

Evaluation of preemptive analgesia with dextromethorphan gargling in patients undergoing tonsillectomy

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BACKGROUND: This double-blind clinical trial was done to attenuate post tonsillectomy pain with preoperative dextromethorphan gargling. **METHODS:** In a clinical trial study, sixty patients who were candidate for elective surgery under general anesthesia were randomly divided into three groups. Group OD (oral dextromethorphan) received 45 mg oral dextromethorphan tablet. Group GD (gargling dextromethorphan) were asked to gargle 45 mg dextromethorphan syrup and group PB (placebo) received placebo tablet preoperatively. Pain-free period (PFP) and severity of pain at rest and swallowing saliva were recorded. Need for additional analgesic and satisfaction after 24 hours were compared between groups. **RESULTS:** Three groups were similar in age, weigh and sex ($p > 0.05$). The PFP was longer in OD and GD groups than placebo group ($p = 0.002$). The severity of pain during swallowing saliva was lower in OD and GD groups than placebo group ($p = 0.047$). The mean dosage of additional analgesic was more in placebo group than OD and GD groups ($p = 0.005$). The median satisfaction after 24 hours was higher in OD and GD groups than placebo group ($p = 0.048$). **CONCLUSIONS:** Preemptive analgesia by eating or gargling dextromethorphan can effectively attenuate post-operative tonsillectomy pain.

KEYWORDS: Tonsillectomy, Dextromethorphan, Preemptive Analgesia, Gargling

BACKGROUND

Postoperative pain is one of the most annoying complications after surgical procedures that may have adverse physiological effects on patient.^[1] Incomplete treatment of postoperative pain in many patients is due to inadequate drug prescription because of the fear of the drugs side effects. Respiratory depression and addiction possibility are the most important causes of insufficient use of opioids as the post-operative analgesics.^[2]

Preemptive analgesia is one of the post-operative pain control methods. Indeed, it is "treating pain prior to its onset" which can decrease the severity and duration of post-operative pain.^[3] Preemptive analgesia is a calmativ treatment with increasing threshold for nociception by reduction in central and peripheral nerve sensitivity.^[4] In fact, afferent fibers create central sensitization to pain through receptor-mediated stimulation of N-methyl-D-aspartic acid (NMDA), therefore the use of NMDA antagonists prevent irritation and reduce sensitivity to pain after surgery.^[5-7]

Preemptive analgesia diminish severity of post-

operative pain and increase the patient ability to tolerate post operation period through the less analgesic consumption and imposes fewer drug side effects.^[8] Tonsillectomy is a common surgical procedure that causes pain and discomfort. Some interferences with adjunct drugs may improve postoperative analgesia and hasten hospital discharge. ^[9] Dextromethorphan is a non-opioid antitussive that also is NMDA receptor antagonist.^[10]

The preemptive analgesic effect of gargling with dextromethorphan on tonsillectomy was not previously evaluated. According to dextromethorphan mechanism effect^[11] and our previous scattered pilot studies, we conducted this study.

METHODS

After Obtaining the University Ethics Committee approval (number 1027) and informed written consent, sixty patients (18–45 years old) with American Society of Anesthesiologists (ASA) physical status I-II, scheduled for bilateral tonsillectomy were enrolled in this double-blind randomized clinical trial in the Imam Reza Hospital.

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Patients were selected through convenience sampling method. Sample size was determined with the use of previous pilot study and the formula ($n = Z^2 \times \delta^2 / d^2$). In this formula n = sample size and z = confidence interval ($\alpha = 0.05$, $\beta = 10\%$, study power 90%). According to our pilot study in which free pain period was scaled on hours, the precision was determined as about one hour ($d = 1$). The sample size was calculated about 14 patients; but to increasing study accuracy, we considered 20 patients for each group.

