Comparison of 4 analgesic agents for venipuncture

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This study compared pain on application, pain on venipuncture, cost, and convenience of 4 analgesic agents used for venipuncture. A convenience sample of 280 preoperative subjects was assigned randomly to 1 of 4 groups. Group 1 received 2.5% lidocaine-2.5% prilocaine cream (LPC) topically, Group 2 received dichlorotetrafluoroethane spray (DCTF), Group 3 received 0.5% lidocaine subcutaneously, and group 4 received normal saline with 0.9% benzyl alcohol (BA) subcutaneously. A 7-point verbal descriptor scale measured pain on application, and a 100-mm visual analogue scale measured pain on venipuncture. Cost was measured and compared on unit-dose basis. Convenience was measured with a questionnaire survey completed by the investigators.

There was no significant difference (P < .05) among the groups for age, sex, ASA physical status, or difficulty of venipuncture. There was a significant difference in pain on application for all 4 agents (P < .05). The DCTF had the highest pain on application score (1.7 ± 0.1), while the LPC had no pain on application (0.0 ± 0). Lidocaine had a higher pain on application score (1.08 ± 0.1) than the BA (0.52 ± 0.1) but a lower score than DCTF. Lidocaine (1.3 ± 0.3) was significantly less painful (P < .05) on venipuncture than LPC (2.18 ± 0.3) and DCTF (2.5 ± 0.3) but was not significantly different than BA (1.92 ± 0.3). (All scores are given as mean ± SEM.)

Introduction
Anesthesia practice requires intravenous access with large-gauge catheters for the administration of fluids and medications. Intravenous catheter insertion, or venipuncture, is perceived as a painful and stressful event to an already anxious surgical patient. The increase in the number of outpatient surgical procedures has fostered the practice of unmedicated patients arriving to the operating room holding area with anticipatory fear of the surgical experience. Many of these patients have had prior encounters with venipuncture in other areas of the hospital, such as the emergency department and inpatient wards. These experiences may have left painful memories because of the failure of the staff to obtund venipuncture pain with analgesics. Therefore, administration of an analgesic agent before catheter insertion is useful to prevent pain and optimize patient comfort and satisfaction.
Current emphasis on healthcare costs and competition for healthcare dollars in terms of patients' satisfaction has prompted reevaluation of simple procedures once taken for granted. If an inexpensive and effective analgesic agent for venipuncture can be identified, healthcare agencies can preserve patient comfort while attempting to minimize the cost of venipuncture.

We identified qualities of the ideal analgesic agent as no pain on application, no pain on venipuncture, low cost, and convenience of use by the anesthesia staff. Past methods of analgesia for venipuncture include stretching the skin, slow injection through tiny needles, pinching, application of cold (cryoanalgesia), normal saline, benzyl alcohol, infiltration of local anesthetics, and topical anesthetics. Various studies have evaluated different analgesic agents that relieve or alleviate venipuncture pain but ignored other important aspects, such as cost and convenience to staff and patient.

The present study analyzed application pain, venipuncture pain, cost, and convenience to staff of 4 commonly used analgesic agents: topical 2.5% lidocaine-2.5% prilocaine cream (LPC) commonly known as EMLA cream, topical dichlorotetrafluoroethane spray (DCTF), superficial subcutaneous 0.5% lidocaine with methylparaben, and superficial subcutaneous bacteriostatic normal saline with 0.9% benzyl alcohol (BA).

Blocking the peripheral pain impulses caused by venipuncture is the proposed mechanism of the 4 analgesic agents used in the present study. The gate control theory of pain first introduced by Melzak and Wall in 1965 hypothesizes that decreasing the number of impulses generated at the periphery will prevent the critical level of impulses received at the "gate" in the substantia gelatinosa, keeping it closed and causing a decreased perception of pain. The introduction of the gate control theory caused an explosion of research on neuronal fibers and the role of the dorsal horns and ascending pathways on pain. This research refuted some of the details of the original 1965 gate control theory (which specific fibers have what role), but the concept of the role of the central nervous system (brain and dorsal horns) in inhibition, excitation, and modulation of inputs has been validated.

LPC is an oil and water emulsion mixture containing equal amounts of 2.5% lidocaine and 2.5% prilocaine. Topical analgesia occurs when the lidocaine and prilocaine are absorbed and directly block the voltage-sensitive sodium channels in the cell membrane of free nerve endings.

