Reduction of adhesion formation after gynaecological adhesiolysis surgery with 4DryField PH – a retrospective, controlled study with second look laparoscopies

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ABSTRACT
Adhesions are a common consequence of abdomino-pelvic surgery. Efficacy of available adhesion prevention agents is discussed controversially. Here, we used the adhesion barrier 4DryField PH: a powder, which is transformed into a barrier gel with saline solution. The study includes 40 consecutive patients with surgeries for adhesiolysis, endometriosis and other gynaecological pathologies and subsequent second look interventions. The intervention group (n = 17) received 4DryField PH gel while control patients (n = 23) did not receive any adhesion prevention. Severity and extent of adhesion formation were scored during both interventions using an established score. Direct comparison between first and second interventions showed that extent and severity of adhesions could be reduced significantly using 4DryField PH gel. In contrast, in the control group, extent was not reduced and severity was even significantly higher. Direct comparison of second look laparoscopies revealed that adhesion extent and severity were significantly lower in the 4DryField PH than in the control group.

IMPACT STATEMENT
- **What is already known on this subject?** Adhesion formation after gynaecologic surgeries is known to be frequent and highly problematic as it directly induces complications and additionally makes subsequent surgeries more difficult. The effectiveness of established adhesion barriers is not sufficient to tackle these problems adequately.
- **What the results of this study add?** This is the first controlled study using the relatively new adhesion barrier 4DryField PH. It yields a significant reduction of extent as well as severity of adhesions, while adhesiolysis surgery alone does not solve the problem.
- **What the implications are of these findings for clinical practice and/or further research?** Usage of 4DryField PH gel seems to be a good approach to solve the adhesion problem of gynaecologic surgery in general and the reformation problem of adhesiolysis surgery specifically. The results should be confirmed in a larger prospective randomised controlled trial.

Introduction
Intraabdominal adhesions still represent an unsolved problem of surgery. They occur after 55–100% of all abdominal surgeries (Diamond 2000). Adhesions are fibrous bands that develop between adjacent tissues after inflammation, surgical interventions or tumours. Once a peritoneal injury occurs, fibrinous strands form between the affected tissues and fill up with different cell types (Menzies and Ellis 1990). In addition to fibrin formation, the intraoperative trauma leads to local activation of the innate immune system, which is associated with increased cytokine release and leukocyte infiltration (Hong et al. 2015). The cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 inhibit fibrinolysis, resulting in an imbalance of the fibrinolytic system on behalf of polyfibrin persistence, which induces and enhances adhesion formation (Hong et al. 2015). In about 10–20% of patients, adhesions cause severe health problems, including chronic pain, ileus and female secondary infertility (Menzies and Ellis 1990). Adhesions even are the most common cause of female secondary infertility. Additionally, adhesions lead to a high incidence of re-admissions and reoperations (Ellis et al. 1999; De Wilde et al. 2017). In the latter case, the treating surgeon often finds himself confronted with difficult accessibility and an unrecognisable anatomy, which significantly prolongs operation time (Hong et al. 2015) and increases the risk of unintentional organ damage. Furthermore, the economic burden of adhesiolysis is estimated at more than 2 billion dollars per year in the USA, not even including follow-up costs associated with decreased quality of life and possible sequelae (Sikirica et al. 2011).

Since adhesions are a major burden for patients, surgeons, hospitals and the healthcare system, many different attempts have been made in order to develop effective adhesion prevention devices (De Wilde et al. 2017). Most of these
products act as barriers that separate impaired neighbouring peritoneum until the mesothelial surfaces have healed. However, in a comprehensive review article, Ahmad et al. (2015) did not find conclusive proof of efficacy for any of the adhesion prevention devices included. Correspondingly, adhesion barriers are still not ubiquitously used (Trew et al. 2009; Schreinemacher et al. 2010).

