**Randomised controlled trial of Hyalobarrier® versus no Hyalobarrier® on the ovulatory status of women with peri-ovarian adhesions: a pilot study**

Ying Cheong1,2, Sarah Bailey1,2, Jane Forbes1

1Southampton University Hospital Foundation NHS Trust; 2Human Development and Health, Faculty of Medicine, University of Southampton, UK

Corresponding author: Ying Cheong. Email y.cheong@soton.ac.uk

Abstract

Introduction

Peri-adnexal adhesions are known to contribute to subfertility. The restoration of the tubo-ovarian anatomy is one the key principles in reproductive surgery, and this involves adhesiolysis. However, adhesion formation/reformation is very common after peri-ovarian adhesiolysis. It is not known if the application of Hyalobarrier®, an anti-adhesion gel around the adnexal post-surgery influence ovulatory status. The study is a randomised controlled pilot study (RCT) randomising women into the application of Hyalobarrier® versus no Hyalobarrier® at the time of laparoscopy, where post-surgical ovulatory status and pregnancy rates were evaluated.

Methods

This was a pilot randomised controlled trial where women were recruited from the gynaecological and subfertility clinic who were deemed to require an operative laparoscopy. If intra-operatively they were found to have peri-ovarian adhesions, they were randomised into having adhesiolysis with and without usage of Hyalobarrier®. Demographic details and intraoperative details including the severity, extent and the ease of use of Hyalobarrier® was recorded. Prior to the surgery, and post operatively, the participants had their serum hormonal status (Day 2 FSH, LH and Day 21 progesterone) evaluated. Post operatively, they underwent a follicular tracking cycle at 3 months.

Results

15 women were randomised into use of Hyalobarrier® (study group), 15 into the no Hyalobarrier® group (control group) between December 2011- January 2014. There was no difference in the patient characteristics in terms of age, BMI, the number of previous pregnancies, the extent, site and severity of adhesions between the two groups. There was no significant difference between the study versus control groups in terms of the hormonal profile (Day 2 FSH and D21 progesterone) before or after surgery. The 3-month post-operative Day 10-12 follicular tracking findings and endometrial thickness were similar between the study and control groups. Four women in the study group (24%) and one in the control group were pregnant cumulatively over 2 years. All the pregnant patients were randomised into the Hyalobarrier® group. The majority of surgeons reported that the Hyalobarrier® Gel Endo was easy to apply.

Conclusion

The use of Hyalobarrier® post salpingo-ovariolysis did not influence follicular development as inferred from the results of the Day 21 progesterone and folliculogram on Day 10-12 3-month post-surgery.

Introduction

Peri-adnexal adhesions are adhesions which enveloped the fimbrae ends, the Fallopian tubes and / or ovaries. These adhesions can develop post-surgically, after infection and inflammation secondary to pelvic inflammatory disease or as a consequence of other intra-abdominal infective source. Peri-adnexal adhesions contribute to subfertility by a combinations of ways; namely by the mechanical distortion of the tubo-ovarian anatomy thereby interfering with the transport of the ovum into the Fallopian tube or the disruption of blood supply to the ovary and its follicular development [1-4]. Indeed, it has been observed that women with peri-ovarian adhesions are significantly more prone to have unruptured follicles [5].

The restoration of the tubo-ovarian anatomy is one the key principles in reproductive surgery, and this involves adhesiolysis. However, adhesion formation/reformation is very common after peri-ovarian adhesiolysis (40%)[6]. The natural anatomical position and density of ovaries precludes hydro floatation mechanism as an effective adhesion prevention strategy after adnexal surgery (Carpenter and Kent 2010). Hence, consideration is required for the application of other forms of adhesion prevention agents such as hyaluronic gel based products.

