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Effect of Ethyl Chloride Spray for Pain Reduction during Amniocentesis: A non – blinded randomized controlled trial

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ABSTRACT

Objectives: To evaluate the cryo-analgesic effect of ethyl chloride spray on reducing pain during second-trimester amniocentesis.

Materials and Methods: A non-blinded randomized controlled trial was performed to compare the post-procedural pain scores during second-trimester amniocentesis between pregnant women who received and did not receive ethyl chloride spray immediately before amniocentesis needle penetration. Outcome was mean of post-procedural pain score measured by using visual analogue scale (VAS).

Results: The study was performed between May and November 2016. One hundred and forty-eight participants were randomly divided into two groups received cryo-analgesia using ethyl chloride spray and did not receive. There were no differences between demographic data and pre-procedural pain scores (anticipated pain) ($p = 0.6$). Mean post-procedural pain score in the cryo-analgesia group was significantly lower than the control group ($p = 0.01$). Six participants in cryo-analgesia group had frostbite skin rash (8%) which was self-limiting condition and persists for about one month with no scar. Most participants (98%) willingly accepted to undergo the procedure again if indicated.

Conclusion: Ethyl chloride spray may be an alternative method for amniocentesis procedural pain management. Women should be informed about the potential risk of complications.

Keywords: Amniocentesis, pain, ethyl chloride spray, visual analogue scale.

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การศึกษาผลของยาชาชนิดพ่นเอทธิลคลอไรด์ (Ethyl chloride) ต่อการลดความเจ็บปวดจากการเจาะน้ำคร่ำในไตรมาสที่สองของการตั้งครรภ์

กฤตกาล เตลผล, สมมาตร บำรุงพืช, ณัฐพงศ์ อิศรางกูร ณ อยุธยา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของยาชาชนิดพ่นเอทธิลคลอไรด์ (ethyl chloride) ต่อการลดความเจ็บปวดจากการเจาะน้ำคร่ำในไตรมาสที่สองของการตั้งครรภ์*

วัสดุและวิธีการ: *ทำการศึกษาแบบควบคุมสุ่มแบบไม่อำพราง (Non-blinded randomized controlled trial) เพื่อเปรียบเทียบคะแนนความเจ็บปวดหลังจากการเจาะน้ำคร่ำในไตรมาสที่สองของการตั้งครรภ์ ระหว่างหญิงตั้งครรภ์ที่ได้รับ และไม่ได้รับยาชาชนิดพ่นเอทธิลคลอไรด์ (ethyl chloride) ก่อนแทงเข็มเจาะน้ำคร่ำ คะแนนความเจ็บปวดวัดด้วยการใช้ visual analogue scale (VAS)*

ผลการศึกษา: *ทำการศึกษาระหว่างเดือนพฤษภาคม ถึง พฤศจิกายน พ.ศ. 2559 ผู้เข้าร่วมการศึกษาจำนวน 148 คน ถูกแบ่งเป็นสองกลุ่มโดยการสุ่ม ได้แก่ กลุ่มทดลองที่ได้รับยาชาชนิดพ่นเอทธิลคลอไรด์ และกลุ่มควบคุม ไม่พบความแตกต่างกันของลักษณะข้อมูลพื้นฐานของผู้เข้าร่วมการศึกษาและคะแนนความเจ็บปวดที่คาดคะเนก่อนทำหัตถการ (p = 0.6) ค่าเฉลี่ยของคะแนนความเจ็บปวดหลังทำหัตถการในกลุ่มที่ได้รับยาชาชนิดพ่นเอทธิลคลอไรด์น้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (p = 0.01) ผู้เข้าร่วมการศึกษาจำนวน 6 คน ในกลุ่มที่ได้รับยาชาชนิดพ่นเอทธิลคลอไรด์เกิดรอยผื่นน้ำแข็งกัด (8%) ซึ่งเป็นภาวะที่สามารถหายได้เอง โดยใช้เวลาประมาณหนึ่งเดือนและจางหายไปไม่มีรอยแผลเป็น ส่วนใหญ่ของผู้เข้าร่วมการศึกษาทั้งหมด (98%) ยินดีเข้ารับการเจาะน้ำคร่ำอีกครั้งหากมีข้อบ่งชี้*

