World J. Surg. 28, 662–665, 2004
DOI: 10.1007/s00268-004-6825-6

WORLD
Journal of
SURGERY

Comparative Effectiveness of Several Agents for Preventing Postoperative Adhesions

Jehat Kutlay, M.D., Yusuf Ozer, M.D., Burak Isık, M.D., Hulagu Kargici, M.D.

2nd General Surgery Department, SSK Ankara Teaching Hospital, Ankara 06090, Turkey

Published Online: June 8, 2004

Abstract. Postoperative adhesions (PAs) are usually clinically asymptomatic. Symptomatic cases, however, may present with chronic abdominal and pelvic pain, infertility, and intestinal obstruction; and they may require intensive, costly therapeutic modalities. Various agents have been used to prevent PAs, but the results indicate general suboptimal effectiveness. Our objective was to evaluate the comparative effectiveness of two pharmacologic agents for preventing PA: nadroparine calcium (low-molecular-weight heparin, or LMWH) and aprotinin, as well as a barrier agent, sodium hyaluronate/carboxymethycellulose (SCMC). Our subjects were 40 male Wistar-Albino rats divided into four groups, each consisting of 10 rats, which underwent standard cecal abrasion preceding midline laparotomy. In the control group (group 1) 1 ml of 0.9% NaCl was administered intraperitoneally before abdominal closure. In the three preventive groups, 100 U AXa (anti factor X activity) LMWH, 1800 IU aprotinin, and SCMC were administered intraperitoneally to groups 2, 3, and 4, respectively. Relaparotomy was performed on the 14th postoperative day. Visceral and abdominal wall adhesions were scored in a blinded fashion. The adhesion scores (mean ± SD) for groups 1, 2, 3, and 4 were 2.00 ± 0.67, 0.6.00 ± 0.84, 1.10 ± 0.74, and 0.20 ± 0.42, respectively. The differences in the adhesion scores among all three preventive groups (groups 2, 3, 4) were statistically significant when compared with the control group ($p < 0.001$, $p = 0.017$, $p < 0.001$, respectively). Intraperitoneal SCMC and administration of LMWH were more effective than giving aprotinin.

Postoperative adhesions (PAs) and their prevention, despite medical progress, remain essentially an unsolved problem. Peritoneal adhesion is the result of injury to the peritoneal surface. Adhesions frequently cause abdominal and pelvic pain, bowel obstruction, and infertility [1, 2]. Autopsy cases demonstrate a strong relation between abdominal surgery and subsequent intraperitoneal adhesions [3]. The incidence of PAs has been reported to be as high as 93%, and 3% of these patients eventually have intestinal obstruction at some point after surgery [4, 5]. In a multicenter study, all patients who had undergone abdominal surgery developed at least one adhesion [6]. Although more than 80% of patients' adhesions form between the incision and the omentum, in 50% of cases they also involve the intestines [7].

Postoperative adhesions account for approximately 70% to 80% of small bowel obstructions, and they are often associated with high morbidity and mortality [8], including chronic abdominal pain, gastrointestinal fistula formation, postsurgical reproductive organ complications, and even ureteral obstruction [9]. In women, abdominal adhesions comprise a major causative factor in infertility [10].

Numerous therapeutic agents have been used in attempts to prevent PA formation [11]. In this experimental study, we evaluated the comparative effectiveness of two pharmacologic agents—nadroparine calcium (Fraxiparine; Sanofi, Winthrop Industrie, Notre Dome de Bonville, France) and aprotinin (Trasylol; Bayer AG, Leverkusen, Germany)—and a commercially available barrier agent, sodium hyaluronate/carboxymethycellulose (SCMC) (Seprafilm; Genzyme Biosurgery, Cambridge MA, USA), which have been proclaimed to be effective in preventing PA formation.

Materials and Methods

Forty male 5-month-old Wistar-Albino rats at Ankara University Faculty of Medicine animal research laboratory, weighing 250 to 300 g, were acclimated to the new environment for 48 hours; they were maintained on standard rat chow and water. None of the rats was fasted before surgical intervention. The 40 rats were randomized into four groups of 10 each. Each rat was anesthetized with intramuscular ketamine (60 mg/kg) and xylazine (10 mg/kg). Each animal was prepared with povidone-iodine and draped in a sterile fashion. Using a lower midline incision, the cecum and terminal ileum were mobilized and a 1 cm^2 area of the cecum was rubbed with gauze until subserosal hemorrhage developed.