Hyalobarrier® Gel Endo is a sterile, transparent and highly viscous gel that forms a barrier to prevent or reduce post-surgical adhesions. A recent randomised controlled trial examining if the instillation of Hyalobarrier® intrauterine after the evacuation of products of conception showed a significant reduction in the formation of intrauterine adhesions post-operatively at second look hysteroscopy [7]. The gel is composed of highly purified, auto-crosslinked polymers of hyaluronic acid. Hyaluronic acid is a main component of the connective tissue in the human body. When applied between tissue surfaces, it ensures that adhesive surfaces of the peritoneum in the ovarian fossae are separated and thus is theoretically effective in peri-ovarian post-operative adhesion prevention. Within the peritoneum, this gel-based product is required to be placed on and adjacent to the ovaries and Fallopian tubes, and the immediate impact on ovulatory function and subsequent reproductive outcome is unclear.

The study is a randomised controlled pilot study (RCT) randomising women into the application of Hyalobarrier® versus no Hyalobarrier® at the time of laparoscopy once surgeon confirmed the presence of salpingo-ovarian adhesions and proceeded to perform salpingo-ovariolysis. The ovarian function of women with peri-ovarian adhesiolysis who had Hyalobarrier® as an anti-adhesion barrier instilled and those who did not was compared. The clinical pregnancy rate of the two groups of women were also evaluated at 2 years post operatively.

**Methods**

This was a pilot randomised controlled trial where women were recruited from the gynaecological and subfertility clinic who were deemed to require an operative laparoscopy. If intra-operatively they were found to have peri-ovarian adhesions, they were randomised into having adhesiolysis with Hyalobarrier® (study group) and without usage of Hyalobarrier® (control group).

The inclusion criteria were 1) Age 18-38; 2) Women were undergoing operative laparoscopy for gynaecological pathology, with possible peri-ovarian adhesions. The exclusion criteria were the 1) Presence of malignancies or a history of malignancies; 2) Women on medications that affected ovulation and 3) Women with known conditions that resulted in anovulation (PCOS, Pituitary causes).

The method of conduct of this RCT is similar to studies previously conducted by our group[8]. Randomisation was performed using computer generated random numbers and the concealed, opaque unlabeled envelope was opened after it had been determined that the patient met the intra-operative criteria. The patients were blinded to the allocation of treatment and the assessor during follow up was blinded to the treatment. The assessor who administered the questionnaires and recruited the patients was the research nurse who did not have prior knowledge of what type of surgery the patients underwent. Consent was obtained prior to any baseline assessments. The operation notes were stored in a sealed enveloped within the patient notes and not accessed except during an emergency. In the latter case, the data would be used to the point of unblinding. The randomisation code was broken at the end of the follow up period and patients who wished to know were informed of their treatment groups.

Laparoscopic surgeons who were skilled in advanced laparoscopy performed the surgery. Entry into the abdomen was either via the traditional Veress needle or a modified Hasson’s technique of open entry. CO2 was used for creating a pneumo-peritoneum of 20 mmHg before a 10 mm trocar was inserted into the intra-umbilical incision. Two or three more lateral ports were inserted depending on the site and extent of surgery. During surgery, the principles of microsurgery were followed, including meticulous haemostatic control and usage of constant irrigation to prevent tissue desiccation. Hyalobarrier® was applied to women randomized intra-operatively to the study group and no Hyalobarrier® was applied to the group randomized to the control group. 10 mls of Hyalobarrier® Gel Endo was applied using the standard applicator in the commercial pack over the operative site(s). A short questionnaire on the ease of use of the Hyalobarrier® was completed by the surgeon post operatively.

The patients’ histories, clinical examination and operative findings were documented on standard proforma. The extent, severity and site of adhesions was noted and the completeness of adhesiolysis was documented. The extent of the adhesions was defined as no adhesions, mild (adhesions covering <26% of total area), moderate (adhesions covering 26-50% of total area) and severe (adhesions covering >51% of total area). The severity of adhesions was defined as no adhesions, mild (filmy and avascular adhesions), moderate (some vascularity and/or dense adhesions), and severe (cohesive) adhesions. All patients’ data and including hormonal and follicular tracking results were entered into a computerised database. Complications during and after the surgery were documented on standard proforma sheets.

