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Misoprostol vaginal insert versus dinoprostone vaginal insert: A comparison of labour and delivery outcomes

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ABSTRACT

Objectives: To compare Misoprostol Vaginal Insert (MVI), a vaginal insert containing 200 μg of misoprostol) versus Dinoprostone Vaginal Insert (DVI), a vaginal insert containing 10 mg of dinoprostone), in the induction of labour.

Study Design: We performed a retrospective analysis of the data between February 2016 and September 2017 of women induced with MVI (n = 100) and DVI in UK (n = 100) at NHS Fife. MVI was used for the same indications as DVI, but specifically indicated in women with a Modified Bishops score ≤ 4. Outcome measures included: the incidence of tachysystole and hyperstimulation; further use of prostaglandins; use of pre-delivery oxytocin; mode of delivery; median insertion-to-delivery-interval; and admission to the neonatal unit. Statistical data analysis was performed. A logistic regression analysis was also performed, adjusting for potential confounders such as body mass index (BMI), gestational age, parity and baseline Modified Bishops score.

Results: Demographics such as parity, BMI, baseline Modified Bishops score and gestational age were assessed. A significantly higher rate of tachysystole and hyperstimulation was noted in the MVI group as compared to the DVI group. Only 8% of women in the MVI group as compared to a third (33%) of women in the DVI group required further prostaglandins. There was no difference in the modes of birth in either group and this result was statistically significant. The median induction to delivery interval was 15 h in the MVI group compared to 33 h in the DVI group. There was no difference in neonatal outcomes in either group. There was no significant difference in the use of pre-delivery oxytocin for subsequent augmentation of labour in either group. All the results, when adjusted to potential confounders using logistic regression, were in keeping with the unadjusted statistical analysis.

Conclusion: The results of this study suggest that MVI significantly reduces the induction to delivery interval, has a similar caesarean section rate and neonatal outcomes, when compared with DVI.

Introduction

Induction of labour (IOL) is a common procedure: approximately one in five pregnant women in high-income countries have induced labours and this rate is slowly increasing [1]. Various methods are available for cervical ripening and IOL. However, no method has been demonstrated to be optimal. Prolonged induction of labour can be perceived as traumatic by women: 40% of women state that speed was the most important aspect they would like to change if they were to undergo another induction [2].

In the United Kingdom (UK), the current NICE guidance from 2008 [6] suggests that IOL should be performed using vaginal prostaglandin (PG) E2 (tablet, gel, controlled release insert) as the first line agent. However, the misoprostol vaginal insert (MVI) was licensed and approved for use in the UK in 2013. Misoprostol is a synthetic analogue of prostaglandin E1. MVI is a vaginal insert containing 200 μg of misoprostol, released at the rate of 7 μg/hour over 24 h [2]. In 2014 the Scottish Medicines Consortium (SMC) accepted MVI for use in IOL in women with an unfavourable cervix (Bishop's score ≤ 4) from 36 weeks' onwards – citing the significant reduction in interval to vaginal delivery [3] and the likely value for money offered despite a higher acquisition cost than DVI. In 2018, MVI was also recommended by the All Wales Medicine Strategy Group as an option for use within NHS Wales for the induction of labour in women with an unfavourable cervix, from 36 weeks' gestation, in whom induction is clinically indicated [7].

A recent multicentre Phase 3 randomised controlled trial compared the efficacy and safety of the MVI versus DVI in 1358 women (EXPEDITE) [4]. This concluded that the misoprostol insert

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was more effective at achieving vaginal birth in 24 h. Overall, there was no significant difference in adverse events for either women or babies. However, there was a significant increase in hyperstimulation with the misoprostol vaginal insert compared with the dinoprostone vaginal insert, although the rate of caesarean sections or number of babies admitted to intensive care were not different between the groups [5].

