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Impact of Polyethylene Glycol and Dextran 70 Treatment on Adhesion Formation after Subtotal Thyroidectomy

Sanem Guler Cimen[1,*], Koray Atila[1], Sertac Cimen[1], Melih Kaan Sozmen[2], Tulay Canda[3]

[1]Department of General Surgery, Dokuz Eylul University Faculty of Medicine, Izmir, 35340, Turkey
[2]Department of Public Health, Dokuz Eylul University Faculty of Medicine, Izmir, 35340, Turkey
[3]Department of Pathology, Dokuz Eylul University Faculty of Medicine, Izmir, 35340, Turkey

Abstract Secondary thyroidectomy can be complicated due to adhesions. This study evaluates the impact of two antiadhesive barriers on adhesion formation after subtotal thyroidectomy in a rat model. Twenty-eight Wistar albino rats were randomized into three groups after subtotal thyroidectomy. Dextran 70 was used in Group 1 (n=10), Polyethylene glycol (PEG) was used in Group 2 (n =10), and the control group was Group 3 (n = 8). At postoperative day 14, surgical fields were scored regarding parameters including extent of fibrosis. All subjects in the control group (8 of 8), 6 of 10 subjects in the Dextran 70 group, and 3 of 10 animals in the PEG group had either filmy or dense adhesions. There was a significant difference in adhesion density scores ($P<.05$) between the PEG and control groups, whereas the difference between the Dextran 70 and control groups was not significant. Histopathological examination results showed significantly lower fibrosis scores in the PEG group compared to the Dextran 70 ($p=0.001$) and control groups ($P<.05$), while there was no significant difference between the fibrosis scores of the Dextran 70 and control groups. The anti-adhesive barrier PEG significantly decreased adhesion formation after subtotal thyroidectomy.

Keywords Polyethylene Glycol, Dextran 70, Thyroidectomy, Adhesion, Anti-adhesive Barrier

1. Introduction

Secondary thyroidectomy, where remnant thyroid tissue is removed, has a crucial role in the treatment of patients with thyroid diseases[1-3]. Main indications of secondary thyroidectomy include detection of thyroid cancer in primary thyroid tissue, recurrent thyroid cancer, occurrence of cancer in the residual thyroid tissue after operation for benign thyroid diseases, symptomatic recurrent nodular or multinodular goiter, and recurrent thyrotoxicosis[4-6].

Primary thyroidectomy leads to postsurgical adhesion formation which results in loss of normal anatomic planes [1]. This increases the risk of recurrent laryngeal nerve injury and hypoparathyroidism. Additionaly, adhesions and scarring make the operation technically more challenging and therefore prolong the operation time[1,2].

One approach in decreasing the complication rate of secondary thyroidectomy is to focus on technical aspects of the surgery[5-7]. Specifically, maintaining precise hemostasis with meticulous surgical technique, avoiding excessive suturing, and cauterizing is crucial for prevention of excessive scarring and adhesion formation[2,8,9]. Furthermore, anti-adhesive barriers can be used in the primary surgery as an additional measure[10].

Polyethyleneglycol (PEG; SprayGel©) and Dextran 70 (Hyskon©) are anti-adhesive barriers which reduced adhesion formation after abdominal and gynecological surgeries[11-14]. However, their effects have never been evaluated in the thyroidectomy surgery setting. The aim of this study was to analyse and compare the efficacy of PEG and Dextran 70 in the prevention of postsurgical adhesion formation in a standardized rat thyroidectomy model.

2. Materials & Methods

This study was designed as a prospective, randomized, double-blinded, controlled, experimental study. Ethical approval of this project was given by the local ethical board of the Experimental Animal Care and Usage Council of Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

Animals: Twenty-eight male Wistar albino rats from the same colony, weighing 275 to 325g, 4 to 6 months of age, were used. All rats were acclimated for at least one week before the surgery for adjustment to the laboratory environment.

Throughout the experiment, animals were given standard rat chow and water. They were housed singly in polycarbonate micro-isolator cages in a controlled environment with a temperature of 20° to 22°C and relative

* Corresponding author:
gulersanem@yahoo.com (Sanem Guler Cimen)
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humidity of 50% to 70% and a 12h light-dark cycle. The animals were cared for according to the principles of the National Institutes of Health publication "Guide for Care and Use of Laboratory Animals"[15].

Surgery: Rats were anesthesized intraperitoneally with 90mg/kg ketamine (Ketalar, Pfizer, Turkey) and 10mg/kg xylazine hydrochloride (Rompun, Bayer, Turkey). All surgical procedures were performed under aseptic conditions. A 2cm midline horizontal skin incision was made on the neck. Submaxillary glands and muscles were separated and lateralized. The trachea was exposed and a right subtotal thyroidectomy was performed (Figure 1).

