Safety and efficacy of the double balloon catheter and the prostaglandin pessary: A multicentre randomised controlled trial

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May 5, 2020

Abstract

Objective We compare the adverse events in the 12 hours after double balloon catheter(DBC) or first prostaglandin(PGE) inserted and the efficacy of DBC to that of PGE in labour induction. Design Multi-centre Randomised controlled Trial (RCT), in 2 centers with 2 arms: (i)DBC (ii)prostaglandin pessary. Setting 2 tertiary hospitals, Singapore and Malaysia Population Southeast-Asian women Method This is a prospective cohort randomised controlled study. 210 women were recruited in each center and assigned randomly to cervical ripening with either DBC or prostaglandin pessary. Main outcome The adverse events in the 12 hours after DBC or first PGE inserted and the efficacy of a DBC to that of a prostaglandin in labour induction were evaluated. Results There were significantly less women with uterine hyperstimulation in the double balloon catheter group (2 vs 24, p=<0.0001) compared to the prostaglandin group. There were no women with uterine hyperstimulation and non-reassuring fetal status in the double balloon group while there were 5 women with uterine hyperstimulation and fetal distress in the prostaglandin group. Use of pain relief was significantly less in the double balloon catheter group (p=0.009). There were no significant differences in both groups in mode and time to delivery, although significant less time was needed to achieve os dilation more than 4cm in the double balloon catheter group (p=<0.0001). Conclusion DBC remains a good alternative method for inducing women in view of low adverse events and a good safety profile with low risk of hyperstimulation. Keywords: Double balloon catheter;prostaglandin;hyperstimulation;induction of labour ClinicalTrials.govIdentifier:NCT02620215.URL:https://clinicaltrials.gov/ct2/show/NCT02620215

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Shortened running Title: Safety and efficacy of the DBC and the PGE

Abstract

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We compare the adverse events in the 12 hours after double balloon catheter(DBC) or first prostaglandin(PGE) inserted and the efficacy of DBC to that of PGE in labour induction.

Design

Multi-centre Randomised controlled Trial (RCT), in 2 centers with 2 arms: (i)DBC (ii)prostaglandin pessary.

Setting

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Population

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This is a prospective cohort randomised controlled study. 210 women were recruited in each center and assigned randomly to cervical ripening with either DBC or prostaglandin pessary.

Main outcome

The adverse events in the 12 hours after DBC or first PGE inserted and the efficacy of a DBC to that of a prostaglandin in labour induction were evaluated.

Results

There were significantly less women with uterine hyperstimulation in the double balloon catheter group (2 vs 24, p=<0.0001) compared to the prostaglandin group. There were no women with uterine hyperstimulation and non-reassuring fetal status in the double balloon group while there were 5 women with uterine hyperstimulation and fetal distress in the prostaglandin group. Use of pain relief was significantly less in the double balloon catheter group (p=0.009). There were no significant differences in both groups in mode and time to delivery, although significant less time was needed to achieve os dilation more than 4cm in the double balloon catheter group (p=<0.0001).

Conclusion

DBC remains a good alternative method for inducing women in view of low adverse events and a good safety profile with low risk of hyperstimulation.

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Tweetable abstract: The double balloon catheter is a good alternative method for inducing women in view of low adverse events and a good safety profile with low risk of hyperstimulation.

Introduction

In light of recent evidence in the literature advocating for elective induction of uncomplicated singleton pregnancies at 39 weeks of gestation, [1] we can expect that induction of labour (IOL), which is one of

the most common procedures a woman may experience in pregnancy, will become even more frequently employed. As such, there is a pressing need to study the most optimal method of cervical ripening among pharmacological, mechanical or surgical methods.

There are increasing amounts of evidence of safety and efficacy of mechanical IOL including an updated publication of the Cochrane Database of Systematic Reviews in 2012 [2] and a NICE interventional procedure guidance on the double balloon catheter (DBC).[3] A well-conducted meta-analysis by Du et al. published in 2016 demonstrated that mechanical IOL with cervical ripening balloons appeared to have similar efficacy profiles, and greater safety and cost-effectiveness than prostaglandin (PGE2) agents. A randomised-controlled study on 98 women in 2018 specifically addressing patient experience between IOL methods found that pain during induction was significantly lower with the double-balloon cervical ripening balloon while other satisfaction and acceptability scores were similar. [4]

To the best of our knowledge, current large randomised controlled trials have not directly examined the immediate effects or potential adverse events that occur in the first 12 hours of double-balloon catheter or first prostaglandin insertion in IOL. [5, 6,7,8,]Outcomes on the efficacy and safety during this period will be valuable to support its clinical application in high risk pregnancies. We conducted a multi-centre study to specifically evaluate the use of DBC in IOL in a Southeast-Asian population with regards to adverse effects in 12 hours after insertion while using a non-incremental balloon-filling regime.

