

A randomized controlled trial of fentanyl for abortion pain

Mollie J. Rawling, MB, ChB, and Ellen R. Wiebe, MD

Vancouver, British Columbia, Canada

OBJECTIVE: Our aim was to find out whether intravenous fentanyl was effective in reducing the pain of first-trimester abortion.

STUDY DESIGN: This randomized controlled trial included 825 women attending a nonhospital abortion facility. Some women chose standard care. Women who did not choose standard care were randomly assigned to receive either 50 to 100 µg of fentanyl, a placebo, or no intervention. With SAS software and a mixed effects analysis of variance model with covariates, we compared mean pain scores of the fentanyl and placebo groups to detect a difference of at least 1 point on an 11-point pain scale.

RESULTS: The mean pain score of the fentanyl group was 1.0 point less than that of the placebo group (95% confidence interval, 3.7-4.3) and 0.9 point less than that of the observational group (95% confidence interval, 4.7-5.1). This pain reduction was statistically significant, but the women who were studied wanted a 2-point reduction from fentanyl.

CONCLUSION: Fentanyl, when compared with the placebo, reduced abortion pain by 1.0 point on an 11-point scale. This reduction was of questionable clinical significance and was less than desired by the women included in the study. (*Am J Obstet Gynecol* 2001;185:103-7.)

Key words: Abortion pain, fentanyl

Physicians who perform abortions disagree about the use of intravenous fentanyl for pain control. Fentanyl is a short-acting opioid used as an analgesic for many brief surgical procedures; it is not always effective.¹ A comprehensive literature review did not discover any report of whether fentanyl is an effective analgesic for abortion.

Approximately 1,400,000 surgical abortions take place in North America each year,² and 450,000 of them are done in National Abortion Federation clinics. When Lichtenberg et al³ surveyed the clinical practice of these clinics, it was found that 17% of them used general anesthesia, although local anesthesia was cheaper and was more acceptable to many women. He also found that 65% of the clinics using local anesthesia supplemented it with conscious sedation. Most used fentanyl in doses of 50 to 100 µg as the intravenous analgesic; 91% of them also offered an intravenous anxiolytic.

The primary objective of our trial was to find out how effective fentanyl is in reducing the pain of first-trimester abortion.

Material and methods

The study design included 2 arms, an observational arm and an experimental arm. The experimental arm was a randomized, double-blind, and placebo-controlled trial. We designed it to test our primary hypothesis that women receiving fentanyl would experience less pain than women receiving a placebo and that the difference would be 1 point or greater on a 0 to 10-point pain scale. Randomization assigned women to the fentanyl, placebo, and no intervention groups in the ratio of 2:1:1. The observational arm of the study ran concurrently with the experimental arm and included women who wanted to answer questions about their experience of abortion pain but did not want to accept the chance of receiving fentanyl (Fig 1).

The trial ran between November 1997 and July 1998 at a nonhospital facility performing 2300 abortions annually with local anesthesia. Women attending for elective first-trimester abortion received information about the study and an invitation to participate. Professional interpreters were available for the large number of women who were not fluent in English; therefore, in contrast to many other studies,⁴ these women had equal opportunity to take part. Standard clinic care was provided for all women, whether or not they participated in the study. It included emotional support, full counseling, the offer of oral analgesic and anxiolytic medication, Rhesus factor and hemoglobin testing, intracervical and paracervical infiltration of 20 mL of 0.5% lidocaine, standard suction curettage abortion, and clinical monitoring during surgery and recovery.

From the Everywoman's Health Centre, and the Department of Family Practice, Faculty of Medicine, University of British Columbia. Presented at the Annual Meeting of the National Abortion Federation, Atlanta, Georgia, April 27, 1999.

Received for publication December 16, 1999; revised February 7, 2001; accepted March 19, 2001.

Reprint requests: Mollie J. Rawling, MD, ChB, Everywoman's Health Centre, 2005 E 44th Ave, Vancouver, British Columbia, Canada, V5P 1N1.