There are generally four strategies to avoid adhesion formation: adapted surgical techniques, pharmaceutical treatments, as well as application of liquid solutions and solid barriers. The adaption of the surgical technique aims at causing the least possible trauma or preventing post-operative contact of injured tissues (Korell 2010). Nevertheless, the widespread deployment of minimally invasive techniques has neither reduced complications nor costs substantially (Kavic and Kavic 2002). Pharmaceuticals (Brochhausen et al. 2012) as well as liquid solutions (Trew et al. 2011) have not convincingly shown to be effective, either. Solid barriers for adhesion prevention include various types of membranes and nonwovens, as well as gels. The latters are more flexible than membranes and usually easier to apply and resorb. The efficacy of a gel barrier particularly depends on the material used and its retention time. These characteristics also influence the safety and biocompatibility of the product, particularly with regard to possible foreign body reactions. The group of gel barriers comprises 4DryField PH (4DF; modified polysaccharide, PlantTec Medical GmbH, Lüneburg, Germany), a starch-based polysaccharide certified for both, adhesion prevention and haemostasis (Pharma central numbers: 3 g unit (PZN: 16000657), 5 g unit (PZN: 16000663)). As powder, 4DF provides haemostasis. When mixed with saline solution, it forms a barrier gel for adhesion prevention. The product has already been shown to effectively reduce adhesion formation in several experimental and clinical studies, including three publications on gynaecological surgery with second look interventions (Korell 2014; Korell et al. 2016; Ziegler et al. 2016). In order to verify the promising results from previous studies and to assess the possible benefits of its usage, we decided to perform a case-control study on patients with the condition of persisting adhesions necessitating adhesiolysis surgery, as well as accompanying pathologies, particularly endometriosis and myoma formation. The outcome of the 4DF-treated group is compared with a control group exhibiting similar pathologies but without adhesion prevention treatment. Over the course of 46 months, consecutive patients with second look surgeries were included in this retrospective study.

Methods and materials

This retrospective, controlled study was approved by the Ethics Committee of the European Medical School Oldenburg-Groningen (no. 129/2016) and has been performed in accordance with the ethical standards laid down to the 1964 Declaration of Helsinki and its later amendments. Participants gave written informed consent before their data was used for the study.

The study comprises 40 patients aged 18–77, who underwent laparoscopic adhesiolysis in the period from November 2012 to August 2016. Adhesions had been caused by surgeries for various pre-existing conditions such as endometriosis, myomas, tumours and others. Only patients with a second look surgery were included in the study. Extent and severity of adhesions were scored during both interventions enabling a direct assessment of the efficacy of the adhesion prevention device. The first 23 consecutive patients received no adhesion barrier, whereas the following 17 were treated with 4DF gel. The product was either applied as a powder and subsequently dripped with saline solution or the gel was premixed extracorporeally. The premixed gel was prepared using either 3 g 4DF powder and about 30 mL saline solution or 5 g 4DF powder and about 50 mL saline solution. The gel was distributed on all surgically affected surfaces in the peritoneal cavity and the lesser pelvis. Examples of the application of 4DF powder with subsequent transformation into a gel are shown in Figure 1(A–F).

Furthermore, patient data like age, body mass index (BMI), number of nulligravida and numbers of patients with previous gynaecologic or visceral surgeries, and number of patients with previous adhesiolysis surgery were collected (statistically significant difference with p < .05 indicated by an asterisk): mean age (a) was 35.6 (±7.6) in the control group vs. 42.9 (±14.5) in the 4DF group (p = .045), mean BMI (kg/m²) was 24.7 (±5.6) vs. 24.1 (±3.3) (p = .973), number of nulligravida was 19 (83% of patients) vs. 7 (41%) (p = .009), the number of patients with previous gynaecologic or visceral surgery was 8 (35%) vs. 13 (77%) (p = .012) and the number of patients with previous adhesiolysis surgery was 0 vs. 6 (35%) (p = .003).

Surgical techniques

All 40 patients underwent adhesiolysis in the lesser pelvis and/or abdominal cavity. Data on surgery duration and length of associated hospital stay, as well as the interval between first and second intervention were collected and compared (Table 1). An overview of additional procedures possibly inducing adhesion formation is provided in Table 2. The total number of these additional procedures is 27 in the control and 20 in the 4DF group, which is about 1.2 per patient for both groups.

