COMPARISON OF THE EFFECTIVENESS OF ETIDOCAINE AND LIDOCAINE AS LOCAL ANESTHETIC AGENTS DURING ORAL SURGERY

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SUMMARY

In a double-blind study conducted in 112 patients undergoing removal of four impacted third molar teeth, etidocaine hydrochloride 1.5% solution with epinephrine 1:200,000 and lidocaine hydrochloride 2.0% solution with epinephrine 1:100,000 were used, one on each side of the face, to produce inferior alveolar nerve block, infiltration anesthesia of the maxillary tooth and hemostasis of the mucoperiosteum around each tooth.

Surgically adequate anesthesia was rapidly produced by both agents but the duration of action of etidocaine was longer than that of lidocaine as reflected in more prolonged numbness of the lip and delayed onset of pain. Moreover, after etidocaine treatment fewer patients reported severe pain as the local anesthesia receded. No adverse local or systemic effects were observed in, or reported by, any of the patients.

Etidocaine is a local anesthetic agent that is both chemically and pharmacologically related to lidocaine but has a longer duration of action.[1-5] It has found rather wide use in medical anesthesia, being used for percutaneous blocks, with maximum single doses for regional anesthesia not exceeding 400 mg. Under similar conditions of use the anesthesia produced by etidocaine exhibits generally faster onset but similar duration to that of bupivacaine, while the motor block with etidocaine is relatively more profound. Etidocaine also produces long retrobulbar blocks. We are not aware of studies in which etidocaine has been compared with another long acting anesthetic solution in dentistry or oral surgery.

While the possible uses of etidocaine in dental practice have not been extensively studied,[2,3] the drug may prove useful in oral, maxillofacial and periodontal surgical procedures following which postoperative discomfort would be alleviated by longer postsurgical analgesia. At present there are only two published studies on the dental use of etidocaine; both studies involved third molar removal. In these studies treatment with etidocaine 1% solution with epinephrine 1:200,000 produced more prolonged postsurgical analgesia than treatment with lidocaine 2% solution with epinephrine 1:100,000.[2,3]

In order to determine whether the use of an even higher concentration of etidocaine would offer some advantages, we conducted a similar study using etidocaine 1.5% solution with epinephrine 1:200,000. Our study was conducted in otherwise healthy men and women who required the removal of four third molar teeth and was designed specifically to allow a comparison of etidocaine and lidocaine with respect to the frequency of surgical anesthesia, the duration of postsurgical anesthesia, and the incidence, type and severity of adverse experiences.

METHODS

Experimental Design

This was a double-blind study in which each subject underwent oral surgery to remove all four third molar teeth during the same session. Each

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subject served as his/her own control, with etidocaine used as the local anesthetic agent on one side and lidocaine used on the opposite side. The conduct of this study was approved by the Institutional Review Committee of Florida Hospital, Orlando, Florida.

Subjects

The study was conducted on 112 subjects. They consisted of 49 men, 15-28 years of age, and 63 non-pregnant women, 15-27 years of age. All subjects were generally in good medical and dental health with no history of previous adverse experience following the use of local anesthetic drugs. Patients with a concurrent disease in an active stage were excluded from the study. The nature of the study and possible discomforts and risks were explained to each subject and a written statement of informed consent was signed by each patient or his or her guardian.

Procedures and Observations

The patients were given suitable intravenous preanesthetic medication, generally consisting of scopolamine (0.3 mg i.v.), diazepam (10-20 mg i.v.) and methohexital (10-118 mg i.v.). Anesthesia was induced by using coded cartridges to produce inferior alveolar nerve block, anesthesia of the long buccal nerve and hemostasis of the mucoperiosteal tissues surrounding the mandibular tooth and for anesthesia and hemostasis of the maxillary tooth and surrounding tissue. Following premedication and at the time of administration of the local anesthetic solutions, all patients were sedated but retained intact reflexes and were responsive to voice commands. The severity and frequency of aversion responses upon injection of the local anesthetic solutions did not appear different in this group from responses expected in similar but unsedated patients. Thus, there was no reason to believe that the premedications compromised the observer's ability to compare the two drugs in terms of the patients' responses to the injections.

