Efficacy of Beta-Aminopropionitrile, Contractubex®, Nigella sativa Oil, Aloe Vera Oil, and Soybean Oil in Preventing Postoperative Adhesions in an Experimental Thyroidectomy Model

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Research Article

Keywords: Thyroidectomy, reoperative surgery, tissue adhesions, fibrosis, beta-aminopropionitrile, anti-adhesive agents

Posted Date: May 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9619483/v1

Additional Declarations: No competing interests reported.

Abstract

Background/Aim:

Adhesions in reoperative thyroid surgery lead to prolonged operation times and an increase in postoperative complications. The use of anti-adhesive agents during the initial surgery may reduce the incidence of recurrent laryngeal nerve injury and permanent hypoparathyroidism, which are among the most significant complications associated with reoperative surgery. The aim of this study was to investigate the efficacy of beta-aminopropionitrile (BAPN), Contractubex→, (CT), nigella sativa oil (NSO), aloe vera oil (AVO), and soybean oil (SO) in preventing adhesions following thyroidectomy in an experimental rat model.

Materials and methods

Thirty-six female Wistar-Albino rats were randomly divided into six equal groups (n = 6 per group). All rats underwent right subtotal thyroidectomy. The following substances were applied to groups 1–5 in order of operation: BAPN, Contractubex→, nigella sativa oil, aloe vera oil, and soybean oil. No substance was applied to the control group (group 6). All rats were sacrificed on postoperative day 14. Adhesions were scored macroscopically and histopathologically.

Results

The BAPN group showed a significantly lower macroscopic adhesion score compared to the control group ($p = 0.015$). The CT group had a significantly lower polymorphonuclear leukocyte (PMNL) score compared to both the control ($p = 0.015$) and NSO ($p = 0.015$) groups. No statistically significant differences were observed in the remaining histopathological adhesion scores between any of the intervention groups and the control group ($p > 0.05$).

Conclusions

BAPN significantly reduced macroscopic adhesion formation following experimental thyroidectomy and may therefore help decrease surgical complications in high-risk candidates for reoperative thyroid, parathyroid, or neck surgery. Further experimental and clinical studies are needed to confirm the anti-adhesive efficacy and safety of BAPN before translation into clinical practice.

1. INTRODUCTION

Adhesions following thyroid surgery may lead to voice changes, swallowing difficulties, cervical scar deformities, and a pulling sensation during neck extension [1, 2]. In reoperative thyroid surgery, disruption of normal tissue planes due to adhesions generally leads to increased operative time, hospital stay duration, and frequency of postoperative complications. The most serious complications are permanent recurrent laryngeal nerve (RLN) injury and permanent hypoparathyroidism. These complications negatively affect patients' quality of life [3] .

There are two important strategies for reducing or preventing postoperative adhesions. The first involves surgical techniques and procedures. The second involves limiting adhesion formation by acting on the inflammatory, coagulatory, and fibrinolytic pathways involved in adhesion formation through various agents [4–6]. Studies aimed at preventing postoperative adhesions have primarily focused on intra-abdominal adhesions, as they are more common in clinical practice and are associated with significant morbidity, mortality, and healthcare costs. Although numerous studies have been conducted to date on reducing or preventing postoperative adhesions, an ideal anti-adhesive agent has not yet been found [7, 8] .

There are very few studies in the literature examining and preventing adhesions formed after thyroidectomy. In some experimental studies, polyethylene glycol 4000 [9], simvastatin [10], and glycerol and flax seed [11] were used and reported to be effective against adhesions.

The lathyrogen Beta-Aminopropionitrile (BAPN) irreversibly inhibits the activity of lysyl oxidase, which is involved in collagen synthesis, resulting in the production of weaker collagen [12, 13]. Topical inhibition of lysyl oxidases has recently been shown to reduce skin scarring and fibrosis in preclinical models, supporting the translational potential of lysyl oxidase-targeted agents in surgery [14]. Contractubex® (CT) contains 10% extractum cepae (onion extract), 50/U sodium heparin, and 1% allantoin as active ingredients. CT is used clinically more often in the treatment of hypertrophic scars and keloids. Onion extract has been shown to be effective against scarring by reducing fibroblast proliferation and inducing matrix metalloproteinase-1 expression in vivo and in vitro [15]. Experimental studies have reported that heparin reduces peritoneal adhesion [16] and that allantoin has epithelializing, keratolytic, moisturizing, and anti-irritant effects [17]. The anti-inflammatory effects of viscous black cumin oil [Nigella Sativa] (NSO), aloe vera oil (AVO), and soybean oil (SO) have been demonstrated [18–20] .

To the best of our knowledge, this is the first study to comparatively evaluate the anti-adhesive efficacy of these five agents—BAPN, CT, NSO, AVO, and SO—in a thyroidectomy model. Notably, BAPN has not previously been tested for adhesion prevention in thyroid surgery. The aim of our study is to investigate the efficacy of BAPN, CT, NSO, AVO, and SO in preventing adhesions after thyroid surgery in an experimental rat model.

2. MATERIALS AND METHODS

Ethics Statement

Approval was obtained from the Istanbul University Animal Experiments Local Ethics Committee (approval no: 50442, date: 16/03/2017). The care and use of the subjects were performed in accordance with the principles of the Guide for the Care and Use of Laboratory Animals (8th edition, National Research Council, 2011).

