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Kemppainen, Venla

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Patient-controlled intravenous versus on-demand oral, intramuscular or mcs intravenous administration of oxycodone during medical induced abortion from 64 to 128 days of Gestation: A randomized controlled trial

Venla Kemppainen[a], Maarit Mentula[a], Vilja Palkama[b], Oskari Heikinheimo[a,*]

[a] The Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University hospital, Helsinki, Finland
[b] The Department of Anesthesiology and Intensive Care Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

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ABSTRACT

Objective: To compare oxycodone administration via intravenous patient-controlled analgesia (IVPCA) vs on-demand administration during late-first- and second-trimester medically induced abortion.
Study design: A prospective randomized controlled study. We enrolled women between 64 to 128 days of gestation in the study between June 2016 and August 2018. Participants were randomized to receive oxycodone either via IVPCA or given on-demand orally, intramuscularly, or intravenously. Pain intensity and satisfaction with care were measured using the visual analogue scale (VAS, 0–100mm).
Results: Altogether 99 participants were randomized: 48 in IVPCA group and 51 in on-demand group. Median gestational age was similar between groups (74 days [Interquartile range, IQR 69–81] in the IVPCA group vs 72 [69–80] in the control group, $p = 0.587$). Peak maximal pain was severe in both groups (median pain VAS was 62 [IQR 44–84] and 71 [IQR 56–90], $p = 0.52$). The odds for severe pain (highest pain VAS≥70) were similar between the groups (IVPCA group OR 0.51 [95% Confidence Interval 0.22–1.18], $p = 0.118$). In contrast, the odds for mild or tolerable pain (highest pain VAS≤40) were higher in the IVPCA group (OR 4.06 [95% CI 1.05–16.04], $p = 0.043$). Nevertheless, satisfaction with care was high (VAS 94 [89–100]) in both groups. Of those experiencing severe pain, 94.0% declared pain medication as adequate.
Conclusion: Women often experience severe pain during medical abortion irrespective of the mode of opiate administration. Oxycodone administration via IVPCA permits women to self-administer analgesics when experiencing pain, raising the odds for mild or tolerable pain during abortion care. Satisfaction with care was high.

Implications

Medical abortion in late-first- and second-trimester is often painful experience. IVPCA offers a good method of choice for analgesia and raises the odds for tolerable pain (pain VAS less than 40) experience when compared to on-demand administration of analgesics.

1. Introduction

Medical abortion has proven safe and effective irrespective of the duration of gestation and in all women, including those later in pregnancy and young women and adolescents [1–6]. Abdominal pain due to uterine cramping is a known consequence of medical abortion. During late-first- and second-trimester medical abortion, pain is often reported as severe (i.e., VAS ≥7, on scale 1–10) [1,7–9]. Advanced duration of gestation, nulliparity, younger age and history of dysmenorrhea predict a more intense pain experience [4,10]. Often the most severe pain is related to fetal expulsion, occurring within few hours after initiation of misoprostol administration [7,8].

Knowledge on optimal pain management during late-first- and second-trimester medical abortion is lacking and practice

* Corresponding author.
E-mail address: oskari.heikinheimo@helsinki.fi (O. Heikinheimo).

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varies between providers [11–13]. The use of non-steroidal anti-inflammatory drugs (NSAIDs) does not interfere with the effect of mifepristone or misoprostol, and prophylactic use of NSAIDs lowers the need for opiates during medical abortion [9].

Reported need for additional narcotic analgesics for pain control during second-trimester medical abortion has varied from less than 10% to more than 80% in different studies [1,7,9,10]. Oxycodone taken orally at onset of abdominal pain did not reduce maximal pain during medical abortion at less than 11 weeks of pregnancy compared to placebo [8]. Study on intravenous patient-controlled analgesia (IVPCA) with different fentanyl doses compared to morphine showed a fentanyl dose 50ug to be most effective [14]. To our knowledge, there are no published studies on oxycodone administration using intravenous patient-controlled analgesia (IVPCA) during second-trimester medical abortion.

The aim of this study was to compare different administration routes of oxycodone during late-first- and second-trimester medical abortion. We compared opioid administration via intravenous patient-controlled analgesia (IVPCA) to opioids administered on-demand either orally, intramuscularly or intravenously according to our hospital policy. As the onset of pain is often unpredictable during medical abortion, we assumed that oxycodone administered via IVPCA gives women faster and more effective analgesia, decreases the intensity of pain experienced, and therefore results in higher satisfaction on abortion care and pain management.

