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COMBINATION OF MIFEPRISTONE AND MISOPROSTOL VERSUS MISOPROSTOL ALONE IN INDUCTION OF LABOR IN INTRAUTERINE FETAL DEATH: A PROSPECTIVE INTERVENTIONAL STUDY

Obstetrics & Gynaecology

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ABSTRACT

Introduction: Impact and outcomes Intra uterine fetal death varies widely between developing and developed nations. But impact is more evident in developing nations due to health care infrastructure availability, utilization & variations in patient provider perspectives. Promptness in decision making between initiating induction & waiting for expectant management post IUFD is vital in preventing mother from facing physiological & psychological trauma.

Objectives: Without standard guidelines for best mode of action post IUFD with multiple differences of opinions among scholars. In this study we evaluated safety, tolerance and efficacy of combination regimen of mifepristone and misoprostol with conventional use of misoprostol alone in a tertiary care hospital in India.

Methodology: Study was conducted in Department of Obstetrics and Gynecology at IMS&SUM Hospital, Bhubaneswar for 2 years between august 2018-2020. Group A received Tab. Misoprotol vaginally; Group B received Tab. Mifepristone 200mg orally followed by Tab. Misoprostol vaginally after 24hrs and the efficacy of drugs were assesd in IUFD patients.

Results: The Mean age in both groups was approximately 28 years; with higher propotion of primigravida (68%) in both groups. There were significant difference between groups with regard to Induction delivery interval, Group B had lesser time 13.6 (±6.5) hours for delivery compared to the other Group A 18.8(±10.1hrs). (P value = 0.03). Primigravidas in both groups, Group B had with a short duration of induction 14.8 (±7.2) hrs however difference was not significant (P value = 0.09).

Conclusion: From results we could conclude that, Induction delivery interval was significantly shorter in combined regimen and the association was more in primigravida than multigravida. The combination of mifepristone and misoprostol is a safe and effective method for labor induction following IUFD resulting in shorter delivery interval with lesser side effects.

KEYWORDS

Intra uterine fetal death (IUFD), Induction, Mifepristone, Misoprostol

INTRODUCTION

Intra uterine fetal death (IUFD) affects the mother both physically and psychologically and entire family psychologically. In 2004 World Health Organization (WHO) defined IUFD as death prior to complete expulsion or extraction of a product of human conception from its mother, irrespective of duration of pregnancy and which is not an induced termination of pregnancy.(WHO,2004) Currently WHO defines IUFD as all fetal deaths weighing 500gm or more occurring both during pregnancy (ante partum death) or during labor (intra partum death) (MacDorman MF, 2012).As definitions evolves constantly WHO defines IUFD as a baby born with no signs of life at or after 28 weeks of gestation for international comparison.(WHO, Maternal, newborn, child and adolescent health, 2016) Globally out of 2.6 million stillbirths in 2015 with a Still Birth Rate (SBR) of 18·4 per 1000 births, the majority occurred in the developing compared to developed Nations. India contributed highest for stillbirths.(Blencowe H, 2016)

Following an IUFD one can wait for spontaneous delivery or expectant management to avoid impending psychological and clinical complications that is when the need for induction arises. (WHO, Maternal, newborn, child and adolescent health, 2016). Usually spontaneous delivery ensues in 80-90% cases within 2 weeks of IUFD. (Silver TM, 2007)(RCOG, 2010)(Cabrol D, 1985) Induction of labor is defined as the process of artificially stimulating the uterus to start labor. (WHO, Managing complication in pregnancy and childbirth: a guide for midwives and doctors, 2000)

In developed nations, the proportion of infants delivered at term following induction of labor can be as high as one in four deliveries (Caughey AB, 2009) (Declercq ER, 2006) (Martin JA, 2007) Complete contrast scenario is in African nations as per unpublished data from WHO Global Survey involving 24 countries on Maternal and Perinatal Health (WHO, Global Survey on Maternal and Perinatal Health. Induction of labour data, 2010)

Globally situation varies depending on various perspectives from patients (shorten the duration of pregnancy or to fix time the birth of the baby), Health works workers (Convenience) & available health-care resources & infrastructure in the settings (Mozurkewich E, 2009) (NICE, 2008).

