Original Article

Prospective Randomized, Double-blinded, Placebo-Controlled Trial of Preoperative Acetaminophen/Tramadol for Pain Relief in Manual Vacuum Aspiration under Paracervical Block

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***Objective*:** To evaluate the analgesic efficacy of pre-operative administration of acetaminophen/tramadol (Ultracet) when compared to placebo in patients undergoing uterine manual vacuum aspiration (MVA) under a standard technique of paracervical block.

***Materials and Methods*:** This double-blinded, randomized, concealed allocation, placebo-controlled trial enrolled 220 women who underwent MVA under a standard technique of paracervical block. One hundred and ten women were randomly assigned to receive ultracet and the others to placebo. The primary outcome was to assess the intensity of pain after procedure in term of visual analog pain score. Student's *t*-tests and Chi-squared test were used to analyze data as proper.

***Results*:** No statistically significant differences in basic characteristics were observed in both groups of patients. The number of patients who had no pain (pain score=0) after MVA were significant increase in Ultracet group (P<0.01). In patients who still reported of pain, there was also lowered in pain intensity in Ultracet group. Only a few minor adverse effect was observed during the study. However this adverse effect showed no significant differences between groups.

***Conclusion*:** We concluded that the addition of the preoperative administration of acetaminophen/tramadol confirmed its efficacy to prevent pain in patients who undergo MVA under a standard technique of paracervical block.

Keywords: ultracet, manual vacuum aspiration (MVA), pain score

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The manual vacuum aspiration (MVA) is commonly used for diagnosis and treatment in obstetrics and gynecology[1-3]. It is usually performed under local anesthesia such as paracervical block[4]. Although paracervical block with lidocaine had a significant analgesic effect in fractional curettage and seem to be safe, inexpensive, and easy to perform, it provides an inadequate and a variable analgesic effect[5-8]. Therefore the adjunctive administration of oral analgesic drugs such as opioid analgesics or anti-inflammatory drugs (NSAIDs) prior to the procedure has been introduced. Presently tramadol, naproxen, ibuprofen and etoricoxib have been shown to be effective in pain reduction during curettage but the degree of pain reduction by this treatment has no clinical importance[9-13]. Importantly these drugs was reported the common adverse effect such as gastrointestinal tract mucosal damage, and avoid in some patients such as old age, history of renal disease, bleeding tendency in NSAIDs use[14].

The acetaminophen/tramadol (Ultracet®), each tablet contains 325 mg of acetaminophen and 37.5 mg of tramadol. Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, there were at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin[15]. Acetaminophen is a non-opiate, non-salicylate analgesic that is considerable evidence that the analgesic effect is central and is due to activation

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of descending serotonergic pathways, but its primary site of action may still be inhibition of prostaglandins synthesis[16]. Moreover acetaminophen/tramadol is not associated with the side effects that can result from NSAID use, such as gastrointestinal ulcers or bleeding[17-19].

The aim of this study was to evaluate the analgesic efficacy of pre-operative administration of acetaminophen/tramadol (Ultracet) when compared with placebo in patients undergoing uterine MVA under paracervical block.

Materials and Methods

The present study was a double-blind, randomized controlled trial comparing acetaminophen/tramadol with placebo for pain relief after MVA under paracervical block. 220 women who had MVA done under paracervical block, after written inform consents were signed, were randomly allocated to receive either acetaminophen/tramadol (Ultracet®) (325 mg of acetaminophen plus 37.5 mg of tramadol) tablet or placebo 60 min before the procedures. The exclusion criteria were; no history of sexual intercourse, hypersensitivity to lidocaine, acetaminophen or tramadol. The randomized sequence was generated with computer. The active tablets and the corresponding placebo tablets were identical in size, shape, and color. They were packed in the opaque sealed envelopes and the envelopes were labeled sequentially with the subject number in the center. Each envelope was then distributed in sequential numerical order to ensure randomization and double-blindness to treatment. The patients, gynecologists performing the procedure, and nurse assistance were blinded to the contents of the oral medications. The code was not broken until the study was completed.

The standard procedure for MVA was performed after waiting 5 minutes for the onset of lidocaine. The paracervical block in the study was standardized, by injecting 1% lidocaine using a 23-gauge spinal needle at 4 and 8 o'clock of cervicovaginal reflection at an estimated depth of 1 cm, 10 ml at each site. Intermittent aspiration was performed before and during injection to avoid paracervical blood vessel puncture. Oxygen and vasopressor were always available for caring of hypersensitive reaction to the medications.

