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The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation

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BACKGROUND: Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the biosynthesis of prostaglandins and concerns have been expressed that they might attenuate the effects of exogenous prostaglandins. This randomized study was conducted to evaluate whether NSAID given during medical abortion with mifepristone/misoprostol in the second trimester has a negative effect on the efficacy of the abortifacient by prolonging the induction-to-abortion interval. METHODS: Seventy-four women were treated with the anti-progesterone mifepristone, followed by repeated doses of misoprostol 36–48 h later. They were randomized to receive a prophylactic pain treatment of either paracetamol and codeine or diclofenac with the first dose of misoprostol. RESULTS: Co-treatment of NSAID with misoprostol did not attenuate the efficacy of mifepristone and misoprostol. There was no significant difference between the NSAID and the non-NSAID group in the induction-to-abortion interval (5.4 versus 6.5 h) or the total doses of misoprostol needed (2 versus 3). The frequency of surgical intervention was similar (55.6 versus 52.6%). Women in the group treated with NSAID required significantly less opiates (P = 0.042). CONCLUSION: Co-treatment with NSAID and misoprostol does not interfere with the action of mifepristone and/or misoprostol to induce uterine contractions and pregnancy expulsion in medical abortion. Prophylactic NSAID administration reduces the need for opiate injections.

Key words: medical abortion/misoprostol/non-steroidal anti-inflammatory drug/pain relief/second trimester

Introduction

The degree of uterine activity during pregnancy is thought to be regulated by the balance between the intrinsic suppressor, progesterone, and the stimulant prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Csapo, 1974). Bygdeman and Swahn (1988) showed that treatment with mifepristone increased contractility in the pregnant uterus and sensitized the myometrium to prostaglandin. The increased contractility occurs 24 h after the administration of mifepristone and is due, in part, to a reversal of the hyperpolarization of the cell membrane and the progesterone-dependent inhibition in gap-junction formation (Garfield *et al*., 1988). Following treatment with mifepristone, there is also an increase in decidual prostaglandin release and reduced activity of prostaglandin dehydrogenase (Norman *et al*., 1991). Like prostaglandin, mifepristone induces softening and ripening of the cervix during pregnancy (Rådestad *et al*., 1993; Ngai *et al*., 1999).

Non-steroidal inflammatory drugs (NSAIDs) inhibit the biosynthesis of prostaglandins. It has been shown that treatment with NSAID significantly prolongs the induction-to-abortion interval in abortions not using exogenous prostaglandin such as intrauterine instillation of hypertonic saline or Rivanol®. An increase in endogenous prostaglandin production is essential for the effect on uterine contractility in this method and the induction-to-abortion time is significantly increased by NSAIDs (Ölund *et al*., 1979). Furthermore, dysmenorrhea is associated with an increased uterine contractility caused by an increased endogenous $PGF_{2\alpha}$ production. In these women, NSAIDs are an effective treatment for pain and are believed to act via the reduction of endogenous prostaglandin. (Lundström *et al*., 1976; Smith, 1987).

Since mifepristone leads to an increase in endogenous prostaglandin production in the uterus, concerns have been expressed that simultaneous administration of NSAIDs might attenuate the effect of mifepristone when used together with prostaglandin for first and second trimester abortion. Because of these theoretical concerns, NSAIDs are frequently avoided and a recommendation against their use given in protocols for medical abortion (Exelgyn, 1998). On the other hand, co-treatment with NSAIDs and exogenous prostaglandin does not seem to influence the effect of prostaglandin with regard to uterine contractility or cervical ripening (Norman *et al*., 1991; Li *et al*., 2003) and does not affect the efficacy in women receiving methotrexate and misoprostol for early abortion (Creinin and Schulman, 1997).

In medical abortion using a combination of mifepristone and prostaglandin, analgesic treatment is important for the acceptability of the method. However, the best treatment schedule remains to be established. The pain is most pronounced following the administration of the prostaglandin (misoprostol or gemeprost). It has not yet been evaluated in a prospective study whether co-administration of a NSAID with misoprostol following mifepristone has an influence on the efficacy of the procedure.