Copyright © 2001 by Mosby, Inc.

0002-9378/2001 \$35.00 + 0 6/1/115860

doi:10.1067/mob.2001.115860

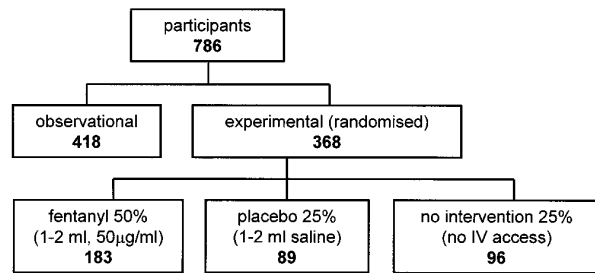


Fig 1. Flow chart of participants.

A counselor gave each woman verbal and written information about the study; explained to her the need for an indwelling intravenous catheter for the administration of fentanyl, as required by the College of Physicians and Surgeons of British Columbia; and informed her of possible side effects of fentanyl, including driving impairment and increased drowsiness. The counselor then invited each woman to participate and obtained signed consent. For each woman entering the experimental arm, the counselor opened a sequentially numbered, opaque envelope with a randomized code that indicated whether the woman would have an intravenous catheter or not. A study assistant prepared sequentially numbered syringes from a randomized list that indicated whether each syringe was to be filled with 2 mL of fentanyl solution (50 µg/mL) or with 2 mL of normal saline solution. Physicians, clinic staff, and women in the study did not know the contents of the syringes. A nurse inserted an intravenous catheter for all women randomized to receive one and tested blood from the catheter for hemoglobin and rhesus factor. The nurse tested blood from a finger stab for all women randomized to be without intravenous access and obtained a pain score for either the finger stab or the venipuncture. For all women in the fentanyl and placebo groups, a nurse took the next sequentially numbered syringe and injected 1 mL of solution intravenously while the speculum was being placed. She injected up to another 1 mL if the woman indicated that she would like more pain control. Thus all doses of fentanyl were between 50 and 100 µg. Uterine evacuation, known to be the most painful part of the procedure for most women,⁵ usually followed 2 to 5 minutes after the initial intravenous injection.

During the 3 minutes after the removal of the speculum, women rated their abortion pain on a verbal 11-point numerical rating scale. A nurse asked each woman, "On a scale of 0 to 10, where 0 is no pain and 10 is pain as bad as it can be, what was that like for you?"

To control for factors known to influence abortion pain,⁶⁻⁸ nurses recorded maternal age, gestational age, and attending physician. Immediately after obtaining informed consent and before dispensing oral medications, counselors asked women to rate their preoperative anxi-

ety and depression on 11-point verbal numerical rating scales that were similar to the 11-point verbal numerical rating scale used for pain measurement. Women rated their preoperative and postoperative nausea on a similar 11-point scale to give information about whether fentanyl affected postoperative nausea.^{9, 10} Nurses asked women whether they would choose fentanyl for a possible future abortion, and, if so, what minimum pain reduction they would want from it.

The Clinical Research Ethics Board of the University of British Columbia granted approval for the study. Because the study facility had not been offering intravenous analgesic medication for the previous 8 years, the introduction of intravenous fentanyl in a placebo-controlled trial was ethically justifiable.

With the assumption of an SD of 2.5 and an α level of 5% and with minimum sample size of 180 in the fentanyl group and 90 in each of the control groups, the power to detect a difference of 1 point on the 11-point numerical rating scale was at least 95%. For examination of the primary hypothesis, we adjusted the pain scores in the 3 experimental groups for physician, maternal age, gestational age, anxiety, depression, and other medication. SAS software (SAS, Cary, NC) afforded a mixed-effects analysis of variance model with covariates and a specific contrast to test the primary hypothesis. We considered randomly assigned treatment to be a fixed effect and the physician performing the procedure to be a random factor. This model specification allowed inference to physicians in general. We used confidence intervals (CI) to report differences in the mean abortion pain in each of the 3 experimental groups and for each of the 3 physicians.¹¹ In addition, we used correlation coefficients with CIs to describe the degree of association between mean abortion pain and both anxiety and depression.

