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Implementation of a piritramide based patient-controlled analgesia (PCA) as a standard of care for pain control in late abortion induction: A prospective cohort study from a patient perspective

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ABSTRACT

Objective: To assess whether the implementation of patient-controlled analgesia (PCA) with piritramide using an automatic pump system under routine conditions is effective to reduce pain in late abortion inductions
Study design: Prospective observational cohort study
Setting: Patients requiring medically indicated abortion induction from 14 weeks of pregnancy onwards between July 2019 and July 2020 at the department of Obstetrics and Prenatal Medicine of the Bonn University Hospital in Germany.
Methods: Evaluation of pain management after implementation of a PCA system compared with previous nurse-controlled tramadol-based standard under routine conditions. Patients answered a validated pain questionnaire and requirement of rescue analgesics was assessed. Pain intensity and satisfaction were measured on a ten-point numeric rating scale. Main Outcome Measure Maximal pain intensity
Results: Forty patients were included. Patients using Piritramide-PCA complained of higher pain sores than those in the standard group (6.90 (± 2.34) vs. 4.83 (± 2.87), ($p < 0.05$)). In both groups the level of satisfaction with the analgesia received was comparable (8.00 (± 2.45) vs 7.67 (± 2.62), ($p = 0.7$)). Patients in the PCA group suffered more nausea (63.2 % vs 30 % respectively, OR 4.0, 95 % CI 1.05–15.20, $p < 0.05$) and expressed more the desire for more analgesic support compared to the control group (OR 5.7 (1–33.25), $p = 0.05$).
Conclusion: Women with abortion induction after 14 weeks of gestation suffer from relevant severe pain, which requires adequate therapy. However, addition of PCA does not seem to bring any advantage in patients undergoing this procedure.

Introduction

Medically-indicated termination of pregnancy (TOP) is one of the most commonly performed procedures in obstetrics. It is estimated that of the 99,948 TOPs performed in Germany in 2020, almost 3900 were due to health conditions and a total of 2874 were performed after the 12th week of pregnancy [1]. The standard approach for TOP in the second and third trimester of gestation in Germany means induction of labor with prostaglandins often after application of mifepristone and feticide.

During second or third trimester abortion induction, notably more complications can be expected. In addition to heavy bleeding and pain, patients may experience higher levels of psychological stress due to longer exposure to pregnancy. It is well established that psychological distress play a relevant role in pain modulation [2].

Higher intensive pain levels during delivery have also been correlated.

with a higher risk of developing postpartum depression [3].

Abbreviations: CI, Confidence Intervall; NRS, Numeric rating scale; OR, Odds-Ratio; PCA, Patient-controlled analgesia; QUIPS, Quality improvement in post-operative pain management-project; SD, Standard deviation; TOP, Termination of pregnancy.

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Unfortunately, these data are missing for later TOP. Opioid-based patient-controlled analgesia (PCA) is an established technique for procedural analgesia, has been demonstrated to provide effective analgesia in many other procedures [4] and is recommended by evidence-based guidelines worldwide [5].

This study represents the first phase of a broader investigation aimed at identifying risk factors for the development of severe pain during obstetrical procedures in daily care. Given that TOP from the second trimester onward is associated with similar pain levels to that experienced during vaginal childbirth and assuming a potential influence due to severe psychological stress, to quantify the pain experience endured by women through TOP is very challenging. Improvement of analgesic management in these procedures is crucial but difficult to achieve through prospective studies with randomized control due to the multifactorial nature of pain and the complex psychological and ethical situation these women go through.

The QUIPS-Project (Quality Improvement in Postoperative Pain Management) is an ongoing initiative initially developed by the University Hospital in Jena. It focuses on internal and cross-clinic quality management of analgesic care. This project leverages the collection of patient-reported outcomes (PRO) and processed parameters in different procedures of the medical scope. Initially developed for assessing pain after surgical procedures, we adapted the main tool of this registry, the PROs-Questionnaire, to the process of TOP. In a second stage of the project other analgesic interventions should be evaluated under daily care conditions using this tool.

