Hydrogen Peroxide Irrigation in Children Undergoing Adenoidectomy: A Preliminary Study for Hemostasis After Surgery

Adenoidektomi Uygulanan Çocuklarda Hidrojen Peroksit Uygulaması: Cerrahi Sonrası Kanama Kontrolü İçin Ön Çalışma

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ABSTRACT

Objective: To evaluate the effectiveness of 0.5% hydrogen peroxide (H2O2) irrigation to control bleeding after adenoidectomy.

Material and Methods: This prospective, controlled, cross sectional study was conducted on 80 children under the age of 10 years undergoing adenoidectomy. After adenoidectomy, nasopharynx was irrigated with 0.5% H₂O₂ in the study group (n=43), or with serum physiologic at 25°C in the control group (n=37). Adenoid volumes and sizes were recorded. Control of bleeding and operation times were measured. Bleeding and hemostasis were scored by the surgeons using visual analogue scale (VAS). **Results:** The ages of the patients ranged between 3 - 9 (mean±SD: 4.9 ± 1.8) years. There were 29 and 22 males, 8 and 21 females respectively, in the control and H₂O₂ groups. The average hemostasis time for the H202 group (4 minutes) was shorter than the control group (5 minutes), but there were no statistical significant differences between

control and H202 groups for operation time (p=0.854), control of bleeding time (p=0.065), or VAS values of subjective bleeding (p=0.961) and control of bleeding (p=0.346). A statistically significantly positive correlation was found between adenoid volume and operation time (r=0.269; p=0.016), but the correlation between adenoid volume and hemostasis was not statistically significant (r=0.213; p=0.058).

Conclusion: There were no statistically significant reductions in hemostasis or operation times in 0.5% H202 group, although the average hemostasis time of the H202 group was shorter than the control group. The studies with large sample groups are required to confirm our results, and show the effectiveness of H_2O_2 irrigation in hemostasis after adenoidectomy.

Keywords

Adenoidectomy; hemostasis; hydrogen peroxide; hemorrhage

ÖZET

Amaç: Yüzde 0,5 hidrojen peroksit (H₂O₂) ile yıkamanın adenoidektomi sonrası kanama kontrolündeki etkinliğini araştırmak.

Gereç ve Yöntemler: Bu prospektif, kontrollü, kesitsel çalışmada 10 yaş altında olan ve adenoidektomi operasyonu uygulanan 80 çocuk çalışmaya alındı. Çalışma grubunda (n=43) adenoidektomi sonrasında nazofarenks %0,5 hidrojen peroksit ile irrige edildi, kontrol grubunda (n=37) 25°C serum fizyolojik ile irrigasyon yapıldı. Adenoid hacmi ve boyutu kaydedildi. Kanama kontrolü ve operasyon süreleri ölçüldü. Cerrahlar tarafından kanama ve kanama kontrolü görsel analog skala (VAS) kullanılarak derecelendirildi.

Bulgular: Çocukların yaşları 3 ve 9 arasında değişmekteydi (ortalama \pm SD: 4,9 \pm 1,8). Kontrol grubunda 29 erkek ve 8 kız çocuk, H₂O₂ grubunda ise 22 erkek ve 21 kız çocuk bulunmaktaydı. H₂O₂ grubu için ortalama hemostaz zamanı (4 dakika) kontrol grubunun ortalama hemostaz zamanından (5 dakika) daha kısaydı. Fakat kontrol ve H₂O₂ grupuları arasında operasyon zamanı (p=0,854), hemostaz zamanı (p=0,065) veya sübjektif kanama (p=0,961) ve hemostaz (p=0,346) VAS skorları açısından istatistiksel olarak anlamlı fark saptanımadı. Adenoid hacmi ve operasyon zamanı arasında istatistiksel olarak anlamlı pozitif korelasyon saptandı (r=0,213; p=0,058).

Sonuç: Yüzde $0,5 H_2O_2$ grubunda hemostaz ve operasyon zamanında istatistiksel olarak anlamlı azalma saptanmadı. Ortalama hemostaz zamanı, H_2O_2 grubunda kontrol grubuna göre daha kısa olarak bulundu. H_2O_2 ile yıkamanın adenoidektomi kanama kontrolündeki etkinliğinin kanıtlanması ve daha iyi anlaşılması için daha çok vaka içeren çalışmalara ihtiyaç vardır.

