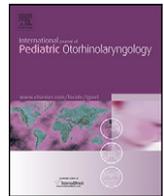




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Prospective, controlled clinical trial of Ankaferd Blood Stopper in children undergoing tonsillectomy

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ABSTRACT

Objectives: This is a prospective study evaluating the efficacy of Ankaferd Blood Stopper as a hemostatic agent compared to hemostasis by means of knot-tie after cold knife dissection tonsillectomy.

Methods: Study design was the use of ABS and the KT to reach hemostasis for patients undergoing tonsillectomy. ABS is applied on right side tonsil fossa and KT is used on left side tonsil fossa. Measured outcomes such as blood loss, surgical time, and complication will be assessed. In total, 47 consecutive patients undergoing cold knife dissection tonsillectomy were studied, in all of whom Ankaferd Blood Stopper wet tampon was used for right side tonsil hemorrhage and knot-tie technique for left side tonsil hemorrhage. Data were collected intraoperatively. Follow-up visits of all patients were completed at postoperative days 1, 3, 7, and 10.

Results: Ankaferd Blood Stopper side had shorter hemostasis time after tonsil removal than knot-tie side (3.19 ± 0.74 min vs 7.29 ± 2.33 min [mean \pm SD], $p < 0.01$) and less blood loss (1.57 ± 2.26 ml vs 14.04 ± 7.23 ml [mean \pm SD], $p < 0.01$). In addition, KT number was less with ABS side as compared to KT side ($p < 0.01$).

Conclusions: The side on which Ankaferd Blood Stopper was used had statistically significant differences in hemostasis time, blood loss, and knot-tie number in the operation period. Ankaferd Blood Stopper is safe and efficient, and it decreases intraoperative bleeding, reduces operating time, as compared to the traditional hemostasis methods after cold knife dissection tonsillectomy.

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1. Introduction

Tonsillectomy is one of the most common operations performed in the otorhinolaryngology practice. Various surgical procedures for tonsillectomy are performed with a wide array of options with each having its own advantages and disadvantages. Although numerous techniques have been introduced and used to perform tonsillectomy, cold knife tonsillectomy is still frequently used by most of the surgeons [1]. After the cold knife dissection, tonsillectomy needs some methods to control the hemorrhage. Hemostasis is achieved by either mechanical (ligation) or electrosurgical means. In an optimal situation of tonsillectomy, a surgical procedure would be the one that generates minimal postoperative pain, little or no bleeding, is completed in minimal operation time, and allows the patient to return to their normal daily activities in the shortest period of time [2,3].

ABS is a hemostatic agent composed of plant extracts which are *Urtica dioica* (0.06 mg/ml), *Vitis vinifera* (0.08 mg/ml), *Glycyrrhiza*

glabra (0.07 mg/ml), *Alpinia officinarum* (0.07 mg/ml), and *Thymus vulgaris* (0.05 mg/ml). Each of the constituents has some effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics and cell mediators. The basic mechanism of action for ABS is the formation of an encapsulated protein network representing focal points for vital erythrocyte aggregation [4,5]. ABS could be used effectively to manage external bleeding in clinical settings such as skin bleeding and/or superficial mucosal blood oozing.

This study will evaluate the clinical efficacy of ABS in children undergoing tonsillectomy. This hemostatic technique will be compared to the traditional technique of knot-tie (KT) hemostasis in cold knife dissection pediatric tonsillectomy. Intraoperative bleeding, time to hemostasis, knot-tie number in the operation period, and postoperative complications were compared for each technique.

2. Patients and methods

This study was performed at ENT Clinic. A prospective, not randomized, nonblinded study was undertaken between November 2008 and February 2009. Setting was tertiary referral center. Study protocol was approved by the Ethics Committee of Hospitals.

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This study was conducted on pediatric population. Patients with chronic tonsillitis, tonsillar hypertrophy, and obstructive sleep apnea syndrome were included in the study. Patients with bleeding disorders, aspirin use within 2 weeks prior to surgery, peritonsillar abscess history, acute tonsillitis within 4 weeks prior to surgery, tonsillectomy due to malignancy suspicion and children with systemic diseases were excluded.

