The University of Texas Medical Branch at Galveston

Research Protocol # 15-0272

Title: Induction of labor in women with unfavorable cervix: randomized control study comparing Dilapan to Foley bulb.

NCT02899689

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1. Introduction and Purpose: Historically, mechanical methods were the first methods developed to ripen the cervix or to induce labor (Thiery 1989). Dilapan®, a hygroscopic cervical dilator made of a patented hydrogel (AQUACRYL), works by stimulating the release of endogenous prostaglandins, which degrade collagen fibers and soften the cervix. Additionally, it dilates the cervix gradually and the effect is gentle as well as predictable. Recently, Dilapan, another form of mechanical dilator, has been approved by the FDA. There are no data comparing this newly approved Dilapan® to the most commonly used mechanical dilator method which is the foley bulb. Therefore, we propose a randomized controlled trial to determine the effectiveness of Dilapan® compared with foley bulb for cervical ripening and induction of labor in pregnant women greater than 37 weeks.

2. Background: Labor induction is a common obstetric procedure, which is generally carried out when the risks of continuing pregnancy outweigh the benefits. To maximize the success of induction of labor in women with an unfavorable cervix, various ripening methods are available. These include drugs such as prostaglandins and mechanical agents such as the foley bulb cervical dilator, which has been used in labor delivery units for decades. Mechanical methods of labor induction are safe, effective and cost effective. Recently, Dilapan® was approved by the FDA as another form of mechanical dilators. Data are lacking regarding the comparative effectiveness of Dilapan® compared with the standard foley bulb in labor induction.

3. Concise Summary of Project: Primary outcome will be to compare the efficacy of achieving a vaginal delivery using the synthetic osmotic cervical dilator Dilapan-S® versus Foley catheter for cervical ripening prior to induction of labor. Secondary outcomes will be to evaluate the efficacy of Dilapan-S® versus Foley catheter on other clinical outcomes such as vaginal delivery rate within 24 and 36 hours post insertion, time to reach active stage of labor defined as $\geq$ 6 cm, change in Bishop score, rate of spontaneous and operative vaginal delivery, rate of caesarean sections and patient satisfaction. Randomization will be performed using a computer generated random list of numbers assigning subjects to the 2 groups of the study. This list of random number assignments will be kept secure in an opaque envelope until the end of the study.

4. Study Procedures:
After institutional review approval, pregnant women that are scheduled for induction of labor will be approached by principal investigator or any of the co-investigators for participation in the study in a private subject room in labor and delivery unit. Prospective subjects presenting for induction of labor in labor and delivery, and willing to participate in the study will be evaluated for their eligibility including, including their bishop score. The latter will be obtained from the subject chart after the initial pelvic exam which is standard of care for these subjects in our unit. After obtaining informed consent, subjects will be randomized.
Group assigned to receive synthetic osmotic cervical dilator:
Before the device placement, patients undergo continuous CTG monitoring for 20 minutes while fetal condition and uterine activity are monitored. The cervix is visualized with a sterile vaginal speculum and cleaned with iodine. As many as possible pieces of synthetic osmotic cervical dilator (Dilapan-S®, Medicem Technology, Kamenne Zehrovice, Czech Republic) are inserted into the cervical canal under direct visualization. Synthetic osmotic dilators are entered to the cervical canal with special attention to cross through the internal os. The number pieces inserted will vary, since different patients will have different pelvic or cervical exam/dilatation. Synthetic osmotic dilators will be inserted as per manufacturer's instructions for use /Appendix 2/. The patient will be instructed to report any excessive bleeding, pain or other concerns. Under no circumstances should patient try to remove Dilapan-S® herself.

The synthetic osmotic dilators will be left in place for at least 12 hours, and no longer than 24 hours. Patient will be allowed to ambulate, shower and perform regular activity as long as a reactive and reassuring NST is documented after placement of device. Reasons for examining or removing dilators earlier include: 1) Spontaneous onset of labor (defined as regular, firm, uterine contractions with an effaced cervix >80% and a cervical dilatation > 3 cm); 2) Category III fetal heart rate tracing; 3) Spontaneous rupture of membranes or need for amniotomy; 4) Spontaneous expulsion of dilators. If cervix remains unfavorable after extraction of the dilators (< 3cm and at most 60% effaced) to provide induction of labor, the second round of Dilapan-S® will be used in this case for maximum of 12 hrs. If cervix remains unfavorable after extraction of second round of cervical dilator, only pharmacological cervical ripening may be provided. Neither Dilapan-S® or Foley will be used in this case. The agent and its total dose will be recorded into the data sheet.