Though induction was described in Sao Paulo, Brazil in 1987 there are no standardized guidelines available for its application till date. Clinicians judge waiting for spontaneous labor to be of greater risk than shortening the duration of pregnancy with induction.

The IUFD itself does not constitute an indication for cesarean section (Mulher, 2000) therefore surgery should be reserved for specific conditions because of increased maternal morbidity without any fetal advantage. (ACOG, 2009) In the absence of emergency, priority must be labor induction with medicine and finishing the pregnancy through the vaginal route (Silver RM, 2010) Deciding for the surgical induction depends fetal and obstetric conditions taking psychological impact on the mother into consideration (Habek D, 2008) (Steel A, 2009).

Royal College of obstetricians & Gynecologists (RCOG) in its Green-top Guideline No. 55 recommends a combination of drugs for IUFD which is also endorsed by the National Institute for health and care excellence(NICE) guidelines (Silver TM, 2007) (Cabrol D, 1985) Whereas WHO recommends single drug usage. There is lack of uniformity in use of misoprostol in specific trimesters and route of administration, taking side effects too into consideration (Eng N, 1997) (Jain J, 1996) Nevertheless, the current evidence has concluded that the most appropriate route of administration is vaginal (Wagaarachchi PT, 2002).

Hence the ideal drug for the termination of pregnancy in cases of IUFD should not only be effective and safe, but also cost effective. With this base Knowledge we aimed to evaluate safety, tolerance and efficacy of combination regimen against conventional single drug for IUFD Induction.

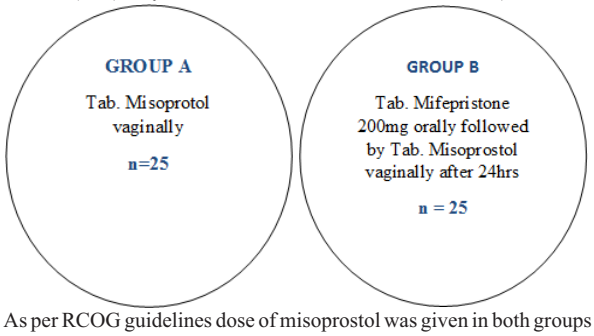
AIMS & OBJECTIVES

Aim of my study is to evaluate safety, tolerance and efficacy of combination regimen of mifepristone and misoprostol with conventional use of misoprostol alone.

MATERIALS & METHODS

This Prospective interventional study was conducted in Department of Obstetrics and Gynecology at a Tertiary care hospital, IMS&SUM Hospital, Bhubaneswar for 2 years between august 2018-2020. Purposive and consecutive sampling was adopted among patients with IUFD as study involved single investigator without specific sample size calculation. Proper randomization was not executed for the same reasons. Hence the principle investigator provided Tab. Mifepristone 200mg orally followed by Tab. Misoprostol vaginally after 24hrs and others administered Tab. Misoprostol vaginally for two years. At the end of two years 25 from each group was taken for analysis. All Women with IUFD attending outpatient department, Gravid up to 4 during study period, >24 week period of gestation**,** Not in labor (no regular contractions or unfavorable cervix) **&** willing for medical management were taken as study participants. Patients with allergy to prostaglandins, asthma, glaucoma, multiple gestation and previous uterine scar were excluded.

After getting written informed consent explaining the purpose of study, a detailed patient history and examination was performed and diagnosis of IUFD was confirmed by ultrasonography based on absence of cardiac activity. A pre tested semi structured questionnaire was used to collect data. Details regarding Demographic data (socioeconomic status by B G Prasad scale), clinical characteristics, presence of any medical illness (Hypertension (HTN), Diabetes Miletus (DM), Thyroid disease, Connective tissue disorders).



As per RCOG guidelines dose of misoprostol was given in both groups as follows. Routine investigations & procedures for mother was done, in addition Bishop score was assesed before induction.

Descriptive details were represented as Proportion, Mean & Standarad Deviaton. Inferential analysis was done using independent T test, chi square & Mcnemar Test. P value < 0.05 was considered significant. The data was entered in excel sheet (version 13) and subjected to statistical analysis using SPSS software(version 20)with help of Department of Community Medicine of the same institute. The study got approval from Institutional ethical committee.

