The effects of lauromacrogol on thyroid tissue in rabbits. 
Is this a safe option for the treatment of nodular thyroid disease?

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The effects of lauromacrogol on thyroid tissue in rabbits. Is this a safe option for the treatment of nodular thyroid disease?

AIM: The effects of lauromacrogol as a sclerosing agent were evaluated on rabbit thyroid tissue.

MATERIAL AND METHODS: Twelve rabbits were divided into two equal groups. Intra-thyroid injections of 0.1 ml lauromacrogol were administered in the study group and 0.1 ml physiologic serum in the control group. The blood levels of free T3, free T4, TSH, postoperative adhesions and histopathologic differences of the thyroid tissues were evaluated.

RESULTS: The values of serum free T3, free T4 and TSH levels did not differ significantly (p>0.05), but the free T3 levels were significantly different in the inter-group analysis (p=0.020). Postoperative macroscopic adhesion scores did not differ significantly (p>0.05). In the histopathologic evaluation, the inflammation and fibrosis scores were significantly higher in the study group (p=0.003).

DISCUSSION: In our study, we found two important outcomes. Firstly, tests of thyroid function were not significantly different between the control and study groups. This important finding suggests lauromacrogol can be safely used without the risk of hypothyroidism or hyperthyroidism. Secondly, the Erlich-Hunt Model histopathologic evaluation results revealed that inflammation and fibrosis were significantly increased in the study group. This finding shows lauromacrogol can be effectively used to treat thyroid nodules by means of fibrosis.

CONCLUSIONS: Lauromacrogol causes fibrosis in thyroid tissue without significant perithyroidal adhesion formation and functional differences. Treatment of nodular thyroid disease with lauromacrogol may be safe.

KEY WORDS: Lauromacrogol, Nodule, Thyroid

Introduction

Thyroid diseases are the most frequent endocrine disorder, and the thyroidectomy is the most frequent endocrine surgical procedure 1. Thyroid surgery is primarily performed for thyroid nodules. The estimated prevalence of palpable thyroid nodules ranges from 3% to 7% 2. During the past two decades, the widespread use of ultrasonography for evaluation of thyroid and non-thyroid neck disease has resulted in a dramatic increase in the prevalence of clinically unapparent thyroid nodules, estimated at 20% to 76% in the general population 3,4. Most thyroid nodules are benign, but some require treatment for the risk of malignant transformation, cosmetic reasons or subjective symptoms 5. Surgery is used to treat benign thyroid nodules. Although surgery is an invasive technique, non-surgical, minimally invasive percutaneous modalities have been described, including
ethanol injection, laser, microwave and radiofrequency ablation.

Lauromacrogol (polidocanol) is a local anesthetic agent. It has a high affinity for vessel endothelium, reacting with endothelium and causing inflammation and sclerosis. Lauromacrogol is used to treat some pathologic processes, including thyroid nodules. There is some literature regarding the use of lauromacrogol for the treatment of thyroid nodules. However, the physiologic and histopathologic effects of lauromacrogol on the thyroid tissue have not been previously evaluated. In this study, we evaluate the effects of lauromacrogol on rabbit thyroid tissue.

Materials and Methods

This study was performed at the Experimental Animal Production and Research Laboratory of Bezmialem Vakif University and was approved by the local Animals Ethics Committee. All protocols were in accordance with the regulations governing the care and use of laboratory animals in the declaration of Helsinki.

According to power analysis with 0.05 accuracy and 0.95 power, the number of rabbits were determined to be six in each of the groups. Twelve female New Zealand white rabbits (mean weight 3120±75 g; mean age 5.5 months; outbred) were divided into two equal groups. The rabbits were housed single in standard cages with stainless steel tops and bottoms and woven wire sides. The cage floors were covered with wood shavings that were changed daily. The rabbits were kept at room temperature with adequate ventilation. Water and feeding containers were made of standard plastic with side entrances. The animals were fed pellets designed for small laboratory animals.

The rabbits were starved overnight and anesthetized with Ketamine (Ketalarâ, Parke Davis and Co. Inc.; 40 mg/kg body weight) and xylazine (Rompunâ Bayer Co.; 5 mg/kg body weight).

