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Effect of Topical Local Anesthetic Application to Skin Harvest Sites for Pain Management in Burn Patients Undergoing Skin-Grafting Procedures

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Objective

To determine if topical administration of local anesthesia, applied to fresh skin-harvest sites, reduces pain and analgesic requirements after surgery.

Summary Background Data

Nonopioid treatments for pain after therapeutic procedures on patients with burns have become popular because of the side effects associated with narcotics. The topical administration of local anesthesia originally offered little advantage because of poor epidermal penetration.

Methods

This study compares 2% lidocaine with 0.5% bupivacaine or saline, topically applied after skin harvest, to determine what effect this may have on pain and narcotic use. Sixty patients with partial- or full-thickness burns to approximately 10% to 15% of their body were randomly divided into three groups: group 1 received normal saline, group 2 had 0.5% bupivacaine, and group 3 had 2% lidocaine sprayed onto areas immediately after skin harvest. Blood samples were subsequently obtained to measure concentrations of the local anesthetic. Hemodynamic variables after surgery, wake-up times, emetic symptoms, pain, and narcotic use were compared.

Results

Higher heart rates were noted in the placebo group than in those receiving lidocaine or bupivacaine. No differences were noted in recovery from anesthesia or emetic symptoms. Pain scores were lower and 24-hour narcotic use was less in patients who received lidocaine. Plasma lidocaine levels were greater than bupivacaine at all time points measured.

Conclusions

Topical lidocaine applied to skin-harvest sites produced an analgesic effect that reduced narcotic requirements compared with patients who received bupivacaine or placebo. Local anesthetic solutions aerosolized onto skin-harvest sites did not affect healing or produce toxic blood concentrations.

One of the major problems faced by patients during recovery from burn injury is the pain of repeated therapeutic procedures.[1] Pain from skin débridement and grafting procedures may be an important factor in the development of psychiatric disorders and depression, especially if control of pain is inadequate. The perception of pain from a given stimulus is influenced by numerous factors, including patient variability, ethnic background, socioeconomic class, previous life experiences, and support systems.[2] About 52% of patients report pain during burn wound débridements, whereas 84% describe extreme pain after therapeutic procedures.[2] The size and depth of the burn injury may also influence the amount of perceived pain.

Opioid administration is the dominant form of analgesic therapy in this patient population.[2] The pharmacokinetics of opioids are altered in patients with burn injury, both immediately after the event and for weeks to come because of changes in the volume of distribution, unbound drug fraction, clearance half-life, and sensitivity. In addition, opioid requirements may increase over time, may reach a ceiling effect, and may not be able to provide complete analgesia in

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all patients.[3] Other analgesic modalities have been tried in this patient population with minimal success. Both intravenous[4] and local injections of ketamine applied to the burn site[5] have been tried with minimal success as a means of reducing pain after burn wound débridements. Topical glucocorticoids,[6] preemptive nerve blocks,[7] and intravenous lidocaine infusions[8] have not been totally successful in reducing pain after therapeutic burn procedures.

The topical administration of local anesthetics to burn wounds has been previously studied as a method to reduce pain in thermal-injured patients.[9,10] However, because of poor skin penetration by local anesthetic mixtures such as lidocaine–prilocaine (EMLA) cream[10] or 0.5% bupivacaine,[9] no apparent advantage in reducing pain was noted after burn injury. No studies to date have examined the analgesic effect of the topical application of local anesthetics to areas where split-thickness skin grafts have been harvested or burn wounds débrided. Because the outer keratinized layers of skin have been removed before application of the local anesthetic, absorption into skin at these sites may be enhanced, producing a better analgesic effect.

This study compares the topical administration of a 2% lidocaine solution with that of a 0.5% bupivacaine or placebo solution, applied to areas immediately after skin harvest and débridement, to determine whether any beneficial effect on patient recovery, pain, and outcome is produced by this therapy. In addition, blood levels of the local anesthetic were measured to determine the amount of absorption from skin and whether this correlated with any beneficial effect.

