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Article

Efficacy of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery

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Abstract. *Background:* Intrauterine adhesions are a relevant short- or long-term result of hysteroscopic surgery, and the rate by which they develop depends mainly on the type of surgical procedure, being particularly high in the case of metroplasty, myomectomy, and endometrial ablations. The authors in this study sought to evaluate the effect of cross-linked hyaluronic acid in the prevention of intrauterine adhesions after different hysteroscopic procedures. *Methods:* The study was conducted on 60 females, the patients underwent different hysteroscopic surgeries (myomectomy and septum resection) then they were randomized to either group A or group B. Group A received 5 ml new crosslinked hyaluronic acid (NCH) intrauterine gel (MateRegen gel, Bioregen Biomedical Co.) at the end of the hysteroscopic procedure. Group B did not receive the gel after the hysteroscopic procedure**.** A second look hysteroscopy was done to all patients to evaluate the intrauterine adhesions. *Results:* Our results showed that on second look hysteroscopy , adhesions was found in 3 patients (10%) in group A and in 9 patients (30.0%) in group B , there was a difference between both group but it was not statistically significant , p value = 0.053. *Conclusion:* It seems hyaluronic acid gel can help reduce the incidence of intrauterine adhesions after hysteroscopy but the results were not statistically significant, further studies are needed with higher number of cases.

Keywords: hyaluronic acid gel; prevention; intrauterine adhesions; hysteroscopic surgery

Introduction

Intrauterine adhesions are the most frequently encountered problems after operative hysteroscopy.[1, 2] It is a condition brought on by damage to the endometrial basal layer. Opposing uterine walls adhere together during the healing process, minimally, marginally, or completely obliterating the uterine cavity.[3]

Multiple scoring systems have been proposed to evaluate the severity of the condition and the prognosis , one of those scoring systems is the AFS adhesion scoring system, it quantifies the condition's severity based on the extent of the adhesions, the type of the adhesions and the presence of menstrual blood.[4] Obliteration of the entire uterine cavity is a serious problem that causes secondary amenorrhea and infertility.[5] Moreover some other consequences have been introduced such recurrent miscarriages, abnormal uterine bleeding, dysmenorrhea, or abnormal placentation.[6, 7] Furthermore, intrauterine adhesions can cause the obliteration of parts of the endometrial cavity, leading to hematometra and chronic pelvic pain.[8]

The most commonly recommended tool for diagnosing and treating these complications is hysteroscopy.[9] Hyaluronic acid gel is one of several anti-adhesive materials that have been used to prevent postoperative adhesions. Hyaluronic acid (HA) molecules have been shown to modulate inflammatory processes, regulate macrophage cytokine secretion, and facilitate scar-free tissue repair.[10]

The aim of our study was to assess the efficacy of new cross linked hyaluronic acid gel in the prevention of postoperative adhesions following hysteroscopic surgery (uterine septum resection and myomectomy).

Materials and methods

The study was a randomized controlled trial conducted on 60 female patients recruited from the gynecology clinic at the university hospital our Inclusion criteria was patients requiring hysteroscopic myomectomy or septum resection (level 2 or level 3 hysteroscopic surgery based on the RCOG classification of operative hysteroscopy levels) and our exclusion criteria was Patients with previous hysteroscopic surgeries , Asherman syndrome and initial intrauterine adhesions , patients with known allergy to HA and patients with contraindication to hysteroscopy.

The Sample size was estimated using PASS Version 20 Program. The minimal hypothesized total sample size of 50 women undergoing level 2 or level 3 hysteroscopic surgeries (25 per group) is needed to determine the efficacy of auto-cross linked hyaluronic acid gel in preventing the intrauterine adhesions after hysteroscopic surgeries assessed by the American Fertility Society Scale compared to control group; taking into consideration 95% confidence level and 80% power using Chi Square-test.(power:0.80,N:50,K:2,n:25,alpha:0.05,beta:0.20,effect size:20.0)

The patients were randomly assigned to 2 groups by choosing themselves a closed opaque envelope. To avoid potential bias from the surgeons, participants randomization and grouping results were revealed at the end of the hysteroscopic procedure.