Dichlorotetrafluoroethane spray is a skin refrigerant similar to ethyl chloride that has been used as a topical analgesic immediately before venipuncture. The 2 proposed mechanisms of action of cryoanalgesia and the relief of acute pain are as follows:

1. A decrease in temperature may slow the neuronal metabolic rate and decrease speed of action potential conduction, blocking impulse transmission.

2. A "counterirritant" effect occurs when thermal receptor stimulation (cold) on the skin overrides a painful stimulus in the same area. This sensory input may partially "close the gate," which reduces the transmission and perception of painful stimuli.

Lidocaine is an amide local anesthetic metabolized by the liver that directly blocks the voltage-sensitive sodium channels. The onset of action of subcutaneous 0.5% lidocaine is rapid, and its duration is 20 to 25 minutes. Methylparaben is a commonly used bacteriostatic and fungistatic preservative used in multidose vials of lidocaine that has not been shown to alter the effect or duration of analgesic agents.

Bacteriostatic isotonic sodium chloride solution (with 0.9% benzyl alcohol) has been found to have an analgesic effect when injected subcutaneously. Benzyl alcohol is used as the bacteriostatic preservative. The proposed analgesic mechanism of action is an increase in membrane fluidity, causing expansion and disorder in the interior of the lipid membrane.

Methods

The purpose of the present study was to determine whether a difference existed in pain on application, pain on venipuncture, cost, and convenience among 4 analgesic agents. Permission to conduct a study involving human subjects was obtained from the institutional review board, and written permission was obtained from all subjects. The population consisted of patients scheduled for surgery at a 425-bed military teaching hospital who required intravenous access.

A 7-point verbal descriptor scale (VDS) with numerically related words to describe pain was used to measure pain on application, and a 100-mm visual analogue scale (VAS) was used to measure the pain of venipuncture (Figure 1). Different tools were chosen to measure pain on application and pain on venipuncture to allow for differentiation between the 2 stimuli by the subjects. The VDS and VAS have been shown to be
valid and sensitive measures of pain intensity in the general population.\textsuperscript{20-22} The 2 scales are highly correlated: $r = 0.88$,\textsuperscript{20} and $r = 0.81$.\textsuperscript{23} Littman and colleagues\textsuperscript{21} used clinical trials involving 1,497 patients to establish a strong correlation among the VDS, the VAS, and the verbal pain relief scale ($r = 0.89$ to 0.93). There were no consistent differences found between the tools, and they concluded that the choice of scale may not be critical.

Cost was measured and compared on a unit-dose basis. The total amount of agent per container was divided by the amount of agent used per application to determine the number of doses per container. The cost of the container was then divided by the number of doses per container to obtain the cost per dose or “unit-dose cost.” The costs of any supplies that were needed for application, such as a syringe, were added to the unit-dose cost.

Convenience was defined conceptually as the ease of use or operation. We designed a survey to operationally measure convenience after data collection was completed. The list of items on the survey was compiled by the 5 authors to answer the question “What makes an analgesic agent convenient to use?” The 4 items on the survey were: (1) convenience of gathering supplies, (2) convenience of agent application, (3) convenience of clean up, and (4) time required for effective analgesia. These items were scored using a 7-point Likert scale with 1 (least convenient) and 7 (most convenient) for each agent.

Subjects meeting inclusion criteria were counseled without the investigator or subject knowing group assignment. Informed consent was obtained, and a randomizing table\textsuperscript{24} was used for group assignment and a data sheet was initiated. Group 1 received 2.5 g of LPC with an occlusive dressing to the dorsum of each hand for a minimum of 60 minutes and a maximum of 240 minutes. Group 2 received DCTF spray for 10 seconds at a distance of 6 inches. Group 3 received a subcutaneous injection, with a 27-gauge needle, of 0.1 mL of 0.5% lidocaine with methylparaben, and group 4 received a subcutaneous injection, with a 27-gauge needle, of 0.1 mL of isotonic sodium chloride solution with 0.9% BA.