METHODS

After approval by the Institutional Review Board for Patient Safety and after obtaining informed written consent, 60 patients with American Society of Anesthesiologists physical status 2 and 3 who had suffered deep partial- or full-thickness burns to approximately 15% of their body were admitted into the study. Patients ranged in age from 18 to 65 years. Patients were excluded from the study if they had severe systemic disease (*e.g.*, renal failure, congestive heart failure) or sepsis, if they were allergic to morphine, if they were pregnant, or if they could not give informed consent. Patients were fluid-resuscitated according to Parkland formula guidelines. All wounds were débrided on admission; burn size was documented and reverified 48 hours after admission. Topical wound care consisted of gauze dressings impregnated with silver sulfadiazine beginning at the time of admission. Excision of burn wounds and grafting procedures were performed under general anesthesia within 5 to 7 days of admission.

Patients were equally divided and randomly assigned by lottery to one of three groups. Group 1 patients, considered the control group, received a placebo composed of normal saline with 1:200,000 epinephrine, aerosolized onto areas where skin harvest had occurred. Group 2 patients received 0.5% bupivacaine with 1:200,000 epinephrine, again aerosolized onto areas of skin harvest. Group 3 patients had 2% lidocaine with 1:200,000 epinephrine sprayed onto skin-harvest areas. The topical application of bupivacaine 0.5% and EMLA cream (2.5% lidocaine and 2.5% prilocaine) to intact skin after burn injury, as a method of reducing pain, has previously been evaluated.[9,10] EMLA application to mucous membranes or open wounds is contraindicated because of the risk of prilocaine toxicity and subsequent methemoglobinemia.[11] Thus, aqueous 2% lidocaine was used instead of EMLA cream as the topical agent for group 3. Both the surgeon and the anesthesiologist involved in the surgical procedure were blinded to all study solutions.

On arrival in the operating room, standard monitors (electrocardiogram, noninvasive blood pressure, pulse oximetry, mass spectrometer, and temperature probe) were placed and used throughout the procedure. Arterial catheters were used for continuous blood-pressure monitoring and blood sample collection. Foley bladder catheters were used for urine collection throughout the procedure. Age, weight, and physical status were recorded along with heart rate (HR) and mean arterial pressure (MAP) when the patient entered the operating room. The severity of overall pain was assessed using a 100-mm visual analog scale (0 = minimal or no pain, 100 = maximal or the most severe pain the patient has ever had) to determine the baseline level of pain before the surgical procedure.

After a 5-minute preoxygenation period, general anesthesia was induced with thiopental (3 to 5 mg/kg) and fentanyl (2 μg/kg) given intravenously. Intubation was facilitated with intravenous vecuronium (0.1 mg/kg). Maintenance anesthesia consisted of isoflurane 0.5% to 2.0% end tidal concentration in a 50% N_2O/O_2 mixture, titrated to maintain HR and MAP to within 20% of preinduction values. During the course of the anesthetic, bradycardia and hypotension (decreases in HR and MAP to <80% of baseline values) were recorded and treated with intravenous ephedrine (5 mg/kg). Tachycardia and hypertension (HR and MAP >120% of baseline values) were treated with increasing concentrations of isoflurane or intravenous esmolol (5 mg).

Skin areas to be harvested were sterilely prepared using chlorhexidine gluconate. Autografts were harvested from donor sites using an air-powered surgical dermatome set at 0.009″ to 0.012″. Immediately after skin removal, the study solution was aerosolized onto the wound, which was then covered with a saline-dampened gauze to prevent excessive hemorrhage. Harvested autografts were either meshed two to one, before application, with a skin-graft mesher or were applied as sheets. The burn recipient site was prepared by serial excision to a viable tissue bed, as assessed by punctate bleeding, and removal of all nonviable tissue by excision to fascia for the deeper burns. All donor sites were treated with BCG-matrix (Brendan Medical, Minneapolis, MN) after skin harvest.

