

Intraoperative Dexamethasone Single Dose and Risk of Postoperative Haemorrhage in Tonsillectomy Patients

Dr. Asif Mahajan¹, Dr. Shahnaz Sheikh², Dr Abdul Qayoom³

¹Senior Resident, Department of ENT H&NS, SKIMS Medical College and Hospital Srinagar, J&K India

²Senior Resident, Department of ENT H&NS, Dr. Ulhas Patil Medical College, Jalgaon, Maharashtra, India

³ENT Specialist, Department of ENT, District Hospital, Baramulla, J&K, India

Abstract: ***Introduction:** Several meta-analyses investigating morbidity following tonsillectomy have demonstrated that under controlled conditions a single intravenous dose of Dexamethasone (DX) is an effective, safe and inexpensive method of reducing the incidence of postoperative nausea and vomiting (PONV) following tonsillectomy in children 1-5. Unfortunately, there is substantial variability across these studies with respect to design, surgical technique, method of acquiring hemostasis and age of patients. We undertook the study to find out the effectiveness of intraoperative single IV dose of dexamethasone on the risk of postoperative haemorrhage in tonsillectomy patients. **Objective:** To assess whether dexamethasone dose-dependently reduces or increases the risk of postoperative haemorrhage in tonsillectomy patients. **Methods:** This study was conducted with 200 patients who underwent tonsillectomy. Patients were divided into four groups of 50, where one group (n=50) received intraoperative dexamethasone of 0.05mg/kg, second group (n=50) received intraoperative dexamethasone of 0.15mg/kg, third group (n=50) received intraoperative dexamethasone of 0.5mg/kg and the fourth group (n=50) were given placebo injection Normal Saline. Bleeding episodes of all the groups were recorded in first 7 days following surgery. Children were randomly assigned to receive dexamethasone injection (0.05, 0.15 or 0.5mg/kg) and placebo intravenous Normal saline after induction of anaesthesia. Acetaminophen-codeine and ibuprofen were given as postoperative analgesics. Follow up continued until the 7th postoperative day. **Results:** At 24 hours, 2 of the 50 children who received placebo (4%; 95% CI, 0.5%-13%), 6 of 50 (12%; 95% CI, 4%-23%) who received dexamethasone, 0.05mg/kg, 2 of 50 (4%; 95% CI, 0.5%-13%) who received dexamethasone, 0.15 mg/kg, and 12 of 50 (24%; 95% CI, 13%-38%) who received dexamethasone, 0.5 mg/kg, had at least 1 bleeding episode (P=.003). The largest dose of dexamethasone 0.5mg/kg was associated with the highest risk of bleeding (24%; 95% CI, 13%-38%). Children who received dexamethasone received significantly less ibuprofen. There were 26 postoperative bleeding episodes in 22 children. Dexamethasone 0.5mg/kg was associated with the highest bleeding risk. **Conclusion:** A single dose of intraoperative intravenous dexamethasone was significantly associated with increased risk of postoperative haemorrhage in tonsillectomy patients.*

Keywords: Tonsillitis, Tonsillectomy, Pain relief, Dexamethasone, PONV- postoperative nausea and vomiting, Haemorrhage

1. Introduction

Several meta-analyses investigating morbidity following tonsillectomy have demonstrated that under controlled conditions a single intravenous dose of Dexamethasone (DX) is an effective, safe and inexpensive method of reducing the incidence of postoperative nausea and vomiting (PONV) following tonsillectomy in children¹⁻⁵.