Before the surgical procedure, blood samples were taken from the ear veins of all subjects and sent to the biochemistry laboratory for free T3, free T4 and TSH levels. The anterior neck was shaved and disinfected with povidone iodine. A 5 cm longitudinal mid-line incision was made. The pretracheal muscles were divided laterally and reached to the thyroid region. Thyroidal lobes were uncovered from para-thyroidal tissues and exposed clearly.

In the study group (n= 6), 0.1 ml lauromacrogol per lobe (aethoxysklerolâ 0.1%, Kreussler Pharma, Germany) was injected intrathyroidally. In the control group (n= 6), the same procedure was performed with 0.1 ml 0.9% physiologic serum (% 0.9 Serum Fizyolojikâ, Eczacibaşı Co, Turkey).

After the procedure, the muscles and skin were stitched separately with 3-0 polypropylene sutures. After examination at 3 hours postoperatively, the rabbits were allowed their usual feed. On postoperative days 5, 10, 20 and 30, blood samples were received from all subjects for re-evaluation of free T3, free T4 and TSH levels. The animals were sacrificed on postoperative day 30 by intraperitoneal injection of 200 mg/kg sodium pentothal. The same neck incision was used for re-exploration after widening it superiorly and inferiorly. Postoperative adhesions were evaluated according to the Evans Model (Table I), and thyroid tissue with tracheal segments were resected for histopathologic examination.

The specimens were fixed in 10% formal, dehydrated, and embedded in paraffin wax. Sections were cut at a thickness of 5 mm and stained with hematoxylin and eosin. The tissue was evaluated in terms of the quantity of inflammatory cells, fibroblasts, neovascularization level, and collagen content according to the Ehrlich-Hunt model (Table II).

The primary evaluation parameters were histopathologic evaluation and differences of secretory function of thyroid tissue, and the secondary parameter was the postoperative adhesion formation grades of the groups.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Ver. 19.0. In addition to descriptive statistical methods (mean, standard deviation, and median), we used the Friedman test and post hoc Dunn test for in-group variables comparisons and the Mann Whitney U test for comparisons of inter-group variables.
Results

The values of serum free T3, free T4 and TSH levels of the groups are shown in Table III, IV, and V. No statistically significant differences were observed in the in-group analysis (p>0.05), and only the free T3 levels differed significantly in the inter-group analysis (p=0.020). When we evaluated the postoperative adhesions, the macroscopic adhesion scores did not differ significantly (p>0.05). In the histopathologic evaluation according to the four parameters, inflammation and fibrosis were significantly different (p=0.003) between the two groups (Table VI).

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**Table III - The serum free T3 levels of the groups**

<table>
<thead>
<tr>
<th>Serum T3 Levels (pg/ml)</th>
<th>Control Group</th>
<th>Study Group</th>
<th>Mann Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Median</td>
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<tr>
<td>Preop</td>
<td>5.6167</td>
<td>1.6916</td>
<td>5.0500</td>
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<tr>
<td>Postop Day 5</td>
<td>6.2667</td>
<td>1.2127</td>
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</tr>
<tr>
<td>Postop Day 10</td>
<td>6.3000</td>
<td>2.2018</td>
<td>6.1000</td>
</tr>
<tr>
<td>Postop Day 20</td>
<td>6.8333</td>
<td>1.5642</td>
<td>6.7000</td>
</tr>
<tr>
<td>Friedman chi-square</td>
<td>3.467</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.483</td>
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**Table IV - The serum free T4 levels of the groups**

<table>
<thead>
<tr>
<th>Serum T4 Levels (pg/ml)</th>
<th>Control Group</th>
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<th>Mann Whitney U</th>
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<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Median</td>
</tr>
<tr>
<td>Preop</td>
<td>17.9833</td>
<td>3.0993</td>
<td>18.1000</td>
</tr>
<tr>
<td>Postop Day 5</td>
<td>17.3000</td>
<td>3.2472</td>
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<tr>
<td>Postop Day 10</td>
<td>17.9000</td>
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<td>Postop Day 20</td>
<td>16.3000</td>
<td>4.3308</td>
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<tr>
<td>Postop Day 30</td>
<td>17.3667</td>
<td>3.7120</td>
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<td>Friedman chi-square</td>
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<tr>
<td>p</td>
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**Table V - The serum TSH levels of the groups**