Donor-site complications were considered to be present when infection occurred or the donor site failed to heal, requiring subsequent skin grafting to achieve wound clo-

Table 1. DEMOGRAPHIC DATA COMPARED BETWEEN THREE DIFFERENT GROUPS

	Age (yrs)	Height (cm)	Weight (kg)	Study Solution Used (mL)	Burn Area %	Gender M/F	Anesthesia Time (min)	Surgery Time (min)
Placebo	32.4 ± 3.6	176 ± 3.0	78.7 ± 5.1	26.2 ± 4.7	10.3 ± 1.7	14/6	131.2 ± 14.3	77.7 ± 13.4
2% lidocaine	48.3 ± 3.8*	171 ± 2.0	82.7 ± 5.3	21.1 ± 4.8	8.1 ± 1.8	11/9	122.0 ± 14.8	80.3 ± 14.2
0.5% bupivacaine	43.6 ± 3.6*	172 ± 3.0	90.4 ± 5.1	30.5 ± 4.6	12.0 ± 1.7	14/6	154.3 ± 15.2	102.2 ± 13.4

All values expressed as mean ± SEM
*$p < 0.05$ when compared to placebo group.

sure. The time for donor-site healing was defined as the time necessary for the reepithelization of the harvest site and no further need for wound dressings.

At the completion of the surgical procedure, all patients were given 100% oxygen and neuromuscular blockade was reversed, if necessary, with neostigmine (70 μg/kg) and glycopyrrolate (0.15 mg/kg) given intravenously. When the patient was responsive with adequate respiratory parameters, the trachea was extubated and the patient was brought to the postanesthesia care unit (PACU) for evaluation. MAP, HR, and oxygenation were assessed every 10 minutes by a research nurse blinded to the study drug administered. Recovery from anesthesia was also determined using Steward recovery scores.[12] This system is based on a 6-point total score, with scores of 0, 1, or 2 assigned to each of three categories: motor activity, level of sedation, and ventilation.

Pain scores were also determined every 10 minutes while in the PACU and at 120 minutes and 6 and 12 hours after surgery. If pain scores exceeded 5, patients were given morphine (2 mg) intravenously every 5 minutes. This was repeated until pain scores dropped to <5 or the respiratory rate was <8. Total morphine administration was recorded every 10 minutes for the first 30 minutes, then at 30-minute intervals until 90 minutes after PACU admission. On discharge from the PACU, patients were given a patient-controlled analgesia (PCA) device, with total morphine use determined at 2, 4, 8, and 24 hours after surgery. PCA dosages were set at 1.5 mg per dose, with an 8-minute lockout time between doses. The total maximal dose over a 4-hour period was 40 mg.

Nausea and vomiting were also documented after surgery. If the patient retched or vomited twice after admission to the PACU, the vomiting was considered severe and intravenous metoclopramide (10 mg) was administered. The severity of nausea was again assessed using a visual analog system (0 = no nausea, 10 = the worst nausea ever experienced). These scores were obtained at the same time intervals used to assess pain, both in the PACU and over the next 24 hours.