The present study aimed to evaluate the periprocedural pain experience after the introduction of an opioid-based intravenous PCA technique in comparison with standard analgesic care for pain control during late abortion induction. For this aim this group introduced a tailored PRO questionnaire for assessing pain perception. Pain intensity was considered the primary outcome.

Methods

In this prospective controlled cohort study consecutive patients undergoing TOP after 14 weeks of gestation at the department of Obstetrics and Prenatal Medicine of the Bonn University Hospital in Germany between August 2019 and July 2020 were included. Women under the age of 18 or having a medical history of opiate abuse or any contraindications for opiate use were excluded from the study.

The procedure of TOP was performed according to standards of the Bonn University Hospital. This consists of taking 600 mg of mifepristone starting in the afternoon on the day of admission, followed by misoprostol the following day at 10:00 pm administered every 4 h. The dose of misoprostol depends on gestational age and obstetrical history (see supplement).

If TOP was indicated after 20 weeks of gestation, feticide was performed by percutaneous ultrasound-guided injection of potassium chloride into the umbilical vein before administration of mifepristone. This study was prospectively planned as an evaluation of introducing a new strategy for pain management in this clinical setting and all patients were included consecutively. Data sampling started on 1st of August 2019. Introduction of PCA as a new standard in our clinic was previously planned and started on April 1st of 2020 after inclusion of 20 patients treated with previous analgesic standard. The initial analgesic management consisted of nurse-controlled administration of ibuprofen 600 mg, paracetamol (acetaminophen) 1 g, metamizole 1 g, tramadol 100 mg or a combination of meptazinol 100 mg and hyoscine butylbromide (HBB) 40 mg as short infusion on demand. Use of medication was at discretion of the nurse depending on pain intensity, time to prior medication and contraindications for each: nonsteroidal anti-inflammatory drugs (NSAID) for mild pain, tramadol for moderate pain and meptazinol combined with HBB for severe pain allowing combination in a three-step strategy patient in analogy to the classic WHO pain ladder [6]. No basic analgesia was provided.

In analogy to analgesic management for labor in this center analgesia was performed depending on pain intensity: nonsteroidal anti-inflammatory drugs (NSAID) for mild pain, tramadol for moderate pain and meptazinol combined with HBB for severe pain allowing combination in a three-step strategy. For comparison of opioid consumption dosage was converted to equivalents of oral morphine using standard literature [7,8]. According to this 100 mg meptazinol are equivalent to 12 mg of oral morphine and 15 mg piritramide are equivalent to 30 mg oral morphine.

On April 1st, 2020, intravenous administration of piritramide via PCA pump was additional implemented as standard care. A dose of 2 mg of piritramide bolus was triggered by the patient as needed. The bolus could be repeated every ten minutes with a maximum dosage of 30 mg in 4 h. Pump records were evaluated (times and intervals of the applications) and the regime was adjusted as needed. Application of ibuprofen, paracetamol or metamizole was also allowed.

The study group consisted of patients treated after the introduction of the PCA pump. The control group was composed of all patients who underwent TOP before the introduction of PCA.

The evaluation was performed according to the QUIPS project (quality improvement in postoperative pain management). Data collection was performed in a highly standardized manner as described in a previous studies [9]. QUIPS is a national multicenter interdisciplinary project for the evaluation of acute pain management included in the german registry for clinical trials (DRKS-ID: DRKS00006153), using patient reported outcomes (PROs). This is the biggest database for acute postoperative pain worldwide with more than 500,000 patient records. For this study pain questionnaire was modified to evaluate pain experience within the TOP procedure. As for QUIPS, focus of this evaluation was the whole pain experience through the procedure so the pain questionnaire was handed out to the patient at admission and they were instructed to fill out the questionnaire anonymously at the time of discharge, after process of abortion was ended. The questionnaire consisted of fifteen (see Table 1). Patients were instructed to use a numeric rating scale (NRS) from 0 (no pain) to 10 (most unbearable pain) for pain intensity to evaluate pain scores since begin of TOP.