2. Materials and methods

This randomized controlled study was conducted between June 20th, 2016 and August 29th, 2018. The study was approved by the ethics committee of the Hospital district of Helsinki and Uusimaa (HUS320/13/03/03/2015) and the Finnish Medical Agency. The EudraCT registration number of the study is 2015-003760-36. The trial was registered at www.clinicaltrials.gov registry (NCT02678897).

Women requesting medical abortion of a singleton pregnancy at between 64 and 170 days of gestation were invited to participate. This interval of gestational age was selected as patients at this duration of gestation are hospitalized for abortion care based on the Finnish national guideline for induced abortion [15]. Other inclusion criteria were age between 15 to35 years, nulliparity and no allergy for the analgesics used in the study. History of miscarriage or induced abortion were not exclusion criteria. We excluded patients seeking abortion due to fetal abnormalities or maternal health conditions. Fetal expulsion before intake of misoprostol, history of opioid or narcotic addiction, severe obesity (body mass index BMI >35 kg/m^2) or baseline illness (ASA 3 or 4) were also exclusion criteria.

Medical abortion was carried out according to the Finnish national guideline [15]. Following clinical examination, and determination of the duration and status of the pregnancy by vaginal ultrasound, mifepristone (200mg) was administered orally at the outpatient clinic (day 1). All participants were admitted to the hospital ward for misoprostol administration 24 to 72 hours later in the morning (day 3 or 4). The first dose of misoprostol (0.8mg) was administered vaginally followed by 0.4mg doses every 4 hours until fetal expulsion. Repeat doses are administered orally or vaginally, depending on whether bleeding has started. Misoprostol was administered orally in cases of heavy bleeding.

Participants were recruited for the study at the outpatient clinic or by phone before they arrived the hospital ward. Participants signed an informed consent after having received written and verbal information on the study. A consent from guardian was requested from minors (aged 15–17 years of age). Participants completed a questionnaire on background information. Reported use of pain medication during menstruation was used as an indicator of history of dysmenorrhea.

Participants were randomized in computer-generated block allocation using sealed envelopes to receive oxycodone either via IVPCA or to administered on-demand. Blinding was not possible in this study setting.

The IVPCA was prepared, and an intra-venous line was established before the first dose of misoprostol. Concentration of oxycodone in IVPCA was 1mg/ml, boluses of 3mg (2.5mg for participants of weighing less than 50kg) with lockout of three minutes, no background infusion, and at maximum of four boluses/hour. Participants in the control group were administered oxycodone orally, intramuscularly or intravenously as participants in the control group did not routinely get an IV line. Administration route and doses were decided case by case at the hospital ward according to local guidelines and a midwife's assessment on pain intensity.

All participants were administered prophylactic analgesics: 600mg of ibuprofen and 1000mg of paracetamol (acetaminophen) simultaneously with first misoprostol intake, to be repeated later up to three times a day if needed. Medication against emesis was administered when needed.

Abortion-related pain and emesis were recorded every 30 minutes or as often as possible after the onset of the pain. We used a paper diary, in which participants were asked to estimate the intensity of pain and emesis. Information on analgesics used was recorded. Intensity of pain and emesis during abortion were measured using a visual analogue scale (VAS). The visual analogue scale is a 100mm long line. At the far left, 0 means no pain at all and at the far right 100 the worst imaginable pain. A woman marks the point in the 100mm long line best describing the intensity of her pain or emesis. Regarding the intensity of pain, VAS $\leq$40 was considered mild or tolerable pain, and VAS $\geq$70 severe pain [16].

Following abortion care at the ward, participants were asked to record pain and analgesics in a paper diary at home. A follow-up visit was scheduled 2 to 4 weeks after abortion. On that visit, the outcome of abortion was verified with ultrasound. Participants also completed questionnaires on memory of pain and overall satisfaction on the care (measured using VAS), adequacy of the analgesics used, and willingness to choose medical abortion again if needed.

The primary outcome was maximal intensity of pain, measured using VAS during medical abortion at the hospital ward. Secondary outcomes included opiate administration (measured by number of doses and total quantity of used oxycodone), emesis experienced during abortion care, and overall satisfaction on pain management and abortion care.