Results

A total of 825 women entered the study. We excluded the results for 39 women who had incomplete questionnaires, whose intravenous access failed, or whose physician performed fewer than 2% of the total number of abortions. Of the 786 women for whom results were available, 183 were in the fentanyl group, 89 were in the placebo group, 96 were in the no intervention group, and 418 were in the observational group (Fig 1). When we compared the 4 groups, we found that they were similar with respect to maternal age, gestational age, anxiety, and depression (Table I). In each group 99% of women accepted oral ibuprofen (600 mg) or acetaminophen (1 g) 1 hour before surgery. In each experimental group 94% of the women accepted sublingual lorazepam (0.5-1.0 mg) 1 hour before surgery, but in the observational group only 68% of the women did so. Numbers of women attended by each physician differed.

Table I. Demographics by groups

	No intervention	Placebo	Fentanyl	Observational
Maternal age (y)				
Mean (SD)	25.6 (5.16)	25.0 (6.34)	25.2 (6.11)	25.9 (6.3)
Min/max	16/38	13/39	15/44	14/45
No.	96	93	184	427
Gestational age (wk from last menses)				
Mean (SD)	9.0 (1.68)	9.0 (1.61)	9.0 (1.63)	8.8 (1.66)
Min/max	5.5/14	6/14.5	6/14.5	4.5/14
No.	96	93	183	426
Preoperative anxiety (0-10)				
Mean (SD)	4.9 (2.89)	4.9 (2.47)	4.9 (2.49)	4.5 (2.45)
Min/max	0/10	0/10	0/10	0/10
No.	96	89	183	420
Preoperative depression (0-10)				
Mean (SD)	3.5 (2.72)	3.4 (2.57)	3.7 (2.72)	3.4 (2.78)
Min/max	0/10	0/10	0/10	0/10
No.	96	89	183	4418
Preoperative nausea (0-10)				
Mean (SD)	3.0 (3.27)	2.3 (2.81)	2.45 (2.78)	2.5 (2.80)
Min/max	0/10	0/10	0/10	0/10
No.	94	86	178	410

The results showed a statistically significant difference between the mean abortion pain reported by women in the fentanyl group and by women in the placebo control group. The adjusted mean abortion pain of the fentanyl group was 1.0 point less than that of the placebo group (95% CI, 0.4-1.6) and 1.2 points less than that of the no intervention group (95% CI, 0.6-1.8) (Table II).

Comparison of the unadjusted mean pain score of the fentanyl group at 4.0 points (95% CI, 3.7-4.3) with that of the observational group at 4.9 points (95% CI, 4.7-5.1) showed a difference of 0.9 point.

When the 4 study groups were combined, the mean difference in abortion pain was 0.8 point (95% CI, 0-1.7) between physicians A and B, 1.5 points (95% CI, 0.7-2.3) between physicians A and C, and 0.7 point (95% CI, 0.1-1.3) between physicians B and C. Comparison between the fentanyl and placebo groups showed that fentanyl reduced the mean pain score for each physician by approximately the same amount (Fig 2).

The Pearson correlation coefficient for anxiety was 0.21 (95% CI, 0.11-0.31) and 0.22 (95% CI, 0.12-0.31) for depression, indicating that increased anxiety and depression are predictors of increased abortion pain.