This study reports our initial experience using MVI in a District General Hospital in NHS Fife in Scotland (3500 deliveries per annum). The labour and delivery outcomes of the first 100 women undergoing induction of labour using MVI are compared to 100 women induced with a DVI. Preliminary results from this study were presented at the British Maternal & Fetal Medicine Society [8] meetings and the Royal College of Obstetrics and Gynaecology [9] meetings in 2017 and 2018.

Methods

Data were collected retrospectively from 100 women who were induced with MVI between February 2016 and September 2017 and 100 women who were induced with DVI over the same time-period.

MVI® was used for the same indications as DVI® but was specifically indicated in women with a Modified Bishop Score ≤ 4. The Score was calculated using the following parameters – cervical dilatation, length, consistency and position, as well as fetal station [10]. The current IOL guidance at NHS Fife suggests users exercise caution with the use of MVI® in women with a parity of ≥ 3, previous precipitate labour, oligohydramnios and suspected fetal compromise.

Outcome measures included: the incidence of tachysystole and hyperstimulation; further use of prostaglandins; use of pre-delivery oxytocin; mode of delivery; mean insertion-to-delivery-interval; and admission to the neonatal unit.

Tachysystole was defined as more than five contractions per 10 min for at least 20 min [6]. Uterine hyperstimulation was defined as a single contraction lasting at least 2 min, or more than five contractions over 20-minute period with adverse changes in the fetal heart rate pattern on cardiotocography [6].

Statistical data analysis was performed using R, version 3.1.1. Fisher's exact test was used for binary data and the Wilcoxon rank sum test was used for continuous data. Logistic regression analysis was performed for the outcome measures, adjusting for potential confounders including body mass index (BMI), gestational age, parity and baseline Modified Bishops score.

Results

Group characteristics

Table 1 summarises the parity, baseline Bishop score, gestational age and body mass index (BMI). 30% of women in the DVI group started with a baseline Modified Bishops Score ≤ 6, although this discrepancy was accounted for in the subsequent analysis of the data.

Labour and delivery outcomes

Table 2 summarises the adjusted estimates of the effect of treatment. The estimates are expressed as odds ratios, comparing the estimated odds of the outcome in question among women treated with DVI compared to women treated with MVI. The rate of delivery between the two treatment groups was compared based on the estimated hazard ratio from a Cox proportional hazards model: a comparison of the rate of delivery in each treatment group amongst those women who are yet to deliver.

Table 1
Group summary statistics for baseline pregnancy characteristics.

	MVI	DVI
Modified Bishop Score	**Number of women**	**Number of women**
0	1	4
1	8	11
2	35	13
3	31	23
4	15	19
5	0	23
6	0	7
Missing	*10*	*0*
Parity	**Number of women**	**Number of women**
0	65	56
1	24	24
2	9	14
≥ 3	1	6
Missing	*1*	*0*
Gestational Age (days)		
Mean (SD)	280.8 (10.1)	279.4 (10.5)
Median (Q25, Q75)	282 (173,291)	281 (273,287)
Missing	*2*	*0*
BMI (kg/m^2)		
Mean (SD)	28.7 (7.0)	28.6 (7.8)
Median (Q25, Q75)	27 (2331)	26.8 (2332.7)
Missing	*5*	*0*

These treatment effects have been adjusted for potential confounders including BMI, gestational age, parity and baseline Modified Bishop score. Nulliparous women were used as the reference group for the parity analysis. The group of women with Modified Bishop score = 0 at baseline was the reference group for this analysis.

Induction delivery interval

The median induction to delivery interval was 15 h in the MVI group compared to 33 h in the DVI group. Results of the Cox proportional hazards model show an estimated hazard ratio of 0.23 suggesting the time taken to achieve delivery is significantly slower in the DVI group compared to the MVI group.

Additional prostaglandin use

Eight women in the MVI and 33 women in the DVI group required further prostaglandins for induction of labour. Following adjustment, this equates to a 32% increase in the estimated odds of requiring additional induction agents in women receiving DVI vs MVI, when controlling for other variables.