2.1. Preoperative assessment

Preoperative studies included full blood count, coagulation tests and serological tests. Risk factors for hemorrhage (hypertension, intake of oral anticoagulants, etc.) were treated preoperatively and patients with lasting abnormal values did not undergo surgery. All patients were examined by an otolaryngologist, a pediatrician, and an anesthetist for operation. 47 children who had no exclusion criteria, and for whom informed consent from the parents were obtained, were included in the study. Study design was the use of ABS and the KT to reach hemostasis for patients undergoing tonsillectomy. ABS (Trend Teknoloji Ilac AS, Istanbul, Turkey) 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. We used ABS wet tampon form (2.5 cm × 7 cm/3 ml). The retail cost of ABS is \$ 20/ml in Turkey. ABS is applied on right side tonsil fossa and KT is used on left side tonsil fossa.

2.2. Tonsillectomy technique

The cold knife dissection technique was used on both tonsils of each patient subject to the study. After cold knife dissection tonsillectomy, the right tonsil hemostasis were to be provided with the ABS and if needed with traditional knot-tie. The contralateral tonsil hemostasis was to be provided with the KT. No other hemostatic technique was used for the patients. All operations were performed by three staff of otorhinolaryngology department. Surgeons were not blinded from the hemostatic technique. The estimated blood loss and time taken to complete each procedure and any abnormalities encountered were noted on the day of operation.

All tonsillectomies were performed under general anesthesia with endotracheal intubation. The patient position was the supine with a roll under the shoulder. A MCiver gag retractor was inserted intraorally and conventional cold knife tonsillectomy was started by an incision overlaying the superior pole of the tonsil with knife and the anterior pillar was separated from tonsillar capsule with a long-curved hemostatic clamp. The cold dissection proceeded along the tonsillar fossa in the peritonsillar plane, keeping as close to the tonsil capsule as possible. Elevator was used for blunt dissection, followed by a snare at the tonsillar base. Tonsil tissue was removed by snare and than hemostasis was achieved on right tonsil by ABS, left tonsil by KT.

2.3. Data collection and follow-up

When the right tonsil was removed, blood was suctioned, then ABS wet tampon was directly applied to the operative site. On the manufacturer's recommendation, the tampon was left in place for 3 min for ABS side in this study. If continued bleeding was noted in the ABS side, the ABS was reapplied. After two unsuccessful ABS applications, the patient was crossed over into the KT application. A saline-moistened pack was placed into left tonsil fossa for 3 min. The saline pack was inserted again if the hemostasis was not achieved. If the bleeding still persisted after these procedures, the hemorrhages were controlled by 2.0 silk KT. Operative time was

recorded from the insertion of the ABS wet tampon through its removal for the right tonsil and for the left tonsil, it was recorded from the insertion of the saline-moistened pack through adequate hemostasis. Blood loss was estimated and recorded for the right tonsil by adding the amount in the suction bottle to the amount in the used ABS wet tampon which is obtained by weighing it. And for the left tonsil it was estimated and recorded by adding the amount in the suction bottle to the amount in the used gauze pack which is obtained by weighing it.

After achieving hemostasis and measurement of the blood loss and hemostasis time, if necessary, additional surgeries, such as adenoidectomy and insertion of a ventilation tube were performed. Then the patients were extubated and taken to the recovery room. After observing for any potential adverse reaction for at least 1 h in recovery room, the patients were transferred to the clinic.

Patients were discharged from hospital the day after tonsillectomy. All children were prescribed as a standard regimen of paracetamol and amoxicillin postoperatively. Each patient was controlled at postoperative days 1, 3, 7, and 10 after surgery. Considering that the children could not differentiate the pain between the tonsils, we did not regard the pain in this study. Bleeding, if any, was recorded. All patients' data including demographic parameters, intraoperative blood loss, operative time, knot-tie number in the operation period, and postoperative complications were recorded.

3. Statistics

For statistical analysis, NCSS 2007&PASS 2008 Statistical Software (Utah, USA) was used for comparison. Data were entered into Wilcoxon test for the quantitative analysis.

4. Results

The study consists of 47 consecutive procedures all performed by the otorhinolaryngology staff. The study population comprised 24 (51.1%) males, 23 (48.9%) females; age range was 4–14 years old (mean ± SD: 6.97–2.68 yrs). 6 (12.8%) had OSAS and 41 had chronic tonsillitis (87.2%) in our study. A detailed database was prepared for prospective recordings.