Unfortunately, there is substantial variability across these studies with respect to design, surgical technique, method of acquiring hemostasis and age of patients. Oropharyngeal pain and irritation of gastric mucosa by swallowed blood are two main contributors towards high incidence of PONV following tonsillectomy. Steroids can have beneficial effects on post-tonsillectomy morbidity due to their anti-inflammatory and antiemetic properties. There is ongoing controversy regarding whether perioperative systemic steroid administration increases post tonsillectomy bleeding. A meta-analysis of 29 randomized trials (n = 2674) found that steroid administration was related to increased frequency of reoperation,⁶ but the findings were limited by the small sample size. We undertook the study to find out the effect of a single IV dose of dexamethasone on postoperative haemorrhage

2. Materials and Methods

This was a prospective study conducted in Department of ENT and HNS of SKIMS Medical College and Hospital, Srinagar tertiary care hospital between January, 2018 to March 2019. 200 patients were enrolled in this study and were randomly divided into four groups of 50 patients each. Patients were divided into four groups of 50, where one group (n=50) received intraoperative dexamethasone of 0.05mg/kg, second group (n=50) received intraoperative dexamethasone of 0.15mg/kg, third group (n=50) received intraoperative dexamethasone of 0.5mg/kg and the fourth group (n=50) were given placebo injection Normal Saline. Bleeding episodes of all the groups were recorded in first 7 days following surgery. The patients were explained about the study and the procedure involved and written and informed consent was taken. Ethical clearance for the study was obtained from the hospital ethical committee. Patients were randomly assigned to receive dexamethasone injection (0.05, 0.15 or 0.5mg/kg) and placebo intravenous saline after induction of anaesthesia. Acetaminophen-codeine and ibuprofen were given as postoperative analgesics. Follow up continued until the 7th postoperative day. Relevant clinical and demographic data were obtained from the concerned patient. They also underwent detailed ENT examination. Patients with coagulopathy, diabetes, gastritis, peptic ulcer,

hypertension and cardiovascular or renal disease or on therapy with corticosteroids, anti-histaminic, or aspirin were excluded. Preoperatively tonsil size was graded into four grades:

- I – Tonsil within tonsillar fold
- II – Just outside the tonsillar fold
- III - Well outside the tonsillar fold
- IV – Reaching uvula or past uvula

Episodes of postoperative bleeding in all the four groups were recorded in first 7 days. Total number of episodes of bleeding for each patient were noted.

Bleeding episodes were separated into three categories:

- Category 1: History of bleeding leading to readmission but without evidence of bleeding at medical examination.
- Category 2: Readmission due to bleeding with evidence of bleeding at medical examination but no need for reiteration.
- Category 3: Emergency reoperation due to bleeding.

After surgery, children were transferred to the postanaesthesia care unit and 2 hours later to the ward, where they stayed overnight. In the ward, analgesia was with oral or rectal acetaminophen-codeine(maximum Daily Dose of Acetaminophen 50mg/kg).When pain relief was inadequate, ibuprofen was added(maximum Daily Dose 30mg/kg).Children were free to eat and drink as soon as the surgeon confirmed through visual examination the absence of bleeding from tonsillar bed.

3. Results

Out of 200 patients, 22 (11%; 95% CI, 6.8%-15.6%) experienced at least 1 bleeding episode; 4 patients had 2 episodes of bleeding. All episodes occurred within the 7-day study follow-up. Out of 22, 15 patients (68.18% [95% CI, 45.1%-86.1%] of those bleeding) had bleeding diagnosed later than the first postoperative day.Two of the 50 children who received placebo (4%; 95% CI, 0.5%- 13%), 6 of 50 (12%; 95% CI, 4%-23%) who received dexamethasone, 0.05mg/kg, 2 of 50 (4%; 95% CI, 0.5%-13%) who received dexamethasone, 0.15 mg/kg, and 12 of 50 (24%; 95% CI, 13%-38%) who received dexamethasone, 0.5 mg/kg, had at least 1 bleeding episode ($P=0.003$). The largest dose of dexamethasone 0.5mg/kg was associated with the highest risk of bleeding (24%; 95% CI, 13%-38%).

Age was significantly associated with bleeding risk i.e. older children had more risk of bleeding. Eight children needed emergency reoperation because of post-tonsillectomy hemorrhage (bleeding category 3); they had all received dexamethasone. With the largest dose of dexamethasone, the risk was highest, although the difference compared with placebo was only borderline significant ($P=0.05$).

