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Role of 400 µg oral Misoprostol versus 0.2mg intravenous Methyl ergometrine for the active management of third stage of labor

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Abstract
Introduction: Postpartum haemorrhage is an important cause of maternal morbidity and mortality, accounting for nearly one quarter of all maternal deaths worldwide. The prophylactic use of oxytocic in the third stage of labor has shown to significantly reduce the risk of postpartum hemorrhaged by about 40%, implying that for every 22 women who are given such an oxytocic, one post partum hemorrhaged is prevented and its use is generally advocated in the management of third stage of labor.
Methods and Material: The present study of 400µg oral misoprostol vs 0.2mg intravenous methylergometrine for the active management of third stage of labor was conducted in the Department of Obstetrics and Gynecology of tertiary care hospital in Dehradun.
Results: In the present study there were 50 cases in each of the two groups. Majority of the cases were from urban area. The mean parity was 0.61±0.52 and 0.67±0.53 in Misoprostol and methylergometrine maleate group respectively (P=>0.05). Majority of the patients in the misoprostol group had third stage of labor of 10-12 minutes duration while in the methylergometrine maleate group, for majority of the patients the duration of third stage of labor was 5-6 minutes. In Misoprostol group side effects noted were shivering in 30% followed by fever 14%, Nausea 8%, vomiting 6% and pyrexia 4% cases, while in methylergometrine maleate group, nausea was observed in 20% followed by shivering 6%, vomiting 4% and Increase in diastolic blood pressure 4% cases.
Conclusion: Although efficacy of both the drugs are comparable, even in presence of shivering which is a serious side effect but self-limiting with oral misoprostol offers. It is the simplest route desirable in developing countries where many of the deliveries are still being conducted at home especially in the rural areas, not attended by medically trained staff.

Keywords: Misoprostol, Postpartum hemorrhaged, 400µg oral misoprostol, haemorrhage

Introduction

Postpartum hemorrhaged is an important cause of maternal morbidity and mortality, accounting for nearly one quarter of all maternal deaths worldwide [1]. The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour [2]. During the third stage of labour, the muscles of the uterus contract, causing constriction of the blood vessels that pass through the uterine wall to the placental surface and stopping the flow of blood. This action also causes the placenta to separate from the uterine wall [3]. Although risk factors may increase a woman's chances of developing postpartum hemorrhaged, 2/3rd of the cases of PPH occur without any predisposing factors, hence all pregnant woman remain at a risk of developing PPH. The prophylactic use of oxytocic in the third stage of labor has shown to significantly reduce the risk of postpartum haemorrhage by about 40%, implying that for every 22 women who are given such an oxytocic, one post partum haemorrhage is prevented and its use is generally advocated in the management of third stage of labor [4]. This intervention has been described in Cochrane review as administration of prophylactic uterotonic after delivery of the baby, early cord clamping and cutting and controlled cord traction. Expectant management involves waiting for signs of separation of placenta and allowing it to deliver spontaneously, or aided by gravity or nipple stimulation [6]. Ergometrine was the first of the injectable oxytocic's used in postpartum haemorrhage and has been in use for past 70 years. It produces prolonged uterine contractions involving the upper and lower uterine segments with a duration of 60-120 minutes. The use of these uterotonic agents in the management of third stage of labour reduces the amount of bleeding and need for transfusion. But it is associated with side effects ranging from nausea, vomiting, and increased blood pressure to postpartum convulsion, intracerebral haemorrhage,

myocardial infarction, cardiac arrest and pulmonary oedema etc. Oral administration of ergometrine has been shown to be ineffective in reducing postpartum blood loss and the oral preparation is not stable under simulated tropical conditions, making it unsuitable for use in tropical countries [7]. Misoprostol is an orally active uterotonic agent; it is a prostaglandin El analogue and was first marketed as an antipeptic ulcer drug. Recently it has been found to be effective in medical evacuation of the uterus in spontaneous abortion, cervical ripening and induction of labor first and second trimester termination of pregnancy [8]. After oral administration it is absorbed rapidly into the blood stream and when taken in early pregnancy, it has been reported to cause an increase in uterine tonus within 7 minutes. It is stable at high temperature and has a long self-life. The use of ergometrine is contraindicated in hypertensive cases as ergometrine stimulate vasoconstriction, causes hypertension, and may cause headache, convulsions and even death in preeclampsia cases. Misoprostol on the other hand has shown to decrease the mean arterial pressure and systemic vascular resistance, hence, may be used as an oxytocic in hypertensive or preeclamptic women undergoing vaginal delivery [9]. WHO has also recently recommended the use of misoprostol for active management of third stage of labor, especially by trained birth attendant in rural areas. Misoprostol has a range of potential benefits including rapid absorption, ease of administration (oral, rectal, sublingual) which does not require any trained personnel and can be administered by traditional birth attendants, cost effectiveness and no special condition for the storage and transport, has a shelf-life of several years and thus it proves to be a suitable uterotonic agent for use in the prophylactic management of third stage of labour especially in resource-poor set-up in developing countries like ours [7, 10] So, the present study is an attempt to assess the effect of oral misoprostol on 3rd stage of labour in comparison with standard methergine regimen.

