

The Acceptability of Misoprostol administered by sublingual, vaginal and rectal route for the induction of labor

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There has been much interest in recent years in using misoprostol to induce labor whenever there is a need for elective labor induction. Clinical trials have been carried out in this respect to evaluate the effectiveness of misoprostol, its most appropriate doses, as well as the maternal and perinatal morbidity associated with the use of different routes of administration of this drug for the induction of labor. However, there are few studies that in addition focus on women's acceptability and satisfaction/dissatisfaction with the use of misoprostol in its different viable routes of administration for the induction of labor. A search of the literature available through Medline reveals only four papers dealing with this subject, three of which were written by the same research group (Shetty et al. 2001, 2002a, 2002b) in England and another one by Hoffmann & Fawcus (2001) in South Africa. In these papers, women were requested to fill out a self-response questionnaire during the post-partum period, before being discharged from hospital. In all cases, "satisfaction" was high, above 80%, with the vaginal, oral and sublingual routes of administration. None of these papers defines what was considered as acceptability, although they conclude that the acceptability of labor induction was good, particularly when the oral route of administration was used.

Objectives

General Objectives:

To evaluate the acceptability of misoprostol, administered by the sublingual, vaginal or rectal route, in inducing labor in pregnant women hospitalized for labor induction at the Assis Chateaubriand Maternity Teaching Hospital of the Federal University of Ceará (MEAC-UFC), at the Sant'Ana Maternity Hospital of the Santa Casa de Misericórdia de

Sobral, Ceará and at the Institute for Maternal and Child Health Care of Pernambuco (IMIP), Recife, Pernambuco.

Specific Objectives:

To compare the satisfaction of expectant mothers with the administration of misoprostol by sublingual, vaginal or rectal route.

To describe the secondary effects of misoprostol administered sublingually, vaginally and rectally as perceived by the expectant mothers.

To determine the expectant mothers' preference regarding the route of administration of misoprostol and the reasons for this preference.

Subjects and Methods

Study Design:

A descriptive study was carried out as a module of the clinical trials “Induction of labor involving a live fetus with misoprostol sublingually or vaginally – a randomized and double-blind clinical trial” and “Comparison of rectal and vaginal misoprostol for the induction of labor in expectant mothers with premature rupture of membranes: a randomized clinical trial”.

Sample Size:

A hundred and one women accepted were admitted to this study. They had been hospitalized with an indication for the elective induction of labor and they were also admitted to the clinical trails mentioned above.

Subject Selection:

On the day following childbirth, each woman who had participated as a subject in one of the fore-mentioned clinical trials was invited to participate in this study. The subject's recruitment was generally done by a psychologists or a resident doctor who works in the participant hospitals.

Exclusion Criteria:

Women who were physically or emotionally unable to participate in the study were excluded.

Instruments for Data Collection:

A structured and pre-tested questionnaire containing pre-coded and open questions was used (see Attachment 1).

Data Collection and Processing:

A trained interviewer identified, on a daily basis, those women who were submitted to labor induction the previous day and who were subjects of one of the previously mentioned clinical trials. The women who agreed to participate in this study were interviewed immediately.

All completed questionnaires were photocopied: the copies are maintained at the sites at which the study took place, under the responsibility of the respective clinical trial investigator; the original documents were sent to Cemicamp for reviewing and filing. Data entry was carried out followed by verification of data bank consistency.

Data Analysis:

The frequency of the studied variables was presented for each one of the three groups (sublingual, vaginal; and rectal administration) according to specific objectives.

Ethical Aspects

The participation of women in this study was voluntary and all participants gave their signed, informed consent. When they were invited to participate in one of the clinical trials, they were informed that a short interview would be carried out the day following childbirth for the purpose of evaluating their opinion regarding the route of

administration of the medication used for labor induction. Attachment 2 contains the Informed Consent Form that was used in these clinical trials. This study adhered strictly to the Ethical Principles for Medical Research Involving Human Subjects laid down in the Declaration of Helsinki (WMA, 2000) and Resolution 196/96 of the Brazilian Ministry of Health (CONSELHO NACIONAL DE SAÚDE 1996).

