SINGLE-BLIND EVALUATION OF POST-TONSILLECTOMY PAIN TREATMENT WITH AN EUTECTIC MIXTURE OF LOCAL ANESTHETICS

G. NERI, C. BAFFA, F. VITULLO, R. DI MASCIO[1] and E. BALLONE[1]

Surgical Experimental and Clinical Sciences Department, ENT Division, "G. d'Annunzio" University of Chieti; [1]Medicine and Ageing Science Department, Laboratory of Biostatistics, University of Chieti, Chieti, Italy

Received March 17, 2006 – Accepted October 5, 2006

The efficacy of an eutectic mixture of local anesthetics (lidocaine and prilocaine) in ointment for topical use (EMLA) in the treatment of post-tonsillectomy pain in both pediatric and adult patients was evaluated. Ninety patients affected by recurring tonsillitis and refractory to antibiotic therapy were submitted to tonsillectomy by dissection. Of the ninety patients 45 random subjects received topical treatment and the remaining 45 did not receive any treatment in the emptied tonsillar compartment. Pain intensity was evaluated at 3, 6 and 9 hours after surgical treatment using a visual subjective evaluation scale (VAS for adults and FES for children). The percentage of adults who referred pain of minor intensity was greater in the treated patients than in the controls: 51.4% vs 14.3% ($p<0.001$) at the third hour, 71.4% vs 2.9% ($p<0.001$) at the sixth hour and 88.6% vs 14.3% ($p<0.001$) at the ninth hour. In the pediatric groups, 80.0% of the treated subjects referred moderate pain at the third hour, compared to 40% of the control group. At the ninth hour all children (100%) referred moderate pain compared to 20% of the control group. No treated patient required analgesic therapy during the post-operative observation period. The application of EMLA in the compartment after tonsillectomy determined an extremely significant reduction of postoperative pain in terms of intensity and duration.

Even though tonsillar pathology can be treated with medical therapy, tonsillectomy, in the child or adult, is without doubt the most frequent surgical procedure in otorhinolaryngology. In Italy, its incidence is approximately three times higher than average and is inferior only to appendectomy (1). The frequency of tonsillectomy is probably linked to the fact that tonsillar pathology strongly influences the quality of life of those affected and their families, in terms of economic and biological costs, by limiting work, scholastic, social, and recreational activities. During the pre-operative evaluation, these details prevail over the modifications of the local-regional immune capacity and the unpleasant postoperative aspects (for example, pain and inflammatory state due to tissue trauma).

Pain after tonsillectomy is thought to be due to a combination of nerve irritation, inflammation and pharyngeal muscle spasm. Primary hyperalgesia (2), due to the liberation of vasoactive, chemotactic and proinflammation substances (bradykinin, serotonin, prostaglandin, etc.), represents the immediate response to the surgical injury and is an alteration of the sensitivity that, reducing pain

Key words: tonsillectomy, pain, lidocaine, prilocaine

Mailing address:
Giampiero Neri,
c/o Ospedale SS Annunziata,
Via dei Vestini,
66013 Chieti, Italy
Tel/Fax: +39 0871 552033
e-mail: neri@unich.it

1721-727X (2006)

threshold, causes an abnormal increase of the pain sensibility (3) induced by a stimulus(4-5). The persistence of pain in time is linked to a "secondary hyperalgesia" whose origin is complex and not yet perfectly clarified Therefore, the treatment of acute pain, especially postoperative pain, besides having an ethical aspect, assumes fundamental importance because it enormously improves patient outcome, significantly reducing mortality and morbidity along with noted systemic effects (neuroendocrine response, incretion of catabolic hormones, inhibition of anabolic substances, modification of A.N.S. and modifications of the cardiovascular and respiratory system) (6-13).

Many studies concerning the treatment of post-tonsillectomy pain have been conducted through local application of medicines (anesthetic and non) injected or sprayed or otherwise applied in the compartment, immediately before or after the abscission of the tonsils. Nevertheless, a publication in the Cochrane register concerning the treatment of pain with local anesthetics after tonsillectomy, concluded that there was no proof that the use of local anesthetic in patients subjected to tonsillectomy improved postoperative pain control (14).

