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Original Article

Dinoprostone vaginal pessary for induction of labour: Safety of use for up to 24 h

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Background: Cervidil® (dinoprostone) intravaginal pessaries are used for induction of labour and maintain serum prostaglandin levels for up to 24 h. The Therapeutic Goods Administration approves Cervidil® for 12-h use. However, twenty-four-hour use of Cervidil® is supported in Europe, New Zealand, America and some Australian hospitals.
Aim: To assess the safety of Cervidil® use for up to 24 h for induction of labour in nulliparous women.
Methods: A retrospective cohort study of 269 consecutive women receiving Cervidil® at the Royal Brisbane and Women's Hospital (RBWH) between July 2007 and December 2008 was performed. The primary outcome measures were frequency of, and time to, uterine tachysystole with or without fetal heart rate (FHR) changes. Secondary outcome measures included frequency of maternal (intrapartum temperature, postpartum haemorrhage) and neonatal (low Apgars, resuscitation, nursery admission) morbidity. Morbidity outcomes of those who received Cervidil® for less than or equal to 12 h were compared with those who received Cervidil® for more than 12 h.
Results: Uterine tachysystole occurred in 9.3% of patients receiving Cervidil®, with a mean time to tachysystole of 10 h. The majority of cases (68%) occurred within 12 h of use. There was no increase in maternal or neonatal morbidity for those who received Cervidil® for longer than 12 h.
Conclusion: Twenty-four-hour use of Cervidil® is likely as safe as 12-h use for induction of labour in nulliparous women.

Key words: Cervidil®, dinoprostone, hyperstimulation, induction of labour, safety, tachysystole.

Introduction

Induction of labour is one of the most common obstetric procedures, performed in 25% of pregnancies in Australia.[1] The most common indications for induction of labour are prolonged pregnancy, pre-eclampsia/hypertension and psychosocial reasons.[1]

Synthetic prostaglandins have been used since the 1960s for induction of labour.[2] Prostaglandin E_2 (PGE_2, dinoprostone) is the preferred form of prostaglandin and compared to placebo, vaginal PGE_2 has been shown to increase the rate of vaginal delivery within 24 h and is generally given when a cervix has a Bishop's score of five or less.[3–6] The most clinically significant side effect is uterine tachysystole, which is reported in the literature to occur in 1–5% of inductions and may cause fetal distress warranting expeditious delivery.[4]

Cervidil® (Registered trademark of Controlled Therapeutics (Scotland) Ltd. Australian sponsor CSL Limited) is an intravaginal pessary used for induction of labour that contains 10 mg of PGE_2. The pessary releases PGE_2 at a rate of 0.3 mg per hour and continues to release PGE_2 and maintain serum levels for up to 24 h.[7] While it has proven efficacy and safety over 12 h, there are no studies that focus on safety of use after 12 h as a primary outcome.[6,8] Recently, Triglia *et al.* (2010) published a randomised control trial comparing 24-h use of vaginal dinoprostone pessary to prostaglandin gel for induction of labour in term pregnancies with a Bishop's score of <4 in an Italian population of 133 patients and found a higher success rate of vaginal delivery for those using the 24-h dinoprostone pessary.[9] However, the side effect profile reported no cases of uterine hyperstimulation or frequency of 'tachysystole' in either group. While the literature seems to suggest benefits in terms of higher vaginal birth rates with longer use, the consequences of this, including maternal and neonatal morbidity, are not well defined. A recent systematic analysis by Austin *et al.* (2010) collated available

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randomised trials to compare the efficacy of dinoprostone 10 mg pessary with misoprostol administration for induction of labour and as a secondary outcome reported on some maternal and neonatal adverse events.[10] However, the adverse event data reported had broad ranges from 0% to 30% for tachysystole and 0% to 27.6% for neonatal nursery admission. Evidently, further research is needed to clarify the side effects of using dinoprostone for longer than 12 h.

