



CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

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[Aesthetic Plast Surg.](#) 2015 Aug; 39(4):597-601. DOI: 10.1007/s00266-015-0509-5. Epub 2015 Jun 5.

Skin Sterility After Application of a Vapocoolant Spray Part 2.

[Mlynek K¹](#), [Lyahn H](#), [Richards B](#), [Schleicher W](#), [Bassiri Gharb B](#), [Procop G](#), [Tuohy M](#), [Zins J](#).

Abstract

INTRODUCTION:

Refrigerant sprays have been used for pain relief at the time of minor office procedures. However, their sterility remains in question. This study investigates the microbiologic effect of this vapocoolant when sprayed after 70 % isopropyl alcohol skin preparation.

MATERIALS AND METHODS:

In 50 healthy volunteers, three skin culture samples were collected: Group 1 prior to alcohol application; Group 2 after preparation with alcohol, and Group 3 after preparation with alcohol followed with vapocoolant spray. Samples were cultured in a blinded fashion and analyzed after 5 days of incubation. Gram staining was performed when cultures were positive.

RESULTS:

Bacterial growth was found in 98 % of samples prior to any skin preparation. This was reduced to 54 % after alcohol use (Group 2). Spraying with the skin refrigerant further reduced bacterial growth to 46 % (Group 3). The results showed a significant reduction in the number of positive bacterial cultures following skin preparation with alcohol and when alcohol prep was followed by vapocoolant spray ($p < 0.001$) compared to initial cultures. No statistical difference was observed between Groups 2 and 3 ($p = 0.74$).

CONCLUSIONS:

The use of the vapocoolant spray does not compromise the sterility of the skin following alcohol prep. Both 70 % isopropyl alcohol antiseptic preparation and skin preparation followed by vapocoolant spray significantly reduce skin colonization when compared to unprepared skin ($p < 0.001$).

PMID: 26044395 [PubMed – in process]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

Plast Surg (Oakv). 2015 Summer; 23(2):71-6.

Microcirculatory effect of topical vapocoolants.

Galdyn I¹, Swanson E², Gordon C², Kwiecien G³, Bena J⁴, Siemionow M⁵, Zins J³.

Abstract

BACKGROUND:

Vapocoolant sprays are commonly used to minimize pain following minor interventions such as venipuncture, shave biopsy or needle insertion. Although these sprays have been widely used in clinical practice, little is known about their effect on microcirculation or cutaneous blood flow.

OBJECTIVE:

To evaluate the real-time effect of a topical vapocoolant using a well-established, rat cremaster muscle microcirculatory model, allowing direct measurement of changes in vessel diameter, capillary density and leukocyte behaviour.

METHODS:

Fifty rats were divided into a control and four experimental groups: group 1: 4 s spray with vapocoolant at 18 cm distance; group 2: 10 s spray at 18 cm distance; group 3: 4 s spray at 8 cm distance; and group 4: 10 s spray at 8 cm distance. Vessel diameters, capillary density and leukocyte behaviour were monitored for 1 h thereafter. Muscle was harvested for immunohistochemistry analysis of proangiogenic markers (vascular endothelial growth factor and von Willebrand factor), leukocyte behaviour markers (E-selectin, vascular cell adhesion molecule, intercellular adhesion molecule), pimonidazole-hypoxia staining and ApopTag (Millipore, USA) staining for apoptosis. Gene expression for inflammatory markers (interleukin [IL]-1 β , IL-2, IL-4, IL-6, IL-10, tumour necrosis factor-alpha and interferon-gamma) was evaluated using polymerase chain reaction and myeloperoxidase assay for inflammation was performed.

RESULTS:

The use of refrigerant spray decreased vessel diameter and capillary density initially, although none of these decreases were statistically significant. Polymerase chain reaction showed no significant changes. The myeloperoxidase assay showed statistically significant increase in myeloperoxidase activity in groups 2, 3 and 4. Immunohistochemistry was negative for angiogenic and proinflammatory markers.

CONCLUSIONS:

The lack of statistically significant changes in vessel diameter and inflammatory markers corroborated the safety on microcirculation.

PMID: 26090345 [PubMed] PMCID: PMC4459411 [Available on 2016-06-01]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

Oral and Maxillofacial Surgery Cases. May 2015. [Epub] DOI: <http://dx.doi.org/10.1016/j.omsc.2015.05.004>

Topical refrigerant spray for pediatric venipuncture for outpatient surgery.

Thomas Schlieve, DDS, MD, Michael Miloro, DMD, MD

Abstract

HIGHLIGHTS:

1. Pediatric anesthesia is a challenge because of poor cooperation from anxious children.
2. The pain of injections in the child may prevent the ability to obtain intravenous access in the outpatient setting and prevent the ability to perform the planned surgical procedure(s).
3. A simple technique using topical refrigerant spray can remove the pain associated with obtaining intravenous access.
4. This simple procedure is well tolerated, and no failures have been observed in the pediatric population undergoing outpatient surgery.
5. This technique should be used by all oral and maxillofacial surgeons.

Anxiety in the pediatric patient population is a problem for outpatient anesthesia because of poor patient compliance during the initiation of the anesthetic technique. A variety of techniques have been used in the outpatient surgery and emergency department settings to improve cooperation in the pediatric age group or those with developmental and cognitive delay. These adjunctive techniques include the growing popularity of the use of eutectic mixtures of local anesthetic cream, nitrous oxide, oral premedication and intramuscular injections. A highly effective technique to use during intravenous catheter insertion is the use of a refrigerant spray, ethyl chloride, to cause a transient local hypoesthesia of the skin at the venipuncture site. This technique is not associated with any significant contraindications or adverse reactions, and it should be considered for both pediatric and adult patients in the oral and maxillofacial surgery practice.

DOI: <http://dx.doi.org/10.1016/j.omsc.2015.05.004>

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[Nurs Manage](#). 2014 Dec; 45(12):21-2. DOI: 10.1097/01.NUMA.0000457135.64967.fd. No abstract available.

So much to gain for nurses who ease the pain.

[Papa A](#).

PMID: 25412376 [PubMed - in process]

[Anesth Analg](#). 2014 Dec; 119(6):1367-72. DOI: 10.1213/ANE.0000000000000469.

