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Ethyl Chloride Spray for Injection Site Analgesia

Ryan Pyles PA-S and Mackenzie Kappe PA-S

Common Abbreviations:

ASSH = American Society for Surgery of the Hand

BTX = Botulinum toxin

Abstract

Objective: To determine if ethyl chloride spray provides adequate analgesia prior to injections.

Design: Systematic literature review. **Methods:** A search was conducted in both Pubmed and Scopus using search terms ethyl chloride and injection. The Pubmed search was narrowed to include studies within a 10-year publication range. Articles were excluded based on: population age range, date of publication, and if ethyl chloride was used in conjunction with another analgesic. There were no relevant articles in the Scopus search. **Results:** *Franko O, Stern P.* demonstrated that there was no statistically significant improvement in anxiety or pain perceived with ethyl chloride treatment as compared to the control.¹ *Irkoren et al.* found that ethyl chloride spray and Eutectic Mixture of Local Anesthetic (EMLA) cream each significantly decreased the pain associated with forehead botulinum toxin (BTX) injections when compared to the control.² The majority of patients preferred the ethyl chloride spray over the EMLA cream as an analgesic.² *Moon et al.* determined lidocaine and ethyl chloride are equally effective methods for decreasing pain associated with injections.³ Ethyl chloride spray had the added benefit of a lack of metallic taste.³ **Conclusion:** We cannot conclude that ethyl chloride spray is an effective analgesic prior to injections in men and women. However, we do recommend its use prior to BTX forehead injections and dorsal hand propofol injections in women age 18 and older, based on results from *Irkoren et al.* and *Moon et al.*^{2,3}

Introduction

The use of injections is a frequently utilized treatment and assessment modality presenting throughout most, if not all, disciplines of medicine. According to the most recent available data, there are around 16 billion injections performed each year.⁴ From vaccinations to nerve blocks, injections are utilized for the benefit of the patient, but are often associated with reasonable pain and distress. Studies estimate that between 2 and 20% of people seeking medical attention experience injection anxiety.⁵ This anxiety, described as an excessive fear in response to the anticipation or experience of an injection, can become a barrier to treatment and has been shown to increase the experience of pain.⁵ Patients that could benefit from an injection may hesitate to receive something that would be therapeutic.⁵ Avoidance of therapeutic measures can have a negative result on the patient's attitude toward health care,

and potentially, their course of treatment. Reducing the levels of pain associated with an injection is an important consideration to lowering a patient's barriers to treatment. One of the most prevalent analgesics for decreasing injection-associated pain is ethyl chloride.

Ethyl chloride is a topical anesthetic approved for use in adults and children and is used to temporarily control pain associated with injections, venipuncture, and minor surgical procedures. The topical anesthetic is administered as a spray to intact skin prior to one of the aforementioned procedures. Ethyl chloride utilizes vapocoolant properties to slow nerve conduction of the C-fibers and A-delta fibers in the peripheral nervous system.⁸ This property slows conduction of the pain fibers to temporarily decrease the central nervous system's capacity to perceive pain.⁸ The effects of the spray can last up to one minute, due to its rapid evaporation time.⁷ This property prevents prolonged loss of sensation for the patient. If the procedure is not completed within one minute, the spray can be reapplied to intact skin without adverse reaction. Side effects of ethyl chloride are rare and include allergic reaction and temporary hypochromia.⁶ Dyschromia occurs with over-freezing of the skin; however, proper use is preventative.⁶

The aim of this study is to compile the most up-to-date evidence to investigate whether there is a statistically significant difference, as well as a clinically significant difference, in the outcome of injection-associated pain for the use of ethyl chloride compared to placebo.

Clinical question

Among adults receiving injections, does ethyl chloride, as compared to a placebo, provide adequate analgesia?

Methods

An initial search was conducted on September 6th, 2017 using the Pubmed database (Figure 1). A total of 199 studies were identified using search terms "ethyl chloride" and "injection". Narrowing the search to include studies within a 10-year publication range produced 55 articles, which were screened for relevance. From these results, 5 full-text articles were assessed for eligibility. Two full-text articles were excluded based on: population age range, date of publication, and if ethyl chloride was used in conjunction with another analgesic. The exclusion criteria left 3 articles that were included in the qualitative synthesis. An additional search was also conducted using the database Scopus for additional peer-reviewed literature. A search using the same terms of "ethyl chloride" and "injections" yielded 19 articles. None of the 19 articles were relevant as there was no discussion of ethyl chloride administration or injection-associated pain.

