

Dinoprostone in First Trimester Miscarriages: A Prospective Observational Study in a Malaysian Tertiary Healthcare Institution

Penggunaan Dinoprostone dalam Keguguran Trimester Pertama: Kajian Prospektif di Pusat Rujukan Perubatan di Malaysia

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ABSTRACT

The objective of this paper was to evaluate the outcome of medical evacuation of first trimester miscarriages using dinoprostone. A prospective observational study in a tertiary centre between 1st January and 31st December 2018 in Obstetrics and Gynaecology unit, UKM Medical Centre. Women diagnosed with incomplete and missed miscarriage (n=41) at or less than 13 weeks of gestation were recruited. Dinoprostone 3 mg was inserted into the posterior fornix, twice within 6 h apart on day-1 followed by similar protocol on day-2. Patients were reassessed clinically and sonographically upon passing out products of conception, at 48 h and day-7. Complete evacuation was defined as closed cervical os and/or endometrial thickness of less than 15 mm sonographically. Treatment failure was defined as failure to achieve complete evacuation by day-7. Overall success rate was 55.3% (n=26) being better in incomplete (n=6, 100%) as compared to missed miscarriage (n=21, 48.8%, p=0.03). Those with successful evacuation required dinoprostone at a mean of 8.4 ± 2.9 mg achieving complete miscarriage within a mean of 27.8 ± 16.6 h. Mean pain score was 5.8 ± 0.8 with mean patient satisfaction score of 8.7 ± 0.8. Mean drop in haemoglobin was 0.7 ± 0.2 g/dL. No major adverse effects were reported. Medical evacuation of miscarriage using intravaginal dinoprostone is safe and promising, with acceptable success rate and high patient satisfaction. This study supported previous studies suggesting presence of prostaglandin E2 receptors in the first trimester.

Keywords: Dinoprostone; first trimester miscarriage; medical evacuation

ABSTRAK

Tujuan kajian ini dijalankan adalah untuk menilai hasil penggunaan ubat untuk rawatan keguguran pada trimester pertama. Ini adalah kajian prospektif yang dijalankan di unit Obstetrik dan Ginekologi, Pusat Perubatan UKM dari 1 Januari hingga 31 Disember 2018. Semua pesakit (n=41) yang dikenal pasti mengalami keguguran pada atau kurang dari 13 minggu kandungan telah dimasukkan ke dalam kajian. Ubat dinoprostone 3 mg telah dimasukkan ke dalam faraj sebanyak 2 kali dalam beza masa selama 6 jam. Ini dilakukan selama 2 hari berturut-turut. Pesakit dinilai secara klinikal dan dengan menggunakan mesin imbasan jika ada perdarahan daripada faraj yang mengandungi tisu kandungan atau selepas 48 jam atau selepas 7 hari dari permulaan rawatan. Keguguran lengkap ditentukan apabila pintu rahim telah tertutup atau imbasan menunjukkan ketebalan dinding rahim kurang daripada 15 mm. Rawatan dianggap gagal jika keguguran lengkap tidak berlaku pada hari ketujuh selepas permulaan rawatan. Kejayaan keseluruhan adalah 55.3% (n=26) dan ia adalah lebih baik dalam kes pesakit yang telah keguguran tidak lengkap (n=6, 100%) berbanding dengan mereka yang tiada langsung keguguran (n=21, 48.8%, p=0.03). Mereka yang telah berjaya memerlukan dinoprostone pada min 8.4 ± 2.9 mg dan kejayaan dicapai pada min masa 27.8 ± 16.6 jam. Min skor kesakitan adalah 5.8 ± 0.8 dan min kepuasan pesakit 8.7 ± 0.8. Min penurunan hemoglobin adalah 0.7 ± 0.2 g/dL. Tidak terdapat komplikasi yang teruk semasa kajian. Rawatan untuk keguguran dengan menggunakan ubat adalah selamat dan mempunyai kadar kejayaan yang baik. Kebanyakan pesakit juga berpuas hati. Ini membuktikan teori bahawa terdapat reseptor untuk prostaglandin E2 pada trimester pertama kandungan.

