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 antiinflamatuars, 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-

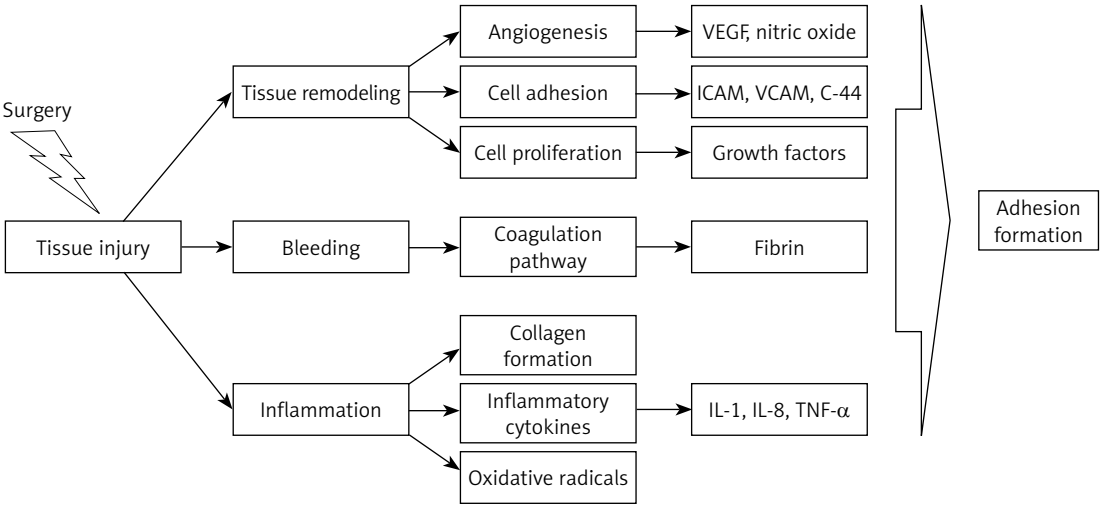

Figure 1. Mechanism of adhesion formation

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 systemic 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

1. Letrozole (anti-estrogenic effect of aromatase inhibitor)
2. Anastrozole (anti-estrogenic effect of aromatase inhibitor)
3. Leuprolide acetate (anti-estrogenic effect of GnRH agonist)
4. Cetrorelix (anti-estrogenic effect of GnRH antagonist)
5. Meloxicam (anti-inflammatory effect of COX2 inhibitor)
6. Resveratrol (anti-inflammatory effect of natural phenol)
7. Linezolid (anti-inflammatory effect of oxazolidinone)
8. Atorvastatin (anti-inflammatory effect of statin)
9. Metformin (anti-inflammatory effect of biguanide)
10. Sildenafil (anti-inflammatory effect of phosphodiesterase inhibitor)
11. Tadalafil (anti-inflammatory effect of phosphodiesterase inhibitor)
12. Trimetazidine (anti-oxidant effect of fatty acid oxidation inhibitor)
13. Ozone therapy (anti-oxidant effect)
14. Melatonin (anti-oxidant effect of N-acetyl-5-methoxytryptamine)
15. Type 1 collagen (anti-oxidant effect)
16. Rosiglitazone (anti-oxidant effect of PPAR-γ agonist)
17. Medroxyprogesterone acetate (anti-estrogenic effect of progesterone)
18. Methylene blue (anti-oxidant effect)
19. Vitamin E (anti-oxidant effect)
20. Bevacizumab (fibrinolytic effect of angiogenesis inhibitor)
21. Ricinus oil (mechanic effect)

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 ischemia 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]. Ozçelik *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-

Table II. Characteristics of included studies

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 day 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.* 2009 [22]	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-inflammatory and immunomodulatory effects of linezolid.
Yilmaz *et al.* 2009 [29]	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.* 2007 [23]	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.* 2012 [24]	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.* 2012 [26]	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.* 2012 [27]	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.
Ozçelik *et al.* 2003 [30]	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.* 2005 [31]	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.* 2009 [32]	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. 15 mg vs. 4 ml vs. film	Single dose 3 weeks before surgery vs. 2 doses 3 weeks before surgery at the end of surgery vs. 3 doses during surgery vs. during surgery	Intramuscular 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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