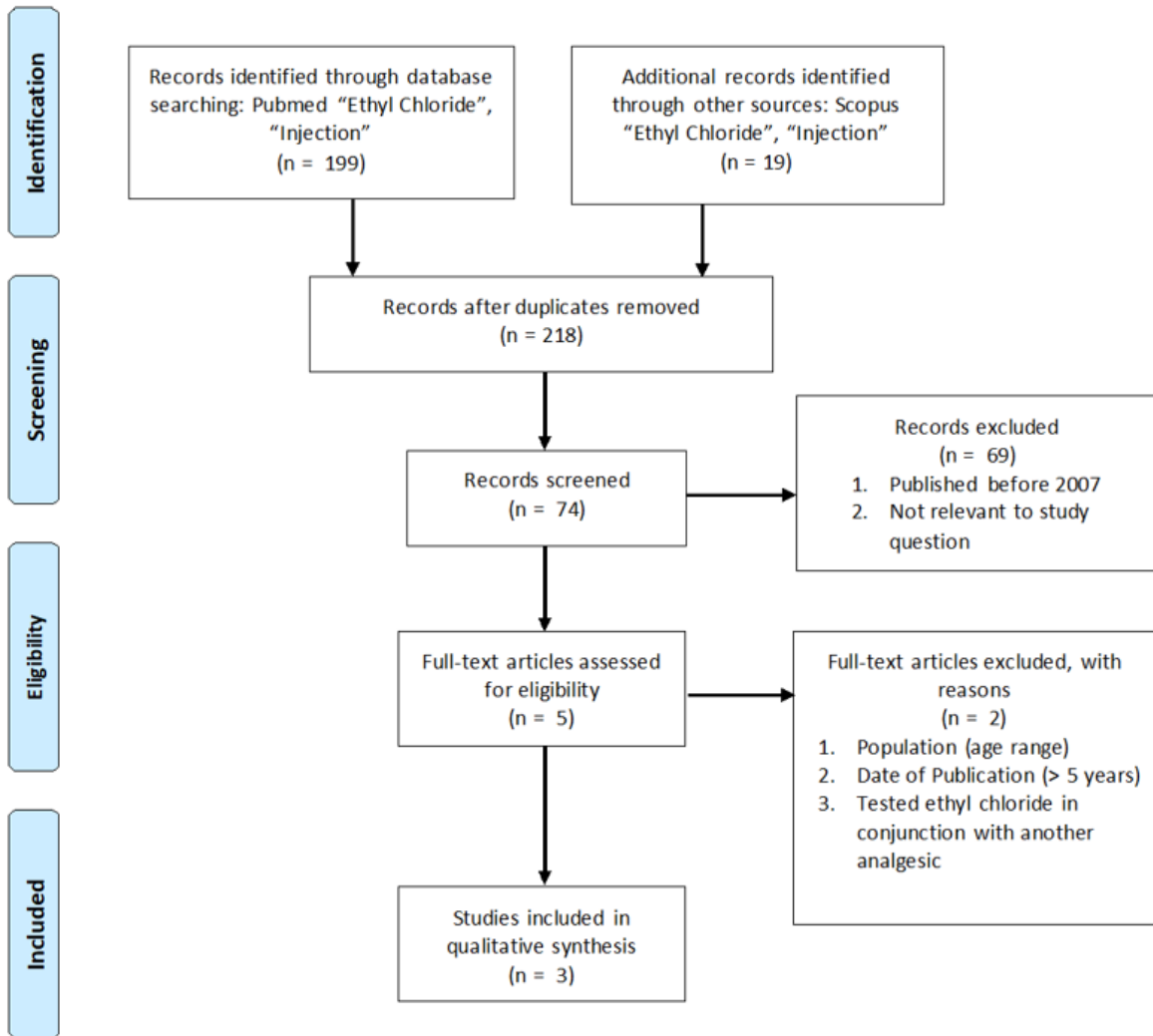


Figure 1. PRISMA flow diagram outlining the methods used to select the articles analyzed in this study.⁹

Results

Study #1: *Use and Effectiveness of Ethyl Chloride for Hand Injections.* Franko O, Stern P.¹

Study Objective:

To determine the efficacy of ethyl chloride on a patient's pain level and injection associated anxiety before and after routine hand injections.

Study Design:

The study begins with an email survey to all members of the American Society for Surgery of the Hand (ASSH). Contact information was obtained through membership records of the ASSH. All members were asked: "In your hand practice, how often do you use ethyl chloride

spray for analgesic effects immediately before a steroid injection (trigger finger, DeQuervain, carpal tunnel, joint injections)?” Response options were Always (>90%), Often (67%-90%), Sometimes (33%-66%), Rarely (10%-32%), and Never (<10%). The survey aimed to characterize each responding surgeon’s usage of ethyl chloride administration prior to injections. Responses were collected over a two week period and reminders were sent to those who had not yet responded. Those responding were analyzed in relation to their years of membership to the ASSH, the region of the United States for which they practiced, as well as their type of practice and specialty.