According to the literature, the use of an eutectic mixture of local anesthetics (EMLA) in ointment for topical use in the treatment of post-tonsillectomy pain has never been considered. This is a basic oleaginous emulsion with a 5% concentration where two local anesthetics, lidocaine and prilocaine, are present in equal proportions. Their mechanism of action is to block Na^+ channels at the axonal membrane level, preventing the transit of nociceptive impulses at the cortical level. This result is obtained by reducing the action potential of the nerve fibers and by increasing the refractory period, avoiding the wind-up phenomenon responsible for post-surgical hyperalgesia.

We evaluate the efficacy of EMLA in the treatment of post-tonsillectomy pain in both pediatric and adults patients.

MATERIALS AND METHODS

Ninety patients were enlisted, equally divided by sex, and affected by recurring tonsillitis and refractory to antibiotic therapy. Of these, 70 were adults (average age 27.3 years, range 18-47) and 20 children (average age 8 years, range 4-13). After a series of preoperative "routine" tests, all patients were informed of the aim of the study, and personal consent was given by the person directly interested or his/her parents (in case of minors). The patients underwent tonsillectomy by dissection in the Rose position, in general anesthesia with assisted ventilation and tracheal intubation. Thirty minutes preceding the surgical treatment, the adult patients were medicated with atropine 0.5 mg and promethazine 0.5 mg im and the children received midazolam 0.5 mg/kg sublingual.

In the emptied tonsillar compartment, the patients randomly received, at the end of the operation and before waking up, 2 ml of an association of lidocaine-prilocaine in ointment (EMLA) applied in the region with the use of a 5 ml syringe equipped with plastic needle cannula (35 adults and 10 children) or no treatment (35 patients). The same methodology was used in pediatric patients, of whom 10 received EMLA treatment and 10 received no treatment (control group). Pain intensity was evaluated for all the patients in the study at 3, 6 and 9 hours after surgical treatment using a visual subjective evaluation scale already amply validated in literature.

For the adults we used a visual analogical scale (VAS) from 0 to 10 points, while in the children pain intensity was evaluated using a facial expressions scale (FES) with up to 6 points. All the patients were requested to assess their pain level on the respective evaluation scale (15-18). The VAS was then categorized into three groups of pain intensity: light <4 points; moderate between 4 and 7 points; and heavy >7 points; the FES was categorized into two groups of pain: moderate ≤4 points and heavy >4 points.

Statistical analysis

The adult sample size was calculated on the basis of a 30% difference in percentage of adult patients with pain intensity >7 at 6 hours assuming a prevalence of 40% among controls. To reach a power of 80% with a type I error of 5%, a minimum of 32 subjects must be enrolled for each adult group.

The randomization of patients into the two groups was determined by sequentially alternating

their assignment following the scheduled order (determined by an administrative office) of the surgical procedures. The study was single-blind since only the patients did not know to which group they were assigned.

Initially, a summary analysis of the ordinal variables of pain intensity (VAS and FES) was performed by mean score and Standard Deviation (SD). Frequencies of VAS and FES <4 for each treated patient categorized values that were compared to their respective control group at 3, 6 and 9 hours using Chi-squared test or Fisher exact test, when appropriate.

The ordinal values obtained for VAS and FES did not have a normal distribution, therefore, we applied a non-parametric test. The Mann-Whitney test was used to compare the treated group with the control group and the Wilcoxon test to compare the different time points for each group.

Statistical analysis was performed using SPSS Advanced Statistical™ 10.0 software (SPSS Inc., Chicago, Ill).

RESULTS

No statistically significant differences were seen between the treated and control groups of both adult and pediatric groups in terms of age and gender (Table I). Patients not treated required analgesic therapy during the post-operative observation period; while 9 adult patients (25.7%) and 4 pediatric patients (40%) in both control groups required analgesic therapy which was administered during the first three post-operative hours after awakening (Table II).

No adult patient in the treated group indicated that they had pain >7 on the VAS scale during the 9 hours of observation (Fig. 1A) compared to 34.3%, 40.0% and 11.4% of the control group at the third, sixth and ninth hours, respectively (Fig. 1B). The percentage of patients that referred pain of a light intensity (VAS<4) was greater in the treated patients than in the controls: 51.4% vs 14.3% ($p<0.001$) at the third hour, 71.4% vs 2.9% ($p<0.001$) at the sixth hour and 88.6% vs 14.3% ($p<0.001$) at the ninth hour (Fig. 1A and 1B).

