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The Effect of Hyaluronic Acid/Carboxymethylcellulose in the Prevention of Postoperative Adhesion in Guinea Pigs

Kobaylarda Postoperatif Adezyonların Önlenmesinde Hyaluronic Acid/Carboxymethylcellulose'un Etkisi

Savaş TEZEL[1], Reha ÖZGÜVEN[1], Selma TUNÇOL[1]

[1] Ankara Eğitim ve Araştırma Hastanesi, 3. Genel Cerrahi Kliniği, ANKARA

SUMMARY

It is well known that appropriate surgical technique alone will help decrease but not prevent intraabdominal adhesion formation. It is necessary to use adjuvant therapy that falls into two main categories, drugs and barriers. This study was designed to determine the effectiveness of HA/CMC (Hyaluronic acid/Carboxymethylcellulose) as a barrier agent for preventing postoperative adhesions and also to determine whether it alters abdominal wound tensile strength.

An adhesion forming state was created by traumatization of peritoneal and serozal surfaces and inoculation of self blood on traumatized areas in 30 guinea pigs. HA/CMC was applied between the viscera and the abdominal wall before laparotomy closure in the experimental group (n= 15). Three weeks after the operation the adhesion scores were obtained and the abdominal wall wound was evaluated for tensile strength.

Adhesion formation was significantly lower in the study group compared to the control group ($U= 197$, $p< 0.05$). There were no statistically significant difference for tensile strength between the two groups ($U=113$, $p> 0.05$).

HA/CMC has no adverse effect on wound tensile strength, while significantly lowering adhesion formation. However, it does not totally prevent it. Future investigations on its insufficient states and causes will help in obtaining successful results.

Anahtar Kelimeler: *Prevention of adhesion formation, hyaluronic acid/carboxymethylcellulose.*

ÖZET

Uygun cerrahi tekniğin tek başına adezyon oluşumunu azaltmaya yardımcı olabileceği fakat adezyon oluşumunu tümden engellemeye yetmeyeceği iyi bilinmektedir. İlaçlar ve bariyerler olmak üzere 2 ana grupta toplanan yardımcı yöntem kullanımı gereklidir. Bizim bu deneysel çalışmadaki amacımız, hem genel cerrahi hem de jinekoloji kliniklerinde giderek daha yaygın kullanılmaya başlanan, bariyer materyali HA-CMC'nin, adezyon oluşumunu engellemedeki etkinliğini, yara gerilim kuvveti üzerine olumsuz etkisinin olup olmadığını belirlemektir.

Laparotomi sırasında peritoneal ve serozal hasar ile kan kullanılarak adezyojenik ortam oluşturulan 30 kobayın yarısına, batın kapatılmadan önce HA-CMC yerleştirildi. 3 haftanın sonunda yüksek doz eter anestezisi ile deneklerin hayatları sonlandırıldıktan sonra adezyon skorlaması ve yara gerilim kuvveti ölçümleri yapıldı.

Adezyon oluşumu, çalışma grubunda kontrol grubuna göre anlamlı ölçüde daha azdı ($U= 197$, $p< 0.05$). Gruplar arasında, yara gerilim kuvvetleri yönünden istatistiksel anlamlı fark gözlenmedi ($U= 113$, $p> 0.05$).

HA-CMC, yara gerilim kuvveti üzerine olumsuz etki yapmadan adezyon oluşumunu anlamlı derecede azaltmış fakat tamamen önleyememiştir. Yetersiz kaldığı durumların irdelenmesi, daha başarılı sonuçların alınmasına yardımcı olacaktır.

Key Words: *Adezyon, hiyaluronik asit, karboksimetilselüloz.*

INTRODUCTION

Postoperative abdominal adhesions are formed following damage to the rnesothelium due to causes such as instrument contact, foreign bodies, dead tissues, powder, drying and excess heat. Adhesion formation is observed following the great majority of surgical interventions. While causing serious complications such as intestinal obstruction, infertility and pain, it is also a clinical problem, which incurs significant economic expenditures (1,2).

Two strategies aimed at preventing or decreasing adhesion formation are appropriate surgical technique and ancillary methods. In general surgical practice:

1. One should be vigilant about the potential adhesive complications of the intervention;

2. The invasiveness of the surgery should be kept at the minimum level;

3. A practice which will reduce surgical trauma, ischemia and foreign body reaction to a minimum should be sustained. It is well known that an appropriate surgical technique alone may help to decrease adhesion formation, although it will not be sufficient to completely prevent adhesion formation (3). Employment of ancillary methods classified under the two main groups of drags and barriers is necessary (3). With this objective, a semitransparent hyaluronic acid/carboxymethylcellulose (HA/CMC) membrane belonging to the barrier group is being used increasingly more frequently in both surgical and gynecological clinics (2).

Our aim in this experimental study is to determine the effectiveness of the hyaluronic acid/carboxymethylcellulose membrane in preventing adhesion formation and to observe whether it has negative effects on wound tension force.

All of the operations have been performed by the same team. Scorings and assessment of the findings have been carried out by a physician who had no information about the groups. The non-parametric Mann-Whitney U test has been used as a statistical method (4).