The side in which the ABS was compared to KT had significantly shorter times to hemostasis (3.19 ± 0.74 min vs 7.29 ± 2.33 min [mean ± SD], $p < 0.01$). The mean blood loss in the ABS side was 1.57 ± 2.26 [mean ± SD] ml, the mean blood loss in the KT side was 14.04 ± 7.23 [mean ± SD] ml. When comparing the ABS side to the KT side, there was statistically significant less blood loss during hemostasis ($p < 0.01$). ABS side did not need any other hemostasis methods when hemostasis was achieved. Only two ABS side were crossed over to KT when adequate hemostasis could not be achieved after 6 min of ABS application on the tonsil fossa. In addition, KT number was less with ABS as compared to KT ($p < 0.01$) (Table 1).

No peritonsillar or uvular edema was noticed in any of the patients. No postoperative hemorrhage or other complication occurred.

Table 1

Assessment of hemostasis time, blood loss, and number of knot-tie (p values were determined using the Wilcoxon test).

	Right tonsil	Left tonsil	p
	Mean ± SD (median)	Mean ± SD (median)	
Operation time (min)	3.19 ± 0.74 (3)	7.29 ± 2.33 (7)	0.001**
Blood loss (ml)	1.57 ± 2.26 (1)	14.04 ± 7.23 (13)	0.001**
Knot-tie number	0.06 ± 0.32 (0)	1.97 ± 1.22 (2)	0.001**

** $p < 0.01$.

5. Discussion

Tonsillectomy continues to be one of the most common surgical procedures performed worldwide in the pediatric population. Despite advances in surgical and hemostatic techniques such as bipolar radiofrequency, laser, coblation, harmonic scalpel and thermal welding, however, post-tonsillectomy morbidity remains a significant problem [6,7]. Actually bleeding after tonsillectomy is associated with significant morbidity and rare mortality. Our prospective study of ABS showed effective hemostasis of tonsillectomy and decreased risk of intraoperative bleeding when compared to KT.

Walker and Gillies [8] identified a difference in the rate of secondary hemorrhage after different techniques for tonsillectomy. They found postoperative bleeding rate to be higher for cauterization technique than cold knife technique. It was determined that cold knife dissection plus hemostasis by means of knot-tie had the lowest risk of post-tonsillectomy bleeding. Also several studies demonstrated that postoperative pain and post-tonsillectomy hemorrhage is encountered frequently after cauterization [9,10]. If ABS is applied in tonsillectomy, use of cauterization would be reduced, pain and hemorrhage would be encountered less after the operation. Generally locally applied vasoconstrictors can assist in the control of bleeding, reduce the time to achieve hemostasis and provide a better defined plane of dissection which minimizes trauma to the surrounding tissue [11]. Oxymetazoline, ksilometazolin, and phenylephrin possess remarkable vasoconstrictive abilities. On the other hand these agents cause postoperative bleeding and adverse reactions after tonsillectomy [12]. In this study we found that ABS causes no side effects and reduces postoperative bleeding, therefore it may be preferred over vasoconstrictors in tonsillectomy.

Our results suggest that ABS achieves statistically significant reduction in intraoperative hemorrhage when compared to the KT as hemostasis technique for pediatric tonsillectomy patients. Since hemostasis starts immediately after application of ABS, intraoperative bleeding is minimized and wound bed remains dry. On average, the ABS side had 12.5 ml lower blood loss than the KT side. The minimal difference in blood loss admittedly has little clinical significance.

Our study demonstrated that ABS achieved hemostasis much more rapidly than the traditional technique of KT. On average, the ABS hemostasis time was 4 min faster than the KT. Although statistically significant, we do not feel that this is a clinically significant difference. But this more rapid hemostasis by ABS reduces the operation time. Furthermore, since learning curve is not required for ABS, operation time is not increased. Finally, the surgeons rated ABS application to be considerably easier to perform than KT for achieving rapid hemostasis on the tonsil fossa. It is a single use, easy-to-use hemostatic agent without the need for special training.