Adhesion classification

One of the most commonly used adhesion scores in gynaecologic surgery is the AFS score. However, this score is restricted to predetermined areas not encompassing all of the areas relevant in the present study, particularly in cases of widespread and extensive adhesiolysis. Therefore, we decided to use a more general score, modified from the one by Corson et al. (1995). Adhesion severity was scored on a five-point scale ranging from 0 to 2 (0 = no adhesions, 1 = filmy, avascular adhesions, 2 = organised, cohesive, vascular, dense adhesions), with half-integral scores (0.5 and 1.5) also being possible. Adhesion extent was likewise scored on
a five-point scale including half-integral scores and quantified the area affected (0 = 0%, 0.5 = below 25%, 1 = between 25 and 50%, 1.5 = between 50 and 75%, 2 = above 75%). Only pelvic and/or abdominal cavity but not intrauterine adhesions were considered.

**Table 1.** Duration of the first surgery, length of hospital stay, time between first and second look surgery.

| Procedure                        | Control        | 4DryField PH   |
|----------------------------------|----------------|----------------|
| Duration of first surgery (min)  | 23–211 74 43  | 20–270 104 67  |
| Hospital stay after first surgery (days) | 0–14 5.3 2.7 | 1–30 7.8 6.6   |
| Interval to second look (weeks)  | 2–103 27 30   | 1–56 11 13     |

AM: arithmetic mean; SD: standard deviation.

*Statistically significant difference (p < .05).

**Table 2.** Frequencies of adhesiogenic procedures performed in addition to adhesiolysis.

| Procedure                        | Control | 4DryField PH |
|----------------------------------|---------|--------------|
| Resection of DE (deep endometriosis) | 11 48 7 41 | .755         |
| LAV resection (deep endometriosis) | 0 0 1 6  | .425         |
| Intramural tumour (adenomyoma)    | 0 0 1 6  | .425         |
| Myomectomy                       | 6 26 6 35 | .729         |
| Adnex-related pathologies        |         |              |
| Adnexa removal (one-sided)       | 1 4 1 6  | > .999       |
| Total extirpation of ovaries     | 2 9 0  | > .999       |
| Adnectomy                        | 2 8 0 0 | > .999       |
| Ovarectomy                       |         |              |
| Ovarian cystectomy               | 1 4 0 0  | > .999       |
| Ovarian tumour                   | 1 4 0 0  | > .999       |
| Tumourectomy (right adnexa)      | 1 4 0 0  | > .999       |
| Resection of ovarian fibroid     | 0 0 1 6  | .425         |
| Deperitonealisation of the lesser pelvis | 0 0 1 6 | .425         |
| Suture of sigmoid colon          | 0 0 1 6  | .425         |
| Tumourectomy of pelvic wall      | 0 0 1 6  | .425         |
| Abscess drainage                 | 1 4 0 0  | > .999       |
| Salpingotomy                     | 1 4 0 0  | > .999       |

**Figure 1.** First (A–F) and second (G–L) surgeries of the same patient from the intervention group: (A, B) adhesions at first surgery, (C, D) application of 4DryField PH as a powder, (E, F) subsequent transformation into a gel by dripping with saline solution; (G–L) sites of former adhesiolysis at second surgery completely free of adhesions.

**Statistical analyses**

Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, Seattle, WA) and GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA). For continuous data, arithmetic means and standard deviations were calculated. Afterwards, it was tested if the data sets were distributed normally using the D’Agostino–Pearson normality test. Depending on this, a test was selected (unpaired t-test for normally distributed data or Mann–Whitney’s test for not normally distributed data) to
determine if the data sets were significantly different. If pre- and postoperative continuous data of the same group had to be compared with each other, a paired t-test (for normally distributed data) or a Wilcoxon matched pairs signed rank test (for not normally distributed data) was employed. For discrete data, the computation was done using Fisher’s exact test. For continuous data describing time intervals (e.g. duration of surgery), the Mantel-Cox test was used. As adhesion scores are rank data, they were evaluated by calculating medians with 25% and 75% percentiles, followed by a statistical comparison using the Mann-Whitney test (for unpaired data) or the Wilcoxon matches pairs signed rank test (for paired data). Correlation of factors within one group was calculated determining Pearson’s correlation coefficients with corresponding 95% confidence intervals. The level of significance ($\alpha$) was always 0.05.