2.1. Sample size

In an earlier study, we reported mean maximal pain VAS of 70 (SD26.5) during second-trimester medical abortion [7]. The study hypothesis was that we can decrease the pain level from VAS 70 to 35 by means of IVPCA. We initially planned to recruit participants in four subgroups of different gestational age and age: late-first- and second-trimester abortions, and teenagers and adult participants separately (ratio 1:2). To demonstrate a decrease of 35 points' change in pain VAS with 90% power and alpha of 5% and to compensate for an estimated 20% of dropouts, we aimed to recruit a total of 16 teenagers or 32 adult participants per group. Thus, the original aim was to enroll altogether 192 patients. We assumed that half of all women eligible for the study would be willing to participate. The aim was to complete the study within two years.

We stopped the recruitment at two years and two months due to slow enrolment. This was partly due to decreasing number of induced abortions, especially among teenagers in Finland. As

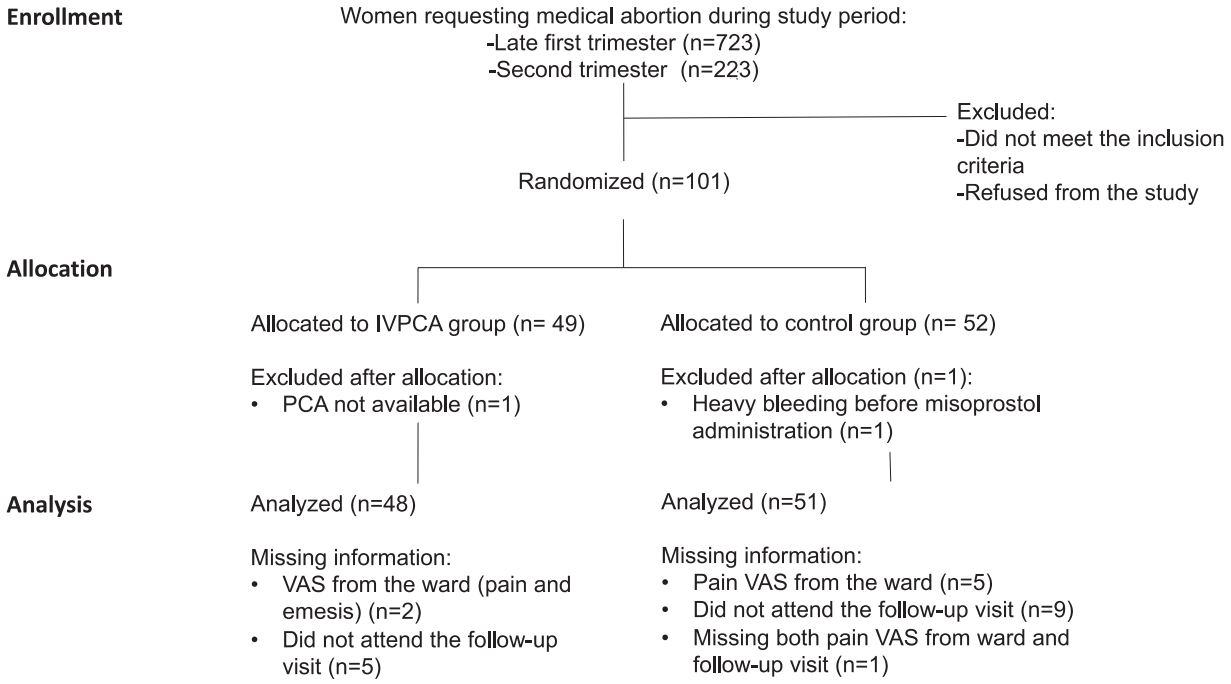

Fig. 1. Flow of the randomized study comparing pain management with IVPCA and on-demand oral, intramuscular or intravenous administration of oxycodone during medical induced abortion from 64 to 128 days of gestation: A study from Finland between years 2016 and 2018.
IVPCA = intravenous patient-controlled analgesia.

the groups of both teenagers and second-trimester abortions were small, we analyzed the results in two groups according to randomization: opioid administration via IVPCA or on-demand. However, randomization of participants into different subgroups resulted in an even distribution of teenagers and adults, and late-first- and second-trimester abortion in both study groups. Results were analyzed on basis of intention-to-treat, even if some of the data were missing for some participants.

2.2. Statistical analysis

We used IBM SPSS version 25 for Mac (IBM Corp.) for analyses. Comparisons were performed using nonparametric tests, Pearson's chi-square test, and Mann-Whitney-U test as appropriate. We used logistic regression for calculating odds ratios (ORs). All statistical tests were two-tailed. A p-value < 0.05 was considered to be statistically significant.

