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RESEARCH ARTICLE

The Efficacy of Carboxymetylcellulose for Prevention Adhesion Formation After Thyroid Region Surgery

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Summary

Aim of this study is to investigate the impact of carboxymetylcellulose about adhesion formation, fibrosis and inflamation after thyroid region surgery in an animal model. Forty rats were grouped into four and a cervical midline skin incision was made. Both thyroid lobe were seen and they were sutured two times per lobe with silk suture in group I, II, III and IV. In addition this procesure a sheet of the Carboxymethylcellulose (CMC) membrane was placed on thyroid glands before closing in goup III and IV. Rats were sacrified at seventh day in groups I, III and at twenty-eighth day in groups II, IV. In all groups adhesion formation, fibrosis and inflamation were evaluated and compared statistically. The comparison of groups in terms of macroscopic adhesion, fibrosis and inflammation scores revealed a statistically significant difference between Group I and Group III, and Group II and Group IV. (P<0,0001) Severe fibroblast proliferation was seen in the control groups and minimal fibroblast proliferation was seen in CMC membrane groups. CMC usage may be proceed to avoid from adhesion in reexploration expected thyroid surgery.

Keywords: *Adhesion, Thyroid surgery, Reoperation, Ccarboxymetylcellulose, Prevention*

Tiroid Bölgesi Ameliyatlarından Sonra Oluşan Adezyonu Önlemede Karboksi Metil Selülozun Etkisi

Özet

Bu çalışmada amaç, ameliyat sonrası yapışıklık oluşmasını önlemek için kullanılan karboksimetil sellüloz (KMC)'un tiroid bölgesi ameliyatlarından sonra oluşan fibrosiz, enflamasyon ve yapışıklıkları önlemedeki etkisini irdelemek. Kırk rat onarlı dört gruba ayrıldı. Tüm ratlara servikal insizyon yapılarak her iki tiroid lobu görüldü ve her bir lob ipek ile iki sefer sütüre edildi. Sütür sonrası kontrol grupları (1,2) kapatılırken çalışma gruplarına (3,4) KMC uygulandı. 1. ve 3. gruplar 7.gün, 2. ve 4. gruplar 28. gün sakrifiye edildiler. Gruplar adezyon oluşumu yönünden karşılaştırıldılar. Makroskopik adezyon yönünden karşılaştırma yapıldığında Grup I ile Grup III arasında ve Grup II ile Grup IV arasında anlamlı fark bulundu (P<0,0001). Histopatolojik incelemede inflamasyon ve fibrozis skorları açısından Grup I ile Grup III arasında ve Grup II ile Grup IV arasında anlamlı fark tespit edildi (P<0,0001). Reexplarasyon beklenen tiroid ameliyatlarında, yapışıklıkları önleyici olarak KMC kullanımı düşünülebilinir.

Anahtar sözcükler: *Yapışıklık, Tiroid cerrahisi, Reoperasyon, Karboksimetil selüloz, Önlem*

INTRODUCTION

While the complication rate of thyroid surgery has been reduced to approximately 1% as a result of the development of novel techniques, it still remains as a problem for the surgeons and endocrine surgeons. Complication rate can be further reduced by increasing of experience, adequate evaluation of the surgical indication, paying utmost care to the application of surgical technique and rules, and

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performing a decent preoperative preparation [1-4] .

Reoperative thyroid surgery carries significantly increased risk of morbidity. The major risk of complications occurs during dissection of the scar tissue surrounding either the recurrent larengeal nerve or the vascular pedicle of the parathyroid glands [5] .

The principal indications for reoperative thyroid surgery are removal of the thyroid remnant for the presence of a thyroid cancer in the initially removed thyroid tissue, recurrent thyroid cancer, occurrence of cancer in the thyroid remnant after operation for benign thyroid diseases, symptomatic recurrent nodular or multinodular goiter, and recurrent thyrotoxicosis [6].