สรุป: *ยาชาชนิดพ่นเอทธิลคลอไรด์ อาจเป็นทางเลือกหนึ่งในการจัดการความเจ็บปวดจากการเจาะน้ำคร่ำโดยผู้ที่จะรับการใช้ยาชาชนิดพ่นนี้ควรได้รับคำแนะนำอย่างเหมาะสมถึงความเสี่ยงต่อภาวะแทรกซ้อน*

คำสำคัญ: *เจาะน้ำคร่ำ, ปวด, เอทธิลคลอไรด์, ยาชาชนิดพ่น*

Introduction

Amniocentesis is a common prenatal diagnosis procedure which is at risks such as abortion (0.2-0.3%), infection, and membrane leakage[1]. This procedure also causes pain which leads to anxiety and some patients may request pain controller or refuse to undergo this procedure.

There are two pathways of amniocentesis-associated pain i.e. somatic and visceral pain[2]. Previous studies evaluated pain-related factors during amniocentesis found that parity, gestational age, body mass index (BMI), previous surgery, needle penetration through the placenta, the thickness of the abdominal wall, and depth of needle penetration have no correlation with the degree or severity of pain[3]. One study had divided uterus into three areas (upper, middle, and lower) and evaluated the degree and severity of pain when needle penetrated through each site and found that pain from penetration in upper part had less pain score than other sites[4].

There have been many previous studies to evaluate analgesic methods. Two studies comparing xylocaine injection and without anesthesia found no difference in pain score between both groups[5, 6]. Other two studies that used a sub-freezing needle and light leg rubbing technique reported the same result[7, 8].

The aim of cryo-analgesia is to inhibit local pain reception by using the cold-producing instrument. One study using cold gel pack placed on skin 5 minutes before needle insertion compared with room temperature gel pack found the lower pain score in cold gel pack group[9]. However, amniocentesis procedural time must be prolonged and cold gel pack may cause unnecessary wide anesthetic area. Ethyl chloride spray is a vapor coolant which induces skin cooling, reduces the sensitivity of pain receptor and causes decreased pain perception[10]. It is used as cryo-analgesia for venipuncture in both adults and children[11, 12]. Although ethyl chloride spray is not sterile, one study showed that ethyl chloride spray did not change sterility on the sprayed skin[13]. This spray is recommended for fetal scalp blood stimulation in fetal scalp blood sampling procedure and had no reports of mutagenicity, embryotoxicity, teratogenicity and reproductive toxicity in human[14-16]. With the benefits of cryo-analgesia and safety in human, this ethyl chloride spray could be one of analgesic methods that improve the amniocentesis pain control. The objective of this study was to assess cryo-analgesic effect of ethyl chloride spray on pain reduction in second trimester amniocentesis.

Materials and Methods

A prospective non-blinded randomized controlled trial was conducted from May to November 2016 at the Prenatal Diagnostic Unit, Ramathibodi Hospital. Pregnant women with indications for amniocentesis were recruited. Inclusion criteria were women who never undergone amniocentesis and no fetal gross structural abnormalities identified by ultrasonographic evaluation. Exclusion criteria included women who had known allergy to cold, ethyl chloride spray, received pain killer for previous 4 hours, required more than 1 puncture in the same procedure, and could not understand the study process or had a poor ability in communication. This study was reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, based on the Declaration of Helsinki.