3. Results

Altogether 101 participants were randomized to the trial. We excluded one from IVPCA group because PCA was not available for her and one from control group due to heavy bleeding and abortion before misoprostol after randomization (Fig. 1). We included 99 participants in the final analysis: 48 in the IVPCA group and 51 in the control group. Data were partly missing for seven participants in the IVPCA and for 15 in the control group.

Background characteristics were similar between the study groups (Table 1). Range of gestational age was 64 to 128 days of gestation. The gestational age was similar between the groups (median 73.5 days [IQR 69.0-81.0] in IVPCA group and 72.0 [69.0-80.0] in control group, $p = 0.59$). Most of the participants (85.9%, n = 85) requested an abortion late in the first-trimester (between 64 and 84 days of gestation). Teenagers (participants aged 15 – 19 years old) covered 24.2% of the study population.

The median maximal pain VAS was 70 (Interquartile range, IQR 50–88) with no difference between the study groups (62 [IQR 44–84] in the IVPCA group vs 71 [IQR 56–90] in the control group, $p = 0.52$). Altogether 46.5% of participants reported severe pain during medical abortion (VAS ≥70). The proportion of participants experiencing mild or tolerable pain (maximal pain VAS ≤40) was higher in the IVPCA group (20.8%) than in the control group (5.9%, $p = 0.03$). The main results are presented in Table 2.

In IVPCA group 89.6% of participants needed opioids compared to 84.3% in control group ($p = 0.44$). In the IVPCA group, total number of opiate doses administered was higher than in the control group (4 [IQR 2–7] vs 2 [IQR 1–3], $p = 0.03$), but total quantity of oxycodone was similar between the study groups (12mg [IQR 6–12] vs 12 mg [IQR 7–20], $p = 0.99$). In control group 16 participants received only per oral opiates, 25 intramuscular opiates and two were administered intravenous opiates in addition to oral and intramuscular doses.

Majority of participants needed antiemetics (72.9% in IVPCA group and 78.4% in control group, $p = 0.52$), proportion being similar regardless of opioid administration: 77.9% (n = 60) of those who were administered opioid and 68.2% (n = 15) of those managed without opioids ($p = 0.35$).

Altogether 47.5% of participants reported pain at home after abortion care and almost all of them also reported analgesic use when experiencing pain; there was no difference between the groups.

Memory of pain was lower in the IVPCA (VAS 68 [46–83]) than in the control group (VAS 82 [64–91], $p = 0.02$). Overall satisfaction with care was high (VAS 94 [89–100]). Altogether 94.0% of participants reported pain medication as adequate and 80.8% would choose medical abortion again if needed. Satisfaction with care was high also among participants who experienced severe pain (memory pain VAS≥70, satisfaction VAS 95 [84–100]) compared to rest of the participants (VAS 94 [90-100], $p = 0.56$).

Factors affecting either severe pain (VAS ≥70) or tolerable pain (VAS ≤40) during medical abortion are presented in Table 3. Primigravids were more likely to experience severe pain (OR 3.76 [95% CI 1.51–9.37], $p = 0.004$. Emesis during abortion raised the odds for severe pain (OR 3.70 [95% CI 1.21–11.38], $p = 0.02$). Odds

Table 1
Background characteristics of the two study groups. Randomized study from Finland between 2016 and 2018.

	IVPCA group (n = 48)	Controls (n=51)	*p*-value
Age (years)	23.2 (19.9–28.2)	23.5 (20.3–26.8)	0.72
BMI (kg/m^2)[a]	22.3 (20.1–24.4)	23.2 (21.0–26.2)	0.38
Gestational age (days)	73.5 (69.0–81.0)	72.0 (69.0–80.0)	0.59
History of induced abortion(s) or miscarriage(s)	16 (33.3)	18 (35.3)	0.84
Reported ovulation pain (VAS)[b]	8 (0–29)	10 (0–49)	0.41
Reported menstrual pain (VAS)[c]	39 (20–64)	47 (12–65)	0.95
Reported use of analgesic during menstruation [d]	24 (54.5)	26 (57.8)	0.76
Reported dyspareunia [e]	8 (17.8)	3 (6.5)	0.10
Smoking [f]	25 (54.3)	26 (51.0)	0.74
In a relationship at the time of abortion	34 (70.8)	30 (58.8)	0.44
Emesis in current pregnancy (VAS)[g]	33 (14–65)	32 (7–55)	0.62