The efforts for decreasing scar formation and adhesion formation after thyroid surgery may decrease the risk of complications after reoperative thyroid surgery. Carboxymethylcellulose (CMS) is a polysaccharide that can prevent adhesion formation when combined with hyalurinic acid (HA) or glicosaminoglycan (GAG). It is used as a barrier method for preventing adhesion formation due to its viscosity and high molecular weight. In the literature the effects of CMS shown very well after abdominal surgery [7-9].

Aim of this study is to investigate the impact of CMS about adhesion formation, fibrosis and inflamation after thyroid surgery in an animal model.

MATERIAL and METHODS

This study was performed in the Haydarpasa Numune Education and Research Hospital Animal Research Laboratory and was approved by Marmara University Medical Faculty, Experimental Research and Experimental Animal Ethical Committee. Fourty male Wistar Albino rats approximately weighing 180-220 g were used. The animals were cared for according to the principles of the National Institutes of Health publication “Guide for Care and Use of Laboratory Animals,” revised 1996.

Surgical Procedure

All rats were anesthetized with 50 mg/kg ketamine (Ketalar, Pfizer, Turkey) and with 10 mg/kg xylazine HCl (Rompun, Bayer, Turkey), both given intramuscularly. The neck was shaved and prepared with povidone-iodine solution. All surgical procedures were performed under aseptic conditions. A 1.5 cm. cervical midline skin incision was made. Submaxillary glands and the muscles were separated to both sides from the midline. The trachea was exposed, and both thyroid lobe were seen *(Fig 1)*. They were sutured two times per lobe with 5/0 silk suture. The muscles and glands were replaced to their original positions. The skin incision was closed with 5-0 polypropylene suture.

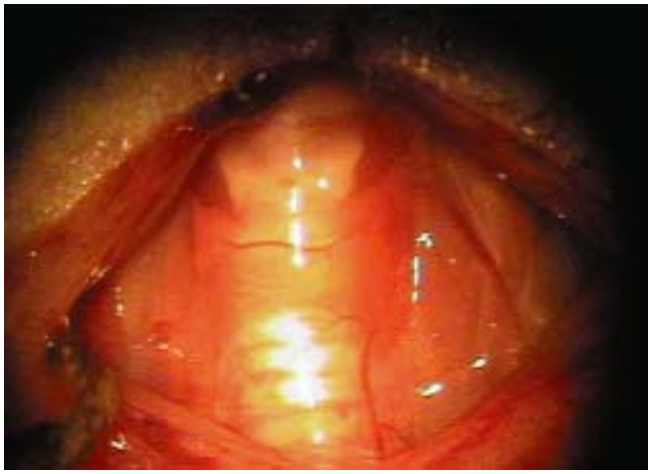

Fig 1. The view of the thyroid lobes under microscope x 25
Şekil 1. Tiroid loblarının görünümü 25x büyütme ile

Rats were grouped into four.

In Group I: Only surgical procedure was performed and rats were sacrified at seventh day.

In Group II: Only surgical procedure was performed and rats were sacrified at twenty-eighth day.

In Group III: Surgical procedure was performed. Before closing a 1x1 cm. sheet of the CMC membrane (Seprafilm, Genzyme Company, Cambridge, MA) was placed on thyroid glands. Rats were sacrified at seventh day.

In Group IV: Surgical procedure was performed. Before closing a 1x1 cm. sheet of the CMC membrane was placed on thyroid glands. Rats were sacrified at twenty-eighth day.

In all groups sacrification was performed with high dose anesthesia.

Evaluation of Adhesion Formation

Adhesion formation was evaluated macroscopicaly and microscopically. Macroscopic evaluation was performed according to a qualitative scale *(Table 1)* at seventh and twenty-eight day after sacrification by a researcher blind to surgery [10].

Histopathologic Evaluation

Histopathologic evaluation was performed by an independent pathologist whom graded amounts of

fibrosis and inflammation at the strap muscles-sutured area interface in each specimen with a semiquantitative scoring system [11] *(Table 2)*.