4. Discussion

Common complications of tonsillectomy are postoperative nausea and vomiting (PONV), pain, and bleeding.⁷ Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used in this setting for their pronounced analgesic efficacy and a lack of the emetogenic effect inherent to opioids. However, classic NSAIDs, through reversible

platelet inhibition, further increase the risk of bleeding after tonsillectomy.^{8,9} Dexamethasone has antiemetic properties in the surgical setting.¹⁰ An international expert panel recommended dexamethasone, alone or as part of a multimodal regimen, for PONV prophylaxis in adults and children.¹¹ It has been suggested that, especially in children undergoing tonsillectomy, dexamethasone is useful, not only for its antiemetic but also for its analgesic effects, and that it should be used routinely because the adverse effects and cost appear negligible.^{12,13,14,15} Indeed, dexamethasone for tonsillectomy has become standard care in many institutions.¹⁶ The dose response of dexamethasone for prevention of PONV symptoms in pediatric tonsillectomy remains unclear, although doses up to 1 mg/kg have been tested.^{17,18,19,20}

The 2008 guidelines of the Association of Paediatric Anaesthetists of Great Britain and Ireland conclude that in patients undergoing tonsillectomy, “dexamethasone 0.15 mg/kg provided good reduction in postoperative vomiting with no adverse effects.”²¹ Expert panels have recommended the widespread use of dexamethasone in surgical patients.²² Prophylactic dexamethasone has become standard care in children undergoing tonsillectomy in many institutions.^{23,24,25,26} Several authors have suggested that dexamethasone should be given in considerably higher doses.^{27,28,29,30}

Observational studies have reported an association between steroid exposure and an increased risk of bleeding in the context of tonsillectomy.^{31,32} A case-control study reported a significant annual 15% increase in posttonsillectomy hemorrhage, and the authors suggested that this may be partially related to the increased use of perioperative steroids.³² A retrospective chart review of 430 tonsillectomy patients found that the use of intraoperative steroids, among other factors, was positively correlated with postoperative bleeding; however, curiously, the authors concluded that the use of steroids could probably be discounted as a causative factor.³¹

Surgical techniques were equally distributed among groups,³³ and we were unable to identify any clustering of the surgeons among the different groups. The baseline risk was not excessively high; similar rates of reoperation after tonsillectomy have been reported before.^{34,35} Also, the distribution of surgical indications was similar in the entire cohort and in the subgroup that had bleeding.

Posttonsillectomy bleeding is categorized as primary or secondary.³⁶ Primary bleeding is defined as bleeding within 24 hours after tonsillectomy and is associated with surgical technique and reopening of blood vessels. Secondary bleeding occurs more than 24 hours after tonsillectomy, often between days 5 and 10.^{37,38,39,40} and usually occurs when the primary scab or necrotic tissue on the tonsil bed sloughs off before the wound has completely healed.

A previous study in the United States found that obstructive sleep apnea syndrome was associated with a lower rate of posttonsillectomy bleeding, which may be explained by the protective effect of upregulation of prothrombotic factors.³⁸

Czarnetzki et al were the first to report a dose related increased risk of post tonsillectomy hemorrhage following the administration of dexamethasone.⁴¹

Several arguments suggest that the association between dexamethasone and bleeding should be considered causal. Reverse causality can be excluded. The magnitude of the association was strong; with the largest dose of dexamethasone, the bleeding risk appeared to be 4 times higher than the risk associated with classic NSAIDs.^{34,35} A biological basis for the increased bleeding risk would support causality. Dexamethasone was shown to interfere with platelet aggregation in animals,⁴² but in humans, glucocorticosteroids did not impair platelet function or primary hemostasis.⁴³ An increased bleeding risk associated with dexamethasone in the absence of a preliminary lesion seems unlikely. In infants with bronchiolitis who received high doses of dexamethasone, no bleeding was reported.⁴⁴ Concomitant use of NSAIDs may have reinforced the bleeding risk. The risk of gastrointestinal hemorrhage in patients taking classic NSAIDs is largely increased by concomitant glucocorticosteroids.⁴⁵ One of our initial hypotheses was that children who were exposed to dexamethasone would need less NSAIDs postoperatively and, subsequently, would be less prone to bleeding. Yet the risk of bleeding was increased in children who received dexamethasone although they were significantly less frequently exposed to ibuprofen. This observation further strengthens the additional bleeding risk that is associated with dexamethasone. The most convincing biological explanation might be related to inhibition of repair processes of wounds by glucocorticosteroids⁴⁶ and to delayed ulcer healing.⁴⁷ Ulcer healing is a programmed and complex repair process.^{46,48} Epidermal and basic fibroblast growth factors regulate the process of mucosal healing and are inhibited by dexamethasone.^{49,50,51} Dexamethasone decreases collagen deposition, epithelization, and fibroblast content of surgical wounds.⁵² This would explain why bleeding sometimes occurred several days after administration of dexamethasone.