IQR, Interquartile range; n, Number of women; BMI, Body mass index; VAS, visual analogue scale (0–100).
Data are presented as median (IQR) or n (%). Percentage of women of whom the data are available.
[a] Data missing from six women in study group and five in control group
[b] Information missing from six women in study group and eight in control group
[c] Information missing from 10 women in study group and nine in control group
[d] Information missing from four women in study group and six in control group
[e] Information missing from three women in study group and five in control group
[f] Information missing from two women in study group
[g] Information missing from five women in study group and eight in control group

Table 2
Reported pain, emesis, and use on pain medication during and after medical abortion in study groups. Randomized study from Finland between 2016 and 2018.

	IVPCA group (n = 48)	Controls (n = 51)	*p*-value
Maximal pain (VAS; median, IQR)[a]	62 (44–84)	71 (56–90)	0.05
Intensity of maximal pain VAS[a]			
Mild/tolerable (VAS ≤40)	10 (22.2)	3 (6.5)	0.03
Moderate (VAS 41-69)	16 (35.6)	16 (31.4)	0.94
Severe (VAS ≥70)	19 (42.2)	27 (58.7)	0.12
Need of narcotic (opioid) analgesics	43 (89.6)	43 (84.3)	0.44
Number of times narcotic analgesic administered	4 (2–7)	2 (1–3)	<0.01
Oxycodone, total dose (mg)	12 (6–21)	12 (7–20)	0.99
Route of opiate administration			
No opiates	5 (10.4)	8 (15.7)	
Oral		16 (31.4)	
Oral and/or intramuscular		25 (49.1)	
Only intravenous	43 (15.7)		
Oral, intramuscular and intravenous		2 (3.9)	
Timing of pain (hours from misoprostol intake)			
Pain onset	1.7 (0.5–3.4)	1.4 (0.8–3.1)	0.94
Time of maximal pain	4.8 (3.5–5.8)	3.7 (2.3–6.5)	0.21
Reported emesis during abortion [a]			
Yes	37 (82.2)	35 (76.1)	0.47
VAS of emesis	19 (1–54)	33 (1–66)	0.47
At home after the abortion			
Reported pain (yes)	26 (54.2)	21 (41.2)	0.14
Highest reported pain (VAS)	49 (31–67)	31 (19–76)	0.19
Use of analgesics (yes)[b]	24 (92.3)	19 (90.5)	0.83
At follow-up visit			
Memory pain VAS[c]	71 (46-83)	83 (64-91)	(0.02
Memory VAS ≥70	22 (52.4)	30 (73.2)	0.05
Memory VAS ≤40	7 (16.7)	6 (14.6)	0.80
Satisfaction on care VAS [d]	95 (84–100)	94 (90–99)	0.89
Analgesia reported as adequate [e]	42 (97.7)	37 (90.2)	0.15
Would you choose medical abortion again? (yes)[f]	40 (95.2)	40 (95.2)	1.00

IQR, interquartile range; BMI, Body mass index; VAS, visual analogue scale (0–100); n, Number of women.
All data are presented as number of participants n (%) or median (IQR). Percentage of women of whom the data are available.
[a] Data (pain diary) missing from three women in study group and five in control group
[b] Use of analgesics amond those who reported pain at home after abortion
[c] Information missing from six women in study group and 10 in control group
[d] Information missing from five women in study group and 10 in control group
[e] Information missing from five women in study group and nine in control group
[f] Information missing from six women in study group and nine in control group

for mild or tolerable pain (VAS ≤40 compared to greater pain) were higher in the IVPCA group (OR 4.06 [95% CI 1.05–16.04], $p = 0.04$).

Ten participants in the IVPCA group (21.3%) and nine in the control group (17.6%, $p = 0.72$) underwent a surgical uterine evacuation due to residual tissue.