Group assigned to receive Foley catheter:

Before the device placement, patients undergo continuous CTG monitoring for 20 minutes while fetal condition and uterine activity are monitored. The cervix is visualized with a sterile vaginal speculum and cleaned with iodine. A Foley catheter is introduced into the cervix and the balloon is filled with 60 ml of sterile 0.9% NaCl. The Foley catheter will be left in place for at least 12 hours, and no longer than 24 hours. Patient will be allowed to ambulate, shower and perform regular activity as long as a reactive and reassuring NST is documented after placement of device. Reasons for examining or removing Foley catheter earlier included: 1) Spontaneous onset of labor (defined as regular, firm, uterine contractions with an effaced cervix >80% and a cervical dilatation > 3 cm); 2) Category III fetal heart rate tracing; 3) Spontaneous rupture of membranes or amniotomy; 4) Spontaneous expulsion of Foley catheter. If cervix remains unfavorable after extraction of the dilators (< 3cm and at most 60% effaced) to provide induction of labor, a second round of Foley catheter will be used in this case for a maximum of 12 hrs. If cervix remains unfavorable after extraction of second round of cervical dilator, only pharmacological cervical ripening may be provided. Neither Dilapan-S® or Foley will be used in this case. The agent and its total dose will be recorded into the data sheet.

Induction of labor:

After expulsion or removal of synthetic osmotic dilators or Foley catheter, induction of labor using either oxytocin infusion or prostaglandins may be performed. Total dose of oxytocin and prostaglandins used will be documented. The oxytocin protocol used in our labor and delivery consists of: oxytocin infused intravenously through a controlled infusion pump at a proximal port on the peripheral IV line. Oxytocin is started at 2 milliunits/min and increased at a rate of 2 milliunits/min or less every 10 minutes until adequate contraction pattern is achieved. Initial maximum dose is 20 milliunits/min. Dose can be increased to 30 milliunits/min after faculty staff approval. Prostaglandins in practice in our facility include: Prepidil: dinoprostone 0.5 mg/3 g (2.5 mL gel), Misoprostol (buccal, sublingual or vaginal) 25 mcg tablets or Cervidil: dinoprostone 10 mg vaginal insert.

The study will be explained as in the consent form and if agreed, subjects will elect either to or not to participate in the study after all risks and benefits are explained. Data to be collected will consist of age gravida/para, gestational age, BMI, time of date of intervention, time date of delivery, mode of delivery, bishop score at admission, bishop score after 12 hrs. of intervention, time and date of rupture of membranes, vaginal delivery within 24 hrs., hospital length of stay, other intrapartum and obstetrical interventions, complications in labor and delivery including but not limited to infections, hemorrhage, fetal decelerations and subject satisfaction. Data will be abstracted from subjects medical records as well as from direct interview with the subject. We will also collect basic neonatal data including birth weight, Apgar scores, rate of admission to neonatal intensive care unit, infections, and other neonatal complications. If elected to participate consents will be obtained and stored in subject chart. A copy of the consent will be given to the subject. Subjects will be consented in either English or Spanish by research personnel familiar with the language. Randomization will be done at time of consents. The study's time frame inclusive will be from 2016 till 2018. Data will be analyzed as per intent to treat.

Sample Size Calculation
The sample size will be calculated for the non-inferiority test.
The significance level of the test is targeted at 0.025, one-sided.
The rate of overall vaginal delivery is 71% and 76% for Foley catheter and Dilapan-S® , respectively. Higher rates are better.
The non-inferiority margin is δ=10%. It is defined as the largest treatment difference of no clinical importance.
The treatment allocation ration will be 1:1.
The power of the non-inferiority test to be achieved is 90%.