MATERIALS and METHODS

In the study conducted in the experimental laboratory of our hospital, 30 each 6-month old, male guinea pigs with weights ranging between 450 to 500 grams were used. The guinea pigs were randomized into S (Study) and C (Control) groups. After the guinea pigs' abdomens were sterilized, the abdomen was opened with a 5 cm median incision over the umbilicus under Ketamine HCL 35 mg/kg and Xylazine HCL 5 mg/kg anesthesia. Serosal drying was applied for 5 minutes by placing two dry sponges on the intestines under the incision. In the meantime, the peritoneum on both sides of the incision was prepared as a flap starting from the edge of the incision and extending 1 cm laterally along the posterior sheath of the rectus muscle. The sponges were removed 5 minutes later. After the intestines were explored first with a sponge and then with talcum powdered gloves and pincettes, two small vessels each behind one of the tube rectus muscles were cut thus allowing a small amount of blood to exude into the inter-intestinal space. No additional procedures were performed on the C group. In the S group, the abdomen was closed with 4/0 silk sutures one by one in a fashion including the peritoneum after two pieces of (HA/CMC) measuring 3 x 3 cm were placed under the incision with a very little overlap in the middle.

At the end of 3 weeks, the guinea pigs were sacrificed under a high dose of ether anesthesia and their abdomens were opened with a U type incision extending from the bilateral costal arch to the pelvis. The adhesions were assessed using a scoring sys-

Table 1. Adhesion scoring method.

Scor	Extension (Adhesion/Incision)	Appearance	Resistance
0	None	None	None
1	< %25	Tulle, transparent, avascular	Easily separated
2	< %50	Opaque, semitransparent, avascular	Separated by traction
3	< %75	Opaque, semitransparent, capillary	Separated by sharp dissection
4	> %75	Opaque, large vessels present	

The adhesion score in equal tothe sum of the scores the adhesion received from each section. The highest possible score is 11.

tem (Table 1). Based on extension, appearance and resistance to snapping. In order to assess wound tension force, a muscle tissue 2 cm inferior to the xiphoid process, measuring 5 x 1 cm was excised from the abdominal wall with its lower side vertical to the incision plane with the incision scar remaining in the middle plane.

The wound tension force measurements were carried out in the Polymer Laboratory of the Department of Chemistry, Faculty of Science at the Middle East Technical University using a tension measurement device called Instron (Tensile testing machine TM1102). For each piece, measurements were taken with a 2.5 cm initial length and 0.62 cm/min elongation rate. The tension forces were recorded in grams (g).

RESULTS

There were postoperative problems in only two of the subjects included in the study: One in the control group who removed the sutures on postoperative day 1 by itself and had a skin gap which healed secondarily, and one in the study group who developed a subcutaneous purulent infection and healed after having been drained on postoperative day (5).

The adhesion scoring results of all 30 subjects included in the study are shown in (Figure 1). Statistically, adhesion formation is significantly less in the study group (Mann-Whitney U; U= 197, $p< 0.05$).

While there are 9 subjects in the group to whom HA/CMC was applied and no adhesion is observed, it is only 2 in the control group (Figuri 1). It is observed that subjects in the control group obtained higher results in the scoring (Figure 1). In a subject in the study group who developed a subcutaneous infection and in whom drainage was done on postoperative day 5, it is a striking finding to observe omental adhesion despite the HA/CMC at the 1 cm incision area matching only that region.

Besides finding no statistical differences between the study and control groups in the tension forces the tissue parts could withstand (Mann-Whitney U; U= 113, $p> 0.05$), in all subjects snapping occurred not at the region of the scar tissue but at the intact muscle tissue.

DISCUSSION

The most suitable antiadhesive material should not be permanent, should not have adhesiogenic properties, should continue to be effective in the presence of blood and should not affect wound healing negatively (5). At present, HA/CMC, which may be said to have all these properties, seems to be ideal in this respect.

In our experimental study, while significantly reducing adhesion formation, HA/CMC has not been able to prevent it completely. In experimental studies in which incisional hernia repair has been performed with polypropylene mesh, it has been shown that HA/CMC is effective in preventing adhesions (6-9). Becker, in a clinical study in which he included patients in whom he performed pouch-anal anastomosis with colectomy and diverting loop ileostomy for ulcerative colitis and familial polyposis, has reported that HA/CMC is effective in preventing the formation of abdominal adhesion and also that it does not negatively affect the safety of the patients (10). In another study including patients in whom excision of the uterus myoma has been performed, Diamond has

