A systemic review of randomized controlled studies about prevention with pharmacologic agents of adhesion formation in the rat uterine horn model

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Abstract

Introduction: Evaluation of treatment attempts in postoperative adhesion formation is pivotal for the prevention of several morbidities including infertility, pelvic pain, bowel obstruction, and subsequent intraoperative complications. The purpose of this systemic review was to assess the literature on the rat uterine horn model for adhesion formation and treatment modalities to prevent adhesion in the most frequently used experimental animal model.

Material and methods: We performed a systemic review of publications from January 1st 2000 to December 31st 2013 via a PubMed search. A high number of agents were evaluated for the prevention of postoperative adhesion formation in the rat uterine horn model.

Results: According to most of the studies, adjuvants such as antiinflammatorys, antiestrogens, antioxidants were effective to prevent adhesion formation.

Conclusions: Prevention of adhesion formation is pivotal and numerous types of agents were described in the literature were summarized in this review.

Key words: adhesion, prevention, rat, uterine horn, systemic review.

Introduction

Adhesion formation is one of the major complications after pelvic surgery and occurs in 60–90% of women after gynecological surgery [1]. Postoperative adhesion formation is associated with several morbidities including infertility, pelvic pain, bowel obstruction, and subsequent intraoperative complications [2, 3]. Adhesions account for approximately 20% of all infertility cases depending on a previous operation and adhesiolysis has been shown to increase pregnancy rates in more than 50% of infertile patients after previous laparotomy [4, 5]. However, the treatments of adhesions including adhesiolysis have an extra cost, hospitalization, and risks of surgery for the patients [6, 7]. Therefore, prevention is much more significant than treatment in postoperative adhesions.

Although there are still major gaps in the pathophysiology of adhesion formation, the development of adhesion formation comprises the inflammatory response, exudation of fibrinogen and imbalance between fibrogenesis and fibrinolysis, blood coagulation, collagen synthesis, cell survival, proliferation, migration, adhesion and invasion, and angiogen-
esis [8]. The molecular pathways involved in these processes are all integrated (Figure 1). Additionally, treatment options in the rat model were performed to consider this pathophysiology. The purpose of these preventive agents was to activate fibrinolysis, hamper coagulation, diminish the inflammatory response, inhibit collagen synthesis or create a barrier between adjacent wound surfaces. In the literature there has been no systematic review focused on the prevention of adhesion formation in the most often used experimental rat model.

Development of peritoneal adhesions has been studied extensively in rat models, but to date there has been no definitive strategy to prevent their formation, as controversies concerning the effectiveness of available preventive agents still exist. In addition, there have been no recommendations or guidelines in the literature. This review summarizes the prevention strategies of postoperative adhesion formation in the rat uterine horn model that might in future enter clinical usage.

Material and methods

We performed a systemic review of the literature available in the PubMed database on experimental adhesion formation in the rat uterine horn model, published in English, from January 1st 2000 to December 31st 2013. Table I shows the list of medications used for this model. Available full text studies and randomized controlled trials were included in this review. Studies without the full text available, case reports, studies that used physical barriers to prevent adhesion formation, and other animal models for adhesion formation such as rabbits were excluded from this study. Inclusion criteria of this study were rat-based studies, studies using chemical agents, and adhesion formed in control groups. In adhesion formation of the rat uterine horn model, there have been several methods preferred to develop adhesions via monopolar or bipolar electrocautery and mechanical damage with a scalpel or both. In the studies, the adhesion model was mostly adapted from the system of Başbuğ et al. [9]. In this system, the uterine horns were visualized and a 2-cm segment of each horn devascularized by creating a window, and traumatized in 10 spots on the anti-mesenteric surface using unipolar cautery. Sometimes absorbable sutures were applied on the serosal surface. All animals were killed within 14 days after surgery. Furthermore, adhesion formations between the groups were evaluated with macroscopic view and histological score or both.

