



Topical blood stopper agents during adenoid surgery in young children; a prospective randomized controlled trial

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Abstract

Objective To investigate the safety and efficacy of two topical blood stopper modulators; Ankaferd blood stopper (ABS) and feracrylum 1% solution (FS) during adenoid surgery.

Study design Prospective randomized trial.

Methods Two hundred and twenty five consecutive pediatric adenoid patients aged from 9 months to 2 years old were studied. Patients were randomly allocated into two haemostatic groups; (ABS, FS) and normal saline (control group).

Results ABS and FS groups showed a significantly less intra operative blood loss ($16.4 \pm 2.6/22 \pm 6.2$), operative time ($9.31 \pm 1.9/11.2 \pm 1.6$ min), use of cautery ($10.6/25.3\%$), postoperative analgesics ($3 \pm 1.1/3.8 \pm 1.2$), duration to return normal diet ($2.4 \pm 1.2/3.9 \pm 0.9$) and operating theatre cost ($233 \pm 48\$$ and $279 \pm 40\$$) than the control group.

Conclusion AFS and FS are easy, safe, and reliable topical haemostatic modulators that could be used in adenoid surgery.

Keywords Topical · Ankaferd · Feracrylum · Haemostatic · Randomised · Controlled · Adenoidectomy

Introduction

Adenoidectomy is a very common operation in children [1]. Various techniques for adenoidectomy operation have been used. Among them, curette adenoidectomy is the most commonly used worldwide. Application of temporary gauze tampons in the nasopharynx represents the main haemostatic tool. If bleeding is not controlled, other methods of homeostasis are used such as saline irrigation, epinephrine tampon or cautery. Excessive cautery carries the risk of nasopharyngeal stenosis, damage of surrounding vital structures, severe postoperative pain and Grisel's syndrome [2–6]. Very rarely, bleeding may require posterior nasopharyngeal pack or even external carotid artery ligation [7–9]. Uncontrolled bleeding increases duration of operation, risk of infection, possibility of blood transfusion, cost of care and morbidity/mortality rates [8, 9]. This is of high importance especially in young children where normal physiological mechanisms are less

adaptable to a rapid blood loss even in small amounts [10, 11].

Achieving quick and effective homeostasis is a critical goal for the surgeon. Topical haemostatic agents are now frequently used in surgical and traumatic sites. Ankaferd blood stopper (ABS) is a blood stopper modulator contains some plant derivatives, including (*Urtica dioica* 0.06 mg/ml), (*Vitis vinifera* 0.08 mg/ml), (*Glycyrrhiza glabra* 0.07 mg/ml), (*Alpinia vinifera officinarum* 0.07 mg/ml) and (*Thymus vulgaris* 0.05 mg/ml). Each of these constituents has some effect on the endothelium, blood cells, angiogenesis, cellular proliferations, vascular dynamics, and cell mediators [12]. Feracrylum contains a mixture of water-soluble (polyacrylic acid) incomplete ferrous salt which composed of 0.05–0.5% of iron in combination with the pharmaceutical solvent which is water or physiologic solution. Feracrylum is obtained by polymerization of acrylic acid inhibited by redox- system in aqueous medium at 50 °C temperature [13]. Understanding how and when to use each of the available haemostatic agents can greatly affect clinical outcomes and help in reducing morbidities and mortalities as well as limiting the overall cost of treatment [14]. Therefore, this study was planned in a prospective randomized controlled fashion to investigate the safety and efficacy of two topical

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haemostatic modulators; ABS and FS, to control bleeding during adenoid surgery in infants.

