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Topical Anesthesia with Lidocaine Aerosol in the Control of Postoperative Pain

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Postoperative pain was assessed in patients undergoing inguinal hernia repair. Ten patients received lidocaine aerosol in the surgical wound before skin closure, ten patients received placebo aerosol devoid of lidocaine, and ten patients were untreated. The lidocaine-treated group had significantly lower pain scores and meperidine requirements during the first postoperative day compared to the control groups. During the second day after surgery, these variables did not differ between groups. Wound anesthesia, assessed by palpation of the wound 24 h after surgery by a blinded investigator, was significantly more pronounced in the group treated with lidocaine aerosol than in the control groups. Similarly, in patients undergoing bilateral herniorraphy, wound pain following palpation was significantly reduced on the lidocaine-treated side compared to the untreated side. Patients in the group receiving lidocaine aerosol indicated less pain in connection with mobilization than untreated patients, but not compared to patients treated with placebo aerosol. Plasma substance P (SP) and beta-endorphin (BE) measured in lidocaine-treated patients and in untreated patients before and after drug administration showed no significant differences regarding SP, while BE was significantly increased 1 h after surgery in the untreated group. Plasma lidocaine concentrations were well below toxic levels. Results show that lidocaine aerosol used as topical anesthetic in the surgical wound is simple to use, and results in a long-lasting reduction of pain after a single administration. Moreover, postoperative mobilization is facilitated, and the requirement for postoperative analgesics is reduced. Wound healing was normal, and no adverse reactions to lidocaine were reported. (Key words: Analgesics: meperidine. Anesthetics, local: lidocaine. Anesthetic techniques: topical. Pain: postoperative. Surgery: herniorraphy. Endorphins. Substance P.)

PAIN AFTER INGUINAL HERNIA repair is mainly due to activation of cutaneous and subcutaneous receptors of afferent nerve fibers involved in the transmission of pain.[1–3] Patients often experience pain necessitating the use of opiate analgesics which may cause undesirable side effects. Furthermore, mobilization of the patient is restricted by pain from the surgical wound.

Several studies in patients undergoing herniorraphy have shown that local anesthetic-induced neural blockade is an effective and simple method of relieving postoperative pain without adverse reactions. Thus, implantation of polyethylene tubes in the surgical wound followed by injection of a local anesthetic[4–7] and infiltration of a long-acting anesthetic solution[8–10] have been shown previously to reduce postoperative pain. In the present study, lidocaine aerosol was used as topical anesthetic in the surgical wound in patients undergoing herniorraphy, and its effect on postoperative pain and mobilization was evaluated.

Materials and Methods

Thirty patients scheduled for elective inguinal hernia repair were investigated in a double-blind, randomized trial. Patients gave informed consent and the study was approved by the Regional Ethical Committee, University of Göteborg. Patients with hepatic, renal, cardiovascular disease or diabetes were excluded. Preanesthetic medication consisted of 20 mg phentiazine intramuscularly. Anesthesia was induced with thiopental (4 mg/kg). After the administration of 1 mg of pancuronium to prevent fasciculations, tracheal intubation was performed with the aid of succinylcholine (1 mg/kg). After intubation, 5 mg of pancuronium was given, with additional doses of 1 mg as indicated during surgery. Anesthesia was maintained with N_2O/O_2 and isoflurane. At the conclusion of surgery, 1 mg of atropine followed by 2.5 mg of neostigmine were administered to reverse neuromuscular blockade.

The patients were randomized into three groups. Hernia repair was carried out by different surgeons using the Shouldice technique.[11] After termination of the hernia repair, before skin closure, one group of patients (group A; n = 10) received 200 mg of lidocaine (100 mg lidocaine/ml, ASTRA) that was sprayed evenly on the cutaneous and subcutaneous surface of the surgical wound after carefully wiping the surface. In a second group (group B; n = 10), placebo aerosol with the same contents except for lidocaine was used while, in a third group (group C; n = 10), no aerosol was administered. Placebo and lidocaine aerosol solutions

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were blinded to the operating surgeons and all investigators by ASTRA. The untreated group was included in the study for comparison with the normal clinical situation. We were, however, unable to obtain an aerosol containing only saline for group C. In order to blind this group, a blinded surgeon, different from the operating surgeons, performed all follow-up of the patients after surgery. All staff at the postoperative ward were blinded to the patient groups.

A separate group of seven patients undergoing bilateral inguinal hernia repair were randomized to receive, double blindly, lidocaine aerosol on one side, the other side serving as untreated control. This part of the study aimed at evaluating postoperative wound anesthesia with patients serving as their own control.