4. Discussion

Participants experienced severe pain during late-first- and second-trimester medical abortions, the median of the highest reported pain VAS was 70 (in scale 0–100). Most of the participants in both groups needed opioid analgesia. These are in line with

Table 3
The odds for maximal pain to be severe (VAS ≥70) or tolerable (VAS ≤40) pain according to different background and abortion related factors. Randomized study from Finland between 2016 and 2018

Variable	Pain max VAS ≥70 OR (95%CI)	*p* value	Pain max VAS ≤40 OR (95%CI)	*p* value
Group: IVPCA	0.51 (0.22–1.18)	0.12	4.10 (1.05–16.04)	0.04
Control	1		1	
Dysmenorrhea[a]	1.12 (0.48–2.62)	0.79	0.91 (0.30–2.79)	0.88
No dysmenorrhea	1		1	
Teenagers	2.04 (0.79–5.31)	0.14	1.19 (0.38–3.76)	0.77
Adult women	1		1	
Smoking: Yes	0.87 (0.38–2.00)	0.75	0.73 (0.23–2.28)	0.60
No	1		1	
History of previous pregnancy				
Primigravid	3.76 (1.51–9.37)	0.004	0.62 (0.19–2.02)	0.62
Yes	1		1	
Relationship status:				
Single	0.50 (0.18–1.37)	0.18	0.88 (0.13–3.66)	0.88
In relationship	1			
Emesis during abortion:				
Yes	3.70 (1.21–11.38)	0.02	1.53 (0.31–7.59)	0.60
No	1		1	
Sufficient pain medication:				
No	2.76 (0.27–27.8)	0.39	[b]	
Yes	1			
Duration of pregnancy:				
Late 1st trimester	1	0.71	1	0.41
2nd trimester	1.24 (0.40–3.89)		0.41 (0.13–2.31)	

OR, odds ratio; CI, Confidence interval; VAS, visual analogue scale (0–100).
Results of univariate regression analyses.
[a] History of menstrual pain
[b] All participants having maximal pain VAS ≤40 declared pain medication as adequate.

previous findings [7]. There was no difference between the study groups in the intensity of maximal pain reported, but the pain was four times more likely to be mild or tolerable, and the memory of pain at follow-up visit was lower when oxycodone was administered via IVPCA compared to on-demand administration. Even if pain experienced was often severe, participants were highly satisfied with treatment, eight out of 10 declared pain medication to be adequate and would choose the medical method again if needed.

As far as we know, our study is the first randomized study evaluating the use of oxycodone via IVPCA in abortion-related pain. Randomization is a strength, but blinding would have been difficult in this study setting. The sample size was smaller than that initially planned due to slow enrollment and difficulty in recruiting participants to the study is a weakness. The doses or routes of oxycodone administrated on-demand were not standardized, decisions were made case-by-case at ward according to our clinic practice. On the other hand, standardization of the opiates in the control group could have led to either under or over treatment of pain. Yet, our goal was to compare IVPCA to current clinical practice, in order to assess whether IVPCA could be an option for pain management in the future during medical abortion. Furthermore, data were partly missing for some of the participants and some questionnaires were not fully completed, leading to a proportion of missed information.

As also reported previously, we found that pain during medical abortion in the late-first- and second-trimester is often severe [1,7–9]. Nevertheless, satisfaction with care in our study was high regardless of pain intensity. This finding is in line with our previous results concerning early first-trimester medical abortion [17]. We argue that short duration of most intense pain and knowledge of expected pain might explain the high acceptance of pain during medical abortion. Nevertheless, we are concerned that a painful abortion experience might trigger negative thoughts about future pregnancies or childbirth.

We found that nine out of 10 women needed opiates for pain during medical abortion, IVPCA offers the possibility to self-administer analgesics at the time of pain and furthermore the effect of oxycodone administered intravenously is faster than if administered orally or intramuscularly. This is an asset of IVPCA, as intense pain often occurs quickly during medical abortion at the time of fetal expulsion and might explain higher odds to keep pain level as mild or tolerable. To our surprise, IVPCA did not reduce the intensity of maximal pain in this study. IVPCA needs an intravenous line, which is not routinely provided for women during a medical abortion in Finnish hospitals. This must be kept in mind in discussions on pain management.

Emesis is a known side effect of both misoprostol and opiates, and it was more often reported by participants experiencing severe pain during abortion. This and our previous study shown that majority of women experienced emesis during medical abortion regardless of opioid administration [8]. As administration of antiemetics was common in the study population, we argue that antiemetic medication should be provided routinely during medical abortion regardless of opioid analgesics / the type of analgesia.