The patients were placed in extended lithotomy position and the procedure was performed under general anesthesia after surgical draping of the field.The cervix

was dilated under transabdominal ultrasound guidance with a Hegar dilator up to size 10, the uterine cavity was assessed for adhesions using AFS adhesion scoring system at the beginning of the procedure then each subject underwent the appropriate hysteroscopic procedure according to the condition found.

For patients with sub mucous myomas (Federation of Gynecology and Obstetrics (FIGO) classification types 0, 1, and 2), hysteroscopic myomectomy was done using the cutting loop of the 26 Fr Karl Storz monopolar resectoscope while for patients with septum the Collin's cutting knife electrode was used.

Patients randomized to group A received at the end of the hysteroscopy procedure, 5 mL of the auto cross-linked hyaluronic acid gel (MateRegen gel, BioRegen Biomedical Ltd Inc., Changzhou, China) which was injected into the uterine cavity through a sterile delivery cannula.

Patients randomized to group B did not receive the gel at the end of the procedure.

In all women, hormone therapy was initiated on the day of the operation, which consists of estradiol valerate at a dose of 4 mg daily for 11 days and then 1 mg norgestrel for 10 days.

A second hysteroscopic examination was performed to all patients at approximately 1 to 2 months postoperatively using the BETTOCCHI 5mm office hysteroscope for the evaluation of IUA.

The evaluation of IUA was based on the American Fertility Society (AFS) scoring system; the score of the adhesions was noted and classified into mild, moderate, and severe adhesions accordingly.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

Results

In Figure 1 the flow-chart of the study is shown.