Anahtar Sözcükler

Adenoidektomi; kanamanın durması; hidrojen peroksid; kanama

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INTRODUCTION

denoidectomy was first described by Meyer in 1868, and it is one of the most common surgical procedures performed in children.¹ Adenoidectomy is advised for the treatment of upper airway obstruction and recurrent or chronic adenoiditis which may present as chronic rhinosinusitis or recurrent acute otitis media.² Adenoidectomy is useful in sleep disturbances, nasal obstruction, chronic rhinitis, speech and swallowing disorders, and emotional distress in children with adenoid tissue hypertrophy.²

Total excision of the adenoid tissue by curette, shaver or coblation is the most important goal of this operation without causing any complications. As adenoidectomy is the most commonly performed surgery, even small improvements in complication control, duration of the procedure and general anesthesia could be important.² Control of bleeding after adenoidectomy is mostly achieved by nasopharyngeal packing, irrigation with solutions, and/or bipolar electrocautery. Hydrogen peroxide (H₂O₂) irrigation has been used to achieve hemostasis during active bleeding in gastrointestinal system.³⁻⁵ Three percent H₂O₂ has been used in animal and human studies to clear blood clots for the better visualization of gastric and duodenal ulcers.³⁻⁶ H₂O₂ has also been used in orthopedics as an effective hemostatic agent.^{7,8}

To the best of our knowledge, H_2O_2 irrigation for control of bleeding after adenoidectomy has not yet been studied in the literature. The aim of this study was to investigate the effectiveness of 0.5% H_2O_2 irrigation for control of bleeding after adenoidectomy.

MATERIAL AND METHODS

Subjects

The study was approved by our institutional Ethics Committee. Written informed consents were obtained from the parents of all participating children. Eighty consecutive children under the age of 10 years undergoing adenoidectomy with or without tonsillectomy for hypertrophic adenoid tissue, persistent nasal obstruction and/or recurrent adenotonsillar infection, were included in our study between September 2010 and June 2012. Children with an underlying chronic illness or bleeding disorder, or to whom another simultaneous procedure was planned in addition to adenotonsillectomy were excluded from the study. There were two groups: 43 cases who had irrigation of nasopharynx after adenoidectomy with 0.5% H_2O_2 constituted the study group, and irrigation of nasopharynx after adenoidectomy with 25°C serum physiologic of 37 cases constituted the control group. The diagnosis and follow-up were made with use of transnasal fiberoptic flexible endoscope in all patients both preoperatively and 1 year postoperatively.

Adenoidectomy Technique

All the operations were performed in an operating room under general anesthesia, as an outpatient procedure. If adenoidectomy was combined with tonsillectomy, adenoidectomy was performed first, and tonsillectomy was performed after the achievement of control of bleeding and acquiring the study data. All operations were performed by experienced 3 surgeons. With a Crowe-Davis mouth gag splint, the mouth was opened, the palate and uvula were seen and palpated to exclude a soft palate cleft. A small, Nelaton Catheter (10 Ch) was passed through the patient's nose, brought out through the oral cavity and then clamped back on itself extra-orally to retract the soft palate. A curette was used to remove the bulk of the adenoids.⁹

