

The effectiveness of intraperitoneal usage of hydroxyprogesterone caproate in prevention of postoperative adhesion: an experimental study

GÜL A.¹, KOTAN Ç.², ŞAHİN G.¹, TİMURKAN H.³, ERYAVUZ Y.⁴

Departments of Gynecology and Obstetrics¹, General Surgery², Experimental IVF Laboratory³, School of Medicine, Yüzüncü Yıl University, Van

Department of Surgery⁴, SSK Okmeydanı Hospital, İstanbul

Objective Postoperative adhesions following intraabdominal surgery are the most important cause of infertility and intestinal obstruction. Progesterones have anti-inflammatory and immunomodulating effects which may be useful in prevention of postoperative adhesions. We aimed to search the efficacy of the hydroxyprogesterone caproate in rats.

Method Twenty rats were randomly divided in to two groups with each group containing 10 rats. After 3 cm midline incisions, serosal defects were performed on the small intestines and anterior peritoneal surface by rubbing with a gauze sponge causing loss of serosal layer and petechial hemorrhages. Prior to closure of the abdomen 50 mg of hydroxyprogesterone caproate was instilled to the denuded area in group 1. The second group received no medication. 2 weeks after the surgery the rats were sacrificed and adhesions were scored according to the classification described by

Goldberg. Chi-square test was used for statistical analysis and statistical significance was defined as $p < 0.05$.

Results In the first group, there was 3 rats with grade 1, 4 rats with grade 2, 2 rats with grade 3 and 1 rat with grade 4 adhesions. In the control group, there was 1 rat with grade 1, 1 rat with grade 2, 4 rats with grade 3, 4 rats with grade 4 adhesions between the abdominal wall and the small intestines. The statistical difference was found between hydroxyprogesterone caproate positive and negative groups according to the adhesion scores.

Conclusion Our data showed that, peroperative intraperitoneally usage of hydroxyprogesterone caproate results with significantly less adhesion formation than control group. Despite this, there is not enough data about antiadhesive properties of progesterones.

Key words Postoperative adhesion, Progestagens.

Introduction

Postoperative adhesions and their complications are of great interest both for general surgeons and gynecologists. Abdominal postsurgical adhesions develop following trauma to the mesothelium, which is damaged often by surgical handling and instrument contact, foreign materials such as sutures and glove dusting powder, desiccation and over-heating. Understanding of the pathogenesis of adhesions has improved recently. Adhesions result from the normal peritoneal wound healing response and develop in the first five to seven days after injury (1). Adhesion formation and adhesion-free re-epitelization are alternative pathways, both of which begin with coagulation initiating a cascade of events resulting in the build-up of fibrin gel matrix. If not removed, the fibrin gel matrix serves as the progenitor to adhesions by forming a band or bridge when two peritoneal surfaces coated with it are opposed. The band or bridge becomes the basis for the organization of an adhesion (1,2).

There is no agreement about how to prevent adhesion formation and, what to use, adjuvants or barriers or any other method. For these purposes corticosteroids and NSAID's had been used frequently. It has been thought that these agents show their anti-adhesive effect by their immunomodulating

Accepted for publication: 18 May 1999

questionable clinical efficacy, possibly because of difficulties in drug delivery.

Modulation of the immune response to peritoneal injury may prevent postoperative adhesion formation (3). There is only few experimental reports about the use of progesterone acetate in the prevention of postoperative adhesions due to its anti-inflammatory and immunomodulating effects (4,5). In this study, we aimed to investigate antiadhesive effect of topical hydroxyprogesterone caproate.

