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Review Article

The Effect of Adjuvant Treatment to Prevent and Treat Intrauterine Adhesions: A Network Meta-Analysis of Randomized Controlled Trials

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ABSTRACT Intrauterine adhesions (IUAs) can lead to partial or complete closure of the uterine cavity, which may result in symptoms including abnormal menstruation, infertility, and pelvic pain. A network meta-analysis was performed to assess the effect of adjuvant therapy on the prevention and treatment of IUAs. We searched electronic databases, including PubMed, Embase, and the Cochrane Library, up to May 5, 2017, without language restrictions. The primary outcomes in the present analysis were the rate of IUAs for prevention and the rate of IUA recurrence for treatment. The secondary outcomes included the IUA score and the rate of severity of IUAs. The treatments were then ranked by the surface under the cumulative ranking curve (SUCRA). We included 20 articles that involved a total of 1891 patients in our analysis. In the outcomes of prevention-related studies, an alginate hyaluronate–carboxymethylcellulose membrane (ACH) (n = 10, SUCRA score = 93.3%) was the adjuvant treatment that most effectively reduced IUA incidence. It was followed by intercoat (n = 10, SUCRA score = 74.7%) and misoprostol (n = 10, SUCRA score = 68.6%). In addition, auto–cross-linked hyaluronic acid (ACP) (n = 3, SUCRA score = 83.2%) and intercoat (n = 3, SUCRA score = 66.4%) each corresponded to a relatively high preventive effect against severe IUAs. In the treatment-related studies, ACP plus a balloon (n = 4, SUCRA score = 96.3%) and a freeze-dried amnion graft plus a balloon (n = 4, SUCRA score = 62.7%) most effectively reduced IUA recurrence and had a high probability of most effectively reducing IUA scores. Therefore, according to the prophylactic analysis, ACH and intercoat were most likely to prevent IUA development. In our analysis of agents used to prevent severe IUAs, we found that ACP and intercoat provided significant advantages and had high reliability. In our analysis of treatments, ACP plus a balloon and freeze-dried amniotic agents plus a balloon were most likely to reduce IUA recurrence and IUA scores after adhesiolysis. Journal of Minimally Invasive Gynecology (2018) 25, 589–599 © 2017 AAGL. All rights reserved.

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Intrauterine adhesions (IUAs), also known as Asherman syndrome, represent a gynecologic disease that leads to the partial or complete closure of the uterine cavity, resulting in symptoms including abnormal menstruation, infertility, and pelvic pain. The presence of IUAs is usually secondary to dilatation and curettage and other operations that can injure the endometrium [1]. Given the variability in presentation, the prevalence of IUAs is difficult to precisely estimate. In the population of women who undergo the placement of an intrauterine device (IUD), the incidence of IUAs is 0.3%, whereas in postpartum curettage patients the incidence is 21.5% [2].

An IUA is characterized by endometrial adhesions and fibrosis and may also affect the myometrium. Any trauma caused by injury of the basal lamina of the endometrium can lead to endometrial wall adhesions. In addition, an IUA can also be secondary to cesarean section, surgery for myoma tumors, and chronic endometritis. This condition is currently a major reason for secondary infertility and recurrent miscarriage [3].

The principal goal of IUA therapy is to treat the adhesions, restore normal structures, and prevent recurrence. Transcervical incision of the adhesions is currently the standard treatment. Hysteroscopy can be used to view the adhesions and avoid causing extra damage resulting from blind intrauterine exploration and uterine perforation [4]. However, whether adjuvant therapies used to prevent the development

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and recurrence of IUAs are effective remains controversial, as does the question of which therapies are most effective. The adjuvant therapies that are currently the most widely applied include IUD placement, high-dose estrogen, or both. However, the optimal choice of doses of estrogen preoperatively is still controversial to prevent adhesion recurrence. The placement of a balloon (such as a Foley catheter) in the uterus separates the uterine walls; amnion grafts may enhance endometrial repairs; and a variety of antiadhesive gels, which are convenient and safe, have been used to protect the endometrium.