Methods

This is a prospective cohort randomized controlled study conducted at the KK Women's and Children's Hospital (KKH) and University Malaya Medical Center (UMMC), teritary hospitals each with an approximate 11000 deliveries annually. The study was conducted from January 2015 to January 2018. Local institutional review board approval was achieved in both centers. 210 women were recruited in each center. ClinicalTrials.gov Identifier: NCT02620215. Funding for the study was supported by SingHealth Duke-NUS OBGYN Academic Clinical Program (ACP) Grant.

The main hypothesis is DBC has no major adverse events including hyperstimulation and non-reassuring fetal status in a 12-hour period after DBC insertion, and its efficacy is non-inferior to prostaglandin insertion. This will allow it to fulfil a current void in offering safer outpatient induction. We attempt to address this hypothesis by monitoring the periods of regular uterine contractions (>1:10) measuring the frequency, length of contractions and its association with adverse events during this period after intervention. We also examined the efficiency of DBC in achieving a favourable cervix for rupture of membranes or active labour at the end of 12 hours compared with PGE2.

NICE guidelines on induction of labour [9] defined uterine hyperstimulation as contractions more than 5 in 10 min for more than 20 min or contractions lasting more than 2 min in duration. A retrospective study involving prostaglandin induction of labour[10] showed that hyperstimulation occurred in 5.8% of cases. Arbitrarily, we considered a relative 80% decrease in hyperstimulation risk (estimated hyperstimulation with DBC 1%) as clinically significant. Hence, assuming a significance level of 5% and power of 80%, and allowing for a 5% dropout rate, we estimated that 210 subjects would be needed per group (one-sided test).

Randomization of the women is achieved with third party sealed envelope allocation. 210 envelopes containing DBC allocation and another 210 identical envelopes containing prostaglandin pessary allocation were prepared by a third party. The 420 envelopes were shuffled according to a computer randomization code after sealing and labelled with a randomization allocation number from 1 to 420. Half of the envelopes were handed to the each center's principal investigator, and kept in the clinical store on labour ward together with the stock of DBC and prostaglandin pessary.

Women requiring term IOL were identified in both centers and screened with the inclusion and exclusion criteria (Box 1. Inclusion and exclusion criteria). Once the written informed consent was obtained a research assistant would disclose the intervention allocation.

In the group allocated the DBC, the catheter was inserted into the cervical canal either under direct visu-

alization with a sterile speculum examination or via vaginal examination. After both balloons have entered the cervical canal, the uterine balloon was filled with 40 ml of saline, the catheter was then retracted and a vaginal examination was done to ensure the DBC is in the cervical canal and the vaginal balloon was inflated to 40 ml of saline. Both balloons were then inflated to 80 ml each. The tubing was then taped to the woman's thigh. After the DBC was put in place, a cardiotocogram was performed for 60 to 120 minutes and the woman was allowed to ambulate. The double balloon catheter was left in place for a maximum of 12 hours as per the manufacturer's advice. Failed induction of labour was defined when labour was not initiated after removal of the DBC.

In the group allocated the vaginal prostaglandin pessary, the pessary was inserted and placed in the posterior vaginal fornix. After insertion of the pessary, a cardiotocogram was performed for 60 to 120 min and the woman was allowed to ambulate. After 6 hours, if the woman is not in labour and the bishop score was still less than 6, a second dose of prostaglandin was inserted and monitored as previously described. Failed induction of labour was defined when labour was not initiated after insertion of 2 pessaries.

The women were continuously monitored for uterine activity and non-reassuring fetal status. During the first 12 hours of the intervention, women were monitored for hyperstimulation defined when there was more than 5 contractions for 10 min and hypertonus defined as a single contraction lasting for more than 2 minutes. The type of pain relief use was recorded (entonox, intramuscular pethidine or epidural). Any vaginal bleeding that was more than a "show" was recorded. Features of any non-reassuring heart rate was recorded and this was defined in accordance to the NICE intrapartum care guidelines.[11] Decisions for caesarean section based on cardiotocographs were made by obstetrician consultants on labour ward.