For each patient, two coded packages of cartridges were prepared*, one containing five cartridges of the "experimental" solution, the other containing five cartridges of the "control" solution. The "experimental" 1.8 ml cartridge contained etidocaine hydrochloride 1.5% solution with epinephrine 1:200,000 and the "control" cartridges were of the same volume and contained lidocaine hydrochloride 2.0% with epinephrine 1:100,000. The packages were labeled for each patient by number, one package labeled for use for the patient's right side and the other labeled for the left side. The packages were coded so as to randomize use of the experimental drug between the two sides.

Anesthesia was produced in the following manner: An inferior alveolar nerve block injection was made using 1.8 ml of solution. If the patient did not feel paresthesia of the lower lip within five minutes after the first injection, another 1.8 ml of the same solution was injected in order to effect a block of the inferior alveolar nerve. When paresthesia of the lower lip developed, hemostasis and anesthesia of the buccal mucosae were produced by injecting 0.5 ml of similar anesthetic solution from a previously unused cartridge.

During the study each patient was attended constantly and observed for objective and subjective evidence of local anesthetic-related adverse conditions, such as nervousness, dizziness, tremors, blurred vision, or other indications of possible effects of local anesthetics upon the central nervous system.

TABLE 1. A Comparison of the Quality of Local Anesthesia During Oral Surgery

Drug	Number of Injections	Mandibular Block		Maxillary Infiltration	
		Number of Patients	Slight Intra-Operative Pain	Number of Patients	Slight Intra-Operative Pain
Lidocaine	1	80	none	112	6 cases
	2	32	5 cases	0	—
	3	0	—	0	—
Etidocaine	1	74	none	112	5 cases
	2	38	4 cases	0	—
	3	0	—	0	—

RESULTS

Local Anesthesia

The quality of the anesthesia produced by the two agents at the time of surgery is summarized in Table 1. Of the 112 subjects, satisfactory inferior alveolar block was produced by a single injection of lidocaine in 80 cases while 32 subjects required a second injection; none required additional inferior alveolar nerve block injections. There was slight intra-operative pain in five of the 32 cases even after the second injection. In six cases there was slight intra-operative pain during extraction of the maxillary tooth. Similar results were obtained with etidocaine, where single injections produced satisfactory mandibular blocks in 74 cases and where intra-operative pain occurred in five cases during maxillary tooth extraction. Thus, the qualities of anesthesia produced by the two drugs were remarkably similar.

Nature of the Surgery

Surgery was started between 3 and 18 minutes after the start of the local anesthetic injections; the mean time interval (± S.E.) was 6.9 ± 0.3 minutes. The mean duration of surgery was 10.8 ± 0.4 minutes. Degree of impaction ranged from complete bone impaction to fully erupted teeth. Removal of the teeth was performed using standard procedures. When the lidocaine-treated side and the etidocaine-treated side were compared, there were no differences in operative techniques employed or in degree of difficulty of the procedures.

Postoperative Analgesic Agents

After surgery each patient was given prescriptions for Mepergan Fortis Capsules® (meperidine 50 mg and promethazine 25 mg) to be used for severe pain, and for mild pain either Darvocet-N® 100 tablets (propoxyphene napsylate 100 mg and acetaminophen 650 mg) or Phenaphen® with codeine #3, and was instructed to complete and return a Patient Report Sheet on which he/she was to indicate hourly the status of lower lip numbness (right and left side), amount of pain (right and left side) and whether analgesic medication had been ingested. Lip numbness was assessed by the patient as being "none", "partial", or "complete", and pain being "none", "light", "moderate", or "severe".

Of the 112 subjects, 98 subjects submitted reports on their analgesic use, and 96 of these took from one to ten doses of analgesic agents over the first fifteen hours after surgery.