A questionnaire concerning adverse reactions to lidocaine (lightheadedness, tinnitus, perioral numbness, drowsiness, and slurred speech) was answered by the patients on the morning of the first postoperative day. All the patients were evaluated during a 12-month period regarding wound healing. The first evaluation of the wound was performed 3 weeks after surgery, when a surgeon or a registered nurse examined the surgical area and interviewed the patients. Abnormalities, such as infection, hematoma, rupture, or abnormal inflammatory reaction in the wound were reported. Three months and 1 yr after surgery, the patients answered a questionnaire concerning wound healing.

Pain Assessment

Pain during the initial 48 h after surgery was assessed using a linear analogue pain scale ranging from 0 (no pain) to 100 (pain as bad as it could be).[12] Starting within 1 h after the return from the operating room, patients scored their pain at 2-h intervals during the first 12 h after surgery and at 4-h intervals during the remaining period of observation. No meperidine was administered before the first pain assessment. When patients complained of pain, they were given intramuscular injections of 50 mg meperidine until pain was relieved. Twenty-four hours after surgery, pain felt by the patient upon firm palpation of the surgical wound was evaluated on a linear pain scale ranging from 0 to 100. Wound palpation was performed in all patients by the same investigator, blinded to the patient groups. Moreover, patients were mobilized after 12–14 h and pain in connection with mobilization was recorded on a five-graded scale (1-no pain, 2-discomfort in the wound but no pain, 3-light pain, 4-moderate pain, 5-severe pain).

Plasma Concentrations of Lidocaine

Venous blood samples were drawn from all the groups in heparinized tubes 10 min, 30 min, 60 min, 90 min, and 24 h after closing the surgical wound. Samples were kept on ice until centrifugation, and plasma was kept frozen at −70° C until analysis. Plasma lidocaine concentrations were determined in the group of patients treated with lidocaine aerosol (n = 10) by mass-fragmentography[13] (ASTRA Research and Development Laboratories, Sweden). Sample-to-sample variation is less than 10%, and sensitivity of assay is 9 ng/ml plasma. Plasma levels of lidocaine are expressed as ng lidocaine/ml plasma.

Plasma Beta-endorphin and Substance P Levels

Venous blood was sampled from all the patients in pre-chilled tubes containing EDTA, 1 h before surgery and 1, 6, and 24 h after drug administration. Samples were analyzed in eight untreated patients and nine lidocaine aerosol-treated patients. Blood from one patient in the lidocaine group and two patients in the control group was discarded due to hemolysis in the tubes. Samples were stored at −70° C until analysis. Immunoreactive (IR) beta-endorphin was quantified using a N-terminally directed rabbit antiserum in a final dilution of 1:30,000. The detection limit was 1.9 pmol/l (0.19 fmol/tube). This antiserum has negligible cross-reactivity against beta-lipotropin, and the intra- and interassay coefficients of variation were below 8%.[14] Immunoreactive substance P (SP) was quantified using a rabbit antiserum (a kind gift from Dr. E. Brodin, Stockholm, Sweden) that has been described in detail previously.[15] The detection limit is 1 pmol/l (0.1 fmol/tube). SP-antiserum detects no known tachykinin besides SP.[15]

Bacteriological Examination

Samples for bacteriological analysis were obtained at random from ten bottles containing lidocaine aerosol that had been in use during a 6-month period. The bottles were stored at room temperature. The samples were cultured aerobically on blood agar plate and selective media for streptococci, staphylococci, and gram-negative enterobacteria. The plates were examined after 18 h at 37° C. The result was scored negative if there was no visible growth on agar.

Statistical Methods

Differences between groups were analyzed using the Wilcoxon rank sum test. Differences in pain scores in the group undergoing bilateral herniorraphy were analyzed using the Wilcoson signed-rank test. The estimated means of the accumulated pain scores during the first and second postoperative days were calculated in each patient, and the differences in means between the groups were analyzed using the Wilcoxon rank sum test. All data were unblinded and analyzed 1 yr after

TABLE 1. Personal and Clinical Data from 30 Patients Undergoing Unilateral Inguinal Hernia Repair under N_2O-O_2-isoflurane and Relaxant Anesthesia (Mean ± SEM)

	Placebo Aerosol	Lidocaine Aerosol	Untreated
Number of patients	10	10	10
Age (yr)	42 ± 4	49 ± 4	35 ± 4
Sex (male/female)	10/0	9/1	9/1
Weight (kg)	77 ± 3	73 ± 4	84 ± 4
Duration of surgery (min)	59 ± 7	60 ± 6	68 ± 4

inclusion of the last patient into the study. Data are expressed as mean ± SEM.