Results

In Table I, the pharmacological agents used in the studies are presented with possible mechanisms of action. In Figure 1, the pathophysiological causes of adhesion formation after surgery are demonstrated by establishing the relation with Table I. Table II summarizes medications in studies, route of administration and doses of agents, technique of adhesion formation, and results and mechanisms of the trials. We found 34 studies on adhesion formation in the rat uterine horn model. Thirteen studies were excluded because of fulfilling exclusion criteria of this study. Twenty-one randomized controlled trials with 1047 rats were involved in this review. In the studies, adhesion formations have been scored with macroscopic and microscopic scoring systems. The macroscopic scoring system used by the adhesion model trials was mostly graded by the clinical adhesion scoring system of Linsky et al. [10]. In Linsky's system, the extent of adhesions was evaluated as follows: 0 = no adhesion, 1 = 25% of surface covered, 2 = 50% of surface covered, 3 = completely covered. The severity of the adhesions was measured...
Table I. Effective pharmacological agents

| No. | Agent                                                                 | Effect                                                                 |
|-----|------------------------------------------------------------------------|------------------------------------------------------------------------|
| 1   | Letrozole (anti-estrogenic effect of aromatase inhibitor)               | Anti-estrogenic effect, prevents adhesion formation                     |
| 2   | Anastrozole (anti-estrogenic effect of aromatase inhibitor)            | Anti-estrogenic effect, prevents adhesion formation                     |
| 3   | Leuprolide acetate (anti-estrogenic effect of GnRH agonist)            | Anti-estrogenic effect, prevents adhesion formation                     |
| 4   | Cetrorelix (anti-estrogenic effect of GnRH antagonist)                 | Anti-estrogenic effect, prevents adhesion formation                     |
| 5   | Meloxicam (anti-inflammatory effect of COX2 inhibitor)                 | Anti-inflammatory effect, prevents adhesion formation                   |
| 6   | Resveratrol (anti-inflammatory effect of natural phenol)               | Anti-inflammatory effect, prevents adhesion formation                   |
| 7   | Linezolid (anti-inflammatory effect of oxazolidinone)                  | Anti-inflammatory effect, prevents adhesion formation                   |
| 8   | Atorvastatin (anti-inflammatory effect of statin)                     | Anti-inflammatory effect, prevents adhesion formation                   |
| 9   | Metformin (anti-inflammatory effect of biguanide)                     | Anti-inflammatory effect, prevents adhesion formation                   |
| 10  | Sildenafil (anti-inflammatory effect of phosphodiesterase inhibitor)   | Anti-inflammatory effect, prevents adhesion formation                   |
| 11  | Tadalafil (anti-inflammatory effect of phosphodiesterase inhibitor)    | Anti-inflammatory effect, prevents adhesion formation                   |
| 12  | Trimetazidine (anti-oxidant effect of fatty acid oxidation inhibitor)  | Anti-oxidant effect, prevents adhesion formation                       |
| 13  | Ozone therapy (anti-oxidant effect)                                    | Anti-oxidant effect, prevents adhesion formation                       |
| 14  | Melatonin (anti-oxidant effect of N-acetyl-5-methoxytryptamine)       | Anti-oxidant effect, prevents adhesion formation                       |
| 15  | Type 1 collagen (anti-oxidant effect)                                  | Anti-oxidant effect, prevents adhesion formation                       |
| 16  | Rosiglitazone (anti-oxidant effect of PPAR-γ agonist)                 | Anti-oxidant effect, prevents adhesion formation                       |
| 17  | Medroxyprogesterone acetate (anti-estrogenic effect of progesterone)   | Anti-estrogenic effect, prevents adhesion formation                     |
| 18  | Methylene blue (anti-oxidant effect)                                   | Anti-oxidant effect, prevents adhesion formation                       |
| 19  | Vitamin E (anti-oxidant effect)                                       | Anti-oxidant effect, prevents adhesion formation                       |
| 20  | Bevacizumab (fibrinolytic effect of angiogenesis inhibitor)            | Fibrinolytic effect, prevents adhesion formation                       |
| 21  | Ricinus oil (mechanic effect)                                         | Mechanic effect, prevents adhesion formation                           |

as follows: 0 = no resistance to separation, 0.5 = some resistance, 1 = sharp dissection needed. The total score was obtained by the addition of two scores. Similarly, the extent and severity of the adhesions might be separately measured [11, 12]. These adhesion specimens were scored by the histological scoring system of Kanbour-Shakir et al. [13] according to the following characteristics: inflammation, fibroblastic activity, foreign body reaction, collagen formation, and vascular proliferation with the grading of 0: none, 1: mild, 2: moderate, 3: marked, and 4: severe. Moreover, another histologic classification was used according to the adhesion classification based on the presence and extent of fibrosis [14].

Discussion

There have been several methods identified to reduce adhesion formation such as reduction of inflammatory response and oxidative radicals, inhibition of coagulation and fibrosis, promotion of fibrinolysis, immunomodulation, and mechanical separation with barriers. This review analyzed all of the rat uterine horn adhesion trials in which pharmacological agents were tested.