Study Design

Adenoid size was assessed subjectively by visual inspection with a mirror and graded according to the threelevel classification described by Wormald and Prescott.¹⁰ This grading system is based on the degree of choanal obstruction caused by the adenoids. The grading system consists of grade 1 (less than one third of posterior choanae obstructed), grade 2 (one third to two thirds of posterior choanae obstructed), and grade 3 (more than two thirds of posterior choanae obstructed). Complete removal was confirmed by mirror and/or by endoscopic examination. At this stage, the volume of the excised tissue was measured. To measure the volume of the adenoid tissue, we used a 10 ml disposable syringe with a needle. The tip of the needle was plugged with wax and its plunger was removed. The barrel was filled with isotonic saline solution up to the level of 5 ml. The adenoid tissue was placed into the barrel. The displacement volume of the fluid was accepted as the volume of the tissue. If the tissue volume was larger than 5 ml, we sliced the tissue and measured each slice separately to be able to measure the volume correctly.9 After adenoidectomy, pressure was applied to the nasopharynx by tonsillar pack for one minute. After tamponade, the nasopharynx was irrigated with either 0.5% H₂O₂ or 25°C serum physiologic (SP). The irrigation was continued until the wash-out fluid was clear. Hemostasis was accepted to have failed at a limit of 10 minutes. In these cases, we used bipolar electrocautery for control of bleeding. The duration between the end of the adenoidectomy and achievement of hemostasis was accepted as the hemostasis time. The duration between application and removal of the mouth gag was accepted as the operation time. Subjective bleeding was measured by visual analogue scale (VAS) values following adenoid pack removal (0: none, 1: minimal/restricted, 2: moderate/diffuse ooze, 3: severe/brisk). The ease of hemostasis was also measured by VAS values (1: extremely difficult, 2: difficult, 3: some effort, 4: usual, 5: easy, 6: very easy).

Statistical Analysis

Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal was determined using the Shapiro Wilk test. Continuous data were expressed as mean±standard deviation or median (minimum-maximum), where appropriate. Mean differences were compared by Student's t test; otherwise, the Mann Whitney U test was applied for comparisons of median values. Nominal data were evaluated by the Pearson Chi-square test. Degrees of association between continuous variables were evaluated with Spearman's rank correlation test. A p value less than 0.05 was considered statistically significant.

RESULTS

Table 1 displays the demographic data, adenoid size and adenoid volume distribution according to the groups. Electrocauterization was employed for hemostasis in 3 patients in the control group and 2 patients in the H_20_2 group.

The average hemostasis time of the H_20_2 group (4 minutes) was shorter than the control group (5 minutes), but there were no statistical significant differences between control and H_20_2 groups with respect to operation time (p=0.854), hemostasis time (p=0.065) or VAS values of subjective bleeding (p=0.961) or hemostasis (p=0.346) (Table 2). The correlation between operation time and size was not significant (r=0.059; p=0.609). There was no correlation between size of adenoid and hemostasis time (r=0.043; p=0.705). There was a significant positive correlation between volume and operation time (r=0.269; p=0.016) (Figure 1). The correlation between volume and hemostasis was not significant (r=0.213; p=0.058).

Finally, there was no statistically significant difference between indications of adenoidectomy of the two groups with respect to operation time (p=0.612) and hemostasis time (p=0.753) (Table 3). There was no complication in either group, including postoperative hemTable 1. Demographic data, adenoid size and adenoid volume.

Variables	Total (n:80)	Control Group (n:37)	H ₂ 0 ₂ Group (n:43)	p-value
Age Gender	(3-9) 4.9±1.8	4.9±1.9	4.8±1.7	0.844 0.012
Male	51 (63.8%)	29 (78.4%)	22 (51.2%)	
Female	29 (36.3%)	8 (21.6%)	21 (48.8%)	
Indication				0.642
OBS	39 (48.8%)	17 (45.9%)	22 (51.2%)	
RI	41 (51.2%)	20 (54.1%)	21 (48.8%)	
Size				0.005
Grade 1	11 (13.8%)	10 (27.0%)	1 (2.3%)	
Grade 2	24 (30.0%)	8 (21.6%)	16 (37.2%)	
Grade 3	45 (56.3%)	19 (51.4%)	26 (60.5%)	
Volume	2.0 (0.5-5.0)	2.0 (0.5-5.0)	2.0 (1.0-4.0)	0.780

OBS: Obstruction; RI: Recurrent infection.

 Table 2. Operation and hemostasis times and VAS values of subjective bleeding and hemostasis.

Variables	Total (n:80)	Control Group (n:37)	H ₂ 0 ₂ Group (n:43)	p-value
Operation time	13 (7-27)	13 (7-27)	14 (8-27)	0.854
Hemostasis time	4 (1-15)	5 (2-15)	4 (1-12)	0.065
VAS BLE	1 (0-3)	2 (1-3)	1 (0-3)	0.961
VAS Hemostasis	4 (2-6)	4 (3-5)	4 (2-6)	0.346

VAS BLE: Visual Analogue Scale of subjective bleeding; VAS Hemostasis: Visual Analogue Scale of ease of hemostasis.

orrhage, blood transfusion, chronic nasopharyngitis or aspiration, after 1 year follow up.

