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Article in Respiratory Medicine · December 2003
Impact Factor: 3.09 · DOI: 10.1016/S0954-6111(03)00226-9 · Source: PubMed

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Topical tetracaine prior to arterial puncture: a randomized, placebo-controlled clinical trial

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**SUMMARY**

The objective of this randomized, double-blind, placebo-controlled clinical trial was to determine whether a topical anesthetic agent (tetracaine) provides effective local analgesia prior to radial arterial puncture. Tetracaine or placebo gel was applied 45 min prior to arterial puncture to patients who were referred for elective arterial blood gas. The primary outcome was the patient’s perception of pain associated with the procedure as measured by a visual analog scale. Fifty patients were randomized into the study, 24 received tetracaine and 26 placebo. Mean pain score on the visual analog scale was 26.2±32.6 for the tetracaine-treated patients and 23.8±27.4 for the placebo-treated patients ($P=0.78$). Mean time from the first skin puncture to successful procurement of 1 ml of arterial blood was 70±103 s in the tetracaine group and 49±48 s in the placebo group ($P=0.40$). Difficulty of arterial puncture as assessed by the respiratory therapist performing the test was identical for the two groups ($P=0.86$). We conclude that tetracaine gel did not decrease patient’s perception of pain associated with arterial puncture, nor did its use facilitate the ABG procedure.

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**KEYWORDS**

Anesthetics local; Anesthesia; Arterial blood gas

**INTRODUCTION**

The arterial blood gas (ABG) is a test that provides important information on patients’ blood pH, oxygenation and CO$_2$ elimination.\textsuperscript{1} ABGs are most often done on an urgent or semi-urgent basis in critically ill patients. However, elective, non-urgent ABGs are also frequently performed, often in outpatient clinics or pulmonary function laboratories.

Arterial blood is usually obtained by percutaneous needle puncture of a palpable radial (wrist) artery. The procedure can be painful for patients because it involves puncture of the skin and the radial artery. Difficulties finding the radial artery are common, and multiple skin punctures are sometimes required before a successful ABG is obtained. Understandably, the pain associated with the procedure can provoke anxiety, especially in patients who require serial ABGs for assessment of their respiratory status.\textsuperscript{2}

The use of local infiltrative anesthetic prior to arterial puncture is supported by results from two clinical trials\textsuperscript{2,3} and is recommended by the British Thoracic Society in order to decrease the pain associated with the procedure.\textsuperscript{4} However, local
infiltrative anesthesia produces pain during its administration, and therefore the use of local anesthesia prior to arterial puncture has not been widely adopted by physicians. An alternative anesthetic option other than local infiltration with lidocaine may be topical anesthetics. Topical anesthetics, such as tetracaine gel and lidocaine-prilocaine cream, bind to neuronal receptor sites in nociceptors below the stratum corneum and provide effective skin analgesia. Tetracaine gel also has the added property of acting in a bi-phasic manner on local blood vessels, and it may act to vasodilate the radial artery and therefore facilitate successful arterial puncture.

The major advantage to topical anesthetics is that, unlike local anesthetics, their administration is painless. The following randomized double-blind, placebo-controlled clinical trial was undertaken to determine whether a topical anesthetic agent (tetracaine) provides effective analgesia prior to arterial puncture.

Methods

Patients

Outpatients referred to the pulmonary function lab for elective ABGs from March to November 2001 were recruited for the study. Four experienced respiratory therapists, certified and licensed by The Canadian College of Respiratory Therapists of Ontario, performed the arterial punctures. All patients 18 years of age or older were eligible to participate. Patients were excluded from the study if they had a history of allergy to local anesthetics, psoriasis affecting the wrists, or if they were taking warfarin. The protocol and consent forms were approved by the Ottawa Hospital Research Ethics Board.

Study design

The study was a double-blind, randomized, placebo-controlled trial. Central computer-generated randomization lists were prepared. The randomization schedule was blocked by four and randomization was stratified according to the respiratory therapist performing the test.

The sample size was calculated to detect a 13 mm between-group difference in the visual analog pain scale score (VAS) with a power of 0.8 and a two-tailed alpha of 0.05. The VAS is a well- validated tool that is used to measure patient’s perception of pain associated with venipuncture or arterial puncture. A standard deviation in the VAS of 15 mm was assumed based on two studies which evaluated subcutaneous anesthetics for pain associated with arterial puncture. A difference of 13 mm was chosen because it has been shown to be the minimal clinically significant difference in pain scores using the VAS. The final a priori calculated sample size was 44 patients (22 patients per group).