Difficulties encountered during the implementation of the study

Data collection took far longer than estimated for several unexpected contingencies: a) a delay in the preparation of the placebo tablets for vaginal and sub-lingual use, specially manufactured for this study by Hebron Laboratories, which delayed the beginning of the clinical trails for several months; b) a strike in the participant hospitals that interrupted the clinical trails for additional two months; c) a serious disease of the father of the principal investigator of the clinical trials, which determines that she left all other commitments for several weeks at the end of the study period. As a consequence, the last 27 forms that were ready to be sent to Cemicamp were “lost” and we could recover them only on December 15, when we received copies by fax.

All the above factors contributed to leave us with only 48 hours for the transferring of the data to the bank and for their analysis. Consequently we can present only an initial analysis at this time. The final analysis of the women’s perception of side effects according to route of administration will not be possible, however, until the secret code of the clinical trial is broken and we will be able to know the route of administration of active misoprostol in the randomized, double blind comparison of vaginal versus sub-lingual misoprostol.

Results

The majority of participant women were 15-24 years old (62%), had 5 or more years of schooling (80%), one delivery (62%), and delivered the current newborn by the vaginal route (64%) (Table 1).

Table 1 – Participants distribution by socio-demographic and reproductive characteristics

| Characteristics | n | % |
|--|------------|-----------|
| Age (completed years)* | | |
| 15 to 19 | 29 | 29 |
| 20 to 24 | 33 | 33 |
| 25 to 29 | 20 | 20 |
| 30 or more | 18 | 18 |
| Scholarship (years)⁺ | | |
| None | 1 | 1 |
| 1 to 4 | 18 | 19 |
| 5 to 8 | 36 | 37 |
| 9 to 11 | 41 | 42 |
| 12 or more | 1 | 1 |
| Deliveries * | | |
| 1 | 62 | 62 |
| 2 to 3 | 27 | 27 |
| 4 or more | 11 | 11 |
| Actual labor route [#] | | |
| Vaginal | 59 | 64 |
| Caesarea | 33 | 36 |
| Total | 101 | |

* Missing information from one participant.

⁺ Missing information from four participants.

[#] Missing information from nine participants.

Only 9% of women were from the Rectal versus Vaginal Misoprostol Clinical Trial, and only 5% received misoprostol by rectal route; 95% of women received the tablets by vaginal route, and 91% by sublingual route also (Table 2).

Table 2 – Participants distribution by clinical trial they had participated and misoprostol administration route

| | n | % |
|--|------------|----------|
| Clinical trial | | |
| Misoprostol: Vaginal versus sublingual | 92 | 91 |
| Misoprostol: Rectal versus vaginal | 9 | 9 |
| Administration route * | | |
| Vaginal | 96 | 95 |
| Sublingual | 92 | 91 |
| Rectal | 5 | 5 |
| Total | 101 | |

* In the vaginal versus sublingual clinical trial all participants had received misoprostol by vaginal and also sublingual route, without knowing which was misoprostol and which one was placebo.

More than twice as many participants who received misoprostol by sub-lingual route were satisfied or very satisfied as compared with those who received the drug by the vagina; route (59% versus 26%). Accordingly, more than twice as many participants were unsatisfied or very unsatisfied with the vaginal than with the sub-lingual route (44 versus 17%) (Table 3).

Table 3 – Participants satisfaction with the misoprostol administration by vaginal or sub-lingual route *

| | Vaginal | | Sub-lingual | |
|--------------------------|---------|-----------|-------------|-----------|
| | n | % | n | % |
| They felt | | | | |
| Very satisfied | 4 | 4 | 14 | 16 |
| Satisfied | 21 | 22 | 38 | 43 |
| Indifferent | 28 | 30 | 21 | 24 |
| Unsatisfied | 22 | 23 | 11 | 13 |
| Very unsatisfied | 20 | 21 | 4 | 4 |
| Total[#] | 95 | | 88 | |

* It is not possible to know, by now, how many women who had misoprostol administrated by vaginal route had in fact received placebo because the clinical trial is double blind and it had not finished yet.