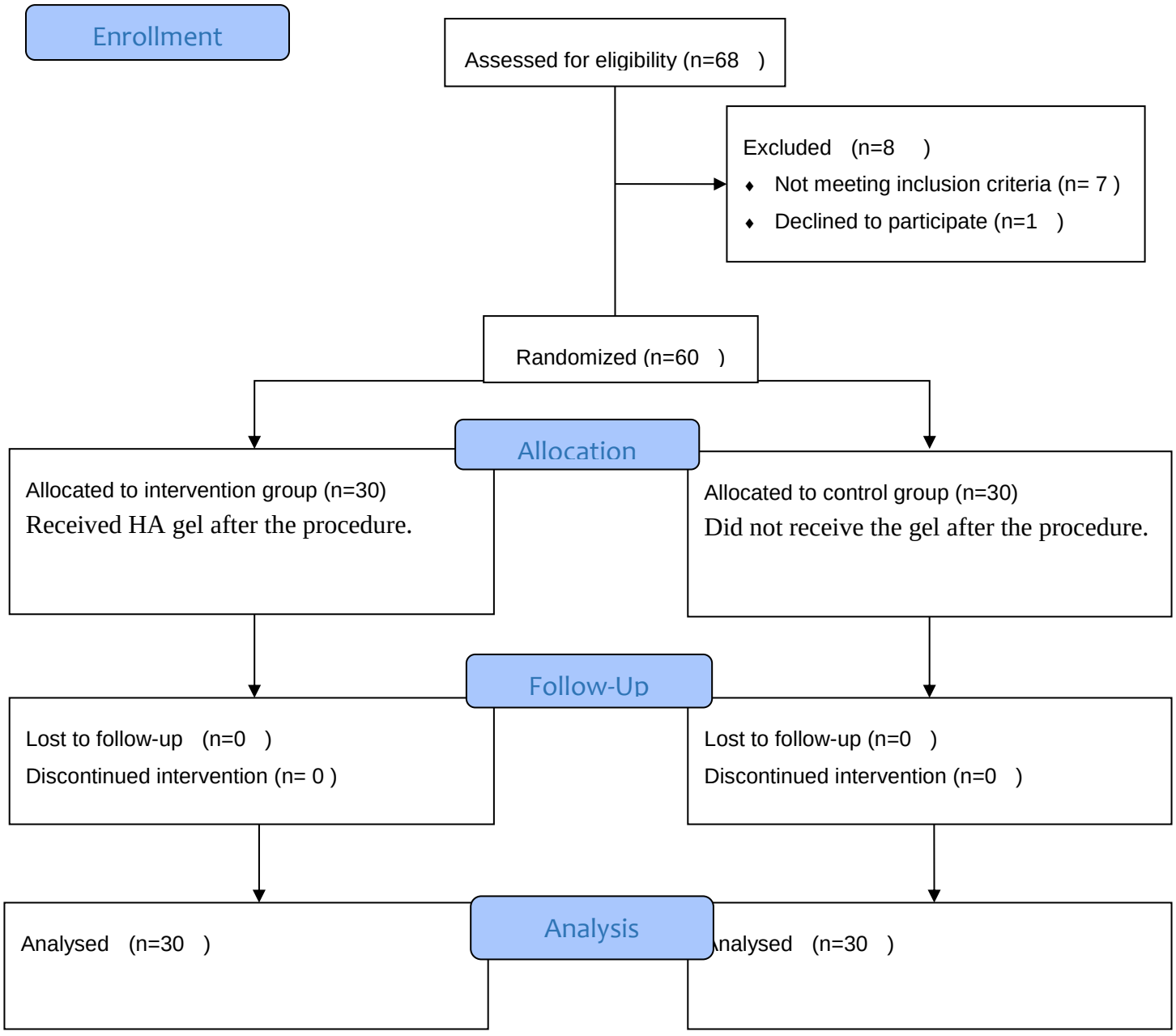


Figure (1): Flow-chart of the study

First with the main characteristics of the study participants there was no statistical difference between both groups. As shown in (Table 1), there was no statistical difference in age between the 2 groups. Age ranged from 21 to 47 years with a mean of 33.47 years ± 8.24 in group A and ranged from 20 to 52 years with a mean of 34.90 years ± 8.30 in group B with p value = 0.505.The mean period of marriage in

group A was 6.23 years± 6.78 while in group B it was 9.67 years ± 8.45 with no statistical difference and the p value = 0.057.

Table (1): Comparison between the two studied groups according to demographic data

Demographic data	Group A (n = 30)	Group B (n = 30)	Test of sig.	p
Age (years)				
Min. – Max.	21.0 – 47.0	20.0 – 52.0	t= 0.671	0.505
Mean ± SD.	33.47 ± 8.24	34.90 ± 8.30		
Median (IQR)	34.0 (25.0 – 40.0)	36.50 (30.0 – 41.0)		
Married since				
Min. – Max.	1.0 – 24.0	1.0 – 30.0	U= 322.0	0.057
Mean ± SD.	6.23 ± 6.78	9.67 ± 8.45		
Median (IQR)	3.50 (1.0 – 10.0)	6.50 (3.0 – 16.0)		

IQR: **Inter quartile range** SD: **Standard deviation** **t: Student t-test** **U: Mann Whitney test**

p: p value for comparing between **Group A and Group B**

Regarding the obstetric history (Table 2) we compared the gravidity, parity, abortion, ectopic pregnancy and mode of delivery in both groups.

In group A 17 patients (56.7%) were nulligravida and 13 (43.3%) had a pregnancy at least once while in group B the numbers were 13 (43.3%) and 17 (56.7%) respectively, there was no statistical difference between both groups with a p value of 0.302.

As for parity, in group A 25 patients (83.3%) were nullipara , 4 Patients (13.3%) were primipara and 1 patient (3.3%) was multipara. While in group B 17 patients (56.7%) were nullipara, 7 Patients (23.3%) were primipara and 6 patients (20%) were multipara, there was no statistical difference between both groups with a p value of 0.052.

As regards to history of abnormal pregnancy (abortion, vesicular mole, ectopic pregnancy) there was no statistical difference concerning abortion when comparing both groups, 8 patients (26.7%) had abortion in group A while 7 patients (23.3%) in group B with a p value of 0.766. Also concerning ectopic pregnancy there was no statistical difference between both groups with a p value of 0.612.There was no history of molar pregnancy in both groups.

