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Auto-cross-linked hyaluronic acid gel after hysteroscopic surgery reduced formation of intrauterine adhesions

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**OBJECTIVE** To determine the efficacy of auto-cross-linked hyaluronic acid (ACP) gel in preventing the formation of de-novo intrauterine adhesions after hysteroscopic surgery.

**DESIGN** Randomized, double-blind (surgeon and assessor), controlled trial. Allocation was by computer-generated randomization list, stratified by type of lesion.

**SETTING** University hospital in Italy.
SUBJECTS A total of 132 premenopausal women, aged ≤50 (mean 37) years and weighing ≤100 (mean 69) kg, who had a single intrauterine lesion (submucous myoma 37%, polyps 51%, or septum 12%) diagnosed by hysteroscopy. Women with more than one lesion or intrauterine adhesions were excluded. An additional six randomized women (4%), a similar proportion in each group, did not return for follow-up and were excluded from the analysis.

INTERVENTION All women underwent appropriate operative hysteroscopy. Randomization allocated 67 women to receive, immediately after the procedure, an intrauterine application of 10 mL ACP gel, and 65 women to receive no additional treatment. Follow-up diagnostic hysteroscopy was performed 3 months after surgery. Assessment of adhesion score was performed by one investigator who was unaware of treatment allocation; the surgery and ACP gel application were performed by a second investigator who was not informed of treatment allocation until after the surgical procedure.

MAIN OUTCOME MEASURES Presence of adhesions, adhesion score (American Fertility Society (AFS) 1988), and staging at 3 months after surgery.

MAIN RESULTS At follow-up, intrauterine adhesions were observed in 7/67 women (10%) in the ACP gel group, compared to 17/65 women (26%) in the control group (p = 0.02, relative risk 0.40, 95% CI 0.18 - 0.87, absolute treatment effect (ATE) 16%, CI 3 - 29, number needed to treat to prevent adhesions in one woman is 6, CI 3 - 38). The mean (±SD) adhesion score was 2.4 ± 0.8 in the ACP gel group and 3.8 ± 1.0 in the control group (p < 0.05, ATE 1.4, CI 1.1 - 1.7). Similar differences between treatment groups in proportion of women with adhesions and mean adhesion score were noted in all three lesion type subgroups, although the differences did not reach significance. When adhesions were present, they were classified as stage I (mild) in 86% of women and stage II (moderate) in 14% in the ACP gel group, compared to 24 and 76%, respectively, in the control group (p=0.01).

CONCLUSION The use of auto-cross-linked hyaluronic acid gel after hysteroscopic surgery reduced the proportion of women with intrauterine adhesions three months later by 60%. The mean adhesion score and adhesion severity were also significantly lower with the use of ACP gel.
This paper presents the results of a prospective, randomized, controlled trial (RCT) that further define the role of an auto-cross-linked hyaluronic acid gel for adhesion prevention after hysteroscopic surgery, including resection of polyps, fibroids, and septa. This study follows on from a previous RCT by the same group, demonstrating the effectiveness of the hyaluronic acid gel for adhesion prevention after hysteroscopic adhesiolysis.\(^1\) Sepra-film, another barrier agent based on a hyaluronic acid derivative, has been shown to be effective in reducing adhesion formation after suction curettage for incomplete and missed abortion.\(^2\) The frequency of postoperative intrauterine adhesions varies between 7 and 40% and depends on the pathology treated.\(^3\) The resection of multiple myomas presents the greatest risk.

The current study protocol adhered to the CONSORT statement. Although not described in much detail, the randomisation process seems to have been adequate, with stratification for type of pathology and blinding of the surgeon until the hysteroscopic resection was complete. The timing of the surgery relative to the menstrual cycle is a potential effect modifier that does not seem to have been taken into account in the analysis. It is conceivable that wound healing is different in different phases of the menstrual cycle. The authors also did not report a sample size calculation and one wonders how they decided when to stop the trial.

The results clearly indicate the benefits of the gel. There was at least a two-fold increased risk of having post-operative intrauterine adhesions if no gel was applied. When adhesions were present after gel application, their severity, as assessed by the AFS classification, was significantly lower. The results appear reliable, because the findings were consistent with those of the previous study\(^1\) and the beneficial effect of the gel was observed for the three types of pathology studied.

The authors used a bipolar energy delivery system (Versa-point, Gynecare; Ethicon Inc) for all surgical procedures. This system is less widely used for hysteroscopic surgery than unipolar systems and it is unclear how this difference may affect the external validity of the results.

Despite both the statistically and clinically significant effect of the gel, 7 out of 67 women randomised to the gel application had adhesions at follow-up hysteroscopy. As gel application does not preclude adhesion formation, it seems likely that a second-look hysteroscopy will still be recommended. However, the relevance of
removing ‘mild’ intracavitary adhesions has not yet been proven. Retaining this additional procedure would, obviously, decrease the cost-effectiveness of this new adhesion-prevention barrier.

**Literature cited**


*Calculated from data in article.*