Animals and Housing

Thirty-six female Wistar-Albino rats with an average weight of 250 ± 25 g were used. The rats were placed in cages with identical characteristics in groups of three and kept for 14 days under a 12-hour dark/light cycle at a room temperature of 22 ± 1°C. They were deprived of food 8 hours before surgery but had free access to water. After thyroidectomy, rats were given unrestricted access to both food and water.

Experimental Design and Grouping

The animals were randomly allocated into six groups of six rats each (n = 6 per group): five intervention groups (BAPN, CT, NSO, AVO, SO) and one control group. The sample size was determined based on similar previously published experimental thyroidectomy adhesion studies in rats, given the exploratory/pilot nature of the study design. All rats underwent the same surgical procedure, and intervention agents were applied locally to the surgical field at the conclusion of surgery.

Anesthesia and Surgical Procedure

All rats were anesthetized using intraperitoneal xylazine hydrochloride (10 mg/kg) and ketamine hydrochloride (80 mg/kg). The neck area where the incision would be made was shaved and antiseptically treated with povidone-iodine solution. After making a 2 cm longitudinal incision in the anterior neck region, the submandibular glands were retracted with gentle traction, and the muscles were separated to the sides to reach the trachea and thyroid lobe. A right subtotal thyroidectomy was performed using bipolar cautery (Fig. 1). The muscles were approximated with one primary suture using 4/0 vicryl. The skin was closed using a continuous suture technique with 3/0 silk suture.

Intervention Agents and Application

Immediately after subtotal thyroidectomy and before closure, 0.1 ml of the following agents were applied locally to the surgical field:

- Group 1 (BAPN): β-aminopropionitrile monofumarate (Sigma Aldrich, USA), 300 mg/kg prepared with distilled water.
- Group 2 (CT): Contractubex® (Merz Co., Germany).
- Group 3 (NSO): Nigella sativa oil (Çörek Otu Yağı®, Arifoğlu Co., Turkey).
- Group 4 (AVO): Pure aloe vera oil (Aloe Vera Yağı®, Arifoğlu Co., Turkey).
- Group 5 (SO): Pure soybean oil (Soya Yağı®, Arifoğlu Co., Turkey).
- Group 6 (Control): No agent applied.

The applied substances were allowed to contact all tissues within the surgical field before muscle and skin closure.

Tissue Sampling and Macroscopic Evaluation

On postoperative day 14, rats were sacrificed with an intraperitoneal injection of thiopental sodium at a dose of 200 mg/kg. The skin overlying the previous surgical site was removed. Macroscopic examination was performed by two expert surgeons who were blinded to group allocation, and adhesions between tissues and muscles in the superficial and deep cervical regions were scored semi-quantitatively. Macroscopic adhesions were scored according to the Evans classification (Table 1) [21]. Subsequently, the larynx-trachea, esophagus, and thyroid tissue were resected en bloc from the floor of the mouth to the thoracic inlet.

Table 1
Scoring system for macroscopic and histopathological parameters.

Macroscopic	**PMNL, Lymphocyte** **Histiocyte, Fibroblast** **Giant cell**	**Vascular proliferation**	**Collagen**	**Score**
No adhesions	Absent or normal	Absent	Absent	**0**
Filmy adhesions, separating spontaneously	Slight increase	1–2 vessels	Thin collagen bundles and slight staining	**1**
Firm adhesions separated by traction	Marked infiltration	3–9 vessels	Patchy thickened collagen bundles with moderate staining	**2**
Dense adhesions requiring sharp dissection	Massive infiltration	10 or more vessels	Collagen forming thick bundles and intense staining	**3**

Tissue Processing and Staining

The resected specimens were fixed in 10% buffered formaldehyde solution for 24 hours. All obtained tissues were sampled by cutting them transversely into 2 mm thick sections. After routine tissue processing, they were embedded in paraffin blocks. Four 5-micron-thick sections were prepared from each case. Two sections were stained with hematoxylin and eosin, and two with Masson trichrome.

Histopathological Evaluation

Histopathological examination was performed by two pathologists blinded to group allocation using light microscopy, focusing on the area containing granulation tissue between the thyroid and striated muscle tissue. The assessment included polymorphonuclear leukocytes (PMNL), lymphocytes, histiocytes, fibroblasts, collagen, vascular proliferation, and giant cells. The histopathological examination was scored semi-quantitatively according to Table 1 [21]. The parameters of PMNL, lymphocytes, and histiocytes were considered criteria for the intensity of inflammation; fibroblast and collagen production extending into the surrounding muscle and connective tissues accompanied by vascular proliferation were considered criteria for the intensity of adhesion (fibrosis); giant cells, thought to form in response to substances placed in the thyroid lobe, were considered criteria for a foreign body reaction. The amount and content of inflammation and the amount of vascular proliferation were evaluated in hematoxylin and eosin stained sections (Fig. 2), and fibrosis was evaluated in Masson trichrome stained sections (Figs. 3–5).

Outcomes

Macroscopic adhesion score was defined as the primary outcome. Histopathological examination scores (PMNL, lymphocyte, histiocyte, fibroblast, collagen, vascular proliferation, giant cell) were defined as secondary outcomes.