Patients and methods

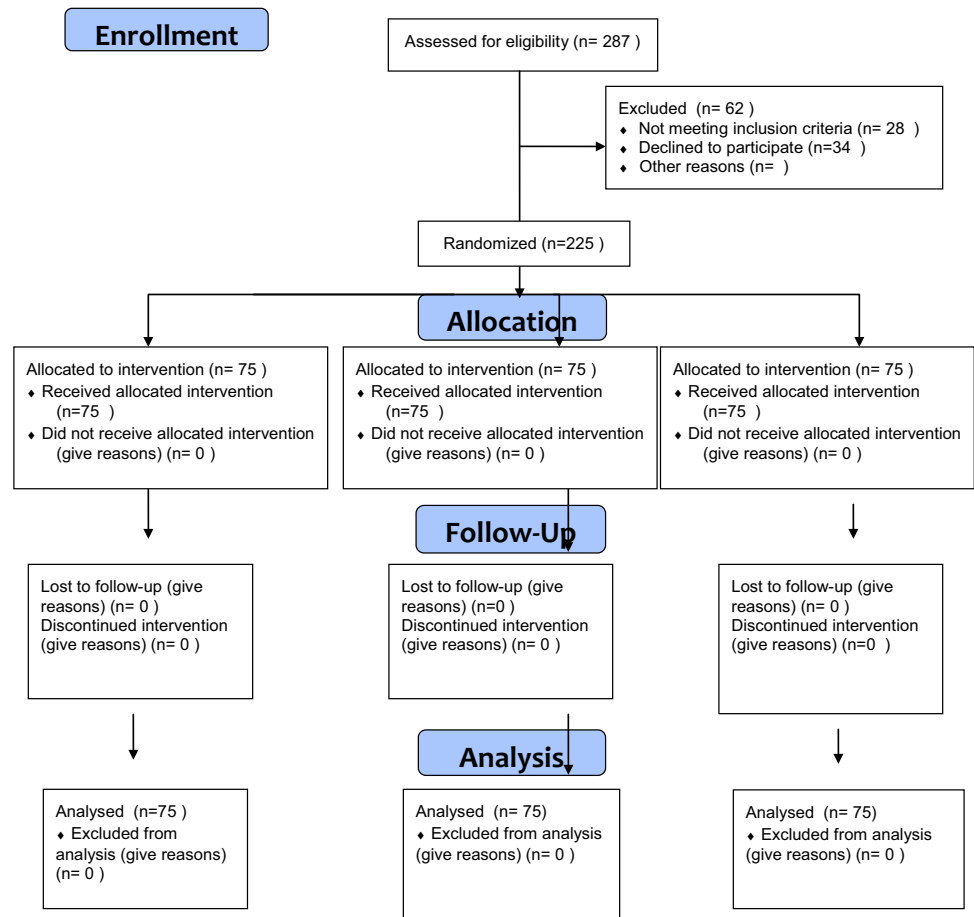
The study was conducted between June 2015 and January 2016, including 225 patients aged 9–24 months, who were planned for adenoidectomy in the department of Otolaryngology-Head and Neck Surgery, Taiba hospital, Kuwait for indications of persistent obstructive breathing (73 cases), chronic mouth breathing (45 cases), obstructive sleep apnea (37 cases), and secretory otitis media with big adenoid (70 cases). All parents were given an oral informed consent for the research. Children were randomized into three equal groups: ABS, FS and control group. Detailed history for all children was taken, clinical examination, and lateral plain X-ray of the nasopharynx. Pre-operatively, hemoglobin level, CBC, and coagulation profile were routinely checked according to our hospital policy. Bleeding disorders, systemic diseases, malnutrition and tonsillectomy patients were excluded from our research study. The research review

committee of Taiba Hospital approved the research protocol and consent. The flow chart of the study was shown in Fig. 1.

Operative technique

All cases were operated under general anesthesia in supine position with an oral endotracheal tube. All cases were done by the same surgeon (RA) and the same anesthetist (MZ). A Boyle–Davis mouth gag was inserted. Palate was palpated to exclude submucosal cleft. The adenoid tissue was directly visualized with a mirror as well as digitally palpated. Adenoidectomy was done by curettage with the largest possible adenoid curette. Complete removal of the adenoid tissue was confirmed by digital palpation and mirror examination. One hundred milliliter saline was put in a bowl and used for intermittent suction. After removing the adenoid, cleaning of blood was done by suction then gauze soaked with a hemostatic agent or normal saline was inserted for 3 min. In the first group, the gauze was soaked with 2 ml of Ankaferd blood stopper, (Trend Teknoloji Ilac AS, Istanbul, Turkey). In the second group, the gauze was soaked with 2 ml of feracrylum 1% sterile solution, (Themis Medicare Limited, India). In the last group, the gauze was soaked with 2 ml of 0.9% physiological saline. If

Fig. 1 CONSORT flow chart of the study



bleeding did not stop, we shifted to suction electro cautery set at 35 watts under mirror visualization until complete homeostasis was achieved.