Blood was collected before induction of anesthesia and at 5, 15, 30, 60, 90, 120, 180, 240, and 360 minutes after the initial application of the study drug for measurement of local anesthetic concentration.[13] Five milliliters of whole blood was placed in tubes containing sodium citrate and chilled until they were centrifuged for 15 minutes. Plasma was separated and placed into plastic tubes and frozen at −70°C until analysis. Plasma concentrations of either bupivacaine or lidocaine were assessed using high-performance liquid chromatography with a C_{18} reverse phase column (Alltech Associates, Deerfield, IL). After thawing, 1 ml of plasma was placed in a glass tube with 100 μl of etidocaine (40 μl/ml) and 1 ml of tetraborate buffer (pH 6.9). In addition, 6 ml of diethyl ether was added, and the solution was mixed thoroughly for 15 minutes and then centrifuged for 10 minutes at 2500 g. After centrifugation, the organic phase was transferred into a clean glass tube containing 500 μl of 0.2 N hydrochloric acid. This mixture was again shaken and centrifuged, and the diethyl ether organic phase was removed and added to 1 ml of tetraborate buffer. To this, 5 ml of extraction solvent was added. The organic solvent was removed and evaporated at ambient temperatures under a gentle stream of nitrogen. The residue was then reconstituted in 200 μl of mobile phase (25 mM phosphate buffer, pH 6.9, and acetonitrile 60:40), 50 μl of which was then injected into the high-performance liquid chromatograph using a programmable injector. Standard curves with known concentrations of local anesthetic were determined, and unknowns were compared against these standards. Sample concentrations are expressed in μg/ml.

Demographic data, along with anesthesia and surgical times, were compared using analysis of variance. Postsurgical hemodynamic data, Steward scores, pain scores, morphine use, and nausea scores were compared in like manner. The incidence of nausea and vomiting was compared among groups using chi square analysis. Plasma local anesthetic levels were compared within and between the groups at the different time points using independent t testing. All values are expressed as mean ± SEM with significance determined at $p \leq 0.05$.

RESULTS

Demographic variables were similar among the groups with the exception of age (Table 1). Total body burn surface

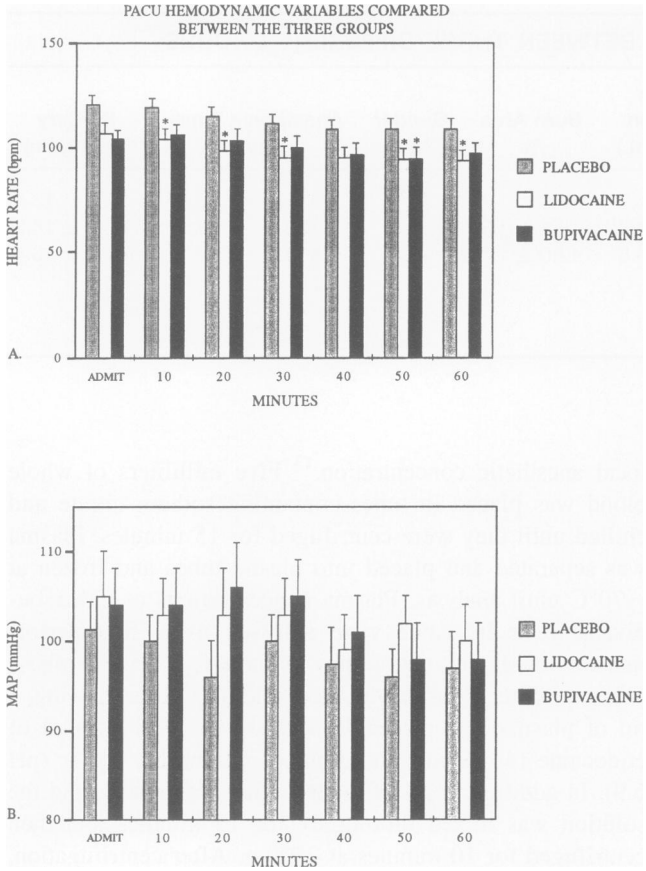

Figure 1. Postanesthesia care unit heart rates (A) and mean arterial pressures (B) during first 60 minutes of admission. *, significant difference ($p < 0.05$) *vs.* the placebo group. Values are expressed as mean ± SEM.

area, amount of study solution aerosolized, sex distribution, and physical status was also similar among the groups (see Table 1). Anesthesia and surgical times were not significantly different.