Statistical Analysis

SPSS software version 28.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Normality assessment of the data was performed using the Kolmogorov–Smirnov test. Non-parametric data were analyzed using the Kruskal–Wallis test, and the Mann–Whitney U test was used for post-hoc pairwise comparisons when statistical significance was detected between groups. A p-value of < 0.05 was considered statistically significant. Data are presented as mean ± SD for descriptive purposes.

3. RESULTS

No surgical site infection, hematoma, morbidity, or mortality was observed in any subject during the 14-day follow-up and care period after thyroidectomy. No side effects were observed against the applied substances.

Details of the statistical analysis of macroscopic and histopathological data for all groups are presented in Table 2. None of the agents used in our study completely prevented adhesion formation. The macroscopic adhesion score in the BAPN group was significantly lower than that in the control group ($p = 0.015$). No statistically significant difference was observed in the macroscopic adhesion score between the CT, NSO, AVO, and SO groups and the control group ($p > 0.05$) (Table 2).

Table 2
Statistical analysis of macroscopic and histopathological parameters according to study groups, with pairwise comparisons.

Macroscopic	CONTROL mean ± sd	BAPN mean ± sd P	CT mean ± sd P	NSO mean ± sd P	AVO mean ± sd P	SO mean ± sd P	P1
	1.83 ± 0.41	**1.0 ± 0.0 0.015**	**1.17 ± 0.41 0.065**	**1.67 ± 0.52 0.699**	**1.67 ± 0.52 0.699**	**1.50 ± 0.55 0.394**	**0.032**
PMNL	0.83 ± 0.41	0.17 ± 0.41 0.065	0.00 ± 0.00 **0.015**	0.83 ± 0.41 1.000	0.50 ± 0.55 0.394	0.50 ± 0.84 0.310	**0.026**
Lymphocyte	1.33 ± 0.52	0.83 ± 0.41 0.240	1.0 ± 0.00 0.394	1.33 ± 0.52 1.000	1.17 ± 0.41 0.699	1.0 ± 0.00 0.394	0.177
Histiocyte	1.33 ± 0.82	1.33 ± 0.82 1.000	1.0 ± 0.89 0.589	0.67 ± 0.82 0.240	1.67 ± 1.03 0.589	1.0 ± 0.63 0.485	0.421
Fibroblast	1.67 ± 0.82	1.17 ± 0.75 0.394	1.17 ± 0.41 0.310	1.33 ± 0.52 0.589	1.67 ± 0.52 0.937	1.0 ± 0.00 0.180	0.228
Collagen	1.67 ± 0.82	0.67 ± 0.52 0.065	1.0 ± 0.00 0.180	1.0 ± 0.63 0.240	1.17 ± 0.41 0.310	0.83 ± 0.41 0.093	0.079
Vascular proliferation	1.83 ± 0.98	1.33 ± 0.52 0.485	1.0 ± 0.00 0.180	1.67 ± 0.52 0.937	1.67 ± 0.52 0.937	1.33 ± 0.52 0.485	0.187
Giant cell	0.67 ± 0.82	1.00 ± 0.63 0.485	1.0 ± 0.89 0.589	0.83 ± 0.98 0.818	1.67 ± 1.03 0.132	0.83 ± 0.75 0.699	0.512

P: pairwise comparison of each intervention group with the control group (Mann–Whitney U test); P1: overall comparison among all groups (Kruskal–Wallis test). Bold values indicate statistical significance ($p < 0.05$). Data are presented as mean ± SD for descriptive purposes.

The PMNL examination score was significantly lower in the CT group than in the control group ($p = 0.015$) and the NSO group ($p = 0.015$). No significant difference in PMNL examination score was observed between the BAPN, NSO, AVO, and SO groups and the control group ($p \geq 0.05$). No statistically significant differences were observed in the lymphocyte, histiocyte, fibroblast, collagen, vascular proliferation, and foreign body reaction examination scores between the BAPN, CT, NSO, AVO, and SO groups and the control group, or in the comparisons made between the groups individually ($p \geq 0.05$) (Table 2).

4. DISCUSSION

Permanent RLN injury and permanent hypoparathyroidism are among the most important complications of thyroid surgery. Compared with primary surgery, the incidence of permanent RLN injury and permanent hypoparathyroidism increases approximately fourfold and fivefold, respectively, during reoperative procedures. The most important reason for this increase is that adhesions disrupt normal tissue planes, making it difficult to identify landmarks in thyroid surgery [3] .

There are a limited number of studies in the literature on anti-adhesive agents following thyroidectomy. To our knowledge, the first experimental adhesion prevention study in the literature following thyroidectomy was conducted in 2002 by Sakarya et al. [9] using polyethylene glycol 4000. The first prospective randomized controlled human study was conducted in 2009 by Park et al. [22] using poloxamer/sodium alginate. Prospective randomized controlled human studies have reported that poloxamer/sodium alginate, oxidized regenerated cellulose, and autocrosslinked polysaccharide gel are effective on voice changes, swallowing difficulties, scars, and wrinkles, while sodium hyaluronate and sodium carboxymethyl cellulose are ineffective [1, 2, 22, 23]. More recently, a multicenter, randomized, double-blind, non-inferiority study by Kim et al. demonstrated the efficacy and safety of a temperature-sensitive acellular dermal matrix in preventing postoperative adhesion after thyroidectomy [24] .