Table1. *Adhesion severity scoring scale* [10]
Tablo 1. *Yapışıklık derecesi skorlama skalası* [10]

Score	Evaluation
0	no adhesion
1	filmy adhesions easily separable with blunt dissection
2	mild to moderate adhesions with freely dissectible plane
3	moderate to dense adhesion with difficult dissection
4	non-dissectible plane

Table 2. *Histopathologic evaluation, according to fibrosis grading scale and inflamation grading scale* [11]
Tablo 2. *Fibrosis ve enflamasyon oluşum skalasına göre yapılan histopatoljik değerlendirme* [11]

Score	Fibrosis grading scale	Inflammation grading scale
0	Nil	Nil
1	Minimal, loose	Giant cells, occasional lymphocytes, and plasma cells
2	Moderate	Giant cells, plasma cells eosinophils, neutrophils
3	Florid, dense	Many in.ammatory cells, microabscesses

Statistical analysis

The Graph Pad Prisma V.3 software package was used for statistical evaluations. For data analysis, in addition to descriptive statistics (mean ± SD), the Mann-Whitney U test for groups comparisons were used. A P value <0.05 at the 95% confidence interval was considered significant.

RESULTS

The standardized surgical procedures and the administration of the protocols were well tolerated by the animals. None of the animal died postoperatively.

The comparison of groups in terms of macroscopic adhesion and inflammation scores revealed a statistically significant difference between Group I and Group III, and Group II and Group IV. (P<0.0001) (*Table 3* and *4*) Severe adhesion *(Fig 2)* and fibroblast proliferation was seen in the control group. In the Seprafilm group, minimal fibroblast proliferation and adhesion were seen *(Fig 3, 4)*.

Table 3. *Frequencies of adhesion scores in the groups*
Tablo 3. *Gruplardaki yapışıklık skorlaması değerlendirmesi*

macroscopic	7th day		28th day	
	Group I	Group III	Group II	Group IV
0	-	-	-	1 (10%)
1	-	-	-	7 (70%)
2	-	8 (80%)	-	2 (20%)
3	6 (60%)	2 (20%)	3 (30%)	-
4	4 (40%)	-	7 (70%)	-

Table 4. *Frequencies of inflammation scores in the groups*
Tablo 4. *Gruplardaki enflamasyon skorlaması değerlendirmesi*

Inflammation	7th day		28th day	
	Control	Sepraflim	Control	Sepraflim
0	-	-	-	-
1	-	8 (80%)	-	7 (70%)
2	2 (20%)	1 (10%)	4 (40%)	3 (30%)
3	8 (80%)	1 (10%)	6 (60%)	-

Fig 2. Macroscopic wiew of adhesions in control group
Şekil 2. Kontrol grubunda yapışıklıkların makroskopik görünümü

The evaluation regarding fibrosis scores demonstrated a statistically significant difference between Group I and Group III, and Grup II and Group IV (P<0.0001) *(Table 5)*.

Table 5. *Frequencies of fibroblast cell density scores in the groups*
Tablo 5. *Gruplardaki fibroblast hücre yoğunluğu skorlamasının değerlendirmesi*

Fibroblast	7th day		28th day	
	Control	Sepraflim	Control	Sepraflim
Stage 0	-	-	-	6 (60%)
Stage 1	-	7 (70%)	2 (20%)	3 (30%)
Stage 2	3 (30%)	2 (20%)	8 (80%)	1 (10%)
Stage 3	7 (70%)	1 (10%)	-	-

Fig 3. Macroscopic wiew of adhesions in CMC membrane group
Şekil 3. KMS grubunda adezyonların makroskopik görünümü