Prior to abdominal closure, group 1 (control), group 2 (LMWH), and group 3 (aprotinin) were given 1 ml of 0.9% NaCl 100 IU AXa (anti factor X activity) nadroparine calcium, and 1800 IU aprotinin intraperitoneally, respectively. In group 4, the area of cecal abrasion was covered with an SCMC sheet before abdominal closure. The abdomen was closed in running fashion with 4/0 polypropylene sutures, and the skin was closed with interrupted 4/0 silk sutures. Animals were allowed to feed ad libitum immediately after operation.

Relaparotomy was performed on the 14th postoperative day. The adhesions were scored by a surgeon (B.I.) blinded to the treatments, according to criteria described elsewhere [12, 13] (Table 1).

Correspondence to: Jehat Kutlay, M.D., Angora Evleri Bulusmalar Caddesi, F5/25 Beysukent, Ankara 06530, Turkey, e-mail: jkutlay@yahoo.com

Table 1. Adhesion classification.

0	No adhesion
1	Filmy thickness, avascular
2	Limited vascularity, moderate thickness
3	Well vascularized, dense thickness

The statistical analysis of adhesion scores between the groups was evaluated by Kruskal-Wallis variance analysis. When the p value from the Kruskal-Wallis test was statistically significant, multiple comparison tests were used to determine the groups that differed from others. Values are expressed as the mean ± 1 SD. A p value of < 0.05 was considered statistically significant.

Results

No deaths or complications were observed. The mean ± SD adhesion scores for groups 1, 2, 3, and 4 were 2.00 ± 0.67, 0.60 ± 0.84, 1.10 ± 0.74, and 0.20 ± 0.42, respectively. Adhesion scores of each group are summarized in Table 2. The rats treated with intraperitoneal aprotinin and LMWH showed a significant decrease in adhesion formation when compared with the no-treatment control rats (Figs. 1, 2). In regard of adhesion scores, there was a statistically significant difference between all three preventive groups [group 2 (LMWH), group 3 (aprotinin), and group 4 (SCMC)] compared with the control group ($p < 0.05$). There was no significant difference between group 2 (LMWH) and group 3 (aprotinin) ($p = 0.095$) or between group 2 (LMWH) and group 4 (SCMC) ($p = 0.205$). However, the difference between group 3 (aprotinin) and group 4 (SCMC) was significant in favor of SCMC ($p = 0.005$).

Discussion

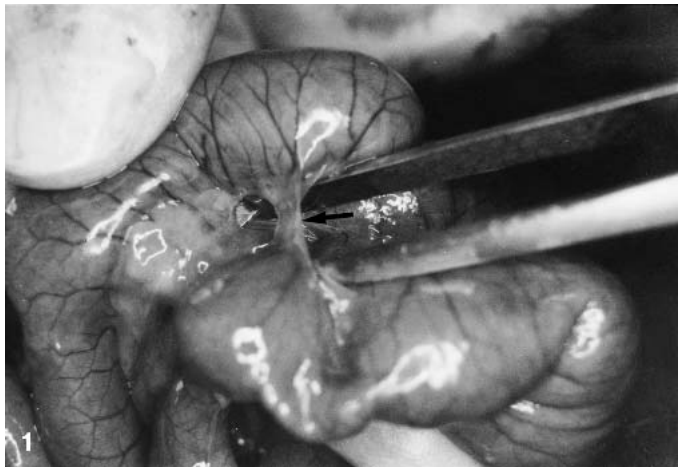
Peritoneal adhesion is the result of injury to the peritoneal surface. Surgical injury is a potent stimulus to the peritoneum, which results in the initial outpouring of a fibrinogen-rich inflammatory exudate that ultimately becomes fibrin. Associated with peritonitis is a substantial decrease in the fibrinolytic activity of the peritoneum, which allows the formed fibrin matrix to persist. Frequently bacteria are loculated in the fibrin matrix. As protected by the fibrin capsule, these bacteria may grow unimpeded by the defense mechanisms of the host. Contaminated fibrin predisposes the peritoneum to repeated bouts of infection and abscess formation. If the fibrin mesh is not cleared by the fibrinolytic process, the fibrin matures into dense adhesions. The extent of fibrin deposition depends on the balance between fibrin formation and fibrinolysis. PA formation, as a result of abnormal peritoneal healing, is due to insufficient fibrinolysis. A large number of therapeutic modalities have been studied clinically and in animal models in an attempt to decrease the frequency and severity of adhesion formation after peritoneal injury. The proposed mechanisms by which they may reduce adhesion formation are as follows: (1) reduce the initial inflammatory response and ensuing exudate release; (2) inhibit exudate coagulation; (3) enhance fibrinolysis; (4) mechanically separate fibrin-covered surfaces; and (5) inhibition of fibroblastic proliferation. Probably the most effective way to reduce PA formation is to diminish surgical trauma via careful surgical technique. However, surgical technique alone cannot eliminate de novo formation and reformation of PAs [14]. Even after adhesiolysis, PAs tend to reform [15] with increased morbidity and frequency of bowel obstruction [16]. Therefore preventing PA formation is of crucial importance.