The analgesic effect of a vapocoolant stream spray in reducing heat nociception on the glabrous skin of rat pups.

[Sethna NF¹](#), [Yahalom B](#), [Schmidt B](#), [Hall AM](#), [Zurkowski D](#).

Abstract

BACKGROUND:

Blood sampling is a common screening and diagnostic test in newborn infants in the neonatal intensive care unit, and heel lancing accounts for two-thirds of these tests. Heel lancing causes acute pain and distress, and most infants rarely receive analgesics because of fear of respiratory depression from opioids and lack of effectiveness of topical local anesthetics on the glabrous skin. To circumvent this latter problem, we investigated the analgesic efficacy and safety of a topical vapocoolant spray.

METHODS:

Forty Sprague-Dawley rat pups aged 7 days old were randomly assigned to receive either vapocoolant or saline spray on the plantar hind paws for 5 to 6 seconds. Forty-five seconds later, the paws were subjected to a modified hotplate test to quantify the nociceptive flexor withdrawal (NFW) thresholds before and after treatment with the sprays. Seven days later, the animals were euthanized and the hind paws were examined histologically. A nested analysis of variance approach was used to account for the triplicate measurements per animal. A 2-tailed $P < 0.05$ was considered significant.

RESULTS:

At baseline, there were no differences in the NFW thresholds between the 2 groups ($P = 0.22$). After treatment, these thresholds were significantly lower in both vapocoolant ($P < 0.001$) and saline ($P = 0.008$) groups relative to baseline values. The vapocoolant group demonstrated a significantly longer NFW latency time compared to the saline group ($P < 0.001$). All specimens in both groups were examined and showed normal skin histology.

CONCLUSIONS:

Vapocoolant spray treatment of the glabrous skin is effective and safe after a single treatment.

PMID: 25313968 [PubMed – indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

Dermatol Surg. 2014 Oct; 40(10):1103-7. DOI: 10.1097/01.DSS.0000452654.29636.56.

Skin sterility after application of a vapocoolant spray.

Schleicher WF¹, Richards BG, Huettner F, Ozturk C, Zuccaro P, Zins JE.

Abstract

BACKGROUND:

Refrigerant sprays have been widely used to reduce pain in the office setting. However, more recently, their use has been limited by both concern regarding flammability and questions of bacterial contamination.

OBJECTIVE:

We investigated the microbiological effect of 1,1,1,3,3 pentafluoropropane and 1,1,1,2-tetrafluoroethane when sprayed after povidone-iodine application in 50 volunteers.

MATERIALS AND METHODS:

In 50 volunteers, 3 cultures were taken (1) at time 0 before antiseptic application, (2) after povidone-iodine topical antiseptic, and (3) after spraying with vapocoolant. Cultures at 3 time intervals were analyzed in a blinded fashion, and Gram stains obtained when cultures were positive.

RESULTS:

Bacterial growth was found in 98% of cultures taken before antiseptic was applied (Group 1), in 28 cultures (56%) after povidone-iodine was applied, and in 24 cultures (48%) after spraying with vapocoolant. There was a statistically significant difference found between Group 1 (no antiseptic) and both Group 2 (after antiseptic but before vapocoolant) and Group 3 (after vapocoolant) ($p < .001$).

CONCLUSION:

The topical antiseptic povidone-iodine significantly reduces skin colonization when compared with unprepared skin ($p < .001$). The vapocoolant 1,1,1,3,3 pentafluoropropane and 1,1,1,2-tetrafluoroethane is sprayed on skin prepared with povidone-iodine; there is no statistically significant increase in bacterial colonization.

PMID: 25229779 [PubMed – indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

Pediatr Emerg Care. 2013 Jan; 29(1):8-12. DOI: 10.1097/PEC.0b013e31827b214b.

Cryotherapeutic topical analgesics for pediatric intravenous catheter placement: ice versus vapocoolant spray.

Waterhouse MR¹, Liu DR, Wang VJ.

Topical refrigerant spray for pediatric

Abstract

OBJECTIVES:

Intravenous catheter placement is one of the most common sources of pain for children in inpatient settings. We sought to compare the efficacy of 2 cryotherapeutic treatments for this procedure: vapocoolant spray versus topical ice pack.

METHODS:

We prospectively enrolled 95 patients, aged 9 to 18 years, in a pediatric emergency department who required intravenous (IV) catheters as part of their treatment. Subjects were randomly assigned to receive vapocoolant spray or topical ice pack for 3 minutes, before IV catheter placement. Subjects completed visual analog scale (VAS) scores for 3 time points: baseline, pretreatment with ice or spray, and IV insertion. The principal investigator and 2 physicians viewing video recordings of the procedure also completed VAS scores for observed pain levels. Visual analog scale scores were compared using the Wilcoxon rank sum test.

RESULTS:

Although median VAS scores were similar, the change in VAS from baseline was of greater magnitude in the Pain Ease group, indicating that it may be more effective. More subjects in the Pain Ease group (76%) felt their treatment worked well, compared with 49% in the ice group. Physician-assigned VAS scores were lower and less variable than those of subjects. Most IV insertions were successful (83%).

CONCLUSIONS:

Vapocoolant spray may be more effective than ice as an analgesic for IV insertion. Subjects were more satisfied with vapocoolant spray. Neither agent caused a decrease in successful IV insertion rates.

PMID: 23283254 [PubMed – indexed for MEDLINE]

PMCID: PMC3985604

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Academic Emergency Medicine. 2013:S4–S336. DOI: 10.1111/acem.12115.

The effect of a vapocoolant spray on pain due to venipuncture in adults: A randomized, blinded, placebo-controlled trial.

Mace, SE.

Abstract

OBJECTIVES:

This study determines that a topical vapocoolant spray is effective and safe in adults undergoing venipuncture in the ED.

RESULTS:

Prospective blinded randomized controlled efficacy and safety trial of vapocoolant spray on pain in adults (≥ 21 years) undergoing venipuncture in the ED at a large urban tertiary care hospital. Adults were randomized to normal saline placebo spray or vapocoolant spray (Gebauer's Pain Ease®, 1,1,1,3,3 pentafluoropropane and 1,1,1,2 tetrafluoroethane) prior to venipuncture. Numeric rating scales (NRS) (1 to 10) were obtained after the spray was given and following venipuncture. Assessment and photographs of the venipuncture site were done pre-and post-application of both sprays. Vital signs and side effects were documented.