Based on the above assumptions, the sample size would be 182 evaluable subjects in either treatment group, i.e. 364 evaluable subjects in total. Assuming that 13% of patients will not qualify for the primary analysis set
(due to protocol deviation or considered as drop-out of loss to follow up), 420 patients are to be enrolled into this study.

5. Sub-Study Procedures: Not applicable.

6. Criteria for Inclusion of Subjects:

- Pregnant woman scheduled for induction of labor
- Age between 18 and 45 years
- Understanding and capable to sign informed consent
- Singleton pregnancy
- Gestational age ≥ 37 $^{0}/_{7}$weeks
- Live fetus in cephalic presentation
- Intact membranes
- Pelvic exam (sterile vaginal exam) of less than or equal to 3cm and at most 60% effaced.

7. Criteria for Exclusion of Subjects:

- Iodine allergy
- Active labor or oxytocin has been administered
- Chorioamnionitis
- Prior uterine or cervical surgery
- Non reassuring fetal status requiring immediate delivery
- Non-cephalic fetal presentation
- Active vaginal bleeding from cervical os
- Placenta previa
- EFW > 5000 gm (non diabetic) or > 4500gm (diabetic)
- ♉Other contraindication to vaginal delivery

8. Sources of Research Material: Medical chart/records.

9. Recruitment Methods and Consenting Process: After institutional review approval, pregnant women scheduled for induction of labor will be approached by perinatal research division staff (PRDS) for participation in the study. Prospective subjects presenting for induction of labor in labor and delivery unit, and willing to participate in the study will be evaluated for their eligibility including their pelvic

exam. The latter will be obtained from the subject chart after the initial pelvic exam which is standard of care for these subjects in our unit. The study will be explained as in the consent form and if agreed, subjects will elect either to or not to participate in the study after all risks and benefits are explained. If willing to participate, written consent will be obtained and a copy placed in patient chart. A copy of the consent will be given to the subject. Subjects will be consented in either English or Spanish by research personnel familiar with the language. Randomization will be done after obtaining consent. Participants are randomly allocated to cervical ripening with either a synthetic Dilapan-S® or Foley catheter. The randomization sequence is created using a computer generated randomization scheme with 1:1 allocation for each arm of the study. The random allocation sequence is concealed from those responsible for recruiting participants into the study by keeping it in a file cabinet with access restricted to research staff. PRDS will disclosure the nature of the assignment only after patient´s consent.

10. Potential Risks:

a. Accidental release of confidential subject information
b. Vaginal bleeding during/after study device´s insertion
c. Subjective pain felt during insertion
d. Vaso-vagal reaction from manipulation of the cervix
e. Contamination of the device during insertion
f. Allergic reaction from hypersensitivity to the components
g. Rupture of membranes or uterine contractions as the feature of the onset of labor
h. Cervix laceration if study device inserted using an incorrect technique
i. Retraction of the device to the uterine cavity if inserted using an incorrect technique
j. Entrapment of the device if removed using an incorrect technique
k. Fragments of the device in the genital tract if removed using an incorrect technique

11. Subject Safety and Data Monitoring: We believe that this intervention confers minimal risk to the subject that participates in this study. One group will be randomized to our standard cervical mechanical dilator at our institution. Adverse events may include rupture of membranes, pain/discomfort, vaginal bleeding. Data will be monitored through chart review and the subject ID will be protected by de-identification. Data will be stored on a UTMB password-protected computer in a locked room.

12. Procedures to Maintain Confidentiality: Each subject will be assigned a study number with personally identifiable information deleted or removed. If needed, charts will be reviewed in the medical records area. Subjects' information will be de-identified and tagged with a number. Data will be collected and stored on a UTMB password-protected computer in a locked room.

13. Potential Benefits:

This study has the potential benefit to show that pre-induction cervical ripening with Dilapan-S® may increase the rate of overall vaginal deliveries as well as the rates of vaginal deliveries reached within 24 and 36 hours. Another benefit is that it may confirm the safety of Dilapan-S® use as compared to foley catheter cervical ripening. In addition, we believe that subject’s satisfaction may be improved, since Dilapan-S® can be placed as an outpatient, and may shorten hospital length of stay. Ultimately, this will reduce the health care costs associated with failed induction (cesarean delivery) and improve maternal neonatal early bonding. We hope that the results of this study will show that Dilapan-S® is a reasonable alternative to Foley catheter cervical ripening in the United States.