Yano et al. described the putative mechanisms of the development of intestinal adhesions [17], stating that fibrin deposition occurs at the damaged serosal membranes, and failure of fibrin resolution induces contact with other serosal surfaces (i.e., fibrinous adhesions). Adhesion formation requires fibrin. Although exudation cannot be prevented, it may be possible to prevent coagulation

Table 2. Distribution of adhesion scores in all groups.

Score	Group 1 (control)	Group 2 (LMWH)	Group 3 (aprotinin)	Group 4 (SCMC)
0	0	6	2	8
1	2	2	5	2
2	6	2	3	0
3	2	0	0	0
Mean	2.0	0.6	1.1	0.2
Median	2	0	1	0

LMWH: low-molecular-weight heparin; SCMC: sodium hyaluronate/carboxymethylcellulose.



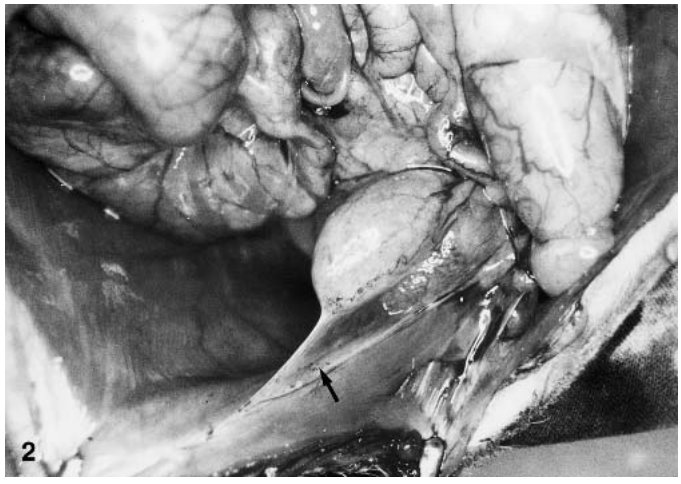


Fig. 1. Control group had extensive intraperitoneal adhesions with dense thickness (arrow).

Fig. 2. Sodium hyaluronate/carboxymethylcellulose (SCMC) group had minimal, avascular filmy thickness (arrow).

of the fibrinous exudate and its ultimate maturation to mature fibrous adhesions. In the case of lower fibrinolytic activity, fibroblast proliferation increases, followed by organization without mesothelial regeneration, causing fibrous adhesion [17].

Methods to prevent PA include (1) pharmacologic approaches aimed at influencing the early cellular and biochemical events involved in normal tissue repair and (2) mechanical approaches that separate damaged tissues during the healing process [18, 19]. Adhesion formation begins 24 to 48 hours after injury, during the inflammatory stage of healing, and the adhesions are usually well formed by the fifth to seventh days after injury [20–22]. Physical barriers such as SCMC, which we used in this study, keeps serosal and peritoneal surfaces separate during the healing phase. Aprotinin decreases PA formation probably by preventing early depression of local fibrinolytic activity [23]. Heparin administered systematically or intraperitoneally has effectively inhibited adhesion and abscess formation in animals with experimental peritoneal damage. The most likely explanation for the mechanism of action of heparin is that it acts as an anticoagulant and activates antithrombin III, resulting in a reduction of fibrin clots. It is also possible that the fibrin matrix is imperfect secondary to the heparin effect, making it more susceptible to plasminogen. Heparin directly stimulates tissue plasminogen activator activity and increases the activation of plasminogen, which would enhance fibrinolysis [24]. In this study we used nadroparine calcium, an LMWH that, compared to unfractionated heparin, has higher antithrombotic activity, more bioavailability, a longer biologic half-life, and reduced risk of hemorrhage [25]. The results presented here confirm and augment the extensive experimental evidence from other laboratories on the efficacy of heparin and SCMC regarding both the grade and incidence of adhesions. No hemorrhagic complication was observed in any group.