In the present study, second trimester patients received treatment with mifepristone followed by repeated doses of misoprostol. The primary outcome of the study was to evaluate whether co-treatment of NSAID with the first dose of misoprostol would affect the induction-to-abortion interval. The secondary outcome was to evaluate whether the combined treatment of NSAID with the first misoprostol dose would be a more effective pain control method than a non-NSAID analgesic during medical abortion with mifepristone and misoprostol.

Materials and methods

Healthy women with a singleton intrauterine pregnancy requesting abortion for socio-economic or fetal indications were asked to participate in the study, which was carried out between October 2003 and November 2004 in the Department of Obstetrics and Gynaecology at the Karolinska University Hospital, Stockholm, Sweden. The pregnancies were between 13 and 22 weeks gestation calculated from the first day of the last menstrual period and confirmed by gynaecological examination and ultrasound. Exclusion criteria were a history of allergy to misoprostol, any signs of local infections, major medical problems or not being able to understand the information provided. The women gave their written informed consent and the study was approved by the Ethics Committee at the Karolinska University Hospital/ Karolinska Institute, Stockholm.

The women received 600 mg mifepristone (Mifegyne®; Exelgyn, Paris, France) orally, swallowed under supervision in the clinic on day 1. They were then allowed home and returned 36–48 h later to receive four misoprostol tablets (a total of 800 μg), which were inserted into the posterior vaginal fornix. Three hours following the first dose of misoprostol, 400 μg doses were administered orally at 3 h intervals until expulsion. A maximum of nine doses of oral misoprostol was offered according to the routine protocol. A similar regimen has been described previously (Ashok and Templeton, 1999).

The women were randomized into two treatment groups according to a computer-generated randomization schedule. Treatment was given with either two tablets of oral paracetamol 500 mg + dihydrocodeine 10 mg (Citodon®) or two tablets of 50 mg Diclofenac (Voltaren®/generic). Diclofenac sodium is a potent NSAID with analgesic and antipyretic properties. It inhibits cyclo-oxygenase activity with a reduction in the endogenous production of prostaglandins. Diclofenac sodium is well absorbed following oral administration and the elimination half-life is 1–2 h (product information).

The tablets for the pain treatment were put in identical-looking opaque-sealed envelopes prepared by a research nurse who did not take part in recruitment. All patients received the study drugs from a midwife at the same time as the first misoprostol dose was administered. The patients were given the envelope containing the drugs by a midwife. The midwife was instructed to look away while they opened and swallowed the drugs. No special preparation of tablets was used. The study did not use placebo tablets, but all the staff and the researchers were unaware of the treatment allocations.

If products of conception were passed on the ward and appeared to be complete, no further interventions were undertaken. Products of conception were identified by visual inspection. Women were observed on the ward for 2 h after passing the products of conception and before discharge home. Patients who did not pass the placenta had a speculum examination performed and any products in the cervical os or vagina were removed. Surgical evacuation was performed if the placenta was not delivered within 1 h of delivery of the fetus.

Where women did not pass products of conception with five doses of misoprostol or within 15 h of administration of the first dose of misoprostol, they were considered to have failed medical abortion and received repeat doses of misoprostol the following day 24 h after the start of the first dose of misoprostol (Ashok and Templeton, 1999). The induction-to-abortion interval was defined as the time interval in hours from administration of the first dose of vaginal misoprostol to passing the products of conception.

Pulse, blood pressure, temperature and systemic symptoms were monitored hourly following misoprostol administration. The women were counselled about the analgesia options available. The same information was provided to all women. Following the initial prophylactic dose of analgesia according to the allocated group, further treatment with paracetamol, codeine or parenteral analgesia (intravenous opiates or para cervical block) was provided as required to all women, but NSAIDs were then excluded. The nature and quantity of analgesia used were recorded.

The pain score was assessed pre- and post- administration of misoprostol. Pain levels were measured according to a 100-mm linear visual analogue scale (VAS; 0 = no pain to 100 = most severe pain). The woman was shown the linear VAS scale by the research nurse and asked to indicate the pain level. The research nurse was blinded to the study group assignment.