As for the mode of delivery, in Group A 1 patient (20%) had a cesarean section and 4 patients (80%) had a normal vaginal delivery while in Group B 5 patients (38.5%) delivered by cesarean delivery and 8 (61.5%) delivered by normal vaginal delivery, there was no statistical difference between both groups with a p value of 0.075.

Table (2): Comparison between the two studied groups according to obstetric history

Obstetric history	Group A (n = 30)		Group B (n = 30)		Test of sig.	p
	No.	%	No.	%		
Gravidity						
Nulli gravida	17	56.7	13	43.3	χ^2=1.067	0.302
Gravida	13	43.3	17	56.7		
Parity						
Nulliparous (0)	25	83.3	17	56.7	χ^2=5.717	^{MC}p=0.052
Primiparous (1)	**4**	**13.3**	**7**	**23.3**		
Multiparous (≥2)	**1**	**3.3**	**6**	**20.0**		
Abortion	8	26.7	7	23.3	χ^2=0.089	0.766
Mode of delivery	**(n = 5)**		**(n = 13)**			
Cesarean section	1	20.0	5	38.5	χ^2=5.281	^{MC}p=0.075
Normal vaginal delivery	4	80.0	8	61.5		
Ectopic pregnancy	3	10.0	1	3.3	χ^2=1.071	^{FE}p=0.612

χ^2: **Chi square test** MC: **Monte Carlo** FE**: Fisher Exact**

p: p value for comparing between **Group A** and **Group B**

Concerning the evaluation of intrauterine adhesions (table 3; figures 2 and 3) our results showed that on second look hysteroscopy , adhesions was found in 3 patients (10%) in group A and in 9 patients (30.0%) in group B , **there was a difference between both group but it was not statistically significant , p value = 0.053**.

As far as concerns the score of severity of intrauterine adhesions, in group A 1 patient (33.3%) had mild intrauterine adhesions and 2 patients (66.7%) had moderate adhesions, while in group B 3 patients (33.3%) had mild adhesions and 6 patients (66.7%) had moderate adhesions, there were no severe adhesions in both groups, there was no statistical difference between both groups.

Table (3): Comparison between the two studied groups according to the presence of IUA and the severity of the adhesions.

	Group A (n = 30)		**Group B (n = 30)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Presence of intrauterine adhesions						
No	27	90.0	21	70.0	χ^2=3.750	0.053
Yes	**3**	**10.0**	**9**	**30.0**		
If Yes	**(n = 3)**		**(n = 9)**			
Mild (1 – 4)	1	33.3	3	33.3	χ^2=0.000	^{FE}p= 1.000
Moderate (5 – 8)	2	66.7	6	66.7		
Severe (9 – 12)	0	0.0	0	0.0		

χ^2: **Chi square test;** FE**: Fisher Exact;** p: p value for comparing between **Group A** and **Group B; Group A: Received 5 ml new cross linked hyaluronic acid (NCH) intrauterine gel; Group B: Did not receive the gel after the hysteroscopic procedure**

Figure (2): Comparison between the two studied groups according to the presence intrauterine adhesions