Results

Figures 1 and 2 contain representative intraoperative images from the first and second interventions showing the outcomes of using an adhesion barrier in comparison to using none. Images from the first interventions can be found in Figure 1(A–F) (4DF group) and Figure 2(A,B) (control group), photographs from the second interventions of the same patients, respectively, in Figure 1(G–L) (4DF group) and Figure 2(C–F) (control group). Adhesion extent and severity scores for both groups can be found in Table 3 and Figure 3.

As indicated in Table 3, both median adhesion severity and extent scores in the 4DF group were 2 in the first surgery but only 0.5 in the second surgery. The statistical evaluation shows that both severity and extent were significantly reduced from first to second surgery when 4DF was used. In contrast, both median adhesion severity and extent scores in the control group were 1 in the first surgery but 1.5 and 1, respectively, in the second surgery. The statistical evaluation reveals that in the control group, the adhesion extent was not reduced in the second surgery (reduction was 0% in the control group, whereas it was 75% in the 4DF group) and the adhesion severity was even significantly higher in the second than in the first surgery (severity increased by 50% in the control group, whereas it decreased by 75% in the 4DF group).
The statistical comparison of the two groups shows that median adhesion severity and extent both were significantly higher in the first surgery in the 4DF group. This indicates unfavourable starting conditions for the 4DF group since detached adhesions are predilection sites for adhesion (re)formation. Nevertheless, the outcome at second surgery was superior in the 4DF group with both adhesion severity and extent being significantly lower than in the control group.

**Discussion**

Several factors were evaluated to rule out the possibility of biased results due to distorted starting conditions (see patient characteristics given under ‘Methods and materials’, as well as Tables 1 and 3). The results show that BMI, surgery duration, hospital stay, as well as the frequencies of procedures performed in addition to adhesiolysis did not differ significantly between the two study limbs, whereas age, number of nulligravida, number of patients with previous gynaecologic or visceral surgery and number of patients with previous adhesiolysis were distributed between the groups to the disadvantage of the 4DF group. Although time between the surgeries was significantly shorter in the 4DF group, there was at least one week between the two interventions. This can be judged sufficient to detect any possible adhesion formation since adhesion formation can only take place until the mesothelial-covered peritoneum has healed, which takes between three and five days (Diamond 2000). Therefore, adhesion extent cannot be influenced by this difference. As formed adhesion might mature and become more severe, validity of the severity score could possibly still be reduced.

In order to examine this question, a correlation analysis of the time between surgeries with adhesion severity scores was carried out. This analysis revealed that there was no correlation (4DF group: $r = 0.048$, 95% CI $= -0.44$ to 0.52, $p > 0.05$).

| Control group | 4DryField PH group |
|---------------|---------------------|
| **Severity**  |                     |
| Median        | 1                   |
| 25% perc.     | 1.5                 |
| 75% perc.     | 2                   |
| **Severity**  |                     |
| Median        | 2                   |
| 25% perc.     | 1.5                 |
| 75% perc.     | 2                   |
| $p$ Value (1st vs. 2nd surgery) | **<0.001** |
| **Extent**    |                     |
| Median        | 1                   |
| 25% perc.     | 1.5                 |
| 75% perc.     | 2                   |
| **Extent**    |                     |
| Median        | 2                   |
| 25% perc.     | 1.5                 |
| 75% perc.     | 2                   |
| $p$ Value (1st vs. 2nd surgery) | **<0.001** |

The table shows the adhesion scores of severity and extent of adhesions at first and second surgery and the statistical comparisons between first and second surgery within one group and between the groups for both surgeries.