While Cervidil® has been used in Australia since 2004, it is currently only approved for up to 12-h use by the Therapeutic Goods Administration. After its introduction at the RBWH in nulliparous women, it was observed that there was a large proportion of patients in whom further cervical priming was required after 12 h of use. This observation was confirmed by other studies where repeat doses of Cervidil® were required in up to 53% of nulliparous women prior to being able to perform amniotomy.[11,12]

Twenty-four-hour use of Cervidil® is supported in Europe, New Zealand and the USA. Although small in absolute numbers, previous studies have suggested the majority of adverse events associated with Cervidil® occur within the first 12 h of use. Following the observation that a number of women required further cervical priming following 12-h use of Cervidil® and review of the literature, a consultant panel at RBWH changed policy to enable Cervidil® use for up to 24 h. Cervidil was used outside of current TGA approval of 12-h use at RBWH, based on the above evidence. The aim of this study was to audit the safety of using Cervidil® for up to 24 h compared to the safety of 12-h use for induction of labour in nulliparous women.

Materials and Methods

A retrospective chart audit of 269 consecutive nulliparous patients who received Cervidil® at the RBWH between July 2007 and December 2008 was performed. The study population was identified through a search of the hospital coding database and correlated with the inductions booking list.

As per the induction of labour guideline at RBWH, Cervidil® was administered to nulliparous women with a Bishop's score of four or less for induction of labour in singleton pregnancies with a vertex presenting fetus, at gestational age ≥ 37 weeks, after a normal thirty-minute cardiotocograph (CTG) was obtained.[13] On a routine basis, patients received a written information sheet on the multiple methods used for induction of labour (including 24-h use of Cervidil), had the opportunity to discuss the process with an obstetrician/obstetric registrar and gave verbal consent for the induction process prior to the commencement of induction. Contraindications were consistent with those given in the Cervidil® product information and included ruptured membranes, previous uterine surgery, hypersensitivity to prostaglandin preparations, unexplained vaginal bleeding and medical contraindications to prostaglandin administration.[14] Patients less than eighteen years of age or with intellectual or mental impairment were excluded from the analysis because of ethical requirements.

A postinsertion thirty-minute CTG was performed, and if normal, Cervidil® was left in situ for 24 h unless labour (defined by three contractions every ten minutes for at least 1 h, confirmed by CTG monitoring), rupture of membranes (ROM) or side effects occurred, in which case Cervidil® was removed early. Women received normal four hourly observations during this time of temperature, pulse and blood pressure. After removal, amniotomy was performed if possible. If further cervical priming was necessary, six-hourly intravaginal PGE_2 gels, up to a maximum of three doses, were used until amniotomy was possible. Oxytocin was used in those women with ruptured membranes who required it for the usual obstetric indications.

A detailed chart review was performed for every eligible patient, and data on demographics and safety were collected. Additional data were obtained from the hospital coding database.

The primary outcome of safety was determined by recording the frequency of uterine tachysystole in the first, and second, 12 h of Cervidil® use, the time since insertion and cervical dilatation during the episode and the mean time to tachysystole. Tachysystole was defined by ≥ 5 contractions in 10 min and was further defined by the presence or absence of FHR changes giving an abnormal CTG.[15] Abnormal CTG was defined as per the Royal Australian and New Zealand College of Obstetricians and Gynaecologists *Intrapartum Fetal Surveillance Clinical Guidelines*.[16] Morbidity outcomes of those who received Cervidil® for less than or equal to 12 h were also compared with those who received Cervidil® for more than 12 h (including maternal nausea, vomiting, diarrohoea, intrapartum temperature, postpartum haemorrhage (PPH) and neonatal Apgars, resuscitation and nursery admission).

PPH was defined as blood loss of ≥ 500 mL following vaginal birth or ≥ 750 mL following caesarean delivery (ICD-10 blood loss criteria[17]) or where a diagnosis of PPH was recorded in the case notes. Those women who received additional PGE_2 gels were excluded from the morbidity comparisons because of the potential of these gels to contribute to adverse outcomes.

The outcome measures were analysed quantitatively with SPSS software. Pearson Chi-squared analyses were performed to compare the frequencies of outcome data between the two groups. Statistical significance was measured at the $P < 0.05$ level. The study has 80% power to detect an increase of 0.08 (doubling) with probability level of 0.05. In addition, Kaplan–Meier analysis was performed. The study was approved by the RBWH Human Research Ethics Committee.