Results

The three groups of patients were comparable with regard to personal and clinical data (table 1). The estimated mean of the accumulated pain scores during the first 24 h after surgery was significantly lower in patients in group A (22 ± 2), treated with lidocaine aerosol, than in those in group B (37 ± 5) ($P < 0.05$) and group C (38 ± 5) ($P < 0.01$) (fig. 1). No significant differences were found between patients in group B and group C. Pain scores during the second postoperative day were not significantly different between group A (19 ± 4), group B (19 ± 4), and group C (19 ± 2).

The need for meperidine during the first day after surgery was significantly reduced in the lidocaine-treated group compared with the group receiving placebo aerosol ($P < 0.01$) and the untreated group ($P < 0.01$) (fig. 2). Meperidine requirements were not significantly different between the groups during the second day after surgery (fig. 2).

Wound tenderness upon palpation 24 h after surgery was significantly reduced in patients in group A compared with those in group B ($P < 0.05$) and group C ($P < 0.05$) (fig. 3). In the group of patients undergoing bilateral herniorraphy, a significantly more pronounced anesthesia in the surgical wound was found on the lidocaine-treated side ($P < 0.01$) (fig. 3).

The severity of pain experienced by the patients upon mobilization was significantly reduced in lidocaine-treated patients (group A) (2.5 ± 0.5) compared to those untreated (group C) (3.6 ± 0.2) ($P < 0.05$), but not compared to those receiving placebo (group B) (3.2 ± 0.5). The difference between group B and group C was not significant.

The follow-up of wound healing revealed one untreated patient with wound infection necessitating only skin revision. Wound healing was prolonged in this patient, but no late complications were found upon renewed inspection 3 weeks later. Normal wound healing was reported in all patients 3 months and 1 yr following surgery. No hernia recurrences were reported in any group 1 yr after surgery.

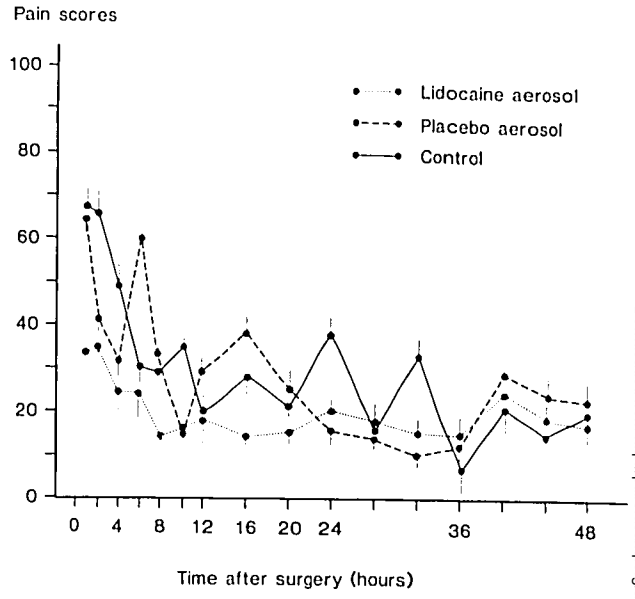

FIG. 1. Pain scores during 48 h after surgery in patients undergoing unilateral hernia repair and treated with lidocaine aerosol or placebo aerosol in the surgical wound and in untreated control patients.

Plasma lidocaine reached a steady-state level ranging between 150 and 166 ng/ml within 30 min after drug administration. Measurable plasma levels of lidocaine were obtained in several patients 24 h after administration of the aerosol (fig. 4).