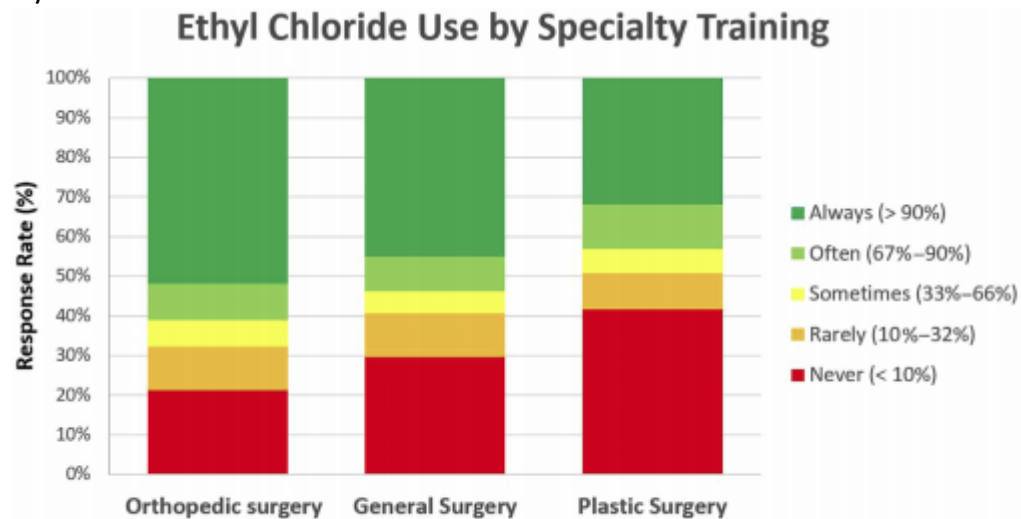


FIGURE 2: Ethyl chloride use among hand surgeons based on training specialty.

Figure 2: Percentage comparison of ethyl chloride usage among responding hand surgeons based on specialty.¹

After completion of the survey, a prospective, randomized study was completed to evaluate the benefit of administering ethyl chloride compared to no-spray on the patient’s perceived pain and anxiety through a questionnaire completed before and after the injection administration. Participants were included in the study if they were receiving a routine injection for trigger finger, DeQuervain tenosynovitis, first carpometacarpal joint osteoarthritis, or carpal tunnel syndrome. Patients were excluded if they were unable to complete an English survey or requested ethyl chloride prior to an injection. Using either ethyl chloride or no spray in alternating months was utilized for the randomization of a patient’s treatment. Informed consent was obtained for all patients prior to each procedure.

After consenting to study enrollment, each patient completed a questionnaire using an 11-point Likert scale ranging from “none” to “extreme” for three questions. The questions are as follows: (1) How painful do you think it will be?, (2) How painful will it be 1 minute after the injection?, and (3) How nervous are you about the injection? A fourth yes or no question was asked not using the scale: (4) Have you had a hand injection before?... and if so, was ethyl chloride/ freeze spray used?

The procedure was performed at two different healthcare institutions with parallel treatment regimens performed by the same surgeon. Aseptic preparation was performed with alcohol swabs, and if in the spray group, ethyl chloride was administered over the injection site

for 7-10 seconds. Then for both groups a 27-gauge needle was inserted with the surgeons customary, consistent technique. For all patients, the same 1:1 ratio of a combination of 1% lidocaine and 4mg/ml dexamethasone was utilized with 1mL utilized for trigger finger or thumb base joint injections and 2mL for a DeQuervain's tenosynovitis or carpal tunnel syndrome.

One minute after the procedure, an additional four item questionnaire was completed asking participants to report their pain on a scale of 1 to 10. The questions asked were for the actual needle pain, the actual pain from the medication, the actual pain one minute after the injection, and their overall anxiety related to the procedure.

Using statistical analysis, it was determined that having 75 participants in the ethyl chloride spray group and 75 participants in the no spray group would be needed to have adequate power to draw conclusions about their differences. The Mann-Whitney U test was implemented to compare the differences between the two groups based on the different patient's answers for pain before the injection, pain after the injection, pain after injection after a minute, and their nervousness before the injection. Additional analysis was also obtained by subgroups for sex, high anxiety, or those with high levels of anticipated pain. There were 16 comparisons made and a Bonferroni correction, a statistical method to overcome multiple comparisons, yielded an alpha level of 0.003.