After the DBC was removed or expelled, and if vaginal examination revealed that the cervical os was more than 3 cm, membranes were ruptured and oxytocin infusion was started for women who were not in labour. For the prostaglandin group, during a vaginal examination, if the cervical os was more than 3 cm, membranes were ruptured and oxytocin infusion started 6 hours after the last dose of prostaglandin. Oxytocin was administered using a standard regime in each hospital. Once in active labour, standardized intrapartum care was given according to hospital protocol.

All decisions for caesarean sections were made by obstetrician consultants on labour ward. Failure to progress in first stage of labour was defined as the absence of cervical change for 4 hours or more in the presence of adequate uterine contractions and cervical dilation of at least 4 cm. During second stage of labour women who were undelivered with no progress with active pushing after at least 2 hours in multiparous women and 3 hours in nulliparous women were diagnosed as failure to progress.

Statistical analysis of outcomes data was performed with Chi squared test and R software.

Results

During the study period, 420 patients were recruited, 210 from each center. (Figure 1. Study Enrolment flowchart.)

In the DBC group, 3 women were excluded because of age criteria and deviation from study protocol. One patient was excluded because of prelabour rupture of membranes after randomisation and before the DBC was inserted and 4 patients had incomplete data. During labour, 5 patients had malpresentation and had to undergo a caesarean section, these patients were excluded from the analysis. In the prostaglandin group, 4 patients were excluded because of age criteria and deviation from study protocol, 4 patients were dilated to more than 3 cm after the randomisation and before the insertion of the vaginal prostaglandin and excluded. One patient was not induced as she declined induction of labour after the randomisation. During labour, 3 patients had malpresentation and had to undergo a caesarean section, they were also excluded from the analysis. The demographics and baseline characteristics were similar in both groups (Table 1). Indications for induction of labour was not significant in both groups (Table S1).

The use of entonox is significantly more in the prostaglandin group than the DBC group, while the use of intramuscular pethidine and epidural was similar in both groups. The average induction to pain relief needed

interval was 6.57 (± 2.83) hours in the prostaglandin group and 7.6 (± 2.72) hours in the DBC group. In the double balloon catheter group, 141 patients (71.9%) did not need pain relief during the first 12 hours of induction (Table 2).

Adverse events during the first 12 hours of induction were recorded (Table 3). All patients who had hyperstimulation had intrauterine resuscitation with a change to left lateral position and intravenous hydration. Three patients needed tocolysis with intravenous terbutaline, none required delivery due to persistent non-reassuring fetal status. There were two cases of hyperstimulation occurred in the DBC arm, but none had an impact on the fetal status. There were no incidences of intrauterine deaths in both groups.

Although there was no difference in the time to delivery in both groups, the time for dilation to 4 cm was significantly less in the DBC group than the vaginal prostaglandin group ($p<0.0001$) (Figure 2.). Oxytocin use for augmentation of labour was significantly higher in the DBC group. 52 patients in the prostaglandin group, underwent spontaneous rupture of membranes ($p<0.0001$). There were no significant differences in the mode of delivery in both groups (Table 4). In the prostaglandin group, a significant number of women had a cesarean section because of failed IOL ($p=0.0369$), while a significant number of patients who had the DBC allocation had a caesarean for failure to progress in the first stage of labour.

Neonatal outcomes were similar in both study groups (Table S2).

Discussion

Main Findings

To the best of our knowledge, this is the largest multi-centre Asian population randomised controlled trial undertaken to evaluate the safety of the DBC as well as the efficacy of the DBC compared to the vaginal prostaglandin. Our findings show that the number of adverse events in hyperstimulation and the use of entonox were significantly less in the women allocated to the DBC group. Our study also showed similar labour outcomes in both groups with regards to recourse to caesarean deliveries. Average time to eventual delivery in both groups was similar.

Strengths and Limitations

The strength of the study include the multi-centre and randomisation design with good power and patient numbers. A limitation of the study was that it was impossible to blind the allocation to the investigator or the patient. However, the investigator had no part in observing any adverse events. The CTGs were interpreted and the need for intervention determined by the attending clinicians. Hyperstimulation was specifically defined and recorded by a third party studying the CTGs and blinded to the patient's allocated group. The patient also reported contractions intervals, pain scores, satisfaction scores with validated standard pain and satisfaction assessment tools to minimize the potential bias. Allocations were omitted from the database so as to blind the analyst in order to prevent manipulation.