In previous meta-analyses, antiadhesive barrier gels (used because of their high viscosity, which protects the wound for a long period of time) were shown to exert a preventive effect [5–7]. Studies have shown that other antiadhesive gels, especially auto–cross-linked hyaluronic acid (ACP) gel, exert a substantial preventive effect against IUAs. However, it remains difficult to choose which barrier gel to use given the diversity of materials. Estrogen therapy did not exert a significant preventive effect against IUAs when compared with the effect of placebo or no treatment controls [6]. Assessments of the effects of other treatments were less reliable because of the small number of studies. In addition, more evidence involving either direct or indirect comparisons is needed to confirm the role of other therapies in preventing and treating IUAs. In this study, we used a network meta-analysis to evaluate adjuvant therapies that are used to prevent and treat IUAs with the goal of providing clinical recommendations.

Methods

Data Search Strategy and Selection Criteria

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched public electronic databases, including PubMed, Embase, and the Cochrane Library, from January 1, 1973, to May 5, 2017. The following search keywords were used: “Asherman’s syndrome,” “Asherman Syndrome,” “intrauterine adhesion,” “IUA,” “uterine atresia,” “cervical atresia,” “uterine atrophy,” “sclerotic endometrium,” “endometrial sclerosis,” “intrauterine synechia,” “Fritsch syndrome,” and “random*”. The literature search and selection were independently performed by 2 authors, and any disagreements were resolved by discussion. The full texts and references of relevant reviews were also checked to ensure that no key studies were inadvertently omitted. The studies included in this meta-analysis were required to meet the following criteria: (1) the study had a randomized clinical trial (RCT) design; (2) it included patients with or at high risk of developing IUAs; (3) adjuvant therapies were used for IUA prevention or treatment; and (4) 1 of the following outcomes was included in the study: IUA incidence or recurrence, rate of severe IUA patients, and IUA score after treatment. The exclusion criteria including the following: (1) not an RCT design, (2) included comparisons between different operations or modified operations, (3) not an adjuvant therapy-related study (e.g., studies of antibiotics or the mindfulness-based stress reduction treatment), (4) anesthesia-related studies, and (5) studies that did not include the desired outcomes. Additionally, conference reports and dissertations that were non–peer-reviewed studies were also excluded because of their lack of reliability. Two authors selected studies independently, and disagreements were solved by discussion to reach consensus.

Data Extraction and Quality Assessment

The following information was independently extracted by 2 investigators from each eligible study: the name of the first author, publication year, study type, sample size, type of patients, surgical type, intervention treatment, control treatment, and follow-up. The primary outcomes were the rate of IUAs for preventive therapies and the rate of IUA recurrences for treatments. Secondary outcomes included IUA scores and the rate of severe IUAs. We assessed the methodological quality of the included studies using the Cochrane Collaboration tool. Studies were graded as having a “low risk,” “unclear risk,” or “high risk” in 7 specified domains [8].

Statistical Analysis

We used a random effects model for mixed multiple treatment comparisons because it allowed us to fully preserve the within-trial randomized treatment comparisons in each trial [9]. Inconsistency between direct and indirect sources of evidence was globally assessed by comparing the fit and parsimony of consistency and inconsistency models and locally assessed by calculating the difference between direct and indirect estimates in all closed loops in the network [10]. For all treatments, we estimated the ranking probability of the treatment being at each possible rank for each intervention using a surface under the cumulative ranking curve (SUCRA) [11]. Comparison-adjusted funnel plots were used to determine whether small study effects were present in our analysis [12]. We performed the analysis in STATA (version 14.0; StataCorp, College Station, TX) with the “metan” commands and the “network” command set.

We used the Grading of Recommendation Assessment, Development and Evaluation guidance tools to assess the quality of our network meta-analysis. We graded quality at 4 levels, from high (best) to very low (worst). This method considered the quality of direct and indirect evidence in addition to the quality of network evidence by identifying inconsistency between direct and indirect evidence and intransitivity among all related evidence [12]. To inform these evaluations, we performed “node splitting” to separate indirect evidence from direct evidence [13]. We also performed a pairwise meta-analysis using a random effects model when an outcome was not included in the network meta-analysis. The standard mean difference (SMD) was calculated as the effect size for continuous data, and the odds ratio was