Eighty percent of the women in the fentanyl group and 26% of the women in the placebo group noticed at least one side effect after the intravenous injection. Dizziness was the most common side effect, with drowsiness second and relaxation third. Clinic staff and physicians did not observe any instances of respiratory depression, and there was no change in the occurrence of occasional vasovagal incidents associated with the abortion procedure. There was no difference in nausea between the fentanyl

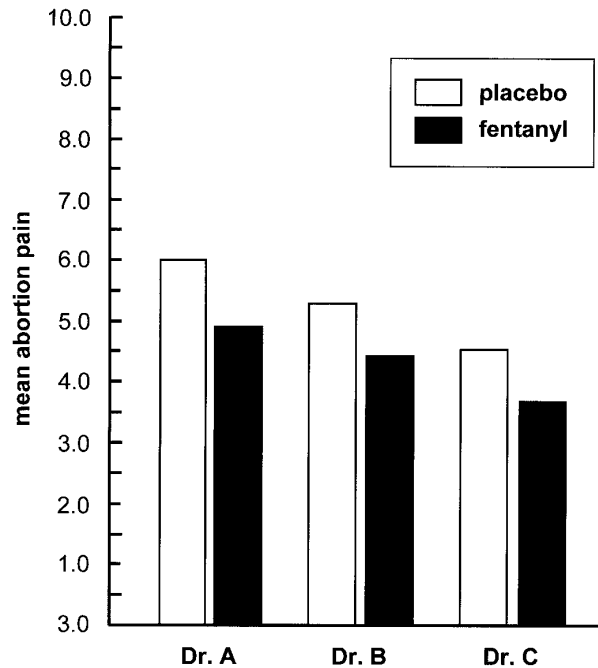


Fig 2. Mean abortion pain by group and physician.

Table II. Adjusted abortion pain in experimental groups

	No. of participants	Mean	SE
Fentanyl	183	4.3*	0.4
Placebo	89	5.3	0.5
No intervention	96	5.6	0.5

*Difference between fentanyl and placebo groups was 1.0 point (95% CI, 0.4-1.6).

and placebo groups, and women rated pain of venipuncture and finger stab equally at 2 points.

Median acceptable abortion pain for women in all groups was 5 points. Preference for future fentanyl was 92% in the fentanyl group, 88% in the placebo group, 62% in the no intervention group, and 23% in the observational group. The 235 women who indicated that they would choose fentanyl for a possible future abortion said that in doing so they would want a median minimum pain reduction of 2 points.

Comment

The background for this study was the wide variation in the use of conscious sedation by North American abortion clinics. In 1996 Lichtenberg et al³ surveyed the clinical practice of National Abortion Federation clinics. The study found that 65% of the clinics offered conscious sedation and that they used at least 7 different medications in varying doses and for varying proportions of women. In 1998 a study comparing pain scores of randomly selected clinics found that those offering conscious sedation scored 1.3 points less pain on an 11-point pain scale

than those not offering it.¹² Moreover, some clinics that never used conscious sedation scored less pain than some clinics that used it freely. We conducted the study because our clinic was trying to decide whether to reintroduce the use of intravenous fentanyl and wanted to know how much it reduced pain. We did not design our randomized controlled trial to evaluate conscious sedation in general; instead, we designed it to measure the specific analgesic effect of fentanyl in the dose most commonly used for abortion, namely 50 to 100 µg.

Because we regarded fentanyl as a major analgesic intervention, we thought that women might expect significant pain relief from it. We asked women questions about their choice of fentanyl for a future abortion during their 30-minute period of postabortal rest. At this time they were very aware of the intensity of their own personal abortion pain, and we had told them that we did not know how effective fentanyl was. A 90% preference for fentanyl for a future abortion in the combined fentanyl and placebo groups and a 23% preference in the observational group suggested that, for most of these women, their abortion experience had not changed their choice. In the no intervention group 38% of women changed their choice after their abortion experience, saying that they would not choose fentanyl in the future. These were women who had wanted intravenous analgesic and knew they had been denied it. We did not ask why they changed their choice and therefore have no evidence-based explanation for it. They may have been satisfied with their nonopioid pain control. Overall preference for fentanyl for a future abortion was 53%.