Postoperative Numbness of the Lip and Pain

With respect to numbness of the lower lip, the mean (± S.E.) time at which numbness was reduced from "complete" to "partial" in 94 subjects with complete data was 3.0 ± 0.1 hours on the lidocaine-treated side and 5.9 ± 0.2 hours on the etidocaine-treated side (Table 2); these values are statistically different ($p<0.0001$, paired t-test). The mean times for reduction from "partial" numbness to "none" in 97 subjects were 5.1 ± 0.3 and 9.9 ± 0.3 hours, respectively; these values were also significantly different ($p<0.001$, paired t-test). The durations of numbness were not different in the subgroups receiving one and two injections of either agent.

The mean times of onset of postoperative pain in those patients given one inferior alveolar nerve block injection was not different from the time in those patients given two injections, regardless of the drug used. For the combined 89 patients for whom complete data were available, the mean duration of painlessness for the lidocaine-treated side of the face was 2.8 ± 0.2 hours and for the etidocaine-treated side was 4.6 ± 0.4 hours. These values were significantly different ($p < 0.0001$, paired t-test).

TABLE 2. A Comparison of the Duration of Numbness of the Lower Lip and Times of Onset of Postoperative Pain

Parameter	Number of Patients	Mean (± S.E.) Time After Treatment (hr)	
		Lidocaine-treatment	Etidocaine-treatment
Reduction in lower lip numbness			
From "complete" to "partial"	94	3.0 ± 0.1	5.9 ± 0.2 (P<0.001*)
From "partial" to "none"	97	5.1 ± 0.3	9.9 ± 0.3 (P<0.001*)
Onset of pain	89	2.8 ± 0.2	4.6 ± 0.4 (P<0.001*)

*Paired t-test

The intensity of postoperative pain as assessed hourly by the patient was graded as 0 = none, 1 = light, 2 = moderate and 3 = severe. Figure 1 shows a plot of the percent of patients reporting various degrees of pain on the lidocaine-injected side at various times after surgery and a similar plot of intensity on the etidocaine-treated side. As can be seen, the majority of patients were free of pain one hour after surgery but, with time, pain returned and it returned earlier on the lidocaine-treated side than on the etidocaine-treated side. The longest duration of painlessness after lidocaine treatment was about three hours but after etidocaine it was about nine hours.

Adverse Experiences

None of the 112 subjects developed episodes of fainting, vomiting, changes in skin color, or intra-operative excessive bleeding. In addition, no nausea, dizziness, or syncope was reported.

DISCUSSION

This study compared the use in oral surgery of two different formulations of local anesthetic agents — lidocaine hydrochloride 2% solution with epinephrine 1:100,000 and etidocaine hydrochloride 1.5% solution with epinephrine 1:200,000. The first drug formulation is widely used in dentistry, and the second is relatively new but has the potential to produce long-lasting postoperative pain relief because, in a variety of situations, the duration of the local anesthetic effect of etidocaine is markedly longer than that of lidocaine[1,4,5].

An important feature of the present study was the use of both formulations simultaneously in the same patient during the removal of four third molars, with one formulation employed on each side of the face. This has the advantage that it minimizes intersubject variability, allowing a more precise comparison of the two formulations.

These experiments have shown that the two formulations of local anesthetic agents produce equivalent surgical anesthesia but that the duration of local anesthetic effect is much longer after an injection of etidocaine 1.5% solution with epinephrine 1:200,000. With respect to efficacy of local anesthesia, it was found that among the 112 subjects the nature of the surgery on the lidocaine-treated side was not different from that on the etidocaine-treated side, as judged from the degree of impaction, the nature of the operative techniques employed for tooth removal and the difficulty of the procedure.

Accordingly, each patient experienced roughly equivalent trauma on each side of the face. Similarly effective local anesthesia also resulted from use of the two formulations: 80 of the 112 patients experienced successful anesthesia after only one injection of lidocaine and 74 after only one injection of etidocaine. Two injections were required for successful anesthesia in 32 areas receiving lidocaine and 38 receiving etidocaine. In no case was a third injection needed. Thus the formulations were equieffective under the conditions of this study.