Pregnant women were informed about the amniocentesis procedure and complications by Maternal-Fetal Medicine (MFM) fellows. Then, the study was explained to patients for participation. They were given ample time for questions and decision and had voluntarily consented to join the study. Then, a visual analogue scale was introduced to all participants. The visual analogue scale (VAS) is a method for pain measurement which consists of a 10-centimeter line with two terminals. The left terminal refers to “no pain” (score=0) and another terminal refers to “full pain in life” (score=10). Each participant must mark a point that represents the level of pain on the 10-centimeter line prior to and

immediately after amniocentesis for anticipated pain and post-procedural pain measurement, respectively. The anticipated pain was level of pain from amniocentesis that they expected and the post-procedural pain was level of pain they truly had from this procedure. General demographic data were collected, including maternal age, body weight, height, gestational age, parity, previous delivery, previous vaginal operation, history of abortion and dilatation and curettage, history of cesarean section, and history of abdominal surgery. They also had to answer a questionnaire about their concern of, or anxiety to amniocentesis.

Block of four was used for randomization to assign study population into 2 groups: cryo-analgesia and control group. For a significant difference in mean pain score, this study needed a sample size of at least 74 cases per group to gain power of 80% at 95% confidence interval. After randomization, participants entered a procedural room for ultrasonographic fetal anomaly screening. An area on skin was marked for needle insertion and applied with an aseptic agent. Spinal needle gauge 22 and a 20 ml syringe were used. Participants in the cryo-analgesic group were sprayed with ethyl chloride on the marked area immediately before needle insertion. The distance of 30 centimeters in perpendicular position from marked skin must be maintained for ethyl chloride spraying and the duration of spray was 4 seconds until a thin snow was coated over the skin. Amniotic fluid was drawn for amount of 15 ml. After needle withdrawing, participants must mark a point that represents the level of their pain on VAS line. Fetal heart activity and immediately procedural associated complications were observed before leaving. Each participant received a card describing possible cryo-analgesia complications and symptoms for self-monitoring and contact information. Participants were asked about overall severity of pain measured by 5-points likert scale that categorized from minimal to marked severe pain. A few days after amniocentesis, participants were followed-up by phone. Participants who had skin lesions with suspected frostbite were counseled and scheduled for further evaluation and treatment by dermatologist. All participants were observed for maternal and fetal complications until postnatal period.

Statistical analysis

Statistical analyses were performed by using Stata version 14.2. Demographic data were presented and compared by using Student t-test and Mann-Whitney U test for continuous variables and Pearson chi-square test and Fisher exact test for categorical variables. Continuous data were presented as mean and standard deviation (SD). Categorical data were presented as frequencies (n (%)). $P < 0.05$ was considered as a significant difference.

Results

One hundred forty-eight participants were recruited. Each group consisted of 74 participants. No participant was excluded from eligibility assessment. Demographic data included maternal age, weight, height, BMI, gestational age, location of placenta, parity, history of vaginal operation, abortion, dilation and curettage, cesarean section, abdominal surgery, showed no difference between both groups (Table 1). All procedures were performed by a single attempt. No participant was excluded. The clear color amniotic fluid samples were obtained from all participants and no immediate post-procedural complication was observed.

Pre-procedural VAS pain score (Table 2) between cryo-analgesic and control showed no significant difference (VAS 5.92 ± 2.00 and 5.67 ± 2.56, respectively, $p = 0.6$). Post-procedural VAS pain score showed a significant difference (VAS 2.42 ± 2.17 and 3.54 ± 2.68, respectively, $p = 0.01$). Most participants in cryo-analgesia group had mild degree of overall pain compared to moderate degree in control group (Fig. 1). Most participants (98%) had voluntarily willing to undergo amniocentesis again if clinically indicated (Table 3). Six out of 74 participants in the cryo-analgesic group (8%) had mild frostbite rash with only itching and superficial skin burn. All

affected participants were scheduled for evaluation, treatment, and follow-up at the outpatient clinic. All frostbite lesions were improved within a few days and completely recovered within a month without any scar. In addition, there were no abortion, infection, and amniotic fluid leakage in the study.

Table 1. Demographic data.