ABS is a novel effective hemostatic agent that has the therapeutic potential to be used in the management of hemorrhage. Blood stopping process is driven based on protein agglutination. ABS stimulates the formation of an encapsulated protein network that provides points for erythrocyte aggregation in the injured vascular area. Furthermore, ABS also interacts with fibrinogen as well as other blood proteins. ABS induced formation of the protein network affected the entire physiological hemostatic process without affecting any individual clotting factor. The levels of coagulation factors II, V, VII, VIII, IX, X, XI, and XIII were not effected by ABS. Therefore, ABS might be used in patients with deficient primary hemostasis and/or secondary hemostasis, including patients with disseminated intravascular coagulation [13–15]. Bilgili et al. [16] showed that acute mucosal toxicity, hematotoxicity, hepatotoxicity, nephrotoxicity, and biochemical

toxicity were not observed after oral ABS administration in rabbits. They suggested that ABS had no signs of toxicity during short-term study. In the literature, there are no reported side effects from the use of this agent [17–19].

ABS induces a very rapid formation of a specific hemostatic protein network within vital erythrocyte aggregation in the injured vascular area. The data on the efficacy of ABS in gastrointestinal system bleeding is limited to case reports only. In addition ABS has been used to control upper gastrointestinal bleeding [17], life-threatening arterial bleeding of the digestive tract [18], and bleeding due to solitary rectal ulcer [19]. To our knowledge, our study is the first application of ABS in tonsillectomy patients. And also, our study is the first to evaluate effectiveness of ABS application as a hemostatic agent during an operation.

The price of equipment involved in tonsillectomy varies with the technique used although the largest cost factor in the operation is the operating time [20]. Cost of ABS is covered by reducing the operation time by an average of 8 min (4 min for each side). Therefore increase in cost due to ABS is offset by reduction in operation room cost because of the advantage of time to hemostasis. It may be preferred by surgeons due to its ease of use which could be a contributing factor in operation cost reduction. The cost of ABS is relatively low, which makes its routine-use seem reasonable. However, this cost-effectiveness remains to be studied.

ABS is a standardized extract from the following plants: *T. vulgaris*, *G. glabra*, *V. vinifera*, *A. officinarum* and *U. dioica*. The antibacterial activity of these plants has been investigated previously. For example, *U. dioica* has been shown to have an antibacterial activity against *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* [21]. Also Tasdelen Fisgin et al. [22] have obtained a rationale for assessing the activity of ABS on infected wounds. We agree that this property may reduce the need for postoperative profilaxi against bacteria. Our study was not designed to answer this, but if it is possible, patients would take less medicine.

There were no complications with either technique, including postoperative tonsillectomy hemorrhage, aspiration, blood transfusion, or hospitalization. We did not observe any potential adverse reaction after the operation. It is important to emphasize that ABS does not leave residual particulate because it is a solution. We did not need irrigation of the oropharynx after the ABS use.

In spite of our promising data, this study does possess certain limitations. As a small pilot study these findings are preliminary and need to be confirmed in a large, blinded, and randomized study.

6. Conclusion

Our results showed that ABS reduces intraoperative hemorrhage and operation time. It is a safe, efficient, and easy to use hemostatic agent with no side effects. Therefore we recommend ABS during routine tonsillectomy for healthy children. Further study could be carried out to determine possible benefits in the post-tonsillectomy hemorrhages.

References

- [1] R.V. Faulconbridge, S. Fowler, J. Horrocks, J.H. Topham, Comparative audit of tonsillectomy, *Clin. Otolaryngol. Allied Sci.* 25 (2000) 110–117.
- [2] J.P. Windfuhr, G. Schloendorff, D. Baburi, B. Kremer, et al., Lethal outcome of post-tonsillectomy hemorrhage, *Eur. Arch. Otorhinolaryngol.* 265 (2008) 1527–1534.
- [3] T.H. Low, P. Harris, A. Esterman, A.S. Karney, Pain versus bleeding risk following tonsillectomy: do patients and doctors agree? *J. Laryngol. Otol.* 20 (2009) 1–6.
- [4] H. Goker, I.C. Haznedaroglu, S. Ercetin, S. Kirazli, U. Akman, Y. Ozturk, et al., Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper, *J. Int. Med. Res.* 36 (2008) 163–170.
- [5] H. Bilgili, A. Kosar, M. Kurt, I.K. Onal, H. Goker, O. Captug, et al., Hemostatic efficacy of Ankaferd Blood Stopper in a swine bleeding model, *Med. Princ. Pract.* 18 (2009) 165–169.