Hemodynamic data obtained during the PACU admission revealed appreciably higher heart rates in the placebo group than in the groups receiving either lidocaine or bupivacaine (Fig. 1A). MAP values in the PACU, however, were not appreciably different among the groups (Fig. 1B). No intergroup differences were noted in Steward scores (which measure emergence from anesthesia), oxygen saturation, or the incidence of nausea and vomiting while in the PACU.

Pain scores were significantly lower when measured immediately after admission in the patients who received lidocaine than in either the bupivacaine or placebo group (Fig. 2A). These scores eventually increased and were similar to the other groups during the remainder of the PACU stay. Pain scores peaked approximately 30 minutes after PACU admission and then slowly declined until a nadir of 4 was reached 12 hours after surgery. Narcotic analgesic requirements were similar among the groups during the PACU stay (Fig. 2B). However, analgesic requirements were significantly lower for the lidocaine group 6, 8, and 24 hours after surgery. The cumulative narcotic requirements for the patients who received either placebo or bupivacaine were almost double those of the patients who were given lidocaine 6 hours (17.6 ± 2.8 *vs.* 8.8 ± 2.9 [$p = 0.08$] and 21.3 ± 2.8 *vs.* 8.8 ± 2.9 [$p = 0.009$]), 8 hours (34.1 ± 4.2 *vs.* 16.2 ± 4.5 [$p = 0.016$] and 35.0 ± 4.4 *vs.* 16.2 ± 4.5 [$p = 0.012$]), and 24 hours (74.9 ± 9.9 *vs.* 38.3 ± 10.9 [$p = 0.043$] and 79.3 ± 10.5 *vs.* 38.3 ± 10.8 [$p = 0.025$]) after surgery, respectively.

Measurements of local anesthetic concentrations in plasma demonstrated significantly higher levels in patients who received lidocaine than in those who received bupivacaine (Fig. 3). Plasma levels were noted at the 5-minute time point, with peak concentrations occurring 30 to 60 minutes after the initial application of the local anesthetic. After this time, concentrations declined, with measurable levels still present at 6 hours.

Evaluations of the donor sites both acutely and over a 2-week period demonstrated no clinical differences in wound healing when patients who received local anesthetic were compared with those who received aerosolized saline.

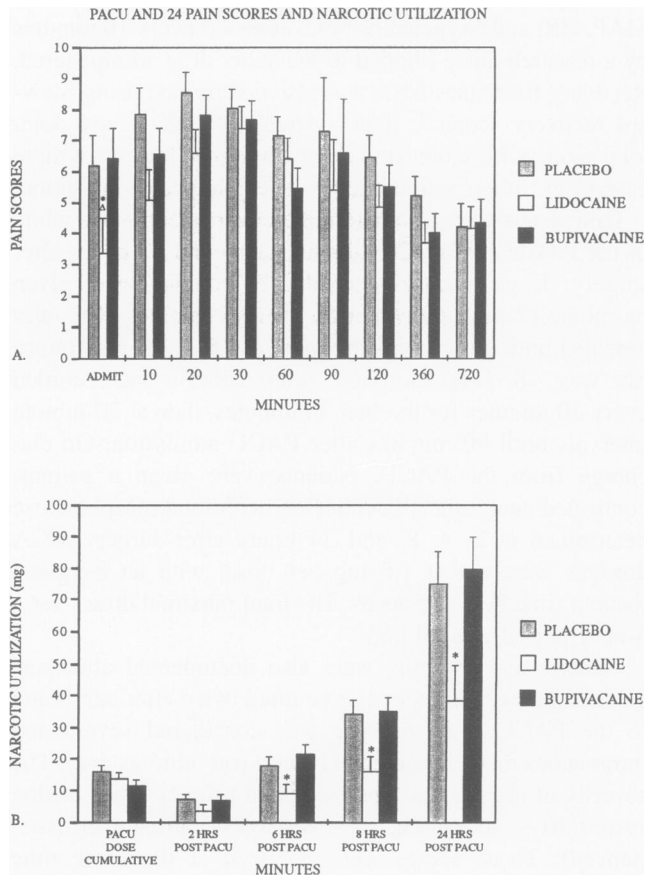

Figure 2. (A) Pain scores during the postanesthesia care unit stay and during the subsequent 7 hours. (B) Narcotic use during this same period and for the remaining 24 hours after surgery. Values are expressed as mean ± SEM. *, significant difference ($p < 0.05$) *vs.* the placebo group; **, significant difference *vs.* the bupivacaine group.