14. Biostatistics:
Completed questionnaires will be analyzed by the study coordinators as well as by the authorized persons of the sponsor. Data will be analyzed as per intent to treat. Statisticians will be masked to treatment assignment. Unmasking of group assignment will be done after analysis completion or post analysis. Statistical analysis of data will be performed by the Leading Clinical Research, s.r.o. Official Member of the Association of International CROs – AICROS, Jana Zajíce 216/29, 170 00 Prague 7, Czech Republic.

Analysis Populations
There will be 4 analysis populations, namely All Randomised Subjects, Safety, Intent-To-Treat (efficacy) and Per-Protocol (efficacy). Criteria for being a member of an analysis population are provided in this section. Study subject classification will be determined and documented after clinical completion of the study.
All study subject classifications, with reasons, will be discussed and agreed in a formal meeting which will be documented. All individuals responsible for determining final classifications will be blinded to treatment allocation. They will be given blind data listings and a list of all protocol violations to make the decision.

All Randomized Subjects (ARS)
The ARS is a set of subjects who entered the study and who were randomized. The ARS will be used for a summary of demographic and other baseline characteristics.

Intent –To-Treat (ITT) Population
It is a subset of all randomized subjects with the primary outcome available. ITT subjects will be analysed in accordance with their randomised study treatment (i.e. in the treatment group they were originally allocated, regardless of treatment actually received). The ITT population will be used:
-A premature withdrawal, except for those who dropped out due to an insufficient treatment effect;
-Missing primary variable value;
-Violation of one or more inclusion/exclusion criteria (ineligibility);
-Error in treatment assignment;
-Use of excluded medication;
-Use of Dilapan-S® or Foley catheter though contraindicated;
-The subject does not deliver during the hospitalization in the study center.

Per Protocol Population (PP)
The PP population is a subset of the ITT and includes all study subjects who:
-Actually used either Dilapan-S® or Foley catheter during their participation in the study;
-Did not experience any major protocol violations that would affect the endpoints being assessed.
The following protocol deviations may be considered major with the implication of data exclusion from the PP analysis population:
-A premature withdrawal, except for those who dropped out due to an insufficient treatment effect;
-Missing primary variable value;
-Violation of one or more inclusion/exclusion criteria (ineligibility);
-Error in treatment assignment;
-Use of excluded medication;
-Use of Dilapan-S® or Foley catheter though contraindicated;
-The subject does not deliver during the hospitalization in the study center.

These criteria will be updated and detailed in the SAP after the data review and before the clinical database has been frozen, without knowing the treatment assignment.

The PP population will be analysed according to their actual study treatment used (i.e. “as treated”). The PP population is the primary efficacy population.

Subject Disposition

All subjects screened and randomised will be accounted for. All post-randomisation discontinuations will be summarised by time of, and reason for, discontinuation. The number of subject screened and not randomised will be presented with the main reason for their non-inclusion.

The number of patients who were randomised will be reported. The patients with wrong assignment to treatment will be summarised by treatment and listed.

Patient Demographics and other Baseline Characteristics

Summary statistics of demographics, medical history, and other baseline characteristics will be presented by treatment group. The ARS population will be used.

Primary Efficacy Variable Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint is the rate of overall vaginal delivery.

Statistical Hypothesis, Model and Method of Analysis

The primary hypothesis testing consists of simultaneous/combined tests for non-inferiority and superiority - a useful strategy proposed for a confirmatory phase III clinical trials [1] and accepted by EMA in 2000 (CPMP/EWP/482/99, PtC on switching between superiority and non-inferiority), provided that the non-inferiority margin has been defined in advance in the study protocol.

Statistical inference involves testing the hypotheses regarding the difference in proportions with a vaginal delivery between the Dilapan group and the foley group. For the non-inferiority test, this can be expressed as HN0: $PD \leq PF - \delta$.

against the alternative HNA: $PD > PF - \delta$.

Where PD and PF denote population proportions for Dilapan and foley group, respectively, and $\delta>0$ is a non-inferiority margin. This type of test is called a test of non-inferiority.