Study Results:

A response rate of 73% was obtained for the email survey from 2,083 members of the American Society for Surgery of the Hand. 59% reported they always or often used ethyl chloride, while 24% never utilized the spray. Experienced surgeons were considered less likely to use ethyl chloride with only 35% reporting utilizing it routinely compared with 66% of younger surgeons. No association for ethyl chloride usage was noted based on region or type of practice. A statistically significant result with a p-value <0.05 was found for decreasing use of ethyl chloride and increased years of practice as well as decreasing usage of ethyl chloride for plastic, orthopedic, and general surgeons. Of the 151 patients that were studied, half received ethyl chloride administration with the other half not receiving a spray. The results showed equivalence in the questionnaire for injection pain, pain after 1 minute, and overall anxiety. A Pearson test was utilized to demonstrate the pain from the injected anesthetic and post-injection pain were highly correlated ($r=0.073$) and a mean of their values was utilized to show injection pain. There was no difference throughout the overall population studied for anticipated versus actual pain and anxiety. However, there was a reduction in post-injection pain in those anticipating high levels of pain before the injection and in females for post-injection pain. No subgroup showed statistically significant improvement in anxiety or pain perceived with ethyl chloride treatment.

Study Critique:

A major strength of this study was the stated degree of patient randomization to initial treatment. Patients were block-randomized in groups of 3 before enrollment. This was completed through simple randomization with a computerized random number generator and sealed envelopes. For further privacy protection, the order was kept in sealed, opaque envelopes and revealed with each patient enrollment. An additional strength of this study is its comparison of similar, commonly used, and affordable forms of topical analgesia. These choices

for study are especially beneficial as they are likely to be applicable to a variety of clinical settings.

A major critique of this study is that patients that requested ethyl chloride were removed from the study. This was done to eliminate bias, but also removes an entire patient population that had presumably received enough prior benefit from ethyl chloride to request its administration again. It was not stated whether the study kept or removed patients that similarly requested to not have ethyl chloride administration. The study is additionally limited by its focus only on patient populations receiving hand injections. This is a highly specific and unique anatomic region that could limit the ability to extrapolate to other areas and types of injections. Additionally, the paper admittedly neglects to consider factors such as anxiety levels and female menstruation which are known to alter a patient's perception of pain. Altered perceptions of pain have the potential to skew the final results. Furthermore, the study did not use a placebo. Without a placebo, there was no blinding to the patient's treatment, which can create bias for accurately reporting pain. Patient's expectations of treatment and their efficacy can influence the expected result in terms of benefit and pain perception. If a patient is receiving an analgesia they have not previously found beneficial, they are more likely to expect a worse outcome than they would be with a novel or previously beneficial analgesia. Finally, the author's of this paper did not specifically declare the source of study funding or any potential conflicts of interest.

Study #2: *A Clinical Comparison of EMLA Cream and Ethyl Chloride Spray Application for Pain Relief of Forehead BTX Injection. Irkoren et al.*²

Study Objective

To determine the efficacy of EMLA cream and ethyl chloride spray application for analgesia prior to BTX injection.

Study Design

This was a prospective, randomized study that consisted of 45 females who volunteered to receive forehead injections of BTX A for reduction of wrinkles. Exclusion criteria included patients who were taking analgesics or anxiolytic drugs, and individuals with known allergies to the study medications. Before study enrollment, simple randomization, using a computer random number generator, was used to block-randomize patients into three groups. The randomized order was kept in sealed opaque envelopes and revealed upon patient enrollment.

The first group included 15 females between ages 35 and 60 with an average age of 46.73 +/- 8.85 years. These women received ethyl chloride spray (Chlorethan 100 mL, ethyl chloride cooling aerosol spray) on one side of the forehead; the opposite side served as the control. The second group of 15 females had an average age of 48.53 +/- 9.04 years with a range of 36 to 64 years. In this group, topical anesthetic cream (EMLA cream 5% 25 g lidocaine, 25 g prilocaine; Astra Zeneca, London, UK) was applied to one side of the forehead while the other side served as a control. The last group of 15 females had an average age of 49.60 +/- 8.71 years with a range of 37 to 66 years. On one side of the forehead the ethyl chloride spray was used and on the other side, topical anesthetic cream was applied.

EMLA cream was applied 45 minutes prior to injection of BTX. Ethyl chloride was sprayed on the injection sites for 4 to 8 seconds or at the first sign of skin blanching. Gauze was used to shield the patients' eyes from the ethyl chloride spray. BTX was diluted with 4mL of 0.9% sodium chloride so that 0.1mL contained 2.5 U of BTX. The skin was sterilized with alcohol before patients had four 0.1mL injections of 2.5 U of BTX (maximum 10U) in their forehead according to the clinical features of the patients. A 30-gauge disposable needle was used for injections, and one doctor performed all injections to decrease variability.

Pain was assessed using the visual analog scale (VAS). Each subject was informed on how to use the VAS prior to scoring. Patients were shown a 10-point scale in which they were to rate their pain on a scale of 1 to 10, 1 representing no pain and 10 representing the worst pain imaginable. Participants in Group 3 were requested to determine which method of analgesia they preferred, the EMLA cream or ethyl chloride spray.