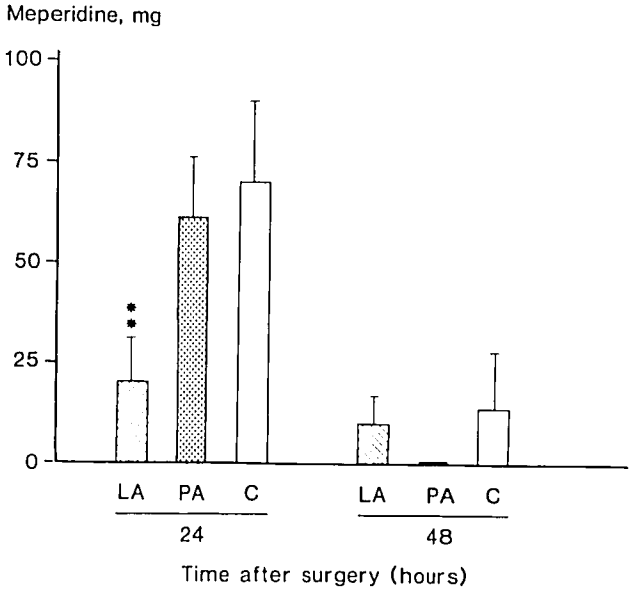

FIG. 2. Meperidine requirements during the first and second postoperative days in patients receiving lidocaine aerosol (LA) or placebo aerosol (PA) in the surgical wound and in untreated control patients (C). **$P < 0.01$ *versus* PA and C. Data are mean ± SEM.

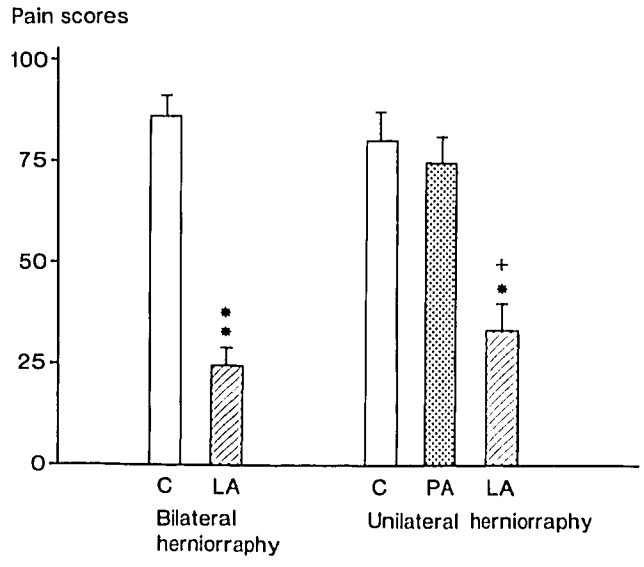

FIG. 3. Pain scores upon palpation of the surgical wound 24 h after surgery to evaluate wound anesthesia. LA = lidocaine aerosol; PA = placebo aerosol; C = untreated control. Left panel illustrates a group of seven patients undergoing bilateral herniorraphy and randomly treated with lidocaine aerosol on one side, the other side serving as untreated control. Significantly lower pain scores ($P < 0.01$) were indicated on the lidocaine-treated side. Right panel illustrates data from three groups of patients undergoing unilateral hernia repair and treated with LA, PA, or C. Pain scores were significantly reduced in the LA-treated group compared to PA ($P < 0.05$) and C ($P < 0.05$). Differences between C and PA were not significant. *$P < 0.05$, **$P < 0.01$ *versus* untreated controls (C), †$P < 0.05$ *versus* placebo aerosol (PA). Data are expressed as mean ± SEM.

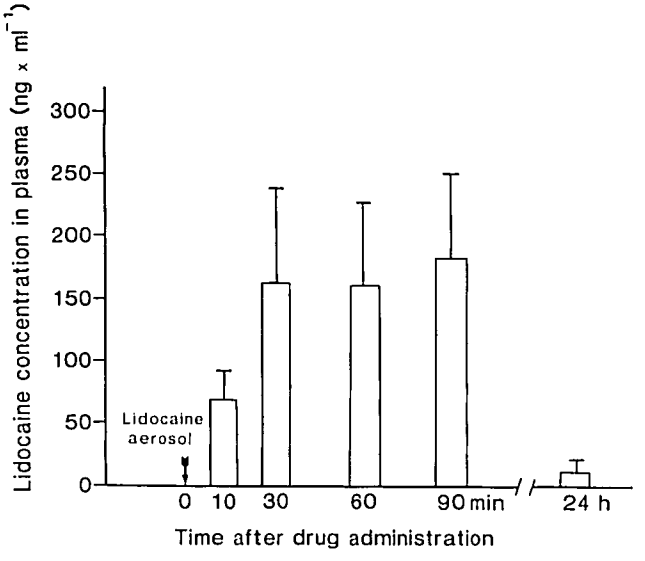

FIG. 4. Plasma lidocaine levels in ten patients treated with lidocaine aerosol (200 mg lidocaine) in the surgical incision following inguinal hernia repair. Plasma levels reached steady state after 30 min and were detectable up to 24 h after drug administration.