Interpretation

Our findings are similar to Du et al. [12] who also showed a 10 times lower risk of hyperstimulation in the double-balloon catheter group to the prostaglandin group. However, the time to first use of pain relief and the percentage not requiring pain relief in the first 12 hours was still similar in both groups, likely an inherent development in labour induction.

A recent systematic review [13] on the safety of the balloon catheter used a random effects model. It included 26 studies (8292 women) which estimated the prevalence of adverse events to be 0 to 0.26%, "pain and discomfort' being most common. In this study, none of the included studies used a double balloon catheter. Our study provides more data to support the good safety profile of the double balloon catheter. Solt et al. [14] compared the Bishop score increment between a DBC and a single balloon catheter, he concluded that the DBC was more effective that the single balloon catheter with decreased time to delivery and decreased caesarean section rates. The usage of a single balloon catheter in induction of labour is off-licensed, and also requires traction.

Outpatient cervical ripening can be an attractive option because of the potential for lower costs and patient satisfaction. This is only possible if the method does not have an adverse effect on the fetus and does not require medical interventions. Less fetal monitoring may be required when DBC is used. In this regard, it may still be difficult for the double catheter balloon to fulfil this role fully, even without hyperstimulation, given the requirement for analgesia in the first 12 hours in 28.1% of the patients.

Wilkinson et al [9] ran a pilot randomised trial comparing inpatient and outpatient balloon induction, they found that patients in the outpatient arm felt less isolated and emotionally alone while medical staff including midwives and doctors were more comfortable with the use of a catheter as an option for outpatient ripening with 90% supporting outpatient ripening with the catheter. A local study[5] also showed that the use of DBC showed similar satisfaction and acceptability in the Singapore population, with 71% of patients recommending the DBC as the mode for IOL.

Du et al's systemic review [12] of 9 randomized controlled studies concluded similar efficacy profiles between the double balloon catheter and the prostaglandin E2. Our study also showed similar labour outcomes in both groups with regards to recourse to caesarean deliveries, but identified the difference in reasons however. Caesarean delivery for failed induction was more common in the prostaglandin group and failure to progress in the first stage of labour more common in the DBC group. Average time to eventual delivery in both groups was similar. Our study, in particular, demonstrated a more predictable course of induction and significantly shorter time required with the DBC from the initiation of IOL to achieving a cervical dilation of more than 4 cm (91.3% vs 67.6%, p=<0.0001), although artificial rupture of membranes and augmentation are more frequently required. We believe this could offer significant advantage to obstetricians in planning inductions for their patients, as well as better patient satisfaction. A cost-efficacy study may be useful in evaluating a best method of induction.

Currently, there are 9 randomized controlled trials[6,15,16,17,18,19,20] involving a double balloon catheter. The balloon-filling regime is not standardized. In this trial, we used a standardized non-incremental balloon-filling regime prescribed according to the manufacturer's advice. This decreased delays in achieving full inflation and decreased the time requiring intensive monitoring of the fetus; hence, we would recommend this as the standard balloon-filling regime for the double balloon catheter.

Conclusion

Our study shows low uterine hyperstimulation and a good safety profile of the double balloon catheter in the induction of labour, with a more predictable and shorter course of induction. DBC may have a place in high risk pregnancies such as growth restricted fetuses.

Acknowledgements

We would like to thank all the participants of the trial, KK Women and Children's Hospital and UMMC hospital labour ward staff providing assistance in data collection. We would like to thank Dr Janice Tung for her contribution to the study.

Disclosure of Interest

No potential conflict of interest was reported by the authors.

Contribution to Authorship

NYHG was involved in conception, planning and carrying out the study with recruitment of women, analysing the results and writing the manuscript. AAA was involved in carrying out the study and recruitment of the patients, collection of data for the study in UMMC and reviewing of the manuscript. TTL was involved in the conception and planning of the study and editing the manuscript. RK was involved in the conception, planning of the study, carrying out of the study in UMMC and reviewing the manuscript. ST was involved in the conception, planning, carrying out of the study and editing of the manuscript. GYSH was involved in the conception, planning, carrying out of the study and reviewing the manuscript.

Details of Ethics approval

Singapore Centralised Institutional Review Board, Date of approval: 16-Oct-2015, Reference number 201506-00112

Funding

Funding for the study was supported by SingHealth Duke-NUS OBGYN Academic Clinical Program (ACP) Grant.