DISCUSSION

Adenoidectomy is one of the most commonly performed procedures in children. Generally there is not significant amount of blood loss during adenoidectomy, consequently the bleeding and hemostasis time are more important than the amount of blood loss.¹¹ Hemostasis after adenoidectomy is provided by choanal packing, irrigation and/or electrocautery. Several new techniques to achieve faster and more effective hemostasis during and following adenoidectomy have been described.¹²⁻¹⁹ Teppo et al. recommended the use of topical adrenalin in adenoidectomy among children.12 Cannon et al. demonstrated that endoscopic-assisted adenoidectomy is not associated with excessive bleeding.¹⁷ Jo et al. evaluated the efficacy of floseal as a hemostatic sealant compared to traditional electrocautery hemostasis after cold knife adenotonsillectomy and found safe and efficient when floseal was used as a hemostatic method in children undergoing adenotonsillectomy.¹⁸ Mathiesan and Cruz advocated the floseal matrix hemostatic sealant as an efficient hemosta-



Figure 1. Graph illustrating the correlation between adenoid volume and duration of operation time.

 Table 3. Patient operation time and hemostasis time with respect to indication.

variables	OBS (n:39)	RI (n:41)	p-value
Operation time	14 (7-27)	13 (7-25)	0.612
Hemostasis time	4 (1-12)	4 (2-15)	0.753

OBS: Obstruction; RI: Recurrent infection.

tic agent for adenoidectomy.^{15,16} However, the cost is questionable. Albirmawy et al. applied tranexamic acid locally in adenoidectomy for intra- and postoperative bleeding, and found that topical application of tranexamic acid after adenoidectomy led to a significant reduction intraoperative blood loss and decreasing in the rate of postoperative blood loss.²⁰ Ozmen and Ozmen also described that 50°C saline irrigation was more efficient for post-adenoidectomy hemostasis compared to 25°C saline irrigation, providing a shorter hemostasis time and requiring less recurettage and electrocauterization.¹⁹

 H_20_2 irrigation has been used to facilitate hemostasis in the presence of active bleeding.³⁻⁵ H_20_2 has a potential hemostatic effect, which may add to other adjunctive therapies in the endoscopic management of acute nonvariceal bleeding and bladder bleeding.³⁻⁵ H_20_2 oxidizes hemoglobin, and facilitates clot dissolution and clearance.^{3-5,21} H_20_2 at biologically relevant concentrations acts as a signaling molecule. Previous investigators described the hemostatic effect via several mechanisms, including thermal injury to vessels, formation of fibrin thrombi, and arteriolar spasm.^{22,23} The mechanism by which hydrogen peroxide affects clotting may in part be from hydrogen peroxide inhibition of adenosine diphosphate-induced platelet aggregation, thereby modulating thrombus generation itself.²⁴ Kalloo et al. have concluded that the powerful oxidizing effects of hydrogen peroxide may also contribute to hemolysis.3 Irrigation with serum physiologic is mostly applied during adenoidectomy to remove blood and clots. However, to our knowledge, H₂0₂ irrigation after adenoidectomy has not been studied before. We hypothesized that H₂O₂ irrigation after adenoidectomy might reduce hemostasis and operation times. In the light of this hypothesis, we aimed to evaluate the effect of H₂O₂ irrigation on hemostasis time after adenoidectomy, in this study. The average hemostasis time for the H_2O_2 group was shorter than the control group, but there was no statistically significant difference between two groups for operation time (p=0.854), hemostasis time (p=0.065) or VAS values of subjective bleeding (p=0.961) and hemostasis (p=0.346). In H₂O₂ study group, there were no postoperative complications such as delayed postoperative bleeding or any complications during the healing process. Although H_20_2 (3%) is known to be relatively non-toxic and, accordingly no adverse effects were encountered in animal and human studies,3-8,21,24 some authors demonstrated that oxidative stress by H₂O₂ induced apoptotic cell death in mature oligodendrocytes.25 In the present study, we used 0.5% H₂O₂ irrigation instead of 3% H₂O₂, and we did not observe any chronic nasopharyngitis which may be an effect of H_2O_2 's powerful oxidation.