DISCUSSION:

There were no significant differences in demographics between the two groups. Normal saline (NS) placebo spray vs. vapocoolant (V): mean age (years) 51.5 (NS) 53 (V). Sex (M/F) 54%/46% (NS), 38%/62% (V), ethnicity – African American 58%, Caucasian 42%. Post venipuncture pain on numeric rating scale 4.72 (NS) 1.76 (V) ($p < 0.001$).

CONCLUSION:

Vapocoolant is effective and safe for treatment of the acute pain of venipuncture in ED patients with a significant ($p < 0.001$) decrease of 3 in mean NRS compared with NS (4.72 saline to 1.76 vapocoolant) and was well tolerated. There were no visible abnormalities at the site post application of the spray. Following application of the spray and prior to venipuncture, there was no significant difference in mean NRS between the sprays with a mean NRS < 1 for either spray, indicating that appropriate application of the vapocoolant spray was not painful or uncomfortable.

UPDATE: Post venipuncture pain on numeric rating scale 4.72 (NS) value changed to 3.72 after final data analysis but did not alter statistical significance.

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Journal of Athletic Training, 2012 May; 47(3)Supplement: S-92

Cold Perception, Surface, Subcutaneous and Intramuscular Temperatures Provided by Gebauer's Ethyl Chloride® Topical Vapocoolant Spray.

Martin KM, Merrick MA.

CONTEXT:

Vapocoolant sprays rapidly cool the skin, providing brief local anesthesia for injections and intravenous cannulation as well as management of minor sports injuries and spray & stretch. Temperature effects in humans and effects of commonly used nozzle types, spray distances or spray durations have never been previously reported.

OBJECTIVE:

To describe cold perception and temperature effects of Ethyl Chloride

DESIGN:

Crossover design

SETTING:

Research laboratory

PATIENTS OR OTHER PARTICIPANTS:

Convenience sample of 10 healthy participants (age=21.9 ± 2.4yr)

INTERVENTIONS:

Ethyl Chloride was applied to the proximal forearm in 8 experimental conditions on different days with at least 48hrs between. Conditions were determined using a 2x2x2 repeated measures factorial based on clinical use instructions. Independent variables were: nozzle type (mist & stream), spray duration (4 & 10 sec [or until skin blanching]) and spray distance (7.6cm [3in] & 17.8cm [7 in]). Treatment order was determined using a balanced Latin Square.

MAIN OUTCOME MEASURES:

Ambient and interface temperature were measured using surface thermocouples. Subcutaneous and 1cm intramuscular temperature were measured using sterile implantable thermocouples inserted via cannulae. Temperatures were recorded at 1sec intervals for 500sec. Cold severity perception was measured via 10cm Visual Analog Scale. Data were analyzed via repeated measures MANOVA with Sidak adjusted pairwise comparisons with $\alpha = 0.05$.

RESULTS:

Ambient (25.5 ± 0.5°C, p=0.52) and baseline temperatures (surface 30.3 ± 1.18°C), SubQ 33.3 ± 0.9°C, IM 33.5 ± 1.1°C, p=0.68) did not differ across conditions. Averaged across conditions, interface

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temperature was $-8.9 \pm 1.3^{\circ}\text{C}$, SubQ temperature was $30.7 \pm 1.1^{\circ}\text{C}$ and IM temperature was $32.3 \pm 0.6^{\circ}\text{C}$. For interface temperature, a nozzle X distance X duration interaction effect occurred ($p=0.007$). Pairwise comparisons showed (mist, 7in, 4sec) did not produce interface temperatures below freezing ($3.05 \pm 1.6^{\circ}\text{C}$) and was warmer than other conditions (ranged -6.27°C to -14.00°C). A main effect for nozzle ($p=0.004$) showed that stream ($-10.94 \pm 0.9^{\circ}\text{C}$) was colder than mist ($-6.89 \pm 0.6^{\circ}\text{C}$). A main effect for distance ($p=0.007$) showed that 3in ($-10.55 \pm 0.7^{\circ}\text{C}$) colder than 7in ($-7.27 \pm 0.7^{\circ}\text{C}$). A main effect for duration ($p<0.001$) showed 4sec ($-6.65 \pm 0.9^{\circ}\text{C}$) was warmer than spraying until skin blanched ($-11.18 \pm 0.5^{\circ}\text{C}$). Subcutaneously, a single main effect for spray duration ($p=0.037$) showed 4sec ($31.37 \pm 0.4^{\circ}\text{C}$) was warmer than spraying until the skin blanched ($30.12 \pm 0.7^{\circ}\text{C}$). No effect was observed intramuscularly ($p=.912$). For cold perception, a main effect for distance ($p=0.015$) showed 3in ($4.9/10 \pm 0.3$) feels colder than 7in ($3.75/10 \pm 0.5$). A main effect for duration ($p<0.001$) showed spraying until the skin blanched ($5.34/10 \pm 0.4$) feels colder than 4sec ($3.3/10 \pm 0.4$).

CONCLUSIONS:

Other than (mist, 7in, 4sec), Ethyl Chloride cools skin to well below freezing without causing skin injury. Temperature changes at SubQ ($\sim -2.8^{\circ}\text{C}$) and IM ($\sim -1.1^{\circ}\text{C}$) are small, short lived and may not be clinically meaningful.

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Journal of Athletic Training, 2012 May; 47(3)Supplement: S-91

Cold Perception, Surface, Subcutaneous and Intramuscular Temperatures Provided by Gebauer's Pain Ease® Topical Vapocoolant Spray.

Merrick MA, Martin KM.

CONTEXT:

Vapocoolant sprays rapidly cool the skin, providing brief local anesthesia for injections and intravenous cannulation as well as management of minor sports injuries and spray & stretch. Temperature effects in humans and effects of commonly used nozzle types, spray distances or spray durations have never been previously reported.