*Statistically significant ($p < 0.05$).

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**Figure 3.** Severity and extent of adhesions at first and second surgeries in the control and 4DryField PH groups (with 25% and 75% percentiles as error bars; *statistically significant difference, $p < 0.05$).
Numerous attempts have been made to develop effective medical devices for adhesion prevention (Torres-De La Roche et al. 2019). As none of the well-known products have been convincingly shown to be effective (Trew et al. 2011; Ahmad et al. 2015; Poehnert et al. 2016; Torres-De La Roche et al. 2019), we decided to use 4DF, a product that has entered clinical routine and has been shown to effectively reduce adhesion formation also in previous clinical studies (Korell et al. 2016; Ziegler et al. 2016; Blumhardt et al. 2018; Ahmad and Crescenti 2019). Using an effective adhesion barrier is crucial in abdominal and pelvic surgery, particularly considering that adhesions form in 67–97% of patients (Weibel and Majno 1973; Operative Laparoscopy Study Group 1991) and are the main cause of chronic pain, secondary female infertility and small bowel obstruction (Ellis et al. 1999; Parker et al. 2007; De Wilde et al. 2016; Torres-De La Roche et al. 2019).

In the present study, adhesion reduction could be achieved by the use of 4DF. Adhesion extent and severity in the second surgery were significantly lower than in the control group. Comparing the first with the second surgery, adhesion reduction could only be achieved by using 4DF, although both scores were even higher at first surgery in the 4DF group. Additionally, age, number of nulligravida, number of patients with previous gynaecologic and visceral surgery, as well as number of patients with previous adhesiolysis were distributed between the groups to the disadvantage of the 4DF group. This shows the challenging clinical condition of the patients in the 4DF group and makes the results even more remarkable. Including only patients with second look intervention was crucial for the significance of the study as only second looks enable a reliable quantification of post-operative adhesion formation. The absence of clinical symptoms in turn does not rule out the presence of adhesions (Ahmad and Crescenti 2019).

Previously, the best results for a single type of adhesion barrier had been achieved with cellulose-based products. A recent review article summarised their usage for the prevention of de novo adhesions after laparoscopic myomectomy in randomised controlled trials (Raimondo et al. 2020). The pooled results of these indicate a significant adhesion reduction by 37% while the product application prolonged the interventions by four minutes. Our results for 4DF show a higher adhesion reduction efficacy, with both extent and severity of adhesions being significantly reduced by 75% when comparing the first and second surgeries of the intervention group. Additionally, adhesion scores were reduced by 50% (extent) and 67% (severity) when comparing the second look outcomes of both groups despite 100% higher extent and severity scores at first surgery in the 4DF group. From our surgical experiences, the application of 4DF also takes less than four minutes.

Haemostats are not generally used in gynaecological surgery but only applied based on individual decisions made by the surgeon (Korell et al. 2016). A subjective assessment of the haemostatic efficacy of 4DF was positive in all patients in whom the product was first given for haemostasis. By reducing blood loss, sufficient haemostasis also reduces the secretion of fibrinogen, the first step for the formation of adhesions. It is, therefore, also important for effective adhesion prevention.

Since no side effects or complications were observed, the use of 4DF is considered safe. Furthermore, no remnants of the product were detected during the second look interventions. Additionally, the combination of 4DF powder for haemostasis and, after transformation, its gel form as a barrier for adhesion prevention is intriguing. The high efficacy observed in the present study is in line with previous experimental and clinical studies.

Conclusions

4DryField PH usage proves to be safe and effective. Despite a patient distribution between the two groups unfavourable to the examined adhesion barrier, its application significantly reduced both adhesion extent and severity in comparison to an untreated control. Correspondingly, adhesion extent and severity were significantly reduced by 4DF also when comparing the adhesion scores of the first and second surgeries, whereas the control group showed a deterioration here. 4DF constitutes a promising supplement in the surgical treatment of adhesions. Further prospective, randomised, controlled trials are recommended to corroborate these results.

Disclosure statement

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