The patient was completely monitored during general anesthesia. Changes in heart rate, blood pressure, respiration, CO₂ levels and oxygen saturation after application of the adenoid pack were reported. Gauzes were weighed before and after operation. Then suction for both nostrils and nasopharynx was done. After that, all the remaining bowel saline was sucked into the suction bottle until all the fluid was emptied into the suction bottle. The amount of intra operative blood loss was calculated by adding the volume of gauze absorbed blood to the suction bottle fluid and subtracting the 100 ml of bowel saline. A digital stopwatch was used by the circulating nurse to record the duration of operation starting from insertion to removal of the mouth gag.

All patients were observed in the ward for 24 h after operation and discharged on the next day. Parents were told to give paracetamol every 6 h as long as patient had pain, fever or did not return to normal diet. Patients were followed for 2 weeks. Duration of paracetamol, the exact time to return to normal diet and adverse events such as postoperative bleeding were recorded.

Statistical methods

Sample size was calculated as 75 patients in each group to give the study a power of 80% at the 5% level of significance. Blood loss was the primary endpoint in this study. To maintain exactly equal number of patients in the three groups, randomization was done using random blocks. At the time of operation and during the follow-up period, both the patient and the surgeon were unaware of the group assignment. Each patient was coded in a separate envelope. The anesthetist who was responsible to instruct the nurse to prepare the soaked gauze with ABS, FS or saline, opened the envelope that contained the cod of the patient to which group, on the day of the operation. The surgeon was unaware of the material soaking the gauze. Statistical presentation and analysis of the present study was conducted, using SPSSV17 (Chicago IL, SPSS Inc®). Data were expressed as (mean $\pm$ SD). *P* values less than 0.05 were considered significant. One way Anova test was used to compare between more than two means. Parametric independent two sample *t* test and analysis of variance were used for data that followed a normal distribution pattern. While nonparametric Chi-square test (χ^2) was used for data that showed abnormal distribution. Analysis was done per protocol.

Table 1 Baseline data

Parameter	ABS (N = 75)	FS (N = 75)	S (N = 75)	<i>p</i> value
Age (months)	17.1 $\pm$ 4.3	16.9 $\pm$ 4.4	17.2 $\pm$ 4.6	> 0.957
Sex	36 male 39 female	34 male 41 female	38 male 37 female	> 0.808
Adenoid size				
Moderate	43 (57.3%)	48 (46%)	43 (57.3%)	> 0.630
Sever	32 (42.7%)	27 (36%)	32 (42.7%)	

No significance difference regarding to the age, sex or the adenoid size *p* value > 0.05

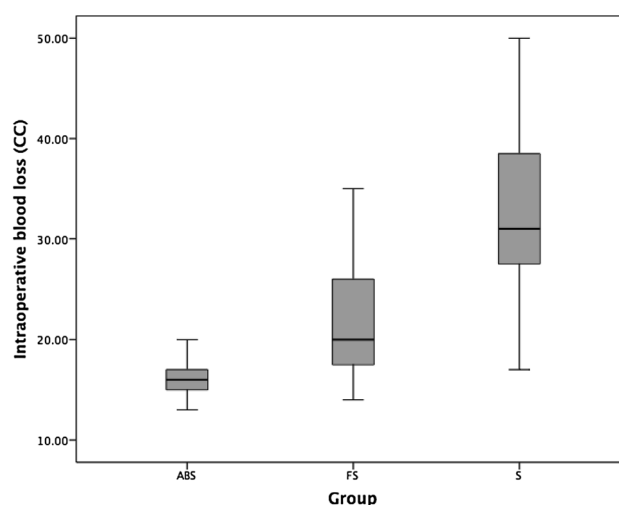


Fig. 2 Boxplots of the intraoperative blood loss

Results

Baseline data

The base line data did not show any statistical significant difference among the three groups regarding the distribution of age, sex, and adenoid size (Table 1).