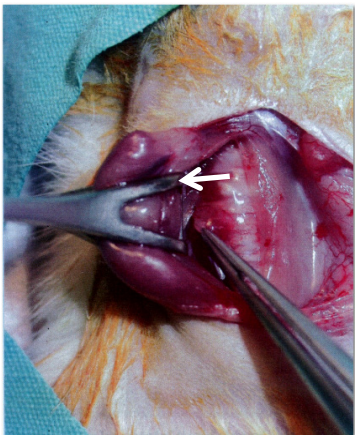


Figure 1. Surgical exposure of the right lobe of the thyroid gland (arrow)

In all subjects bleeding was controlled by application of pressure to the wound. No suturing or cauterizing was used (except for the skin level) during the thyroidectomy procedures. Animals were randomized into three groups:

Group 1 (Dextran 70 group) consisted of 10 animals. Right subtotal thyroidectomy was performed and then 1 ml of 32% Dextran 70 was administered to the thyroidectomy field. Muscles and submaxillary glands were replaced to their original positions before skin closure. Skin incision was closed with 5–0 polypropylene monofilament nonabsorbable suture.

Group 2 (PEG group) consisted of 10 animals. Right subtotal thyroidectomy was performed and then PEG solution was sprayed to the thyroidectomy field. Muscles, submaxillary glands were replaced and skin incision was closed as in Group 1.

Group 3 (control group) consisted of 8 animals in which no agent was administered to the thyroidectomy field. Right subtotal thyroidectomy was performed. Muscles, submaxillary glands were replaced and skin incision was closed as in Group 1.

Evaluation: The subjects were returned to their cages after the operation and were fed with standard rat chow for a period of 14 days. On day 14, surgical fields were exposed under general anesthesia for blinded evaluation of adhesion formation by K.A., who was not involved in the primary surgical procedures. Adhesion tenacity was scored (adhesion density score) using a semi-quantitative scale. Scoring was based on the dominant adhesion type (filmy or dense) and required adhesion dissection technique (blunt or sharp dissection) (see Table 1).

Table 1. Adhesion Density Score Scale

Grade	Adhesion
0	No adhesions
1	Adhesions resolved by blunt dissection (filmy adhesions)
2	Adhesions required sharp dissection (dense adhesions)

After scoring, subjects were sacrificed and *en bloc* excision of the entire surgical field, including the remaining thyroid tissue and trachea, was performed. Specimens were fixed in 10% neutral buffered formalin for 24h. Tissues were processed, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin-eosin and Masson's trichrome stain. A pathologist, blinded to the experimental groups and adhesion density evaluations, scored the histopathologic slides for fibrosis using a semi-quantitative scale (Table 2).

Table 2. Scale for Microscopic Assessment of Fibrosis

Grade	Histopathological Signs
0	No fibrosis
1	Thin bunches of fibrosis
2	Wide areas of fibrosis with reduced vascularization
3	Areas of fibrosis formed by thick bunch of collagen

Tissue sections were also examined and graded in terms of vascular proliferation, edema, necrosis, congestion, polymorphonuclear leukocytes (PMNL), fibroblasts, histiocytes, and macrophages. These parameters were scored as 0, 1, 2 and 3 for absent, light, moderate and severe, respectively. Absence or presence of microorganisms was also noted as an indicator of infection.

Statistics: Adhesion density scores were analyzed using the Chi-square test. The non-parametric Kruskal-Wallis variance analysis was used to determine the statistical difference in the histopathological scores between groups and Mann-Whitney U test was used to find out the source of difference. A P value of less than 0.05 was considered statistically significant.

3. Results

The standardized surgical procedures were well tolerated by all animals and all animals survived throughout the study. All surgical fields were intact with no obvious surgical site infection or hematoma. No apparent allergic reaction to the administered agents was encountered. On day 14, no residual adhesion barrier was observed in the surgical field. The model we used proved to be effective in terms of adhesion formation given that 100% of the subjects of the control group developed adhesions.

In the control group, 75% of the animals (6 in 8) had filmy adhesions while the remaining 25% (2 in 8) had dense adhesions. No adhesions were found in 7 of the 10 animals in the PEG group, but 6 of the 10 animals in the Dextran 70 group did have adhesions. Both PEG and Dextran 70

groups had 1 subject with dense adhesions which required sharp dissection in order to expose the surgical field. The mean adhesion density score for PEG was significantly lower (p=0.016) than the control group (Figure 2).