<table>
<thead>
<tr>
<th>Serum TSH Levels (µIU/mL)</th>
<th>Control Group</th>
<th>Study Group</th>
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<tr>
<td>Preop</td>
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<td>0.0010</td>
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<tr>
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<td>0.0015</td>
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<td>0.0018</td>
<td>0.0008</td>
<td>0.0020</td>
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<tr>
<td>Postop Day 20</td>
<td>0.0018</td>
<td>0.0004</td>
<td>0.0020</td>
</tr>
<tr>
<td>Postop Day 30</td>
<td>0.0015</td>
<td>0.0008</td>
<td>0.0010</td>
</tr>
<tr>
<td>Friedman chi-square</td>
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<td></td>
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</tr>
<tr>
<td>p</td>
<td>0.241</td>
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Table VI - The histopathologic evaluation and macroscopic adhesion score results of the groups.

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
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<th>Study Group</th>
<th></th>
<th>Mann Whitney U</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Standard</td>
<td>Median</td>
<td>Mean Standard</td>
<td>Median</td>
<td>z</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0.5000</td>
<td>0.5477 0.5000</td>
<td>3.3333</td>
<td>0.5164 3.0000</td>
<td>-2.983</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.5000</td>
<td>0.5477 0.5000</td>
<td>2.3333</td>
<td>0.5164 2.0000</td>
<td>-2.983</td>
</tr>
<tr>
<td>Neovasc. Collagen</td>
<td>0.5000</td>
<td>0.5477 0.5000</td>
<td>0.6667</td>
<td>0.5164 1.0000</td>
<td>-0.561</td>
</tr>
<tr>
<td>Deposition</td>
<td>0.8333</td>
<td>0.7528 1.0000</td>
<td>0.8333</td>
<td>0.7528 1.0000</td>
<td>0.000</td>
</tr>
<tr>
<td>Macroscopic Adhesion score</td>
<td>1.8333</td>
<td>0.7528 2.0000</td>
<td>2.5000</td>
<td>0.5477 2.5000</td>
<td>-1.573</td>
</tr>
</tbody>
</table>

Discussion

Knowing that the majority of thyroid nodules are benign, alternates to surgical treatment have been proposed. Ethanol injection, laser, microwave and radiofrequency ablation are the most popular methods. 6-17. The ethanol injection is very effective when used to treat cystic thyroid nodules 6-12. Ethanol works as a sclerosing agent via cellular dehydration and protein denaturation that leads to coagulation necrosis and fibrosis. Yasuda et al. reported the cystic nodule volume decreased more than half in 72% of the patients treated with ethanol sclerotherapy. 21. Cho et al. reported 68% of the patients had more than a 50% decrease in thyroid nodule volume after ethanol injection. 22. Others suggest ethanol can be a safe and effective treatment for cystic nodules that are proven to be benign and cause cosmetic or local discomfort.

Tetracycline-based sclerotherapy is one of the sclerosing treatment methods proven effective for cystic lesions. Treece et al. 23 and Goldfarb et al. 24 used tetracycline for the treatment of cystic nodules and suggested the mechanism of action might be the result of tetracycline’s low pH.

Ultrasound guided interstitial laser photocoagulation (ILP) is a non-invasive method of local tissue ablation that was first described to treat advanced cancers. Use of the laser causes a coagulation necrosis by thermal effect, and the necrotic area, which is induced by laser can be controlled unlike with ethanol administration. Studies indicated a need for controlled trials to establish the role of ILP in routine practice. 13-15.

Radiofrequency ablation (RFA) is an effective treatment for various malignant tumors such as those of the liver. Recently, RFA was used to treat thyroid nodules and recurrent thyroid cancers. Lee et al. reported the initial experience of RFA for treatment of thyroid nodules. The volume reduction rate in their study was 84%. The major side effect was recurrent laryngeal nerve injury, which occurred in 3.3 % of patients. 12.