A questionnaire was given to the women to assess side effects (nausea, vomiting, diarrhoea, shivering, lethargy, headache, hot flushes and dizziness). The women were asked to fill in the questionnaire during the abortion and to complete it before being discharged home.

The volume of blood loss was estimated by collecting and weighing the sanitary pads and extracting their dry weight. In addition, capillary haemoglobin (Hb) was obtained on admission and before the woman was discharged home.

All women were advised to return for a follow-up ~4 weeks after the induced abortion according to the clinical routine.

The sample size was estimated using Altman's nomogram (Gore and Altman, 1992). A total sample size of 70 patents would give, at the 5% significance level, 80% power of detecting a standard difference of 0.67 of the induction to abortion time measured from the first dose of misoprostol to expulsion. Based on previous studies in the second trimester (El-Refaey *et al*., 1993), this would account for a clinically significant difference of ~2 h between the two groups.

The required dose of misoprostol, bleeding, pain intensity, use of analgesia and need for surgery were compared between the two groups as secondary outcome of the study.

A subgroup analysis was performed blindly before the code was broken for nulliparous/parous women and for two different gestional age groups (<105 days and >105 days). This was done to increase the understanding of the data obtained. Parity and duration of pregnancy are both factors known to influence the need for analgesia and the induction-to- abortion interval.

Data were analysed using the StatsDirect Statistical Software, version 2.4.4 (www.Statsdirect.com).

Continuous variables with a normal distribution are presented as mean and SD. Comparison was made using the Independent *t*-test.

Non-parametric continuous variables are presented as medians and ranges, and assessed for normality and comparison using the Mann–

Whitney *U*-test. The χ^2 test was used for independent nominal data. Results were considered statistically significant if *P* was <0.05.

Results

During the study, 129 women requesting second trimester termination of pregnancy were screened. Among them, a total of 80 women met the recruitment criteria and agreed to participate. All women completed the study. A total of 40 women took Citodon®/misoprostol and 40 women took diclofenac sodium/misoprostol. Only those who aborted within 24 h were analysed further; 39 women in the non-NSAID group and 38 in the NSAID group. Retrospectively those with a missed abortion at entry were also excluded, i.e. one patient in the non-NSAID group and two patients in the NSAID group. The number of women in the final analysis was 38 and 36, respectively. There were a total of 38 (51.4%) nulliparous women (21 and 17 per group, respectively) (Fig.1).

None of the patients aborted following mifepristone administration prior to misoprostol. Thirty-four (85%) and 37 (92.5%) aborted within 15 h in the non-NSAID and the NSAID group, respectively, and all but three women (*n* = 77, 96%) aborted within 24 h and were included in further analysis. All three women had no prior vaginal delivery.

The clinical characteristics of the subjects are summarized in Table I. Women in the two groups were comparable in age, height, weight, gestational age, indication and history of previous births and abortions (Table I). The median induction-to-abortion interval was shorter in the NSAID group— 5.4 h compared with 6.5 h in the non-NSAID group, but the difference was not statistically significant (*P* = 0.13) (Table II). Surgical evacuation of the placenta for incomplete abortion was required by 20 women (52.6%) in the non-NSAID group and 20 women (55.6%) in the NSAID group (Table II). The number of additional oral doses of misoprostol needed following the initial vaginal dose did not differ significantly between