Material and Method

Twenty rats weighing 200 to 250 gr were randomly divided in to two groups with each group containing 10 rats. The rats were anesthetized with 100mg/kg Ketamin given intramuscularly. Abdomen of the rats were shaved and prepared with polyvidone-iodine before surgery. The drapes, instruments and operative staff were all sterile. All of the rats underwent laparotomy trough a 3cm midline incision. Serosal defects were induced by abrading a 4cm segment of ileum near the ileocecal valve with rubbing a gauze sponge causing loss of serosal layer and petechial hemorrhages. 50 mg of hydroxyprogesterone caproate (HPC) was instilled to the denuded area in group 1. The second group received no medication. Abdominal wall of the all rats were sutured continuously with 2/0 Vicryl®.

Two weeks after the surgery, the rats were sacrificed and a second laparotomy was performed. The adhesions that had formed were divided and graded on a scale of 1-4 as previously described by Goldberg et al (6) (Table I).

Table I. Adhesion scores, described by Goldberg.

Grade 1	No adhesions
Grade 2	Fine filmy adhesions localized to the area of injury
Grade 3	Dense adhesions requiring sharp dissection but localized to the area of injury
Grade 4	Widespread adhesions outside the area of initial injury

Results

Table II. The number and grade of adhesions in study and control groups

	n	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)
Hydroxyprogesterone group	10	3	4	2	1
Control Group	10	1	1	4	4

Discussion

The major strategies for adhesion prevention or reduction are adjusting surgical practice and applying adjuvants. Surgeons should adjust their major practices by: 1- Becoming aware of the potential adhesive complications of a procedure; 2-Minimizing the invasiveness of surgery ;and 3-Minimizing surgical trauma, ischemia, exposure to intestinal contents, introduction of foreign material into the body, and use of talc or starch containing gloves (1). In this study adhesion model was designed with peritoneal trauma. And adhesions were developed in 9 of 10 rats in the control group. This result showed that, peritoneal trauma is effective way for developing experimental adhesion model. Postsurgical adhesions have four major negative impacts on health care outcomes: First; adhesion causes significant morbidity, including intestinal obstruction, infertility and pelvic pain. Second; adhesions are associated with multiple surgical complications. Third; these complications lead to greater surgical workload and utilization of hospital and other health care resources. Fourth; all these negative impacts result in significant economic burden to society (2,7).

The progenitor to adhesions is the fibrin gel matrix which develops in several steps. These include the formation and insolubilization of fibrin polymer and interaction with fibronectin and a series of amino acids. Protective fibrinolytic enzyme systems of the peritoneal mesothelium, such as the tissue plasminogen activator (tPA) system, can remove the fibrin gel matrix. However surgery dramatically diminishes fibrinolytic activity (8). This occur in at

In the early and late postoperative period there was no morbidity in any group. In group 1 to which hydroxyprogesterone caproate (HPC) was instilled to the denuded area, there were 3 rats with grade1, 4 rats with grade2, 2 rats with grade3 and 1 rat with grade 4 adhesions. In the control group there was 1 rat with grade 1,1 rat with grade 2, 4 rats with grade 3, 4 rats with grade 4 adhesions between the abdominal wall and the small intestines. Adhesion formation was significantly less in group1 when compared with the untreated control group (Table II).

Statistical analysis was performed using Chi-square test and statistical significance was defined as $p < 0.05$.

least two ways: first by increasing the levels of plasminogen activator inhibitors and second by reducing tissue oxygenation. Peritoneal re-epithelization and adhesion formation thus can be seen as alternative pathways following peritoneal injury (2). Improvements in surgical technique will help decrease but not prevent adhesion formation. Adjuvant therapy is necessary. Adjuvants fall into two main categories, drugs and barriers (7,9). NSAID's have shown questionable clinical efficacy, possibly because of difficulties in drug delivery (10). Corticosteroids alone also have equivocal clinical results and may be immunosuppressive and delay wound healing (3,10). Although topical use of HPC did not cause any hemorrhage or infectious complications, experimentally, fibrinolytics such as tissue plasminogen activator (tPA), administered systematically or intraperitoneally have demonstrated conflicting results and hemorrhage complications (8). Barriers, by separating traumatized surfaces for the critical first five to seven days of peritoneal re-epithelization, are useful adjuvants, and include macromolecular solutions and mechanical devices (7,9)