In the pediatric groups, 80.0% of the children referred pain with an intensity ≤ 4 (FES) at the third hour, compared to 40% of the control group, at the sixth and ninth hour all children (100%) referred pain with an intensity ≤ 4; in the control group the children referred pain with an intensity > 4 in 60% of subjects at the third hour in 60% at the sixth hour ($p<0.05$) and in 80% at the ninth hour ($p<0.01$) (Fig. 2A and 2B).

In the adults, the mean values (± SD) of pain intensity of the VAS at the third, sixth and ninth hours were 4.07 (1.66), 3.27 (1.43) and 2.51 (1.06) in treated patients and 6.19 (1.32), 6.35 (1.25) and 5.35 (1.10) in the control group, respectively. A comparison of the means indicated a statistically significant difference between the treated group and the control group at each time point (Mann-Whitney test, $p<0.01$) (Fig. 3). A significant reduction in pain intensity was already registered at the sixth hour for the treated group and at the ninth hour for both groups (Wilcoxon test, $p<0.001$).

In the children, the mean values (±SD) of pain intensity of the VAS at the third, sixth and ninth hours were 3.1 (0.87), 2.2 (0.63) and 1.7 (0.67) in the treated patients and 4.7 (1.16), 5.0 (0.82) and 5.0 (0.67) in the control group. A comparison of the means indicated a statistically significant difference between treated patients and the control group at each time point (Mann-Whitney test, $p<0.05$ at the third hour and $p<0.01$ at both the sixth and ninth hours) (Fig. 4) with a statistically significant reduction in pain intensity (Wilcoxon test, $p<0.001$) over the observation time in the treated group. We did not observe any collateral effects in the treated patients.

DISCUSSION

Pain has been defined by the International Association for the study of pain as "an unpleasant sensory and emotional experience, associated to potential or real tissue damage or described in terms of such damage" (19-20). "Pathological" pain and its correlated problems constitute a serious problem in postoperative management; because an operation determines two types of pain:

1. intraoperative pain: extremely violent due to surgical maneuvers;
2. postoperative pain: following surgery, due to tissue lesions and produced by the stimulation of peripheral receptors.

