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Effect of paracetamol, dexketoprofen trometamol, lidocaine spray, pethidine & diclofenac sodium application for pain relief during fractional curettage: A randomized controlled trial

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***Background & objectives*: Patients frequently experience pain of moderate to severe degree during gynaecologic procedures. This prospective, randomized, placebo-controlled trial was aimed to investigate the analgesic efficacy of preoperative oral dexketoprofen trometamol, intravenous paracetamol, lidocaine spray, pethidine and diclofenac sodium on fractional curettage procedure.**

***Methods*: A total of 144 mutiparous women were randomly allocated to one of the six groups. The first group (control group) consisted of 22 participants and they did not receive any treatment. The second group had 26 participants receiving oral 25 mg dexketoprofen trometamol. The 23 participants of the third group received two puff lidocaine sprays on cervical mucosa. The forth group consisted of 25 participants receiving 100 mg pethidine. In the fifth group, the 23 participants received 1000 mg intravenous paracetamol and the sixth group consisted of 25 participants receiving diclofenac sodium.**

***Results*: Pethidine was the best choice for reducing pain score during curettage procedure (t2:intra-operative). All analgesic procedures were significantly effective in reducing pain during postoperative period (t3). Significant pain reduction was achieved for both intra- and postoperative period by using analgesics.**

***Interpretation & conclusions*: The results of our study showed that lidocaine puffs provided the best pain relief than the other analgesics used. Therefore, lidocaine may be considered as the first choice analgesic in fractional curettage (NCT ID: 01993589).**

Key words Analgesia - curettage - dexketoprofen trometamol - diclofenac - lidocaine - paracetamol - pethidine - VAS score

Fractional curettage, a surgical procedure, is commonly used for the diagnosis of abnormal uterine bleeding[1]. Curettage related moderate to severe pain during the procedure is an important issue. Blumenthal and Remsburg[2] showed that curettage might be performed on an outpatient basis under local anaesthesia and cost of procedure could also be reduced.

Non steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and dexketoprofen trometamol have an established role in the management of dysmenorrhoea and related inflammatory disorders[3]. The diclofenac is an inhibitor of cyclo-oxygenase, the key enzyme involved in the metabolism of arachidonic acid into various prostaglandin mediators of inflammation and pain[4]. It has been shown that lidocaine spray can be used for pain relief during gynaecologic operations. Lidocaine shows its effect by reduction of generation and conduction of peripheral pain impulses in dysfunctional or damaged nociceptors situated directly below the application site[5].

Paracetamol is believed to primarily act upon the central nervous system by inhibiting central cyclooxygenase, and probably has an indirect influence on the serotoninergic system. Paracetamol has a good safety profile and can easily pass through the blood brain barrier, which assures it as an effective analgesic[2]. Pethidine is a synthetic opioid and is most commonly prescribed systemic opioid for labour pain relief[6].

This prospective, randomized, placebo-controlled trial was undertaken to investigate the analgesic efficacy of preoperative oral dexketoprofen trometamol, intravenous paracetamol, lidocaine spray pethidin and diclofenac sodium in women undergoing fractional curettage procedure for abnormal uterine bleeding.

Material & Methods

This randomized, placebo controlled trial was conducted between November 2012 - May 2013 at the Gynaecology clinic of Kayseri Education and Research Hospital of Medicine at Kayseri, Turkery. The study protocol was approved by the ethics committee of Erciyes University.

Multiparous women scheduled for fractional curettage procedure with the indications of abnormal uterine bleeding, postmenopausal bleeding, uterine myoma causing menometrorrhagia, cervical polyp, tamoxifen treatment for breast cancer, and adnexial mass, were included in the study. Some of the medications may have analgesic effect on gynaecologic procedures[7], therefore, none of the participants received medication such as analgesics, misoprostol up to seven days. Exclusion criteria were all types of abortions (complete, incomplete), primiparity, pregnancy, diabetes mellitus, tendency to bleed such as thrombocytopenia, factor deficiency and functional disorders of platelets, pelvic infection, known cervical stenosis, impaired respiratory or cardiac conduction functions, active liver disease, renal disease, previous adverse reaction to any of the drugs used in the study, and patients who are unable to understand how to score a 10-cm visual analogue scale (VAS) pain score. Patients with chronic pelvic pain prior to the study or patients who rated their pain level on a continuous 100-mm VAS different from 0 (no pain) before the study were also excluded.