- [6] S.P. Parsons, S.R. Cordes, B. Comer, Comparison of posttonsillectomy pain using the ultrasonic scalpel, coblator, and electrocautery, *Otolaryngol. Head Neck Surg.* 134 (2006) 106–113.
- [7] T. Chimona, E. Proimos, C. Mamoulakis, M. Tzanakakis, C.E. Skoulakis, C.E. Papadakis, Multiparametric comparison of cold knife tonsillectomy, radiofrequency excision and thermal welding tonsillectomy in children, *Int. J. Pediatr. Otorhinolaryngol.* 72 (2008) 1431–1436.
- [8] P. Walker, D. Gillies, Post-tonsillectomy hemorrhage rates: are they technique-dependent? *Otolaryngol. Head Neck Surg.* 136 (2007) 27–31.
- [9] S. Mitic, M. Twinnereim, E. Lie, B.J. Saltyte, A pilot randomized controlled trial of coblation tonsillectomy versus dissection tonsillectomy with bipolar diathermy haemostasis, *Clin. Otolaryngol.* 32 (2007) 261–267.
- [10] E. Ferri, E. Armato, P. Capuzzo, Argon plasma coagulation versus cold dissection tonsillectomy in adults: a clinical prospective randomized study, *Am. J. Otolaryngol.* 28 (2007) 384–387.
- [11] L.M. Broadman, R.I. Patel, B.A. Feldman, G.L. Sellman, G. Milmoie, F. Camilon, The effects of peritonsillar infiltration on the reduction of intraoperative blood loss and post-tonsillectomy pain in children, *Laryngoscope* 99 (1989) 578–581.
- [12] B.M. Rasgon, R.M. Cruz, R.L. Hilsinger Jr., H.W. Korol, E. Callon, R.A. Wolgat, et al., Infiltration of epinephrine in tonsillectomy: a randomized, prospective, double-blind study, *Laryngoscope* 101 (1991) 114–118.
- [13] C. Uçar Albayrak, U. Calişkan, I.C. Haznedaroglu, H. Goker, Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper, *J. Int. Med. Res.* 36 (2008) 1447–1448.
- [14] H.S. Cıgil, A. Kosar, A. Kaya, B. Uz, I.C. Haznedaroglu, H. Goker, et al., In vivo hemostatic effect of the medicinal plant extract Ankaferd Blood Stopper in rats pretreated with warfarin, *Clin. Appl. Thromb. Hemost.* 15 (2009) 270–276.
- [15] S. Aydin, Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper, *J. Int. Med. Res.* 37 (2009) 279.
- [16] H. Bilgili, O. Captug, A. Kosar, M. Kurt, M. Kekilli, A. Shorbagi, et al., Oral systemic administration of Ankaferd Blood Stopper has no short-Term toxicity in an in vivo rabbit experimental model, *Clin. Appl. Thromb. Hemost.* (July) (2009) [Epub ahead of print].
- [17] M. Kurt, S. Disibeyaz, M. Akdogan, N. Sasmaz, S. Aksu, I.C. Haznedaroglu, Endoscopic application of Ankaferd Blood Stopper as a novel experimental treatment modality for upper gastrointestinal bleeding: a case report, *Am. J. Gastroenterol.* 103 (2008) 2156–2158.
- [18] M. Kurt, S. Kacar, I.K. Onal, M. Akdogan, I.C. Haznedaroglu, Ankaferd Blood Stopper as an effective adjunctive hemostatic agent for the management of life-threatening arterial bleeding of the digestive tract, *Endoscopy* 40 (2008) 262.
- [19] M. Ibis, M. Kurt, I.K. Onal, I.C. Haznedaroglu, Successful management of bleeding due to solitary rectal ulcer via topical application of Ankaferd Blood Stopper, *J. Altern. Complement Med.* 14 (2008) 1073–1074.
- [20] A.N. Messner, Tonsillectomy, *Operative Tech. Otolaryngol.* 16 (2005) 224–228.
- [21] A.M. Janssen, J.J. Scheffer, Acetoxychavicol acetate, an antifungal component of ALPINIA galangal, *Planta Med.* 51 (1985) 507–511.
- [22] N. Tasdelen Fisgin, Y. Tanriverdi Cayci, A.Y. Coban, D. Ozatli, E. Tanyel, B. Durupinar, et al., Antimicrobial activity of plant extract Ankaferd Blood Stopper, *Fitoterapia* 80 (2009) 48–50.