Both adequate pain medication and good information on expected pain should be offered to every woman undergoing medical abortion. Even though we lack knowledge concerning optimal pain management during medical abortion, patients' wishes and needs should be considered when planning abortion care. The IVPCA is one option for pain management during medical abortion.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Dzuba IG, Chong E, Hannum C, Lichtenberg ES, Lugo Hernández EM, Ngoc N, et al. A non-inferiority study of outpatient mifepristone-misoprostol medical abortion at 64–70 days a, nd 71–77 days of gestation. Contraception 2020;101:302–8. doi:10.1016/j.contraception.2020.01.009.

[2] Niinimäki M, Suhonen S, Mentula M, Hemminki E, Heikinheimo O, Gissler M. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: Population register based study. BMJ 2011;342:d2111. doi:10.1136/bmj.d2111.

[3] Männistö J, Mentula M, Bloigu A, Gissler M, Niinimäki M, Heikinheimo O. Medical termination of pregnancy during the second versus the first trimester and its effects on subsequent pregnancy. Contraception 2014;89:109–15. doi:10.1016/j.contraception.2013.10.015.

[4] Vitner D, Deutsch M, Paz Y, Khatib N, Baltiter T, Rosenberg S, et al. Association between gestational age and induction-to-abortion interval in mid-trimester pregnancy termination using misoprostol. Eur J Obstet Gynecol Reprod Biol 2011;156:140–3. doi:10.1016/j.ejogrb.2010.12.035.

[5] Gemzell-Danielsson K, Lalitkumar S. Second Trimester Medical Abortion with Mifepristone-Misoprostol and Misoprostol Alone: A Review of Methods and Management. Reprod Health Matters 2008;16:162–72. doi:10.1016/S0968-8080(08)31371-8.

[6] Hamoda H, Ashok PW, Flett GMM, Templeton A. Medical abortion at 9-13 weeks' gestation: A review of 1076 consecutive cases. Contraception 2005;71:327–32. doi:10.1016/j.contraception.2004.10.015.

[7] Mentula M, Kalso E, Heikinheimo O. Same-day and delayed reports of pain intensity in second-trimester medical termination of pregnancy: A brief report. Contraception 2014;90:609–11. doi:10.1016/j.contraception.2014.06.031.

[8] Colwill AC, Bayer LL, Bednarek P, Garg B, Jensen JT, Edelman AB. Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2019;134:1163–70. doi:10.1097/AOG.0000000000003576.

[9] Fiala C, Swahn ML, Stephansson O, Gemzell-Danielsson K. The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13-22 weeks gestation. Hum Reprod 2005;20:3072–7. doi:10.1093/humrep/dei216.

[10] Hamoda H, Ashok PW, Flett GMM, Templeton A. Analgesia requirements and predictors of analgesia use for women undergoing medical abortion up to 22 weeks of gestation. BJOG 2004;111:996–1000. doi:10.1111/j.1471-0528.2004.00235.x.

[11] Jackson E, Kapp N. Pain control in first-trimester and second-trimester medical termination of pregnancy: A systematic review. Contraception 2011;83:116–26. doi:10.1016/j.contraception.2010.07.014.

[12] Fiala C, Cameron S, Bombas T, Parachini M, Saya L, Gemzell-Danielsson K. Pain during medical abortion, the impact of the regimen: A neglected issue? A review. Eur J Contracept Reprod Health Care 2014;19:404–19. doi:10.3109/13625187.2014.950730.

[13] Carlsson T. Management of physical pain during induced second-trimester medical abortions: a cross-sectional study of methodological quality and recommendations in local clinical practice guidelines at Swedish hospitals. Scand J Caring Sci 2019;33:111–18. doi:10.1111/scs.12608.

[14] Castro C, Tharmaratnam U, Brockhurst N, Tureanu L, Tam K, Windrim R. Patient-controlled analgesia with fentanyl provides effective analgesia for second trimester labour: a randomized controlled study [L'analgésie auto-contrôlée avec du fentanyl est efficace pendant le travail obstétrical du second trimestre : une étude randomisée et contrôlée]. Can J Anesth 2003;50(10):1039–46.

[15] Finnish National guideline on Induced abortion. Working group of the Finnish Medical Society Duodecim, the Finnish Society of Obstetrics and Gynaecology. https://www.kaypahoito.fi/hoi27050 (15.1.2022)

[16] Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995;61:277–84.

[17] Kemppainen V, Mentula M, Palkama V, Heikinheimo O. Pain during medical abortion in early pregnancy in teenage and adult women. Acta Obstet Gynecol Scand 2020;99. doi:10.1111/aogs.13920.