It has been shown that a difference of at least 2.73 cm between the pain scores can be regarded as a clinically significant difference[8]. As per the estimate at least 18 women were required in each arm to detect a difference of 2.73 cm between the two groups on a 10-cm VAS with a power of 80 per cent at a type I error of 0.05 and SD of 2.7 cm[8]. Because of expected dropouts from the study, it was decided to include 156 participants. At the end of six months 144 women were registered in the trial (Figure). Because of diabetes (n=2), cervical stenos (n=1) and renal disease (n=1), four participants were excluded from the control group. Two patients who rated their pain level on a continuous 100-mm VAS different from 0 (no pain) just before the study and had impaired cardiac function (1 subject), were not included into the lidocaine group. Because of the impaired respiratory function one participant was excluded from the pethidine group. Two patients who are unable to understand how to score on a 10-cm visual analog scale and one patient who had tendency to bleed were excluded from the paracetamol group. Because of data loss, one patient was excluded from the diclofenac group.

After providing their informed consent, a total of 144 participants were randomly assigned into the six study groups. They received 25 mg of oral dexketoprofen trometamol, 1000 mg iv paracetamol, two puff xylocain administration on cervical surface, diclofenac sodium 75 mg and 100 mg subcutaneous pethidine or similar-appearing placebo drugs by using a computer-generated random number chart [PAS W Statistics 18 program (2009 SPSS Inc. SPSS (Hong Kong) Ltd,) Rm 1804, 18/F, Westlands Centre)] before the study. The first group (control group) consisted

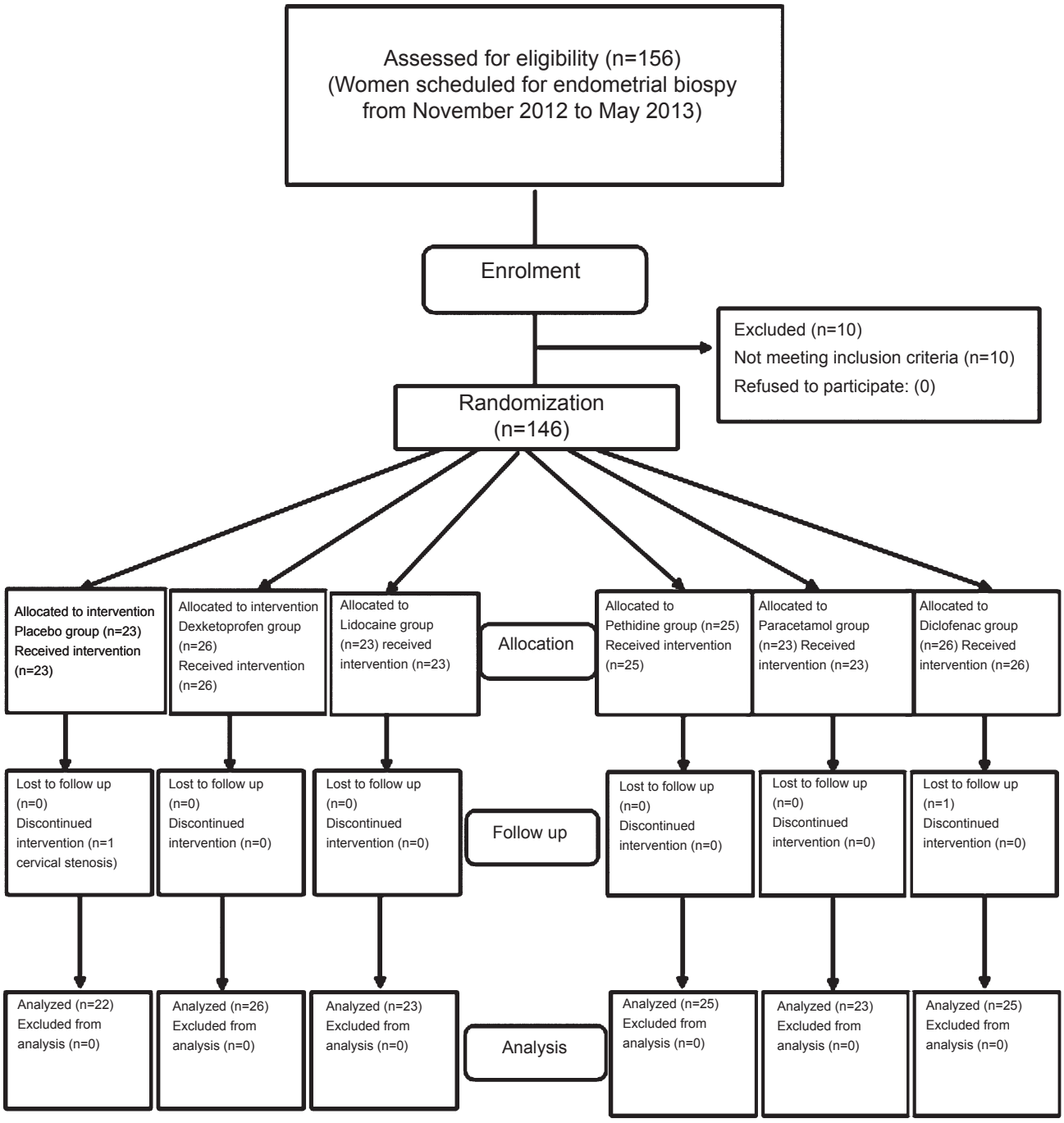

Figure. Flow chart showing study groups.