Tonsillectomy is not comparable with most other surgical interventions because the wound created by the excision of the tonsils is neither sutured nor covered by sealing or hemostatic material. It remains a large wound surface, which is covered by crusting and exposed to food, inhaled air, and saliva. The vascular supply of the tonsils is rich. Posttonsillectomy hemorrhage is a potentially lethal complication because the upper airways are unprotected and manual compression is nearly impossible. If hemorrhage does not stop spontaneously, reintervention is unavoidable. Blood loss becomes evident only when the child is hemodynamically instable or vomits the swallowed blood.⁵³

5. Conclusion

In our study, in children undergoing tonsillectomy, dexamethasone has a significant and dose dependent effect on increasing the risk of bleeding in tonsillectomy patients. However, it cannot be excluded that dexamethasone, possibly through inhibition of wound healing, increases the risk of postoperative bleeding in this specific setting.

References

- [1] Steward DL, Welge JA, Myer CM. Steroids for improving recovery following tonsillectomy in children. *Cochrane Database Syst Rev.* 2003(1): CD003997.
- [2] Bolton CM, Myles PS, Nolan T, Sterne JA. Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth.* 2006; 97(5): 593-604.
- [3] Afman CE, Welge JA, Steward DL. Steroids for post-tonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg.* 2006; 134(2): 181-6.
- [4] Steward DL, Welge JA, Myer CM. Do steroids reduce morbidity of tonsillectomy? Meta-analysis of randomized trials. *Laryngoscope.* 2001; 111(10): 1712-8.
- [5] Goldman AC, Govindaraj S, Rosenfeld RM. A meta-analysis of Dexamethasone use with tonsillectomy. *Otolaryngol Head Neck Surg.* 2000; 123(6): 682-6.
- [6] Plante J, Turgeon AF, Zarychanski R, et al. Effect of systemic steroids on post-tonsillectomy bleeding and reinterventions: systematic review and meta-analysis of randomised controlled trials. *BMJ.* 2012; 345(August): e5389.
- [7] Hilton M. Tonsillectomy technique—tradition versus technology. *Lancet.* 2004; 364(9435): 642-643.
- [8] Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, nonsteroidal anti-inflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized controlled trials. *Anesthesiology.* 2003; 98(6): 1497-1502.
- [9] Moiniche S, Rømsing J, Dahl JB, Tramèr MR. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg.* 2003; 96(1): 68-77.
- [10] Henzi I, Walder B, Tramèr MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg.* 2000; 90(1): 186-194.
- [11] Gan TJ, Meyer TA, Apfel CC, et al; Society for Ambulatory Anesthesia. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2007; 105(6): 1615-1628.
- [12] Bolton CM, Myles PS, Nolan T, Sterne JA. Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth.* 2006; 97(5): 593-604.
- [13] Afman CE, Welge JA, Steward DL. Steroids for posttonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg.* 2006; 134(2): 181-186.
- [14] Steward DL, Welge JA, Myer CM. Do steroids reduce morbidity of tonsillectomy? meta-analysis of randomized trials. *Laryngoscope.* 2001; 111(10): 1712-1718.
- [15] Kehlet H. Glucocorticoids for peri-operative analgesia: how far are we from general recommendations? *Acta Anaesthesiol Scand.* 2007; 51(9): 1133-1135.