Several factors, including adenoid size, adenoid volume, adenoidectomy technique, surgeon experience, and indication of adenoidectomy may influence the operation and hemostasis times. Therefore we investigated the correlation between operation time and adenoid size and volume. We used volume of the adenoid tissue to define the amount of the total removed adenoid tissue instead of weight, unlike previous studies.¹⁷ Obstruction is a result of adenoid tissue volume; therefore volume might define the tissue amount much better than weight.9 The correlation between the size of adenoid and operation time (r=0.059; p=0.609) or hemostasis time (r=-0.043; p=0.705) were not significant. The positive correlation between adenoid volume and operation time was found in this study (r=0.269; p=0.016). But the correlation between adenoid volume and hemostasis was not significant (r=0.213; p=0.058). Consequently, the adenoid volume which has the main impact on the operation time, did not influence the hemostasis time. The volume distribution between the two groups was also the same. The technique of adenoidectomy was consistent in the present study. While in the literature 3% H₂0₂ was applied in acute upper gastrointestinal bleeding, in our study we used 0.5% H₂0₂ due to the fact that there was extensive bubbling that obstructed our aspirator in the operation field when we irrigated with 3% H₂0₂ in the few cases before the study.

There are some limitations of the present study,. First, the sample size was not large enough, therefore we could not reach statistically significant results. Second, the adenoidectomies were not performed by the same surgeon. However, all surgeons were experienced. Third, the bleeding and size were rated and evaluated subjectively by three different surgeons. The main reason of the subjective evaluation of bleeding instead of bleeding volume was due to the small amount of blood loss during adenoidectomy. In addition, the surgeons' subjective bleeding scores and hemostasis time were also counterbalanced.

CONCLUSION

This study investigated the effectiveness of 0.5% H₂O₂ irrigation in hemostasis after adenoidectomy. Although there was no significant decrease in hemostasis or operation time in the H₂O₂ irrigation group, the average hemostasis time of the H₂O₂ group was shorter than the control group. In conclusion, studies with large sample groups are required to confirm our results, and reveal the effectiveness of H₂O₂ irrigation in hemostasis after adenoidectomy.

REFERENCES

- Thornval A. Wilhelm Meyer and the adenoids. Arch Otolaryngol 1969;90(3):383-6.
- Joshua B, Bahar G, Sulkes J, Shpitzer T, Raveh E. Adenoidectomy: long-term follow-up. Otolaryngol Head Neck Surg 2006;135(4):576-80.
- Kalloo AN, Canto MI, Wadwa KS, Smith CL, Gislason GT, Okolo GI 3rd, et al. Clinical usefulness of 3% hydrogen peroxide in acute upper GI bleeding: a pilot study. Gastrointest Endosc 1999;49(4 Pt 1):518-21.
- Wu DC, Lu CY, Lu CH, Su YC, Perng DS, Wang WM, et al. Endoscopic hydrogen peroxide spray may facilitate localization of the bleeding site in acute gastrointestinal bleeding. Endoscopy 1999;31(3):237-41.
- Sridhar S, Chamberlain S, Thiruvaiyaru D, Sethuraman S, Patel J, Schubert M, et al. Hydrogen peroxide improves the visibility of ulcer bases in acute non-variceal upper gastrointestinal bleeding: a single-center prospective study. Dig Dis Sci 2009;54(11):2427-33.
- Hu B, Chung SC, Sun LC, Lau YV, Kawashima K, Yamamoto T, et al. Developing an animal model of massive ulcer bleeding for assessing endoscopic hemostatic devices. Endoscopy 2005;37(9):847-51.
- Hankin FM, Campbell SE, Goldstein SA, Matthews LS. Hydrogen peroxide as a topical hemostatic agent. Clin Orthop 1984;186:244-8.
- Guerin S, Harty J, Thompson N, Bryan K. Hydrogen peroxide as an irrigation solution in arthroplasty - a potential contributing factor to the development of aseptic loosening. Med Hypotheses 2006;66(6):1142-5.
- Ark N, Kurtaran H, Ugur KS, Yilmaz T, Ozboduroglu AA, Mutlu C. Comparison of adenoidectomy methods: examining with digital palpation vs. visualizing the placement of the curette. J Pediatr Otorhinolaryngol 2010;74(6):649-51.
- Wormald PJ, Prescott CA. Adenoids: comparison of radiological assessment methods with clinical and endoscopic findings. J Laryngol Otol 1992;106(4):342-4.
- Clemens J, McMurray JS, Willging JP. Electrocautery versus curette adenoidectomy: comparison of postoperative results. Int J Pediatr Otorhinolaryngol 1998;43(2):115-22.
- Teppo H, Virkkunen H, Revonta M. Topical adrenaline in the control of intraoperative bleeding in adenoidectomy: a randomized, controlled trial. Clin Otolaryngol 2006;31(4): 303-9.
- Stanislaw P Jr, Koltai PJ, Feustel PJ. Comparison of power-assisted adenoidectomy vs adenoid curette adenoidectomy. Arch Otolaryngol Head Neck Surg 2000;126(7):845-9.