The primary outcome was the overall pain after MVA. The patients used a visual analog pain score to evaluate the intensity of pain. They were asked to identify how much overall pain they had by choosing a number from 0 to 10, 0 means no pain and 10 means the worst pain their ever experienced. The participants were asked for the overall pain at 30 minutes after MVA. They were advised to ask for another potent analgesic drugs at any time if she wanted for more pain relief or otherwise wish to leave the study. Patient's satisfactions were assessed at the end of the procedure. Data recorded included marital status, educational level, income, history of menstruation, vaginal delivery, previous vaginal obstetrical procedure, marital status and previous uterine curettage, indication of MVA, size of uterus, size of Karman canula, level of residents who performed the procedure, difficulty of MVA (which was rated by a surgeon; 1= not difficult, 2= rather difficult,3= very difficult and 4= extremely difficult) and complications of the procedure.

Before this study was instituted, a power analysis was performed with respect to visual analog pain score after MVA. With an alpha of 0.05, a power of 80%, a two-side analysis resulted in 110 patients per group. Statistical analysis were performed with SPSS 12.0 for Windows (SPSS Inc., Chicago, IL). The student's *t*-test and the Chi-square test was used to analyze proportion. *P-value* <0.05 (two-tailed test) was considered as statistically significances.

Results

A total of 220 patients were randomized two treatment groups: 110 received acetaminophen/tramadol, and 110 received placebo. The demographical characteristics of the two groups were not difference in age, body mass index, educational levels, income, history of vaginal delivery, history of vaginal obstetrics procedures, history of miscarriage, history of previous curettage, indications for manual vacuum aspiration, and depth of uterine cavity (Table 1). There were no different in the size of Karman canula and difficulty level of the procedure, (Table 2).

The number of patients had no pain (pain score=0) after MVA was 58 and 23 in acetaminophen/tramadol and placebo group, respectively. There were also a significantly difference in visual analog scores ($P < 0.001$), (Table 3). The visual analog score for the acetaminophen/tramadol group was no significantly lower after operative procedure (median visual analog scores (interquartile range) 0 (0-8) vs. 3 (0-9), P=0.49). Patient's satisfactions were not different between two groups.

There was no serious adverse complication from the procedure then there were 7 cases of acetaminophen/tramadol had dizziness. During the study no patient requested another analgesic drugs or left the study (Table 4).

Table 1. Baseline characteristic of patient

Characteristics	Drug group (n = 110)	Placebo group (n = 110)
Age* (y)	48.1±9.1	49.5±10.1
BMI (kg/m^2)	27.1±16.9	25.2±4.3
Education levels		
Primary &secondary school	52 (47.3%)	45 (40.9%)
College	34 (30.9%)	31 (28.2%)
University	24 (21.8%)	34 (30.9%)
Parity		
Nulliparous	21 (19.1%)	9 (8.2%)
Multiparous	89 (90.9%)	101(91.8%)
Previous vaginal delivery	56 (50.9%)	71 (54.5%)
Previous vaginal obstetrics procedure	7 (6.4%)	10 (9.1%)
Previous abortion	38 (34.5%)	28 (25.4%)
Previous curettage	45 (40.9%)	39 (45.5%)
Type of previous curettage		
Fractional curettage	33 (30.0%)	28 (28.5)
Dilatational&curettage	12 (10.9%)	11 (10.0%)

*Data presented as mean±standard deviation or number (%), *p*-values were >0.05 for all comparisons.

Table 2. Indication and baseline characteristic of procedure

Characteristics	Drug group (n = 110)	Placebo group (n = 110)
Indications for MVA		
Menometrorrhagia	65 (59.1%)	57 (51.8%)
Perimenopausal bleeding	26 (23.6%)	36 (32.7%)
Postmenopausal bleeding	19 (27.3%)	17 25.5%)
Depth of uterine cavity(cm)	7.9 ± 1.6	7.6 ± 1.6
Size of Karman canula (K)	5 (4 to 7)	5 (4 to 7)
Difficulty level of procedure		
Level 1	78 (39.4%)	65 (59.1%)
Level 2	21 (10.6%)	37 (3.6%)
Level 3	8 (4.0%)	5 (4.5%)
Level 4	3 (1.5%)	3 (2.7%)