Prior to the surgery, and post operatively, the participants had their serum hormonal status (Day 2 FSH, LH and Day 21 progesterone) evaluated. Post operatively, they underwent a follicular tracking cycle at 3 months. Ovulation was compared as a continuous outcome of day 21 progesterone levels with follicular scan performed on day 10-12 used as supportive evidence. The patient flow of this trial is as per Figure 1.

Statistical analysis

Given that adhesion reformation is significant after adnexal surgery (up to 90%), taking the mean of day 21 progesterone (+/-s.d.) for the control group to be 33 (7) nmol/l and the study group to be 51 (15.7) (Hamilton et al, 1986), the sample size for each group required to show a statistical significance at p=0.05 level between the study and control groups was calculated to be n=15 (total sample size = 30).

The outcome measures were post operative Day 2/3 FSH, LH, Day 21 progesterone, evidence of follicular development during follicular tracking at D10-14 and clinical pregnancy defined as the presence of fetal heart at the 6-week scan.

The ethics number of this study was 11/H0504/6 and the ISRCTN number was ISRCTN1833588. The data analysis was performed using SPSS. T-test comparisons will be used for continuous variables, and chi-2 for discrete variables.

This research conformed to the CONSORT guidelines.

**Results**

A total of43 women were screened, 15 randomised into use of study group, 15 into the control group between December 2011- January 2014). There was no difference in the patient characteristics (Table 1-3) in terms of age, BMI, the number of previous pregnancies, the extent, site and severity of adhesions between the two groups. None of the patients had endometriosis.

There was no significant difference in the mean +/- s.d between the study versus control groups in terms of the hormonal profile (Day 2 FSH and D21 progesterone) before or after surgery (Table 3). The 3-month post-operative Day 10-12 follicular scan showed similar development of mature follicles in the study group (mean diameter of follicle 18.1+/- 3.9mm) and the control group (mean diameter of follicle 19.8 +/- 5.6mm). There was also no difference in the endometrial thickness in the study (10.4 +/- 2.2 mm) versus the control group (8.7 +/- 0.6mm) at the 3-month scan post operatively.

Four women were pregnant in the study group (24%), one in the control group cumulatively over 2 years. All the pregnant patients were randomised into the study group; one patient underwent a successful IVF cycle, the other 3 patients fell pregnant spontaneously. In the control group, 2 patients underwent IVF but were not pregnant at the conclusion of this study. There was one woman with spontaneous pregnancy.

The majority of surgeons reported that the Hyalobarrier® Gel Endo was easy to apply. There was one questionnaire which was not returned.

**Discussion**

The use of Hyalobarrier® post salpingo-ovariolysis did not influence follicular development as inferred from the results of the Day 21 progesterone and folliculogram on Day 10-12 3-month post-surgery. This finding will need to be confirmed in larger studies, however, preliminary data suggests that the application of the Hyalobarrier® is not detrimental to follicular development as denoted by follicular scan and hormonal evaluation post operatively.

Reproductive surgeons and gynaecologists are often confronted with the conundrum of whether or not to remove adhesions around the adnexal area involving the Fallopian tubes and ovaries, in the presence of apparently patent Fallopian tubes. This dilemma is in part resolved with the advent of in-vitro fertilization (IVF) technology, where fully functional Fallopian tubes are not required for conception, and hence intra-operatively, if IVF was thought to be a viable option for the patient, that their adnexal adhesions are often left unlysed to save operative time and unnecessary operative complications. Unfortunately, whilst IVF offers a real and tangible option for a successful conception, the pregnancy rate per cycle is stagnated at around 30% per cycle (HFEA). In vast majority of regions in the United Kingdom, only one cycle of IVF is publicly funded. The cost of a private cycle of IVF often prohibit significant number of patients accessing this treatment for conception. This means that in real terms, about two-thirds of patients who did not manage to achieve a pregnancy after their IVF treatment will continue to suffer from infertility.