of 22 participants and in this group, five patients received placebo tablet, five received saline solution, three received intramuscular (im) isotonic solution, four received subcutaneous isotonic solution and five received puff saline solution. The second group consisted of 26 participants receiving oral 25 mg dexketoprofen trometamol. The third group consisted of 23 participants receiving cervical lidocaine puff. The participants (n=25) in the forth group received 100 mg subcutaneous pethidine, and those in the fifth group (n=23) received 1 g intravenous (iv) paracetamol. The sixth group participants (n=25) received 75 mg

intramuscular (im) diclofenac sodium. In all, 144 consecutive patients were included. Random allocation was done during curettage. The envelope with the patient number on its cover was opened to reveal the randomization by the responsible nurse and the trial medication was given accordingly.

The patients, the anaesthetist performing VAS and the gynaecologist performing the procedure were blinded to the contents of the oral, intravenous, intramuscular, subcutaneous and puff medications. The oral and intravenous medications were given 30 min before the suction curettage due to their pharmacokinetic properties. The suction curettage was performed by the same gynaecologist to maintain consistency and limit confounding variables. Lidocain spray (2 puffs) was done on the cervical surface and allowed for three min to have the anaesthetic effect.

Curettage and VAS procedure: The procedure of curettage was performed as described earlier[9]. After curette was placed into the uterus, the suction machine was turned on, and closed the suction valve on the handle of the curette. A rotary, slightly in-and-out motion was used until an increased resistance to rotation was achieved. Both endocervical and endometrial tissues were sampled.

Pain scoring was performed at three different time points: prior to the procedure (t1), during the procedure (immediately following the removal of the speculum from the vagina at the end of the fractional curettage, the patients were asked to score their pain level experienced during the procedure) (t2), and 30 min after the procedure (t3). Patients were asked to rate their pain level on a continuous 100-mm VAS from 0 (no pain) to 10 (worst pain ever). The patients were observed for 30 min after the curettage procedure. No further follow up was scheduled.

Statistical analysis: Shapiro-Wilk and Kolmogorov-Simirnov tests were used to test the normality assumption of the data. Variance homogeneity assumption was tested with Levene test for the variables age and BMI. Values were expressed as mean ± standard deviation or median (25^{th}-75^{th} percentile). One-way analysis of variance (ANOVA) test or Kruskal-Wallis H test were performed for the comparison of differences between the groups. Tukey HSD post hoc tests were used for the multiple comparisons for the variables age and BMI. Non-parametric test (Kruskal-Wallis H test) and Mann-Whitney U test were used for double comparisons. PAS W Statistics 18 programme (2009 SPSS Inc., SPSS, Hong Kong) was used for all statistical analysis.

Results

The age of the patients ranged from 39 to 67 yr. The groups were comparable for age, BMI and parity. All participants reported their pain level 0 on a continuous 10 cm VAS prior to the study.

There was no significant difference between the lidocaine spray and pethidine groups for pain scores (Table I). All analgesic procedures were significantly effective to reduce pain in both intra- and postoperative periods. There were no significant differences among analgesics in postoperative period (t3). Side effects of the medications are illustrated in Table II. One of the participants in the control group and one in the pethidine group had nausea during application of the procedure.

Table I. General characteristics and pain scores of study groups

Variables	Control (n=22)	Dexketoprofen (n=26)	Lidocaine (n=23)	Pethidine (n=25)	Paracetamol (n=23)	Diclofenac sodium (n=25)	*P* value
Age (yr)	45.59 ± 8.56	44.69 ± 3.64	45.52 ± 8.69	45.04 ± 6.62	44.48 ± 6.64	42.52 ± 8.77	0.723
BMI (kg/m^2)	30.32 ± 6.14	28.96 ± 4.72	28.73 ± 4.27	29.29 ± 5.98	28.70 ± 4.59	29.56 ± 4.45	0.892
Parity	3 (3-4)	3.5 (2-4.25)	2 (2-3)	3 (2.5-4)	3 (2-4)	3 (2.5-4)	0.149
VAS t2 (intraoperative)	9 (7-10)[a]	5.5 (4-8)[b]	4 (2-6)[c]	5 (4-5.5)[cbd]	6 (2-8)[bde]	5 (5-7.5)[bdf]	<0.001
VAS t3 (postoperative)	1 (0-2)[a]	0 (0-0)[b]	0 (0-0)[b]	0 (0-0)[b]	0 (0-0)[b]	0 (0-0)[b]	<0.001