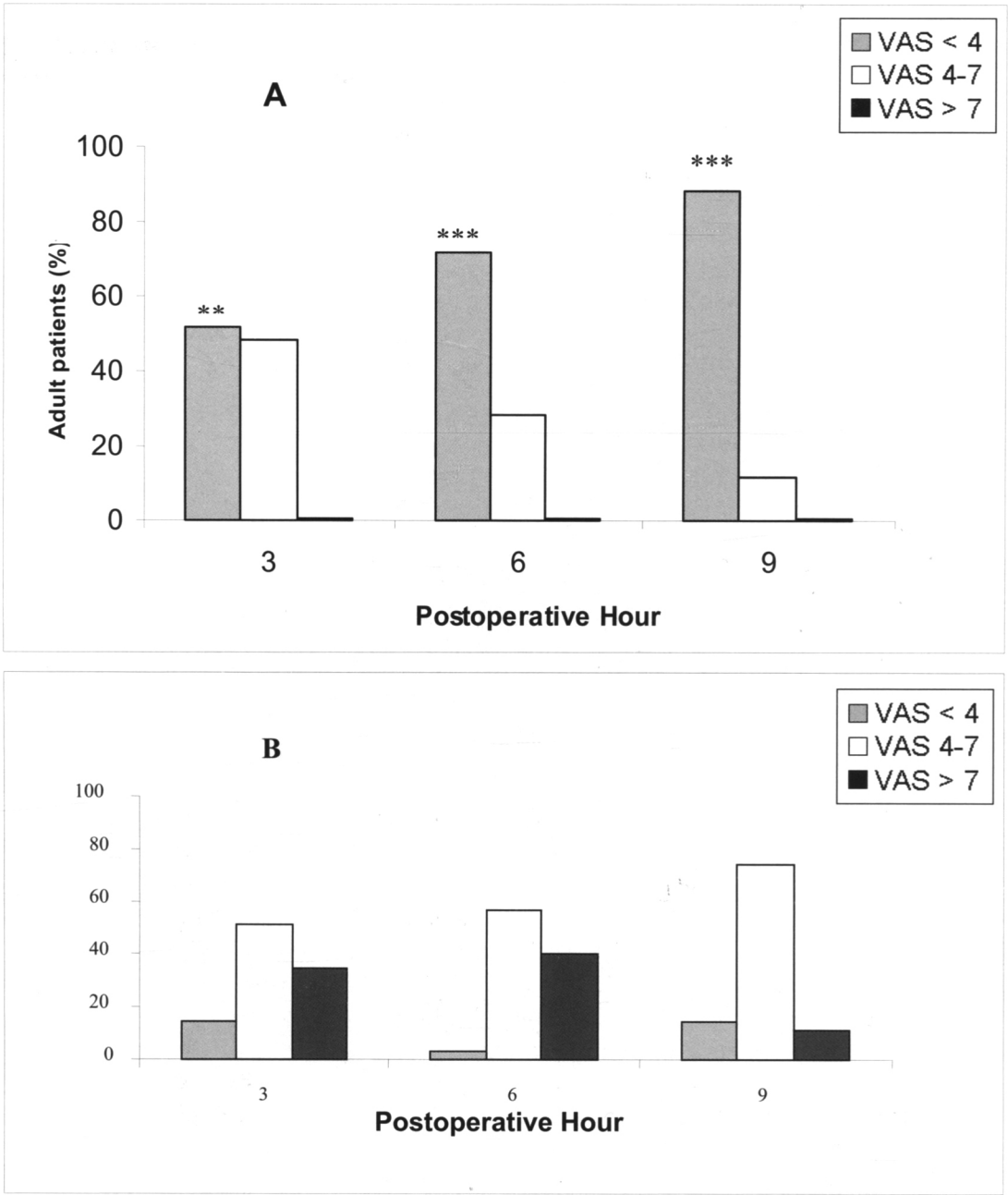
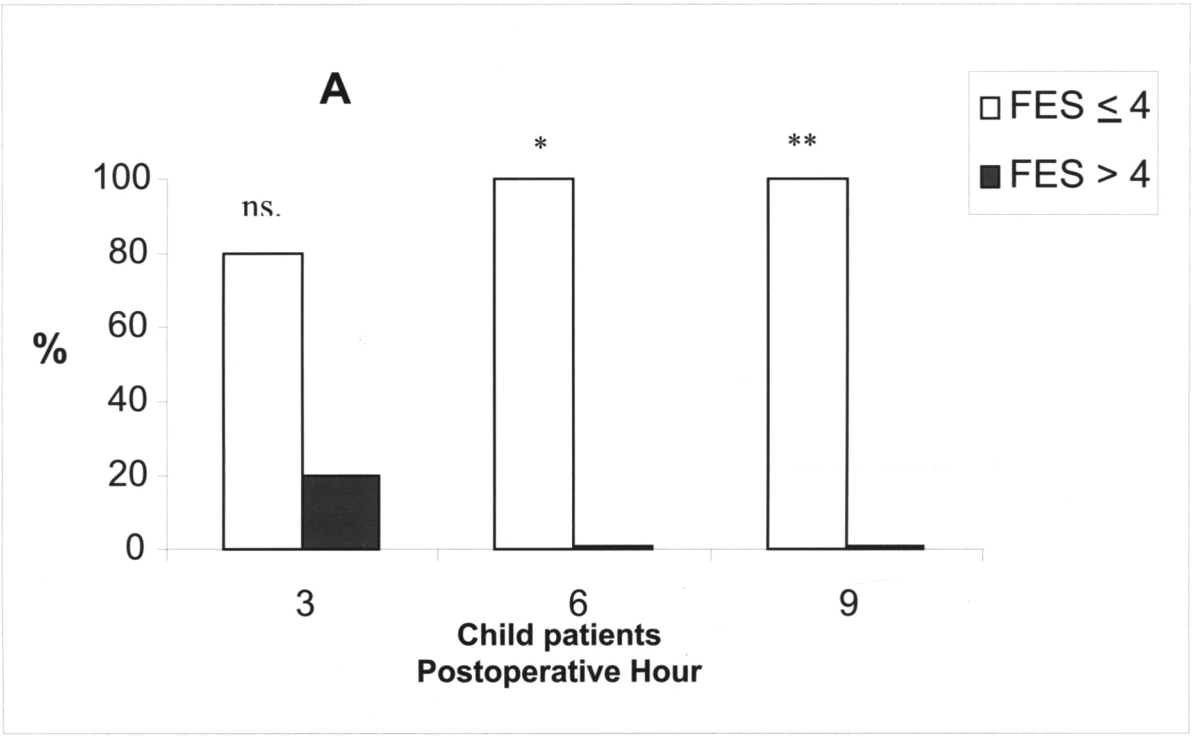