Lauromacrogol (Polidocanol®, Aethoxysklerol®) is an effective sclerosing agent consisting of 95% hydroxy-polyethoxydodecane and 5% ethyl alcohol. It has a high affinity for vessel endothelium, reacting with the endothelium and causing inflammation and sclerosis. Conrad et al. investigated the efficacy and safety of lauromacrogol on leg varices, noting a low risk of systemic and local complications. 18. Lauromacrogol is used for the treatment of some pathologic processes. Guglielmi et al. used lauromacrogol to treat gastroduodenal ulcer and esophageal variceal bleeding. 20. Lopes et al. used it to treat recurrent tracheoesophageal fistulas. 27. Ormeci et al. used it for sclerosing liver and spleen cyst hydatic disease. 28-30, and Angelini et al. used it for palliative treatment of unresectable esophageal tumors. 30. Kaneko et al. compared different agents for portal vein embolization and found lauromacrogol was the most effective at inducing hypertrophy and was the most suitable agent for portal vein embolization. 31.

Although there are many studies in other areas, there is limited literature regarding the use of lauromacrogol for the treatment of thyroid nodules. Kuznetsov et al. studied 37 patients with nodular thyroid disease and found lauromacrogol can be used for hot nodules. 32.

Lauromacrogol is known to be an effective and safe sclerosing agent and can be easily used in routine clinical practice. The functional and histopathologic effects of lauromacrogol on thyroid tissue have not been previously evaluated.

In our study, we found two important outcomes. Firstly, tests of thyroid function were not significantly different between the control and study groups. This important finding suggests lauromacrogol can be safely used without the risk of hypothyroidism or hyperthyroidism. Secondly, the Erlich-Hunt Model histopathologic evaluation results revealed that inflammation and fibrosis were significantly increased in the study group. This finding shows lauromacrogol can be effectively used to treat thyroid nodules by means of fibrosis. More adhesion formation was found in the study group, but the result was not statistically significant. It is not surprising to see excess adhesions after sclerosing agent induction, but we did not see any adhesion related complications in the observation period.
Conclusions

In summary, we revealed lauromacrogol causes fibrosis in thyroid tissue without significant perithyroidal adhesion formation and functional differences. Treatment of nodular thyroid disease with lauromacrogol may be safe.

Riassunto

Lo studio è finalizzato al rilevamento degli effetti del lauromacrogol, un agente sierosante, sul tessuto tiroideo del coniglio, utilizzando 12 conigli divisi in due gruppi di sei ciascuno. Nel gruppo di studio è stato iniettato nel tessuto tiorideo 0,1 ml di lauromacrogol, ed in quello di controllo lo stesso volume di soluzione fisologica. Al controllo postoperatorio sono stati valutati il tasso di FT3, FT4, TSH, la presenza di aderenze e le differenze istopatologiche dei tessuti tiroidei.

Non sono risultate differenze significative nel livelli di FT3, FT4, TSH (p>0,05) ma i livelli di , la presenza di aderenze e le differenze istopatologiche dei tessuti tiroidei.

Ai controlli i livelli di FT3, FT4 e TSH non sono risultati significativamente differenti (p>0,05), mentre i livelli di FT3, FT4, TSH sono stati significativamente differenti all'interno dei due gruppi (p<0,05). Non sono state riscontrate differenze macroscopicamente significative delle aderenze postoperatorie (p>0,05), ma flogosi e fibrosi sono state riscontrate istologicamente più elevate nel gruppo di studio (p<0,003).

Due sono i risultati importanti dello studio: la differenza non significativa dei test di funzione tiroidea tra i due gruppi, suggerendo che il lauromacrogol può essere usato con sicurezza senza rischi di ipotiroidismo e peritiroidei; la valutazione istopatologica su modello Erlich-Hunt ha dimostrato che flogosi e fibrosi sono state riscontrate nel gruppo di studio, indicando che il lauromacrogol può essere usato efficacemente e con sicurezza per il trattamento dei noduli tiroidei per provocare fibrosi, senza significative aderenze peritiroidee e differenze della funzione.

References

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ERRATA CORRIGE

In the paper of Pavicevic, et al. "Efficacy of Magnetic Resonance urography in detecting crossing renal vessels in children with ureteropelvic junction obstruction" published in Annali Italiani di Chirurgia 2015; 86:443-49, a must be done correction of the Authors that should be:


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