OBJECTIVE:

To describe cold perception and temperature effects of Pain Ease

DESIGN:

Crossover design

SETTING:

Research laboratory

PATIENTS OR OTHER PARTICIPANTS:

Convenience sample of 10 healthy participants (age =22.3 ± 1.9yrs)

INTERVENTIONS:

Pain Ease was applied to the proximal forearm under 8 experimental conditions on different days at least 48hrs apart. Conditions were determined using a 2x2x2 repeated measures factorial based on clinical use instructions. Independent variables were: nozzle type (mist & stream), spray duration (4 & 10 seconds) and spray distance (7.6cm [3 in] & 12.7cm [5 in]). Order of testing was determined using a balanced Latin Square.

MAIN OUTCOME MEASURES:

Ambient and interface temperature were measured using surface thermocouples. Subcutaneous and 1cm intramuscular temperatures were measured using sterile implantable thermocouples inserted via cannulae. Temperatures were recorded at 1sec intervals for 500sec. Cold severity perception was measured via 10cm Visual Analog Scale. Data were analyzed via repeated measures MANOVA with Sidak adjusted pairwise comparisons with $\alpha=0.05$.

RESULTS:

Ambient (25.9 ± 0.4°C, p=0.79) and baseline temperatures (surface 31.1 ± 0.4°C, SubQ 34.0 ± 0.4°C, IM 34.5 ± 0.4°C, p=0.68) did not differ across conditions. Interface temperature fell to -11.4 ± 1.1°C and

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re-warmed within 4-5 minutes. SubQ temperature fell to $28.1 \pm 1.0^{\circ}\text{C}$. IM temperature fell to $33.1 \pm 0.5^{\circ}\text{C}$. A main effect was observed for spray duration on cold perception (4sec = 3.9/10, 10sec = 5.9/10, $p < 0.001$) and on lowest temperature at all 3 depths (surface 4sec = $-9.4 \pm 0.7^{\circ}\text{C}$, 10sec = $13.4 \pm 0.4^{\circ}\text{C}$, $p = 0.001$; SubQ 4sec = $30.5 \pm 0.6^{\circ}\text{C}$, 10sec = $25.7 \pm 0.5^{\circ}\text{C}$, $p < 0.001$; IM 4sec = $33.5 \pm .3^{\circ}\text{C}$, 10sec = $32.7 \pm 0.3^{\circ}\text{C}$, $p = 0.05$). A main effect for nozzle was observed on cold perception (stream = 4.1/10, mist = 5.7/10, $p = 0.003$) and on lowest temperature at only surface (stream = $-7.5 \pm 0.6^{\circ}\text{C}$, mist = $-15.4 \pm 0.7^{\circ}\text{C}$, $p < 0.001$) and SubQ depths (stream = $29.3 \pm 0.5^{\circ}\text{C}$, mist = $26.9 \pm 0.6^{\circ}\text{C}$, $p = 0.03$). All 3 subjects receiving mist nozzle/5in/10sec had adverse skin reactions consistent with mild frostbite and the condition was terminated. Temperatures for it were $-17.9 \pm 1.4^{\circ}\text{C}$.

CONCLUSIONS:

Pain Ease cools skin to well below freezing regardless of application technique. This does not produce skin injury except in a single condition (mist, 5in, 10sec). Temperature changes at SubQ ($\sim -5.9^{\circ}\text{C}$) and IM ($\sim -1.4^{\circ}\text{C}$) are small, short lived and may not be clinically meaningful. Mist nozzle produces much colder temperatures and feels colder regardless of spray distance or duration. Spraying for 10sec feels colder and is colder than 4sec. Spraying for 10 seconds with the mist nozzle should not be used clinically.

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

J Bone Joint Surg Am. 2012 Jan 18; 94(2):118-20. DOI: 10.2106/JBJS.K.00229.

Skin sterility after application of ethyl chloride spray.

Polishchuk D¹, Gehrmann R, Tan V.

Abstract

BACKGROUND:

Ethyl chloride topical anesthetic spray is labeled as nonsterile, yet it is widely used during injection procedures performed in an outpatient setting. The purpose of this study was to investigate the sterility of ethyl chloride topical anesthetic spray applied before an injection. Our a priori hypothesis was that application of the spray after the skin has been prepared would not alter the sterility of the injection site.

METHODS:

We conducted a prospective, blinded, controlled study to assess the effect of ethyl chloride spray on skin sterility. Fifteen healthy adult subjects (age, twenty-three to sixty-one years) were prepared for mock injections into both shoulders and both knees, although no injection was actually performed. Three culture samples were obtained from each site on the skin: one before skin preparation with isopropyl alcohol, one after skin preparation and before application of ethyl chloride, and one after ethyl chloride had been sprayed on the site. In addition, the sterility of the ethyl chloride was tested directly by inoculating cultures with spray from the bottles.

RESULTS:

Growth occurred in 70% of the samples obtained before skin preparation, 3% of the samples obtained after skin preparation but before application of ethyl chloride, and 5% of the samples obtained after the injection site had been sprayed with ethyl chloride. The percentage of positive cultures did not increase significantly after application of ethyl chloride ($p = 0.65$). Spraying of ethyl chloride directly on agar plates resulted in growth on 13% of these plates compared with 11% of the control plates; this difference was also not significant ($p = 0.80$).

CONCLUSIONS:

Although ethyl chloride spray is not sterile, its application did not alter the sterility of the injection sites in the shoulder and knee.

PMID: 22257997 [PubMed – indexed for MEDLINE]

[Int J Med Sci.](#) 2011; 8(7):623-7. Epub 2011 Oct 12.

Vapocoolant spray vs lidocaine/prilocaine cream for reducing the pain of venipuncture in hemodialysis patients: a randomized, placebo-controlled, crossover study.

[Çelik G¹](#), [Özbek O](#), [Yılmaz M](#), [Duman I](#), [Özbek S](#), [Apilioğullari S](#).

Abstract

OBJECTIVE:

Patients undergoing hemodialysis are repeatedly exposed to stress and pain from approximately 300 punctures per year to their arteriovenous fistula. This study was designed to measure pain associated with venepuncture during AVF cannulation and to compare the effectiveness of ethyl chloride vapocoolant spray, topical eutectic mixture of local anesthetics (EMLA) cream and placebo in controlling pain caused by venepuncture of arteriovenous fistula patients undergoing chronic hemodialysis.