Characteristics	Cryo-analgesia group (n=74)	Control group (n=74)	p value
Age, yr*	37.80 (2.83)	37.35 (2.54)	0.71
Weight, kg*	60.01 (10.59)	60.75 (10.34)	0.72
Height, kg*	156.97 (5.24)	158.69 (6.05)	0.22
Body mass index, kg/m^2*	24.34 (4.07)	24.11 (3.82)	0.68
GA, wk*	21.95 (0.88)	22.02 (0.80)	0.86
Placental Location**			0.50
- Anterior	33 (44.59)	29 (39.19)	
- Posterior	41 (55.41)	45 (60.81)	
Parity**			0.38
- Nulliparous	22 (29.73)	27 (36.49)	
- Multiparous	52 (70.27)	47 (63.51)	
Route of previous delivery**			0.83
- No	30 (40.54)	33 (44.59)	
- Normal delivery	23 (31.08)	23 (31.08)	
- Cesarean section	21 (28.38)	18 (24.32)	
Previous intrapartum procedure**	2 (2.27)	1 (1.35)	1.00
Previous abortion**	24 (32.43)	20 (27.03)	0.47
Previous curettage**	10 (13.51)	13 (17.57)	0.50
Previous cesarean section**	21 (28.38)	18 (24.32)	1.00
Previous abdominal surgery**	10 (13.51)	8 (10.81)	0.62

* Data were presented in mean (SD) and using Student t-test and Mann-Whitney U test
** Data were presented in n (%) and using Pearson chi-square test and Fisher exact test
GA = gestational age

Table 2. Visual analogue scale pain score.

Group	Cryo-analgesia group (n=74)	Control group (n=74)	p value
Anticipated pain*	5.92 (2.00)	5.67 (2.56)	0.60
Post-procedural pain*	2.42 (2.17)	3.54 (2.68)	0.01

* Data were presented in Mean (SD) and using Mann-Whitney U test

Table 3. Voluntarily willing to undergo amniocentesis again if indicated.

Group	Cryo-analgesia group (n=74)	Control group (n=74)
Yes*	73 (98.65)	73 (98.65)
No*	1 (1.35)	1 (1.35)

* Data were presented in n (%)