Modulation of the immune response to peritoneal injury may prevent postoperative adhesion formation (3). In one study NSAID's (tolmetin, ibuprofen, aspirin and indomethacin) were tested for their anti-adhesive effect and showed significant and comparable efficacy. These results further support the view that NSAID's act to prevent adhesions through a common mechanism. Thus, drugs which have anti-inflammatory effect and modulating immune response to peritoneal injury, by this mechanism, prevent postoperative adhesion formation (10). A lot of adjuvant and barrier agents

have been used experimentally and clinically for preventing adhesion formation. There are only few experimental reports about the systemic use of medroxyprogesterone acetate in the prevention of postoperative adhesions (4,5). But we did not find any report about the topical use of progestagens. Montanino et al, compared antiadhesive effect of the medroxyprogesterone acetate and leprolide acetate in an experimental study, and showed that medroxyprogesterone acetate was more effective in preventing adhesion formation (4). The authors suggested that this result may be due to anti-inflammatory and immunomodulating effects of progestagens (4). In an another experimentally study Baysal et al., used medroxyprogesterone acetate systemically, in rats, and showed that, it reduces adhesion formation significantly than control group (5). In this study we observed that local use of the HPC is effective as systemic use of the progestagens in the prevention of the adhesion formation.

Although our data showed that, adhesion formation rate was significantly lower in the hydroxyprogesterone caproate used group when compared with the untreated group; there are not sufficient studies about the usage of progestagens locally or systemically for anti-adhesive purpose, further studies are needed.

References

1. Holmdahl L, Risberg B, Beck DE, Burns JW, Chegini N, di Zerega GS, Ellis
2. Adhesions: pathogenesis and prevention-panel discussion and summary. Eur J Surg. Suppl. 577:56-62;1997.
3. Di Zerega GS. Biochemical events in peritoneal tissue repair. Eur J Surg Suppl 577:10-6;1997.
4. Holschinder CH, Cristoforoni PM, Ghosh K, Punyasavatsut M, Abed E, Montz FJ. Endogenous versus exogenous IL-10 in postoperative intraperitoneal adhesion formation in a murine model. J Surg Res 70(2):138-43;1997
5. Montanino OM, Metzger DA, Luciano AA. Use of medroxyprogesterone acetate in the prevention of postoperative adhesions. Fiftieth Annual Meeting of The American Fertility Society, 5:260;1994.
6. Baysal B, Eserol F, Buyru F, Kovacý E, Serdarođlu H, Sevilen F. Postoperatif adezyonlary önlemede medroxyprogesterone acetat'yn etkinliđi. Türk Fertilité Dergisi 4 (1):58-62;1996.
7. Goldberg EP, Sheets JW, Habal MB. Peritoneal adhesions. Prevention with the use of hydrophilic polymer coatings Arc Surg 115:776-80;1980.
8. Risberg B. Adhesions: preventive strategies. Eur J Surg Suppl ; (577):32-9;1997.
9. Rattery AT. Effect of peritoneal trauma on peritoneal fibrinolytic activity and intraperitoneal adhesion formation. Eur Surg Res 13:397-401;1981.
10. Luciano AA, Hauser KS, Benda J. Evaluation of commonly used adjuvants in the prevention of postoperative adhesions. Am J obtet Gynecol 146:88-92;1985.
11. Le Grand EK, Rodgers KE, Girgis W, Campeau JD, Di Zerega GS. Comperative efficacy of nonsteroidal anti-inflammatory drugs and anti-tromboxane agents in a rabbit adhesion-prevention model. J Invest Surg 8(3):187-94;1995

Correspondance to:

Dr. Abdulaziz GÜL
Yüzüncü Yıl Üniversitesi Tıp Fakültesi
Kadın Hastalıkları ve Doğum ABD
Van / TÜRKİYE