One hour after surgery, beta-endorphin levels were significantly increased in patients in the untreated group compared to lidocaine-treated patients. Six hours postoperatively, beta-endorphin concentrations had returned to preoperative levels (fig. 5). Plasma substance *P* levels showed no significant differences between the two groups (fig. 5).

The microbiological culture revealed no bacterial growth in any of the lidocaine aerosol solutions examined.

Discussion

The analgesia induced by topical lidocaine was surprisingly long lasting, taking into account that infiltration of lidocaine in intact tissue normally blocks nerve conduction for only about 1–3 h.[16] There may be several possible explanations for this long-lasting effect. Reduced venous outflow, capillary and venous stasis, and slowed capillary blood flow in the incisional area due to shunting or thrombosis of injured vessels[17] would all tend to reduce wash-out of the drug from the incisional area and, thus, prolong its effect.

Another possible explanation could be that lidocaine forms microdroplets with polyethyleneglycol (PEG 400) that act as slow-release units with ultra-long duration, a mechanism reminiscent of that recently shown in a study of lecithin-coated methoxyflurane microdroplets.[18] Such an interpretation is supported by the fact that plasma concentrations of lidocaine were measurable up to 24 h after administration of a single dose.

Another plausible explanation for the extended analgesic effect of lidocaine aerosol would be the potent anti-inflammatory actions that amide local anesthetics posses due to their structural similarity to steroid agents.[19] Trauma to the skin is known to cause release of potent inflammatory agents, such as histamine, serotonin, bradykinin, and prostaglandins (PG).[20] These agents act directly by activation of free nerve endings of pain afferent A-delta and C-fibers[21–23] and, indirectly, by sensitization of receptors to stimulation.[24] This inflammatory reaction in the area of surgery is probably responsible for the activation and maintenance of pain during several days after the mechanical trauma. The anti-inflammatory effect of amide local anesthetics is potent[25] and long lasting,[26] and can be mediated through several mechanisms. These include inhibition of the effects of PGs,[27] inhibition of the migration of leucocytes to the inflammatory area[28] and their activation,[29,30] inhibition of the release of lysosomal enzymes from leucocytes,[31] and reduction of vascular permeability.[32] Such effects would inhibit the release and actions of noxious inflammatory agents in the tissue, and prevent the initiation and maintenance of wound tenderness and pain.

Accumulated data support the hypothesis that the endorphin system is an important link in the endogenous control and perception of pain.[33] Increased plasma beta-endorphin levels due to surgery are effectively reduced by regional anesthesia.[34] Along with the inhibition of pain, our study showed a transient reduction of plasma beta-endorphin in the group treated with lidocaine aerosol.

There is strong evidence that substance P (SP) is localized in a great number of unmyelinated somatosensory neurones[35] and is involved in the transmission of sensory information from these afferent neurons to the CNS. Noxious stimuli will cause release of SP antidromically and elicit a local inflammatory reaction.[36] Intense stimulation of primary afferents will also cause release of SP in the CNS.[37] Surprisingly, plasma SP-levels were not elevated compared to pre-anesthetic values in any of the groups, possibly reflecting a magnitude of surgical trauma too small to induce sufficient release of SP locally.

In addition to lidocaine, lidocaine aerosol contains a number of other agents. PEG 400 is a clear, colorless, viscous liquid which is practically inert.[38] Cetylpyridine chloride (9.7 mg/100 g solution) is a cationic surface active agent with bactericidal effect on gram-positive and gram-negative bacteria.[39] It is used in the aerosol due to its emulsifying actions, and is known to have a relatively low systemic toxicity and no reported effects on nerve tissue.[40] The concentration of ethanol in the solution is 7.3 g/100 g solution (7.3%). Ethanol is used in this preparation to dissolve the lidocaine base. The concentration of alcohol needed to block conduction in peripheral nerves has previously been reported to be in the range of 5–10%,[41] *i.e.*, similar to the concentration used in the present aerosol solution. Besides blocking nerve conduction, alcohol also possesses anti-inflammatory properties.[42,43] This combined effect of alcohol may explain the tendency towards reduced pain in patients treated with placebo aerosol compared with untreated patients.