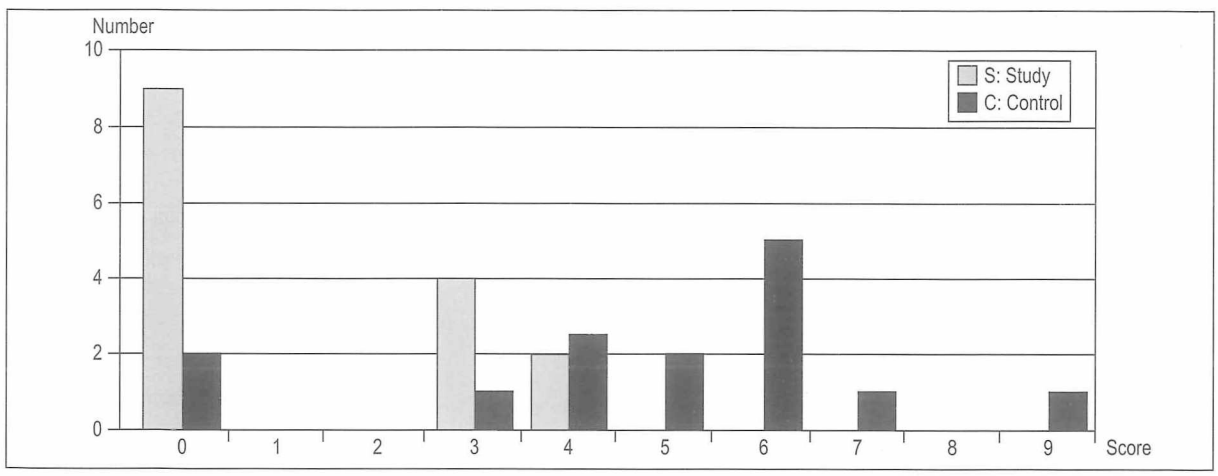

Figure 1. The distribution of adhesion scores in the study and control groups.

again found HA/CMC to be successful without observing increases in postoperative complication rates (11).

The main mechanism for the antiadhesive effect of HA/CMC is its forming a transient mechanic barrier between surfaces having an adhesive potential in the postoperative healing phase (7). Although the mechanism of action of carboxymethylcellulose (CMC), which is one of its components, is not clearly understood, there are experimental studies reporting its effectiveness in preventing adhesions (12-16). CMC may be exerting this effect by preventing direct contact of serosal surfaces by accumulating fluids around itself (hydrofloatation effect) and by preventing the damaged surfaces from facing each other by covering the intraperitoneal surfaces (siliconization effect). In some experimental studies CMC is reported not to have a pronounced effect in preventing adhesions (17,18), while in some others it is reported to significantly suppress wound healing (6,12,17,18). The negative effect of the material on wound healing has been attributed to the suppression of the release of the fibroblast activating cytokines from platelets, endothelial and inflammatory cells or to the induction of fibroblast growth inhibitors released from macrophages (12). This mechanism may be contributing to the antiadhesive action of CMC at the same time (16).

Shushan has indicated that hyaluronic acid, which is the other component of HA/CMC, has an antiadhesive effect and that it may be exerting this effect by its inhibitor effect on platelet aggregation or via receptors on epithelium, macrophage and other mononuclear phagocytes (19). There are data indicating that HA suppresses inflammation, prevents fibrin formation and speeds up the healing of peritoneal tissue (20-22). It is known that inflammation plays a key role in adhesion formation (23-25). Macrophages carry the hyaluronate-CD44 receptors known to regulate cytokine response (26,27). All these data indicate that HA plays a regulatory role in inflammation and wound healing. Hyaluronic acid also speeds up wound healing without causing excessive development in the connective tissue in some tissues, including the peritoneum (22). Despite the well-known negative effect of CMC on wound healing, this effect of HA may account for the absence of negative effects on wound healing in the experimental studies in which HA/CMC is used (6,8). In our study too, the absence of differences between the study and control groups in the tension forces the tissues could withstand as well as the occurrence of snapping at the intact muscle tissue and not at the scar region may be suggesting that HA/CMC does not affect wound healing negatively. There are also studies reporting that this material does not negatively affect anastomosis safety (28-30).

In the study group, the observation of omental adhesion despite HA/CMC in the 1 cm incision area matching only that region in one subject who developed subcutaneous infection and who had it drained on postoperative 5th day is a striking finding. Reijnen, Medina, and Moreira have reported that HA/CMC has been ineffective in preventing adhesion formation successively in intraperitoneal infection, incomplete colonic anastomosis with enteric ooze and in the presence of enterotomy (5,20,29). Bothin, on the other hand, in a study he conducted on rats has reported that contamination with intestinal flora increases adhesion (31). As Harris has pointed out, the prolongation of the critical period (at least 36 hours) required for the successful action of the barrier materials due to infection, inflammation and ischemia or the increased power of the stimulant playing a role in adhesion formation may render HA/CMC inadequate in preventing adhesion formation (14).

Although we have not encountered a similar pathology in our study, it has been reported that HA/CMC may cause extensive peritoneal inflammatory reaction with intensive foreign body reaction (32). In the case presented, while corticosteroid use has been said to improve the clinical course of the patient, the application of a skin test prior to the use of similar materials has been recommended, especially in patients having a history of allergy.

CONCLUSION

In our study simulating a surgical technique inappropriate for adhesion formation, HA/CMC has significantly decreased adhesion formation without negatively affecting wound tension force, but it has not been able to prevent it completely. We believe that the investigation of the cases in which it has been inadequate and their reasons will help to achieve more successful results in preventing adhesion formation.

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