformation of adhesions is focused on the use of careful surgical techniques and anti-adhesive agents. Auto cross linked hyaluronic acid gel barrier appeared to be a reasonable, effective and easily applied with high safety profile substance that can help in reducing formation of adhesions after laparoscopic ovarian drilling for PCOS patients.

REFERENCES

- Arda I, Huseyn E, Sma L, Sma LY, Den ZF, Orhan C, Kemal P, Hakan G (2015). Rectal Lymphoma- Kolon Rektum Hast Derg. 25: 106-108.
- Arda I, Ismail D, Ismayil Y, Huseyin E (2016). Effectiveness of Manual Knotting at Laparoscopic Appendectomy. Gazi Medical Journal. 27(1):19-20.
- Balen A (2006). Surgical treatment of polycystic ovary syndrome. Best Pract Res Clin Endocrinol Metab. 20:271-280.
- Bosteels J, Weyers S, Mol BWJ, D'Hooghe T (2014). Anti-adhesion barrier gels following operative hysteroscopy for treating female infertility: a systematic review and meta-analysis. Gynecol Surg.11:113-127.
- Chen WY, Abatangelo G (1999). Functions of hyaluronan in wound repair. Wound Repair Regen. 7, 79-89.
- Di Zerega GS, Verco SJS, Young P, Kettle M, Kobak W, Martin D, Sanfilippo J, Peers EM, Scrimgeour A, Brown CB (2002). A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. Human Reproduction. Vol 17, No. 4 pp. 1031-1038.
- Fernandez H, Morin-Surruca M, Torre A, Faivre E, Deffieux X, Gervaise A (2011). Ovarian drilling for surgical treatment of

- polycystic ovarian syndrome: a comprehensive review. *Reprod Biomed Online*. 22:556–568.
- Flyckt RL, Goldberg JM (2011). Laparoscopic Ovarian Drilling for Clomiphene-Resistant Polycystic Ovary Syndrome. *Semin Reprod Med*. 29(2): 138-146.
- Hawthorn RJS, Lower A, Clark D, Knight AD, Crowe AM (2003). Adhesion-related readmissions following gynecological laparoscopy in Scotland, an epidemiological study of 24,046 patients. *Reviews in Gynecological Practice*. 3, 1.
- Hershlag A, Diamond MP, Decherney AH (1991). Adhesiolysis. *Clinical Obstetrics and Gynecology*. 34, 395-402.
- Litta P, Pluchino N, Freschi L, Borgato S, Angioni S (2013). Evaluation of adhesions after laparoscopic myomectomy using the Harmonic Ace and the auto-crosslinked hyaluronan gel vs Ringer's lactate solution. *Clin Exp Obstet Gynecol*. 40 (2):210-4.
- Mais V, Bracco GL, Litta P, Gargiulo T, Melis GB (2006). Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study *Human Reproduction*. Vol.21, No.5 pp. 1248–1254.
- Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB (2012). Efficacy of auto-crosslinked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy: a systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol*. Jan; 160(1):1-5.
- Menzies D, Ellis H (1990). Intestinal obstruction from adhesions—How big is the problem? *Annals of the Royal College of Surgeons of England*. 72, 60-63.
- Mercorio F, Mercorio A, Di Spiezio SA, Barba GV, Pellicano M, Nappi C (2008). Evaluation of ovarian adhesion formation after laparoscopic ovarian drilling by second-look minilaparoscopy. *Fertil Steril*. 89:1229–1233.
- Mettler L (2014). Effect of cross linked sodium hyaluronate in adhesion reduction within the gynecologic surgical window. *L. Open Journal of Obstetrics and Gynecology*. 4: 120-129.
- Miller CE (2000). Myomectomy; Comparison of open and laparoscopic techniques. *Obstet Gynecol Clin North Am*. 27,407–420.
- Mitra S, Nayak PK, Agrawal S (2015). Laparoscopic ovarian drilling: an alternative but not the ultimate in the management of polycystic ovary syndrome. *J Nat Sci Biol Med*. 6(1):40-8.
- Practice Committee of American Society for Reproductive Medicine in Collaboration with Society of Reproductive Surgeons (2013). Pathogenesis, consequences, and control of peritoneal adhesions in gynecologic surgery: A committee opinion. *Fertility and Sterility*, 99, 1550.
- Renier D, Bellato PA, Bellini D, Pavesio A, Pressato D, Borriero A (2005). Pharmacokinetic behaviour of ACP gel, an autocrosslinked hyaluronan derivative, after intraperitoneal administration. *Biomaterials*. 26:5368–74.
- Ruiz A, Flanagan CE, Masters KS (2013). Differential support of cell adhesion and growth by copolymers of polyurethane with hyaluronic acid. *Journal of Biomedical Materials Research, Part A*, 101, 2870-2882.
- Watson A, Vandekerckhove P, Lilford R (2000). Liquid and fluid agents for preventing adhesions after surgery for subfertility. *Cochrane Database Syst Rev*. CD001298.
- Zou F, Xiao S, Wan Y, Ye M, Deng H, Ma J, Wei Y, Tan C, Xue M (2015). Prevention of intrauterine adhesion with auto-crosslinked hyaluronic acid gel: a prospective, randomized, controlled clinical study. *Zhonghua Fu Chan Ke Za Zhi*. 50(1):32-6.

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