Intrapartum oxytocin

Thirty-three women in the MVI and thirty women in the DVI group required additional intrapartum oxytocin for augmentation of labour. This equated to an estimated odds ratio of 1.05. However, this difference was not statistically significant ($p = 0.4747$).

Mode of birth

In the MVI group, sixty-one women had spontaneous vaginal birth, ten women had an assisted vaginal birth and twenty-nine women underwent a caesarean section. In the DVI group, sixty women had spontaneous vaginal birth, eighteen women had an assisted vaginal birth and twenty-two women underwent a caesarean section. These differences were not statistically significant. When adjusted for potential confounding factors there was no significant difference between the treatment groups in the odds of having a spontaneous vaginal delivery or a caesarean section.

Table 2
Summary Table of Adjusted Treatment Effects.

DVI VERSUS MVI	Estimated Odds Ratio	95% confidence interval	p-value	Interpretation of outcomes
Tachysystole	0.78	(0.702,0.866)	< 0.01	28% increase in the odds of experiencing Tachysystole with MVI
Hyperstimulation	0.844	(0.768,0.929)	< 0.01	18.5% increase in the odds of experiencing Hyperstimulation with MVI
Additional prostaglandin use	1.32	(1.160,1.496)	< 0.01	32% increase in odds of needing PGs with DVI
Intrapartum oxytocin	1.056	(0.909,1.228)	0.4747	No difference in either group
Mode of delivery: spontaneous vaginal delivery	0.916	(0.794,1.058)	0.233	No difference in either group
Mode of delivery: caesarean section	0.975	(0.850,1.119)	0.722	No difference in either group

DVI VERSUS MVI	Estimated Hazard Ratio	95% confidence interval	p-value	Interpretation of outcomes
Induction-delivery interval	0.23	(0.151,0.349)	< 0.01	In women yet to deliver, delivery is 77% slower with DVI use

Tachysystole

Thirty women in the MVI group and two women in the DVI group were noted to have tachysystole. Following adjustment for potential confounding factors, this equates to an estimated odds ratio of 0.78 (i.e. a 28% increase in the odds of experiencing tachysystole with MVI versus DVI for a given parity, gestational age, BMI, Modified Bishops score) (1/0.780 = 1.28).

Hyperstimulation

Seventeen women in the MVI group experienced hyperstimulation and five of these women required a caesarean section; two of these were category 1. Two women in the DVI group experienced hyperstimulation – both of whom ultimately progressed to a spontaneous vaginal delivery. Following adjustment for confounders there was a 18.5% increase in the estimated odds of developing hyperstimulation in the MVI group when compared to DVI for a given parity, gestational age, BMI, Modified Bishops score (1/0.844 = 1.185).

Neonatal outcomes

Four neonates in the MVI group and six in the DVI group were admitted to the neonatal unit. Three babies in the MVI group were admitted to the neonatal unit with suspected sepsis, and one baby was admitted with respiratory distress syndrome. Four babies in the DVI group were admitted to the neonatal unit for suspected sepsis, one baby for prematurity (34 weeks) with gestational diabetes and one baby for evaluation of cardiac disease. The early neonatal sepsis rate at our unit is 1.25/1000 births. All the babies recovered uneventfully and were discharged. Cord gas evaluation was performed in 46 babies in each group. The lowest arterial pH was very similar in each group (MVI 7.08; DVI 7.04) and the mean arterial pH was the same (7.22) in each group.

Table 3 summarises the results discussed above.

Discussion

Our obstetric unit was one of the first to adopt the use of MVI for IOL in the UK. Currently, MVI for IOL has been incorporated into more obstetric units in the UK. The clinical evidence to support use of MVI comes from the EXPEDITE study which randomised 1358 women to receive either 200-microgram misoprostol vaginal insert or the 10 mg dinoprostone vaginal insert for labour induction [3]. The aim of the current study was to compare labour and delivery outcomes in our local UK context when using these induction agents and to compare these to the results of this large, well-designed study.