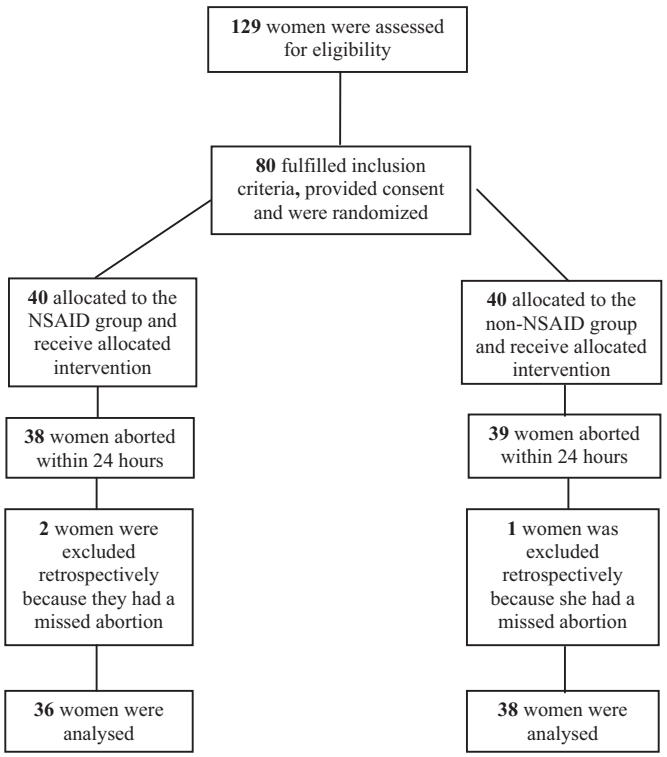

Figure 1. Flow chart for the trial of the effect of NSAIDs on medical abortion.

Table I. Demographic characteristics of participants in the study‡

	non-NSAID (*n* = 38)	NSAID (*n* = 36)	*P*-value
Age (years)*	27.3 (8.1)	28.6 (8.1)	0.50
Weight (kg)*	66.9 (13.1)	68.2 (15.7)	0.75
Height (cm)*	168.5 (7.6)	167.3 (9.5)	0.62
Gestational age (days)*	110.8 (16.4)	106.3 (14.8)	0.22
Number of pregnancies*	2.5 (1.3)	3.1 (1.9)	0.15
Parity**			0.49
Nulliparous, *n* (%)	21 (55.3)	17 (47.2)	
Parous, *n* (%)	17 (44.7)	19 (52.8)	
Previous spontaneous abortion**			0.69
Yes, *n* (%)	8 (21.1)	9 (25.0)	
No, *n* (%)	30 (78.9)	27 (75.0)	
Previous induced abortion**			0.78
Yes, *n* (%)	16 (42.1)	14 (38.9)	
No, *n* (%)	22 (57.9)	22 (61.1)	
Previous caesarean section†			0.99
Yes, *n* (%)	2 (5.3)	2 (5.6)	
No, *n* (%)	36 (94.7)	34 (94.4)	
Indication for induced abortion**			0.16
Fetal, malformation, *n* (%)	9 (23.7)	4 (11.1)	
Socio-economic, *n* (%)	29 (76.3)	32 (88.9)	

*Student's *t*-test; ** χ^2 test; †Fisher's exact test; ‡ Mean (SD) or *n* (%).

Table II. Treatment outcomes‡

	non-NSAID (*n* = 38)	NSAID (*n* = 36)	*P*-value
Induction-to-abortion interval (hours)*	6.5 (2.8–22.0)	5.4 (2.1–23.2)	0.13
Additional (oral) doses of misoprostol*	2 (0–7)	1 (0–8)	0.15
Surgical evacuation**			0.80
Yes, *n* (%)	20 (52.6)	20 (55.6)	
No, *n* (%)	18 (47.3)	16 (44.4)	
Estimated blood loss (ml)*	231 (40–1766)	407 (9–2097)	0.14
Hb difference (g/l)*	7.5 (–30.0 to 34.0)	5.0 (–20.0 to 30.0)	0.81
Para cervical block†			0.42
Yes, *n* (%)	2 (5.3)	4 (11.1)	
No, *n* (%)	36 (94.7)	32 (88.9)	
Additional oral pain treatment**			0.12
Yes, *n* (%)	16 (42.1)	9 (25.0)	
No, *n* (%)	22 (57.9)	27 (75.0)	
Additional intravenous opiate injections**			0.91
Yes, *n* (%)	31 (81.6)	29 (80.6)	
No, *n* (%)	7 (18.4)	7 (19.4)	
Opiates intravenously (mg)*	7.0 (0–53.0)	3.5 (0–25.0)	0.042
VAS max score*	7 (2–10)	7 (4–9)	0.70
Vomiting**			0.20
Yes, *n* (%)	16 (42.1)	10 (27.8)	
No, *n* (%)	22 (57.9)	26 (72.2)	

*Mann–Whitney *U* test; ** χ^2 test; †Fisher's exact test; ‡ Mean (SD) or *n* (%).

the groups with a median of two doses in the non-NSAID group compared with one dose in the NSAID group ($P = 0.15$) (Table II). When the material was stratified for parity, the difference between the two groups in the induction-to-abortion time and the doses of misoprostol needed was most pronounced among nulliparous women ($P = 0.096$ and $P = 0.058$, respectively) than among parous women ($P = 0.61$ and $P = 0.91$, respectively) (Table III).