Study Results

In group 1, comparing ethyl chloride and the control, the average pain score for ethyl chloride was 3.20 +/- 1.20 with a range of 1-5. The average pain score for the control was 7.26 +/- 1.94 (range, 4-10). In group 2, comparing EMLA cream and the control, the average pain score for EMLA cream was 4.20 +/- 1.37 (range, 2-7). The average pain score for the control was 7.66 +/- 1.54 (range, 5-10). Group 3's average pain score using the EMLA cream and the ethyl chloride was 6.80 +/- 1.37 (range, 4-9) and 2.93 +/- 1.03 (range, 1-5), respectively. Pain relief scores for group 1 and 2 were determined by subtracting the pain score of the anesthetized side from the pain score of the control side for each patient. Group 1 and group 2 pain relief scores were 4.06 +/- 1.79 and 3.46 +/- 1.35, respectively.

This study showed that ethyl chloride and EMLA cream are effective at reducing pain with local injections. Both the ethyl chloride group and EMLA cream, (group 1 and group 2, respectively) had a statistically significant reduction in pain as compared to the control ($p < 0.05$). Pain relief scores were higher for group 1 than group 2, indicating a greater reduction in pain with the use of ethyl chloride. Ethyl chloride was more effective than EMLA cream at reduction in pain overall. Patients in group 3 rated pain lower with use of ethyl chloride as compared to use of the EMLA cream, and results were statistically significant ($p < 0.05$). Most patients preferred the ethyl chloride spray over the EMLA cream. This study determined that skin cooling ethyl chloride spray significantly decreased the pain associated with forehead BTX injections.

Study Critique

This study chose to randomize the participants into one of three study groups. Randomization was performed using a computer random number generator and concealed, until patient enrollment, using sealed envelopes. Randomization is a strength of this study because it helps to minimize bias.

The two major limitations of the study were: a small, female only study population and lack of placebo. This study population was small, with 45 participants, and included only females. A larger sample size which includes men, would be a more accurate representative of the general population and would increase confidence in applying results of the study to patients in real practices. The study could not replicate the cooling effect of the ethyl chloride

which prevented them from using a placebo. Without a placebo, patients were not blinded and were aware of which side of their forehead had treatment and which was the control. This could create bias in reporting pain. Participants who want the treatment to work may report lower pain scores when in fact there is no difference between the treatment or control. This issue also correlates with the study using subjective data to score pain rather than objective data. Each patient has a different pain threshold and may report pain differently on a numbered scale. This could affect true pain score and thus, results of the study. The authors did not declare conflicts of study or sources of funding.

Study #3: *Preventive effect of a vapocoolant spray on propofol-induced pain: a prospective, double-blind, randomized study. Moon et al.*³

Study Objective

To compare the effect of ethyl chloride spray to lidocaine as a pre-treatment for propofol injection pain.

Study Design

This prospective, double-blind, randomized study included 90 American Society of Anesthesiologists (ASA) physical status I or II females, aged 20-65 years, scheduled for elective gynecological hysteroscopy via ambulatory surgical care at Seoul Saint Mary's Hospital in South Korea. Exclusion criteria consisted of a history of allergy to the study drug, history of a suspicious or known difficult airway, peripheral vascular disease, chronic pain syndrome, use of an analgesic or topical anesthetic within 24 hours of surgery, psychiatric history, history of cold intolerance, abnormal upper arm sensations, infection at the injection site, body mass index >35 kg/m², pregnancy, or breastfeeding.

Participants were randomized into three groups using computer-generated codes sealed in opaque envelopes. The groups were: group V (vapocoolant spray), group L (lidocaine), or group C (control). Before the start of the study, participants assessed their pain level using a visual analogue scale (VAS) where 0 cm= no pain and 10 cm = worst pain imaginable. A 20-gauge angiocatheter was inserted into the dorsum of the participant's non-dominant hand and ringer's lactate solution, at a rate of 10 ml/min, was attached. Preoperative medication was omitted. Electrocardiogram, non-invasive blood pressure, heart rate, pulse oximetry, and bispectral index monitor were attached in the operating room. Operating room temperature was kept at 25°C.

Two placebos were used: 1% lidocaine (0.05 ml/kg) vs. the same amount of normal saline and vapocoolant spray vs. a placebo spray. The vapocoolant spray was Walter Ritter GmbH & Co., Hamburg, Germany ethyl chloride spray, and the placebo spray was Evian Eau Minerale Naturelle. Labels on syringes were changed so contents could not be identified by participants, and sprays were masked with opaque paper.