Values are expressed as mean ± standard deviation or median (25^{th}-75^{th} percentile). Groups with different superscript letters were found to have significant differences

Table II. Side effects of the medications in study groups

	Control (n=22)	Lidocaine spray (n=23)	Dexketoprofen (n=26)	Paracetamol (n=23)	Pethidine (n=25)	Diclofenac sodium (n=25)
Nausea	1 (4.54)	1 (4.34)	0 (0)	0 (0)	1(4)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)
Rash	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stomach complaints	0 (0)	0 (0)	3 (11.53)	1 (4.34)	0 (0)	1 (4)
Bradycardia	0 (0)	0 (0)	0 (0)	0 (0)	1(4)	0 (0)
Total complications	1 (4.54)	1 (4.34)	3 (11.53)	1 (4.34)	1 (3)	1 (4)

Values are expressed as n (%)

Discussion

Theoretically, topical anaesthetic application reduces the pain because of cervical manipulation/ dilatation but not the pain component because of uterine instrumentation and contraction, because the upper part of the uterus derives its sensory innervation different from the cervix[10].

In a study on the effect of lignocaine gel application for pain relief during suction termination of first-trimester pregnancy it was found that it reduced overall intraoperative pain in multiparous women undergoing suction termination of first-trimester pregnancy preceded by misoprostol cervical priming and premedication for conscious sedation[11]. Xu *et al*[12] claimed that dicaine-containing lubricant jelly for suction termination of first-trimester pregnancy had no effect on pain scores. They reported significantly more satisfactory cervical dilatation in the group using dicaine-containing lubricant jelly compared with the group using lignocaine injection[12]. Our results showed that lidocaine puffs provided the best pain relief than the other analgesics and placebo group. The reason could be that lidocaine might be absorbed by the vessels of cervix. Subsequently, the serum level of xylocaine might increase and this situation led to a decrease in overall pain scores.

Api *et al*[8] conducted a double-blind, randomized, placebo-controlled trial with paracetamol and investigated analgesic efficacy of 1 g intravenous paracetamol during fractional curettage. They concluded that there was no significant difference in pain scores of patients undergoing fractional curettage when the use of i.v. paracetamol was compared with placebo. Conversely, Arici *et al*[13] assessed the efficacy of 1 g iv paracetamol in hysterectomy and concluded that preemptive i.v. paracetamol (1 g) provided good quality postoperative analgesia with decreased consumption of morphine and minimal side effects. We found that 1 g iv paracetamol was effective for reducing pain score in both intra- and postoperative periods.

The analgesic efficacy of NSAIDs during minor gynaecologic surgery is limited. The central mechanism of pain reduction with NSAIDs is mainly attributable to the inhibition of prostaglandin synthesis by the cyclooxygenase enzyme. It is assumed that pain during fractional curettage occurs from the direct stimulation of the uterine wall and disruption of endometrium during the procedure. Consequently, this mechanism was thought to cause prostaglandin release leading to uterine contraction and pain sensation in the upper part of the uterus[14,15]. Both dexketoprofen and diclofenac inhibit cyclooxygenase enzyme. In our study dexketoprofen and diclofenac reduced pain scores during both intra- and postoperative periods, however, there was no significant difference between the two drugs. Api *et al*[16] also showed that administration of oral dexketoprofen was effective in relieving fractional curettage associated pain.

There appears to be a trend toward more use of opioid due to increased attention paid to the treatment of acute, chronic, and cancer-related pain[17,18]. Pethidine, an opioid with predominantly κ-receptor agonist properties, is a phenylpiperidine derivative with a chemical structure similar to local anesthetics. Because of its local anaesthetic effect on peripheral nerves pethidine may be the ideal analgesic for curettage. Previous *in vivo* studies demonstrated that when given intrathecally pethidine was effective as the sole anaesthetic for surgery of the perineum[19] and caesarean delivery[20]. Pethidine with a short duration of action,

has been widely and routinely prescribed for moderate to severe pain in medical and surgical patients[21,22].

Our study had a limitation as we did not evaluate anxiety or pain tolerance prior to the procedure. In conclusion, all analgesic procedures were significantly effective to reduce pain in both intra- and postoperative periods. Although lidocaine group had lower VAS score than the pethidine group during intra-operative period, there were no significant differences between the two groups at the point of t2 and t3. Therefore, we suggest that lidocaine may be the first choice analgesic followed by pethidine in fractional curettage. Further studies need to be done to confirm these findings further and to study the mechanisms of action.

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Conflicts of Interest: None.

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