Data collectors included the authors of the study and 2 assistants who routinely started intravenous fluids in the preoperative hold area. A 16-gauge catheter was chosen for venipuncture so all subjects received a consistent stimulus. Time of application for the LPC was written on the occlusive dressing, and length of application was recorded on the data collection sheet. The DCTF spray, lidocaine, or BA was applied initially to one hand. Spray distance was measured using a 6-inch string secured to the DCTF can. One tenth milliliter (0.1 mL) of lidocaine or BA was drawn up and administered using an insulin syringe with a 27-gauge needle. If a second venipuncture attempt was required, the same analgesic agent was

Figure 1. Data collection worksheet

Date: Code #: Tx Group: Age: Gender: M F ASA: IV site: Number of attempts: LPC* application time: Difficulty of venipuncture: 0-10, 11-20, >20 seconds Complications: Premedications given: Data collector:

Horizontal Visual Analogue Scale

No pain Worst pain possible

Verbal Descriptor Scale

(6) Pain as bad as it could be
(5) Extreme pain
(4) Severe pain
(3) Moderate pain
(2) Mild pain
(1) Slight pain
(0) No pain

*LPC indicates topical 2.5% lidocaine - 2.5% prilocaine cream.
applied to the second hand. The subject was excluded from the study after 2 unsuccessful venipuncture attempts. The sites were disinfected with an alcohol pad before venipuncture. All investigators used a stopwatch to measure the time needed to successfully complete the venipuncture and to time the application of DCTF spray. The venipuncture time (time from skin insertion to blood flashback into stylet) was recorded on the data collection sheet by checking the appropriate category: 0 to 10 seconds, 11 to 20 seconds, and more than 20 seconds. Venipuncture time was interpreted as venipuncture difficulty and used to control for the extraneous variable of venipuncture difficulty that may have affected venipuncture pain. All subjects assessed the pain on application immediately after the agent was applied by using the VDS and the pain on venipuncture by using the VAS after the intravenous line was secured. Data are given as mean ± SEM unless otherwise indicated.

Results

The required sample size was estimated by doing a power analysis. We wanted to detect a difference of 1.0 VAS unit in a 2-tailed test with 80% power and a significance of $P<.05$. By using an equation for independent samples from Snedecor
and Cochran, it was determined that 64 subjects were required for each group.

Data collection took place during a 14-week period with 246 subjects participating in the study. Of the 246, the required time of application for LPC (minimum of 60 minutes and maximum of 240 minutes) was not met for 8 subjects. Statistical analysis of pain of venipuncture included data for only the 238 participants for whom the application protocol was followed correctly. Statistical analysis for pain of application included data for all 246 participants.

Chi-square was used for statistical analysis of the demographic data to include group size, sex, subject age, ASA physical status, and venipuncture difficulty. There was no significant difference in the number of subjects, sex distribution, or ages of the subjects among the treatment groups (Table 1). The mean age for the sample was 40.4 years, and patients in the ASA physical status II category constituted 56% of the sample. There was no significant difference in the distribution of ASA physical status categories or in venipuncture difficulty among treatment groups (Table 2).

Analysis of variance and the Student t test were used to analyze the data pertaining to application pain, venipuncture pain, and convenience. The DCTF group had the highest pain on application score (1.7 ± 0.1), while the LPC group had no pain on application (0 ± 0). The lidocaine group (1.08 ± 0.1) had a higher pain on application score than the BA group (0.52 ± 0.1) but had a lower score than the DCTF group. There was a significant difference (P<.05) in pain on application among all 4 agents (Figure 2).

The DCTF group (2.5 ± 0.3) and the LPC group (2.18 ± 0.3) had significantly higher (P<.05) pain on venipuncture scores than the lidocaine group (1.3 ± 0.3). The BA group (1.92 ± 0.3) had a higher pain on venipuncture score than the lidocaine group, but it was not statistically significant (Figure 3).

A cost analysis was done based on cost per

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**Figure 2. Comparison of mean application pain scores**

Comparison of verbal descriptor scale pain scores measuring the pain on application for each analgesic agent. The measured pain on application is expressed as mean ± SEM for each of the agents. Subjects evaluated application pain immediately after the agent was applied. The asterisk (*) indicates an analysis of variance revealed a significant difference among the analgesic agent groups (P<.05). LPC indicates topical 2.5% lidocaine-2.5% prilocaine cream; DCTF indicates topical dichlorotetrafluoroethane spray; Lidocaine indicates superficial subcutaneous 0.5% lidocaine with methylparaben; BA indicates superficial subcutaneous bacteriostatic isotonic sodium chloride solution with 0.9% benzyl alcohol.