In two recent studies, the aromatase inhibitors letrozole and anastrozole significantly reduced macroscopic and histologic adhesion formation compared with tamoxifen and the control [15, 16]. Results of tamoxifen were similar to the control in both studies and tamoxifen did not prevent adhesion. A hypoestrogenic milieu reduced estrogen-dependent angiogenic growth factors, epidermal growth factor and platelet-derived growth factor caused fibrovascular bands. Estrogen also may modulate the expression of vascular endothelial growth factor and basic fibroblast growth factor, which leads to expansion of capillary perfusion of the adhesion [16]. However, the exact mechanism of adhesion prevention effects for aromatase inhibitors is unclear. Considering the same pathophysiology, GnRH analogs and antagonist are used to prevent adhesion formation [17].

Inflammation develops in the first stage of the adhesion formation pathway after tissue injury, which is followed by an increase in vascular permeability and inflammatory cytokines. Therefore anti-inflammatory effects of agents including resveratrol, meloxicam, cyclooxygenase inhibitor nimesulide, and linezolid might have protective activity against adhesion formation in the rat uterine horn model [18–22]. Additionally, phosphodiesterase-5 inhibitors diminished adhesion formation with local perfusion of nitric oxide and cGMP inhibition, which was pivotal in inflammation and collagen formation [23, 24]. Studies showed that reactive oxygen radicals during inflammation led to an increase in vascular permeability and exudation, which play a role in the formation of adhesion [25]. Anti-oxidant effects of some drugs including trimetazidine were studied for the prevention of adhesion [26–28]. Atorvastatin and metformin reduced adhesion formation with the anti-inflammatory, antioxidant, and anti-fibrinolytic effects of drugs [29]. Özçelik et al. were the first to show that melatonin, which has an antioxidant property, was effective in preventing adhesion formation [30]. Then combination treatment modalities with melatonin such as hyaluronate/carboxymethylcellulose membrane, type I collagen, and rosiglitazone were used to try to prevent adhesion formation and were found significantly effective [31–34]. Rosiglitazone with peroxisome proliferator-activated receptor-γ agonist activity reduced the formation of intraperitoneal adhesion, possibly by reducing the initial inflammatory response and subsequent exudation [33]. In a study, the re-
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| Study ID          | Number of rats | Medication                  | Dose                        | Duration       | Route of administration | Technique of adhesion formation | Outcomes                                           | Mechanism                                                                 |
|-------------------|----------------|-----------------------------|-----------------------------|----------------|--------------------------|--------------------------------|-----------------------------|---------------------------------------------------------------------------|
| Keskin et al. 2013 [15] | 30             | Tamoxifen vs. letrozole     | 500 μg/day vs. 1 mg/kg/day  | 7 days after surgery | Enteric tube             | Unipolar electrocautery and scalpel | Letrozole significantly reduced adhesion histologically and macroscopically whereas tamoxifen did not. | Hypoestrogenic milieu reduced fibrovascular bands caused by estrogen-dependent growth factors. |
| Kaya et al. 2007 [16]       | 45             | Tamoxifen vs. anastrozole  | 500 μg/day vs. 0.2 mg/kg/day | 5 days before surgery, 14 days after surgery | Enteric tube | Unipolar electrocautery | Anastrozole significantly reduced adhesion histologically and macroscopically whereas tamoxifen did not. | Hypoestrogenic milieu reduced estrogen-dependent growth factors. |
| Tamay et al. 2011 [17]     | 21             | GnRH analog (leuprolide acetate) vs. GnRH antagonist (cetrorelix) | 3 mg/kg/day vs. 0.5 mg/kg/day | 7 days before surgery | Subcutaneous | Scalpel | GnRH analog and GnRH antagonist reduced postoperative adhesion formation. | Hypoestrogenic milieu reduced estrogen-dependent growth factors. |
| Keskin et al. 2013 [18]    | 30             | Dexketoprofen vs. meloxicam | 0.5 mg/kg vs. 0.5 mg/kg    | 2 days before surgery, 5 days after surgery | Intramuscular injection | Unipolar electrocautery and scalpel | Meloxicam significantly reduced adhesion histologically and macroscopically whereas dexketoprofen did not. | Anti-inflammatory effect of meloxicam. |
| Orçan et al. 2012 [19]     | 30             | Resveratrol                 | 5.9 mg/kg/day               | 10 days before surgery, 20 days after surgery | Enteric tube | Unipolar cautery | Resveratrol significantly reduced adhesion histologically and macroscopically. | Anti-oxidant and anti-inflammatory effects of resveratrol. |
| Üstün et al. 2007 [20]     | 70             | Resveratrol                 | 10 mg/kg                    | During or 5 days after surgery | Intraperitoneal, subcutaneous | Unipolar cautery | Subcutaneous resveratrol reduced adhesion formation. | Anti-oxidant and anti-inflammatory effects of resveratrol. |
### Table II. Cont.