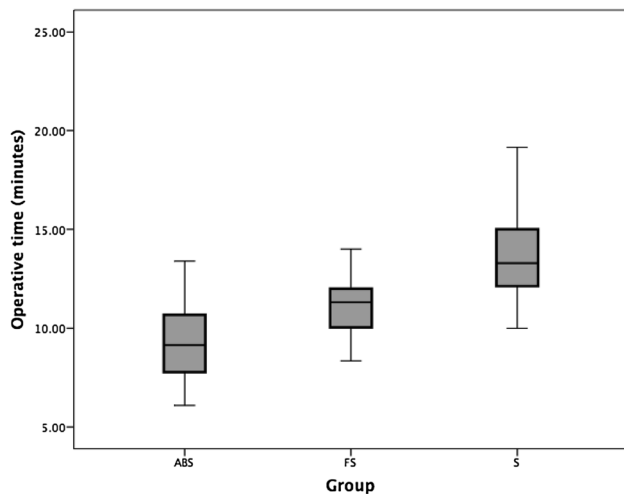
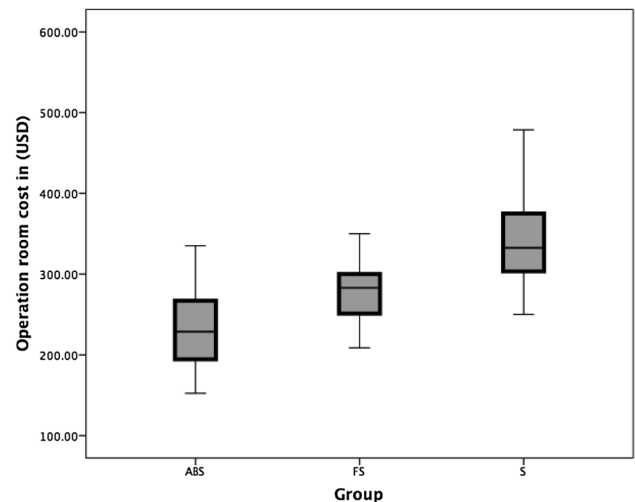
Intra operative blood loss

The mean amount of intra operative blood was 16.4 $\pm$ 2.6, 22 $\pm$ 6.2 and 32 $\pm$ 7.9 for ABS, FS and control group, respectively. It was significantly less in both haemostatic groups when compared to the control group (*p* value < 0.05). In the same time it was also significantly less in the ABS group than FS (*p* value < 0.05) (Fig. 2; Table 2).

Table 2 Parameters of the three surgical groups

Parameter	ABS (<i>N</i> = 75)	FS (<i>N</i> = 75)	S (<i>N</i> = 75)	<i>p</i> value
Intra operative blood loss (CC)	16.4 ± 2.6	22 ± 6.2	32 ± 7.9	0.000
Operative duration (minutes)	9.3 ± 1.9	11.2 ± 1.6	13.8 ± 2.3	0.000
Haemostatic agent cost (US dollars)	40	0.80	0.04	0.000
Operating theatre time cost (US dollars)	233 ± 48	279 ± 40	347 ± 56	0.000
Use of cautery (%)	10.6	25.3	42.7	0.000
Postoperative use of analgesics (days)	3 ± 1.1	3.8 ± 1.2	5.2 ± 1.3	0.000
Return to normal diet (days)	2.4 ± 1.2	3.9 ± 0.9	5.0 ± 1.0	0.000

There is a significant difference (*p* value < 0.001) for all parameters using ANOVA test comparing all groups. There is also a significant difference (*p* value < 0.001) for all parameters between ABS and FS groups as well as between FS and S groups

**Fig. 3** Boxplots of the operative time**Fig. 4** Boxplots of the operating room time cost

Operative time

There was a significantly shorter operative time in both haemostatic groups in comparison with the control group (*p* value < 0.05). The operative time in ABS group was significantly shorter than FS group (*p* value < 0.05). The mean operative time was 9.31 ± 1.9 min for the ABS group, 11.2 ± 1.6 min for the FS group and 13.8 ± 2.3 min for the control group as shown in (Fig. 3; Table 2).