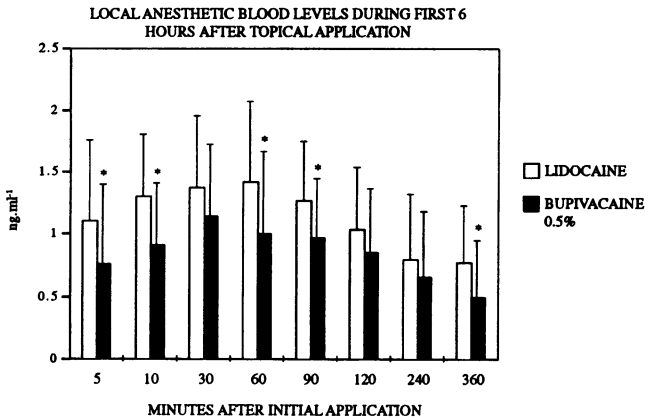

Figure 3. Local anesthetic blood concentrations immediately after topical application to skin and over the next 6 hours after initial application. Values are expressed as mean ± SEM. *, significant difference ($p < 0.05$) *vs.* the bupivacaine group.

DISCUSSION

Although intravenous opioids, administered after therapeutic burn procedures, are the primary method of pain management, nonopioid-based approaches have recently become popular. This change relates to the realization that narcotics may be underused by clinical staff in an effort to reduce side effects such as depression of ventilation and consciousness, decreased gastrointestinal motility and constipation, nausea and vomiting, urinary retention, and physical dependence.[1] These side effects increase the morbidity associated with thermal injury and prolong recovery time. In addition, opioid pharmacodynamics are altered in patients with burns, with requirements increasing over time so that even high doses of opioids may not totally relieve the pain in some patients.[2]

This study demonstrates that the topical application of a local anesthetic to freshly harvested or débrided skin areas affects the hemodynamic response to pain as well as analgesic requirements after surgery. The application of 2% topical lidocaine seemed to have the most beneficial effect, significantly reducing heart rate in the PACU and the need for morphine over a 24-hour period after surgery. Plasma levels of the local anesthetic may also support this observation: lidocaine levels were found to be significantly greater than bupivacaine levels in these patients. Lidocaine is more rapidly absorbed into the blood from the skin than is bupivacaine. This is because of bupivacaine's greater tissue binding and higher lipid solubility.[14] Low-dose intravenous lidocaine infusions have been shown to reduce pain after surgery and narcotic requirements after therapeutic procedures in patients with burns.[8] The topical application of lidocaine after skin harvest may have produced not only a local reduction in pain response, but also blood levels great enough to reduce the perception of pain systemically. Another study demonstrated a beneficial effect of preinjury infiltration of skin with lidocaine in reducing the development of mechanical hyperalgesia and pain surrounding a thermal injury.[15] This effect was noted to last approximately 40 to 70 minutes and may be similar to the effect of topical lidocaine applied to skin-harvest sites, as presented in the present study. The absorption of lidocaine into the skin after subcutaneous injection or after topical application to areas where skin has been removed may similarly reduce the release of substance P, a chemical known to increase plasma and albumin extravasation into the skin secondary to increased vasodilation and vascular permeability.[9] This would decrease peripheral sensitization and the need for analgesics after surgery. In addition, lidocaine applied to the skin may also reduce humoral inflammatory processes with the production and release of phospholipases and superoxide anions and further decrease plasma and albumin extravasation into the skin that leads to postinjury edema.[16–18]