**Figure 3. Comparison of mean venipuncture pain scores**

Comparison of visual analogue scale pain scores measuring pain on venipuncture with each agent. The measured pain on venipuncture is expressed as mean ± SEM for each of the agents. Subjects evaluated pain after venous cannulation. The asterisk (*) indicates an analysis of variance revealed a significant difference between the LPC and lidocaine groups (P<.05). The dagger (†) indicates analysis of variance revealed a significant difference between the DCTF group and the lidocaine group (P<.05). LPC indicates topical 2.5% lidocaine-2.5% prilocaine cream; DCTF indicates topical dichlorotetrafluoroethane spray; Lidocaine indicates superficial subcutaneous 0.5% lidocaine with methylparaben; BA indicates superficial subcutaneous bacteriostatic isotonic sodium chloride solution with 0.9% benzyl alcohol.
unit dose of each agent (Department of Defense Distribution and Pricing Agreement Contract, February 14, 1996) (Table 3). Three agents (DCTF, lidocaine, and BA) were in multidose containers, and 1 agent (LPC) was provided as a single-dose unit. Unit-dose cost was calculated based upon the amount of agent needed per application. The total cost column included the syringe needed for application of the lidocaine and benzyl alcohol solution. The BA and lidocaine were by far the least expensive analgesic agents, at $0.07 and $0.08 per application, respectively. The cost of DCTF spray ($0.91) was almost 15 times more expensive than the cost of an application of BA or lidocaine, while use of the LPC ($7.51) was more than 100 times more expensive than BA or lidocaine.

There was no significant difference in convenience of gathering supplies (Figure 4). The LPC was significantly less convenient to apply than BA or lidocaine ($P<.05$). The LPC also was significantly less convenient to clean up after the treatment and significantly less convenient in terms of time required for effective analgesia than the other 3 agents. The DCTF also was less convenient to apply than BA or lidocaine, but this difference was not significant.

Four subjects reported complications with DCTF, which included blister formation (3) and hypopigmentation (1). No complications were reported with the other agents.

**Discussion**

Pain on application, pain on venipuncture, cost, and staff convenience for use of 4 venipuncture analgesics were studied. The lower pain on application of BA compared with lidocaine found in the present study is supported in the literature. The painless application of LPC also is consistent with the literature and is the principal advantage of using LPC, especially with children.

Other studies reported complaints of cold, burning, and itching with the use of a skin refrigerant; these complaints were similar to the complaints reported anecdotally in the present study. Unlike the present study, Armstrong and colleagues reported no significant difference in pain on application between a skin refrigerant and intradermal lidocaine. One reason for this could be the difference in time and distance of spray in the two studies. Cook and Georgouras reported edema and blister formation as the most common complications of a skin refrigerant.

The DCTF and LPC had higher pain on venipuncture scores than BA, but the difference was not significant. We were surprised to find such high pain on venipuncture scores with LPC. Further evaluation of the data revealed that the patients with an LPC application time of between 60 and 90 minutes had a very high pain on venipuncture score. The patients with LPC application times of greater than 90 minutes had pain on venipuncture scores lower than for lidocaine, a result similar to the results reported by Lycka. Lidocaine had a lower mean pain on venipuncture score than that for BA, but the difference was not statistically significant ($P<.05$). We also noted that none of the 4 analgesic agents interfered with the venipuncture process.

Costs of the 4 analgesic agents were measured on a unit-dose basis and included the costs of all

<table>
<thead>
<tr>
<th>Agent</th>
<th>Agent cost per container</th>
<th>Unit-dose cost</th>
<th>Other supplies</th>
<th>Total cost per application</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPC, 1 box, 5 g, 1 dose</td>
<td>7.51</td>
<td>7.51</td>
<td>None</td>
<td>7.51</td>
</tr>
<tr>
<td>DCTF spray, one 6-fl-oz can, 10-s spray, 23 doses</td>
<td>20.93</td>
<td>0.91</td>
<td>None</td>
<td>0.91</td>
</tr>
<tr>
<td>Lidocaine, one 50-mL bottle; average 0.1 mL, 500 doses</td>
<td>9.91</td>
<td>0.02</td>
<td>Syringe, 0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>BA, one 30-mL bottle; average 0.1 mL, 300 doses</td>
<td>1.44</td>
<td>0.005</td>
<td>Syringe, 0.06</td>
<td>0.07</td>
</tr>
</tbody>
</table>