RESULTS

In this study over 2 years, Fifty (N=50) participants with IUFD were included. The comparison with regard to patient's characteristics was done in both Group A (n=25) & B (n=25) socially and clinically, as it's a comparative study. Similarity was found in patient's characteristics with respect to Age, Parity, Period of gestation, along with amount of drug used (Syntocinon & Misoprostol) across the groups when expressed categorically as in Table 1. Mean age of the participants was approximately 28 years; similarly proportion of primigravida (68%) was higher in both groups compared to multigravida as shown in Table 2.

Table 1: Comparison Of Characteristics Categorically Among Study Participants In Group A & Group B.

Characteristics	GROUP A	GROUP B	χ= Chisquare	P value
	Misoprostol only	Mifepristone & Misoprostol		
Age group n (%)				
<20 years	0	1(04%)	χ =2.37	P= 0.66
20 – 25 years	9 (36%)	8 (32%)		
26 – 30 years	7 (28%)	9 (36%)		
31 – 35 years	8 (32%)	7 (28%)		
36 – 40 years	1 (04%)	0		
Parity n (%)				
G1	17 (68%)	17 (68%)	χ =1.03	P= 0.79
G2	03(12%)	05 (20%)		
G3	02(08%)	01 (04%)		
G4	03 (12%)	02 (08%)		
Total	25 (100%)	25 (100%)		
Gestational period in week's n (%)				
Up to 24 weeks	0	1 (04%)	χ =1.85	P= 0.76
25- 28 weeks	5 (20%)	3 (12%)		
29 – 32 weeks	6 (24%)	6 (24%)		
33 – 36 weeks	6 (24%)	8 (32%)		
37 – 40 weeks	8 (32%)	7 (28%)		
Risk factors n (%)				
Hypertensive Disorders	7 (28%)	9 (36%)	χ =5.63	0.77
Diabetes	3 (12%)	1 (04%)		
Congenital anomalies	1 (04%)	2 (08%)		
Oligohydromnios	2 (08%)	2 (08%)		
Burns	2 (08%)	1 (04%)		
Hypothyroid	5 (20%)	2 (08%)		
Eclampsia	1 (04%)	0		
Anemia	3(12%)	2 (08%)		
Rh negative	0	1 (04%)		
Breech	0	2 (08%)		
VDRL Positive	0	1 (04%)		
Complication n (%)				
Fever	02 (08%)	01 (04%)	χ = 2.75	0.58
Nausea/vomiting	01 (04%)	01 (04%)		
Diarrhoea	01 (04%)	0		
Retained placenta	01 (04%)	01 (04%)		
Fever Severe Bleeding/ Uterine rupture	0	0		
Syntocinon n (%)				
Provided	10 (40%)	13 (52%)	χ =0.72	0.39
Not Provided	15 (60%)	12 (48%)		
Number of doses of Misoprostol Doses n (%)				
One	02 (08%)	08 (32%)	χ =2.75	0.58
Two	10 (40%)	09 (36%)		
Three	06 (24%)	06 (24%)		
Four	04 (16%)	01 (04%)		
More than five	03 (12%)	01 (04%)		

P value <0.05 is considered Significant.

As per the main objective we tried to assess the tolerance to drugs among both groups. Chi square test was applied and there was significant difference between two groups with regard to the following characteristics, Induction delivery interval & Hemoglobin (Hb) concentration.

Table 2: Comparison of social and clinical characteristics as continuous variable among participants in Group A & Group B

Characteristics		Group A Misoprostol n=25 Mean (SD)	Group B Mifepristone Misoprostol n=25 Mean (SD)	P Value
Age(years)		28.7(±4.7)	27.3(±4.5)	0.30
POG		33.7(±4.6)	33.6(±4.6)	0.45
BMI		23.14(±1.3)	23.55(±3.1)	0.54
Hb(gm/dl)		11.68(±1.2)	11(±1.2)	0.03*
Baby weight(grams)		1696.2(±923.5)	1628.4(±890.4)	0.39
Bishop score		3.8(±1.8)	3.6(±1.2)	0.62
Induction delivery interval(hours)		18.8(±10.1)	13.6(±6.5)	0.01*
Induction delivery time VS Gravida				
Primi gravida	n=17	20.5(±11.3)	14.8(±7.2)	0.09
Multigravida	n=8	15.3(±6.2)	11.1(±3.8)	0.12

P value* < 0.05 is considered Significant

As shown in Table 2, It was found that Group B which received combination regimen had lesser time 13.6 (±6.5) hours for delivery since induction compared to the other group(A) whose mean duration was 18.8(±10.1) hours and the difference was statistically significant (P value = 0.01). There was also significant difference based on Hemoglobin (Hb) concentration (P value = 0.03). Similarly the drug combination in group B had better and tolerance effectiveness among

primigravida with a short duration of induction 14.8 (±7.2) as compared to other group but difference was not found significant statistically (P value = 0.09).