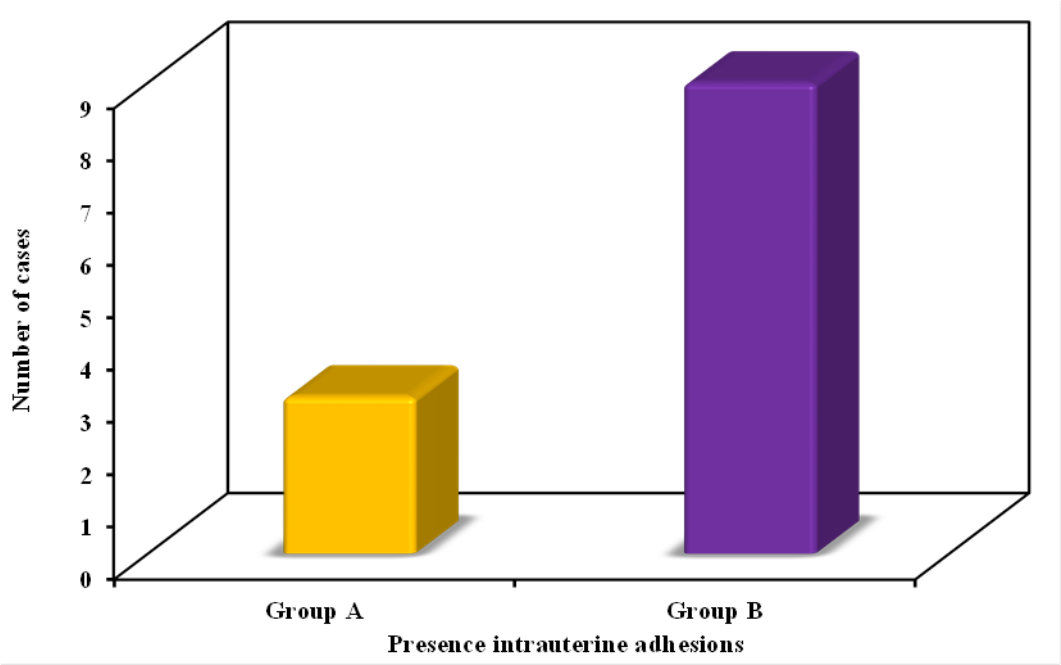
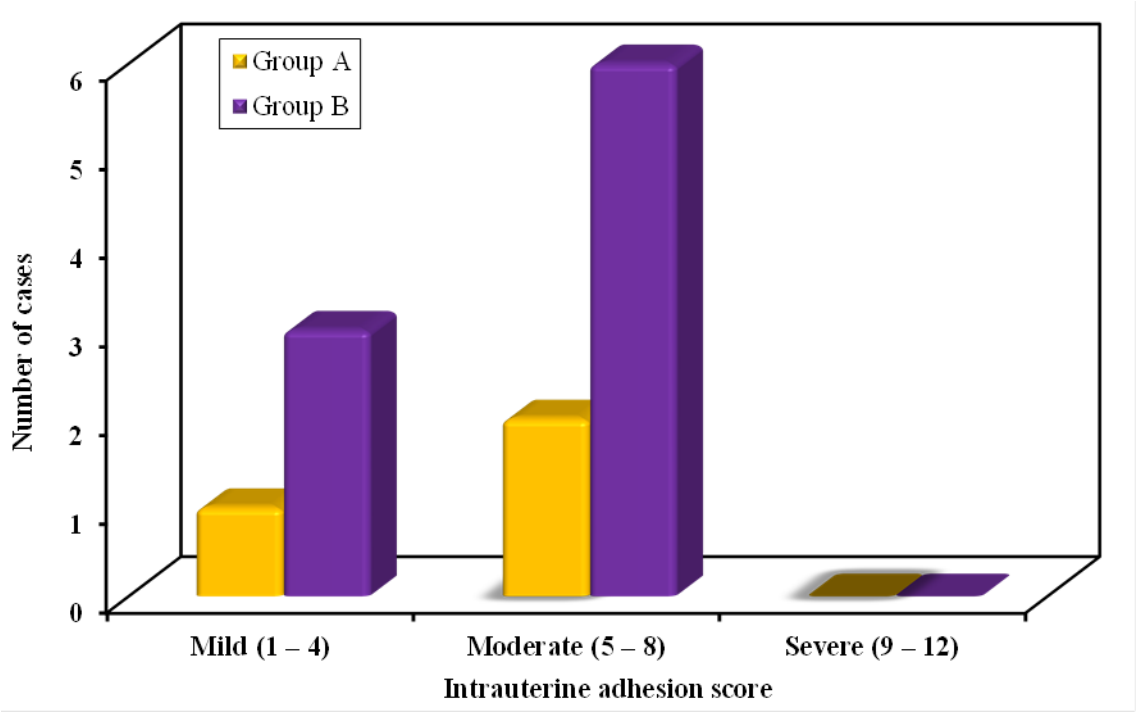


Figure (3): Comparison between the two studied groups according IUA severity score