EXPEDITE demonstrated a statistically significant difference in the hazard rate of vaginal delivery [4]. Our results align with this finding; we also demonstrated a significant reduction in induction-delivery interval (17.7 h) with MVI compared to DVI.

In the EXPEDITE study, the rate of uterine hyperstimulation was 3 times higher with the misoprostol vaginal insert compared with the dinoprostone vaginal inserts (relative risk 3.34) [4]. In our local UK context, we also demonstrated a significant increase in uterine hyperstimulation with MVI compared to DV (estimated odds ratio 1.185). However, this higher rate of hyperstimulation did not equate to a significant difference in mode of delivery or neonatal outcomes between the two groups. Again, the results of our study are in alignment with those of the EXPEDITE study.

In the EXPEDITE study 9.0% of babies were admitted to the neonatal unit in the misoprostol group and 10.4% babies in the dinoprostone group [4]. These results were not statistically significant. The authors suggest that the incidence of some important neonatal events was too low to allow statistical comparison - and this is certainly also a limitation of our small cohorts. In our population, 4% of babies in the MVI group and 6% in the DVI group were admitted to the neonatal unit.

Our study differs from the results of the EXPEDITE trial in that our study demonstrated no significant differences between the two treatment groups for the need for augmentation with intrapartum oxytocin. This is a surprising result - particularly given the significant reduction in the induction to delivery interval for the MVI group. This may be an interesting divergence between the controlled nature of a clinical trial and clinical practise. Initially, when there was little experience with MVI, the MVI insert may have been removed earlier than necessary, thus leading to lower

Table 3
Summary of Results.

DVI VERSUS MVI	MVI (n = 100)	DVI (n = 100)	p-value
Tachysystole	30	2	p<0.0001
Hyperstimulation	17	2	p = 0.0004
Additional prostaglandin use	8	33	p<0.0001
Intrapartum oxytocin	30	33	p = 0.7609
Mode of delivery: spontaneous vaginal delivery	61	60	p = 0.20
Mode of delivery: caesarean section	29	22	
Mode of delivery: Instrumental Births	10	18	
Neonatal Admissions	4	6	p = 0.7475

drug exposure and the need for further augmentation with oxytocin in this group. This perhaps may also suggest that MVI makes the most significant difference in accelerating the latent phase of labour induction when oxytocin is not needed. We do not currently have data on the amount or duration of oxytocin required for each group; this data may provide an interesting insight into this finding.

Conclusion

The results of this study suggest that MVI significantly reduces the induction to delivery interval, has a similar caesarean section rate and neonatal outcomes, when compared with DVI.

Limitations

This is retrospective observational data with the associated biases of a retrospective study. However, we have attempted to adjust for potential confounding factors. Moreover, small patient numbers limit the conclusions that we can draw. However, this data only reflects the start of our experience with MVI. We plan to continue to collect this data on an ongoing basis and hope to collaborate with other maternity units in Scotland. It is reassuring that the majority of our findings align with the EXPEDITE study for both efficacy and safety outcomes.

Future research

The majority of research on this subject is quantitative in nature and focuses on objective measurements - such as the reduction in the time taken to achieve delivery. However, whilst some women may find a prolonged induction difficult, others may find a very rapid labour stressful. Qualitative research is therefore required to augment this data and provide clinicians with an insight into the breadth of patient experience of induction of labour with these agents. This will allow for better understanding of the experience of induction of labour with both agents and thus more informative pre-induction counselling. Speed of delivery is often used as a marker of induction success: the arbitrary primary outcome of vaginal delivery within 24 h being commonly used [11]. However, as Hofmeyer observes in his commentary on the PROBAAT II trial results – which showed misoprostol to be superior to Foley catheter when the chosen end point was delivery within 24 h – the outcome of the study would be reversed if a longer end point (36 h) were to be chosen [11]. We must therefore be cognisant of a broader definition of “success” when considering the induction process and consider maternal satisfaction in the labour process as of paramount importance - rather than any predefined time limits.

Conflict of interest

The authors received support from Ferring Pharmaceuticals for the statistical analysis.

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