METHODS:

This randomized, placebo-controlled, crossover study, included 41 patients undergoing conventional hemodialysis three times a week. First intervention was conducted as baseline pain assessment (control). In the three consecutive dialysis sessions, every patient randomly received 1) ethyl chloride vapocoolant spray, 2) EMLA, or 3) placebo cream before venepuncture. Pain perception was recorded by patients immediately after cannulation on a 0-100 mm visual analogue scale (VAS). $P < 0.05$ was considered as significant.

RESULTS:

VAS scores presented a marked inter-individual variation during venepuncture. EMLA application resulted in significantly lower total pain scores compared to control and all other interventions ($p < 0.05$). No patient experienced severe pain with EMLA or vapocoolant. The patients reported less moderate and severe pain with EMLA, and vapocoolant spray compared to control and placebo interventions. Moderate and severe pain scores were similar between EMLA and vapocoolant spray ($p > 0.05$).

CONCLUSION:

Venipuncture for AVF cannulation causes mild to moderate pain in hemodialysis patients. Although local application of EMLA is more effective than in preventing venepuncture pain, ethyl chloride vapocoolant is as effective as EMLA for preventing mild to moderate puncture pain in patients undergoing hemodialysis.

PMID: 22022215 [PubMed – indexed for MEDLINE] PMCID: PMC3198258

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[J Plast Reconstr Aesthet Surg](#). 2010 Sep; 63(9):1443-6. DOI: 10.1016/j.bjps.2009.07.045. Epub 2009 Aug 27.

Botulinum toxin injection pain relief using a topical anesthetic skin refrigerant.

Engel SJ¹, Afifi AM, Zins JE.

Abstract

BACKGROUND:

This study was performed to determine if pretreatment application of a topical anesthetic skin refrigerant reduced discomfort during botulinum toxin injection.

METHODS:

Twenty patients were assigned to four groups determined by side of the face pretreated with skin refrigerant and side receiving the first injection. On a Visual Analog Scale of 0-10 patients rated discomfort levels after injections in the glabellar complex with and without pretreatment.

RESULTS:

Mean discomfort rating for the pretreated side was 3.1, while the mean discomfort rating for the non-pretreated side was 4.5. Discomfort was not affected by the side sprayed ($p=0.33$) nor by administering the injection to the sprayed side first ($p=0.37$). The paired t-test revealed a significant difference between discomfort levels on the pretreated and non-pretreated sides ($p=0.038$) yielding a 95% confidence interval of (-2.71, -0.09).

CONCLUSIONS:

Topical anesthetic skin refrigerant significantly reduces discomfort in a cost-effective manner for reported by patients undergoing botulinum injections.

PMID: 19716355 [PubMed – indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

Pediatrics. 2009 Aug; 124(2):e203-9. DOI: 10.1542/peds.2007-3466. Epub 2009 Jul 13.

Reducing immunization discomfort in 4- to 6-year-old children: a randomized clinical trial.

Berberich FR¹, Landman Z.

Abstract

OBJECTIVE:

The goal was to test a multifaceted distraction method designed to reduce injection-associated pain in school-aged children.

METHODS:

A clinical trial evaluated 41 children, 4 to 6 years of age, who were given 3 standard prekindergarten immunizations; 21 were assigned randomly to an office routine control group, whereas 20 received a multifaceted, discomfort-reducing intervention. The intervention added verbal suggestions of diminished sensation and a visual focusing activity to the use of ethyl chloride, an established pain-reducing measure. The distraction materials used for the intervention consisted of topical ethyl chloride spray, an improvised, plastic, multipronged arm gripper, and a vibrating instrument descending on the contralateral arm, which provided the focusing task and visual distraction.

RESULTS:

According to patient and parent Faces Pain Scale-Revised scores and nonblinded, video-taped observations scored according to the face-legs-activity-crying-consolability method, the intervention group showed highly significant reductions in pain and discomfort, compared with the control group (patient self-report, $P < .0013$; parent report, $P < .0002$; observation score, $P < .0001$).

CONCLUSION:

This multifaceted distraction intervention reduced significantly the pain and discomfort of childhood immunizations in children 4 to 6 years of age.

PMID: 19596729 [PubMed – indexed for MEDLINE]

J Emerg Nurs. 2009 Jul; 35(4):379-82. DOI: 10.1016/j.jen.2009.02.015. Epub 2009 Apr 14. No abstract available.

Reducing pain in pediatric procedures in the emergency department.

Ramponi D¹.

PMID: 19591743 [PubMed – indexed for MEDLINE]

Ophthalm Plast Reconstr Surg. 2009 May-Jun; 25(3):173-7. DOI: 10.1097/IOP.0b013e3181a145ca.

Reduction of pain and anxiety prior to botulinum toxin injections with a new topical anesthetic method.

Weiss RA¹, Lavin PT.

Abstract

PURPOSE:

To evaluate the safety and efficacy of vapocoolants (topical skin refrigerants) to induce skin anesthesia and relieve patient anxiety and pain prior to cosmetic botulinum injections.

METHODS:

A paired (split-face) design was used in 52 patients where patient side (left vs. right) was randomized to receive either vapocoolant spray or no treatment control to test the study hypothesis of better anesthetic efficacy of vapocoolant spray versus no treatment control.

A pain and anxiety questionnaire was administered before, during, and after the injections.

RESULTS:

A considerable percentage of patients either expected pain (35% of naïve patients expected moderate pain) or had experienced pain from their prior treatment (35% had experienced moderate pain). Among naïve patients, 15% had moderate or severe anxiety and among experienced patients, 31% had moderate anxiety. Pain was a factor in delaying the scheduling of cosmetic botulinum toxin treatments in 19% of naïve patients and 31% of experienced patients. Pain reported from actual injections was higher than what was anticipated prior to treatment. There was a significant reduction in pain at injection sites treated with vapocoolant ($p < 0.001$, paired t test). Overall, 67% of all patients reported that the vapocoolant method had less pain than no anesthesia and 54% preferred vapocoolant for their next treatment. Overall, 6% of all patients would schedule their next botulinum toxin treatment sooner if vapocoolant were available.

