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Comparison of Interlukin-10, Tumor Necrosis Factor-α and Complement-3 Levels among Bangladeshi Pregnant Women with or without Hepatitis E Virus Infection

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Abstract

Background: Several plasma proteins are proposed as biomarkers for acute HEV infected patients, but have not been validated among pregnant Bangladeshi women infected with HEV. **Objective:** In this present study, levels of interlukin-10 (IL-10), tumor necrosis factor α (TNF-α) and complement-3 (C3) were measured among HEV infected pregnant women and were compared with pregnant and HEV infected women. **Methodology:** This comparative cross-sectional study was conducted among the pregnant women who were admitted to the Department of Medicine, Department of Obstetrics & Gynecology, and Department of Hepatology of Dhaka Medical College Hospital (DMCH) and Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh for 1 year period. The study population included acute HEV infected pregnant women (HEV-P), healthy pregnant women (HPC) and HEV-infected non-pregnant women (HEV-NP) of the same age group. Interlukin-10 (IL-10), Tumor necrosis factor α (TNF-α) and complement 3(C3) levels were quantified by enzyme linked immunosorbent assay (ELISA) and turbidometry, respectively. **Result:** A total number of 81 women were recruited for this study of which 31 cases were acute HEV infected pregnant women (HEV-P); 25 cases were healthy pregnant women (HPC) and 25 cases were HEV infected non-pregnant women (HEV-NP) of the same age group. The mean levels with SD of the C3 level showed significant difference (P; 0.05) between groups of HEV-P (67.73±38.24 mg/dl), HEV-NP (147.9±22.28 mg/dl) and HPC (182.6±17.49 mg/dl). Though plasma TNF-α did not show any significant change (P; .05) in any of the groups, the IL-10 level was elevated significantly (p; 0.05) in HEV infected pregnant patients (0.187±0.3 ng/ml) then the non-pregnant HEV patients (0.027 + .08 ng/ml) and pregnant women group (0.012±0.04 ng/ml). **Conclusion:** In conclusion, increased levels of C3 and IL-10 observed in HEV infected pregnant women. *[Journal of National Institute of Neurosciences Bangladesh, July 2022;8(2):157-161]*

Keywords: Safety and efficacy; misoprostol; clinical management; early pregnancy loss

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Introduction

The using of misoprostol as an alternative to surgery is highly acceptable and instead of aspiration in outpatient setting reduces the cost of services[1-4]. Medical evacuation by using misoprostol is a simple, non invasive method and may be preferred by women[5]. It may be a treatment option where there is lack of skilled personnel or no access to surgical intervention.

Chemically misoprostol is a synthetic prostaglandin E1 (PGE1) analogue. Formula of misoprostol is C22H38)53 systematic (IUPAC) name is methyl 7-{3 Hydroxy-2-[(E)-4-hydroxy-4-nethyloet-1-enyl]-5 oxocyclo pentyl} hepatanoate. Regarding pharmacokiretic properties it is extensively absorbed, de-esterified to misoprostol acid, then to prostaglandin F analogue its half life is 20-40 minutes and excreted mainly through renal system (80%) and also through fecal route (15%)[6]. It can be administered oral, vaginal, sublingual and per rectal route[7]. Other studies showed that vaginal application of misoprostol increase the success rate and reduces the side effects[8,9,10]. It is a drug that is FDA approved in the United States for the prevention of NSAID induced gastric ulcers. It is also used (and approved in other countries) to induce labour and as an abortificient[11]. There are also other medical measure to manage early pregnancy loss such as misoprostol with methotrexate or mifepriston. The lowest effective dose of misoprostol for each condition for which it is used not yet clear and the dose differs in different categories of pregnancy loss[12,13].

There are some side effects of misoprostol, such as abdominal cramping and per vaginal bleeding they are also hallmark of abortion process itself. Many women report cramps and abdominal pain similar to those associated with heavy menstrual period. Vaginal bleeding can vary significantly in both duration and severity. Other side effects include nausea, vomiting, diarrhoea, dizziness headache, fever, chills, rashes and pelvic pain. In most cases, side effects and pelvic pain can be managed with oral analgesics.

That's why the main aim of this study is to evaluate the efficacy, safety and acceptability of the treatment with misoprostol in cases of early pregnancy losses and ultimately to reduce the maternal mortality and morbidity from unsafe abortions. The purpose of the present study was to see safety and efficacy of misoprostol for the management of early pregnancy loss.