Kata kunci: Dinoprostone; evakuasi perubatan; keguguran trimester pertama

INTRODUCTION

Spontaneous miscarriage is defined as pregnancy loss before viability, occurring in about 10% of all clinically recognised pregnancies (Wilcox et al. 1988). About 50% occurred in the first trimester due to genetic abnormalities

(Eiben et al. 1990). Miscarriage can be classified as incomplete, complete, and missed. The diagnosis of intrauterine pregnancy must be confirmed via ultrasound examination and the subsequent management depends on the type of miscarriage. Both incomplete and missed

miscarriages require intervention to ensure complete evacuation of the product of conception (POC) in order to prevent further complications.

Different modalities in the management of these miscarriages are available. Each method namely expectant, surgical, and medical treatment has its own risks and benefits. Various published papers had looked into the superiority of a method to another. Conservative or expectant management may reduce the risks involved in surgical evacuation. However, it requires multiple follow-ups with unpredictable achievement of complete miscarriage. On the other hand, surgical evacuation is a faster way of managing the problem definitively but is associated with risks of excessive curettage, uterine perforation, endometritis and incomplete evacuation (Nadarajah et al. 2014).

Medical management is another safe option gaining more popularity. Its efficacy was comparable to the surgical evacuation and was preferred due to the safety profile (Nanda et al. 2012). The known drug that had been recognised for the licensed use in first trimester miscarriages was misoprostol, a prostaglandin E_1 synthetic analogue (WHO 2018). The success rate of achieving complete evacuation in incomplete miscarriages was comparable to surgical management (Kim et al. 2017).

Since 2017, the Ministry of Health, Malaysia had stopped the use of misoprostol. Therefore, the aim of this study was to find a replacement for misoprostol to be used as a medical treatment for first trimester miscarriages in our local setting. This will allow the patients to have more than one option of treatment and avoid unwanted complications arising from surgical evacuation.

MATERIALS AND METHODS

This was a prospective observational study from 1st January to 31st December 2018. Inclusion criteria were women with pregnancies of less than 14 weeks of gestation. Exclusion criteria were age less than 18 years old, inability to understand English or Malay, allergy to prostaglandin, factors necessitating immediate surgical evacuation such as excessive vaginal bleeding, haemodynamic instability and septic miscarriage, current use of anticoagulant, abnormal clotting profile, anaemia, suspected molar or ectopic pregnancy, pregnancy of unknown location (PUL) and high risk patients such as immunocompromised, haematological disorders, severe asthma and heart disease. Ethics approval was obtained from the local ethics committee (FF-2018-189).

All suitable patients were assessed in the patient admission centre (PAC). Complete history, physical examination and ultrasound were performed. Intrauterine pregnancy was confirmed *via* ultrasound examination finding of an intrauterine gestational sac. The gestational age was determined based on the last menstrual period or a dating scan.

Incomplete miscarriage was diagnosed based on opened cervical os and endometrial thickness (ET) of 15 mm or more. The ultrasound criteria for missed miscarriage were (Doubilet et al. 2014) mean gestational sac diameter of > 25 mm without a measurable embryonic pole, an embryo with crown rump length of > 7 mm without cardiac activity, absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac and absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac.

Full blood count was taken prior to treatment and repeated at the end of the protocol. Dinoprostone 3 mg was inserted twice into the posterior fornix, 6 h apart within 24 h. The next day similar protocol was followed. Parameters that were documented during treatment period were blood pressure, pulse rate and temperature, pain score using visual analogue scale, analgesia required (paracetamol 1 g), side effects, treatment administered, number of dinoprostone used, achievement of complete miscarriage and change in the haemoglobin level. The end of the protocol was achieved either within 48 h of admission or after 7 days from the initiation of treatment.

Patients who passed out POC were assessed clinically and transvaginal ultrasound performed. Complete evacuation was diagnosed when the cervical os was close on vaginal examination and transvaginal ultrasound showed ET of less than 15 mm. POC was collected and sent for histopathological examination (HPE). After 48 h of treatment protocol, patients who did not pass out any POC without any excessive vaginal bleeding or side effects were allowed home. Once the POC was passed out or if they developed excessive vaginal bleeding, they were advised to return to the PAC immediately. They were also counseled to document the date and time of passing out POC.

If there was no progress at home, the patients were reviewed after 7 days in the gynaecology clinic and haemoglobin level was repeated along with vaginal examination and ultrasound. If there was still retained POC, patients were subjected to surgical evacuation. In the event of excessive vaginal bleeding, foul smelling discharge or fever, or if the patient refused to continue, surgical evacuation was carried out at any point of time. Treatment failure was defined as failure in achieving complete evacuation after 7 days. The contact number of the main researcher and PAC were provided.