CONCLUSIONS:

Vapocoolants represent a safe and effective means to reduce patient discomfort and anxiety before and during botulinum toxin type A treatments for glabellar area indications.

PMID: 19454924 [PubMed - indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[CMAJ](#). 2008 Jul 1;179(1):31-6. DOI: 10.1503/cmaj.070874.

The effect of vapocoolant spray on pain due to intravenous cannulation in children: a randomized controlled trial.

[Farion KJ](#)¹, [Splinter KL](#), [Newhook K](#), [Gaboury I](#), [Splinter WM](#).

Abstract

BACKGROUND:

Established noninvasive pharmacologic means of alleviating pain and anxiety in children undergoing intravenous cannulation are time-consuming, and thus impractical for routine use in the emergency department. Vapocoolant sprays provide transient skin anesthesia within seconds of application. We compared the effect of a new vapocoolant spray to placebo on pain due to intravenous cannulation in children.

METHODS:

In this double-blind randomized controlled trial, which we conducted between June 1 and Sept. 12, 2006, 80 children aged 6-12 years received either vapocoolant spray or placebo before cannulation. Children rated their pain using a 100-mm colour visual analogue scale. Secondary outcomes included success rate on first attempt at cannulation and pain ratings by the children's parents, nurses and child life specialists.

RESULTS:

We found a modest but significant reduction in pain with the use of vapocoolant spray (mean difference 19 mm, 95% confidence interval [CI] 6-32 mm; $p < 0.01$). Cannulation on first attempt was more often successful with the use of vapocoolant spray (85.0%) than with placebo (62.5%) (mean difference 22.5%, 95% CI 3.2%-39.9%; $p = 0.03$). The number needed to treat to prevent 1 cannulation failure was 5 (95% CI 3-32). Parents ($p = 0.04$), nurses ($p = 0.01$) and child life specialists ($p < 0.01$) considered the children's pain to be reduced with the use of vapocoolant spray.

INTERPRETATION:

The vapocoolant spray in our study quickly and effectively reduced pain due to intravenous cannulation in children and improved the success rate of cannulation. It is an important option to reduce childhood procedural pain in emergency situations, especially when time precludes traditional interventions.

PMID: 18591524 [PubMed - indexed for MEDLINE] PMCID: PMC3267474

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

CDC MMWR Recommendations and Reports, December 1, 2006: 55(RR15); 1-48

Recommendations of the Advisory Committee on Immunization Practices (ACIP).

Kroger AT, Atkinson W, Marcuse E, Pickering L.

SUMMARY:

This report is a revision of General Recommendations on Immunization and updates the 2002 statement by the Advisory Committee on Immunization Practices (ACIP) (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices and the American Academy of Family Physicians. MMWR 2002;51[No. RR-2]). This report is intended to serve as a general reference on vaccines and immunization. The principal changes include 1) expansion of the discussion of vaccination spacing and timing; 2) an increased emphasis on the importance of injection technique/age/body mass in determining appropriate needle length; 3) expansion of the discussion of storage and handling of vaccines, with a table defining the appropriate storage temperature range for inactivated and live vaccines; 4) expansion of the discussion of altered immunocompetence, including new recommendations about use of live-attenuated vaccines with therapeutic monoclonal antibodies; and 5) minor changes to the recommendations about vaccination during pregnancy and vaccination of internationally adopted children, in accordance with new ACIP vaccine-specific recommendations for use of inactivated influenza vaccine and hepatitis B vaccine. The most recent ACIP recommendations for each specific vaccine should be consulted for comprehensive discussion. This report, ACIP recommendations for each vaccine, and other information about vaccination can be accessed at CDC's National Center for Immunization and Respiratory Diseases (proposed) (formerly known as the National Immunization Program) website at: <http://www.cdc.gov/nip>

UNDER: VACCINE ADMINISTRATION- METHODS FOR ALLEVIATING DISCOMFORT AND PAIN ASSOCIATED WITH VACCINATION:

Comfort measures, such as distraction (e.g., playing music or pretending to blow away the pain), ingestion of sweet liquids, breast feeding, cooling of the injection site, and topical or oral analgesia, can help infants or children cope with the discomfort associated with vaccination (77,78). Pretreatment (30--60 minutes before injection) with 5% topical lidocaine-prilocaine emulsion can decrease the pain of vaccination by causing superficial anesthesia (79,80). Evidence indicates that this cream does not interfere with the immune response to MMR (81). Topical lidocaine-prilocaine emulsion should not be used on infants aged <12 months who are receiving treatment with methemoglobin-inducing agents because of the possible development of methemoglobinemia (82).

Acetaminophen has been used among children to reduce the discomfort and fever associated with DTP vaccination (83). However, acetaminophen can cause formation of methemoglobin and might interact

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with lidocaine-prilocaine cream if used concurrently (82). Use of a topical refrigerant (vapocoolant) spray immediately before vaccination can reduce the short-term pain associated with injections and can be as effective as lidocaine-prilocaine cream (84).

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm>

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

J Travel Med. 2004 Sep-Oct; 11(5):267-72.

Topical vapocoolant quickly and effectively reduces vaccine-associated pain: results of a randomized, single-blinded, placebo-controlled study.

Mawhorter S¹, Daugherty L, Ford A, Hughes R, Metzger D, Easley K.

Abstract

BACKGROUND:

Comprehensive international travel preparation often requires several vaccines. Up to 90% of adults have some fear of injections, mostly due to injection-related pain. Pediatric studies with routine vaccines have shown topical anesthetic EMLA cream (lidocaine and prilocaine, Astra Pharmaceuticals, Inc.) and the topical vapocoolant Fluori-Methane (dichlorodifluoromethane and trichlorodifluoromethane, Gebauer Co.) to be equally effective in reducing pain from vaccinations. EMLA cream is expensive and requires a 60-min application, while Fluori-Methane (FM) is immediate in onset of action and inexpensive. Skin anesthesia begins at 10 degrees C. Fluori-Methane can briefly cool the skin to 0 degrees C.