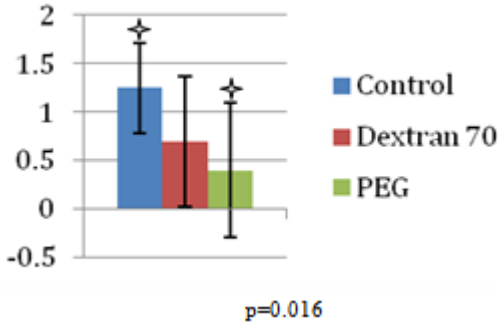


Figure 2. Mean Adhesion Density Scores in Control, Dextran 70 and PEG Groups

Mean scores for each histopathological parameter were calculated for each group. The mean fibrosis score of the PEG group was signifcantly lower than that of the Dextran 70 and control groups (p=0.002, p=0.006 respectively; Figure 3, Picture).

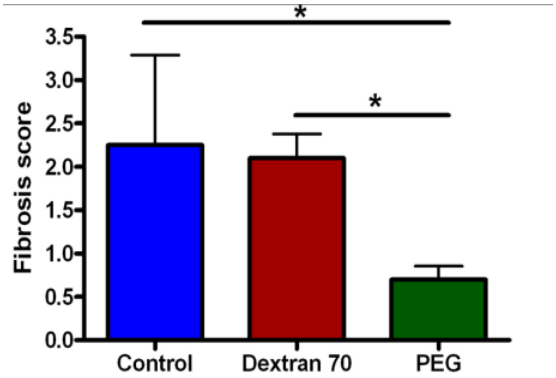


Figure 3. Mean Fibrosis Scores

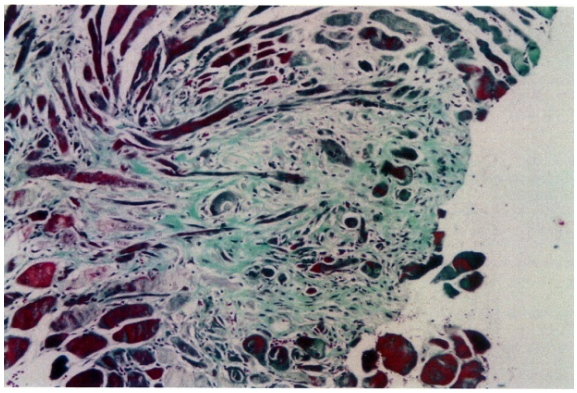


Figure 4. Decreased peri-thyroidal fibrosis in PEG group (Masson's trichrome stain, x200 magnification)

Vascular proliferation, microorganism and histiocyte were not seen and therefore scored as 0 by the pathologist in all three groups. Comparison of histopathologic scores of PEG and control groups revealed that the fibroblast score was significantly lower in the PEG group (p=0.006, Table 3).

Table 3. Statistical Analysis of Histopathological Markers in Control and PEG Groups

	Control (n=8)		PEG (n=10)		
	Mean	SD	Mean	SD	P
Vascular proliferation	0	0	0	0	-
Edema	0.13	0.35	0	0	0.696
Congestion	1.25	0.46	0.80	0.42	0.173
Microorganism	0	0	0	0	-
PMNL	0	0	0.20	0.63	0.762
Fibroblast	2.25	1.04	0.70	0.48	0.006*
Histiocyte	0	0	0	0	-
Macrophage	1.38	0.92	1.00	0.47	0.408
Necrosis	1.38	0.92	1.00	0.47	0.408

Mean fibrosis and fibroblast scores of the Dextran 70 group were calculated as 2.10. These scores were not significantly different when compared with the fibrosis and fibroblast scores of the control group (2.25, p>0.05). There was no significant difference in terms of all of the remaining histopathological parameters as well (Table 4).

Table 4. Statistical Analysis of Histopathological Markers in Control and Dextran 70 Groups

	Control (n=8)		Dextran 70 (n=10)		
	Mean	SD	Mean	SD	P
Vascular proliferation	0	0	0	0	-
Edema	0.13	0.35	0	0	0.696
Congestion	1.25	0.46	0.90	0.74	0.360
Microorganism	0	0	0	0	-
PMNL	0	0	0	0	-
Fibroblast	2.25	1.04	2.10	0.88	0.696
Histiocyte	0	0	0	0	-
Macrophage	1.38	0.92	0.80	0.42	0.203
Necrosis	1.38	0.92	0.82	0.42	0.203

Comparison between PEG and Dextran 70 groups regarding the parameters in question have shown that PEG group had significantly lower fibrosis and fibroblast scores (p=0.001). There was no difference among these groups in terms of the other parameters (Table 5).