Methodology

Study Settings and Population: This was a non-randomized clinical trial. This present study was conducted in the Department of Obstetrics and Gynaecology in Shaheed Ziaur Rahman Medical College Hospital, Bogra, Bangladesh from January 2007 to December 2007 for a period of 12 months. Women with early pregnancy loss who were fulfilling the selection criteria were selected as the study population during the study period. Women presented with the missed abortion of ≤12 weeks of gestation, women with the incomplete abortion of ≤12 weeks of gestation with minimum per vaginal bleeding and anembryomic gestation were included in this study. Women with incomplete abortion or missed abortion of more than 12 weeks of gestation or threatened abortion or history of medical disorders, like cardiac, respiratory renal, hepatic or adrenal disease. H/O thromboembolism, hypertension, coagulopathy, pregnant women with fibroid uterus o incomplete abortion with excessive per vaginal bleeding and anaemic patient with the haemoglobin level of 8 gram/dL were excluded from this study. Womefirimester pregnancy loss were randomly assigned to give treatment with misoprostol. Gestational age was measured from Day 1 of last menstruation according to menstrual history and transabdominal ultrasonogrophy. Medical history was taken and a physical examination was performed. A baseline blood sample was obtained for Hb%, blood sugar, blood for ABO grouping and Rh typing.

Allocation: On admission in hospital all women fulfilling the selection criteria were received a vaginal administration of 800 μg misoprostol by digital insertion into the posterior fornix through a speculum (4 tablets of 200 μg misoprostol). The interval between administration of misoprostol and expulsion of product of conception were recorded. If expulsion of product of conception occurred, after 48 hours of application of 1st does of misoprostol a transabdominal ultrasonography were done to see the completeness of expulsion of product of conception. If complete expulsion occur they were discharged from the hospital. If complete expulsion does not occur after given of 1st dose of misoprostol within 24 hours then 2nd dose of 800 g of misoprostol were given per vaginally in the same manner. Then they were discharged from the hospital.

Follow up and Outcomes Measure: After 7 days (8th day) they were instructed to come to the hospital to see the completeness of expulsion of product of conception by ultrasonography. If sonography shows incomplete expulsion then surgical evacuation was done. Every woman were advised to come for follow-up on 15th day. Then they were complete a questionnaire about the duration and intensity of bleeding, intensity of pain and other side effects of the treatment like fever, diarrhoea, headache etc. ultimately to the acceptability of the treatment. Misoprostol treatment were consider failed if there were persistent abnormal vaginal bleeding and sign of retained product of conception by sonography if endometerial thickness less than 20 mm it was regarded as complete evacuation. All the relevant information for each of the study subjects were recorded in predesigned

data collection sheet.

Statistical Analysis: Data were analyzed using computer based programme statistical package for social science (SPSS) for windows version 12. The written informed consent was obtained from all patients were enable to respond or attendants unable to respond.

Results

A total of 200 women with first trimester pregnancy loss were randomly assigned to give treatment with misoprostol. Most of the women belonged to age group 20 to 25 years (55.0%). The mean with the SD of the study population was 24.95±4.17 years (Table 1).

Table 1: Demography of the Study Population

Age group	Frequency	Percent
15 to 20 Years	55	27.5
20 to 25 Years	110	55
25 to 30 Years	20	10
30 to 35 Years	15	7.5
Total	200	**100.0**
Mean±SD	24.95±4.17	

In most cases expulsion occurs within 24 hours of application of misoprostol, 142(71.0%) complete expulsion within 48 hours, 168(84.0%) cases within 7 days, 170 cases out of 200 cases (85.0%) complete expulsion occurred (Table 2).

Table 2: Length of Time between Insertion of Misoprostol and Expulsion of Product of Conception

Time	Frequency	Percent
Less than 6 hours	20	10.0
6 to 12 hours	100	50.0
12 to 24 hours	142	71.0
24 to 48 hours	168	84.0
48 to 168 hours (7 days)	170	85.0

Complete evacuation after the first dose was in 142(71%) cases and remained incomplete was 58(29%) cases. After administration of the second dose (85%) complete evacuation occurred and 30(15%) cases remained complete that needed surgical evacuation. Analysis was reveled statistically significant ($P < 0.05$) (Table 3).

Vaginal misoprostol treatment appeared to be well tolerated. Only few percent shows mild side effects (Table 4).

About 190(95.0%) cases required no blood transfusion (Table 5).

Table 3: Expulsion Following Insertion of Misoprostol

Types of Expulsion	Frequency	Percent	P value
Complete evacuation after 1st dose (n=200)	142	71	
Incomplete evacuation after 1st dose (n=200)	58	29	0.001
Complete evacuation after 2nd dose (n=58)	28	85	
Incomplete evacuation after 2nd dose (n=58)	30	15	0.001
Need surgical evacuation (n=200)	30	15	

Table 4: Adverse Events reported by the Patients

Adverse Events	Frequency	Percent
Nausea	12	6.0
Vomiting	4	2.0
Diarrhoea	4	2.0
Fever	8	4.0
Headache	2	1.0
Hot flushes	2	1.0
Dizziness	1	0.05

Table 5: Status of Blood Transfusion

Blood Transfusion	Frequency	Percent
Required	10	5.0
Not Required	190	95.0
Total	**200**	**100.0**

Discussion

Misoprostol has selected in this study as it is cheap, stable at room temperature, easy to transport, does not require refrigeration and readily available in most areas of the country. It interacts with prostaglandin receptors, cause the cervix to soften and the uterus to contact, resulting in the expulsion of the uterine content[14].