All patients aged 18 to 45 years who were referred for tonsillectomy under general anesthesia in Imam Reza Hospital were included. Patients with a previous history of chronic oral pain, regular intake of analgesic drugs, or psychiatric disorders were excluded. The patients were divided into 3 groups with the aid of a computer generated random number table. All investigators and patients were blinded to the study group assignment. Patients in OD (oral dextromethorphan) group received 45mg dextromethorphan oral tablet 60 min before the surgery. In GD (gargling dextromethorphan) group, 45 mg dextromethorphan syrup dissolved in 30 cc of water was gargled for 60 seconds immediately before entering the operating room. The recommended oral dose of dextromethorphan varies from 0.5 mg/kg to 150 mg.¹² In PB (placebo) Group, placebo tablet was administered by a nurse 60 min before the surgery.

After entering the operating room, all patients underwent general anesthesia with a same protocol and received 5cc/kg normal saline as preload fluid and midazolam 0.03 mg/kg as a premedication. Anesthesia induction was performed by intravenous (IV) administration of 3µg/kg fentanyl and 5 mg/kg sodium thiopental. Tracheal intubation was facilitated by IV administration of 0.5 mg/kg atracurium. Anesthesia was maintained with 50% nitrous oxide in oxygen and isof

lurane (1-1.5 MAC). At the end of surgery, patients were extubated and transferred to post anesthetic care unit (PACU). In PACU, time to the first analgesic request and severity of post-operative pain at rest and during swallowing saliva were evaluated by Visual Analog Scale (VAS) each 6 hours and recorded for 24 hours. VAS score of 3 or more was the criterion for administering IV pethidine 0.5 mg/kg. VAS measured pain based on the length of 100 cm scale ruler which zero indicated no pain and 100 indicated the most severe pain and was categorized as mild ≤ 30 cm, moderate 30-70 cm and severe >70 cm. Any dextromethorphan adverse effects, such as vomiting, somnolence, respiratory distress, drowsiness, hallucination, blurred vision, skin rashes or itching were recorded and compared.

Collected data was analyzed by SPSS for windows software (version 16.0, SPSS Inc., Chicago, IL). For comparison between quantitative variables such as age, weight and the pain-free period (PFP: painless period after discharging from the operation room) and mean dosage of additional analgesic and the time to first analgesic demand in three groups were compared using ANOVA test. For evaluating ranking variables such as the median satisfaction after 24 hours and the pain severity during swallowing saliva and at rest, Chi-square test was used. We used the chi-square test for analyzing sex distribution in three groups. To assess the normal distribution of variables, Kolmogorov-Smirnov test was used. Data are expressed as mean \pm SD or (median, range).

RESULTS

Baseline characteristics of the patients are presented in table 1. Three groups were not significantly different in the baseline characteristics. Normal distribution of variables was confirmed using Kolmogorov-Smirnov test.

Table 1. Comparison of demographic factors between the three study groups

	Oral dextromethorphan	Gargling dextromethorphan	Placebo	P-value
Age (years)	40.6 \pm 6.6	39.7 \pm 6.7	41.8 \pm 4.3	0.7*
Weight (kg)	75.5 \pm 5.2	76.5 \pm 5.3	75 \pm 2.7	0.9*
Sex (M/F)	9 / 11	12 / 8	10 / 10	0.6**

Data are expressed as mean \pm standard deviation

* ANOVA Test, **Chi-square test

Duration of surgery averaged 60 ± 9 minutes and the mean PACU stay averaged 45 ± 7 minutes. These variables were similar in the three groups ($p = 0.115$ and $p = 0.123$, respectively). The median sedation level according to Ramsay Sedation Scale in different time intervals were identical in the three groups ($p = 0.089$). It was shown that the mean PFP and the first time to analgesic demand in OD group were longer than the GD and placebo groups. The mean dosage of additional analgesic was more in placebo group than OD and GD groups (Table 2).

The intensity of oral pain was significantly different during swallowing saliva but not at rest. There was significant difference between the three groups regarding median satisfaction after 24 hours (Table 3). The Post Hoc test analysis showed significant difference in PFP between three groups ($p = 0.002$).