- [16] Kim MS, Cote CJ, Cristoloveanu C, et al. There is no dose-escalation response to dexamethasone (0.0625-1.0 mg/kg) in pediatric tonsillectomy or adenotonsillectomy patients for preventing vomiting, reducing pain, shortening time to first liquid intake, or the incidence of voice change. *Anesth Analg.* 2007;104(5):1052-1058.
- [17] April MM, Callan ND, Nowak DM, Hausdorff MA. The effect of intravenous dexamethasone in pediatric adenotonsillectomy. *Arch Otolaryngol Head Neck Surg.* 1996; 122(2):117-120.
- [18] Tom LW, Templeton JJ, Thompson ME, Marsh RR. Dexamethasone in adenotonsillectomy. *Int J Pediatr Otorhinolaryngol.* 1996; 37(2): 115-120.
- [19] Pappas AL, Sukhani R, Hotaling AJ, et al. The effect of preoperative dexamethasone on the immediate and delayed postoperative morbidity in children undergoing adenotonsillectomy. *Anesth Analg.* 1998; 87(1): 57-61.
- [20] Hanasono MM, Lalakea ML, Mikulec AA, Shepard KG, Wellis V, Messner AH. Perioperative steroids in tonsillectomy using electrocautery and sharp dissection techniques. *Arch Otolaryngol Head Neck Surg.* 2004; 130(8): 917-921.
- [21] Association of Paediatric Anaesthetists of Great Britain and Ireland. Guidelines on the Prevention of Post-operative Vomiting in Children. Spring 2008. http://www.apagbi.org.uk/docs/APA%20Draft_POV_guidelines_%20Jan08.pdf.
- [22] Gan TJ, Meyer TA, Apfel CC, et al; Society for Ambulatory Anesthesia. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2007; 105(6): 1615-1628.
- [23] Bolton CM, Myles PS, Nolan T, Sterne JA. Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth.* 2006; 97(5): 593-604.
- [24] Afman CE, Welge JA, Steward DL. Steroids for posttonsillectomy pain reduction: meta-analysis of randomized controlled trials. *Otolaryngol Head Neck Surg.* 2006; 134(2): 181-186.
- [25] Steward DL, Welge JA, Myer CM. Do steroids reduce morbidity of tonsillectomy? meta-analysis of randomized trials. *Laryngoscope.* 2001; 111(10): 1712-1718.
- [26] Kim MS, Cote CJ, Cristoloveanu C, et al. There is no dose-escalation response to dexamethasone (0.0625-1.0 mg/kg) in pediatric tonsillectomy or adenotonsillectomy patients for preventing vomiting, reducing pain, shortening time to first liquid intake, or the incidence of voice change. *Anesth Analg.* 2007; 104(5): 1052-1058.
- [27] April MM, Callan ND, Nowak DM, Hausdorff MA. The effect of intravenous dexamethasone in pediatric adenotonsillectomy. *Arch Otolaryngol Head Neck Surg.* 1996; 122(2): 117-120.
- [28] Tom LW, Templeton JJ, Thompson ME, Marsh RR. Dexamethasone in adenotonsillectomy. *Int J Pediatr Otorhinolaryngol.* 1996; 37(2): 115-120.
- [29] Pappas AL, Sukhani R, Hotaling AJ, et al. The effect of preoperative dexamethasone on the immediate and delayed postoperative morbidity in children undergoing adenotonsillectomy. *Anesth Analg.* 1998; 87(1): 57-61.
- [30] Hanasono MM, Lalakea ML, Mikulec AA, Shepard KG, Wellis V, Messner AH. Perioperative steroids in tonsillectomy using electrocautery and sharp dissection techniques. *Arch Otolaryngol Head Neck Surg.* 2004; 130(8): 917-921.
- [31] Collison PJ, Mettler B. Factors associated with posttonsillectomy hemorrhage. *Ear Nose Throat J.* 2000; 79(8): 640-642.
- [32] Macassey EA, Baguley C, Dawes P, Gray A. 15-year audit of post-tonsillectomy haemorrhage at Dunedin Hospital. *ANZ J Surg.* 2007; 77(7): 579-582.
- [33] Lowe D, van der Meulen J; National Prospective Tonsillectomy Audit. Tonsillectomy technique as a risk factor for postoperative haemorrhage. *Lancet.* 2004; 364(9435): 697-702.
- [34] Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, nonsteroidal anti-inflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized controlled trials. *Anesthesiology.* 2003;98(6):1497-1502.
- [35] Møiniche S, Rømsing J, Dahl JB, Tramèr MR. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. *Anesth Analg.* 2003; 96(1): 68-77.
- [36] Baugh RF, Archer SM, Mitchell RB, et al. American Academy of Otolaryngology-Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg.* 2011; 144(1)(suppl): S1-S30.
- [37] Collison PJ, Mettler B. Factors associated with post-tonsillectomy hemorrhage. *Ear Nose Throat J.* 2000; 79(8): 640-646.
- [38] Perkins JN, Liang C, Gao D, Shultz L, Friedman NR. Risk of post-tonsillectomy hemorrhage by clinical diagnosis. *Laryngoscope.* 2012; 122(10): 2311-2315.
- [39] Tolska HK, Takala A, Pitkaniemi J, Jero J. Post-tonsillectomy haemorrhage more common than previously described: an institutional chart review. *Acta Otolaryngol.* 2013; 133(2): 181-186.
- [40] Windfuhr JP, Chen YS, Remmert S. Hemorrhage following tonsillectomy and adenoidectomy in 15,218 patients. *Otolaryngol Head Neck Surg.* 2005; 132(2): 281-286.
- [41] Czarnetzki C, Elia N, Lysakowski C, Dumont I, Landis BN, Giger R, et al. Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. *JAMA* 2008 Dec 10; 300(22): 2621-30.
- [42] van Giezen JJ, Brakkee JG, Dreteler GH, Bouma BN, Jansen JW. Dexamethasone affects platelet aggregation and fibrinolytic activity in rats at different doses which is reflected by their effect on arterial thrombosis. *Blood Coagul Fibrinolysis.* 1994; 5(2): 249-255.
- [43] Thong KL, Mant MJ, Grace MG. Lack of effect of prednisone administration on bleeding time and platelet function of normal subjects. *Br J Haematol.* 1978; 38(3): 373-380.
- [44] Corneli HM, Zorc JJ, Majahan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med.* 2007; 357(4): 331-339.