Traditionally in reproductive surgery, adnexal adhesions can be dealt with by adhesiolysis. It has been reported that the cumulative pregnancy rate 1 year after adhesiolysis can be as high as 67% although a substantial number of patients were observed to have adhesion reformation at second-look laparoscopy [9] but the increased risk of ectopic pregnancy remains high, especially if salpingostomy was also performed [10].

However, there is very little data on the use of these agents on fertility and pregnancy outcomes whether when applied intra-abdominally or intra-uterine [11]. Very often, randomised controlled trials on these agents evaluate end-points pertaining to adhesion reformation rather than pregnancy outcomes [12]. No studies have examined the post-surgical ovulatory status, endometrial thickness and the clinical pregnancy rates after application of the anti-adheison gel around the adnexal region (s). Our study suggests that there is no difference between the ovulatory status and endometrial development of women who had the Hyalobarrier® gel applied intra-operatively versus those who had not as observed from day 21 progesterone hormonal profile and follicular tracking scans performed in 3 months post operatively.

Whilst this study did not provide second look adhesion formation data, adhesion formation post application of the Hyalobarrier® gel has been evaluated after other forms of gynaecological surgery [13, 14] with some evidence of benefit. As the anti-adhesion gel is easy to use, surgeons should consider the application of anti-adhesion treatment around the adnexal region after salpingo-ovariolysis and adhesiolysis in relation to adhesive pelvic disorders [15, 16] to reduce the incidence of post-operative adhesions.

Acknowledgements

Funding

This study was an investigator led study funded by Nordic Pharma. Sponsorship for this study and article processing charges was funded by Nordic Pharma.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. YC conceived the idea, design the study, analysed the data, wrote the manuscript. SB and JF conducted the study, wrote and edited the manuscript.

Disclosure

Ying Cheong is the recipient of the Nordic grant for this study. This study was an investigator led study with the support of an education grant from Nordic Pharma. Sarah Bailey and Jane Forbes has nothing to disclose.

Compliance to Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

 Figure 1. Flow diagram showing the patient flow of the trial.

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient characteristics** | **Hyalobarrier®**  **(n=15)** | **No Hyalobarrier®**  **(n=15)** | **Significance** |
| Age (mean +/- s.d) | 32.7 +/- 4.7 | 31.5 +/- 3.8 | ns |
| BMI (mean +/- s.d) | 23.4 +/- 2.8 | 24.0 +/- 3.9 | ns |
| Number of previous surgeries (mean +/-range) | 0.8 (0-5) | 0.8 (0-4) | ns |
| Number of previous pregnancies (mean +/- range) | 0.9 (0-4) | 1.1 (0-9) | ns |

Table 1. Comparison of characteristics of patients between the study (Hyalobarrier®) and control (no Hyalobarrier®) groups

|  |  |  |  |
| --- | --- | --- | --- |
| **Adhesion sites** | **Hyalobarrier®**  **(n=15)** | **No Hyalobarrier®**  **(n=15)** | **Significance** |
| Bladder | 2 | 2 | ns |
| Posterior uterus | 3 | 2 | ns |
| Adnexa adhesions | 51 | 53 | ns |

Table 2. The number of patients with adhesions at the various sites within the pelvis.

|  |  |  |
| --- | --- | --- |
| **Adhesion severity and extent** | **Hyalobarrier®**  **(n=15)** | **No Hyalobarrier®**  **(n=15)** |
| Mild | 12 | 7 |
| Moderate | 1 | 8 |
| Severe | 2 | 0 |

Table 3. Severity and extent of adhesions in the comparison groups.