Fig. 1. ***Percentage of adult patients in 3 classes of VAS at 3, 6 and 9 postoperative hours.***
*** $p<0.05$; *** $p<0.001$; Chi squared test, A compared with B. Non-treated patients (A) referred pain > 7 and pain is reduced progressively in all patients while in the control group (B) at the sixth hour the moderate and strong pain increased while the light pain is reduced. At the ninth hour a reduction of heavy pain corresponds to an increase in moderate and light pain.*

The results obtained in the present study demonstrate that the application of EMLA cream in the tonsillar compartment at the end of the operation significantly reduces post-tonsillectomy pain. In both treated groups (adults and children), from the first registration, pain was progressively reduced, such that at the ninth hour all the patients treated presented pain referable to the lowest VAS or FES range (Fig. 1A, 2A); whereas, in the control group, postoperative pain was significantly greater than that



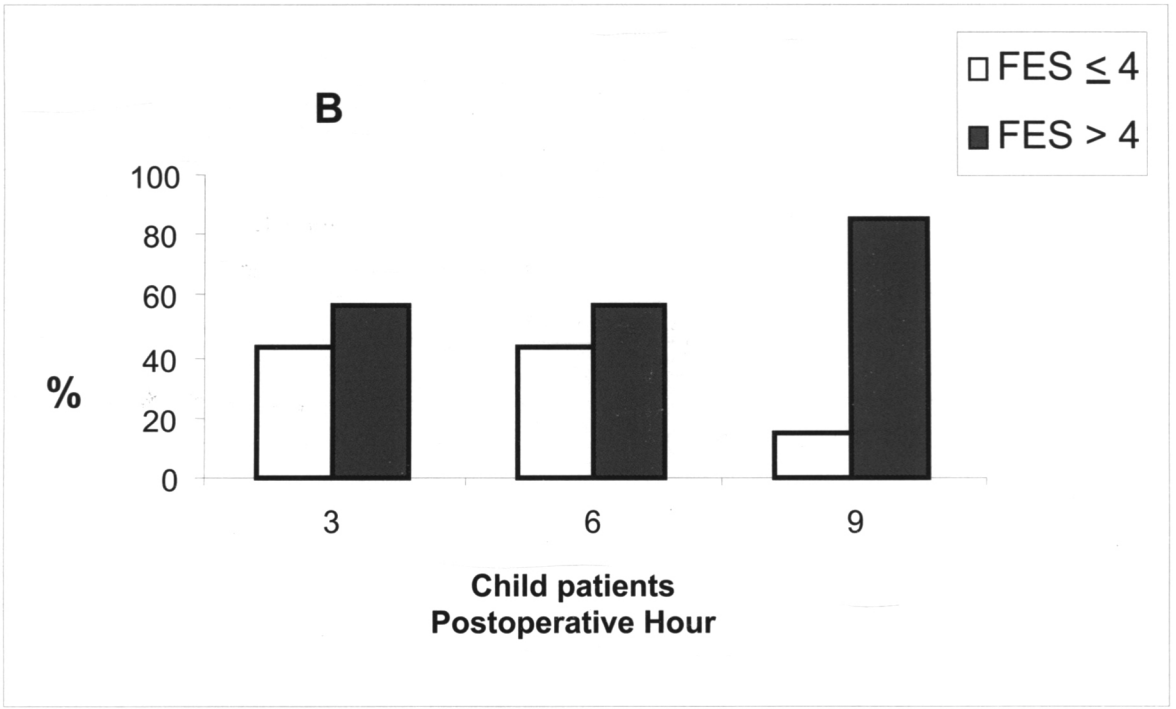


Fig. 2. ***Percentage distribution of children in two classes of FES at 3, 6 and 9 postoperative hours. A: treated with EMLA; B: control group.***