Conclusions

Minimal surgical trauma by a diligent technique seems to be the most effective way to reduce postoperative adhesion formation. Adjuvant preventive interventions that decrease the incidence and intensity of Pas as well as SCMC application and administration of intraperitoneal nadroparine calcium were found to be more effective than aprotinin. Clinical application of antiadhesive agents may be recommended during abdominal surgery.

Résumé. Les adhérences postopératoires (AP) sont habituellement cliniquement asymptomatiques. Par contre, lorsqu'elles sont symptomatiques, elles se présentent sous forme de douleurs abdominales et pelviennes chroniques, et peuvent être une cause d'infertilité et d'occlusion intestinale: les modalités thérapeutiques peuvent être importantes et coûteuses. De nombreux agents ont été utilisés pour prévenir les AP; les résultats, cependant, indiquent une efficience générale en dessous des effets attendus. Notre objectif a été d'évaluer l'efficience comparative de deux agents pharmacologiques, la nadroparine calcique [l'héparine à bas poids moléculaire (LMWH)]; et l'aprotinine, et un agent de protection mécanique la carboxyméthycellulose/hyaluronate calcique (SCMC) dans la prévention des AP. Quarante rats mâles Wistar-Albino, divisés en quatre groupes de 10, ont eu une abrasion cécale avant de subir une laparotomie médiane. Dans le groupe de contrôle (groupe 1), on a administré en intrapéritonéale 1 ml de NaCl à 0.9% avant la fermeture de l'abdomen. On a administré de l'Axa LMWH, 100 U, de l'aprotinine, 1800 UI, et de la SCMC en intrapéritonéale dans les trois autres groupes, dits de prévention, respectivement, groupes 2, 3 et 4. Une relaparotomie a été réalisée au 14è jour postopératoire. Les adhérences ont été cotées d'une manière à simple insu. Les scores d'adhérences (moyen ± ET) ont été 2.0 ± 0.67, 0.60 ± 0.84, 1.10 ± 0.74, et 0.20 ± 0.42 pour, respectivement, les groupes 1, 2, 3, et 4. Les résultats de scores d'adhérences ont été statistiquement significativement différentes parmi les trois groupes de prévention (groupes 2, 3, et 4) comparées au groupe de contrôle (respectivement, $p < 0.001$, $p = 0.017$, et $p < 0.001$). L'administration intrapéritonéale de SCMC et l'application de LMWH ont été moins efficientes que l'aprotinine.

Resumen. Las adherencias postoperatorias (AP) generalmente son clínicamente asintomáticas. Sin embargo, los casos sintomáticos pueden presentar dolor abdominal y pélvico, infertilidad y obstrucción intestinal que pueden implicar modalidades terapéuticas intensas y costosas. Diversos agentes han sido utilizados en su prevención, pero los resultados señalan una eficacia menos que óptima. Nuestro propósito fue evaluar la eficacia comparativa de dos agentes farmacológicos, nadroparina cálcica (heparina de bajo peso molecular—HBPM) y aprotinina, y un agente de barrera, la carboximetilcelulosa/hialorunato sódico (CMCH) en cuanto a la prevención de AP. Se tomaron 40 ratas macho Wistar-Albino en 4 grupos, cada uno de 10 ratas, que fueron sometidas a abrasión cecal estándar por laparotomía de línea media. En el grupo control (grupo 1) se administró 1 ml de NaCl 0.9% por vía intraperitoneal antes del cierre de la pared abdominal. En los tres grupos de prevención se administraron 100 U AXa HBPM, 1800 U de aproptinina y CMCH por vía intraperitoneal en los grupos 2, 3, y 4 respectivamente. Se practicaron relaparotomías en el día 14 postoperatorio, registrando de manera ciega las adherencias viscerales y a la pared abdominal. Los "scores" promedio de adherencia, para los grupos 1, 2, 3, y 4 fueron 2.0 ± 0.67, 0.60 ± 0.84, 1.10 ± 0.74, y 0.20 ± 0.42, respectivamente. Las diferencias en los "scores" de adherencias en los tres grupos de prevención (grupos 2, 3, 4) resultaron estadísticamente significativas en comparación con el grupo control ($p < 0.001$, $p = 0.017$, $p < 0.001$, respectivamente). La administración intraperitoneal de CMCH y la aplicación de HBPM aparecieron más eficaces que la aprotinina.

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