The sample size of this study was calculated using an online sample size calculator available at www.sample-size.net/sample-size-conf-interval-proportion/ using the formula for sample size assessment for a descriptive study of a dichotomous variable. The sample size was determined based on 95% confidence interval with a total confidence interval (CI) width of 0.2, assuming 60% rate of complete miscarriage after medical treatment.

Data entry and analysis were performed using SPSS Statistics Version 23. All outcome measures were analysed using Chi Square, Fisher Exact and Students t-test. Difference between two groups was expressed as

odds ratio (OR) or mean difference (β)(95% Confidence Interval). P value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

There were 59 women recruited but 8 of them did not complete the protocol, leaving 47 women with missed (n=41) and incomplete (n=6) miscarriages. All participants

were Malay with majority of them multiparous and diagnosed with missed miscarriage (Table 1). Their main presentations were abdominal pain and vaginal bleeding at mean gestational age of 10.4 ± 1.6 weeks. Twenty-six (55.3%) had successful medical evacuation, at a mean gestational age of 10 ± 1.8 weeks. Successful evacuation was achieved in 55.3% of women.

Table 2 shows the demographic data and baseline characteristics of patients based on the treatment outcome.

TABLE 1. Demographic data and baseline clinical characteristics of study population (n=47)

Mean age, years \pm SD (range)	33.9 \pm 4.9 (25 - 45)
Mean Body Mass Index, kg/m ² \pm SD (range)	27.7 \pm 5.5 (16.3 - 44)
Mean gestational age at diagnosis, weeks \pm SD (range)	10.4 \pm 1.6 (6.4 - 12.6)
Parity, n (%)	
Nulliparous	11 (23.4)
Multiparous	36 (76.6)
Type of miscarriage, n (%)	
Missed	41 (74.5)
Incomplete	6 (25.5)
Previous miscarriage, n (%)	
Yes	14 (29.8)
No	33 (70.2)
Vaginal bleeding, n (%)	
Yes	35 (74.5)
No	12 (25.5)
Abdominal pain, n (%)	
Yes	24 (51.1)
No	23 (48.9)
Treatment outcome, n (%)	
Successful	26 (55.3)
Failed	21 (44.7)

TABLE 2. Demographic and baseline clinical characteristics of study population by treatment outcome (n=47)

	Successful 26 (55.3%)	Failed 21 (44.7%)	OR/ β (95% CI) p-value
Mean age, years \pm SD (range)	34.8 \pm 4.8 (25 - 45)	32.9 \pm 4.9 (25 - 45)	1.8 (-1.0 - 4.7) 0.2**
Mean Body Mass Index, kg/m ² \pm SD (range)	27.2 \pm 5.7 (16.3 - 44.0)	28.1 \pm 5.4 (19.8 - 43.0)	-1.0 (-4.2 - 2.3) 0.6
Mean gestational age at diagnosis, weeks \pm SD (range)	10.0 \pm 1.8 (6.4 - 12.6)	10.7 \pm 1.1 (8.6 - 12.4)	-0.7 (-1.6 - 0.2) 0.13**
Type of miscarriage, n (%)			
Missed	20 (76.9)	21 (100)	0.5 (0.4 - 0.7)
Incomplete	6 (23.1)	0	0.03*
Parity, n (%)			
Nulliparous	7 (26.9)	4 (19)	1.6 (0.4 - 6.3)
Multiparous	19 (73.1)	17 (81)	0.7*
Mean drop in haemoglobin level, g/dL \pm SD (range)	0.6 \pm 0.3 (0 - 1.1)	0.3 \pm 0.2 (0 - 0.8)	0.3 (0.1 - 0.4) <0.001
Mean patient satisfaction score \pm SD, (range)	8.5 \pm 1.0 (6 - 10)	3.0 \pm 1.1 (1 - 5)	5.5 (4.9 - 6.2) <0.001

*data analysed using Fisher exact test, **data analysed using Student t-test

TABLE 3. Clinical characteristics and detail of treatment in study population by type of miscarriage (n=47)