[#]Missing information from one participant on the vaginal route and from four participants on the sub-lingual route.

All the five women who received the tablets by rectal route referred they felt unsatisfied or very unsatisfied with this form of treatment (Table 4).

Table 4 – Participants satisfaction with the misoprostol administration by rectal route

| They felt | n | % |
|------------------|---|-----------|
| Very satisfied | 0 | 0 |
| Satisfied | 0 | 0 |
| Indifferent | 0 | 0 |
| Unsatisfied | 2 | 40 |
| Very unsatisfied | 3 | 60 |
| Total | 5 | |

Almost two thirds of the women who received the tablets both by vaginal and sublingual route referred secondary effects that they attributed to the misoprostol. The most frequently referred complaint was pain (89%). Two of four women who received misoprostol only by vaginal route, and two of five women who used the tablets by rectal route also referred they felt pain (Table 5).

Table 5 – Participants perception of the secondary effects according to the route they received misoprostol.

| Perceived secondary effects | They received misoprostol | | | | | |
|-----------------------------|--|-----------|-----------------------|------------|----------------------|------------|
| | By vaginal and sublingual route [*] | | Only by vaginal route | | Only by rectal route | |
| | n | % | n | % | n | % |
| Yes | 56 | 62 | 2 | 50 | 2 | 40 |
| Total | 91 | | 4 | | 5 | |
| What they felt | | | | | | |
| Pain | 49 | 89 | 2 | 100 | 2 | 100 |
| Other answers # | 12 | 22 | 0 | | 0 | |
| Total | 56 | | 2 | | 2 | |

^{*} Missing information from one participant.

Others included answers like: Vomit, nauseas, head pain, cramp, diarrhea, pain/ burning under the tongue.

Sublingual was the route of administration favored by most women: 66% of those who received the tablets both by vaginal and sublingual route, 3 of 4 women who received misoprostol only by vaginal route and 4 of 5 who received by rectal route (Table 6).

Table 6– Participants favored administration route according to the route they received misoprostol

| Favored administration route | They received misoprostol | | | | | |
|------------------------------|----------------------------------|-----------|-----------------------|-----------|----------------------|-----------|
| | By vaginal and sublingual route* | | Only by vaginal route | | Only by rectal route | |
| | n | % | n | % | n | % |
| Vaginal | 17 | 19 | 1 | 25 | 1 | 20 |
| Sublingual | 59 | 66 | 3 | 75 | 4 | 80 |
| Vaginal e Sublingual | 6 | 7 | 0 | | 0 | |
| Other | 7 | 8 | 0 | | 0 | |
| Rectal | 0 | | 0 | | 0 | |
| Total | 89 * | | 4 | | 5 | |

* Missing information from three participants.

Coherently, the majority of the participants said they would indicate sublingual route to another woman (Table 7).

Table 7 – Administration route that participants would indicate to another woman according to the route they received misoprostol

| They would indicate the route | They received misoprostol | | | | | |
|-------------------------------|----------------------------------|----|-----------------------|----|----------------------|----|
| | By vaginal and sublingual route* | | Only by vaginal route | | Only by rectal route | |
| | n | % | n | % | n | % |
| Vaginal | 18 | 21 | 1 | 25 | 1 | 20 |
| Sublingual | 62 | 71 | 3 | 75 | 4 | 80 |
| Vagina e Sublingual | 5 | 6 | 0 | | 0 | |
| Other | 2 | 2 | 0 | | 0 | |
| Rectal | 0 | | 0 | | 0 | |
| Total | 87 | | 4 | | 5 | |

* Missing information from four participants and one participant said she did not know which route she would indicate.

Conclusions

Women who received misoprostol by sublingual route referred to be satisfied or very satisfied more frequently than those who received the tablets by other routes of administration.

The few subjects who receive misoprostol by the rectal route were all unsatisfied with this route of administration.

