Comparison between Lidocaine Spray and Oral Paracetamol for Pain Reduction during Amniocentesis in Second Trimester Pregnancy; A Randomize Controlled Trial

Chanokrak Sriwattanapong, M.D.[1], Densak Pongrojpaw, M.D.[1], Athita Chanthasenanont, M.D.[1], Junya Pattaraarchachai, Ph.D.[2], Komsun Suwannarurk, M.D.[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand, [2]Chulabhorn International College of Medicine, Thammasat University, Pathum Thani, Thailand.

ABSTRACT

Objective: The aim of this study was to compare the efficacy of lidocaine spray and oral paracetamol on pain reduction in pregnant women in the second trimester during amniocentesis.

Materials and Methods: This was a prospective randomized-controlled trial study conducted at Maternal and Fetal Medicine unit, Thammasat University Hospital, Pathum Thani, Thailand between June 2022 and April 2023. Participants were pregnant women who underwent amniocentesis during gestational age between 15 and 20 weeks. They were allocated into three groups namely lidocaine, paracetamol and control groups. Subjects in lidocaine group received 8 puffs of 10% lidocaine (80 mg) spray onto the marked puncture site for five minutes before amniocentesis and ingested 1 placebo tablet 1 hour before procedure. Paracetamol group ingested 650 mg paracetamol orally 1 hour before amniocentesis and received 8 puffs of normal saline spray on the marked puncture site. Control group received 8 puffs of normal saline spray onto the marked puncture site for five minutes before amniocentesis and ingested 1 placebo tablet 1 hour before amniocentesis. Expected pain (Te), during procedure (T0), 15 and 30 minutes after procedure (T15 and T30) were evaluated based on 10-cm visual analog scale (VAS).

Results: A total of 510 pregnant women were recruited and divided equally (170 cases per group). Mean maternal age was 36.1 years old. Demographic characters of three groups were comparable. Lidocaine had more pain reduction than paracetamol and control group at T0, T15 and T30 (at T0: 3.06±2.16 vs 3.96±2.42 vs 3.92±2.35, P value < 0.001, T15: 1.12±1.38 vs 1.92±1.47 vs 1.98±1.87, P value < 0.001, T30: 0.64±0.95 vs 1.33±0.97 vs 1.09±1.44, P value < 0.001). However, paracetamol had no significant difference in pain reduction compared to control group.

Conclusion: Lidocaine spray before amniocentesis had more efficacy on pain reduction during amniocentesis, 15 and 30 minutes after procedure.

Keywords: Lidocaine spray; paracetamol; amniocentesis; pain (Siriraj Med J 2024; 76: 8-13)

INTRODUCTION

Amniocentesis during the second trimester of pregnancy is the most common invasive prenatal procedure. Most common indications for amniocentesis were advanced maternal age, parental chromosome abnormalities, previous offspring with chromosome abnormalities and prior diagnosis of fetal malformations. This procedure consisted of transabdominal puncture under ultrasonographic guidance to obtain amniotic fluid. Pain from the procedure was frequently reported

Corresponding author: Densak Pongrojpaw
E-mail: pongrojpaw@gmail.com
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ORCID ID:http://orcid.org/0000-0002-8315-0447
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from previous literature.[1] Some pregnant women refuse to undergo amniocentesis when indicated due to fear of the pain during and after the procedure. Many pregnant women might request pain control to avoid pain during amniocentesis. Factors related to pain during amniocentesis included numbers of parity, gestational age, maternal body mass index (BMI), history of abdominal surgery and location of needle.[2]

There have been various prior studies regarding pain reduction in patients who underwent amniocentesis. Local anesthesia by using lidocaine (infiltration, spray and topical cream), oral paracetamol premedication and cryoanalgesia before amniocentesis had been reported to decrease procedural pain.[3-11]

Paracetamol is a common pain relieving medication and is safe for pregnancy. The peak effect of paracetamol was around 1 to 3 hour after ingestion.[12] Thanita and colleagues reported in 2018 that oral paracetamol one hour before amniocentesis could significantly reduce pain from the procedure than placebo group.[3]

Lidocaine is an amide anesthetic agent with a short onset of local anesthetic action, safe for pregnant women to use. Gordon and Elimian reported in 2007 and 2013 that local infiltration of 1% lidocaine could relieve pain from amniocentesis among pregnant women in the second trimester, compared to placebo with statistical significance.[4,5] Homkrun reported that application of lidocaine spray at amniocentetic puncture site before the procedure could significantly reduce pain compared to the placebo in 2019.[6] However Pongrojpaw reported in 2007 that application of lidocaine cream at the amniocentetic puncture site could not reduce pain from the procedure.[7]

Nonpharmacological pain reduction from amniocentesis, namely music therapy, aroma therapy and cryotherapy were also reported to possibly reduce pain.[13,14]

Lidocaine spray and oral paracetamol are both non-invasive and easy to apply. To date, there has been no comparative efficacy study between lidocaine spray and oral paracetamol for pain reduction during amniocentesis. The aim of this study was to compare the efficacy of pain reduction during amniocentesis between lidocaine spray and oral paracetamol.