*Data presented as mean±standard deviation, median (range) or number (%). *p*-value >0.05 for all comparisons

Table 3. Number of patient who had no pain (pain score 0)

	Drug group (n = 110)	Placebo group (n = 110)	*p*-value
No pain	58 (52.7%)	23 (20.9%)	<0.001
Pain	52 (47.3%)	87 (79.1%)	

*Data presented as number (%)

Table 4. Complication of the procedure

	Drug group (*n* = 110)	Placebo group (*n* = 110)
Dizziness	7 (6.36%)	0

*Data presented as number (%)

Discussion

Several studies have demonstrated the benefits of adding the non-steroidal anti-inflamatory drugs such as celecoxib, rofecoxib, and etoricoxib into the paracervical block. These benefits include minimized the pain score after the procedure[11,12]. This present study, authors showed the acetaminophen/tramadol can relieve the pain in patient who underwent MVA combined to a standard regimen of paracervical block. Our data suggested that an Ultracet (325 mg of acetaminophen plus 37.5 mg of tramadol) tablet 60 min before do the MVA was sufficient to reduce the overall pain score after finish the procedure. Therefore our result showed a significant difference of number of patients who score no pain (pain score = 0) in acetaminophen/tramadol when compare with placebo group (p-value $\leq$ 0.01) also the significant lowered of patients who complaint of pain after the procedure in acetaminophen/tramadol group. Moreover the patient who reported of non-zero pain score, there was a trend to lowered pain scoring in patients who took acetaminophen/tramadol. The average of pain scores were 1.7 and 3.1 in acetaminophen/tramadol and placebo group, respectively (p-value = 0.083). Similarly, it has been demonstrated that NSAID can provide effective analgesia after fractional curettage under paracervical block[11,12]. Acetaminophen/tramadol is a centrally acting synthetic opioid analgesic and acetaminophen is generally considered to be a weak inhibitor of the synthesis of prostaglandins. It could be explained that pain during endometrial injury occurs from the direct stimulation to the uterine wall and disruption of endometrium during the procedure. This can cause prostaglandin release leading to uterine contraction and pain sensation in the upper part of the uterus[10]. Therefore the mechanism of acetaminophen/tramadol might be relieved the pain due to both effect. In our study we selected acetaminophen/tramadol because there are minimal side effects when compared with NSAIDs use, such as gastrointestinal ulcers or bleeding. Also in our study we found only minimal minor adverse reactions, such as dizziness, were reported in patients received acetaminophen/tramadol. No serious adverse reaction was reported in both groups.

Therefore, adding the oral acetaminophen/tramadol prior MVA could be an effective way to

prevent pain related procedure with minimum adverse effects. Because of its efficacy and safety, we propose that acetaminophen/tramadol could be used as the analgesic form of choice to prevent pain during and post MVA procedure. However, a limitation of this study is that we are only able to show the benefit of ultracet in the overall pain for MVA under a standard technique of paracervical block is our sole outcome. Although, the overall pain after procedure is generally well accepted as one of the positive parameters for operation, other parameters should also be investigated. Hence, we suggest that the future study be evaluated in the patient's satisfaction.

Conclusion

We concluded that the addition of the preoperative administration of acetaminophen/tramadol confirmed its efficacy to prevent pain in patients who undergo MVA under a standard technique of paracervical block.

What is already known on this topic?

Several studies have demonstrated the benefits of adding the non-steroidal anti-inflamatory drugs such as celecoxib, rofecoxib, and etoricoxib into the paracervical block. These benefits include minimized the pain score after the procedure. The new analgesic drug, acetaminophen/tramadol was other one medication that researcher team interest because It's not have ADR like NSAIDs groups and gave some of sedative effect to patients who underwent the minor procedure. Then, we conduct RCT to prove the efficacy and benefits or risks of this medication.

What this study adds?

This present study showed the acetaminophen/tramadol can relieve the pain in patient who underwent MVA combined to a standard regimen of paracervical block. This present data suggested an Ultracet (325 mg of acetaminophen plus 37.5 mg of tramadol) tablet 60 min before do the MVA was sufficient to reduce the overall pain score after finish the procedure and no serious ADR was reported.

Potential conflicts of interest

The authors declare no conflicts of interest.

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