METHODS:

We studied the effectiveness of topical vapocoolant on adult clients at our international travel clinic in a randomized, controlled trial of topical FM vs. cold (4 degrees C) saline placebo. Using a preset randomization table, participants served as their own controls, receiving placebo/control or active agent (participant blinded) in one arm (left or right), and a similar number of vaccines in the untreated arm. Vaccines were administered according to a set protocol per arm to minimize the risk of bias. Pain was measured using a modified McGill present pain intensity (PPI) pain index. Subjects rated their pain immediately and at 5 min on a six-level scale, noting treated and untreated arms separately. A questionnaire was completed on intervention preferences. Sample size was predetermined to achieve 90% statistical power estimating 25% efficacy (minimum n=172).

RESULTS:

One hundred and eighty-five participants were enrolled; 93 FM and 92 cold saline placebo. FM-treated arms had a significant reduction in immediate pain compared to untreated arms (pain scale mean 2.2 vs. 3.1; $p < .0001$), and compared to placebo (mean 2.2 vs. 2.8; $p < .01$). Delayed pain at 5 min was not affected by FM or control (mean 1.9 vs. 2.0) compared to no intervention (pain scale 1.9). The intervention preference questionnaire indicated that participants did not find FM therapy uncomfortable. They would choose FM therapy in the future, over a cream, especially if a wait was involved.

CONCLUSION:

The topical vapocoolant Fluori-Methane is an effective, quick, preferred, inexpensive agent for reducing vaccine-associated injection pain for international travel clients.

PMID: 15544709 [PubMed - indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[Otolaryngol Head Neck Surg.](#) 1999 Apr; 120(4):458-9.

Fine-needle aspiration biopsy: is anesthesia necessary?

Cannon CR¹, Replogle B.

Abstract

Fine-needle aspiration (FNA) of inflammatory and neoplastic head and neck masses has become a widely used procedure in otolaryngology-head and neck surgery. Using both subjective (patient perception) and objective (complication rate, accuracy) criteria, this prospective study evaluated patients undergoing FNA with and without anesthesia. Seventy-five patients were enrolled into 1 of 3 study groups: group I, no anesthesia; group II, ethyl chloride spray; and group III, lidocaine infiltrative anesthesia. In general, the ease of FNA, complication rates, and accuracy rates were the same for the 3 groups. Patient perception and satisfaction rates were improved in groups II and III. Use of topical or infiltrative anesthesia may enhance the use of FNA in the anxious nervous patient undergoing FNA of a neck mass.

PMID: 10187933 [PubMed - indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[J Perianesth Nurs](#). 1999 Apr; 14(2):95-101, 112.

Reducing the pain of venipuncture.

Fetzer SJ¹.

Abstract

Patient satisfaction with nursing care is the strongest predictor of overall satisfaction.

Reducing discomfort of routine procedures, such as venipuncture for an intravenous insertion, can contribute to perceived satisfaction. This article reviews three common pharmacological interventions that can be used by perianesthesia nurses to reduce the pain of venipuncture.

PMID: 10418420 [PubMed - indexed for MEDLINE]

[Drug Saf.](#) 1997 Apr; 16(4):279-87.

A risk-benefit assessment of topical percutaneous local anaesthetics in children.

[Russell SC](#)¹, [Doyle E](#).

Abstract

Since its introduction, eutectic lidocaine-prilocaine cream ('EMLA')¹ has been found to be an effective topical an aesthetic agent, with a high degree of efficacy, particularly for venepuncture and venous cannulation, and an impressive tolerability profile. Reports of adverse effects are remarkable for their rarity. The only problems that are likely to be encountered are oral ingestion of the cream (which may lead to anaesthesia of the oropharynx and possible toxicity secondary to rapid absorption of local anaesthetic from oral mucous membranes) and methaemoglobinaemia following repeated applications in neonates and infants. Analysis of the risks and benefits associated with its use comes down heavily in favour of the preparation. More recently, a preparation of tetracaine (amethocaine) has been marketed as a gel. Its advantages are a faster onset, and longer duration, of action than 'EMLA'. Although less widely used, it too has an impressive tolerability record. Concerns over the potential for anaphylactic type reactions due to its ester structure have not been realised in clinical practice. Of the other available preparations, lidocaine (lignocaine), applied iontophoretically, is unlikely to become popular because of the complexity of administration. A paste made of tetracaine, epinephrine (adrenaline) and cocaine (TAC) appears to be a far more toxic preparation on theoretical grounds, and this has been borne out in clinical practice; it is not as well tolerated as 'EMLA' or tetracaine gel. Ethyl chloride, although not a local anaesthetic, can safely provide cutaneous analgesia in children in circumstances when it is impractical to wait for a local anaesthetic preparation to take effect.

PMID: 9113495 [PubMed - indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[Pediatrics](#). 1997 Dec; 100(6):E5.

Vapocoolant spray is equally effective as EMLA cream in reducing immunization pain in school-aged children.

Cohen Reis E¹, Holubkov R.

Abstract

BACKGROUND:

Untreated immunization pain causes undue distress and contributes to under immunization through physician, and possibly parental, resistance to multiple simultaneous injections.

OBJECTIVE:

To compare the efficacies of two pain management methods in reducing immediate immunization injection pain and distress in school-aged children.

DESIGN:

A randomized, controlled clinical trial of eutectic mixture of local anesthetics (EMLA) cream and vapocoolant spray.

PATIENTS:

Children aged 4 to 6 years and scheduled to receive diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) during health supervision visits.

INTERVENTIONS:

Enrolled children were randomized to one of three treatment groups: 1) EMLA cream + distraction; 2) vapocoolant spray + distraction; or 3) distraction alone (control). The specific pharmacologic pain control interventions consisted of EMLA cream (2.5% lidocaine, 2.5% prilocaine [Astra Pharmaceutical Products, Inc., Westborough, MA] \$15. 00/patient; applied 60 minutes before injection) and vapocoolant spray (Fluori-Methane [Gebauer Company, Cleveland, OH] \$0. 50/patient; applied via spray-saturated cotton ball for 15 seconds immediately before injection).

MAIN OUTCOME MEASURES:

The blinded investigator (BI) measured (by edited videotape) cry duration and the number of pain behaviors using the Observational Scale of Behavioral Distress. Pain visual analog scales (linear and faces scales) were completed by the child, parent, nurse, and the BI.