Discussion

Our data showed that the application of the hyaluronic acid gel, just after the surgical intervention, may be beneficial as it decreased the incidence of intrauterine adhesions when compared to the control group (10% vs 30%), although our results

were not statistically significant but we could still see a potential benefit of the HA gel and our p value was very close to being statistically significant p value = 0.053
Our results were comparable to multiple other studies that also evaluated the effect of hyaluronic acid in the prevention of intrauterine adhesions.
A Turkish study by Kutlu et al. evaluated the HA gel after septum resection, a total of 45 infertile women who underwent hysteroscopic septum resection were randomly assigned to two groups, a group with HA gel applied following septum resection (n=23) and a group without hyaluronic acid gel application (n=22), groups were assessed 3 months later. There was a significant difference between both groups in terms of intrauterine adhesions (4% versus 31%, P<0.05).
Another randomized controlled study on 132 patients by Guida et al. confirmed that HA significantly reduces the incidence and severity of de novo formation of IUA after resectoscopic removal of myomas, polyps and septa (10.44% versus 26.15%; $P < 0.05$).[11]In this study the results were statistically significant because they had a bigger sample size.
A more recent study by Huang et al. assessed the use of HA gel in the prevention of IUA after hysteroscopic myomectomy , the study involved a total of 70 patients, 48 patients were randomly assigned to the anti-adhesive gel treatment group and the other 23 patients were not treated with any anti-adhesive agent gel (no-treatment group). The follow-up hysteroscopy showed that 12.8% of the patients (n = 6) in the anti-adhesive agent gel treatment group had a development of IUA, while 39.1% did (n = 9) in the no-treatment group, denoting a statistically significant difference between the two groups (p = 0.012).[12]
Accumulated data were presented by two recent meta analyses, Fei et al. in 2020 evaluated the use of HA to prevent intrauterine adhesions, he included 7 RCTs , all the subjects were divided into treatment group which received HA after an intrauterine operation or the control group that did not receive any treatment .A total of 952 women were included in the study, from these 455 had been treated with HA and 497 were control patients. The results showed a reduced incidence of IUA in the HA group and also a reduced IUA score.[13]
Finally a very recent meta-analysis published in May 2022 by Liu et al. evaluated the efficacy of hyaluronic acid on the prevention of intrauterine adhesion and the improvement of fertility, it included 11 RCTs and based on their results there was a significant reduction of IUA after using hyaluronic acid gel during intrauterine operation (OR 0.39, 95% CI 0.29 to 0.52). In addition, the analysis showed that the hyaluronic acid gel group was associated with a significant increased incidence of pregnancy (OR 1.64, 95% CI 1.08 to 2.50).[14]
On the other hand in other studies the effect of the gel was not statistically significant, in a study by De Iaco et al., 40 patients underwent different hysteroscopic procedures (endometrial ablation or removal of myomas, polyps, septum or adhesions) and then were randomly assigned either to a treatment with HA gel (Group 1 = 18 patients) or to a control group (Group 2 = 22 patients). Second-look

hysteroscopy, showed a higher incidence of IUA formation in Group 2 (27.8% vs 31.8%) but the difference was not statistically significant.[15]
As shown above most of the studies found are in line with our study and all of them found a decrease in intrauterine adhesions when using HA gel.
The current study has the following strengths; the randomization was conducted at the end of the hysteroscopic procedure. All patients were treated by the same surgical team, suggesting that the study population was homogeneous. Finally, other possible precipitating factors, such as age, gravidity, parity, abortion history, mode of delivery, previous uterine surgery as well as the patient complaint were not dominant key factors and there was no difference between both groups concerning them.
There are some limitations in the current study; the results of the current study are only applicable for the patients treated with a hysteroscopic myomectomy or septum resection.
We did not evaluate the effect of the HA gel in the secondary prevention of intrauterine adhesions after hysteroscopic adhesiolysis as we did not include patients with initial intrauterine adhesions. Furthermore, the sample size of the current study was small.
Moreover, we did not evaluate the reproductive performance of these patients; therefore, we do not know if the beneficial role of using anti-adhesive gels is actually present in women who have a need of future pregnancy.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

None to declare.

Data availability

The data are available upon request.

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