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ORIGINAL RESEARCH

The Efficacy of Ankaferd Blood Stopper for the Management of Bleeding Following Total Thyroidectomy

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ABSTRACT

Purpose: Postoperative hematoma remains an uncommon but potentially life-threaten complication of thyroid surgery. The aim of this study is to assess the efficacy of Ankaferd Blood Stopper (ABS) in comparison to hemostasis by conventional technique (HCT) for the controlling of oozing-type bleeding following total thyroidectomy. *Methods*: We randomized 61 patients with benign euthyroid multinodular goiter who underwent total thyroidectomy subject to one of the two different hemostasis techniques. There were 31 patients in the HCT group and 30 patients in the ABS group. The study was designed prospectively to compare ABS and HCT groups in terms of operation time, postoperative drainage, duration of postoperative stay, and complications. *Results*: Mean postoperative drainage from the closed suction drains at first 24 hr were 24.6 ± 8.6 ml and 12.0 ± 9.2 ml ($p = .001$) and mean total postoperative drainage were 38.5 ± 13.2 ml and 20.6 ± 12.2 ml ($p = .001$) in the HCT and ABS groups, respectively, indicating statistically significant differences. *Conclusions*: On the basis of the results of this trial, the use of ABS seems to be more effective than HCT to control hemorrhage following total thyroidectomy.

Keywords: thyroidectomy; bleeding; hemostatic agent; ankaferd blood stopper

INTRODUCTION

Total thyroidectomy is a commonly performed surgical procedure for the treatment of benign and malign thyroid disease. The main aims of the thyroidectomy process are the conservation of the parathyroid glands, avoidance of injury to recurrent laryngeal nerve (RLN), and a perfect hemostasis [1]. Thompson et al. developed capsular dissection technique to decrease the complication rate in thyroid surgery in 1973 [2]. Nevertheless, postoperative hematoma remains an uncommon but potentially life-threaten complication of thyroid surgery. Post-thyroidectomy hemorrhage has a reported incidence in the literature of between 0.5% and 4.3% [3]. The conventional techniques for hemostasis are suture ligatures and electrocoagulation. The use of electrocoagulation has the potential risk of lateral thermal damage to the surrounding structures. Difficulties in the control of oozing-type bleeding may also obscure adjacent anatomical structures and may cause indirect morbidities related to RLN and parathyroid glands. In the last decade, new hemostatic agents have been designed to support hemostasis in thyroid surgery [1, 4, 5].

Ankaferd Blood Stopper (ABS) is a novel topical hemostatic agent. The hemostatic mechanism of ABS involves the formation of an encapsulated protein network representing focal points for vital erythrocyte aggregation [6]. The use of ABS in swine bleeding model, in an experimental liver laceration model, upper gastrointestinal hemorrhage, and tonsillectomy, have been reported in the literature [7–10]. The aim of this study was to compare the effectiveness of ABS as a haemostatic agent to control oozing-type bleeding from small vessel after specimen removal in total thyroidectomy versus hemostasis by conventional technique (HCT) to our knowledge, this is the first controlled study testing the effectiveness of ABS in total thyroidectomy.

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MATERIAL AND METHODS

The study was conducted in accordance with the Declaration of Helsinki, as revised in 2000. The protocol of study was approved by the Ethical Committee of Clinical Research of Gaziantep University, Turkey. The setting was a tertiary referral center. The study was planned as a prospective, randomized, controlled trial.

Between July 2008 and March 2010, 169 consecutive patients underwent total thyroidectomy in our institution. Fifty patients were excluded due to diagnoses other than benign euthyroid multinodular goiter, and 119 patients were invited to join the study. Inclusion criteria included bilateral benign multinodular goiter with thyroid masses of less than 5 cm, no suspicion of malignancy, no previous thyroid surgery, no need to use the thoracic approach, and no associated parathyroid gland disease. In order to ensure homogeneity, we also excluded patients with Graves' or hyperfunctioning thyroid diseases and thyroiditis. In addition, patients with a preexisting history of bleeding disorders, or treatment with anticoagulants, and the presence of uncontrolled hypertension were excluded from the study. Sixty-one patients agreed to participate and gave their written informed consent before entering into the study (Figure 1).