RESULTS:

Sixty-two children, aged 4.5 +/- 0.4 years (mean +/- SD) were randomized. The three treatment groups had similar subject characteristics. All pain measures and cry duration were similar for EMLA and vapocoolant spray. Both EMLA and spray were significantly better than control. Results for spray vs control: cry duration (seconds): 8.5 +/- 21.0 vs 38.6 +/- 50.5; number of pain behaviors: 1.2 +/- 1.9 vs. 3.1 +/- 2.1; child-scored faces scale: 2.0 +/- 2.4 vs. 4.1 +/- 2.3; parent-scored faces scale:

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1.6 +/- 1.6 vs. 3.0 +/- 1.7; nurse-scored faces scale: 1.6 +/- 1.2 vs. 3.1 +/- 1.4; and BI-scored faces scale: 1.0 +/- 1.5 vs. 2.4 +/- 1.4.

CONCLUSIONS:

When combined with distraction, vapocoolant spray significantly reduces immediate injection pain compared with distraction alone, and is equally effective as, less expensive, and faster-acting than EMLA cream. As an effective, inexpensive, and convenient pain control method, vapocoolant spray may help overcome physician and parent resistance to multiple injections that lead to missed opportunities to immunize.

PMID: 9374583 [PubMed - indexed for MEDLINE]

CLINICAL REFERENCES, ABSTRACTS AND JOURNAL ARTICLES

[J R Soc Med.](#) 1995 May; 88(5):264-7.

Analgesia for venous cannulation: a comparison of EMLA (5 minutes application), lignocaine, ethyl chloride, and nothing.

[Selby IR](#)¹, [Bowles BJ](#).

Abstract

Three commonly available local anaesthetics were compared, in a controlled trial, for use before venous cannulation. The pain of application of the local anaesthetic, the pain of cannulation, and the rate of successful cannulations were compared. The value of EMLA cream applied for 5 min was questioned. Venous cannulation with a 20G venflon was found to be significantly more painful than the application of any of the local anaesthetics ($P < 0.01$). Lignocaine 1%, injected subcutaneously, and ethyl chloride spray significantly reduced the pain of venous cannulation ($P < 0.01$). The use of lignocaine did not result in significantly more failed cannulations than the control group. It was concluded that local anaesthesia should be used before venous cannulation, even for 20G cannulae.

PMID: 7636819 [PubMed - indexed for MEDLINE] PMCID: PMC1295196

[J Pain Symptom Manage.](#) 1995 Nov; 10(8):584-90.

The use of a topical refrigerant anesthetic to reduce injection pain in children.

Abbott K¹, Fowler-Kerry S.

Abstract

Early childhood experiences with painful injections may lead to anxiety and fear. These reactions need not develop if steps are taken to reduce the pain associated with injections. The purpose of this study was to assess the efficacy of a refrigerant topical anesthetic in reducing injection pain in preschool children experiencing routine diphtheria-pertussis-tetanus (DPT) immunizations. This double-blind placebo-controlled study was conducted in community health clinics in conjunction with ongoing immunization programs. Ninety subjects, aged 4-5.5 years, were randomly assigned to one of three groups: (a) refrigerant topical anesthetic; (b) placebo topical spray; and (c) no-spray control. Pain was measured subjectively using a four-point visual analogue scale. Both the refrigerant topical anesthetic spray and the placebo spray significantly reduced injection pain. Age was found to be an important factor influencing pain response in this study. Parental anxiety was not a significant factor influencing pain response. In addition, parents were not good at predicting their child's pain. The results of the study support the use of an intervention, such as refrigerant topical anesthetic, as a practical, simple, and effective treatment strategy for reduction of short-term painful procedures like injections.

PMID: 8594118 [PubMed - indexed for MEDLINE]

[Cancer Nurs.](#) 1992 Apr; 15(2):130-6.

Use of ethyl chloride topical anesthetic to reduce procedural pain in pediatric oncology patients.

[Zappa SC¹](#), [Nabors SB.](#)

Abstract

Pediatric cancer patients often become anxious, agitated, combative, and uncooperative due to the pain or fear of pain during invasive procedures. Generally, it is not the actual administration of medicines that produces this reaction, but the fear of the needle stick itself. Increased education and implementation of coping mechanisms is often not enough to allay this fear. The tangible solution of using ethyl chloride, an anesthetic spray, before port sticks, lumbar punctures, and bone marrow aspirations, was instituted by the hematology-oncology clinic to determine if the pain, emotional trauma, and fear of cancer treatments could be reduced in oncology patients. Survey results on 60 patients and 60 parents/caretakers showed that when given the choice to use the spray or to refuse its use, 68% of the parents thought that the patient had more of a sense of control and, thus, involvement in their treatment. Seventy-eight percent of the patients reported experiencing less pain associated with procedures. Staff noted an increase in cooperation, less combativeness, and more compliance with treatment. Perceiving the child's discomfort diminished, 87% of the parents/caretakers report feeling less anxious and, therefore, more capable of being supportive to each other and their child. These results verified the staff's perceptions of the advantages of using this noninvasive anesthetic. Ethyl chloride is an easy, effective, concrete approach to reducing procedural pain in pediatric oncology patients.

PMID: 1617619 [PubMed - indexed for MEDLINE]

[Can J Anaesth.](#) 1990 Sep; 37(6):656-8.

Ethyl chloride and venepuncture pain: a comparison with intradermal lidocaine.

Armstrong P¹, Young C, McKeown D.

Abstract

One hundred and twenty unmedicated patients undergoing gynaecological surgery were randomly allocated to one of three equal treatment groups to assess the effectiveness of ethyl chloride in producing instant skin anaesthesia to prevent the pain of venepuncture from a 20 G cannula. They received either no anaesthetic, 0.2 ml one per cent lidocaine plain intradermally or a ten-second spray of ethyl chloride at the cannulation site. Ethyl chloride produced skin anaesthesia that significantly reduced the pain of venepuncture. However, it was not as effective as intradermal lidocaine. It had no effect on vein visualisation or ease of cannulation. Ethyl chloride can be recommended as a method of producing instant skin anaesthesia.

PMID: 2208537 [PubMed - indexed for MEDLINE]