The median blood loss in the non-NSAID group was estimated as 231 ml compared with 407 ml in the NSAID group ($P = 0.14$) (Table II). The difference was not statistically significant. No woman needed a blood transfusion. Hb levels obtained before treatment and those obtained prior to discharge from the ward were available for 22 women in each group and did not differ significantly between the groups.. The median difference before and after treatment was a decrease of 7.5 g/l in the non-NSAID group and 5 g/l in the NSAID group ($P = 0.81$). When data were stratified by parity and gestational length, there was no difference in estimated blood loss between the two groups in nulliparous or in early pregnancy (<105 days) ($P = 0.92$ and $P = 0.49$, respectively) (Tables III, IV). In parous women, the estimated blood loss was greater among women in the NSAID group ($P = 0.039$) although Hb measurements did not differ significantly ($P = 0.46$) (Table III).

The median of the highest pain score reported on the VAS scale was 7 in both groups. A significant difference between the groups in the use of analgesia was observed. Women who had received NSAID prophylaxis required less opiate injections ($P = 0.042$) (Table II).

When stratified for gestational age, there was a significant difference between the two groups in the use of opiates. Less opiate injections were required in the NSAID group only in women with a later gestational age (>105 days) ($P = 0.02$) (Table IV).

Side effects fever, nausea and diarrhoea were comparable in the two groups (data not shown). Vomiting was slightly but not significantly more common in the non-NSAID group (P = 0.20) (Table II). No serious complications were reported in either group.

Discussion

Abdominal pain is one of the most common adverse effects of medical abortion (Spitz *et al*., 1998; Honkanen *et al*., 2004). However, the analgesia requirements and regimens for medical abortion reported in the literature vary widely (Wiebe *et al*., 2001). Due to theoretical concerns about prostaglandin inhibition by NSAIDs, such drugs are frequently avoided or recommended against in protocols for medical abortion.

This is the first prospective randomized study which showed that co-treatment of diclofenac sodium with misoprostol did not affect the induction-to-abortion interval of mifepristone and misoprostol in late medical abortion. A potential weakness with the study design is that, because no placebo or special preparations were available, this could have introduced bias. However, the staff attending the patients and the researchers involved with analysing the results was blinded to treatment allocation.

Previously, and consistent with our results, it was shown that increased uterine contractility still occurs after mifepristone if prostaglandin synthesis is inhibited by co-administration of indomethacin (Norman *et al*., 1991) and that pre-treatment with NSAID did not interfere with the effect of mifepristone on cervical ripening (Rådestad *et al*., 1992). Furthermore, co-treatment with diclofenac and misoprostol did not adversely affect cervical priming during early pregnancy compared with

Table III. Stratified analysis by parity*

	Nulliparous			Parous		
	non-NSAID ($n = 21$)	NSAID ($n = 17$)	*P*-value	non-NSAID ($n = 17$)	NSAID ($n = 19$)	*P*-value
Induction-to-abortion interval (hours)	8.5 (2.8–22.0)	5.7 (3.5–11.2)	0.096	4.9 (3.0–17.2)	5.2 (2.1–23.2)	0.61
Additional doses of misoprostol	2 (0–7)	1 (1–3)	0.058	1 (0–5)	1 (0–8)	0.91
Estimated blood loss (ml)	258 (50–1190)	200 (9–1500)	0.92	206 (40–1766)	500 (20–2097)	0.039
Hb difference (g/l)	6.5 (0–13.0)	4.0 (–10.0 to 5.0)	0.15	7.5 (–30.0 to 34.0)	13.0 (–20.0 to 30.0)	0.46
Opiates injected (mg)	10.0 (0–53.0)	7.0 (0–25.0)	0.18	5.5 (0–20.0)	3.0 (0–11.0)	0.25

*Median (range). Mann–Whitney *U*-test.