Pain was the most frequent secondary effect of misoprostol mentioned by all participant women.

Sublingual was the route favored by the majority of the women in the sample..

References

Conselho Nacional de Saúde. Resolução nº 196, de 10 de outubro de 1996 do **Bioética** 1996; 4(2-supl.):15-25.

Hoffmann RAM. & Fawcus AS. Oral misoprostol vs. placebo in the management of prelabor rupture of membranes at term. **International Journal of Gynecology & Obstetrics** 2001; 72: 215-221.

Shetty A. & Danielian AT.; Templeton A. A comparison of oral and vaginal misoprostol tablets in induction of labour at term. **Br J of Obstet Gynaecol** 2001; 108: 238-243.

Shetty, A.; Mackie L.; Danielian P.; Rice P.; Templeton A. Sublingual compared with oral misoprostol in term labour induction: A randomized controlled trial. **Br J of Obstet Gynaecol** 2002; 109: 645-650.

Shetty, A.; Danielian P.; Templeton A. Sublingual misoprostol for the induction of labor at term. **Am J Obstet Gynecol** 2002; 186 (1):72-76.

WMA - World Medical Association. **Declaration of Helsinki**. Current version: 2002. Available at: <http://www.wma.net/e/policy/b3.htm> .

Annex 1 – Questionnaire



Cemicamp

Aceitabilidade do misoprostol na indução do parto

Nº |__|__|__|

ENTREVISTADORA: _____

DATA: __/__/__

LOCAL: |1| IMIP |2| MEAC |3| MATERNIDADE SANT'ANA

=====

OBSERVAÇÕES:

=====

1ª REVISÃO

NOME _____ RESULTADO _____ DATA _____

2ª REVISÃO

NOME _____ RESULTADO _____ DATA _____

3ª REVISÃO

NOME _____ RESULTADO _____ DATA _____

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DIGITAÇÃO

1ª VEZ

2ª VEZ

PRÉ-CODIFICADAS

TEXTUAIS

**INSTRUÇÃO PARA A ENTREVISTADORA
ANTES DE FALAR COM A MULHER ANOTE:**

1. USOU MISOPROSTOL

|1| VAGINAL
RETAL

|2| SUBLINGUAL

|3|

**DEPOIS, EXPLIQUE À MULHER: GOSTARIA DE CONVERSAR
COM A SENHORA SOBRE SUA EXPERIÊNCIA DE TER TIDO DE
INDUZIR O SEU PARTO**

2. Qual dessas figuras representa como a senhora se sentiu durante o tempo em que esteve induzindo o parto?



|1|



|2|



|3|



|4|



|5|

3. Quais as coisas que mais contribuíram para a senhora ter se sentido assim? (mais alguma coisa?)

INSTRUÇÃO PARA A ENTREVISTADORA

**EXPLIQUE À MULHER: A SENHORA SABE QUE FOI USADO UM
COMPRIMIDO PARA AJUDAR NA INDUÇÃO DO PARTO. AGORA EU
GOSTARIA DE SABER UM POUCO SOBRE SUA EXPERIÊNCIA DE
TER TIDO QUE USAR ESSE COMPRIMIDO**

4. Qual dessas figuras representa melhor como a senhora se sentiu usando o comprimido dentro da vagina?



|1|



|2|



|3|



|4|



|5|

5. Por que a senhora se sentiu assim?

ATENÇÃO, ENTREVISTADORA: ANOTE A RESPOSTA À PERGUNTA 1 E PROSSIGA COM O QUESTIONÁRIO CONFORME INDICADO

|1| P1 = 1 E 2 → SIGA COM A PERGUNTA 6

|2| P1 = 1 E 3 → PASSE À PERGUNTA 8

6. Qual dessas figuras representa melhor como a senhora se sentiu usando o comprimido embaixo da língua?



|1|



|2|



|3|



|4|



|5|

7. Por que a senhora se sentiu assim?

8. Qual dessas figuras representa melhor como a senhora se sentiu usando o comprimido dentro do ânus?



|1| |2| |3| |4| |5|

9. Por que a senhora se sentiu assim?

10. Durante o tempo em que esteve induzindo o parto, a senhora sentiu alguma coisa que acha que foi causada por esse comprimido que teve de usar?