Results

During the 18-month study period, 2665 nulliparous women delivered at RBWH and 25% of these required

Table 1 Baseline characteristics

	Total group (n = 269)	≤12-hr Cervidil (± further prostin) (n = 122)	>12-hr Cervidil (± further prostin) (n = 147)
Mean maternal age (years)	28.8	28	29
Mean BMI (kg/m^2)	27.9	27.4	28.4
Mean gestational age at IOL (weeks)	40 ± 4	40 ± 4	40 ± 4
Indication for IOL			
Postdates	62.5%	64.8%	60.5%
Maternal concerns	29.7%	28.7%	30.6%
Fetal concerns	7.8%	6.6%	8.8%
Mean starting Bishop score	2.8	2.8	2.7
Mean Birth weight (g) (P = 0.006)	3565	3464 (2912–4016)	3648 (3107–4189)

induction of labour. Of these, 269 women received Cervidil®, with more than half of women (147/269) receiving Cervidil® for longer than 12 h. Table 1 shows baseline characteristics of the women.

Just over one-third of women receiving Cervidil® progressed to labour or ROM (either spontaneous or artificial) within the first 12 h (Fig. 1). A further third progressed to labour or ROM over the following 12 h of Cervidil® use. One in five women received further intravaginal PGE_2 gel (1–5 mg) despite 24 h of Cervidil®. A small number of women had Cervidil® removed prematurely, at or before 12 h, and subsequently required further cervical priming with PGE_2 gels. Reasons for early removal included staff and/or the woman believing active labour had occurred when it had not and Cervidil® falling out. There were no statistical differences in the mode of delivery between the two groups (P = 0.80), the 12-h group had a caesarean delivery rate of 43.4%, instrumental delivery rate of 17.2% and spontaneous vaginal delivery rate of 39.3%. This is compared to the more than 12-h group where the caesarean delivery rate was 45.6%,

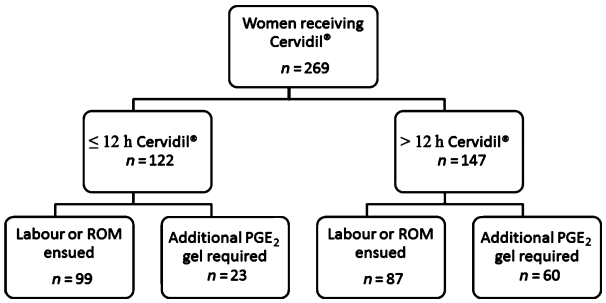

Figure 1 Diagram showing the flow of participants through the induction of labour process.

instrumental deliveries were 14.3% and spontaneous vaginal delivery rate was 40.1%. The most common indications recorded for caesarean delivery in both groups were the same and included fetal distress and failure to progress.

Uterine tachysystole occurred in 25 (9.3%) women receiving Cervidil® with 17 (68%) of these occurring within the first 12 h of Cervidil® use (Tables 2, 3). Tachysystole with FHR changes occurred in 8 (3%) cases and was more likely to occur within the first 12 h of Cervidil® use. Kaplan–Meier analysis confirms that the majority of cases occurred within the first 12 h, with no additional cases occurring between 18 and 24 h (Fig. 2). The mean time to tachysystole was 10 h and standard deviation 4.5 h, with the shortest and longest time to tachysystole of four and 18 h, respectively. The majority (93%) resolved within an hour of pessary removal. Less than one per cent of women receiving Cervidil® required treatment with tocolysis and subsequent delivery (Table 2). The two cases that required expedited delivery occurred in the initial 12 h of use. The first occurred at 4 h postinsertion at 0 cm cervical dilatation and required caesarean delivery with normal neonatal cord gases. The second case that warranted expeditious delivery was at 11 h postinsertion and full dilatation. Staff had been unaware that the woman had ruptured her membranes and the pessary was left in situ after this event. Delivery was expedited by ventouse delivery. Cord gases were consistent with fetal acidosis, and a maternal PPH was also documented. There was no

Table 2 Incidence of uterine tachysystole†

		First 12 h of Cervidil® use		Second 12 h of Cervidil® use	
	All cases n = 269	0–6 h (n = 269)	7–12 h (n = 243)	13–18 h (n = 147)	19–24 h (n = 90)
Uterine tachysystole	25 (9.3%)	7	10	8	0
Uterine tachysystole with FHR changes	8 (3%)	2	5	1	0
Uterine tachysystole requiring tocolysis and delivery	2 (0.74%)	1	1	0	0

Data are presented as n (%).
†Tachysystole defined as ≥ 5 contractions in 10 min.