There are very few studies on the adhesion effectiveness of BAPN, CT, NSO, AVO, and SO, and—to our knowledge—none of these agents has previously been tested for adhesion prevention in thyroid surgery. The present study is therefore the first to comparatively evaluate these five agents in a thyroidectomy model.

In an experimental rat model, BAPN administered intraperitoneally at a dose of 500 mg/kg once daily for 28 days was shown to be effective against stenosis/fibrosis following caustic esophageal burns [25]. In another experimental mouse study, after creating an intraperitoneal adhesion model with carbon nanotubes, BAPN was administered intraperitoneally at a dose of approximately 1 g/kg daily for one week; light and electron microscopy examinations revealed that BAPN reduced fibrosis and collagen accumulation [26]. In our study, although BAPN was seen to reduce adhesion macroscopically with a single local dose of 300 mg/kg, the histopathological examination results did not reach statistical significance. The discrepancy between histopathological findings and macroscopic observations may be related to the dose and duration of BAPN administration.

Two different experimental studies have shown that CT reduces epidural fibrosis after laminectomy [27, 28]. Another experimental study using CT reported that simultaneous CT application with surgery was not effective in preventing adhesion [29]. Although no statistically significant difference was observed in our study, we observed that CT application macroscopically facilitated secondary surgery compared to the control group ($p=.065$). We believe that the low number of subjects compared to other studies may have affected our results, particularly in the CT group.

Sahbaz et al. [30] NSO, Karatas et al. [31] reported that volatile oil and ethanolic extract produced from nigella sativa, and Bozdag et al. [32] thymoquinone, the bioactive component of nigella sativa, used in peritoneal adhesion studies, were effective on adhesion, unlike our results.

Aysan et al. [33, 34] used intraperitoneal aloe vera gel and SO in two different rat studies. The results of both studies were consistent with our study; it was observed that the application of aloe vera gel/SO immediately after the procedure did not reduce adhesion, but aloe vera gel/SO applied to the abdomen before surgery reduced adhesion. Similar to some of the studies mentioned in the literature, our study shows that the application of NSO, aloe vera gel, or SO immediately after surgery does not reduce adhesions at both the macroscopic and microscopic levels and is not effective in preventing adhesions after thyroidectomy.

In our study, the difference in scoring systems used for macroscopic and histopathological evaluation, and the lack of histopathological examination specifically targeting areas with macroscopic adhesions, may explain the statistical inconsistency between macroscopic and histopathological findings, particularly in the BAPN group. Considering that adhesion is primarily based on the surgeon's macroscopic observation and that there are no objective criteria for histopathological evaluation in the literature, we believe that the macroscopic examination result is more important in surgical adhesion studies.

Since there are no studies investigating the effectiveness of the agents we used in this study on post-thyroidectomy adhesions, we made comparisons and discussions based on the limited number of intraabdominal studies conducted on this subject. Unlike abdominal surgeries, thyroid/neck surgeries do not have a natural anti-adhesive barrier such as the peritoneum and involve the presence of peritoneal fluid, which may lead to different results in anti-adhesive studies.

The lack of consensus in the literature on which criteria should be used in the histopathological examination of adhesions makes it difficult to interpret the results of adhesion studies and reach a common conclusion.

This experimental study model and its results, conducted specifically for thyroid surgery, will also be useful and applicable for parathyroid and neck surgeries. Parathyroid and neck surgeries, which are performed in a similar area to the thyroid, may necessitate reoperation, leading to longer operative times and an increased risk of complications such as RLN injury and hypoparathyroidism.

We can list some limitations of our study as follows. Since our study was designed only to examine adhesions after thyroidectomy, the complication rates after reoperation were not directly examined, histopathological and macroscopic examination was scored semi-quantitatively, the number of subjects was limited, the short follow-up period, i.e., the inability to observe the final stages of wound healing, namely maturation and remodeling, within the 14-day postoperative period, which may lead to different results in the future, the lack of knowledge regarding the optimal duration and effective doses of the agents used for maximum adhesion efficacy, and the absence of tests such as blood and urine tests to assess the biochemical effects and side effects of the agents used. Despite these limitations, our findings have direct translational relevance for clinical practice. Reoperative thyroid, parathyroid, and neck surgeries are increasingly common due to rising rates of differentiated thyroid cancer, recurrent goiter, and persistent hyperparathyroidism [35]; in these settings, adhesion-related disruption of tissue planes remains a leading cause of recurrent laryngeal nerve injury and permanent hypoparathyroidism. An effective, locally applied anti-adhesive agent used during the index operation could therefore meaningfully reduce the morbidity associated with subsequent interventions. The significant macroscopic reduction in adhesions observed with BAPN in this pilot experimental model provides a rationale for larger-scale preclinical studies with dose-response and biochemical safety evaluation, which are essential steps before translation to clinical trials in high-risk surgical candidates.

5. CONCLUSION

In our experimental study, we observed that BAPN may have anti-adhesive effects in thyroid surgery. BAPN may reduce surgical complications, particularly in high-risk patients who may require reoperative thyroid, parathyroid, or neck surgery. Further studies are needed on the anti-adhesive efficacy and clinical use of BAPN.