|1| SIM
LEMBRA

|2| NÃO

|8| NÃO SABE/NÃO

PASSE À PERGUNTA 12

PASSE À PERGUNTA 12

11. O que a senhora sentiu?

12. Se a senhora precisasse usar esse comprimido outra vez, em outra gravidez, onde preferiria que ele fosse colocado?

|1| VAGINA

|3| NO ÂNUS

|2| EMBAIXO DA LÍNGUA

|4| EM OUTRO LUGAR. QUAL? _____

13. Por que preferiria esse lugar?

14. Se a senhora fosse recomendar para uma amiga que precisasse usar o mesmo comprimido, qual lugar diria para ela que é melhor?

|1| VAGINA

|3| NO ÂNUS

|2| EMBAIXO DA LÍNGUA

|4| EM OUTRO LUGAR. QUAL? _____

**ENTREVISTADORA, DIGA: PARA TERMINAR, QUERO FAZER
ALGUMAS PERGUNTAS SOBRE A SENHORA**

15. Qual a sua idade? |__|__| ANOS

16. Qual a última série (ano) que completou na escola?

_____ SÉRIE DO _____ |8| NÃO SABE/NÃO
LEMBRA

17. Quantos partos a senhora já teve, incluindo este? |__|__| PARTOS

**ENTREVISTADORA: ENCERRE A ENTREVISTA,
AGRADECENDO A COLABORAÇÃO DA MULHER**

Anexx 2 – Informed Consent Forms

**CONSENTIMENTO LIVRE E ESCLARECIDO PARA PESQUISA EM SERES
HUMANOS**

A – INDUÇÃO DO PARTO COM FETO VIVO COM MISOPROSTOL SUBLINGUAL OU VAGINAL – ENSAIO CLÍNICO, RANDOMIZADO E DUPLO-CEGO.

B – Pesquisador – Francisco Edson de Lucena Feitosa

C– Nome da Paciente - _____

Idade _____ RG _____ Pront. _____

D – Em virtude dos elevados índices de cesárea e dos maiores riscos que esta operação acarreta para a paciente, quando comparada ao parto normal, nos propomos a estudar um medicamento com o intuito de induzir o parto normal e diminuir as taxas de cesáreas conseqüentemente suas complicações.

E – A senhora será submetida a ecografia obstétrica abdominal e pela vagina, a exame para avaliar as batidas do coração do bebê e as contrações (cardiotocografia) e ao exame de toque. Estes procedimentos não acarretam riscos para sua saúde ou para a saúde do seu bebê.

F – Através da ecografia avaliaremos o peso do seu bebê aproximadamente e a quantidade do líquido amniótico. Através do toque saberemos como está o colo do seu útero.

G – Será administrado misoprostol por via sublingual e vaginal a cada 6 horas.

H – Este medicamento ocasionalmente pode ocasionar o surgimento de náuseas, vômitos e diarreia. Ele também aumenta a frequência e a intensidade das suas contrações. Ao participar da pesquisa a senhora estará submetida aos riscos inerentes ao trabalho de parto.

I – Após o início do medicamento o exame para avaliar as batidas do coração do bebê e as contrações será realizado a cada 2 horas em conjunto com o exame de toque. Para tanto, há necessidade que a senhora esteja internada no Hospital.

J – Depois que a senhora tiver tido o parto, vamos fazer algumas perguntas sobre como se sentiu usando o medicamento na vagina e embaixo da língua.

K- A sua participação deverá ser de livre e espontânea vontade.

L – A sua identificação será mantida em segredo e sua identificação não será exposta nas conclusões ou publicações.

M- Você poderá desistir de participar, a qualquer momento, sem qualquer prejuízo de sua assistência.