- Koltai PJ, Kalathia AS, Stanislaw P, Heras HA. Power-assisted adenoidectomy. Arch Otolaryngol Head Neck Surg 1997; 123(7):685-8.
- Mathiasen RA, Cruz RM. Prospective, randomized, controlled clinical trial of a novel matrix hemostatic sealant in children undergoing adenoidectomy. Otolaryngol Head Neck Surg 2004; 131(5):601-5.
- Mathiasen RA, Cruz RM. Prospective, randomized, controlled clinical trial of a novel matrix hemostatic sealant in patients with acute anterior epistaxis. Laryngoscope 2005;115(5):899-902.
- Cannon CR, Replogle WH, Schenk MP. Endoscopic-assisted adenoidectomy. Otolaryngol Head Neck Surg 1999;121(6): 740-4.
- Jo SH, Mathiasen RA, Gurushanthaiah D. Prospective, randomized, controlled trial of a hemostatic sealant in children undergoing adenotonsillectomy. Otolaryngol Head Neck Surg 2007; 137(3):454-8.
- Ozmen S, Ozmen OA. Hot saline irrigation for control of intraoperative bleeding in adenoidectomy: a randomized controlled trial. Otolaryngol Head Neck Surg 2010;142(6): 893-7.
- Albirmawy OA, Saafran ME, Shehata EM, Basuni AS, Eldaba AA. Topical application of tranexamic acid after adenoidectomy: a double-blind, prospective, randomized, controlled study. Int J Pediatr Otorhinolaryngol 2013;77(7): 1139-42.
- Warlick CA, Mouli SK, Allaf ME, Wagner AA, Kavoussi LR. Bladder irrigation using hydrogen peroxide for clot evacuation. Urology 2006;68(6):1331-2.
- Sabetkar M, Low SY, Bradley NJ, Jacobs M, Naseem KM, Richard Bruckdorfer K. The nitration of platelet vasodilator stimulated phosphoprotein following exposure to low concentrations of hydrogen peroxide. Platelets 2008;19(4):282-92.
- Belisario MA, Tafuri S, Di Domenico C, Squillacioti C, Della Morte R, Lucisano A, et al. H₂O₂ activity on platelet adhesion to fibrinogen and protein tyrosine phosphorylation. Biochim Biophys Acta 2000;1495(2):183-93.
- Potyondy L, Lottenberg L, Anderson J, Mozingo DW. The use of hydrogen peroxide for achieving dermal hemostasis after burn excision in a patient with platelet dysfunction. J Burn Care Res 2006;27(1):99-101.
- 25. Fragoso G, Martínez-Bermúdez AK, Liu HN, Khorchid A, Chemtob S, Mushynski WE, Almazan G. Developmental differences in HO-induced oligodendrocyte cell death: role of glutathione, mitogen-activated protein kinases and caspase 3. J Neurochem 2004;90(2):392-404.