Pain levels of seven or more were considered severe for the analysis of risk factors for severe pain.

Statistical analysis

A two-point reduction on the NRS was defined as clinically relevant for the sample size calculation. Based on earlier publications [10], a mean pain score for maximal pain of 4.6 with standard variation of 2.2 was used. Nineteen patients were needed in each arm to see a reduction of two points on the NRS with 80 % power and assuming a 5 % type 1 error.

The Mann-Whitney-U-test was used for the analysis of the ordinal

Table 1
Overview of outcome measures on the questionnaire (translated from German).

Outcome measure	Scale
Pain on ambulation/stress	NRS 0–10*
Maximum pain intensity since TOP	NRS 0–10*
Minimum pain intensity since TOP	NRS 0–10*
Is pain interfering with your mobility or movement?	Yes/no
Are you experiencing pain when you cough or breathe deeply?	Yes/no
Were you woken up by pain last night?	Yes/no
Is pain interfering with your mood?	Yes/no
Have you felt very tired since your TOP?	Yes/no
Have you felt nausea since your TOP?	Yes/no
Have you vomited since your TOP?	Yes/no
Would you have liked to have received more pain medication?	Yes/no
How satisfied are you with your pain treatment since TOP?	NRS 0–10**

* Numeric Rating Scale (NRS) for pain: 0 =no pain, 10 =most intense pain imaginable.

** NRS for satisfaction: 0 = completely unsatisfied, 10 = completely satisfied.

variables since no normal distribution was observed. The Student's t-test was performed for continuous variables. Descriptive categorical variables were analyzed using X^2 or Fischer's exact test as appropriate. Results are expressed as mean, plus/minus standard deviation (SD) for continuous variables and as percentage or odd ratio with 95 % confidence interval for categorical variables. Statistical analysis was performed using SPSS version 19.0 (SPSS inc. Chicago, IL).

An approval of the local ethics committee was provided (Registration Number: 208/18).

Results

Forty patients were included in the study. Demographic and baseline characteristics between groups were comparable (Table 2).

Women in the study group reported higher maximum NRS pain levels (6.90 (± 2.34) vs. 4.83 (± 2.87), ($p < 0.05$)). No difference was observed in satisfaction levels between groups (8.00 (± 2.45) vs. 7.67 (± 2.62), ($p = 0.7$)) (Fig. 1). Nausea was significantly more frequent with piritramide PCA (OR 4.0 (95 % CI 1.05–15.20). These women were also more often awake at night due to pain (OR 4.8 (95 % CI 4.2–19.9). No differences between the two groups were observed for dizziness, fatigue or other items of the questionnaire (Table 3).

Regarding the use of analgesic drugs, non-opioids were rarely used in both groups (two women received paracetamol in the control group and one woman in the PCA group) except HBB, since this was administrated in a fixed combination with meptazinol in the control group. Opioid consumption was similar in both groups. Sixteen patients (80 %) in the control group received opioids for analgesia while nineteen women (95 %) used the piritramide pump in the study group ($p = 0.34$). The analysis of the cumulated dosage of opioid drugs administrated thorough the whole procedure did not significantly differ between the groups (15 mg (± 13.5) vs. 20 mg (± 20.6) respectively, $p = 0.37$).

Sub analysis of the effect of relevant pain levels shows that reporting pain levels of seven or more increases the risk of nausea or vomiting (OR 8.5, 95 % CI 1.96–36.79) and dizziness (OR 6.6, 95 % CI 1.62–26.87) and impairment of mobility (OR 6.79, 95 % CI 1.60–28.86). The wish of more medication was also higher in these patients (OR 5.73 (95 % CI 1.0–33.25). Feticide performed prior to induction of labor and fetal weight over 350 g increased the risk of severe pain. The OR was the same for both variables: feticide and fetal weight over 350 g; (4.19 (95 % CI 1.1–15.9). No correlation was found between severe pain and any other study variable such as need of curettage, maternal age, induction time, etc.