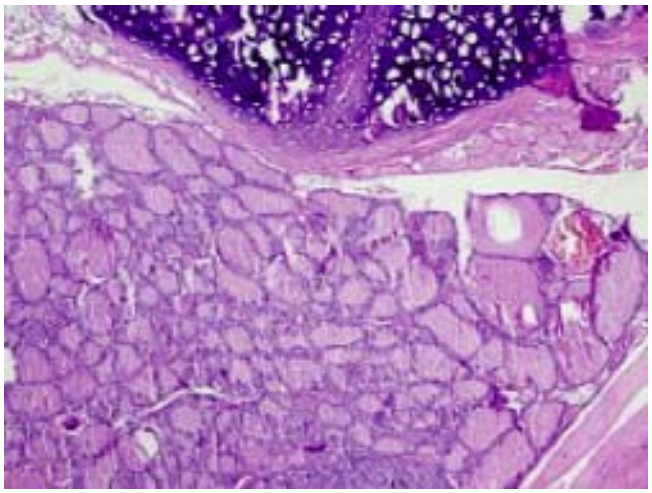

Fig 4. Minimal fibroblast proliferation was seen in thyroid gland at CMC group (H&EX100)
Şekil 4. KMC grubunda thyroid de minimal fibroblat proliferasyonu

DISCUSSION

Reoperative thyroid surgery is an operation associated with a higher complication rate than that seen with the initial operation. Some surgeons hesitate to perform reoperative thyroid surgery for fear of the complications, such as hypoparathyroidism which is seen in an incedence of 3% to 15 % for reoperative thyroid surgery, or injury to the recurrent laryngeal nerve which is seen in an incedence of 17%, but as technique and experience have improved, this incedence of complications has gradually decreased [2]. In the literature incidence of transient recurrent laryngeal nerve (RLN) injury is reported as 3% and in another study consisting of 165 patients who underwent completion thyroidectomy, transient RLN palsy also occurred in 3%, and permanent RLN palsy occurred in 5.5% 12,13. Pasieka et al.[14] reported in their series of patients treated for differentiated thyroid carcinoma with a thyroid reoperation, the incidence of RLN injury was 5%, and transient hypoparathyroidism was found to be 8%. These complications may occure during dissection of the scar tissue surrounding either the reccurent laryngeal nerve or the vascular pedicle of the parathyroid glands [2].

The efforts for decreasing scar formation and adhesion formation after thyroid surgery may decrease the risk of complications after reoperative thyroid surgery. Many approaches to prevent adhesions have been suggested, but they either have not withstood rigorous clinical examination or they have major practical limitations. Some approaches that have been investigated include pharmaceutical agents (corticosteroids, nonsteroidal anti-inflammatory drugs), fluid instillations (dextran, carboxymethylcellulose, lactated Ringer's solution), and physical barriers (oxidized-regenerated cellulose, expanded polytetrafluoroethylene) [15].

Seprafilm Bioresorbable Membrane (Genzyme Corparation, Cambridge, MA) is an adhesion prevention barrier composed of chemically derivatized Na-HA and CMC. Na-HA is a naturally occurring GAG found in connective tissue, synovial fluid, umblical cord, and vitrous humor [9]. This formulation was developed to prevent contact between viscera -the so- called hydroflotation effect. The hydroflotation effect of CMC membrane may have helped to prevent adhesions between serosal surfaces [16,17]. The resorption of this material from the peritoneal cavity occurres within seven days and its excretion from the body occures within twentyeight days [9].

Although it has been suggested that the completion thyroidectomy should be performed either during same hospital stay or 3-4 month period to avoid technical difficulties and to decrease the incidence of complications, Chao et al.[2] concluded that they did not find the timing as a contributory factor for complication formation. Also in our study there was no statistically significance (P= 0, 18) between control groups according to macroscopic adhesion scoring. We have encountered similar macroscopic dense adhesions at seventh and twenty-eighth days. So the timing of the second operation is debatable.

In our study we encountered that macroscopic adhesion scoring, inflammation grading, and fibrosis grading were high in control groups in comparison to seprafilm groups and the results are statistically significant.

In conclusion, further clinical investigations are needed to evaluate the effects of CMC membrane after thyroid surgery, but it is considered advisable to use CMC membrane as an anti-adhesive barrier after thyroid surgery if reexploration is expected.

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