| Study ID          | Number of rats | Medication                          | Dose                              | Duration                              | Route of administration | Technique of adhesion formation | Outcomes                          | Mechanism                                                        |
|-------------------|----------------|-------------------------------------|-----------------------------------|---------------------------------------|--------------------------|---------------------------------|-----------------------------------|------------------------------------------------------------------|
| Aytan et al.      | 90             | Linezolid                           | 5 mg/kg, 15 mg/kg, 50 mg/kg, 100 mg/kg, 150 mg/kg | 3 days before surgery, 14 days after surgery | Enteric tube             | Bipolar cautery                 | More than 50 mg doses of linezolid reduced adhesion formation. | Anti-inflammator and immunomodulatory effects of linezolid.      |
| Yilmaz et al.     | 40             | Atorvastatin vs. metformin          | 2.5 mg/kg/day, 30 mg/kg/day vs. 50 mg/kg/day | 14 days after surgery                 | Enteric tube             | Bipolar cautery                 | Metformin and atorvastatin reduced adhesion formation.            | Anti-inflammatory, antioxidant, anti-fibrinolytic effects.      |
| Batukan et al.    | 32             | Sildenafil                          | 15 mg/kg, 7.5 mg/kg, 3.75 mg/kg    | 1 h before surgery and 5 days after surgery | Enteric tube             | Unipolar cautery and scalpel   | Sildenafil diminished adhesion formation.                          | Increased local perfusion with nitric oxide and cGMP inhibition might decrease adhesion formation. |
| Kutuk et al.      | 22             | Tadalafil                           | 10 mg/kg                           | 14 days after second look laparotomy  | Enteric tube             | Unipolar cautery                | Tadalafil reduced adhesion formation.                            | Increased local perfusion with nitric oxide and cGMP inhibition might reduce adhesion formation. |
| Erdemoglu et al.  | 40             | Trimetazidine                        | 5 mg/kg                            | 5 days after surgery                 | Intraperitoneal          | Unipolar cautery and scalpel   | Trimetazidine reduced adhesion formation.                        | Trimetazidine reduced intracellular acidosis and inhibited oxygen-derived free radicals. |
| Uysal et al.      | 30             | Ozone therapy                       | 0.7 mg/kg                          | 3 days                               | Intraperitoneal          | Unipolar cautery and scalpel   | Ozone therapy prevented adhesion formation.                      | Ozone therapy modulated TNF-α and had anti-oxidative effect.   |
| Özçelik et al.    | 91             | Melatonin                           | 2 mg/ml                            | Single dose                          | Onto uterine horns, subcutaneous | Unipolar cautery               | Single dose melatonin therapy was effective for prevention of adhesion formation. | Anti-oxidant property.                                             |
| Demirbag et al.   | 35             | Hyaluronate/carboxymethylcellulose membrane vs. melatonin | Film vs. 2 mg/ml                   | Single dose                          | Onto uterine horns       | Bipolar cautery                | Hyaluronate/carboxymethylcellulose membrane and melatonin prevented adhesion formation. | Anti-oxidant property of melatonin and physical barriers limited tissue opposition and minimized fibrin matrix. |
| Koc et al.        | 40             | Melatonin vs. type 1 collagen       | 1 mg/ml vs. 10 mg/ml               | Single dose                          | Intraperitoneal          | Bipolar cautery                | Low dose melatonin and type 1 collagen reduced adhesion formation. | Anti-oxidant property and lipid peroxidation prevention.        |
### Table II. Cont.