- [45] Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med.* 1991; 114(9): 735-740.
- [46] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. *N Engl J Med.* 2005; 353(16): 1711-1723.
- [47] Carpani de Kaski M, Rentsch R, Levi S, Hodgson HJ. Corticosteroids reduce regenerative repair of epithelium in experimental gastric ulcers. *Gut.* 1995; 37(5): 613-616.
- [48] Luo JC, Chi CW, Lin HY, et al. Dexamethasone inhibits epidermal growth factor-stimulated gastric epithelial cell proliferation. *J Pharmacol Exp Ther.* 2007; 320(2): 687-694.
- [49] Tarnawski A, Stachura J, Durbin T, Sarfeh IJ, Gergely H. Increased expression of epidermal growth factor receptor during gastric ulcer healing in rats. *Gastroenterology.* 1992; 102(2): 695-698.
- [50] Szabo S, Khomenko T, Gombos Z, Deng XM, Jadus MR, Yoshida M. Review article: transcription factors and growth factors in ulcer healing. *Aliment Pharmacol Ther.* 2000; 14(suppl 1): 33-43.
- [51] Chakraborti S, Mandal M, Das S, Mandal A, Chakraborti T. Regulation of matrix metalloproteinases: an overview. *Mol Cell Biochem.* 2003;253 (1-2): 269-285.
- [52] Durmus M, Karaaslan E, Ozturk E, et al. The effects of single-dose dexamethasone on wound healing in rats. *Anesth Analg.* 2003;97(5):1377-1380.
- [53] Windfuhr JP, Chen YS, Remmert S. Hemorrhage following tonsillectomy and adenoidectomy in 15,218 patients. *Otolaryngol Head Neck Surg.* 2005;132 (2): 281-286.