Table 5. Statistical Analysis of Histopathological Markers in PEG and Dextran 70 groups

	PEG (n=10)		Dextran 70 (n=10)		
	Mean	SD	Mean	SD	P
Vascular proliferation	0	0	0	0	-
Fibrosis	0.70	0.48	2.10	0.88	0.002*
Edema	0	0	0	0	-
Congestion	0.80	0.42	0.90	0.74	0.853
Microorganism	0	0	0	0	-
PMNL	0.20	0.63	0	0	0.317
Fibroblast	0.70	0.48	2.10	0.88	0.002*
Histiocyte	0	0	0	0	-
Macrophage	1.00	0.47	0.80	0.42	0.329
Necrosis	1.00	0.47	0.80	0.42	0.329

4. Discussion

Several agents were investigated with the aim of decreasing adhesion formation after a surgical procedure [15,18]. Steroids, non-steroidal anti-inflammatory drugs, phospholipids and anti-adhesive barriers are the most well-known agents in this respect[18-20]. Administration of anti-adhesive barriers onto the surgical field in the primary surgery keeps the surgically traumatized surfaces covered during the mesothelial regeneration phase and therefore adherence of adjacent structures is prevented[10,19, 20].

All of the anti-adhesive barriers have their unique state (liquid or solid), composition and characteristics. However, an ideal barrier must be resorbable, adherent to the traumatized surface, effective on oozing surfaces, easily available, highly biocompatible and it must reside at the site of injury well after the critical period of adhesion formation. In addition, it must not hinder wound healing and predispose to infection[21]. It has been shown that the majority of adhesions are transient and are naturally lysed within 72 hours. Formation of persistent adhesions begins in the third postoperative day[9,10,19]. Thus, using barrier agents which reside at the site of injury for several days post-surgery is an appealing strategy.

The thyroid surgery model used in our study was based on a model developed by Yigit et al[22]. Our study is the first to compare two anti-adhesive barriers in this model. We compared PEG with Dextran 70 because they are both in liquid forms and they can both be administered by topical route[10]. Thus, a potential bias caused by the difference in administration route was prevented.

Dextran 70 was commonly used intraperitoneally in fertility surgery as part of prophylactic antiadhesive protocols in 1980s[13,14]. It decreases adhesion formation by inducing transudation of serum into the peritoneal cavity and generating ascites, displacing adjacent raw surfaces that can make adhesions[23]. Some authors have hypothesized that the beneficial effect of Dextran 70 might also be due a dextran-induced alteration in the structure of fibrin which makes it more susceptible to degradation by plasmin[23,24].

Rosenberg and Board performed a prospective study in which 44 women undergoing infertility-related surgery were given either Dextran 70 or Ringer's lactate solution intraperitoneally[25]. Six weeks later, a second-look laparoscopy was done where significant reduction in adhesion formation was noted in the patient group treated with Dextran 70. Nagelschmidt et al and Ortega also reported similar findings with Dextran 70, but other studies did not find any benefit[26-30].

In our study we noted a difference in adhesion density scores of the Dextran 70 and control groups, but it was not statistically significant. Furthermore, the fibrosis scores between the Dextran 70 and control groups were not significantly different. However, we believe that the relatively low number of subjects and the relatively narrow surgical field of right subtotal thyroidectomy procedure might have contributed to this finding.

PEG consists of two synthetic liquid precursors that, when mixed together, rapidly crosslink to form a solid, absorbable biocompatible hydrogel[31]. PEG forms an absorbable, flexible and adherent gel barrier when sprayed onto the target tissue, which can be easily visualized with the added PEG colorant . It must be sprayed until a optimal thickness of 1-2mm[31] is achieved so that fine tissue structures become difficult to visualize under the barrier. The barrier remains intact for approximately five to seven days during the healing period and then it is gradually hydrolyzed, absorbed and rapidly cleared by the kidneys.

The efficacy of PEG in abdominal adhesion models has been previously assessed in rats[26], rabbits[31], and pigs [32]. All of these experimental animal studies demonstrated the ability of PEG to reduce post-surgical adhesions.

Two clinical trials showed a significant reduction in post-surgical adhesions by PEG pretreatment[12, 33]. Mettler et al performed a prospective clinical trial in women undergoing myomectomy[33]. In the second-look laparoscopy they noted that adhesion formation on and in the vicinity of the uterus was significantly less in the PEG group in comparison to the control group. Furthermore, Tjandra et al showed that PEG facilitated the closure of loop ileostomy by reducing postoperative and peri-stomal adhesions[12]. In accord with these studies, our results suggest that the PEG is effective in decreasing the post-operative adhesion formations after subtotal thyroidectomy in rats.

5. Conclusions

In this experimental animal study PEG exerted more promising results than Dextran 70 as an anti-adhesive barrier in thyroidectomy setting. PEG reduced post-surgical adhesion formation significantly in an animal model of subtotal thyroidectomy.

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