Declarations

Ethics Approval: This experimental study was conducted following approval from the Istanbul University Animal Experiments Local Ethics Committee (approval date: 16 March 2017, approval no: 50442). All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals (8th edition, National Research Council, 2011).

Prior Presentation: This study is based on the general surgery residency thesis of Mazlum Yavaş, accepted in 2017. Preliminary results of this work were previously presented as an oral presentation at the 16th Medical-Surgical Endocrinology Postgraduate Education Course in Antalya, Turkey (November 2–5, 2017).

Competing Interests: The authors have no competing interests to declare that are relevant to the content of this article.

Funding: No external funding was received for this work. The experimental animals used in this study were provided by Istanbul Training and Research Hospital, whose institutional support is gratefully acknowledged.

Author Contributions: Conceptualization: M.Y., S.S.; Study Design: M.Y., S.S., M.S.G.; Supervision: S.S., F.E.; Data Collection and Processing: M.Y., E.G., G.E., F.G., M.S.G.; Formal Analysis and Interpretation: M.Y., S.S., G.E., M.S.G.; Literature Search: M.Y., T.C.Ş., K.A., M.S.G.; Writing – Original Draft: M.Y., M.S.G.; Writing – Review and Editing: S.S., E.G., F.E., T.C.Ş., K.A., M.S.G.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process: During the preparation of this work, the authors used Claude (Anthropic, San Francisco, CA, USA; claude.ai) for the purpose of language editing and improvement of manuscript clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

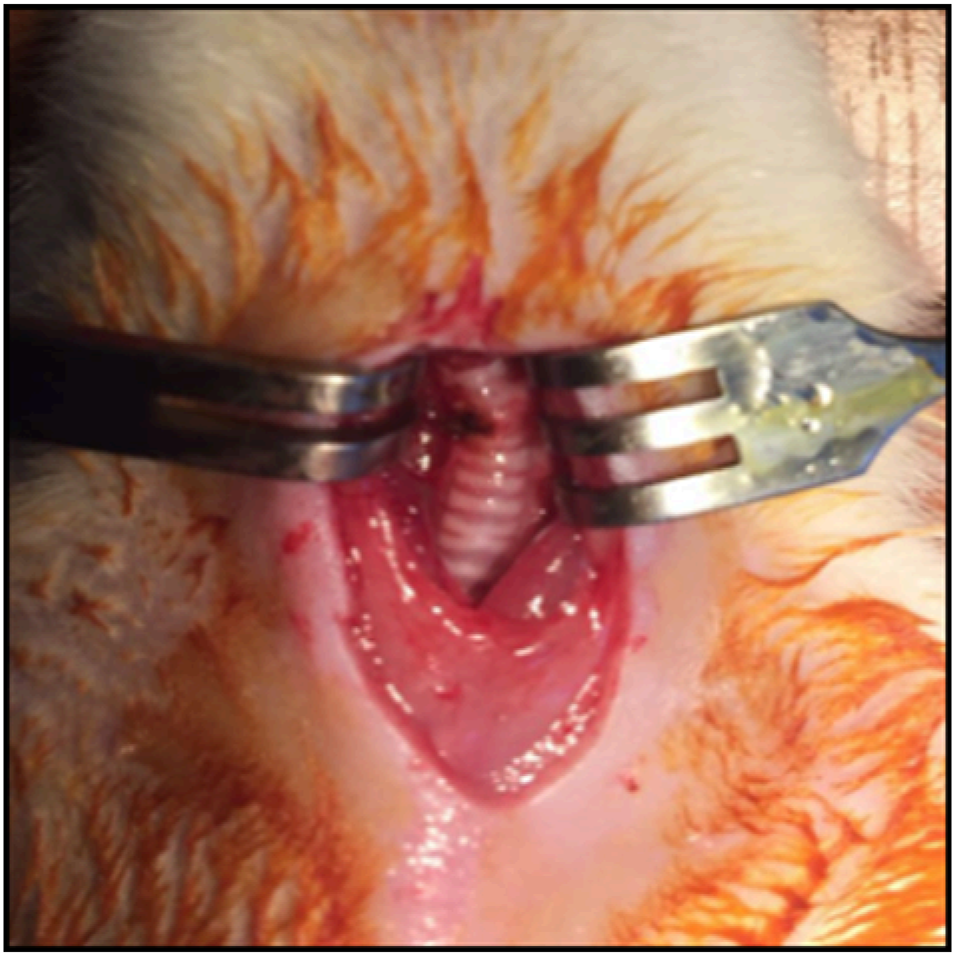

Figure 1

Surgical view following right subtotal thyroidectomy with bipolar cautery. The residual thyroid tissue is visible in the operative field.