Table IV. Stratified analysis by gestational age*

	Early up to 105 days			Late >105 days		
	non-NSAID ($n = 18$)	NSAID ($n = 20$)	*P*-value	non-NSAID ($n = 20$)	NSAID ($n = 16$)	*P*-value
Induction-to-abortion interval (hours)	6.7 (2.8–22.0)	4.7 (2.1–8.7)	0.12	6.5 (3.1–21.8)	5.5 (3.0–23.2)	0.87
Additional doses of misoprostol	1.5 (0–6)	1 (0–3)	0.39	2 (0–7)	1 (0–8)	0.36
Estimated blood loss (ml)	200 (40–1766)	240 (9–2097)	0.49	286 (50–734)	480 (35–1784)	0.14
Hb difference (g/l)	9.5 (-30.0–25.0)	14.0 (-20.0–30.0)	0.65	2.5 (-11.0–34.0)	4.5 (-7.0–12.0)	0.95
Opiates injected (mg)	5.0 (0–22.5)	3.0 (0–15.0)	0.88	10.5 (3.5–53.0)	5.5 (0–25.0)	0.02

*Median (range). Mann–Whitney *U*-test.

treatment with misoprostol alone (Li *et al*., 2003). A retrospective analysis revealed that NSAIDs did not seem to have interfered with the action of misoprostol to induce uterine contractions and pregnancy expulsion in women receiving methotrexate and misoprostol for early abortion compared with a group of women who did not receive NSAIDs (Creinin and Schulman, 1997).

It has previously been shown that vaginal administration of misoprostol following mifepristone is more effective than oral administration for second trimester induced abortion (Ho *et al*., 1997)—probably due to increased bioavailability and a more pronounced effect of misoprostol on the myometrium following vaginal administration as demonstrated in the first trimester (Zieman *et al*., 1997; Gemzell-Danielsson *et al*., 1999). However, most women prefer the oral route of administration (Ho *et al*., 1997). The results of the present study confirm previous reports which have shown no decrease in efficacy in the second trimester with subsequent oral doses of misoprostol provided the first dose is administered vaginally (El-Refaey *et al*., 1995; Ashok *et al*., 2004). In our study, 89% of women aborted within 15 h and 96% within 24 h, with no significant difference between the groups.

The median induction-to-abortion interval was comparable with that previously reported with a similar regimen (Ashok *et al*., 2004). Women who received prophylactic NSAID treatment tended to have a shorter induction-to-abortion time and needed less misoprostol. Although not significant with the present sample size, a difference between the groups in the dose of misoprostol required was observed in nulliparous women with a tendency for lower doses of misoprostol required by NSAID treated women. A difference between one or two doses may seem marginal, but still reflects differences in the induction-to-abortion time. Furthermore, a higher dose of misoprostol means more side effects and more pain. It is tempting to speculate that NSAID pain management in these women led to better relaxation and thus a shorter induction-to-abortion interval. The number of surgical interventions were higher than that reported with a similar regimen (Ashok *et al*., 2004), which probably reflects local practice. However, there was no difference in the number of surgical interventions between the groups.

Estimated blood loss did not differ between the groups in women with a shorter gestational length (<105 days), but seemed to be higher at a longer gestational length in women treated with prophylactic NSAID despite a shorter induction-to-abortion interval in this group. When stratified by parity, there was no difference in bleeding among the groups in nulliparous women while a significant difference was noted among parous women. In this group, there was no difference in the induction-to-abortion time. Caution has to be shown when interpreting the data on the reported blood loss since this was carried out by the routine staff and depended on their willingness and ability to collect and weigh sanitary pads and to estimate the bleeding; data were sometimes totally or partly missing. Moreover, in those women where Hb levels were obtained before and after the abortion, there was no significant difference between the groups in the observed Hb changes.