*n.s. not significant; *p<0.05; **p<0.01; Fisher exact test, A compared with B. In the treated patients at the third hour 80.0% referred moderate pain and at the sixth and ninth hour all children (100%) referred moderate pain; in the control group only 40% of the children referred pain with an intensity <4 that remained stationary at the third hour and increased in ninth hour.*

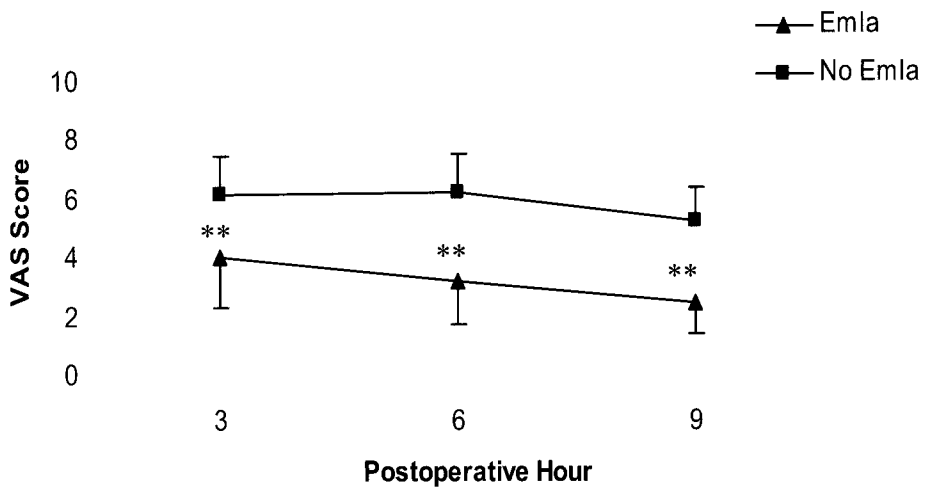


Fig. 3. ***Mean ± SD of VAS for adult patients.***
*** p<0.01; Mann-Whitney test, treated group versus control group.*
A comparison of the means indicated a statistically significant difference between the treated group and the control group at each time point (Mann-Whitney test, p<0.01).

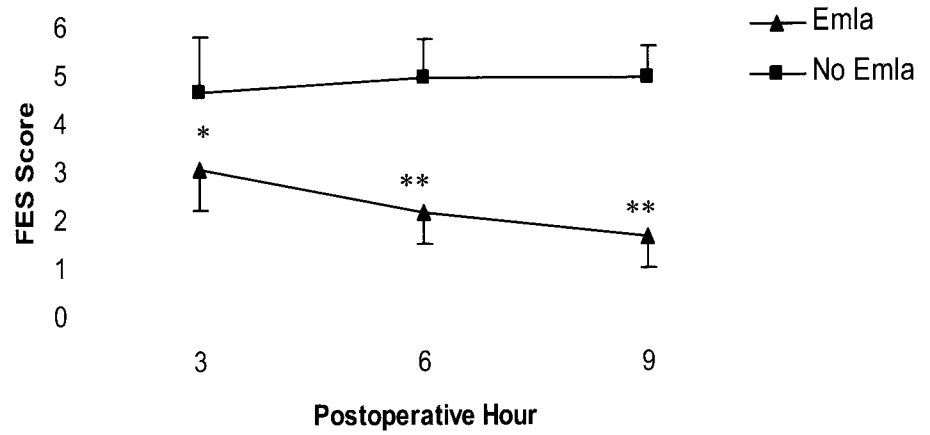


Fig. 4. ***Mean±SD of FES for children.***
** p<0.05; ** p<0.01; Mann-Whitney test, treated group versus control group. A comparison of the means indicated a statistically significant difference between treated patients and the control group at each time point (Mann-Whitney test, p<0.05 at the third hour and p<0.01 at both the sixth and ninth hours) with a statistically significant reduction in pain intensity (Wilcoxon test, p<0.001) over the observation time in the treated group.*

Table I . *The distribution of patients by age and sex in all groups considered.*