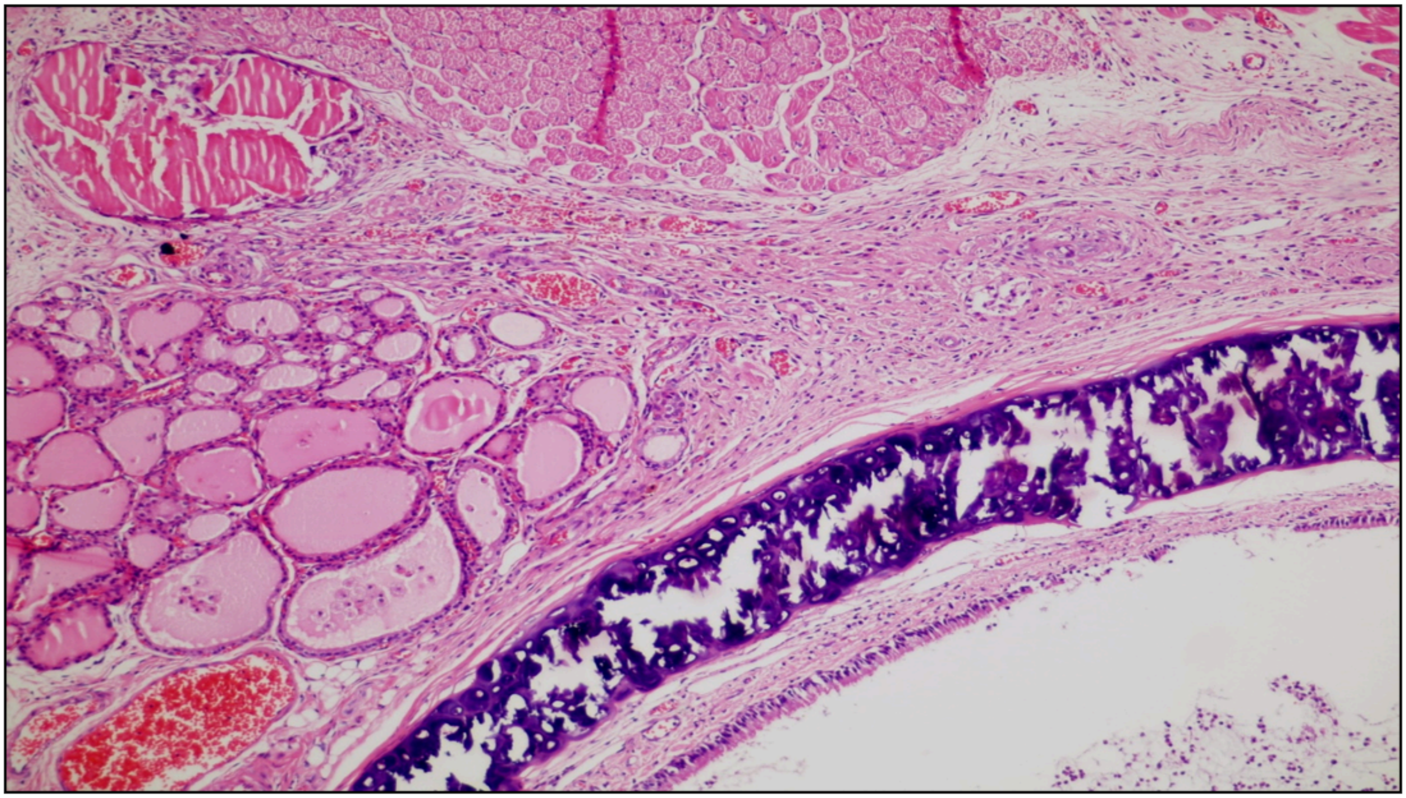

Figure 2

Representative histopathological section from the SO group (hematoxylin and eosin, ×100). PMNL, lymphocyte, and histiocyte infiltration scored 1; fibroblast and vascular proliferation scored 2; foreign body–type giant cells scored 1.