The inclusion in our study of an observational arm provided information from women who did not want an intravenous opioid. The pain score of women in the observational group differed by less than 1 point from the pain score of women in the fentanyl group. Because the observational group was self-selected, statistical bias was inherent in its composition, and its mean pain score was not corrected for covariance. Inclusion of the no intervention group controlled for placebo effect; no blinding was involved, although the group was part of the randomized experimental arm of the study. The placebo effect of 0.3 point was small and validated the 1.0 point analgesic effect of fentanyl. Our study design and our rating scales proved suitable for those women who were not fluent in English. In future studies we will look at how ethnic background and culture influence abortion pain.

The 11-point verbal numerical rating scale that we chose for scoring pain was easy to administer, could be scored when women were lying down, and was known to provide satisfactory results.^{13, 15} In 1997 a study involving 14 National Abortion Federation clinics found that they all used the 11-point verbal numerical rating scale effectively and without difficulty.¹² The authors of a 1998 study comparing 3 pain scales during abortion commented

that the use of an 11-point verbal numerical rating scale for abortion was appealing because it was simple and because women could provide verbal responses at any time regardless of their position.⁵

In a 1988 abortion pain study, clinicians used standardized psychometric measures to assess anxiety and depression,⁷ whereas in our study women answered a single question to score each of these emotions on an 11-point scale. The observed Pearson correlation coefficients of 0.21 for anxiety and 0.22 for depression in our study were only a little lower than those of the 1988 study, which found coefficients of 0.23 for anxiety and 0.28 for depression. This confirmed that our rapid evaluation of anxiety and depression on an 11-point verbal numerical rating scale was adequate to correct for covariance between our experimental groups.

Stubblefield⁸ found that pain varied with the physician doing the procedure, but Borgatta and Nickinovich¹⁴ reported no consistent association between the operator and the pain score. In our previous studies we found consistent differences in the pain scores of our physicians,^{12, 13, 15} and in this study we quantified the differences. Our results showed that fentanyl decreased the mean pain score for each physician by approximately the same amount. Therefore physicians who cause less pain can expect fentanyl to decrease their pain scores by the same amount as physicians who cause more pain. The operating techniques of our 3 physicians were similar, with no wait between the infiltration of lidocaine and the start of cervical dilatation. Although it was interesting to speculate on the reasons for the differences in physician pain scores, we came up with no explanation and hope that future studies will clarify this aspect of abortion pain.

Our observed pain reduction of 1.0 point was statistically significant. Smith et al⁶ published a landmark study on abortion pain in 1979. They and subsequent investigators used statistical significance to detect demographic and clinical predictors of abortion pain such as gestational age, maternal age, anxiety, and depression.^{7, 13, 14} Statistically significant differences in pain, sometimes of less than 1 point, have allowed other researchers to determine the effects of oral medications and the effects of changes in local anesthetic formulations and techniques of cervical block.^{8, 12, 13, 15} These minor changes in management have improved our control of abortion pain. The introduction of an intravenous opioid, however, is not a minor change. Women notice the side effects of fentanyl. Additional monitoring and resuscitative equipment is required, and antidote must be on hand. Although we noticed no change in level of consciousness in our fentanyl and placebo groups, we recognized that fentanyl might produce inadvertent deep sedation and were prepared to deal with this.

In the past 5 years reports have been published on clinically, as distinct from statistically, significant differences

in short-term pain scores. In 1998 an interesting study by Stahmer et al¹⁶ correlated percentage change in pain with perceived relief. It reported that a 30% decrease in pain was perceived as some or partial relief, whereas a 57% decrease in pain was perceived as significant or complete relief. The 2-point pain reduction that women in the current study said they wanted from fentanyl fell within this 30% to 57% range. We tried to evaluate the clinical significance of our results by correlating them with those of other researchers. In an emergency room study, Todd et al¹⁷ found that the minimum change in short-term pain that patients could detect was 13 points on a 101-point scale. In a subsequent study, Kelly¹⁸ found that a difference of 0.9 point on an 11-point scale was the minimum pain change that was clinically significant. Our results showed that fentanyl reduced pain by 1.0 point.