All procedures were carried out under general anesthesia. Anesthesia was induced with propofol 2 mg/kg, sufentanil 0.2 μg/kg, and rocuronium 0.6 mg/kg. Anesthesia was maintained with sevoflurane in oxygen and 50% nitrous oxide. All thyroidectomies were performed by two surgeons (Mehmet Guler and Gokturk Maralcan) with 10 years experience in thyroid surgery. Sixty-one patients were randomized to

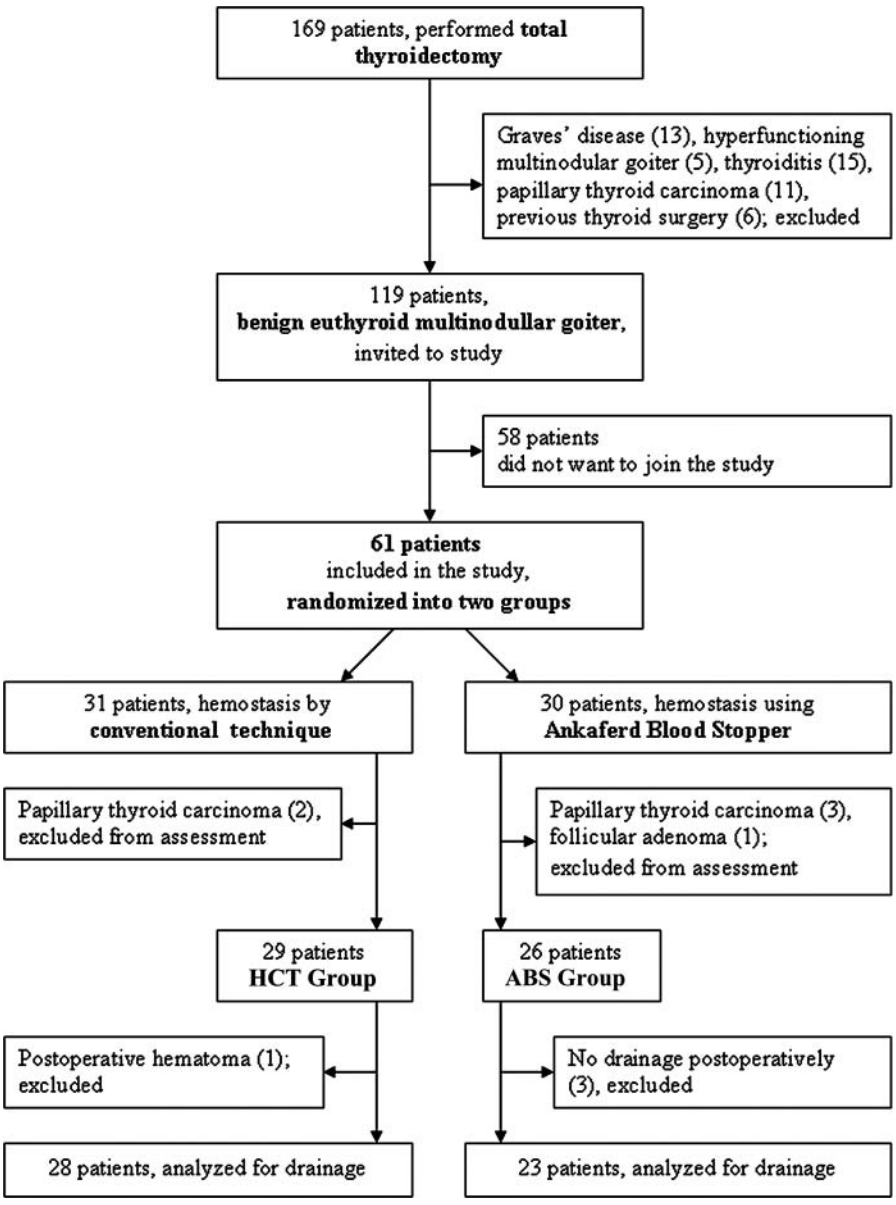

FIGURE 1 Flowchart of trial design.

two groups: The first group (HCT) achieved hemostasis by the conventional technique, and the second group (ABS) received the ABS hemostatic agent. Randomization was performed using numbered and sealed envelopes. The surgeons were blinded to the hemostasis technique until the sealed envelopes were opened in the operating room for each patient, after specimen removal. The procedure was then completed using the assigned hemostasis technique to control oozing-type bleeding from small vessels. In the HCT group, meticulous hemostasis was achieved by the clamp and tie technique, using 4/0 absorbable suture and monopolar electrocoagulation avoiding areas close to the nerves and parathyroid glands. In the ABS group, hemostasis was achieved by topically applied 1 ml liquid form ABS by sterile technique, using an injection syringe squirt to each side of the thyroid lobectomy field. We waited 2 min to observe whether hemostasis was sufficient before wound closure and left the liquid in place. It was planned that if continued bleeding was noted, the procedure would be completed by conventional technique and the patient would be excluded from the study. Before closing the wound, a closed suction drain was placed and withheld for 48 hr in all patients. Postoperative analgesia was consisted of intravenous administration of 2 mg/kg tramadol 30 min before the end of surgery. Paracetamol (1 g) or tramadol (100 mg) were given upon patient request every 6 hr.