Discussion

In this study, patients reported high pain scores during late medically indicated TOP, even when using patient-controlled analgesia with an automatic intravenous PCA device. To the best of the authors' knowledge, this is the first study evaluating the use of opioid based PCA for analgesia during TOP in the second and third trimester under standardized conditions. The available evidence shows unexpectedly high levels of pain intensity related to this procedure [11,12]. Therefore, this study group was unable to find any noteworthy evidence, written guidelines or recommendations regarding pain management for women undergoing late medical abortion. Although the TOP procedure itself is subject of heterogeneous regulations in each country and different medical societies have issued different guidelines, pain management is not part of these guidelines [13,14].

By introducing PCA as a new standard of care for pain management, the authors expected to observe a reduction of pain levels and an increased satisfaction with pain therapy. However, higher pain levels were observed with the new analgetic management. Other studies came to a similar conclusion when opioids were added in early TOP. Colwill et al. observed that adding oxycodone does not reduce the pain intensity for medical abortion in early pregnancy [15].

Opioid consumption was over 80 % in both groups, but equivalent cumulative dosages seem to be rather low with 15 mg and 20 mg respectively. Several studies have shown that administering opioids as analgesics not only does not reduce pain satisfactorily after surgical TOP but also causes relevant side effects, such as nausea or vomiting [16], increasing discomfort during this stressful process.

Considering the lower administration rates of non-opioid in both groups, sufficiency of analgesic treatment can be questioned and considered a plausible explanation for the high pain levels in the present study. Since HBB was always administrated in a fixed combination with meptazinol in the control group, an additional effect of this drug on the observed difference between groups cannot be clearly excluded in this study. Although the analgesic effect of this drug it is not clear, it has been demonstrated, that HBB reduces the duration of labor, and this could have an effect on the whole pain experience [17].

Dufresne et al. studied whether hypnosis before and during TOP had a positive influence on pain management, showing lower intravenous analgesia requirements but reporting similar pain levels [18]. The pain questionnaire used for the present study also included one question about the use of non-pharmacological interventions, but patients used these strategies very rarely.

The pain levels reported in this manuscript were unexpectedly high and should be of concern. As a comparison, similar NRS pain levels have been reported after cesarean sections in a recent publication [19]. This is relevant since cesarean section can be considered one of the most painful surgeries compared with non-gynecological procedures [20] and the most painful surgical procedure in the gynecological spectrum [19].

Pain scores for operative TOP in the first trimester are not as high as for later medical abortion induction [21]. This can probably be explained by the controlled conditions under which surgical procedures are performed, the use of anesthesia during the process, but also the availability of clear guidelines and recommendations.

Since medical abortion induces psychological stress and pain modulation is also affected by psychological factors, it could be assumed that these women have a higher perception of pain. This has been already described for catastrophizing and anxiety regarding other medical procedures [2,22]. Pur et al. for example showed that patients with higher scores for anxiety in the STAI (State-Trait-Anxiety Inventory) questionnaire tended to report higher pain levels after first trimester termination of pregnancy [23].

Insufficient pain control during abortion procedures is also related with a worse whole health care experience [24]. The present data are in line with these findings since patients who reported high pain scores were less satisfied with the whole management.

Recommendations for pain management for second trimester medical abortion have been described as poor and heterogeneous by other groups [25]. Due to the lack of qualitative evidence for analgesic strategies in these patients, each center tends to use local guidelines which are inconsistent and not well evaluated [25].

To our knowledge, this is the first study evaluating different pain

Table 2
Demographic data and baseline characteristics.

	Study Group (n = 20)	Control Group (n = 20)
Mean maternal age in years (SD)	33 (5.6)	34 (7.1)
Primiparity – n (%)	6 (30 %)	9 (45 %)
Mean fetal weight in grams (SD)	417 (291.5)	320 (380.2)
Mean gestational age in weeks (SD)	20 (5.4)	20 (4.1)
Prior cesarean section – n (%)	2 (10 %)	2 (10 %)
Mean induction time in hours (SD)	13 (13)	10.5 (5.6)
Feticide – n (%)	12 (60 %)	6 (30 %)
Curettage – n (%)	3 (15 %)	4 (20 %)

$p > 0.05$ for each item.