		Adults		Children	
		Emla (n=35)	**No Emla** (n=35)	**Emla** (n=10)	**No Emla** (n=10)
Age (mean±SD)		26.91±7.36	27.09±7.40	7.50±3.10	8.70±2.45
Sex n (%)	Male	17 (48.6)	18 (51.4)	4 (50.0)	4 (50.0)
	Female	18 (51.4)	17 (48.6)	6 (50.0)	6 (50.0)

Table II . *The distribution of patients that requested analgesic therapy.*
Nine adults, (5 males and 4 females) and 4 children (2 males and 2 females requested analgesics in the postoperative period. It is evident that treatment with Emla prevents the necessity of administering additional analgesics.

		Adults		Children	
		Emla (n=35)	**No Emla** (n=35)	**Emla** (n=10)	**No Emla** (n=10)
Sex n (%)	Male	0	**5** (14.3)	0	**2** (20)
	Female	0	**4** (11.4)	0	**2** (20)

indicated by the treated group at the first registration, and with the progression of the postoperative period, pain increased (Fig. 1B, 2B). Moreover, of the control group, 25.7% of adults and 40.0% of children asked for an analgesic therapy whereas this therapy was not requested by any of the treated patients. This data confirms, even if indirectly, the effectiveness of the postoperative treatment effectuated and explains how at the ninth hour the intensity of pain was significantly reduced with respect to the preceding observations. Moreover, excluding those patients that had assumed the analgesic, the modification of pain in time did not vary. The diversity between the results in our experience and those in literature could be due to the pharmacological characteristics of the preparations used or to the diverse modality of application.

In the literature, many studies have been conducted on the treatment of post-tonsillectomy pain through the local use of anesthetic, not injected, in the tonsillar region immediately before or after the removal of tonsils, or sprayed or otherwise applied in the compartment only after the surgical procedure. In all cases it has been observed that this did not significantly improve the control of postoperative pain (14). In the other studies, in fact, generally only one type of anesthetic (bupivacaine or lidocaine), and not an association, was used.

Bupivacaine is characterized by a long-lasting effects (120-300 minutes for a dosage of 2.5 mg/Kg) but a slow action time. Lidocaine has a rapid action time but a brief duration (30-60 minutes for a dosage rate of 7 mg/kg if used with adrenaline). These two drugs have never been used together in any previous study. In our study, we used an association of lidocaine and prilocaine that presents a longer action time than lidocaine alone and a duration slightly inferior to that of bupivacaine alone (60-240 minutes for a dose of 2 gr).

In some studies the anesthetic was sprayed into the tonsillar region at the end of operation, and this probably determined a dispersion and consequently the reduction of local anesthetic concentration (14). In other studies the anesthetic was injected into the compartment before the removal of tonsils (17, 21) or at the end of the operation (14, 22). In the first case, the rich vascularization of the tonsillar region

could have favored the rapid displacement of the drug through the vessel network with a consequent reduction of local concentration. In the second case, the slowness of bupivacaine action, the only one experimented in literature, would not permit the inhibition of the wind-up phenomenon with subsequent postoperative hyperalgesia.

In our study we used EMLA cream applied to the tonsillar compartment, in direct contact with the muscular fascia, after tonsillectomy. This permitted the anesthetics to penetrate without causing excessive modifications of their concentration. The pharmacological characteristics and the application method used in our study definitely permitted a rapid action on the genesis of postoperative pain. The association of lidocaine and prilocaine, taking into consideration action time and the diverse duration of these drugs, permitted us to achieve a winning "combination" against postoperative pain. Moreover, the reduction of pain in the first hours favors the precocious recovery of muscular activity. This phenomenon is translated in a rapid removal by the lymphatic pathway of degradation products and of phlogistic neurotransmitters that are at the basis of postoperative pain. This explains the velocity of pain reduction verified at the 6^{th} and 9^{th} hour (Fig. 3, 4).

In conclusion, on the basis of our experience, the application of EMLA in the compartment after tonsillectomy, determined an extremely significant reduction of postoperative pain, either as absolute intensity or duration of pain. In fact, in all patients a significant difference in the intensity of pain was observed between the treated patients and the control group. These differences increased in the subsequent registration, such that in the treated group a progressive reduction of pain was observed whereas in the group not treated pain tended to increase in the post-operative period. This resulted in greater patient comfort and a reduction of economic and biological postoperative costs. In fact, better tolerability of postoperative pain reduces the request of analgesic drugs, which on one hand increases health care costs, while on the other can be the cause of allergic and metabolic collateral effects.