MATERIALS AND METHODS

Participants

Pregnant women in the second trimester (gestational age between 15-20 weeks) who underwent genetic amniocentesis during June 2022 to April 2023 and had no severe congenital anomalies that were prior detected by ultrasonography were enrolled in this prospective randomized controlled trial at Maternal-Fetal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University Hospital, Pathum Thani, Thailand. The exclusion criteria were multifetal pregnancy, severe congenital anomaly detected previously by ultrasonography, contraindication to perform amniocentesis, more than one attempt of needle puncture during procedure, changing the puncture site due to fetal behavior, psychiatric disorder, skin infection at abdominal area, those who had side effects of paracetamol or lidocaine spray, and those who refused to participate in this study.

Trial design

This study was approved from Human Ethics Committee of Thammasat University (MTU-EC-OB-2-369/64) and registered with Thai Clinical Trials Registry. Thai clinical trials registry identification number is TCTR20220530009. Pregnant women who underwent second trimester amniocentesis were approached by certified Maternal Fetal Medicine (MFM) staffs. Pre-procedural counseling was performed, with the procedure being explained to the pregnant women with indications for genetic amniocentesis. After thorough counseling, signed informed consent was done after the study was explained and understood. The patients were recruited and randomized into three groups with simple random sampling methods. Inclusion and exclusion criteria were reviewed before informed consent was given by the patients. Eligible pregnant women were interviewed about demographic data including age, body weight, height, education, occupation, income, gestational age, parity, previous delivery, history of abortion, underlying illness, previous obstetrical or gynecological surgery, parity and history of genetic amniocentesis in the previous gestation. The visual analog scale (VAS) was used for evaluation before the procedure to qualify their anticipated pain level. The VAS is a subjective pain measuring method, which is recorded by making a mark along a 10-cm horizontal line (0 to 10) from no pain or anxiety (score 0) to the worst pain (score 10).

Interventions

All participants were divided into three groups, namely lidocaine, paracetamol and control group. The first group is lidocaine spray. The participants were sprayed with lidocaine spray 8 puffs for 15 minutes and ingested 1 placebo tablet 1 hour before procedure. The second group is paracetamol group. In this group the participants took paracetamol (Tylenol®) (650 mg) 1 tablet orally 1 hour and normal saline spray 8 puffs

15 minutes before procedure. Third group is the control group. The participants received 1 placebo tablet orally 1 hour before procedure and normal saline spray 8 puffs 15 minutes prior to procedure as shown in Fig 1.

All participants (3 groups) underwent ultrasonography to investigate gestational age, fetal anomalies, amniotic fluid and the location of placenta. Genetic amniocentesis procedure was performed by staffs at Maternal Fetal Medicine Units (MFM Units) under ultrasonographic continuous guidance, free-handed, antiseptic technique, using a 22-gauge spinal needle. Pain control methods (paracetamol tablet, lidocaine spray or placebo) were used during the procedure. Commonly, 18-20 mL of amniotic fluid was aspirated and collected in a sterile container. Fetal cardiac activity was auscultated immediately after procedure. The puncture site was covered with a waterproof occlusive dressing by an assistant nurse. Immediately after the intervention, the participants were interviewed to qualify their pain score before (Te: expected pain), during (T0), 15 minutes (T15) and 30 minutes (T30) after the amniocentesis by using the same VAS. Following the procedure, the participants were observed for 30 minutes. While the patients laid, post-procedural, any paracetamol tablet and lidocaine spray complications were observed and fetal heart sound was auscultated by the medical team before discharge. In this study all physicians, participants and nurses were blinded during the procedure. The data was opened after complete the study.

Sample size and statistical analysis

The sample size was calculated from standard deviation of post-procedure pain and anxiety of the control group (SD = 1.58), which was based on the study of Thanitha T. et al.[3] The alpha and beta were set at 0.05 and 0.10 respectively. The authors calculated that at least 154 subjects in each group would provide 80% power at the 0.05 significance level. Given a 10% dropout rate, the total participants to be recruited was 170 in each group.