In a study such as this it is difficult precisely to define and measure the duration of action of the local anesthetic agents, but two kinds of observations are generally used for this purpose. These are (1) the duration of postoperative lip numbness and (2) the duration of postoperative painlessness (i.e., the time to the onset of postoperative pain). In this regard the present study has shown also that the duration of action of the etidocaine formulation was much longer than that of the lidocaine formulation. Specifically, there was more prolonged numbness of the lower lip on the etidocaine-injected side and more prolonged postoperative painlessness. The mean duration of the lower lip numbness was 9.9 hours after etidocaine treatment and only 5.1 hours after lidocaine treatment, a difference of almost five hours. Similar differences were also seen in the duration of postoperative pain relief. The mean time to first perception of postoperative pain was 4.6 hours on the etidocaine-treated side and 2.8 hours on the lidocaine-treated side, a difference of almost two hours.

With respect to the duration of action it should be appreciated, however, that the pain-free interval between injection and the first perception of postoperative pain does not represent, in fact, the total duration of local anesthetic action of the injected agents. It measures only one aspect of pain relief: that is, the time until the drug effect regresses sufficiently for traumatized tissue to be perceived as painful. In fact, the effect of the drug should persist, albeit reduced, and should provide partial pain relief for some time. Measuring only the pain-free period clearly underestimates the ability of agents to provide relief from pain.

In order to better evaluate the postoperative pain relief, we had our subjects grade the intensity of their pain each hour for 15 hours. From their reports we prepared Figure 1 which allows a more complete assessment of the duration of action of the two formulations. The upper part of the figure shows that postoperative pain developed rapidly on the lidocaine-treated side of the face and that after three hours no further patients report the development of pain. Thus,