If the purpose of the test is to prove the superiority of Dilapan to foley superiority, then

HS0: $PD \leq PF$

will be tested against the alternative

HSA: $PD > PF$

This setting generates the usual one-sided test of superiority.

These two tests can be performed simultaneously by employing the closed testing procedure (CTP) while controlling the overall type I error at the level α. In this special case, the resulting procedure is as follows:

1. First, the test of non-inferiority should be performed at the $\alpha=0.025$, one-sided. If HN0 is rejected, the test of superiority should be done at the $\alpha=0.025$, one-sided. Otherwise we can conclude that not even non-inferiority of Dilapan-S can be drawn.
2. In the test of superiority at the second step, if HS0 is rejected at the $\alpha=0.025$, one-sided, we should conclude that Dilapan-S is superior to the control. Otherwise non-inferiority can be concluded.

It can be shown that this testing procedure is equivalent to a (1-2α) 2-sided confidence interval (CI) approach. The CI approach will be used in accordance with ICH E9 recommendations. The 95% 2-sided CI for Dilapan-S – Foley catheter difference will be calculated. A decision will be made as follows:

1. If the 95% CI is completely on the right side to the zero point, it will be concluded that Dilapan is superior over foley.
2. Otherwise, if the 95% CI is completely on the right side to the non-inferiority margin, it will be concluded that Dilapan-S is non-inferior to Foley catheter.

3. Otherwise no conclusion will be drawn.

For the non-inferiority test, the PP analysis population is often chosen as the primary population. To control type I error at the pre-specified level, the same population should be used for the superiority test within the frame of the closed testing procedure. As a result, PP set will be used for both tests as the primary analysis population. However, to demonstrate robustness to the alternative choice, the primary endpoint will also be performed using the ITT analysis population. The ITT analysis for the primary efficacy endpoint will be used to support the primary analysis using the PP population.

Secondary Variables Analysis
Rate of vaginal deliveries within 24 hours, rate of vaginal deliveries within 36 hours, rate of spontaneous vaginal deliveries, rate of operative vaginal deliveries and rate of caesarean sections will be analysed using similar statistical methods as described above for the primary endpoint, except for the definition of the non-inferiority margin and for the non-inferiority test. The 95% 2-sided CIs will be calculated for the treatment differences.
Time to reach active stage of labour defined as ≥ 6 cm (mins) will be analysed using survival analysis methods. Detailed methodology including set-up of censored values will be described in the final SAP.
Change in Bishop score from baseline will be summarised by treatment group.
All rates above, time to reach active stage of labour and Bishop score are related to the secondary objectives and simultaneously, they are supportive measurements related to the primary objective.
Patient satisfaction associated with the device used for cervical ripening (Patient Satisfaction Survey, question No. 12) will be evaluated as a secondary objective. Counts and proportions in all categories will be presented by treatment group. The location shift in response categories between the two treatment groups will calculated and tested at the $\alpha = 0.05$ level of significance, two-sided.

Exploratory Variables Analysis
Exploratory variables will be summarised by treatment group.

Safety Variables Analysis
Safety variables will be summarised by treatment group.

Procedure for Accounting for Missing Data
Study subjects with missing primary variable will be evaluable neither for the ITT nor for the PPS population.
Missing primary variable data is expected to be very rare. If not, a different procedure may be refined in the SAP (e.g. a conservative imputation technique or sensitivity analyses) with the knowledge of the clinical data.

Procedure for Protocol Deviations
All protocol deviations will be listed by treatment group. Study subjects with a major protocol deviation will be excluded from the PPS analysis which makes demonstration of lack of sensitivity to protocol deviations possible (robustness).

Procedures for Deviations from the Original Statistical Plan
The SAP will contain more detailed description of the statistical analysis. If a need to change procedures of the analysis arises, an appropriate SAP update will be made. Major changes will require a protocol amendment.
Since the study is open-label, the risk of influencing the results has to be discussed in the report. A part of the final analysis will also be the originally planned analysis and its results will be provided in the report whenever technically possible. Every effort will be made to avoid such changes.

Particular attention will be paid to any differences between the planned analysis and the actual analysis as described in the protocol, protocol amendments or the updated statistical analysis plan based on a review of study data. Every effort will be made to avoid such deviations.