| Study ID | Number of rats | Medication | Dose | Duration | Route of administration | Technique of adhesion formation | Outcomes | Mechanism |
|----------|----------------|------------|------|----------|-------------------------|---------------------------------|----------|-----------|
| Demirturk et al. 2006 [33] | 80 | Rosiglitazone | 0.1 mg/kg vs. 0.3 mg/kg vs. 1 mg/kg vs. 3 mg/kg | 3 days before surgery | Enteric tube | Bipolar cautery | 1 mg/kg rosiglitazone reduced adhesion formation. | Anti-inflammatory. |
| Aksakal et al. 2010 [34] | 30 | Melatonin vs. rosiglitazone | 2 mg/ml vs. 1 mg/kg | Single dose vs. 15 days after surgery | Onto uterine horns vs. enteric tube | Bipolar cautery | Rosiglitazone but not melatonin was effective in preventing adhesion formation. | Anti-oxidant and anti-inflammatory effects of rosiglitazone. |
| Yoldemir et al. 2002 [35] | 200 | Leuprolide acetate vs. oxidized regenerated cellulose vs. medroxyprogesterone acetate vs. sodium hyaluronate vs. hyaluronate/carboxymethyl cellulose | 0.75 mg vs. 1.5 mg vs. 4 ml vs. film | Single dose vs. 3 weeks before surgery vs. 2 doses 3 weeks before surgery at the end of surgery vs. 3 doses during surgery vs. during surgery | Intra muscular vs. intramuscular vs. onto horn vs. onto horn | Scalpel | All the preparations minimized adhesion formation. | Decrease of estrogen, anti-inflammation, immunomodulatory, physical barrier. |
| Yildiz et al. 2011 [28] | 37 | Methylene blue vs. vitamin E | 2 ml 1% vs. 10 mg | Single dose | Intraperitoneal | Scalpel | Methylene blue prevented adhesion formation. | Anti-oxidant effect of methylene blue blocked the oxidative stress which reduced peritoneal fibrinolytic activity. |
| Moraloglu et al. 2011 [36] | 30 | Bevacizumab | 5 IU and 7.5 IU | Single dose | Intraperitoneal | Unipolar cautery and scalpel | Bevacizumab prevented adhesion formation. | Bevacizumab had inhibitory effect on vascular endothelial growth factor and fibrinolytic activity. |
| Kahyaoglu et al. 2012 [38] | 24 | Ricinus oil | 0.13 g | 8 days after surgery | Enteric tube | Bipolar electrocautery and suture | Although Ricinus oil reduced total adhesion score, there was no difference in histologic, extent and severity scores. | Increased bowel movement may cause mechanical separation. |
duction effect of two barriers, sodium hyaluronate and sodium hyaluronate/carboxymethylcellulose, and two pharmacological agents, medroxyprogesterone acetate and leuprolide acetate, was compared [35]. In this study, physical barrier effects, anti-inflammatory and immunomodulatory effects, and anti-estrogenic effects might be the reasons for the prevention of adhesion formation.

Fibrin and thrombin formation is a part of wound healing after injury, but the exaggeration in this formation is the main accused reason for adhesion formation. Thus, fibrinolytic and thrombolytic agents in the prevention of adhesion formation were examined in the rat uterine horn model [28, 36, 37].

Interestingly, oral Ricinus oil was used postoperatively for 8 days to prevent adhesion formation with the effect of increased bowel movements [38]. Therefore adhesion formation might be decreased by this mechanic effect. Although Ricinus oil reduced the total adhesion score, there was no difference in histologic, extent and severity scores of adhesion formation. The effects of lots of barriers were evaluated for preventing adhesion formation in the rat model and all of them had preventive action on adhesion formation with the effect of a physical barrier [39–42].

In this review, the agents were effective to prevent adhesion formation in rat models. However, these were preliminary studies and cannot be extrapolated to human beings. In fact, even immunological properties of the animals in the same species are not identical [43]. But small animal models such as the rat are the most frequently used models for screening experiments. Although it has advantages such as low cost, ease of handling, and ready availability, it has some controversial disadvantages such as inconsistency and unreliability. Animal models are the first step to analyze the effects of drugs on pathologies. When the efficacy and safety of agents are revealed in sufficient animal models, case reports and clinical investigations may begin. Adhesion formation is pivotal, especially in laparoscopic, infertility, and pelvic surgery [44]. Especially surgeries such as laparoscopic endometrioma, myoma uteri, and hydrosalpinx excisions are commonly used for the treatment of infertility [45]. However, the efficiency of these attempts is not clear. The main disadvantage and limitation of these operations is postoperative adhesion formation and anatomical disruption. Finally, prevention of adhesion formation after surgery must be taken into consideration.

In conclusion, analysis of the studies showed that most of the agents were effective for prevention of adhesion formation in the rat uterine horn model. This is the first review to analyze the trials about the prevention of adhesion formation with pharmacologic agents. Further studies evaluating the efficacy of the pharmacological agents in the experimental and clinical models are needed to clarify the prevention of adhesion formation after surgery.

**Conflict of interest**

The authors declare no conflict of interest.

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