Treatments

After obtaining written informed consent, the respiratory therapist performed an Allen’s test to determine which wrist would be used. The chosen site was prepared by abrading the skin over the radial area with 3M Red Dot tracing prep paper. This was done five times to facilitate diffusion of the gel across the stratum corneum. Eligible patients were randomly assigned to receive treatment with 1 g of tetracaine gel 4%, or placebo gel that was odorless and identical in appearance and texture to the tetracaine gel. The gel was applied to the site of the radial artery pulsation 45 min prior to the arterial puncture and the gel was covered with an occlusive dressing. After 45 min, the dressing and excess gel was removed and the skin was cleansed with an alcohol swab. The respiratory therapist palpated the radial artery and inserted a 23-guage needle for arterial puncture.

At the time the needle made physical contact with the patient’s skin a co-worker activated a stopwatch. The procedure was considered complete as soon as one milliliter of arterial blood was obtained, and at this point the needle was withdrawn, and the time on the stopwatch was recorded.

The individual respiratory therapist was allowed two puncture attempts. If the second skin puncture was unsuccessful the procedure was considered to have ‘failed’ and the time was recorded.

Immediately following the procedure the respiratory therapist who performed the ABG left the room and the co-worker asked the patient to assess the discomfort that was caused by the puncture. The patient was asked to place a slash on a 100 mm visual analogue pain score (VAS). The VAS showed “no pain” at 0 mm and “worst pain” at 100 mm. To ensure that the patients understood how to use a VAS they were given practice questions during their 45 min wait period that asked them to grade extremes of temperature on a visual analogue scale. Their ability to correctly fill out the VAS was verified before the arterial puncture was attempted.
The respiratory therapist documented the difficulty of the arterial puncture by using a graded points scale, i.e. grade 1 = easy, grade 2 = moderately difficult, grade 3 = difficult and grade 4 = failed.\textsuperscript{10} At 24 h patients were asked to report the presence of any local adverse effects such as redness, bruising, swelling, or itching, by returning a self-addressed questionnaire to the coordinating center.

Data analysis

The primary analysis was performed on all patients randomized into the study using the intent to treat principle. VAS pain scores and the time to successful ABG were analyzed using independent $t$-tests. The difficulty of the ABG procedure was analyzed using Somers’ $d$-test for ordinal data. The proportion of failed ABGs was calculated using the Fisher’s exact test. All reported $P$ values are two-tailed.

Results

A total of 71 patients who were referred to the Ottawa Hospital Pulmonary function laboratory for elective ABGs from March to November 2001 were screened for entry into the study, and 50 patients were randomized. Among the patients who were screened but were not randomized, 12 patients were ineligible because they were taking warfarin, and 9 patients declined to participate. One patient who declined to participate had already brought her own anesthetic cream to the laboratory. The mean age of the randomized patients was 60 ± 12 years, and 34 (68%) were male. Patient baseline characteristics were evenly distributed between the two randomized treatment groups (Table 1). Twenty-four of the patients were randomized to tetracaine and 26 to placebo gel.

Results of the VASs are shown in Table 2. Lower scores on the VAS imply less pain. Mean VAS pain score was 26.2 ± 32.6 for the tetracaine-treated patients and 23.8 ± 27.4 for the placebo-treated patients ($P = 0.78$).

The difficulty associated with the arterial puncture and the likelihood of successful puncture was assessed using several outcome measurements. One of 24 ABGs failed in the tetracaine group, and 3 of 26 failed in the placebo group ($P = 0.61$). Six of 24 (25%) of the tetracaine-treated patients required more than one puncture sites for successful ABG, versus 4 of 26 (15%) in the placebo group ($P = 0.40$). The mean time from the first skin puncture to successful procurement of 1 mL of arterial blood for the ABG was 70 ± 103 s in the tetracaine group and 49 ± 48 s in the placebo group ($P = 0.40$) (Table 2). Difficulty of arterial puncture as assessed by the respiratory therapist performing the test was identical for the two groups. Overall 63% and 62% of the tetracaine and placebo-treated arterial punctures respectively were graded by the therapist as ‘easy’, 29% and 27% were graded as ‘moderately difficult’, and 8% and 12% were graded as ‘difficult’ or ‘failed’ ($P = 0.86$).

There were no significant differences in adverse effects associated with tetracaine therapy (Table 2).

Discussion

The aim of this study was to determine whether the application of 4% topical tetracaine gel to the wrist of patients prior to ABG was effective at decreasing the pain associated with the ABG procedure. The study was powered, a priori, to detect a difference in VAS pain scores of 13 mm between the two groups with 80% power. A difference in VAS pain score of 13 has been previously established to be the minimal clinically significant difference appreciated by patients.\textsuperscript{8} Based on our a priori power
calculation, the study required 22 patients in each group to show this difference.

The results of this randomized, placebo-controlled, double-blind clinical trial suggest that application of tetracaine gel prior to arterial puncture had no effect at decreasing the pain associated with the arterial puncture and that tetracaine did not significantly facilitate procedural success.

It is unlikely that this study was unable to show a positive outcome because it was under-powered. In fact, patients in the tetracaine-treated group had slightly higher VAS pain scores than placebo-treated patients, indicating that there was not even a trend towards greater pain relief in tetracaine-treated patients.