The main advantage of using the combination of NSAID with misoprostol as pain prophylaxis or advanced administration was that the use of opiates could be reduced. In accordance with previous reports, more opiate injections were needed in nulliparous women and at later gestational length (Hamoda *et al*., 2004). Although the maximal pain score reported did not differ between the groups, significantly less opiate injections were needed following NSAID treatment. This difference was most pronounced in more advanced pregnancies (>105 days) and was probably reflected also in less vomiting in the NSAID treated group. Less need for opiate injections also saved on the cost and associated pain.

This is the first randomized study to show a difference in analgesic requirement following prophylactic pain medication. Pain is a complex perception involving both physical and psychological components. Despite the fact that pain experienced in medical abortion causes significant distress, it has been only scarcely studied. No studies were identified which directly compared different analgesic regimens or prophylactic pain medication for the relief of pain experienced at the time of medical abortion with mifepriston and misoprostol. However, a placebo-controlled, randomized trial evaluated the relative efficacies of ibuprofen or acetaminophen (paracetamol) with codeine as prophylaxis in the context of early medical abortion with methotrexate and misoprostol (Wiebe, 2001). The agents were taken as prophylaxis at the time of misoprostol administration, prior to the onset of pain. Severe pain scores were reported by almost a quarter of women and there were no significant differences in pain scores between groups (placebo, ibuprofen or acetaminophen with codeine). Women given acetaminophen with codeine reported taking less of the same medication later. In a non-concurrent cohort study on early medical abortion, the use of opiate analgesia was shown to be lower with prohpyactic acetaminophen compared with a control group without prophylactic treatment (Jain *et al*., 2001).

The proportion of women undergoing late medical abortion who use narcotic analgesia varies among studies, but is generally ~80–100% (Gemzell-Danielsson and Östlund, 2000; Ashok *et al*., 2004). This is comparable with the 91% in the present study. Analgesia use varies markedly between centres. Across different studies, the following patient characteristics emerge consistently as predictors of narcotic analgesic use: higher gestational age; younger patient age; and lower parity (Westhoff *et al*., 2000a, Hamoda *et al*., 2004). Typically, pain is most severe on the day of prostaglandin administration (Westhoff *et al*., 2000b; Fiala *et al*., 2004). Consistence with our results, it was found that analgesia requirement was significantly higher in late medical abortion in women of younger age, higher gestation, and longer induction-to-abortion interval and with increased number of misoprostol doses used, while women with previous live birth were significantly less likely to use analgesia (Hamoda *et al*., 2004).

In conclusion, this randomized study has demonstrated that co-administration of NSAID with misoprostol does not negatively affect the abortion process. Women who received advanced or prophylactic NSAID treatment tended to have a shorter induction-to-abortion time and needed fewer doses of misoprostol, especially among nulliparous women. The

differences did not reach statistical significance with the number of women included. There was less need for opiates following NSAID prophylaxis, especially at gestations of >105 days, although caution has to be shown when interpreting the data since the study was not double blinded. NSAID treatment did not seem to affect blood loss in nulliparous women and in women with earlier gestation. The estimated blood loss based on weighing and counting of sanitary pads seemed to be greater in parous women, although this was not supported by the changes in Hb levels.

There are no previous randomized comparative studies to guide the choice of analgesic regimen for use in abortion care. Despite theoretical concerns about prostaglandin inhibition by NSAIDs, available evidence indicates—and the present results support—that such agents can be used in abortion care without loss of abortifacient efficacy.

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References

Ashok PW and Templeton A (1999) Non-surgical mid-trimester termination of pregnancy: a review of 500 consecutive cases. Br J Obstet Gynaecol 106,706–710.

Ashok PW, Templeton A, Wagaarachchi PT and Flett GM (2004) Mid-trimester medical termination of pregnancy: a review of 1002 consecutive cases. Contraception 69,51–58.

Bygdeman M and Swahn ML (1985) Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. Contraception 32,45–51.

Creinin M.D and Shulman T (1997) Effect of non-steroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. Contraception 56,165–168.

Csapo AI (1974) Prostaglandin impact inverted, question mark for menstrua induction. Popul Rep G. 4,33–40.