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Table 1. Demographics and baseline characteristics.

	DBC	DBC	Prostin	Prostin	P
IOL to >4cm dilation,hr (n)	13.87 (179)	±7.51	19.08 (134)	±10.59	**<0.0001**
IOL to full dilation, hr (n)	20.23 (117)	±8.37	20.21 (120)	±11.48	0.5061
IOL to vaginal delivery, hr (n)	20.16 (130)	±8.38	20.87 (143)	±11.54	0.2794
IOL to delivery, hr (n)	22.42 (196)	±8.84	23.78 (198)	±13.4	0.1173
Duration of 2nd stage, hr (os full to delivery) (n)	0.78 (117)	±0.99	0.79 (120)	±1.13	0.4711
Delivery within 24h (Vaginal Delivery)	91		94		0.9147
Failed IOL	12		28		**0.01358**
Number of PGE used	Number of PGE used	Number of PGE used	Number of PGE used	Number of PGE used	Number of PGE used
1	6		99		NA
2	4		71		
3	-		24		
4	-		4		
Use of oxytocin for augmentation	152		109		**<0.0001**
SROM	20		52		**<0.0001**

	DBC	DBC	Prostin	Prostin	P
Use of Epidural \soutuse	86		84		0.8497
Vaginal delivery	112		119		0.6214
Instrumental delivery	18		24		0.4345
Caesarean section	66		55		0.2464
Indication for CS	Indication for CS	Indication for CS	Indication for CS	Indication for CS	Indication for CS
Failed IOL	3		12		**0.03697**
FTP in 1st stage of labour	41		18		**0.0016**
FTP in 2nd stage of labour	2		2		1
NRFS (Non-reassuring fetal status)	20		22		0.8978
Pyrexia in labour Temperature >37.5 C	30		20		0.1613
WICU admission	2		2		1

Table 2. Pain relief during the first 12h of induction

	DBC	DBC	Prostin	Prostin	P
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Table 3. Adverse events during the first 12h of induction

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Pyrexia in labour Temperature >37.5 C	30		20		0.1613
WICU admission	2		2		1

Table 4. Labour outcomes of women undergoing cervical ripening balloon (DBC and Prostin (PGE)

	DBC	DBC	Prostin	Prostin	P
IOL to >4cm dilation,hr (n)	13.87 (179)	±7.51	19.08 (134)	±10.59	**<0.0001**
IOL to full dilation, hr (n)	20.23 (117)	±8.37	20.21 (120)	±11.48	0.5061

	DBC	DBC	Prostin	Prostin	P
IOL to vaginal delivery, hr (n)	20.16 (130)	±8.38	20.87 (143)	±11.54	0.2794
IOL to delivery, hr (n)	22.42 (196)	±8.84	23.78 (198)	±13.4	0.1173
Duration of 2nd stage, hr (os full to delivery) (n)	0.78 (117)	±0.99	0.79 (120)	±1.13	0.4711
Delivery within 24h (Vaginal Delivery)	91		94		0.9147
Failed IOL	12		28		**0.01358**
Number of PGE used	Number of PGE used	Number of PGE used	Number of PGE used	Number of PGE used	Number of PGE used
1	6		99		NA
2	4		71		
3	-		24		
4	-		4		
Use of oxytocin for augmentation	152		109		**<0.0001**
SROM	20		52		**<0.0001**
Use of Epidural \soutuse	86		84		0.8497
Vaginal delivery	112		119		0.6214
Instrumental delivery	18		24		0.4345
Caesarean section	66		55		0.2464
Indication for CS	Indication for CS	Indication for CS	Indication for CS	Indication for CS	Indication for CS
Failed IOL	3		12		**0.03697**
FTP in 1st stage of labour	41		18		**0.0016**
FTP in 2nd stage of labour	2		2		1
NRFS (Non-reassuring fetal status)	20		22		0.8978
Pyrexia in labour	30		20		0.1613
Temperature >37.5 C					
WICU admission	2		2		1

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Figure 1 enrolment.doc available at https://authorea.com/users/302719/articles/432806-safety-and-efficacy-of-the-double-balloon-catheter-and-the-prostaglandin-pessary-a-multicentre-randomised-controlled-trial

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Figure 2 Kaplan.docx available at https://authorea.com/users/302719/articles/432806-safety-and-efficacy-of-the-double-balloon-catheter-and-the-prostaglandin-pessary-a-multicentre-randomised-controlled-trial