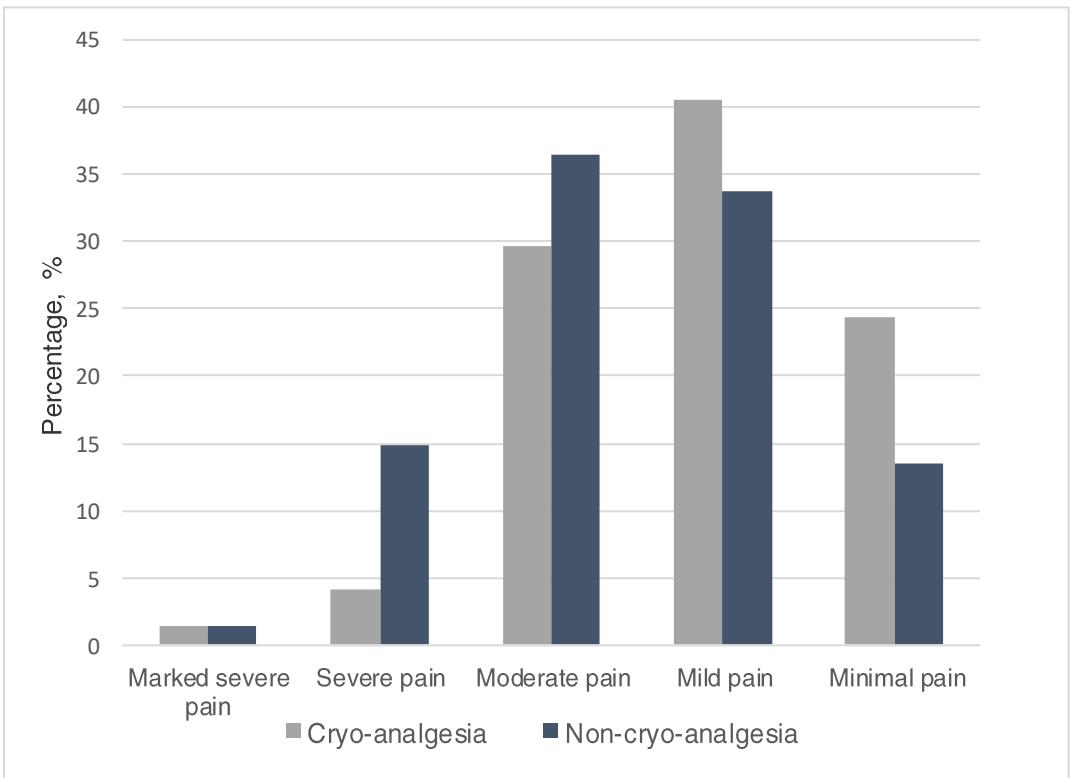

Fig. 1. Overall severity of pain in cryo-analgesia and control group.

Discussion

Amniocentesis associated pain is a common problem that some women are reluctant to undergo this procedure. This study found that cryo-analgesia with ethyl chloride spray significantly decreased post-procedural VAS pain score. Most participants (98%) demonstrated their willingness to undergo the amniocentesis again if clinically indicated.

Amniocentesis-associated pain controlling methods were previously studied by comparing xylocaine injection to no intervention, sub-freezing needle, and legs rubbing, all methods had no significant difference in pain reduction[5-8]. The subsequent study comparing xylocaine injection to placebo found that xylocaine injection can control pain during amniocentesis[17]. This result, however, was conflicted with other previous studies[5,6] due to anesthetic injection-associated pain. Another study of cryo-analgesia used cold gel pack placing on the marked skin for 5 minutes before needle penetration[9]. The

cold gel pack decreased post-procedural VAS pain score significantly and participants had no anesthetic injection-associated pain, but the procedural time was prolonged and it might cause unnecessary analgesic area. Likewise, ethyl chloride spray is a quick and easy method that can reduce VAS pain score without injection-associated pain. The mechanism of ethyl chloride spray might reduce somatic pain at superficial layer of skin by inducing skin cooling and therefore reduce the sensitivity of pain receptor.

All procedures in this study were performed by attending staffs and MFM-fellows in Maternal-Fetal Medicine Unit, Ramathibodi Hospital. Participants did not know whether they had cryo-analgesia or not until a few seconds before needle penetration. So, there was no Hawthorne effect and no significant difference in anticipated VAS pain score. Amniocentesis was performed in all participants with a single attempt. No complication from amniocentesis, such as abortion, procedural site infection, and membrane leakage was found. Although this study was a randomized controlled trial, there was still limitation regard to the placebo effect of spraying. There had a study suggested that needle penetration through upper one-third part of uterus had less pain score than other sites, however, the penetration site could not be controlled due to the position of placenta and fetus. The major adverse effect of ethyl chloride spray is frostbite. The frostbite lesion occurred in 8%, with a small decrease in pain score, but all affected participants had mild symptoms and self-limited course of this type of skin complication. The lesions were limited in dermis layer and classified as 1st degree frostbite that could be improved by moisturizer. These skin lesions were subsided within one month without any scar.

Ethyl chloride spray significantly decreased post-procedural VAS pain score by reducing somatic pain at superficial layer of skin. However, other mechanisms of amniocentesis associated pain including somatic pain at deep layer of skin and visceral pain could not be controlled by this method. Also, this anesthetic method might provide a psychological support which affects pain perception.

Although, there were statistical significantly difference in post-procedural VAS pain scores. Pain scores were categorized as mild pain in both groups, so, it might not showed a clinical significant. The difference of mean between both groups might be needed 13 mm. of VAS to represent the minimal change in acute pain that was clinically significant[18].

Conclusion

Ethyl chloride spray might be an alternative method for amniocentesis procedural pain management. A small decrease in pain scores in this study must be interpreted with caution; this was possibly caused by Hawthorne effect because of non-blinded approach. Women should be informed about the potential risk of complications.