In the operating room, maintenance fluid was discontinued. With the participant in supine position, a blinded partition was set between the upper arm where the propofol would be injected and the investigator, who stood at the head of the participant. Participants were asked to focus on the propofol injection pain "after the tourniquet was released". A nurse who did not participate in the assessment, opened the envelope assigned to each participant and

then, performed the study process behind the blinded partition. This allowed blinding of both the participant and the investigator.

For group V, an automated blood pressure cuff was applied 10-15 cm proximal to the intravenous access point and inflated at 50 mmHg for venous occlusion. Normal saline was injected as a placebo for lidocaine. One minute later, the propofol injection site was sprayed with ethyl chloride spray, 30 cm from arm for 5 seconds. In group L, venous occlusion was performed the same way as group V and lidocaine was injected. After one minute, the propofol injection site was sprayed with the placebo spray in the same way. Group C methods were the same as group V and L except placebo was used for both the injection and spray. To prevent unblinding due to differences in sound, both vapocoolant and placebo sprays were used at the same time with the assigned one targeted to the propofol injection site and the other targeted to the open air.

Immediately after finishing the methods described above, the tourniquet was released and 0.5 mg/kg of propofol-medium-chain triglyceride/long-chain triglyceride (10 mg/ml ampule; Fresenius, Ankara, Turkey) was injected for 5 seconds. Blinded investigators assessed the participant's VAS pain score and occurrence of metallic taste (yes or no). After assessment completion, Fentanyl (1 µg/kg) was injected and 2 mg/kg of propofol was administered to complete anesthetic induction. A laryngeal mask airway was inserted after unconsciousness. Anesthesia was maintained with 1.5–2.5% sevoflurane in a 50% oxygen/air mixture.

Inhaled anesthetics were discontinued after surgery. The laryngeal mask airway was removed, and participants were moved to the post anesthesia care unit (PACU) once they regained consciousness and full muscle strength. After recovery, participants rated their level of satisfaction with the methods used to prevent propofol injection pain using a five-point scale (5: strongly satisfied, 4: satisfied, 3: undecided, 2: dissatisfied, and 1: strongly dissatisfied). The propofol injection site was observed for redness, swelling, itching, or injury from cold.

Study Results

Table 1. Participants' characteristics.³

	Group V (n = 30)	Group L (n = 30)	Group C (n = 30)
Age (years)	37.6 (9.9)	39.9 (9.4)	41.3 (12.5)
Weight (kg)	55.9 (8.6)	57.7 (9.3)	55.8 (7.3)
Height (cm)	159.5 (6.0)	162.2 (5.9)	159.6 (6.8)
ASA I/ II	27/3	24/6	23/7

Of the 90 people enrolled, no participants dropped out of the study (Figure 3).³ Study reported no significant differences in participant characteristics between the groups (Table 1).³