DISCUSSION

One preferred method of reducing postoperative pain is inducing analgesia (preemptive analgesia) through pathways involved in pain transmission. This can be done by several ways including the use of topical anesthetics, nerve blocks, intravenous analgesics and anti-inflammatory medications.^[13- 16] In this study we assessed the effect of preemptive analgesia method by gargling with dextromethorphan syrup on pain status after tonsillectomy.

Kawamata et al. used 45 mg dextromethorphan tablet, 60 minutes before tonsillectomy to evaluate effects of oral dextromethorphan and showed that dextromethorphan reduces oral pain during swallowing saliva and at rest by preventing central sensitization.^[17] On the other hand, Rose et al. showed no analgesic effect by dextromethorphan when a dose of 0.5-1 mg/kg was used in children.^[18] In study of Henderson et al., patients that were given oral dextromethorphan before and after surgery had a significant reduction in

pain score at rest, but not on movement and there was a trend to lower morphine requirements in the first 24 hours.^[19]

Our findings were in accordance with that of Kawamata et al. study regarding the relief of post tonsillectomy pain during swallowing saliva but not in resting pain. One reason could be that our study was carried on a noticeably larger group of patients. Numerous studies have shown no analgesic effect for dextromethorphan. In contrast, other studies suggested that it acts as a receptor antagonist which modifies posterior spinal pathways and decreases central nerves sensitivity to pain.^[20]

Regarding the dextromethorphan mechanism of action, our study indicated that gargling for 60 seconds with 45mg dextromethorphan syrup dissolved in 30cc of water before entering the operating room compared with the placebo group had some beneficial effects on factors such as duration of postoperative pain and severity of pain at rest and during swallowing; however, it was less effective compared to oral dextromethorphan tablets.

Presumably, a mechanism by which the gargling with dextromethorphan syrup (as preemptive analgesia) reduces postoperative pain is the absorption that occurs through pharyngeal mucosa. It decreases the sensitivity of cough receptors and interrupts impulse transmission by depressing the medullary cough center via sigma receptor stimulation that is structurally related to codeine.^[20]

Perceiving longer time of PFP in OD group but lower frequency of severe pain and higher frequency of moderate pain in GD group could be discussed with another hypothesis that dextromethorphan produces some local anesthetic effects at pharyngeal area; however, all of these possibilities require further investigations.

Table 2. Comparison of postoperative factors between the three study groups

	Oral dextromethorphan	Gargling dextromethorphan	Placebo	P-value*
Pain-free period (min)	5.2 ± 1.2	4 ± 1.7	1.4 ± 0.6	0.002
Dosage of additional pethidine (mg)	48.7 ± 6.8	73.5 ± 7.9	99.5 ± 8.7	0.005
Time to the first analgesic request (min)	5.2 ± 0.02	4.1 ± 0.02	1.4 ± 0.4	0.005

Data are expressed as mean \pm SD,
*ANOVA test

Table 3. Comparison of postoperative pain severity and patient satisfaction between the three study groups

	Pain severity at Rest			Pain severity during swallowing saliva			satisfaction after 24 hour		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Low	Medium	High
Oral dextromethorphan	9	8	3	10	6	4	2	5	13
Gargling dextromethorphan	8	8	4	9	8	3	2	7	11
Placebo	6	9	5	4	8	8	8	6	6
P-value*		0.058			0.047			0.048	