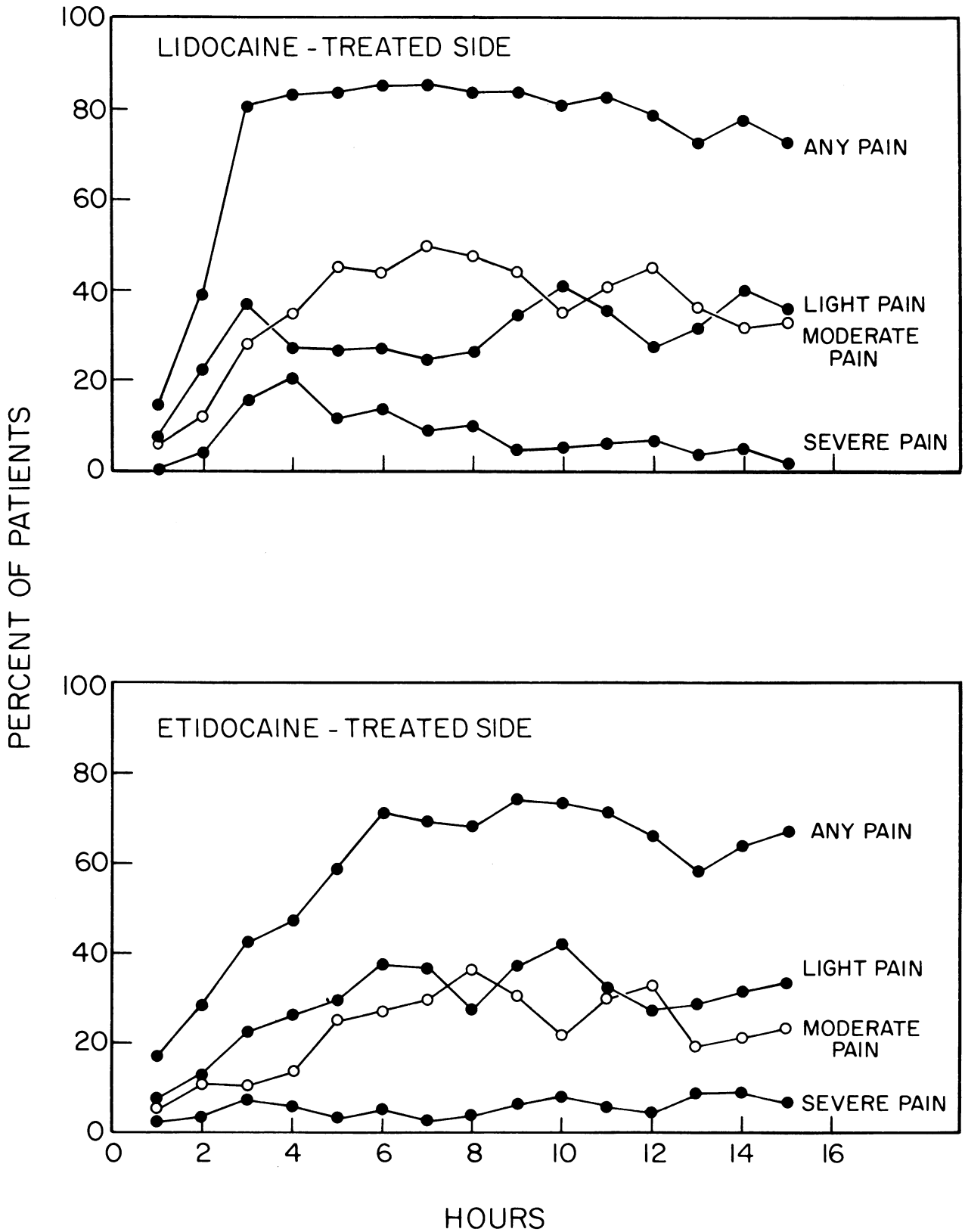

FIG. 1—The incidence of pain after two third-molar extractions on the side of the face injected with lidocaine 2% solution with epinephrine 1:100,000 and two third-molar extractions on the side of the face injected with etidocaine 1.5% solution with epinephrine 1:200,000. The ordinates represent the time after surgery, and the abscissae represent the percent of patients reporting severe pain, moderate pain or light pain. The "any pain" line represents the total numbers of patients who reported pain. The patients who reported no pain are not represented here.

the duration of perceptible pain relief in this patient population was equal to, or only slightly less than, three hours.

The duration of action of the etidocaine formulation can be estimated similarly from the bottom of Figure 1. In this case the number of patients experiencing pain becomes maximum much later than that of the lidocaine formulation, the difference in time being about six hours or three times the length of the lidocaine induced pain-free period. Accordingly, it can be concluded that etidocaine 1.5% solution with epinephrine 1:200,000 produced a longer period of absolute pain relief (4.6 hr vs. 2.8 hr) and a longer total duration of combined complete and partial pain relief (about 9 hr vs. about 3 hr) than lidocaine 2% solution with epinephrine 1:100,000.

In addition to differences in duration of action, Figure 1 also reveals one other difference between the two formulations which seems particularly important. This is the much greater protection against severe postoperative pain provided by treatment with the etidocaine formulation. As can be seen in the figure, the highest incidence of "severe pain" on the lidocaine-treated side was 21%, reported four hours after treatment, while the incidence of "severe pain" on the etidocaine-treated side varied between 3 and 10% over the same period of time. Since it is particularly desirable to reduce the incidence of severe pain and since the effect lasted several hours, this is a particularly striking advantage of treatment with the etidocaine formulation.

Finally, it should be stressed that in this study the use of the local anesthetic agents was free of adverse effects. No adverse local or systemic effects were observed in, or reported by, any of the 112 patients. Thus, both lidocaine 2% solution with epinephrine 1:100,000 and etidocaine 1.5% solution with epinephrine 1:200,000 were used effectively and safely for oral surgery involving the extraction of third molars with the latter formulation providing considerably longer postoperative relief of pain in general and of severe pain in particular.

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