E1-Refaey H, Hinshaw K and Templeton A (1993) The abortifacient effect of misoprostol in the second trimester. A randomized comparison with gemeprost in patients pre-treated with mifepristone (RU 486). Hum Reprod 8,1744–6.

El-Refaey H and Templeton A (1995) Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimens. Hum Reprod 10,475–478.

Exelgyne SA (1998) Summary of product characteristics. Exelgyne, Paris, France.

Fiala C, Winikoff B, Helstrom L, Hellborg M and Gemzell-Danielsson K (2004) Acceptability of home-use of misoprostol in medical abortion. Contraception 70,387–392.

Garfield RE, Blennerhasset MG and Miller SM (1988) Control of myometrial contractility: Role and regulation of gap junctions. In: Oxford Reviews of Reproductive Biology 10,436–90.

Gemzell Danielsson K, Marions L, Rodriguez A, Spur BW, Wong PY and Bygdeman M (1999) Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 93,275–280.

Gemzell-Danielsson K and Östlund E (2000) Termination of second trimester pregnancy with mifepristone and gemeprost. The clinical experience of 197 consecutive cases. Acta Obstet Gynecol Scand 79,702–706.

Gore SM and Altman DG (1992) Statistics in practice. British Medical Association, London, UK, pp. 6–9.

Hamoda H, Ashok PW, Flett GM and Templeton A (2004) Analgesia requirements and predictors of analgesia use for women undergoing medical abortion up to 22 weeks of gestation. BJOG 111,996–1000.

Ho PC, Ngai S.W, Liu KL, Wong GC and Lee SW (1997) Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstet Gynecol 90,735–738.

Honkanen H, Piaggio G, Hertzen H, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, Gopalan S, Horga M, Jerve F, Mittal S, et al. WHO Research Group on Post-Ovulatory Methods for Fertility Regulation (2004) WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. BJOG 111,715–725.

Jain JK, Harwood B, Meckstroth KR and Mishell DR (2001) Early pregnancy termination with vaginal misoprostol and acetaminophen prophylaxis. Contraception 63,217–221.

Li CFI, Wong CYG, Chan CPB and Ho PC (2003) A study of co-treatment of non-steroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. Contraception 67,101–105.

Lundström V, Green K and Wiqvist N (1976) Prostaglandins, indomethacin and dysmenorrhea. Prostaglandins 11,893–907.

Ngai SW, Chan YM, Tang OS and Ho PC (1999) The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. Hum Reprod 14,2139–2142.

Norman JE, Kelly RW and Baird DT (1991) Uterine activity and decidual prostaglandin production in women in early pregnancy in response to mifepristone with or without indomethacin *in vivo*. Hum Reprod 6,740–744.

Ölund A (1979) The effect of indomethacin on the instillation-abortion interval in rivanol-induced mid-trimester abortion. Acta Obstet Gynecol Scand 58,121–122.

Rådestad A and Bygdeman M (1992) Cervical softening with mifepristone (RU 486) after pretreatment with naproxen. A double-blind randomized study. Contraception 45,221–227.

Rådestad A, Thyberg J and Christensen NJ (1993) Cervical ripening with mifepristone (RU 486) in first trimester abortion. An electron microscope study. Hum Reprod 8,1136–1142.

Smith RP (1987) The dynamics of nonsteroidal anti-inflammatory therapy for primary dysmenorrhoea. Obstet Gynecol 70,785–788.

Spitz IM, Bardin CW, Benton L and Robbins A (1998) Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 338,1241–1247.

Westhoff C, Dasmahapatra R, Winikoff B and Clarke S. Mifepristone Clinical Trials Group. (2000a) Predictors of analgesia use during supervised medical abortion. Contraception 61,225–229.

Westhoff C, Dasmahapatra R and Schaff E (2000b) Analgesia during at-home use of misoprostol as part of a medical abortion regimen. Contraception 62,311–314.

Wiebe ER (2001) Pain control in medical abortion. Int J Gynecol Obstet 74,275–280.

Zieman M, Fong SK, Benowitz NL, Banskter D and Darney PD (1997) Absorption kinetics of misoprostol with oral or vagina administration. Obstet Gynecol 90,88–92.

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