Operating theatre time cost

The mean operating theatre time cost was 233 ± 48 , 279 ± 40 and 347 ± 56 US dollars for ABS, FS and control group, respectively. The operating room time cost was significantly less in both haemostatic groups when compared to the control group (*p* value < 0.05). The operating room time cost in the ABS group was significantly less than FS (*p* value < 0.05) as shown in (Fig. 4; Table 2).

Use of cautery

Electric cautery was used for eight patients (10.6%) in the ABS group, 19 patients (25.3%) in the FS group and 32 patients (42.6%) in the control group. The use of cautery was significantly less in both haemostatic groups when compared to the non-haemostatic control one (*p* value < 0.05). The use of cautery in the ABS group was significantly less than FS (*p* value < 0.05) as in (Table 2).

Duration of postoperative analgesics use

It showed a significant difference between the haemostatic groups and the control group with (*p* value < 0.05). The ABS group was significantly less than the FS group (*p* value < 0.05). The mean duration of analgesics was (3 ± 1.1) in the ABS group, (3.8 ± 1.2) and (5.2 ± 1.3) days in the control group (Table 2).

Post operative duration to return to usual diet

The mean duration to return to normal diet was 2.4 ± 1.2 in the ABS group, 3.9 ± 0.9 in the FS group, and 5.0 ± 1.0 days in the control group. It was significantly different, for both haemostatic groups comparing to the third control one with (p value < 0.05). The ABS group was significantly less than the FS group (p value < 0.05) (Table 2).

Post operative adverse events

No serious adverse events were reported in the three groups. No patient in any group had postoperative hemorrhage, hospitalization or blood transfusion. There was no significant difference among the three groups in postoperative adverse events.

Discussion

Adenoidectomy is one of the commonest operations performed by the ENT doctors for children. Adenoid-curette technique still represents the commonest method in adenoidectomy. Severe bleeding after adenoid removal was reported in 0.2% of cases and very rarely required external carotid artery ligation [7–9]. One of the most important targets of the surgeon is to reduce blood loss after the removal of the adenoids especially in young children and infants. Minimal amount of intra operative blood loss and short time of operation help to prevent postoperative complications such as hypovolemia and the other airway problems such pulmonary edema, especially in the young susceptible children who were previously diagnosed as marked sleep apnea [10, 11]. An ideal haemostatic agent should be easy, quick, safe, with cost effective and does not inflict any increase in postoperative post operative pain severity and duration to return to normal diet. Topical haemostatic agents offer an important haemostatic effect which is not yet well explored in the field of adenoidectomy [14]. Therefore, the present study was conducted to investigate the safety and efficacy of two topical haemostatic agents, ABS and FS, in controlling bleeding during adenoid surgery in infant and young children.

In this study, ABS and FS groups expressed a significant reduction for all parameters: intra operative blood loss, duration of operative, intra operative use of electric cautery, use of post operative painkillers, duration taken to return to usual diet and operation room time cost than that for the control group. Moreover, ABS group was significantly better than FS group. ABS and FS, respectively, allowed (16.4 ± 2.6 and 22 ± 6.2) less mean intra operative blood loss, (9.3 ± 1.9 and 11.2 ± 1.6) less mean operative time, (10.6 and 25.3%) less intra operative use of cautery, (3 ± 1.1 and 3.8 ± 1.2) less mean days of analgesics, (2.4 ± 1.2 and 3.9 ± 0.9) less mean

post operative days to return to the usual diet and (233 ± 48 279 ± 40) less mean operating room time cost than that expressed by the non haemostatic control group. Unfortunately, few studies have discussed use of topical haemostatic modulators in adenoidectomy, Iynen et al. [15] compared ABS to physiological saline control group during adenoidectomy. They reported a significant reduction in amount of intra operative blood loss, operation time, use of cautery and the duration of postoperative analgesics in the ABS group. The shortened postoperative duration of analgesia with ABS could be explained by less use of cautery to control bleeding in such group. Hot methods of hemostasis are known to be associated with increased postoperative pain and the duration of postoperative analgesia [16].