ABS (Trend Teknoloji Ilac AS, Istanbul, Turkey) is a haemostatic agent composed of the following plant extracts: *Urtica dioica* (0.06 mg/ml), *Vitis vinifera* (0.08 mg/ml), *Glycyrrhiza glabra* (0.07 mg/ml), *Alpinia offcinarum* (0.07 mg/ml), and *Thymus vulgaris* (0.05 mg/ml). The basic mechanism of action for ABS is the formation of an encapsulated protein network representing focal points for vital erythrocyte aggregation [6]. ABS could be used effectively to manage external bleeding in clinical settings such as skin bleeding and/or superficial mucosal blood oozing [7]. ABS is a registered product for direct application, spraying, or incorporation in dressing material to injured skin or mucosa. It is a licensed medicinal plant product that provides active hemostasis and is approved in Turkey by the Ministry of Health.

Whole blood count, blood chemistry (blood urea nitrogen [BUN], creatinine, alanine transaminase [ALT], aspartate transaminase [AST], gamma glutamyl transferase [GGT]), and coagulation tests (bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, and international normalized ratio) were determined for all patients preoperatively and 24 hr after operation. Postoperative drainage per 24 hr for each patient was determined. In addition, outcome measures included duration of operation, length of postoperative hospital stay, and incidence of postoperative complications. Indirect laryngoscopy was performed in all patients preoperatively, and at 24 hr postoperatively, by specialists from the Otolaryngology Department, to detect any RLN injury. Serum calcium levels were determined preoperatively and at 24 hr postoperatively to test parathyroid function. The operative time was calculated from skin incision to skin closure. Drains were withheld for 48 hr and then removed if the daily drainage was less than 10 ml. Hospital discharge was at 48 hr after the operation if no signs of complications were present. All patients were seen for follow-up clinical visits at 7 days and 1 month.

Statistical Analysis

Sample size was estimated using a power calculation based on a 50% reduction in total drainage in ABS group. It was estimated that after using ABS at least 12 patients would be required to detect a significant difference between two groups at 80% power level and an alpha error of 5%. The study data were analyzed using SPSS (Version 13.0, Chicago, IL). Demographic data were collected and presented as mean ± *SD*. Student's *t* test and Mann–Whitney *U* test were used for means, and the Chi-square test was used for percentages. A 95% confidence interval was used and *p* values less than .05 were considered significant.

RESULTS

The mean age was 43.2 years (range 19–72 years) and 83.6% of participants were female. The two groups were homogeneous for age and sex ($p > .05$). Routine hemogram, blood chemistry, and coagulation parameters **were** within **normal ranges** in all patients preoperatively. Twenty-four hours after total thyroidectomy, these test results were also within normal ranges in all patients except one patient in the HCT group, who developed postoperative wound hematoma. Of the 61 patients included in the study, 5 patients who were diagnosed with papillary thyroid carcinoma and 1 patient diagnosed with follicular adenoma in postoperative pathological examination were excluded from the analysis. After exclusion of those 6 patients, a total of 55 patients were recruited: 29 in the HCT and 26 in the ABS group. Mean operation time was 9 min shorter in the ABS group, but the difference between the two groups was not significant ($p > .05$).