Data are expressed as frequency

REFERENCES

- Sutters KA, Holdridge-Zeuner D, Waite S, Paul SM, Savedra MC, Lanier B, et al. A Descriptive Feasibility Study to Evaluate Scheduled Oral Analgesic Dosing at Home for the Management of Postoperative Pain in Preschool Children Following Tonsillectomy. *Pain Med* 2012. [Epub ahead of print].
- Stewart DW, Ragg PG, Sheppard S, Chalkiadis GA. The severity and duration of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair. *Paediatr Anaesth* 2012; 22(2): 136-43.
- Dionne R. Preemptive vs preventive analgesia: which approach improves clinical outcomes? *Compend Contin Educ Dent* 2000; 21(1): 48, 51-4, 56.
- Dashti GA, Amini S, Zanguee E. The prophylactic effect of rectal acetaminophen on postoperative pain and opioid requirements after adenotonsillectomy in children. *Middle East J Anesthesiol* 2009; 20(2): 245-9.
- El Sonbaty MI, Abo el DH, Mostafa A, Abo SO. Preemptive peritonsillar ketamine infiltration: postoperative analgesic efficacy versus meperidine. *Middle East J Anesthesiol* 2011; 21(1): 43-51.
- Gemma M, Piccioni LO, Gioia L, Beretta L, Bussi M. Ropivacaine peritonsillar infiltration for analgesia after adenotonsillectomy in children: a randomized, double-blind, placebo-controlled study. *Ann Otol Rhinol Laryngol* 2009; 118(3): 227-31.
- Zhuang PJ, Wang X, Zhang XF, Zhou ZJ, Wang Q. Postoperative respiratory and analgesic effects of dexmedetomidine or morphine for adenotonsillectomy in children with obstructive sleep apnoea. *Anaesthesia* 2011; 66(11): 989-93.
- Abu-Samra MM, Ismaeil WA. Pre-emptive oral dextromethorphan reduces both postoperative and packing removal pain in patients undergoing nasal surgery. *Saudi Med J* 2009; 30(2): 214-8.
- Elshammaa N, Chidambaran V, Housny W, Thomas J, Zhang X, Michael R. Ketamine as an adjunct to fentanyl improves postoperative analgesia and hastens discharge in children following tonsillectomy - a prospective, double-blinded, randomized study. *Paediatr Anaesth* 2011; 21(10): 1009-14.
- Helmy SA, Bali A. The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements. *Anesth Analg* 2001; 92(3): 739-44.
- Ali SM, Shahrbano S, Ulhaq TS. Tramadol for pain relief in children undergoing adenotonsillectomy: a comparison with dextromethorphan. *Laryngoscope* 2008; 118(9): 1547-9.
- Abu-Shahwan I. Ketamine does not reduce postoperative morphine consumption after tonsillectomy in children. *Clin J Pain* 2008; 24(5): 395-8.
- Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. *Can J Anaesth* 2001; 48(10): 1000-10.
- Chatterjee US. Preemptive analgesia in paediatric surgery. *Afr J Paediatr Surg* 2011; 8(3): 267-8.
- Behdad A, Hosseinpour M, Khorasani P. Preemptive use of ketamine on post operative pain of appendectomy. *Korean J Pain* 2011; 24(3): 137-40.
- Isiordia-Espinoza MA, Pozos-Guillen AJ, Martinez-Rider R, Herrera-Abarca JE, Perez-Urizar J. Preemptive analgesic effectiveness of oral ketorolac plus local tramadol after impacted mandibular third molar surgery. *Med Oral Patol Oral Cir Bucal* 2011; 16(6): e776-e780.
- Kawamata T, Omote K, Kawamata M, Namiki A. Premedication with oral dextromethorphan reduces postoperative pain after tonsillectomy. *Anesth Analg* 1998; 86(3): 594-7.
- Rose JB, Cuy R, Cohen DE, Schreiner MS. Preoperative oral dextromethorphan does not reduce pain or analgesic consumption in children after adenotonsillectomy. *Anesth Analg* 1999; 88(4): 749-53.
- Henderson DJ, Withington BS, Wilson JA, Morrison LM. Perioperative dextromethorphan reduces postoperative pain after hysterectomy. *Anesth Analg* 1999; 89(2): 399-402.
- Siu A, Drachtman R. Dextromethorphan: a review of N-methyl-D-aspartate receptor antagonist in the management of pain. *CNS Drug Rev* 2007; 13(1): 96-106.

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