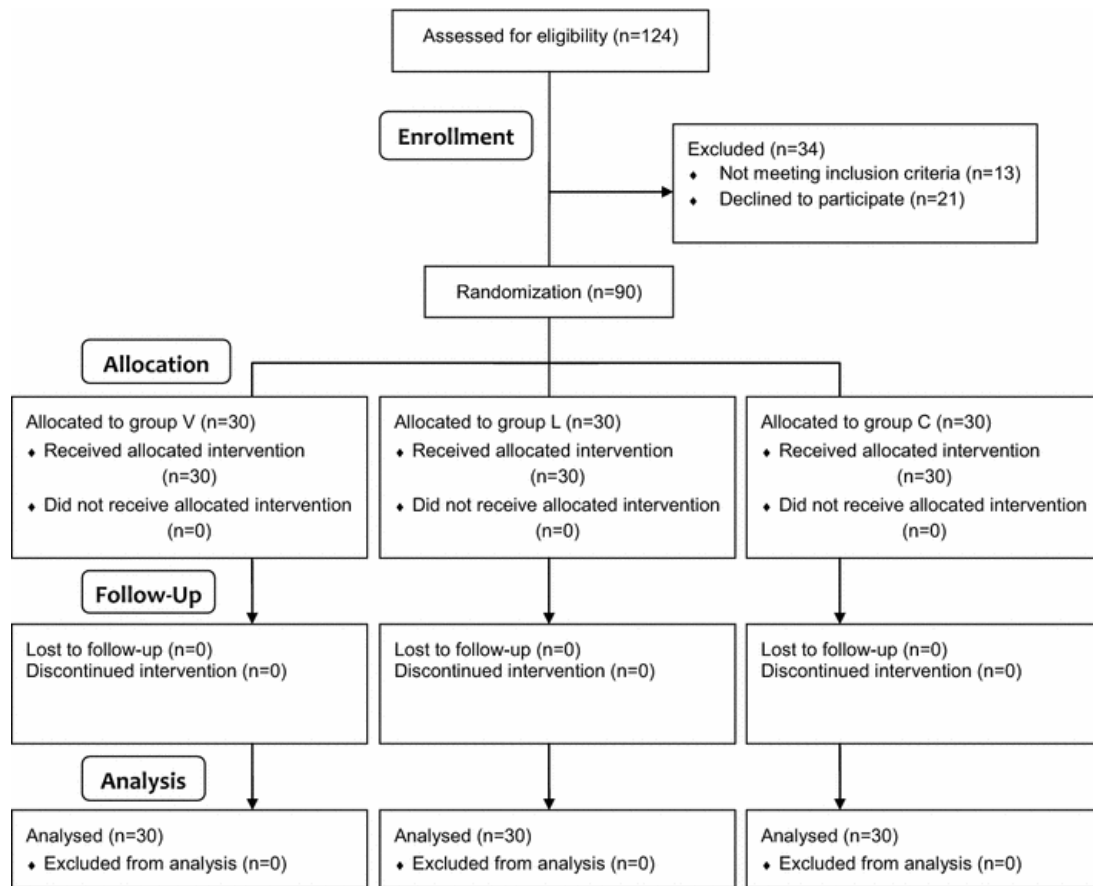


Figure 3. CONSORT flow diagram demonstrating the distribution of participants.³

There was significantly lower pain from the propofol injection in groups V and L than in group C ($p < 0.001$). Group V's, L's, and C's average pain intensity scores were 0.5, 0.5, and 5, respectively ($p < 0.001$). Although the pain score for group V ranged from 0 to 2.25 and group L's pain score ranged from 0 to 1, there was no significant difference in pain intensity between the two groups ($p = 0.413$).

Participants in group V and C did not report metallic taste. Of the 30 people in group L, 23% reported metallic taste. Group L had a statistically significant increase in the incidences of metallic taste when compared to Group V and C ($p < 0.001$). There was no difference between group V and C.

Satisfaction scores for each group were assessed and showed that participants in groups V and L were more satisfied with prevention of propofol induced pain than those in group C ($p < 0.001$). The average satisfaction score for group V was 5 with a range of 4 to 5. The average score for group L and C were 4 (3.75-5) and 2 (2-3), respectively. There was no significant difference between group V and L ($p = 0.012$). Redness, swelling, itching, or injury from cold was not observed at the propofol injection site.

The study found that lidocaine and ethyl chloride are equally effective methods for decreasing pain associated with injections. Participants in the study reported lower pain scores and greater comfort in groups that used lidocaine or ethyl chloride. The ethyl chloride group (group V) had the benefit of a lack of metallic taste.

Study Critique

The strengths of this study include: randomization of participants into one of three study groups, blinding of participants and investigators to treatment allocation, and maintenance of blinding to treatment via placebos. As stated previously, randomization of participants limits biases within the study by distributing lurking variables at chance levels across treatment groups. The blinding of participants and investigators to the treatment allocation (vapocoolant spray, lidocaine, or control) was ensured by sealing the computer randomized numbers in envelopes which were opened by a nurse not participating in the study. The investigators stood behind a curtain as the treatment was carried out by the nurse. Placebos were used for the vapocoolant spray and the lidocaine which further ensured blinding of participants. For the vapocoolant spray, the investigators used Evian Eau Minerale Naturelle, a pure water spray of approximately the same size as the vapocoolant spray, and for the lidocaine, investigators used normal saline. Since each participant received an injection and a spray, they stayed blinded to the actual treatment used (vapocoolant spray vs lidocaine). A double blinded study, such as this one, eliminates bias of the investigator and the participant. Neither will be bias of the result and thus, unable to consciously or subconsciously influence experimental observations.

Like other studies that measure pain in relation to an intervention, this study used a subjective method to assess pain. Pain is a subjective symptom; however, each individual has a different pain threshold and rates pain differently on a numbered scale. This could lead to major variations in results. An objective measurement of pain would be more reliable. Another issue with this study is the use of only females. In order to confidently apply the study results to the general population, male participants should have been included. Again, there are considerable differences in pain threshold and reporting between individuals, and especially between males and females. What may be beneficial to a female population may not be for a male population. There were no conflicts of interest or sources of funding for this study.

Discussion

To summarize, ethyl chloride administration was shown to provide statistically significant benefit for females receiving forehead BTX injections ($p < 0.005$) and females receiving propofol injections prior to surgery ($p < 0.001$), but this significance was not shown for a study of males and females receiving various hand injections.¹⁻³ These conclusions were reached after scanning the literature for articles comparing ethyl chloride with a control and reviewing these three selected articles. Furthermore, there is conflicting and insufficient data to make a sweeping, evidence-based recommendation to endorse the use of ethyl chloride for the general population and the majority of injections due to the narrow scope of these studies. The studies vary in numerous areas including, but not limited to, their methods, measurements of treatment endpoints, injection types, and populations studied. These variations confound results. This limits analysis and the ability to compare their results for the purpose of drawing

more general conclusions about the efficacy of ethyl chloride. Finding more homogenous and broad data on this topic was difficult as additional studies scanned were frequently examining ethyl chloride only in comparison to other analgesics as opposed to placebo or no treatment controls. Ethyl chloride compared to other analgesics is outside the scope of this review. Additionally, each study has its own limitations, differing levels of reliability, and varying levels of bias toward a specific recommendation.