Adequate hemostasis was achieved after topical application of ABS in all patients, and there was no patient excluded because of inadequate hemostasis in ABS group. Three patients in the ABS group observed no drainage postoperatively and one patient in the HCT group who developed wound hematoma were excluded from the statistical analysis for drainage. Mean postoperative drainage from closed suction drains during the first 24 hr was significantly different between the two groups, with 24.6 ± 8.6 ml in the HCT group and 12.0 ± 9.2 ml in the ABS group ($p = .001$). The

TABLE 1 Patients characteristics and outcome

Variables	HCT group ($n = 29$)	ABS group ($n = 26$)	p
Age, mean (year)	42.4	44.1	.783
Sex			
Female/male	25/4	21/5	
Operation time (min)	113	104	.087
Postoperative drainage* (ml)			
1 day, mean (±*SD*)	24.6 ± 8.6	12.0 ± 9.2	.001
2 day, mean (±*SD*)	13.9 ± 9.8	8.6 ± 6.7	.172
Total, mean (±*SD*)	38.5 ± 13.2	20.6 ± 12.2	.001
LOS, mean (range)	3.2 (2–7)	2.7 (2–4)	.069

Note: *SD*, standard deviation; LOS, length of stay.
*Hematoma (1 patient in HCT group) and no drainage (3 patients in ABS group) excluded.

mean total postoperative drainage from closed suction drain was also significantly different between the HCT and ABS groups (38.5 ± 13.2 ml and 20.6 ± 12.2 ml, respectively, $p = .001$). Drainage during the second 24 hr and length of postoperative hospital stay were similar in both groups ($p > .05$; Table 1; Figure 2).

There was no operative mortality in any group. There were no significant differences in postoperative morbidity between the two groups (Table 2). Postoperative hemorrhage occurred in one patient in the conventional hemostasis group. The patient underwent reoperation 4 hr later, made a normal recovery, and was discharged from hospital on the sixth postoperative day. All seven patients with postoperative hypocalcaemia were discharged on a combination therapy of oral calcium and cholecalciferol. Parathyroid function recovered in a mean period of 22 days (range 4–49). RLN palsy developed in one patient but resolved spontaneously in 5 weeks.

DISCUSSION

The thyroid gland is a highly vascular organ, and meticulous intraoperative hemostasis is fundamental to prevent postoperative hemorrhage. Significant postoperative bleeding occurs in less than 1% of patients, but a rapidly expanding hematoma can cause airway compression and sometimes an emergency tracheotomy is required [11]. The risk factors for hemorrhage following thyroid surgery include inadequate surgical skill; preexisting conditions such as uncontrolled hypertension, disorders of hemostasis, and coagulation; treatments such as anticoagulation therapy; and the presence of Graves' or hyperfunctioning thyroid diseases [4]. Suture ligation of individual vessels has been the standard technique in most centers but is time consuming. Most surgeons have therefore been adopting electro coagulation. The onset of hemorrhage is usually within the first 24 hr after the operation [12]. In cases of postoperative hematoma, the bleeding vessel cannot be found in 24% of patients upon reoperation [13]. This suggested that postoperative hematomas may be related to oozing-type hemorrhage observed after specimen removal.

Effective hemostasis after specimen removal is an integral part of safe outcome, but there is a challenge for the surgeon in this last stage of the operation. Careless and blindness maneuvers to obtain hemostasis may cause hemostasis-related complications such as permanent or transient RLN palsy or damage to

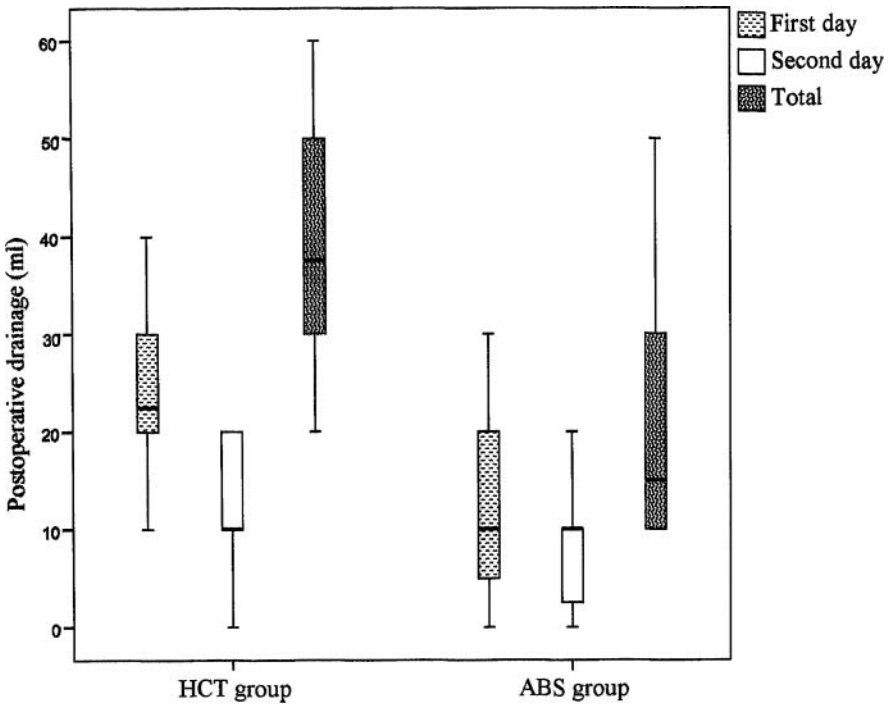

FIGURE 2 Postoperative drainage from closed suction drain after total thyroidectomy.