	Missed 41 (87.2%)	Incomplete 6(12.8%)	OR/β (95% CI) p-value
Mean duration from first dinoprostone insertion to evacuation, hours ± SD (range)	33.3 ± 36.6 (2.5 - 131)	27.8 ± 16.6 (9 - 48)	5.4 (-26.6 - 37.5) 0.73
Mean dose of dinoprostone required, mg ± SD, (range)	10.2 ± 3.3 (3 - 12)	8.4 ± 2.9 (6 - 12)	1.6 (-1.3 - 4.4) 0.26
Mean pain score ± SD, (range)	4.0 ± 1.9 (0 - 8)	5.8 ± 0.8 (5 - 7)	-1.8 [-3.4 - (-0.2)] 0.03
Mean drop in haemoglobin level, g/dL ± SD (range)	0.4 ± 0.3 (0 - 1.1)	0.7 ± 0.2 (0.3 - 0.9)	-0.2 (-0.4 - 0.04) 0.1
Mean patient satisfaction score ± SD, (range)	5.7 ± 3.0 (1 - 10)	8.7 ± 0.8 (8 - 10)	-1.8 [-2.7 - (-0.9)] 0.001

data analysed using Fisher exact test

TABLE 4. A subgroup analysis of demographic data, clinical characteristics and detail of treatment in patients with successful evacuation by type of miscarriage (n=26)

	Missed 20 (76.9%)	Incomplete 6 (23.1%)	OR/β (95% CI) p value
Mean age, years ± SD (range)	35.0 ± 4.9 (25 - 45)	34.3 ± 3.9 (28 - 41)	0.6 (-4.1-5.3) 0.8**
Mean Body Mass Index, kg/m ² ± SD (range)	26.4 ± 6.2 (16.3 - 44.0)	30.0 ± 2.2 (27.5 - 32.6)	-3.6 (-9.0-1.8) 0.2**
Mean gestational age at diagnosis, weeks ± SD (range)	10.1 ± 1.8 (7.4 - 12.4)	10.0 ± 2.2 (6.4 - 12.6)	0.1 (-1.6 - 1.9) 0.9**
Parity, n (%)			
Nulliparous	3 (42.9)	4 (66.7)	0.08 (0.01 - 0.7)
Multiparous	17 (89.5)	2 (33.3)	0.03*
Mean pain score, mm ± SD (range)	1.2 ± 1.5 (0 - 6)	3.8 ± 1.0 (3 - 5)	-2.1 [-3.8 - (-0.5)] 0.01*
Mean duration from first dinoprostone insertion to evacuation, hours ± SD (range)	33.3 ± 36.6 (2.5 - 131.0)	27.8 ± 16.6 (9 - 48)	5.4 (26.7 - 37.5) 0.7
Mean dose of dinoprostone required, mg ± SD, (range)	8.1 ± 3.8 (3 - 12)	8.5 ± 2.9 (6 - 12)	-0.4 (-3.9 - 3.1) 0.8
Mean drop in haemoglobin level, g/dL ± SD (range)	0.6 ± 0.3 (0.0 - 1.1)	0.7 ± 0.2 (0.3 - 0.9)	-0.1 (-0.3 - 0.2) 0.6
Mean patient satisfaction score ± SD, (range)	8.5 ± 1.1 (6 - 10)	8.7 ± 0.8 (8 - 10)	-0.2 (-1.1 - 0.8) 0.7

*data analysed using Fisher exact test, **data analysed using Student t-test

There were significantly more patients with missed miscarriage who had failed medical treatment with dinoprostone as compare to incomplete miscarriage (p=0.03), more significant drop in haemoglobin levels in patients with successful treatment (p<0.001) and higher patients' satisfaction in the group who succeeded (p<0.001). There was no difference between the two groups in regards to age, body mass index, parity and gestational age.

The success rate with dinoprostone was 55.3% with 100% success rate for incomplete and 48.8% for missed miscarriage (data not shown). Table 3 demonstrated the clinical characteristics and detail of treatment based on the type of miscarriage. The patients with incomplete miscarriage experienced significantly more abdominal pain

(p=0.03) but higher satisfaction rate (p=0.001). There was no significant difference in the mean duration from initiation of treatment to achievement of complete evacuation, mean dose of dinoprostone required and mean drop in haemoglobin levels.

Table 4 shows the demographic data, clinical characteristics and detail of treatment in patients who had successful evacuation. There were significantly more multiparous women in the missed miscarriage group (p=0.03) and more women with incomplete miscarriage experienced higher pain score (p=0.01). Both groups were similar in regards to the mean age, mean body mass index, mean gestational age, duration from commencement of treatment to complete evacuation, mean dose of

dinoprostone required, mean drop in haemoglobin levels and satisfaction score.