Study one is limited by its focus exclusively on the hand as an injection site.¹ The hand's specific anatomy and syndromes make it difficult to compare to injections of other anatomic locations. Additionally, it is limited by the fact that patients who requested ethyl chloride administration were excluded. This limits the population of study to those naïve to ethyl chloride spray. This is excluding a group that has potentially received benefit from it previously. This population exclusion, as well as not addressing whether those that requested to not receive ethyl chloride spray were included, creates doubts about the reliability of the study results.¹ This exclusion of one population that presumably experiences benefit from ethyl chloride and not one that had a negative experience with in the past is concerning for bias toward ethyl chloride not being an effective analgesia. This potential bias is consistent with the conclusion of the study, which states that no statistically significant benefit was discovered with ethyl chloride usage.¹ Furthermore, the study is limited by admitted lack of blinding by patients and observers to the mechanism of treatment.¹ A lack of blinding is concerning for creating a bias in pain reporting and interpretation of results.¹ There are no conflicts of interest noted.¹

Study two is limited as it was completed with a population of a small group of only females.² The population of the study was limited to 45 participants in total.² Increasing the sample size and with a similar amount of men and women would more accurately represent a typical population and allow for drawing broader conclusions from the research. The study was limited exclusively to BTX injections of the forehead as well.² This limits not just the site that conclusions can be extrapolated from, but also the types of injection needles utilized, as only those suitable for forehead BTX injections are being studied.² Similar to study one, the patients were not blinded to their treatment as the effects of a cooling spray could not be easily replicated.² The knowledge of treatment by the patient, observer, and provider can create bias and concerns about the reliability of pain reported.² Those with a desire for a treatment to work or not to work can alter the results of the study if they have the knowledge that they are or are not receiving the treatment. Results consisting exclusively of subjective data, such as in this study and study one, are more prone to such bias and can skew the results.^{1,2} There are no conflicts of interest noted.²

Study three, similar to the aforementioned studies, is limited by the need to measure pain subjectively.³ Due to varying pain thresholds among patients and their correlation between specific pain perceived to the scale in the study, there is likely great variability to the study results.³ Like study two, this study used an exclusively female population and therefore cannot be extrapolated to the general population.³ No conflicts of interest were noted.³

Overall, this review is weakened by a lack of available studies with large, diverse sample sizes that have various injection sites studied. Two out of three studies were limited by sample size and population studied, but all three were limited in scope to a specific type of injection.¹⁻³ Therefore, these studies are unable to contribute sufficient evidence to support ethyl chloride as clearly providing clinically significant analgesia for the general population for all, or even

most, injection types. However, statistically significant results were found in studies two ($p < 0.005$) and three ($p < 0.001$) showing that for their female population studied ethyl chloride provided pain reduction for forehead BTX and upper arm propofol injections.^{2,3} There are no conflicts of interest to report for this review and no funding was received.

Conclusion

Injection fear plays a major role in whether a patient receives appropriate care and treatment. Diminishing or eliminating pain with injections helps build good rapport with patients and can reduce a major barrier to treatment. Since injections occur in all areas of healthcare, many methods of analgesia have been studied.

Ethyl chloride spray may be a promising method of analgesia due to its quick onset of action, ease of use, and good safety profile. However, in this review, we cannot conclude that ethyl chloride spray is an effective analgesic prior to all injections in both men and women due to the differences in conclusions and variations between each study. The narrow scope of studied injection types and sites limit our recommendations for ethyl chloride spray use. We do recommend its use prior to BTX forehead injections and dorsal hand propofol injections in women age 18 and older, based on results from *Irkoren et al.* and *Moon et al.*^{2,3}

Futures studies should be performed on a large population size that includes both men and women in order for conclusions to be drawn about the analgesic effect of ethyl chloride in the general population. Studies should also attempt to observe objective measurements of pain to assess efficacy of ethyl chloride spray. This would be beneficial as individual pain thresholds and scoring of pain differs. Objective measurements of pain will provide accurate data free of subjective variation. Lastly, it would be beneficial for studies to assess ethyl chloride spray in a variety of injection locations. Innervation differs in varying regions of the body which makes it difficult to conclude that ethyl chloride spray is effective everywhere. Ideally, studies would also evaluate different injection types.

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