Blood levels of the local anesthetic observed in this study are similar to those found by investigators using topical lidocaine sprayed on mucous membranes of the vaginal canal for pain control during childbirth.[19] Local anesthetic blood concentrations in that study were independent of the dose of lidocaine used or the type of membrane sprayed. This suggests that the effect is at the tissue site and is not the result of systemic absorption. A more probable explanation for the beneficial effect of topical lidocaine is that it may have remained at the tissue site for a prolonged period because epinephrine was added to the solution. The addition of epinephrine to lidocaine solutions has been demonstrated to decrease the systemic absorption of the drug by one third.[20] This effect is not noted with bupivacaine. The higher concentration of lidocaine (2% *vs.* 0.5%) administered at the skin surface, coupled with the reduced systemic absorption produced by the addition of epinephrine, may have created a depot effect for lidocaine and prolonged its analgesic action, reducing the need for narcotic analgesics over the 24-hour period after surgery compared with either the bupivacaine or placebo patients. This observation is supported by the fact that similar volumes of study solution were sprayed onto the skin surface, but the blood concentration of the local anesthetic in the lidocaine group (which was administered at four times the concentration of bupivacaine [2% *vs.* 0.5%]) was not four times greater than that of the bupivacaine group.

Other investigators have looked at the effect of either topical 5% EMLA cream or subcutaneous injection of 0.5% bupivacaine on the inflammatory and pain response after body surface trauma.[9,10] However, both of these local anesthetics have been shown to be ineffectual in reducing pain secondary to their poor absorption into the skin. These findings are similar to those of the present study, which demonstrated that 0.5% bupivacaine had little effect on reducing analgesia requirements after surgery over a 24-hour period and had a lesser effect than 2% lidocaine on possible hemodynamic responses to pain.

Other nonopioid analgesia therapies have been used after therapeutic procedures in burned patients with limited success. Intravenous ketorolac has been used successfully to

decrease narcotic requirements during burn dressing changes.[4] However, these patients were ventilator-dependent, were more debilitated, and were undergoing much less stressful procedures than were the patients in the present study. Thus, it is questionable whether this therapy would have been as effective in reducing the narcotic requirements in our patients. Topical applications of ketorolac[21] and glucocorticoids[6] have also been tried in an effort to reduce inflammation, pain, and hyperalgesia; both have been found to have minimal, if any, effect on these parameters. In addition, forms of hypnotherapy and distraction procedures have been tried in an effort to reduce anxiety in patients undergoing burn dressing changes and débridement procedures.[22,23] Although successful, these techniques could not be applied to the postsurgical patient who has undergone much more extensive surgery, encompassing skin harvest and grafting techniques, and whose sensorium is affected by general anesthesia.

Finally, this study could be faulted by the fact that some of the differences noted in the perception of pain after surgery and the physiologic response to it may have been influenced by age differences between the groups. We do not believe this to be the case. Although the placebo group was statistically younger than either the bupivacaine or lidocaine group, these age differences are clinically insignificant, with all of our patients considered to be adults and middle-aged. In addition, age has been shown to be a poor predictor to gauge a patient's response to pain.[1] Thus, we believe the responses observed are strictly the result of differences in treatment rather than in age.

In conclusion, we believe that topical lidocaine, applied directly to freshly harvested skin-graft sites, produces an analgesic effect that reduces the amount of narcotics needed to generate an equianalgesic condition when compared with patients who received either topical bupivacaine or placebo. This method did not produce toxic blood levels of local anesthetic and was well tolerated by the patients. Further evaluations of topical anesthetics for analgesia after burn procedures should be done, focusing on new methods for drug delivery or ways of prolonging lidocaine's action (depot effect) at the skin site.

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