Table 3 Comparison of maternal and neonatal adverse events

	≤12-h Cervidil® *n* = 99	>12-h Cervidil® *n* = 87	*P*-value	Total group *n* = 186
Maternal adverse events				
Intrapartum temperature ≥37.8°C	6 (6.1%)	6 (6.9%)	0.82	12 (6.5%)
Postpartum haemorrhage	17 (17.2%)	16 (18.4%)	0.83	33 (17.7%)
Neonatal adverse events				
1-min Apgar ≤6	14 (14.1%)	8 (9.2%)	0.30	22 (11.8%)
5-min Apgar ≤6	2 (2.0%)	1 (1.1%)	0.64	3 (1.6%)
Need for resuscitation†	30 (30.3%)	29 (33.3%)	0.66	59 (31.7%)
Nursery admission‡	29 (29.3%)	24 (27.6%)	0.80	53 (28.5%)

This table specifically excludes women who received additional prostaglandins for induction of labour
Data are presented as *n* (%).
†Resuscitation requiring at least positive pressure ventilation.
‡Intensive care or special care admission included.

significant relationship between the occurrence of tachysystole and the initial Bishop score ($P = 0.21$), and the mean cervical dilatation at the time of tachysystole was 2.5 cm (SD ± 1.3 cm).

There were no significant differences in any of the maternal or neonatal morbidity factors measured between those women who received up to 12 h of Cervidil® compared with those who received more than 12 h of Cervidil® (Table 3). There were a total of nine other adverse events (excluding tachysystole), these included nausea, vomiting and diarrohoea, and three women were treated with metoclopromide. Kaplan–Meier analysis indicates that these events, including tachysystole, are more likely to occur within the first 12 h. There was no significant difference between the rates of PPH, being 17.2 and 18.4%, respectively. There were six women in each group who recorded an intrapartum temperature. Neonatal outcomes for neonatal resuscitation were 30.3%, 29.3% and for nursery admission were 33.3% and 27.6% for less than 12- and more than 12-h dinoprostone use. The main reasons for neonatal admission were for infection risk (37.4%), blood sugar monitoring (12%) and respiratory observations (12%).Of these, 68 were to Special Care Nursery only and 23 were to neonatal intensive care unit. Other less reported reasons included congenital abnormality, small for dates and other common newborn ailments (eg hypoglycaemia, vomiting, jaundice, etc). Only three babies subsequently were proven to have an infection.

Discussion

This is the largest study to date that focusses primarily on the safety of Cervidil® when used for more than 12 h. Previous studies have suggested that Cervidil® 'can be left in longer with no apparent detriment'.[18–20] However, this study has confirmed that Cervidil® use for up to 24 h is at least as safe as 12-h use, both in terms of uterine tachysystole and neonatal and maternal morbidity.

Uterine tachysystole is considered the most significant side effect of prostaglandin induction of labour with consequences to the health of both the mother and baby. The American College of Obstetricians and Gynecologists (ACOG) have recently advised the abandonment of the term hyperstimulation and defined tachysystole as more than five contractions in 10 min, averaged over a 30-min window.[21] Our study demonstrates a frequency of tachysystole, with and without FHR changes, that is, similar to previous studies and confirms that the majority of cases occur within the initial 12 h of Cervidil® use.[18–20] This is in contrast to the recent results reported by Triglia *et al.* who reported no tachysystole at all.[9] Both Wing and Kho *et al.* found that 95% of tachysystole occurred within the first 12 h of use, while our study showed 68% occurred within the same time frame.[5,18] While the frequency of tachysystole appears high, it is reassuring to know that less than one per cent of women who received Cervidil® required delivery for unresolving tachysystole associated with FHR changes.

It is well documented that induction of labour and prolonged first stage of labour are risk factors for postpartum haemorrhage, and that prolonged labour is a risk factor for intrapartum fever.[22,23] It was therefore hypothesised that those women receiving Cervidil® for longer than 12 h may have a higher incidence of these morbidities. However, our data demonstrate no additional risk. The higher incidence of PPH in this study compared to a similar dinoprostone pessary study (17.7% compared to 5.5% and 6%) may be explained by the use of the ICD-10 criteria, which has lower thresholds for documenting a PPH.[17,20] As this definition is currently used in medical coding in many Australian hospitals to access Medicare rebate funding, it may in fact more accurately reflect the true cost to Australian obstetric departments in managing PPH associated with induction of labour using Cervidil®.