Statistical analyses were performed by using statistic packaged for social science (SPSS Inc., Chicago, IL USA) for windows version 27. Continuous and category data were analyzed for statistical differences by using ANOVA and post hoc test (pairwise comparison of groups). when clinically applicable. A p-value of less than 0.05 indicates a statistically significant difference.

The primary outcome was a measurement of visual analogue scale (VAS) before amniocentesis, during the procedure, 15 minutes and 30 minutes after the procedure.

RESULTS

A total 510 pregnant women who underwent amniocentesis during the study period were recruited. They were divided in to three groups equally, namely lidocaine, paracetamol and control groups.

Table 1 shows mean maternal age was 36.1 years old. One-third of participants were nulliparous. Half of the participants had an education level equal to or more than a bachelor degree and less than of 10 percent of participants had experience of amniocentesis.

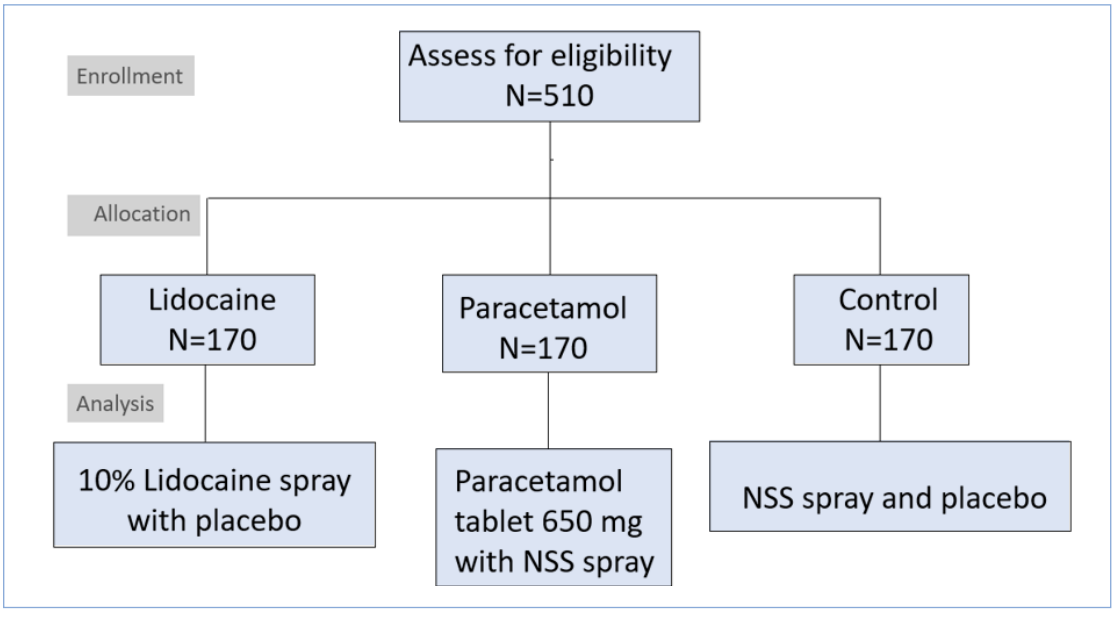

Fig 1. Flow chart of study.

Lidocaine: application of lidocaine spray at amniocentesis site, Paracetamol: ingestion of paracetamol tablet before amniocentesis, Control: application of normal saline spray at amniocentesis site and ingestion of paracetamol tablet before amniocentesis.

All physicians, participants and nurses were blinded during the procedure. The data was opened after complete the study.

TABLE 1. Demographic characters of amniocentesis cases (n=170 cases per group).

	Control	Paracetamol	Lidocaine	*p*-value
Age (years) (mean±SD)	36.22 ± 4.25	35.94 ± 4.32	35.81 ± 4.73	0.69
BMI (kg/m^2) (mean±SD)	24.51 ± 3.96	25.88 ± 4.20	25.39 ± 4.41	0.204
Nulliparity*	57 (33.5)	63 (37.1)	64 (37.6)	0.694
Education level*				0.06
≤ Secondary	102 (60)	89 (52.4)	82 (48.3)	
≥Bachelor	68 (40.0)	81 (47.6)	88 (51.8)	
Occupation*				0.067
Government officer	28 (16.5)	21 (12.4)	17 (10)	
Business owner	26 (15.3)	29 (17.1)	24 (14.1)	
Employee	105 (61.8)	108 (63.6)	116 (68.3)	
Housewife	11 (6.5)	12 (7.1)	13 (7.6)	
No history of surgery*	116 (68.2)	130 (76.5)	122 (71.8)	0.236
History	13 (7.6)	13 (7.6)	14 (8.2)	0.973
Indication				
Advanced age	139 (82.3)	140 (82.4)	144 (85.2)	
Family history	15 (8.9)	21 (12.4)	14 (8.3)	
Abnormal test	6 (3.6)	7 (4.1)	6 (3.6)	
Patient's need	3 (1.2)	2 (1.2)	3 (1.2)	
Previous abnormality	7 (4.1)	0 (0.0)	3 (1.8)	