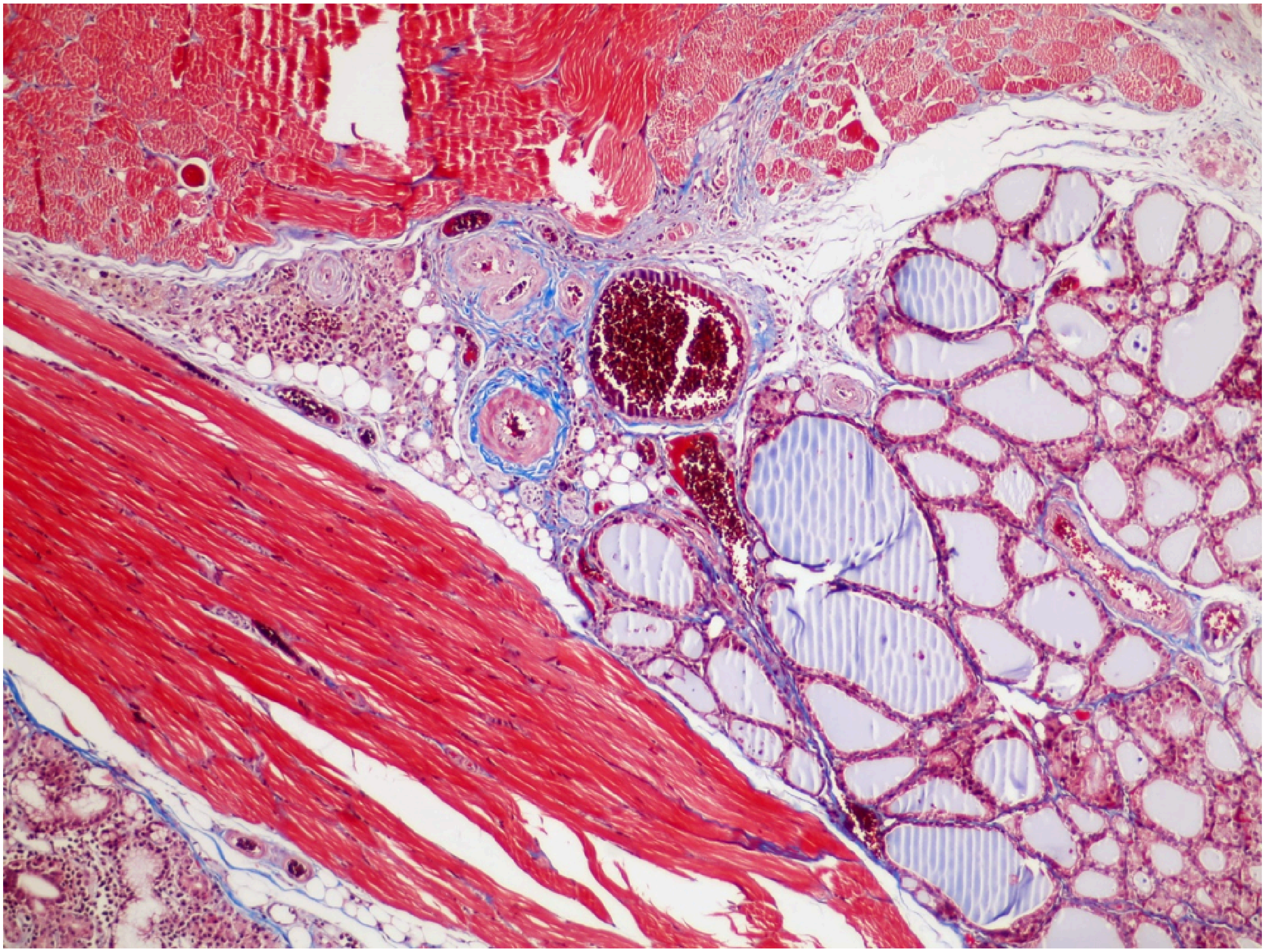

Figure 3

Representative Masson trichrome–stained section from the NSO group (×100). Fibrosis (blue) is observed around the thyroid follicles and extending into the surrounding connective tissue, scored 1.