Previous investigators have used implantation of polyethylene catheters in the surgical wound in order to obtain long-lasting analgesia.[4–7] This technique allows repeated injections of a local anesthetic at regular intervals after surgery. However, implantation of a foreign body in the surgical wound may cause irritation and maintain the inflammatory reaction. Moreover, an increased risk for postoperative infections is apparent, as was demonstrated in a recent study.[44] The introduction of an agent into the surgical wound, *i.e.*, lidocaine, known to suppress leucocyte phagocytic activity[31] might also pose an increased risk for wound infections. On the other hand, the aerosol solution contains several potent bactericidal or bacteriostatic agents, such as cetylpyridine,[39] lidocaine,[45] and alcohol, that may also explain the negative results from the bacteriological examination of the bottles. In our study, no significant differences were observed regarding postoperative wound infections between the three groups, although the small number of patients do not allow conclusions to be drawn on this issue. The potent anti-inflammatory actions of lidocaine could also suppress wound healing in the postoperative period by interfering with the normal reparative process. However, the follow-up examinations do not lend support to such effects.

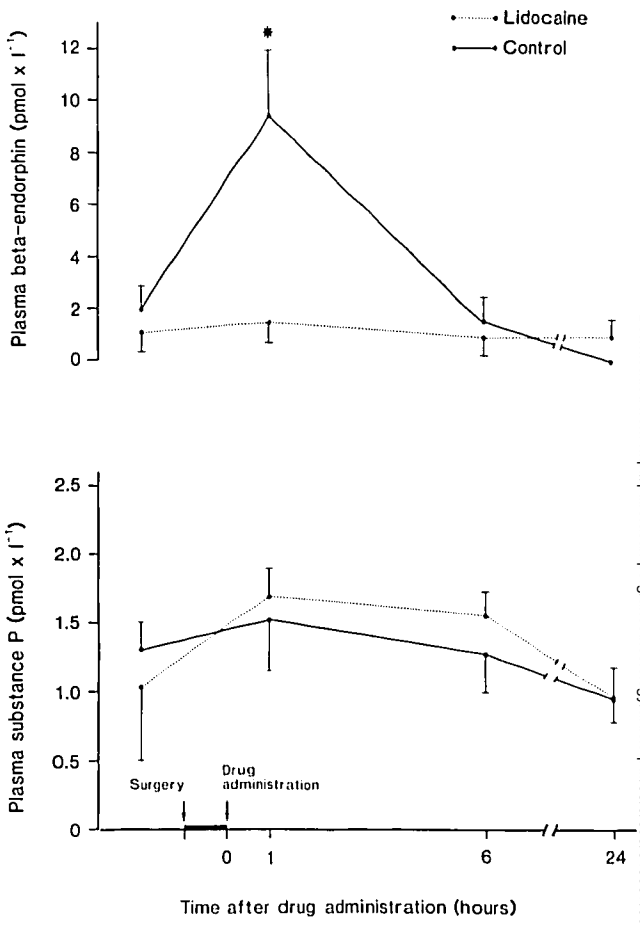

FIG. 5. Plasma beta-endorphin and substance P concentrations in patients undergoing unilateral herniorraphy and treated with lidocaine aerosol on the cutaneous and subcutaneous surface of the surgical wound and in untreated controls. $*P < 0.05$ *versus* control. Data are given as mean ± SEM.

Most local anesthetics can cause histological changes in skeletal muscle.[46] Muscle regeneration is, however, complete within 2 weeks following administration of the drug.[46] In this study, lidocaine was administered after closing the muscular fascia, and no complications related to muscle damage, such as hernia recurrence, were reported.

The possibility that the concentration of lidocaine used in the present solution may cause a long-lasting blockade of nerve conduction due to histopathological nerve changes must be considered. However, considerably higher concentrations than those used clinically are required.[47] In conclusion, the present aerosol technique is simple to use, does not require implantation of a foreign body in the wound, and results in a long-lasting reduction of pain after a single administration. Furthermore, postoperative mobilization is facilitated, and the requirement for potent analgesics is reduced. Wound healing was not affected, and no systemic adverse reactions to lidocaine were reported. The present results are valid in patients undergoing minor plastic surgery and skin surgery where activation of cutaneous and subcutaneous nociceptors dominate. It remains to be shown if topical wound anesthesia is equally effective in the control of postoperative pain in patients undergoing major surgery.