A limitation of our study was our failure to statistically correlate 10 µg incremental doses of fentanyl between 50 and 100 µg with corresponding pain scores. Thus women receiving 75 to 100 µg of fentanyl may have had an adjusted pain score difference of more than 1.0 point.

The women in our study said that a median acceptable pain level on the 0 to 10-point scale would be 5 points. They wanted 2.0 points pain reduction from intravenous fentanyl, but they received only a 1.0-point reduction. We need to know how much pain relief is achieved by other forms of conscious sedation. Increasingly, physicians are combining opioids with midazolam, but there are no published reports on the effectiveness of this combination for abortion or on the effectiveness of midazolam or other anxiolytics used alone. Further randomized controlled trials are needed to find out what effectively controls abortion pain.

Intravenous fentanyl reduced the pain of abortion by 1.0 point on an 11-point numerical rating scale. The clinical significance of this in abortion practice is a matter for individual providers and patients to decide.

We thank Ms Laurie Ainsworth for statistical analysis, Ms Meera Selvakone for data entry, the Department of Family Practice of Vancouver General Hospital for financial assistance with statistical analysis, and the staff and

physicians of Everywoman's Health Centre for patient care and data collection.

REFERENCES

1. Rasmussen YH, Dahl C. Analgesic requirements for ESWL treatment. *Scand J Urol Nephrol* 1994;28:225-7.
2. Henshaw SK. Abortion incidence and services in the United States, 1995-1996. *Fam Plann Perspect* 1998;30:263-70, 287.
3. Lichtenberg ES, Paul ME, Saporta V. 1997 Provider clinical survey; first trimester surgical abortion practice. Washington (DC): National Abortion Federation; 1997.
4. Hankins C, Lapoint N, Walmsley S. Participation in clinical trials among women living with HIV in Canada. Canadian Women's HIV Study Group. *Can Med Assoc J* 1998;159:1359-65.
5. Jensen MP, Miller L, Fisher L. Assessment of pain during medical procedures: a comparison of three scales. *Clin J Pain* 1998; 14:343-349.
6. Smith GM, Stubblefield PG, Chirchirillo L, McCarthy MH. Pain of first-trimester abortion: its quantification and relations with other variables. *Am J Obstet Gynecol* 1979;133:489-98.
7. Belanger E, Melzack R, Lauzon P. Pain of first-trimester abortion: a study of psychosocial and medical predictors. *Pain* 1989;36:339-50.
8. Stubblefield PG. Control of pain for women undergoing abortion. *Int J Gynecol Obstet* 1989;3:131-40.
9. Woodhouse A, Mather LE. Nausea and vomiting in the postoperative patient-controlled analgesia environment. *Anaesth* 1997; 52:770-5.
10. Cepeda MS, Gonzalez F, Granados V, Cuervo R, Carr DB. Incidence of nausea and vomiting in outpatients undergoing general anesthesia in relation to selection of intraoperative opioid. *J Clin Anesth* 1995;8:324-8.
11. Mantha S, Thisted R, Foss J, Ellis JE, Roizen MF. A proposal to use confidence intervals for visual analog scale data for pain measurement to determine clinical significance. *Anesth Analg* 1993;77:1041-7.
12. Rawling MJ, Wiebe ER. Pain control in abortion clinics. *Int J Gynecol Obstet* 1998;60:293-5.
13. Wiebe ER. Comparison of the efficacy of different local anesthetics and techniques of local anesthesia in therapeutic abortions. *Am J Obstet Gynecol* 1992;167:131-4.
14. Borgatta L, Nickinovich D. Pain during early abortion. *J Reprod Med* 1997;42:287-93.
15. Wiebe ER, Rawling M. Pain control in abortion. *Int J Gynaecol Obstet* 1995;50:41-6.
16. Stahmer SA, Shofer FS, Marino A, Shepherd S, Abbuhl S. Do quantitative changes in pain intensity correlate with pain relief and satisfaction? *Acad Emerg Med* 1998;5:851-7.
17. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996;27: 485-9.
18. Kelly A. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? *Acad Emerg Med* 1998;5:1086-90.