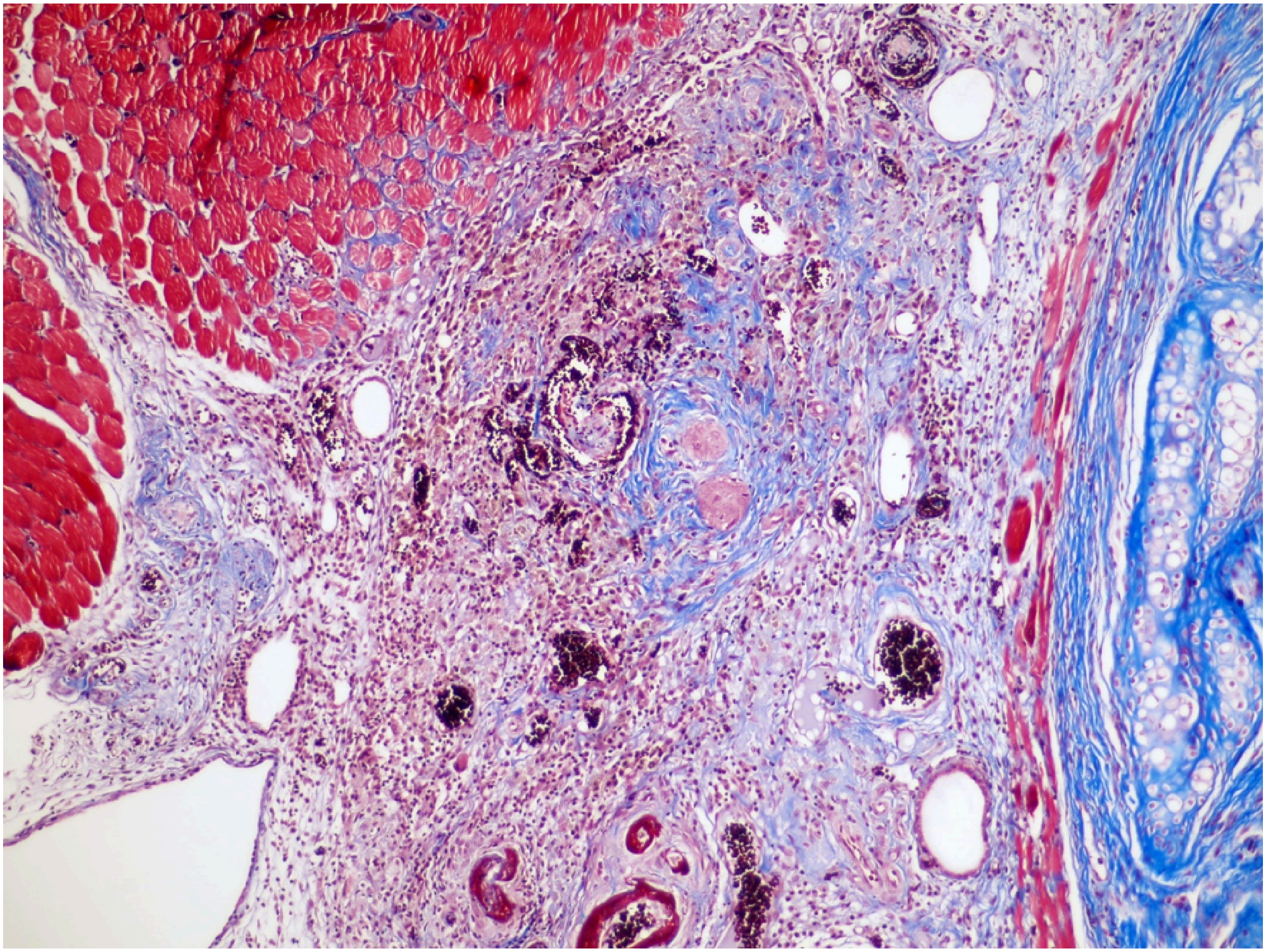

Figure 4

Representative Masson trichrome–stained section from the CT group (×100). Fibrosis (blue) is observed in the connective tissue surrounding the muscle tissue, scored 2.

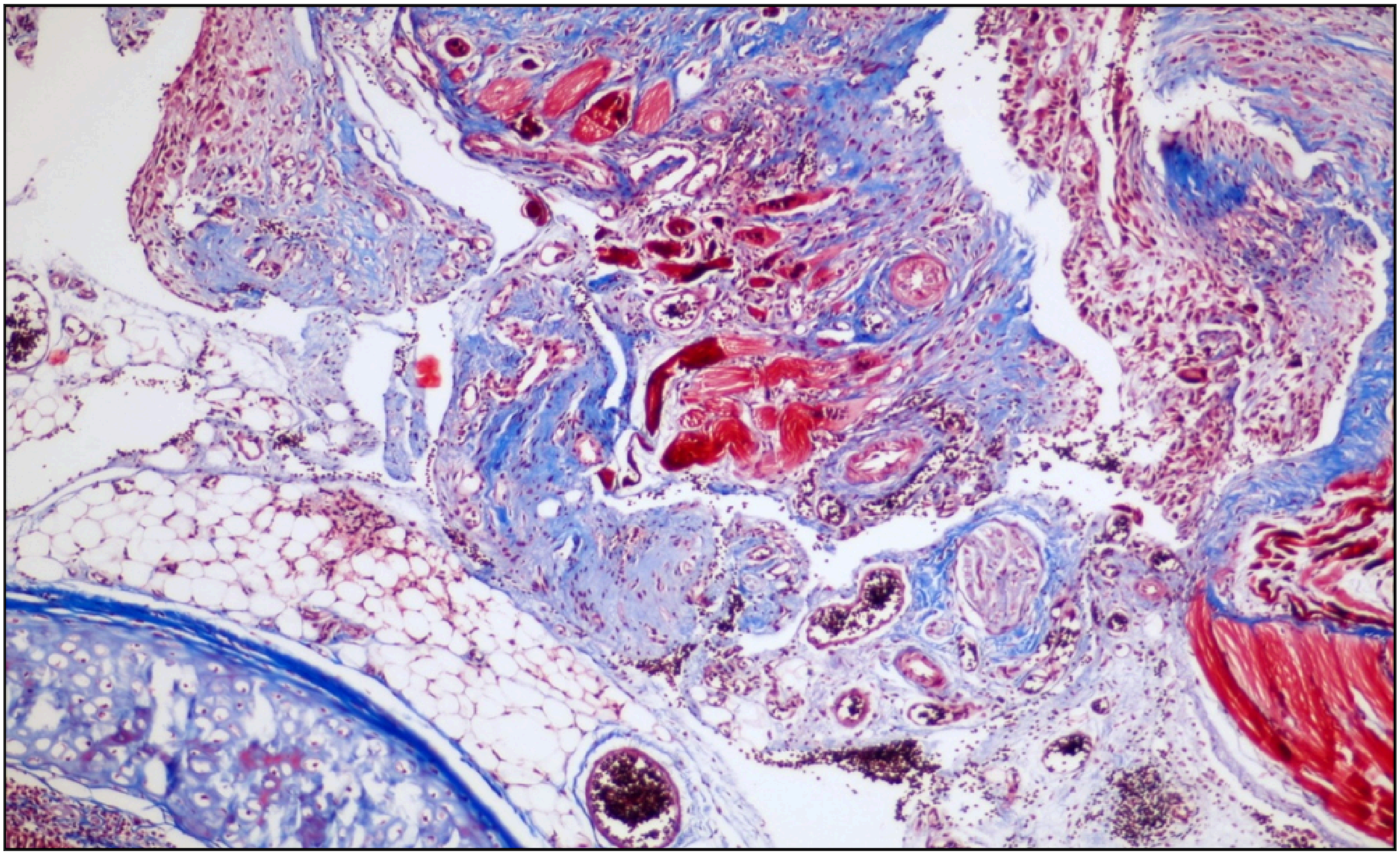

Figure 5

Representative Masson trichrome–stained section from the control group (×100). Marked fibrosis (blue) is observed around the muscle tissue, scored 3.