REFERENCES

1. **Blair R.L., W.S. McKerrow, N.W. Carter et al.** 1996. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J. Laryngol. Otol. 20:1.*
2. **W. Colburn and R. Muglani.** 2003. Central and peripheral components of neuropathic pain. In *Pain.* William K. Schmidt, Chas Bountra, Rajesh Munglani, Marcel Dekker Inc., New York, p. 45.
3. **Raja S.N., R.A. Meyer and S.N. Campbell.** 1984. Evidence for different mechanism of primary and secondary hyperalgesia. *Brain 107:1179.*
4. **Hardy J.D.** 1950. Cutaneous hyperalgesia. *J. Clin. Invest. 29:115.*
5. **Raja S.N., R.A. Meyer and S.N. Campbell.** 1988. Peripheral mechanism of somatic pain. *Anesthesiology 68:571.*
6. **Donovan I.A. and J. Alexander-Williams.** 1976. Postoperative gastric retention and delayed gastric emptying. *Surg. Clin. North Am. 56:1413.*
7. **Garcia-Frade L.J.** 1987. Changes in fibrinolysis in the intensive care patient. *Thromb. Res. 47:593.*
8. **Kehlet H.** 1982. Influence of anesthesia and surgery on immunocompetence. *Reg. Anesth. 7:68.*
9. **Cousins M.J.** 1989. Acute pain injury response: immediate and prolonged effects. *Regional Anaesthesia 14:162.*
10. **Pollock R.E.** 1991. Mechanism of surgical stress impairment of human perioperative natural killer cell cytoxicity. *Arch. Surg. 126:3.*
11. **Rawal N., U. Sjostrand, E. Christoffersson, B. Dahlstrom, A. Arvill and H. Rydman.** 1984. Comparison of intramuscular and epidural morphine for postoperative analgesia in grossly obese. Influence of postoperative ambulation and pulmonary function. *Anesth. Analg. 63:583.*
12. **Krishna P., M.J. La Page, L.F. Hughes and S.Y. Lin.** 2004. Current practice patterns in tonsillectomy and perioperative care. *Int. J. Ped. Otorhinolaryngology 68:779.*
13. **Nikanne E., H. Kokki, J. Salo and T.J. Linna.** 2005. Celecoxib and ketoprofen for pain management during tonsillectomy: A placebo-controlled clinical trial. *Otolaryngology - Head and Neck Surgery 132:287.*
14. **Hollis L.J., M.J. Burton and J.M. Millar.** 2000. Perioperative local anaesthesia for reducing pain following tonsillectomy.

Cochrane Database of Systematic Reviews Issue 4 art. No. CD001874.

15. **Dixon J.S.** 1986. Ageement between horizontal and vertical visual analogue scale. *Br. J. Rheumatol. 24:415.*
16. **Kabn E.A.** 1966. On facial expression. *Clin. Neurosurg. 12:9.*
17. **Le Resche L. and S.F. Dworkin.** 1984. Facial expression accompanying pain. *Soc. Sci. Med. 19:1325.*
18. **Le Resche L.** 1982. Facial expression in pain: a study of candid photographs. *J. Non Verbal Behav. 7:46.*
19. **Merkey H., D.G. Albe-fessard and J.J. Bonica.** 1979. Pain Terms: a list with definitions and notes on usage. *Pain 6:249.*
20. **Helgadóttir H.L. and M.E. Wilson.** 2004. Temperament and pain in 3 to 7-year-old children undergoing tonsillectomy. *Journal of Pediatric Nursing 19:204.*
21. **Kountakis S.E.** 2002. Effectiveness of perioperative bupivacaine infiltration in tonsillectomy patients. *Am. J. Otolaryngol. 23:76.*
22. **Hung T., V. Moore-Gillon, J. Hern, A. Hinton and N. Patel.** 2002. Topical bupivacaine in pediatric day-case tonsillectomy: a prospective randomized controlled trial. *J. Laryngol Otol. 116:33.*