*n(%), Control: no intervention before amniocentesis, Paracetamol: ingestion of paracetamol before amniocentesis, Lidocaine: application of lidocaine spray at amniocentesis site BMI: body mass index, C/S: cesarean delivery, History: History of amniocentesis, Control: no intervention before amniocentesis, Paracetamol: ingestion of paracetamol before amniocentesis, Lidocaine: application of lidocaine spray at amniocentesis site, Advance age: maternal age ≥ 35 years old, Family history: family history of chromosome abnormality, Abnormal screening test: Abnormal prenatal screening test, Previous abnormality: previous child with chromosome abnormality *n(%)

Demographic characteristics between the groups were comparable in terms of maternal age, BMI, parity, education, occupation, history of abdominal surgery at randomization. The majority of cases were advanced maternal age (95%).

Table 2 shows the VAS score among the three groups of participants. The expected pain (Te) and the pain during amniocentesis (T0) were comparable. However, the lidocaine group showed significantly lower value of VAS score at 15 and 30 minutes after the procedure compared to the control group and paracetamol group

Comparison of pain scores (VAS) during amniocentesis at timely manner: expected pain before amniocentesis (Te), during amniocentesis (T0), 15 minutes (T15) and 30 minutes after amniocentesis (T30) were presented in Fig 2.

DISCUSSION

Amniocentesis is a procedure that can cause mild to moderate pain. There are previous studies that investigated various pain reduction methods such as lidocaine, paracetamol premedication, aromatic therapy and cryoanalgesia.[3-14] The current study reported the efficacy of lidocaine spray for pain reduction during amniocentesis. Lidocaine spray shows pain reduction during amniocentesis at timely manner: expected pain before amniocentesis (Te), during amniocentesis (T0), 15 minutes (T15) and 30 minutes after amniocentesis (T30). While paracetamol did not show pain reduction during amniocentesis.

Lidocaine is the most effective and commonly used anesthetic agents which has various routes of administration (intravenous, cream, or spray). Its main mechanism

TABLE 2. Comparison pain score (VAS score) in amniocentesis among control, paracetamol and lidocaine group (n=170 cases per group).

	Control*	Paracetamol*	Lidocaine*	*p*-value (Bonferroni) Con vs Para	Con vs Lido	Para vs Lido	*p*-value (F-test)
Te	5.92 ± 2.18	6.15 ± 2.27	6.11 ± 1.81	0.984	0.710	0.601	0.58
T0	3.92 ± 2.35	3.96 ± 2.42	3.06 ± 2.16	0.987	0.003	0.002	< 0.001
T15	1.98 ± 1.87	1.92 ± 1.47	1.12 ± 1.38	0.943	< 0.001	< 0.001	< 0.001
T30	1.09 ± 1.44	1.33 ± 0.97	0.64 ± 0.95	0.166	0.001	< 0.001	< 0.001

VAS: visual analog scale (range 0-10), Control : no intervention before amniocentesis, Paracetamol: ingestion of paracetamol before amniocentesis, Lidocaine: application of lidocaine spray at amniocentesis site, * mean ± standard deviation(SD), Te: expected pain before amniocentesis, T0: pain during amniocentesis, T15: pain at 15 minutes after amniocentesis, T30: pain at 30 minutes after amniocentesis, Con vs Para: between control and paracetamol, Con vs Lido: between control and lidocaine group, Para vs Lido: between paracetamol and lidocaine group