Other authors have discussed the use of different topical haemostatic agents in adenoidectomy. Mathiasen and cruz [1] had a study comparing Floseal hemostatic sealant with suction cautery to achieve haemostatic during adenoidectomy operation in his patients. Floseal patients had significantly less blood loss, shorter homeostasis time, less subjective bleeding and subjectively easier procedure. In addition, Floseal patients returned to their usual diet earlier and had less use of painkillers. Three patients in the cautery group were shifted to the Floseal group, but no Floseal subjects were shifted to the cautery group. ABS and FS have the advantage of being in liquid form which is safer than Floseal particles which may be aspirated by patients causing respiratory complications. Teppo et al. [2], evaluated the efficacy of topical racemic adrenaline in control of intra operative bleeding during adenoidectomy among children. Adrenaline significantly decreased surgeons' subjective estimate of the amount of intra operative bleeding, reduced the mean number of packs needed and the use of electro cautery and shortened the mean duration of the procedure. ABS and FS are safer than adrenaline since elevation of heart rate was observed more often in the adrenaline group.

Cost effectiveness remains a crucial issue in discussing any novel procedure in surgery. The use of topical haemostatic agents in adenoidectomy incurs an extra cost to the procedure. ABS was 20\$/ml, whereas FS was 0.4\$/ml. The operating theatre time cost varies from country to another but it was estimated at 12–58\$/min [1]. In our region, the operating theatre time cost was estimated at 25 US dollars per minute. In this study, ABS and FS were more cost effective than the control group and ABS represented the most cost-effective group. There was a reduction of the mean operating theatre time cost in the ABS and FS groups by about 114 and 68 US dollars, respectively, when compared to the control group. The mean operating theatre time cost in the ABS group was reduced by 46 US dollars when compared to the FS group. Mathiasen and cruz [1] reported a reduction of the cost of the operating theatre by 106 US dollars in the Floseal group through reducing the operative

time, whereas the retail cost of Floseal was US 85 dollars. Teker et al. [12] reported that the cost of ABS was offset by reduction of the operation room time cost due to the shortened time spent in homeostasis.

No serious adverse events were reported in the three studied groups. Both ABS and FS are safe locally and systemically [17, 18]. ABS was orally administered to rabbits without any signs of acute mucosal toxicity, hematotoxicity, hepatotoxicity, nephrotoxicity, or biochemical toxicity [17]. No further side effects were reported in the literature [18, 19]. FS was safely used topically in deep burns [20], oral mucosa [21] and urethral mucosa [22], with no adverse events as well. The basic mechanism of action of ABS is formation of an (encapsulated network of protein) that affects the entire haemostatic process without affecting any individual clotting factors. The haemostatic effect of Feracrylum is provided by the formation of a synthetic complex with plasma proteins principally albumin on the wound surface. They do not interfere with any step in the normal coagulation process. The level of coagulation factors is not affected. Thus, they may be useful for patients with deficient primary or secondary homeostasis, including patients with hemophilia, over dosage of anticoagulant drugs administration and disseminated intravascular coagulopathy [18, 23]. Further studies were advised to investigate the use of ABS and FS in patients with bleeding and coagulation disorders.

Ankaferd blood stopper and feracrylum 1% solution are easy, safe, and reliable topical haemostatic modulators that potentially add to adenoid surgery in infants. ABS is superior to FS in minimizing intra operative blood loss, reducing operative time, avoiding excessive use of analgesics, and fastening return to normal diet. **ABS is more expensive than FS but at the same time more cost effective as it significantly reduces operating theatre time cost.**

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all parents of individual participants included in the study.

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