TABLE 2 Postoperative complications after total thyroidectomy

	HCT group ($n = 29$)	ABS group ($n = 26$)	p
Transient postoperative hypoparathyroidism, n (%)	4 (13.8)	3 (11.5)	.881
Transient recurrent laryngeal nerve palsy, n (%)	1 (3.4)	0	.945
Postoperative hematoma, n (%)	1 (3.4)	0	.945

parathyroid glands with secondary transient or permanent hypoparathyroidism. Electrocautery used in conventional techniques may harm the adjacent tissues due to lateral thermal damage. After suspensory ligament of Berry dissection, it is common for oozing-type bleeding to appear close to the RLN. This area presents a particular challenge for the surgeon, as hemostasis must be achieved using methods other than electrocautery and ligatures. In addition, the presence of intraoperative hypotension could result in the surgeon failing to recognize some small vessel that should be tied, thus leading to postoperative hematoma.

In recent years, various topical hemostatic agents with different action mechanisms were used effectively for hemostasis in thyroid surgery. For example, Merocel (Medtronic Xomed, Jacksonville, Florida, USA) and Floseal (Baxter Health Care Corp., Deerfield, IL, USA) have been described for use in controlling hemorrhage in thyroidectomy [1, 4]. They are useful to assist in the control of capillary, venous, small arterial hemorrhage, and "oozing" bleeding when ligation or other conventional techniques of control are ineffective. To the best of our knowledge, the present study is the first reported use of ABS for control of oozing-type hemorrhage after specimen removal in thyroidectomy.

ABS is a novel hemostatic agent. ABS-induced formation of the protein network with vital erythroid aggregation covers the entire physiological hemostatic process [7]. Generally, there are three main components of the ABS-induced hemostatic network. Vital erythroid aggregation takes place with the spectrin and ankyrin receptors on the surface of red blood cells. Those proteins and the required ATP bioenergy are included in the ABS protein library. Ankaferd also up regulates the GATA/FOG transcription system affecting erythroid functions. Urotensin II is also an essential component of Ankaferd and represents the link between injured vascular endothelium, adhesive proteins, and active erythroid cells. Those concepts have been developed via MALDI-TOF proteomic molecular analyses, cytometric arrays, transcription analysis, and scanning electron microscope (SEM) ultrastructural examinations, as well as numerous investigations interacting with in vitro and in vivo research settings [14–17]. Three ABS phase III studies, performed in post-tonsillectomy hemorrhages, vascular port insertion bleeds, and anterior epistaxis provide support for its approval as a hemostatic agent in Turkey [10, 18, 19]. In addition, recently there were several reports on the topical application of ABS for gastrointestinal bleeding and presacral bleeding [20, 21].

On the basis of our results, the application of 2 ml dose of ABS to total thyroidectomy field has no effect on systemic parameters commonly used in clinical practice, such as whole blood count and blood chemistry. In addition, although not statistically significant, certain postoperative complications of total thyroidectomy, such as RLN injury and hypocalcaemia, were seen to be lower in the ABS group than the HCT group.

Although some centers no longer consider drainage useful after total thyroidectomy, we used closed suction drain routinely as a part of the study protocol, in order to objectively measure the amount of postoperative bleeding from the surgical field. A statistically significant reduction in drainage during the first postoperative 24 hr after topical ABS application suggests that the usage of ABS might be more effective in preventing hematoma by stopping oozing-type bleeding without causing an increase in hemostasis-related complications.

CONCLUSION

In conclusion, ABS is not intended as a substitute for meticulous surgical technique but, on the basis of this initial experience, it seems to be an effective hemostatic agent for patients undergoing total thyroidectomy, significantly reducing first 24-hr drainage. Preliminary experience using ABS has been encouraging, but prospective randomized trials using adequate patient numbers are needed to confirm effectiveness and safety.

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