DISCUSSION

Medical management of miscarriage is an option gaining popularity with high efficacy and patient acceptability. The Ministry of Health Malaysia has approved the off-label use of misoprostol for treatment of first trimester miscarriage in 2011. Recently the privilege for off-label use of misoprostol was revoked and the import of the drug was stopped. This was due to the several reported cases with adverse side effects in patients who received misoprostol for induction of labour in the third trimester. Hence, medical management of patient with first trimester miscarriage is currently limited to surgical evacuation only. Although gemeprost is an available option with 76.7% success rate in missed miscarriage, the price is expensive in our centre (Egarter et al. 1995).

To date, published data on the use of prostaglandin E₂ in first trimester miscarriages is limited. Wagner et al. (2011) had investigated the use of misoprostol, gemeprost and dinoprostone for termination of pregnancy between 11 and 24 weeks' gestation for fetal anomalies. Eleven women had gone through the dinoprostone gel protocol of 0.5 mg 4 to 6 hourly till adequate contractions were achieved. Overall, the reported success of fetal expulsion 24 h after first induction was 90% but it was not mentioned in detail of which agent was the main contributor.

Al Inizi and Ezimokhai (2003) had published the only paper that compared misoprostol and dinoprostone in a prospective randomised study for the management of missed miscarriage. Dinoprostone 3 mg tablets were inserted vaginally 6 h apart for a maximum dose of 36 mg over 6 days. The success rate was 24.2% and the use of dinoprostone was associated with significantly more surgical evacuation and longer hospital stay. However, there was no difference in requirement for analgesia and drop in the haemoglobin levels. In contrast, our study had shown higher success rate for missed miscarriage i.e. 55.3% as compared to misoprostol which was reported to have higher success rate of 76.7% (Egarter et al. 1995). Despite the lower success rate in our study, this result was still promising.

To the best of our knowledge, this was the first study that had used dinoprostone 3 mg tablet for medical treatment in women with incomplete miscarriages in Malaysia. Although the number of women was small but the success rate was 100%. This is comparable to the use of misoprostol in incomplete miscarriage with reported success rate of 92.7% and 92.9% (Egarter et al. 1995; Ng et al. 2015; Ngoc et al. 2013). However, none of the patients with either successful or failed evacuation had excessive bleeding, developed infection or required emergency surgical evacuation. Among those who had failed treatment and required surgical evacuation, no complications from the procedure were reported. This was most likely due to the cervical ripening effect prior to procedure, which had

been demonstrated in previous studies (MacKenzie 1981; Sparrow et al. 1998). No side effect of dinoprostone was reported in this study. Only one patient required analgesia due to excessive abdominal cramps with pain score of 8 and as expected, the mean patient satisfaction score was higher in those who had successful evacuation.

The results of this study support findings from earlier studies on the use of PGE₂ analogue in the first trimester. The cervix produces prostaglandin in early pregnancy and the concentration increases with gestational age (Ellwood et al. 1980). It has been proven that cervical ripening in the first trimester prior to surgical evacuation was beneficial in reducing the cervical resistance during dilatation and hence reduced complications namely uterine perforation. The side effects were minimal with 5 mg as compared to 10 mg which was in agreement with the results of our study (Anthony et al. 1984; MacKenzie 1981). This is highly suggestive of the presence of prostaglandin E₂ receptors in the first trimester.

Limitation of this study was it is an observational study. However, based on the findings we obtained general overview on efficacy as well as its safety profile. This will become our basis as to how we are going to move forward for future research. Apart from that, our sample size was small with all participants were Malay. We hoped to recruit other ethnicity as well in our future study. This will be more representative of Malaysian population. Our population sample was limited to Asian ethnicity, which cannot be extrapolated to women in other ethnic origin. Randomised clinical trial using higher dose comparing dinoprostone with other agents should be conducted in the future.

The use of prostaglandin E₂ for medical evacuation of miscarriage is promising with successful evacuation rate of 56.5% and high patient satisfaction. Additionally, in those who failed medical evacuation still benefit from the cervical ripening prior to surgical evacuation which avoids the associated complications. Similar studies involving larger population size are recommended. Randomised controlled trial between dinoprostone and other pre-existing agents used for medical termination such as misoprostol or gemeprost will be beneficial.

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