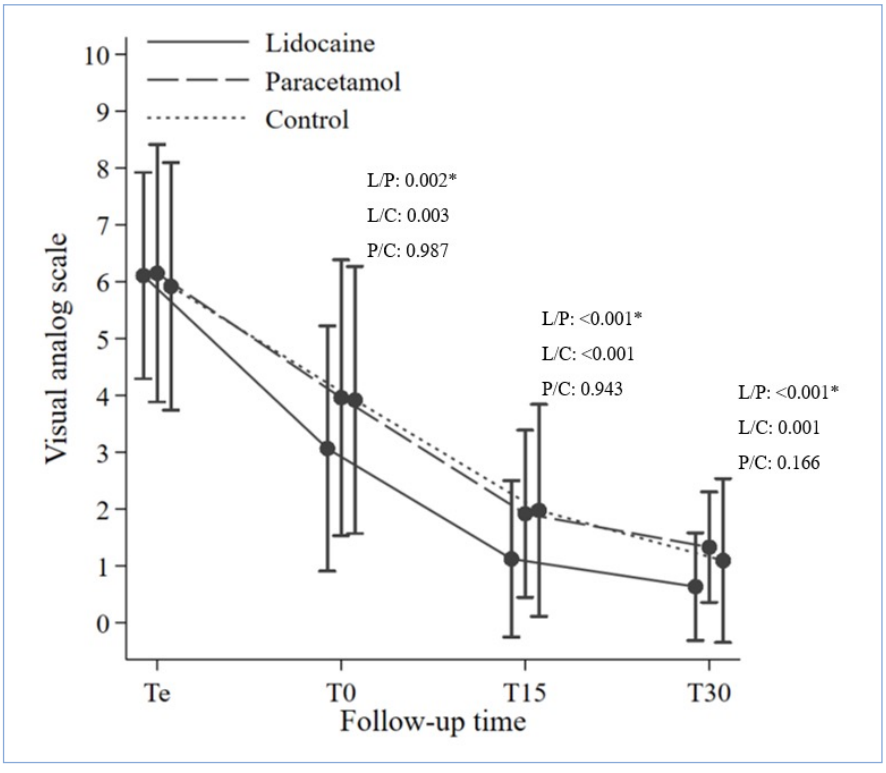

Fig 2. Comparison pain score (VAS score) in amniocentesis among control, paracetamol and lidocaine group.

Lidocaine: application of lidocaine spray at amniocentesis site, Paracetamol: ingestion of paracetamol tablet before amniocentesis, Control: application of normal saline spray at amniocentesis site and ingestion of paracetamol tablext before amniocentesis

*L/P: Lidocaine compare to paracetamol group, L/C: Lidocaine compare to control group, P/C : Paracetamol compare to control group

of action is blocking voltage-gated Na^+ channels.[15] From previous studies, lidocaine-prilocaine cream skin application[7] (Pongrojpaw et al. 2007) were not effective in reducing the pain in amniocentesis. However, Elimian et al. (2013)[5] has proved contrary. In 2019 Homkrun et al[6] reported that lidocaine spray can significantly decrease pain during amniocentesis. Due to different consistency of the product and drug component in previous study may affect the efficacy in pain reduction.

Paracetamol is an analgesic and antipyretic drug that is commonly used to relieve mild to moderate pain and is safe for pregnant women. Mechanism of action for relieve pain is it's bind to arachidonic acid which created N-arachidonyl-phynolamin (AM404) then AM404 stimulates Capsaicin receptor (TRPV1) and Canabinoid CB1 receptor in central nervous system which leads to relieve the pain.[16] In 2018, Thanita T.[3] reported that paracetamol 650 mg orally 1 hour before amniocentesis

compared with placebo could reduce pain during the procedure and 2 hours afterward.

Previous studies have shown that using lidocaine spray and paracetamol can reduce pain during amniocentesis but there is still no study that has compared the efficacy on pain reduction between lidocaine spray and paracetamol. According to this study result, the median procedural pain (T0) was lower in women who received lidocaine spray compared to paracetamol and control group and after 15 minutes and 30 minutes post procedure shows that lidocaine spray can significantly reduce pain. Conversely, neither the paracetamol nor control group had significant pain reduction during the procedure, 15 and 30 minutes after the procedure.

This study showed several strengths. First, this study is a prospective randomized controlled trial and was designed to have three arms. This allow the researcher to create a double blinded trial which can reduce the possible confounding bias that may occur. Moreover, this study involved a large number of participants and has comparable demographic characteristics in each group. However, there are still some limitations in this study. This study is a single center study. In addition, the participants took paracetamol (650 mg) 1 hour orally prior to amniocentesis while peak plasma level of paracetamol is 2 hours, which may affect the efficacy of paracetamol in pain reduction.

Also, the control group (placebo and normal saline spray) can have placebo effect or Hawthorne effect (the participants feel better due to realization of receiving therapy) that can make the comparison between paracetamol group and control group to have no significant difference in VAS score during and after amniocentesis.

From current study shows that lidocaine spray has efficacy in pain reduction during amniocentesis. The author suggests that lidocaine spray used before amniocentesis was recommend due to its profile, convenience and easy to use in clinical practice.

CONCLUSION

Lidocaine spray before amniocentesis had more efficacy on pain reduction than paracetamol during amniocentesis, 15 and 30 minutes after procedure.

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