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient Characteristics** | **Hyalobarrier®** | **No Hyalobarrier®** | **Significance** |
| Pre-surgery D2 FSH | 7.2 +/- 2.4 | 6.24 +/- 1.5 | 0.22 |
| Pre-surgery D21 progesterone | 27.3 +/- 14.8 | 32.2 +/- 17.5 | 0.31 |
| Post-surgery FSH | 6.2 +/- 1.7 | 4.5 +/- 1.0 | 0.19 |
| Post-surgery D21 progesterone | 17.4 +/- 13.3 | 24.1 +/- 11.3 | 0.37 |
| Post-surgery Day 10-12 follicular scan | 18.1 +/- 3.9 | 19.8 +/- 5.6 | 0.78 |
| Post-surgery Endometrial thickness | 10.4 +/-2.2 | 8.7 +/- 0.6 | 0.28 |

Table 4. Hormonal and ultrasound results in the Hyalobarrier® and no Hyalobarrier® groups.

**Reference:**

1. Caspi, E. and Y. Halperin, *Surgical management of periadnexal adhesions.* Int J Fertil, 1981. **26**(1): p. 49-52.

2. Mahadevan, M.M., et al., *The effects of ovarian adhesive disease upon follicular development in cycles of controlled stimulation for in vitro fertilization.* Fertil Steril, 1985. **44**(4): p. 489-92.

3. Bowman, M.C., I.D. Cooke, and E.A. Lenton, *Investigation of impaired ovarian function as a contributing factor to infertility in women with pelvic adhesions.* Hum Reprod, 1993. **8**(10): p. 1654-6.

4. Nagata, Y., et al., *Peri-ovarian adhesions interfere with the diffusion of gonadotrophin into the follicular fluid.* Hum Reprod, 1998. **13**(8): p. 2072-6.

5. Hamilton, C.J., J.L. Evers, and H.J. Hoogland, *Ovulatory disorders and inflammatory adnexal damage: a neglected cause of the failure of fertility microsurgery.* Br J Obstet Gynaecol, 1986. **93**(3): p. 282-4.

6. Alborzi, S., S. Motazedian, and M.E. Parsanezhad, *Chance of adhesion formation after laparoscopic salpingo-ovariolysis: is there a place for second-look laparoscopy?* J Am Assoc Gynecol Laparosc, 2003. **10**(2): p. 172-6.

7. Hooker, A., et al., *Prevention of adhesions post (spontaneous) abortion (PAPA study); a randomized controlled trial evaluating application of hyaluronic acid (HA).* Hum Reprod, 2016. **31**(Supp 1): p. 39.

8. Cheong, Y.C., et al., *Should women with chronic pelvic pain have adhesiolysis?* BMC Womens Health, 2014. **14**(1): p. 36.

9. Tulandi, T., T. Falcone, and I. Kafka, *Second-look operative laparoscopy 1 year following reproductive surgery.* Fertil Steril, 1989. **52**(3): p. 421-4.

10. Gomel, V., *Salpingo-ovariolysis by laparoscopy in infertility.* Fertil Steril, 1983. **40**(5): p. 607-11.

11. Bosteels, J., et al., *Anti-adhesion barrier gels following operative hysteroscopy for treating female infertility: a systematic review and meta-analysis.* Gynecol Surg, 2014. **11**: p. 113-127.

12. Ahmad, G., et al., *Barrier agents for adhesion prevention after gynaecological surgery.* Cochrane Database Syst Rev, 2015(4): p. CD000475.

13. Metwally, M., Y. Cheong, and T.C. Li, *A review of techniques for adhesion prevention after gynaecological surgery.* Curr Opin Obstet Gynecol, 2008. **20**(4): p. 345-52.

14. Hooker, A., et al., *Prevention of adhesions post (spontaneous) abortion (PAPA study); a randomized controlled trial evaluating application of hyaluronic acid (HA).* Hum Reprod, 2016. **31, Supp 1**: p. 39-40.

15. De Wilde, R.L., et al., *Adhesions and endometriosis: challenges in subfertility management : (An expert opinion of the ANGEL-The ANti-Adhesions in Gynaecology Expert PaneL-group).* Arch Gynecol Obstet, 2016. **294**(2): p. 299-301.

16. Scientific Impact paper, R.C.O.G., *The use of Adhesion Prevention Agents in Obstetrics and Gynaecology.* Royal College of Obstetricians & Gynaecologist Scientific Impact Paper, 2013. **39**.