PESQUISA: MISOPROSTOL RETAL X VAGINAL PARA INDUÇÃO DO PARTO EM GESTANTES COM AMNIORREXE PREMATURA

Pesquisador responsável (IMIP): Dra. Melania Maria Ramos de Amorim

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Nome da paciente _____ **Idade**

Registro no IMIP _____ **RG** _____ **CPF**

Leia com atenção as seguintes proposições e assinie caso concorde em participar da pesquisa:

- ❖ Em virtude dos elevados índices de cesárea e dos maiores riscos que esta operação acarreta para a paciente, quando comparada ao parto normal, nos propomos a estudar um medicamento com o objetivo de induzir o parto normal e diminuir a taxas de cesárea e, conseqüentemente, suas complicações.
- ❖ A senhora será submetida a ultra-sonografia obstétrica para avaliar seu bebê, a um exame que avalia as batidas do coração do bebê e as contrações (cardiotocografia), bem como ao exame de toque. Estes procedimentos não acarretam riscos para sua saúde ou para a saúde do seu bebê.
- ❖ Depois destes exames, a senhora poderá vir a receber o medicamento que estudamos (MISOPROSTOL) por via retal ou vaginal. Esse medicamento já é utilizado há vários anos neste hospital em casos como o seu, mas sempre foi usado somente por via vaginal. Esta pesquisa se propõe a comparar o uso vaginal com o retal.
- ❖ Em qualquer das vias, o medicamento será administrado por toque, o toque vaginal com dois dedos e o retal com um dedo, a cada seis horas, até que a senhora comece a ter as contrações do trabalho de parto.
- ❖ Este medicamento ocasionalmente pode ocasionar o surgimento de náuseas, vômitos e diarreia. Ele também aumenta a frequência e a intensidade das suas contrações. Algumas vezes essas contrações podem ser muito frequentes e pode haver necessidade de uso de remédios para diminuí-las.
- ❖ Existem casos descritos na literatura de ruptura do útero, hemorragia e até morte materna depois do uso de misoprostol, porém em doses bem mais altas do que as usadas neste estudo. Esses efeitos não foram relatados com doses baixas, como 25mcg, que será a dose recebida pela senhora.

- ❖ Após o início do medicamento o exame para avaliar as batidas do coração do bebê e as contrações será realizado a cada duas horas, junto com o exame de toque. Para tanto, há necessidade que a senhora esteja internada no Hospital.
- ❖ Depois que a senhora tiver tido o parto vamos fazer algumas perguntas sobre como se sentiu usando o medicamento na vagina ou por via retal.
- ❖ A sua participação deverá ser de livre e espontânea vontade.
- ❖ Caso recuse participar do estudo, não haverá nenhum prejuízo para a senhora, que continuará sendo atendida neste hospital da mesma forma, passando a receber o tratamento padrão para o seu caso, que é o misoprostol por via vaginal.
- ❖ A sua identificação será mantida em segredo e sua identificação não será exposta nas conclusões ou publicações.
- ❖ A senhora poderá desistir de participar, a qualquer momento, sem qualquer prejuízo de sua assistência, passando a receber o tratamento padrão (misoprostol vaginal).
- ❖ Será permitido o acesso às informações sobre procedimentos relacionados à pesquisa.
- ❖ Somente após devidamente esclarecida e ter entendido o que foi explicado, deverá assinar este documento, caracterizando a sua autorização para participar da pesquisa.
- ❖ A senhora terá direito a tratamento médico custeado pelo órgão financiador em casos de danos que o justifiquem, diretamente causados pela pesquisa.
- ❖ Os gastos adicionais, se houver, serão cobertos pelo orçamento da pesquisa.
- ❖ Em caso de dúvidas, poderá comunicar-se com a pesquisadora responsável, Dra. Melania Maria Ramos de Amorim, no próprio IMIP, ou pelo telefone 9143-3078.
- ❖ O Comitê de Ética em Pesquisa do IMIP também se encontra à sua disposição para esclarecer qualquer dúvida.

Recife, _____ de _____ de _____

Paciente

Entrevistador responsável