LPC indicates topical 2.5% lidocaine-2.5% prilocaine cream; DCTF indicates topical dichlorotetrafluoroethane spray; lidocaine indicates superficial subcutaneous 0.5% lidocaine with methylparaben; BA indicates superficial subcutaneous bacteriostatic isotonic sodium chloride solution with 0.9% benzyl alcohol.

The LPC was the least convenient agent to use because it was more time consuming, resulted in more supplies to apply and clean-up, and had a longer onset before effective analgesia. Hallen et al noted that the time between application and onset of action for LPC made it impractical for anything other than routine scheduled procedures. Lidocaine and BA were deemed the most convenient agents.

The strengths of the present study include the use of a power analysis to determine an adequate sample size, a large population from which to draw our sample, and the use of a 16-gauge cannula, which provided a valid test of the efficacy of the analgesic agents. The design of this study did not control for premedication before venipuncture. However, only 1 patient received a premedication before participating in the study. This lack of premedication may have contributed to the internal validity of this study by allowing the patients to more accurately assess and report pain on application and venipuncture.

Several weaknesses of the study also were noted. First, we chose to spray DCTF for a specified time and distance instead of spraying until frost appears, as the manufacturer recommends. We chose to do this to eliminate the subjective observation of frost, which may have varied between data collectors. Some investigators believe it is important to control for pH when comparing analgesic agents. We wanted to use analgesic agents that were easy to use and readily available, so we chose not to alter the pH of the agents. The aspects of convenience were rated according to the investigators’ perceptions. An empirical measurement would have decreased the bias of opinion.

**Conclusion**

Four conclusions were supported from the findings of this study. The DCTF spray had high pain on application and high pain on venipunc-
ture and cannot be recommended for venipuncture analgesia. The LPC had high pain on venipuncture for application times of 60 to 90 minutes and is expensive and inconvenient to use. It cannot be recommended as a first choice or for routine use for venipuncture analgesia because a minimum of 90 minutes’ application time (but preferably more) is needed for adequate analgesia. Lidocaine had low pain on venipuncture and was inexpensive and convenient to use. The BA had all 4 qualities of an ideal venipuncture analgesic: it had low pain on application and venipuncture and was inexpensive and convenient to use. Therefore, BA is recommended for use as a venipuncture analgesic.

The present study offers several implications for nursing practice. Venipuncture analgesia is used routinely within the anesthesia department, and lidocaine is the standard agent of choice. However, BA is readily available, has all of the ideal qualities of an analgesic agent, and should be considered for venipuncture analgesia, especially for patients with an amide local anesthetic allergy, although this allergy is rare.18

Few nurses outside the anesthesia department use venipuncture analgesia. Perhaps this is because nurses view venipuncture analgesia as requiring too much additional time or not effective, or they believe 1 needle stick is better than 2. Nurses’ attitudes about venipuncture analgesia can be improved through education. Departments of nursing should incorporate the benefits of venipuncture analgesia into practice by writing venipuncture standard operating procedures. The standard operating procedures should incorporate the use of BA and lidocaine.

Venipuncture analgesia is also a consumer issue. Patients want the best care with the least amount of pain and expense. Providing quality care is a nursing goal, and venipuncture analgesia is a part of quality care. Venipuncture analgesia is effective and convenient and increases patient satisfaction.

We have the following recommendations for further research. Benzyl alcohol and lidocaine should be studied more intensely with a randomized, double-blind, experimental study design, which would eliminate subject and researcher bias. A study of this design may result in statistically significant results of pain on venipuncture. Dichlorotetrafluoroethane should be studied again using a different application time and distance. A different application time and distance may decrease the pain on application and venipuncture, decrease the incidence of skin reactions and blister formation, increase efficacy, or all of these. A study comparing the convenience of the analgesic agents should be performed using specific measurable aspects of convenience, thus eliminating the bias associated with investigators’ perception of convenience.

REFERENCES


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