In addition, neonatal outcomes were also reassuring with no differences in adverse outcomes between less than and more than 12 h of use and very low rates of poor Apgar scores. Previous studies have not well documented the need for neonatal resuscitation and nursery admission

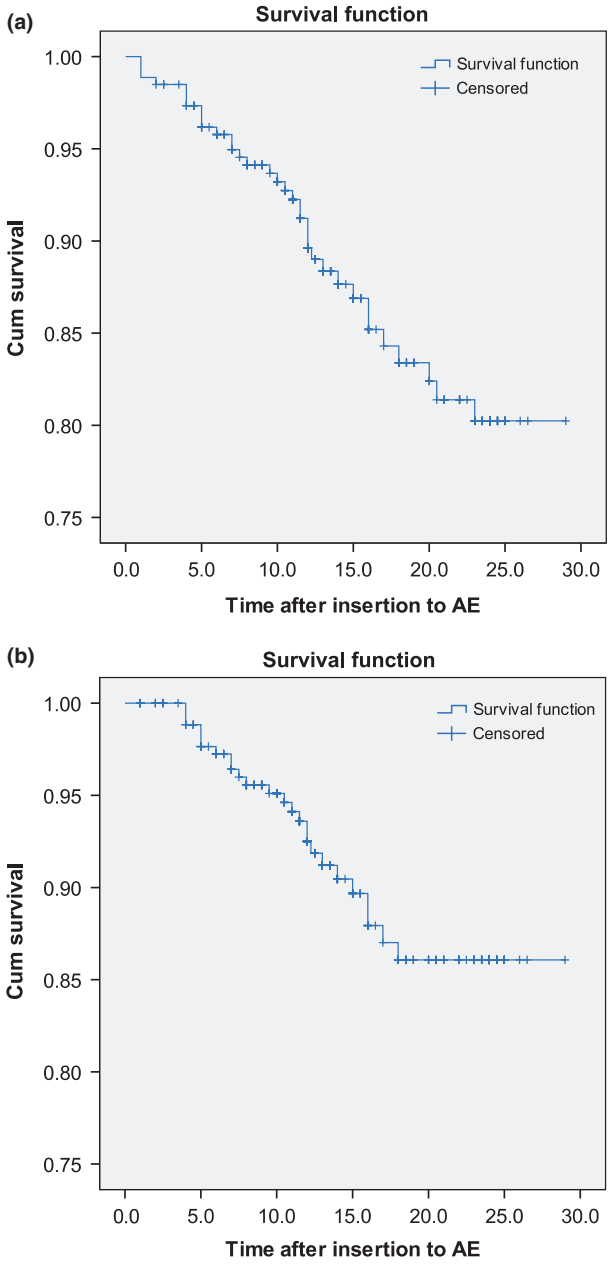

Figure 2 (a) Kaplan Meier curve for total adverse events. (b) Kaplan Meier curve for tachystole.

following administration of dinoprostone pessaries for longer than 12 h. Our study found similarly high rates of neonatal resuscitation and nursery admission to those reported by Wing (1997).[19] However, importantly there was no difference between less than 12- or more than 12-h use. The high rates of neonatal admission in this study may be due to the high risk obstetric population characteristics of a tertiary centre and the neonatal nursery criteria for all babies who require any resuscitation effort, become febrile or with any risk factors for infection to be monitored in the nursery and receive intravenous antibiotics postdelivery. Results from this study are only generalisable to similar nulliparous populations, and discrepancies between numbers reported for adverse outcomes between this and other studies may be due to different patient population characteristics, definitions of terms or inclusion criteria.

Having established the safety of Cervidil® use for up to 24 h in an Australian population, future research is required to determine whether this practice results in improved efficacy and cost effectiveness in the clinical setting. This has important implications for women requiring induction of labour, including the potential for fewer invasive vaginal examinations, as well as possible cost savings to healthcare institutions and governments by reducing the number of induction agents used. However, current TGA guidelines only approve 12-h use of Cervidil®, and hospitals seeking to implement this practice need to ensure they have appropriate approval within their own institutions. Further, a randomised trial specifically designed to assess the efficacy and economic benefit in the Australian population is needed to develop a better understanding of the overall value of this practice. In the interim, this analysis provides evidence that clinicians can be reassured that there is no significant difference in maternal or neonatal morbidity when using Cervidil® for up to 24 h.

Conclusions

Cervidil® use for up to 24 h is likely as safe as 12-h use in terms of uterine tachystystole and maternal and neonatal morbidity for induction of labour. Further research is required to determine whether this practice improves clinical efficiency and cost effectiveness for obstetric departments.

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