Acknowledgement

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Cunningham FG, Levono JK, Bloom LS, Hauth JC, Rouse JD, Spong YC. Prenatal Diagnosis. Williams Obstetrics. 24th ed. New York: McGraw Hill 2014:283-305.
2. Dafny N. Pain Principles [Internet]. Houston: Department of Neurobiology and Anatomy, The UT Medical School at Houston 1997 [cited 2015 Oct 20]. Available from: http://neuroscience.uth.tmc.edu/s2/chapter06.html.
3. Suntornlimsiri W, Naunkeaw K. Clinical correlates of pain with second-trimester genetic amniocentesis. J Med Assoc Thai 2009;92:1567-71.
4. Lekskul N, Tannirandorn Y. The location of needle insertion effect on maternal pain in amniocentesis. J Med Assoc Thai 2006;89:S137-41.
5. Gordon MC, Ventura-Braswell A, Higby K, Ward JA. Does local anesthesia decrease pain perception in women undergoing amniocentesis? Am J Obstet Gynecol 2007; 196:55.e1-55.e4.

6. Van Schoubroeck D, Verhaeghe J. Does local anesthesia at mid-trimester amniocentesis decrease pain experience? A randomized trial in 220 patients. Ultrasound Obstet Gynecol 2000;16:536-8.
7. Fisher RL, Bianculli KW, Sehdev H, Hediger ML. Does light pressure effleurage reduce pain and anxiety associated with genetic amniocentesis? A randomized clinical trial. J Matern Fetal Med 2000;9:294-7.
8. Wax J, Pinette MG, Carpenter M, Chard R, Blackstone J, Cartin A. A randomized single blinded trial of subfreezing versus room temperature needles to reduce pain with amniocentesis. Ultrasound Obstet Gynecol 2005;26:430-1.
9. Hanprasertpong T, Kor-anantakul O, Prasartwanakit V, Leetanaporn R, Suntharasaj T, Suwanrath C. Efficacy of cryo-analgesia in decreasing pain during second trimester genetic amniocentesis: a randomized trial. Arch Gynecol Obstet 2012;286:563-66.
10. Kunesch E, Schmidt R, Nordin M, Wallin U, Hagbarth KE. Peripheral neural correlates of cutaneous anesthesia induced by skin cooling in man. Acta Physiol Scand 1987; 129:247–57.
11. Farion KJ, Splinter KL, Newhook K, Gaboury I, Splinter WM. The effect of vapocoolant spray on pain due to intravenous cannulation in children: a randomized controlled trial. Can Med Assoc J 2008;179:31-6.
12. Page DE, Taylor DM. Vapocoolant sprays vs subcutaneous lidocaine injection for reducing the pain of intravenous cannulation: a randomized, controlled clinical trial. Br J Anaesth 2010;105:519-25.
13. Polishchuk D, Gehrmann R, Tan V. Skin sterility after application of ethyl chloride spray. J Bone Joint Surg Am 2011;94:118-20.
14. MESA specialty gases and equipment. Ethyl chloride, safety data sheet [Internet]. 2015 [updated 2015 May 29; cited 2015 Oct 20]. Available from: https://www.mesagas.com/images/Ethyl%20Chloride.pdf.
15. Colchester Hospital University NHS Foundation Trust. Guideline; Fetal blood sampling [Internet]. 1997 [updated 2012 Oct; cited 2015 Oct 20]. Available from: http://www.colchesterhospital.nhs.uk/maternity_guidelines/Fetal%20Blood%20Sampling.pdf.
16. Henderson Z., Ecker JL. Fetal scalp blood sampling limited role in contemporary obstetric practice: Part II [Internet]. 2003 [updated 2003; cited 2015 Oct 20] Available from: http://labmed.ascpjournals.org/content/34/8/594.full.pdf.
17. Elimian A, Goodman JR, Knudtson E, Wagner A, Wilson P, Williams M. Local anesthesia and pain perception during amniocentesis: a randomized double blind placebo – controlled trial. Prenat Diagn 2013;33:1158-61.
18. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001;38:639-43.