In Bangladesh, many women go for and suffer from the complication of clandestine of induced abortion. These are very vulnerable to short and long-term morbidities. These morbidities are in the form of haemorrhage, infection and physical damage to reproductive organ[15]. It has been estimated that 13% of all maternal death worldwide are due to unsafe abortions[16].

This study indicates that treatment of early pregnancy loss with 800µg of misoprostol vaginally the dose repeated after 24 hours when necessary is efficacious. The success rate by day 15 was 85.0%. The risk of haemorrhage and pelvic infection were very low and the side effects were tolerable. In study of Zhang et al[22] showed treatment of early pregnancy failure 800µg of

misoprostol vaginally with the dose repeated after 48 hours, the success rate by day 30 was 84.0% cases.

Zalanyi[23] treated 25 women with missed abortion at less than 13 week gestational using 200 µg of intravaginal misoprostol at every 4 hour for a total 4 doses and the study reported 88.0% success rate after the third dose and no further success after the fourth. Absence of echogenic structures more than 15 mm in anteroposterior diameter in transvaginal ultrasound is used as a criterion for success. Greinin et al[24] showed 88.0% success rate in treating early missed abortion with vaginal misoprostol (800µg), in two doses 24 hours apart. They used the absence of an intrauterine gestational sac as a criterion for complete evacuation.

Begum et al[25] and Herabutya et al[26] showed 94.0% and 83.3% success rate respectively in treating missed abortion at or below 14 weeks gestation with intravaginal misoprostol, 400µg 6 hourly with maximum 3 doses. Complete expulsion and cervical dilatation with protrusion of product of conception at cervical os are used as the criteria for success. The present study using the 800µg of misoprostol vaginally 24 hours apart 85.0% success rate by day 15 and the criterion for complete expulsion was same but here ultrasound were done transabdominally instead of transvaginally.

The advantage of the regimen of the present study require fewer vaginally application of drug; it avoid considerable number of operations and when complete expulsion dose not occur it usually provides adequate cervical dilation making surgical evacuation easy and less complicated; duration of hospital stay is less.

No significant side effect were observed in the various studies described above[23-26]. About 1.0% to 6.0% of women developed intense bleeding and only 5.0% required blood transfusion. Misoprostol treatment was acceptable to most women. We found that women with incomplete or inevitable spontaneous abortion were more likely to have complete expulsion after one dose of misoporstol than were women with embryonic or fetal death or women with an anembryonic gestation. However by using a second dose, if expulsion is incomplete, a similarly high success rate.

It was waited 24 hours between doses in an attempt to allow sufficient time for the initial dose to be effective. The majority of the women in this study reported satisfaction with this approach. In our study almost all women with an endometrial thickness of less than 20 mm by ultrasonography after misoprostol treatment completed expulsion uneventfully. It is not known whether 800µg of misoprostol represents the lowest effective dose for all subtypes of early pregnancy loss.

Another observation in this study were the additional benefits of using misoprostol treatment which were not completely successful. All the patient who needed surgical evacuation had soft and dilated cervix at the time of surgical evacuation, which reduced the risk of perforation & cervical injury. From this study it is anticipated that medical management of early pregnancy loss with vaginal misoprostol will prove to be a good.

The result of this study should be combined with the results of future studies to provide more precise estimates on the subject. Furthermore, research on optimal dose findings in order to increase evacuation rates for misoprostol treatment are warranted. This trial involved a 15 days follow up period. The vast majority of patients recovered satisfactorily within this period (85%). But a small number required surgical evacuation even after 2 weeks. In some patients tissue was often seen in internal os who came for follow up visit, it was removed in many cases with sponge-holding forceps without further treatment.

This study included women presented with incomplete abortion, inevitable abortion, missed abortion, anembryonic gestation less than 12 weeks, size. In addition women who were having active heavy bleeding when they presented to the hospital were ineligible. Since they had a medical indication for emergency vacuum aspiration. We studied only vaginal administration of misoprostol. Previous randomized trials have indicated that efficacy of misoprostol is similar whether it is administered vaginally or orally, whereas the incidence of nausea, vomiting and diarrhoea was higher when the agent was administered orally alternative to surgical evacuation.

Conclusion

In conclusion, the efficacy of misoprostol for the management of early pregnancy loss gives a good results with minimum adverse events. As this was a small study, conducted only a very small number of cases, the study may not reflect the real picture. A large-scale study is needed to be performed to find out the best route, dose and frequency of using this drug for complete expulsion of product of conception of early pregnancy loss with safety. If the dose is increased, the number of cases of complete expulsion may be increased, but at the same time side effects may develop.

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