DISCUSSION:

Several induction methods following late IUFD have been described. A variety of routes of administration of prostaglandin analogues including PGE_2 and PGF_2 have been used with success. (Meckstroth KR, 2006) (El-Refaey H, 1995) Studies have confirmed the benefits of misprostol and combinations with mifeprestone in second and first trimesters with mifeprestone respectively. (Scher J, 1980) (Filshie GM, 1971) However, there are limited studies using a combined regimen for induction of labor in IUFD. In this study no new regimen was designed specifically, we tried to compare those already described in the literature and tried to capture how well these published regimens perform in India among women undergoing induction for IUFD.

Age in Years

Patients belonged to age group of 19 to 40 years, majority of the patients were of 20-25years (68%). Mean age in Group A, B was 28.72 years 27.36years respectively. Similar age distribution was in other studies (Cabrol D e. a., 1990) (Urquhart DR, 1990)

Parity

There was a uniform distribution of primigravida and multigravida patients in both the groups, however most were primigravida. Similar representation was in study with tenfold higher participant's (Ashok PW, 1999)

Gestational age

The mean gestational age in Group A and B was 33.76 weeks, 33.60 weeks. However lower mean gestational age was found in studies which could be attributed to very early induction (Cabrol D e. a., 1990) (Ashok PW, 1999)

Side effects:

In Group A and Group B, 84%, 92% of patients had nil side effects. However abdominal cramps, nausea, vomiting, diarrhea was the utmost side effects occurred in both groups. Side effects were similar in other studies (Natthinee Prachasilpchai, 2006)

(Paul A. le Roux, 2001)(Fairley, 2005)(Wagaarachchi PT A. P., 2002)

Based on drug dosage the mean induction to delivery interval was relatively shorter with increased dosage (7 hrs with 400mg vaginal/oral misoprostol with mifepristone tablets) (Fairley, 2005). But those patients had 15% higher incidence of gastrointestinal side effects. Emphasizing the fact while using combined regimen there should be a fine balance between the dose, route of administration, induction to delivery interval and side effects as in current study for optimum results.

Complications

Serious complications like uterine rupture were not seen in the present study. In 4% of cases retained placenta was another complication encountered and managed, similar to other studies (Paul A. le Roux, 2001)

Prostaglandins

Using Prostaglandins in IUFD the success rate ranges from 67% to 100%. It has limited dose related side effects by vaginal administration or by giving relatively low dose at frequent intervals.Due to misoprostol usage, Uterine tachysystole, hypertonus and hyper stimulation were reported in few studies (Srisomboon J, 1998) (Bartha, 2000).

In current study we did not encounter uterine tachysystole or hyper stimulus this might be due to decreased sensitivity of prostaglandin to uterus or because of less intense monitoring because of dead fetus. Potential risk of uterine rupture was also not found.

Uterine sensitivity to prostaglandins is known to increase with advancing gestation as reported in (Buglaho A, 1994)Depending upon the dosage, gravida, trimester in which the prostaglandins are being provided, the duration since induction was shorter compared to current study as found in these studies (Mendilcioglu, 2002) (Goh SE, 2006) (Kapp N, 2007)

LIMITATIONS

The core aim could have been well explored using a proper randomized control trial. Limited sample size was adopted as it's a single investigator study. If limitations are rectified, study conclusions would hold a stronger validation.

CONCLUSION

From results we could conclude that, Induction delivery interval was significantly shorter in Mifepristone & Misoprostol group compared to Misoprostol only group and the association was more in primigravida than multigravida. The combination of mifepristone and misoprostol is a safe and effective method for labor induction following IUFD. The induction to delivery interval is shorter with a better side effects profile in combined regimen.

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