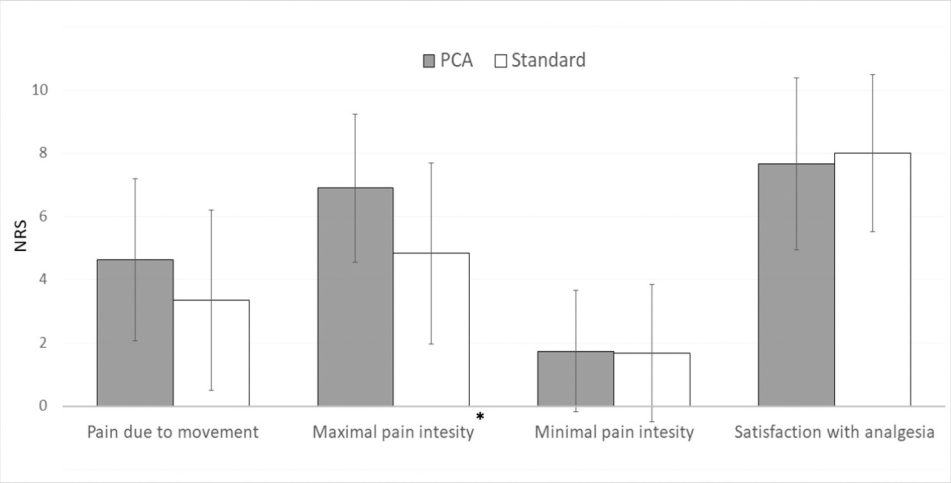

Fig. 1. Comparison NRS for pain intensity at different situations and Satisfaction with pain management.

Table 3
Side effects of pain and pain medication.

	Study group, n = 20	Control group, n = 20	OR (95 % CI)
Awoken due to pain - n, (%)	11 (55)	4 (20)	**4.89 (1.2–19.94)**
Impairement on movement- n (%)	11 (55)	3 (15)	**6.93 (1.53–31.30)**
Nausea - n, (%)	12 (63.2)	6 (30)	**4.0 (1.05–15.21)**
Tiredness - n, (%)	16 (84.2)	12 (60)	3.56 (0.78–16.31)
Dizziness - n, (%)	9 (45)	7 (35)	1.52 (0.43–5.43)
Mood - n, (%)	6 (30)	7 (35)	0.80 (0.21–3.00)
Desire more analgesia - n, (%)	6 (30)	2 (10)	3.86 (0.67–22.11)

Bold text indicates $p < 0.05$ for Chi-Squared test for this comparison.

management modalities in patients undergoing medically induced termination of pregnancy after the first trimester. The strength of this prospective study is the use of a validated high standardized tool for evaluation of acute pain management based on PROs. Since the purpose of this study was to evaluate the introduction of a PCA pump under daily standard hospital conditions, randomization or blinding was not performed, so selection bias cannot be excluded. In order to address this issue no member of the obstetric team was involved in the data collection and external assessors were responsible for data input. Patients were not aware of the different interventions being evaluated.

The present study has certain limitations. A small sample size was calculated for the primary outcome. Consequently, the evaluation of secondary outcomes could be statistically underpowered. The study did not evaluate the stress or anxiety levels of the women undergoing TOP, so an effect of these factors on not be ruled out.

Conclusion

TOP in the late trimester is associated with high pain intensity. Using piritramide PCA for this procedure was associated with higher pain intensity, nausea and. Higher fetal weight and feticide seem to be associated with higher pain levels. Since very little is known about appropriate pain management in these women, more studies are needed to improve patient care.

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Declaration of Competing Interest

The authors report no conflict of interests.

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Details of ethics approval

The authors confirm that the study was approved by the appropriate institutional and/or national research ethics committee (ethics committee of Bonn University Hospital, Registration Number: 208/18). Informed consent Informed consent was obtained from all individual participants included in the study.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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