References

1. Iggo A: Cutaneous mechanoreceptors with afferent C-fibers. J Physiol (Lond) 152:337–353, 1960
2. Burgess PR, Perl ER: Cutaneous mechanoreceptors and nociceptors, Handbook of Sensory Physiology. Edited by Iggo A. Heidelberg, Springer Verlag, 1973, pp 29–78
3. Bessou P, Perl ER: Response of cutaneous sensory units with myelinated fibers to noxious stimuli. J Neurophysiol 32:1025–1043, 1969
4. Blades B, Ford WB: A method for the control of postoperative pain. Surg Gynecol Obstet 91:524–526, 1950
5. Hashemi K, Middleton MD: Subcutaneous bupivacaine for postoperative analgesia after herniorrhaphy. Ann R Coll Surg Engl 65:38–39, 1983
6. Thomas DFM, Lambert WG, Lloyd Williams K: The direct perfusion of surgical wounds with local anaesthetic solution: an approach to postoperative pain ? Ann R Coll Surg Engl 65:226–229, 1983
7. Levach ID, Robertson GS: The direct perfusion of surgical wounds with local anaesthetic solution. Ann R Coll Surg Engl 66:146, 1984
8. Owen H, Galloway DJ, Mitchell KG: Analgesia by wound infiltration after surgical excision of benign breast lumps. Ann R Coll Surg Engl 67:114–115, 1985
9. Moss G, Regal ME, Lichtig L: Reducing postoperative pain, narcotics, and length of hospitalization. Surgery 99:206–210, 1986
10. Kingsnorth AN, Wijesinha SS, Grixti CJ: Evaluation of dextran with local anaesthesia for short-stay inguinal herniorraphy. Ann R Coll Surg Engl 61:456–458, 1979
11. Glassow F: Inguinal hernia repair using local anaesthesia. Ann R Coll Surg Engl 66:382–387, 1984
12. Revill SI, Robinson JO, Rosen M, Hogg MI: The reliability of a linear analogue for evaluating pain. Anaesthesia 31:1191–1198, 1976
13. Hignite CE, Tschantz CH, Steiner J, Huffman DH, Arnoff DL: Quantitation of lidocaine and its de-ethylated metabolites in plasma and urine by gas chromatography-mass fragmentography. J Chromatogr 161:243–249, 1978
14. Brannert M, Ekman R, Larsson I, Thorell JI: Characterization and application of a radioimmunoassay for beta-endorphin using an antiserum with negligible crossreactivity against beta-lipotropin. Regul Pept 5:65–75, 1982
15. Brodin E, Lindefors N, Theodorsson-Norheim S, Peterson L, Bartfai T, Ögren S-O, Rossell S: Tachykinins in rat central nervous system: Distribution, molecular forms, release and effects of chronic treatment with antidepressant drugs, Tachykinin Agonists. Edited by Håkansson R, Sundler F. Amsterdam, Elsevier Science Publishers, 1985, pp 15–27
16. Covino BG, Vassallo HG: Local Anesthetics, Mechanisms of Action and Clinical Use. New York, Grune & Straton, 1976, pp 131–140
17. Zwefach BW: Microvascular aspects of tissue injury, Advances in Pain Research and Therapy, Vol. I. Edited by Bonica JJ, Albe-Fessard D. New York, Raven Press, 1976, pp 17–28
18. Haynes DH, Kirkpatrick AF: Ultra-long-duration local anesthesia produced by injection of lecithin-coated methoxyflurane microdroplets. ANESTHESIOLOGY 63:490–499, 1985
19. Seeman P: The membrane actions of anesthetics and tranquilizers. Pharmacol Rev 24:583–655, 1972
20. DiRosa M, Giroud JP, Willoughby DA: Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. J Pathol 104:15–29, 1971
21. Juan H: The pain enhancing effect of PGI_2. Agents Actions 6:204–212, 1979
22. Chahl LA, Iggo A: The effects of bradykinin and prostaglandin E_1 on rat cutaneous afferent nerve activity. Br J Pharmacol 59:343–347, 1977
23. Chahl LA: Pain induced by inflammatory mediators, Mechanisms of Pain and Analgesic Compounds. Edited by Beers Jr RF, Basset EG. New York, Raven Press, 1979, pp 273–284
24. Perl ER: Sensitization of nociceptors and its relation to sensation, Advances in Pain Research and Therapy, Vol. I. Edited by Bonica JJ, Albe-Fessard D. New York, Raven Press, 1976, pp 17–28
25. McGreggor RR, Thorner RE, Wright DM: Lidocaine inhibits granulocyte adherence and prevents delivery to inflammatory sites. Blood 56:203–209, 1980
26. Dickstein R, Kiremidjian-Schumacher L, Stotzky G: Effect of lidocaine on the function of immunocompetent cells. II. Chronic in vivo exposure and its effects on mouse lymphocyte activation and expression of immunity. Immunopharmacology 9:127–139, 1985
27. Horrobin DF, Manku MS: Roles of prostaglandins suggested by the agonist/antagonist actions of local anaesthetic, antiarrhythmic, anti-malarial, tricyclic anti-depressant and methyl xanthine compounds, effects on membranes and on nucleic acid function. Med Hypotheses 3:71–86, 1977
28. Hammer R, Dahlgren C, Stendahl O: Inhibition of human leucocyte metabolism and random motility by local anesthesia. Acta Anaesthesiol Scand 29:520–523, 1985
29. Cullen BF, Haschke RH: Local anesthetic inhibition of phagocytosis and metabolism of human leucocytes. ANESTHESIOLOGY 40:142–146, 1974
30. Sinclair R, Cassuto J, Thomsen P: Local anesthetics inhibit leucocyte activation induced by immune complexes and opsonized zymosan particles (abstract). Acta Anaesthesiol Scand (Suppl) 86:144, 1987
31. Goldstein IM, Lind S, Hoffstein S, Weissmann G: Influence of local anesthetics upon human polymorphonuclear leucocyte function in vitro. Reduction of lysosomal enzyme release and superoxide anion production. J Exp Med 146:483–494, 1977
32. Cassuto J, Rimbäck G, Sinclair R, Nellgård P, Wesstlander G: Inhibition of peritonitis by local anesthetics (abstract). Acta Anaesthesiol Scand (Suppl) 86:145, 1987