However, one limitation to interpretation of our study results is that the observed variances around the VAS score for both the active and placebo-treated patients were wider than had been assumed a priori based on results of prior published trials. We hypothesize that increased pain score variances may have occurred because of the 45-min delay between application of the tetracaine gel and the subsequent ABG procedure. In a proportion of patients, this 45-min delay accentuated pre-procedure anticipatory anxiety and this may have contributed to more variation in patient’s individual perception of pain associated with the ABG procedure.

Tetracaine does have a bi-phasic effect on blood vessels and potential vasodilatory properties, and we theorized that prior application of tetracaine might cause vasodilatation of the radial artery, and thus facilitate a successful arterial puncture. However, this effect was not seen; the time to successful ABG, number of failed ABGs, number of skin puncture attempts, and difficulty of the ABG, as assessed by the respiratory therapist performing the test, were not different in the tetracaine and placebo-treated groups.

There are two trials in the literature that support the use of local anesthesia with subcutaneous lidocaine prior to arterial puncture. One study randomized 101 patients undergoing arterial puncture to infiltration with 2% lidocaine, infiltration with normal saline, or no infiltration. Significantly lower pain ratings, assessed by patients and physicians, were noted in the group that received lidocaine infiltration compared to the other two groups. The difficulty of the procedure was not adversely affected by the use of lidocaine. A similar study randomized 140 patients to infiltration with lidocaine versus normal saline. This study showed that mean VAS score was significantly lower in the group that received lidocaine compared to the group that received placebo (VAS pain score of 1.50 ± 1.54 cm in the lidocaine group versus 3.06 ± 2.15 cm for the group that received placebo, P = 0.00001).

Despite its demonstrated efficacy, local infiltration with lidocaine prior to arterial puncture is not routinely practiced. A telephone survey of 100 junior hospital physicians established that 84% never used local anesthetic prior to performing a radial artery puncture. Forty-seven percent of the 100 physicians surveyed considered the injection of local anesthetic to be as painful as the procedure itself.

A recent study by Tran et al. has evaluated the effect of topical amethocaine (tetracaine) 4% in reducing pain during arterial puncture. This rando-

### Table 2  Study results.

<table>
<thead>
<tr>
<th></th>
<th>Tetracaine gel (n = 24)</th>
<th>Placebo gel (n = 26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analog pain scale score*</td>
<td>26.2 ± 32.6</td>
<td>23.8 ± 27.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Time to successful ABG* (seconds)</td>
<td>70 ± 103</td>
<td>49 ± 48</td>
<td>0.61</td>
</tr>
<tr>
<td>≥ 1 Puncture site (%)</td>
<td>6 (25)</td>
<td>4 (15)</td>
<td>0.40</td>
</tr>
<tr>
<td>Successful ABG (%)</td>
<td>23 (96)</td>
<td>23 (88)</td>
<td>0.61</td>
</tr>
<tr>
<td>Adverse effects (within 24 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>1</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>Swelling</td>
<td>1</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>0</td>
<td>0.43</td>
</tr>
<tr>
<td>Bruising</td>
<td>0</td>
<td>3</td>
<td>0.25</td>
</tr>
<tr>
<td>Any adverse effect</td>
<td>2 (8)</td>
<td>5 (19)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

The visual analog pain scale scores, and the ease of the arterial puncture, were not significantly different in the tetracaine-treated group as compared to the group which received placebo gel. There were no significant differences in adverse effects associated with tetracaine therapy.

*Mean ± SD.
mized, placebo-controlled trial enrolled 81 patients and used a design similar to ours. Results of the Tran study showed that the application of 4% tetracaine gel applied 30 min before radial artery puncture had no effect on reducing the pain associated with the procedure.\textsuperscript{11}

It is not obvious why topical tetracaine does not seem to provide effective analgesia prior to arterial puncture, however our hypothesis is that a longer application time may be needed to anesthetize deeper structures. Previous studies of tetracaine show that skin analgesia is assured within 45 min\textsuperscript{12} and an application time of 45 min is consistent with the manufacturer’s recommendation for venipuncture. However, the radial artery does lie deeper under the skin than the superficial veins, and it is possible that the tetracaine gel did not have sufficient time to diffuse below the epithelial basement membrane in a sufficient concentration gradient to anesthetize deeper pain fibers surrounding the artery.

In conclusion, our study has shown that tetracaine gel applied for 45 min after tape stripping, did not provide improved analgesia or facilitate arterial puncture compared to placebo. Further studies, with longer anesthetic application times, may be needed to confirm our results. In the meantime, clinicians who use local anesthetics prior to arterial puncture should choose infiltration with 2% lidocaine since this is the only method of analgesia that has thus far been proven to be effective in randomized controlled trials.

**References**