33. Hedner T, Cassuto J: Opioids and opioid receptors in peripheral tissues. Scand J Gastroenterol (Suppl) 130:27–46, 1987
34. Abboud TK, Noueihed R, Khoo S, Hoffman DI, Varakian L, Henriksen E, Goebbelsmann U: Effects of general and regional anesthesia for cesarian section on maternal β-endorphin levels. Am J Obstet Gynecol 146:927–930, 1983
35. Hökfelt T, Kellerth JO, Nilsson G, Pernow B: Experimental immunohistochemical studies on the localization and distribution of substance P in cat primary sensory neurons. Brain Res 100:235–252, 1975
36. Lembeck F, Holzer P: Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn Schmiedebergs Arch Pharmacol 310:175–183, 1979
37. Yaksh TL, Jessel TM, Gamse R, Mudge AW, Leeman SE: Intrathecal morphine inhibits substance P release from mammalian spinal cord in vivo. Nature 286:155–157, 1980
38. Swinyard EA, Pathak MA: Surface-acting drugs, The Pharmacological Basis of Therapeutics, 7th edition. Edited by Goodman Gilman A, Goodman LS, Rall TW, Murad F. New York, MacMillan, 1985, pp 959–979
39. Lawrence CA: Quarternary ammonium surface-active disinfectants, Disinfection, Sterilization and Preservation. Edited by Lawrence CA, Block SS. Philadelphia, Lea & Febiger, 1968, pp 430–452
40. Harvey SC: Antiseptics and disinfectants; fungoids; ectoparacides, The Pharmacological Basis of Therapeutics, 7th edition. Edited by Goodman Gilman A, Goodman LS, Rall TW, Murad F. New York, MacMillan, 1985, pp 959–979
41. Murdoch Ritchie J: The aliphatic alcoholos, The Pharmacological Basis of Therapeutics, 7th edition. Edited by Goodman Gilman A, Goodman LS, Rall TW, Murad F. New York, MacMillan, 1985, pp 372–386
42. Buckley RM, Ventura ES, MacGreggor RR: Propranolol antagonizes the anti-inflammatory effect of alcohol and improves survuval of infected intoxicated rabbits. J Clin Invest 62:554–559, 1978
43. Gluckman SJ, MacGreggor RR: Effect of acute alcohol intoxication on granulocyte mobilization and kinetics. Blood 52:551–559, 1978
44. Cameron AE, Cross FW: Pain and mobility after inguinal herniorraphy: Ineffectiveness of subcutaneous bupivacaine. Br J Surg 72:68–69, 1985
45. Schmidt RM, Rosenkrantz HS: Antimicrobial activity of local anesthetics: Lidocaine and procaine. J Infect Dis 121:597–607, 1970
46. Benoit PW, Belt WD: Some effects of local anesthetic agents on skeletal muscle. Exp Neurol 34:264–278, 1972
47. Adams HJ, Mastri AR, Eicholzer AW, Kilpatrick G: Morphologic effects of intrathecal etidocaine and tetracaine on the rabbit spinal cord. Anesth Analg 53:904–908, 1974