Methods and Material

The present study of 400µg oral misoprostol VS 0.2mg intravenous methylergometrine for the active management of third stage of labor was conducted in the Department of Obstetrics and Gynecology of tertiary care hospital. After a detailed history, general and obstetric examination and routine investigation, 100 patients who fulfilled the selection criteria were included in the study. The comparative study evaluated 100 selected cases admitted during the above mentioned period for delivery. A control group of 50 cases being administered methylergometrine maleate was compared with a study group of 50 cases administered oral misoprostol. A total of 100 cases were studied with 50 cases in each group. An informed consent was taken from the patient in both the groups. In the third stage of labour, immediately after the delivery of the baby, the cord was clamped and cut. The women were given either intravenous Methyl ergometrine 0.2 mg at the delivery of anterior shoulder of fetus or Oral misoprostol 400 µg immediately after the delivery of fetus randomly. Postpartum hemorrhage in the present study is defined as blood loss ≥500 ml in 1st hour after delivery. Once the diagnosis of postpartum hemorrhage was made, the patients were managed as per the needs by giving additional oxytocic's drugs (IV oxytocin infusion or injection prostodin). Third stage complication if any like retained placenta, inversion of the uterus, PPH & side effect if any were observed, and managed symptomatically.

Results

In the present study there were 50 cases in each of the two groups. Majority of the cases were from urban area. The mean parity was 0.61±0.52 and 0.67±0.53 in Misoprostol and methylergometrine maleate group respectively (P=>0.05)

The mean duration third stage of labor in misoprostol in Methylergometrine maleate group. Majority of the patients in the misoprostol group had third stage of labor of 10-12 minutes duration while in the methylergometrine maleate group, for majority of the patients the duration of third stage of labor was 5-6 minutes. In Misoprostol group side effects noted were shivering in 30% followed by fever 14%, Nausea 8%, vomiting 6% and pyrexia 4% cases, while in methylergometrine maleate group, nausea was observed in 20% followed by shivering 6%, vomiting 4% and Increase in diastolic blood pressure 4% cases.

Table 1: Distribution of cases according to factor in the third stage of labor in the two groups

Factors	Misoprostol n=50	Methylergometrine maleate n=50	P Value
Urban	40	35	>0.05
Mean parity	0.61±0.52	0.67±0.53	>0.05
Mean age in years	24.87±5.33	24.98±3.69	>0.05
Mean duration of 1st stage of labor (in hrs.)	10.87±1.97	9.96±1.53	>0.05
Mean duration of 2nd stage of labor (in min)	24.12±8.82	24.87±8.18	<0.05

Table 2: Distribution of cases according to duration of 3rd stage of labor in the two groups

Duration in (min)	Misoprostol n=100		Methylergometrine maleate n=100		P Value
	N	%	N	%	
1-2	1	2	1	2	<0.001
3-4	6	12	14	28	<0.001
5-6	7	14	20	40	<0.001
7-9	15	30	14	28	<0.001
10-12	21	42	1	2	<0.001
Total	50	100	50	100	

Table 3: Distribution of cases according to amount of blood loss in the third stage of labor in the two groups

Amount of blood loss	Misoprostol n=100		Methylergometrine maleate n=100		P Value
	N	%	N	%	
<50 ml	4	8	3	6	<0.001
51-100	23	46	25	50	<0.001
101-200	20	40	16	32	<0.001
201-300	03	6	6	12	<0.001
301-500	0	0	0	0	<0.001
>500	0	0	0	0	
Total	50	100	50	100	

Table 4: Distribution of cases according to side effects

Symptoms	Misoprostol n=100		Methylergometrine maleate n=100	
	N	%	N	%
Nausea	4	8	10	20
Vomiting	3	6	2	4
Shivering	15	30	3	6
Fever	7	14	-	-
Pyrexia	2	4	-	-
Increase in diastolic blood pressure	-	-	2	4

Discussion

The third stage is considered from the delivery of fetus to delivery of placenta. Separation of placenta and membrane is brought about by uterine contraction. Methylergometrine maleate when given intravenously acts directly on the myometrium, producing tetanic uterine contractions and hastens the separation of placenta and minimizes blood loss. Misoprostol is a prostaglandin E1 analogue, which has been shown to have myometrial stimulating property which can be administered orally and is rapidly absorbed, stable at room temperature, has low cost [7, 10]. In high risk cases where PPH can be anticipated, use of misoprostol can help in preventing PPH even in the hands of trained birth attendants or dais due to its simplicity of administration and manageable side-effects. Its use in 3rd stage of labour was first suggested by El-Refaey H [11]. Amant, *et al.* conducted the study comparing efficacy and side-effects of Injection methyl ergometrine 0.2mg intravenously with misoprostol 400 µg given orally for prevention of postpartum haemorrhage [12]. Therefore, the present study was undertaken to evaluate the efficacy of oral misoprostol in the active management of 3rd stage of labour and compare it with injection methylergometrine used intravenously in high risk women anticipating full term vaginal delivery. The onset of the action methylergometrine maleate when given by intravenous route is within 30-45 seconds while the action of misoprostol when given orally starts in few minutes, reaches a peak within 12-3 minutes and persist for 20-40 minutes. Nearly half of the cases had separation of placenta in 10-12 minutes after the delivery of fetus in misoprostol group while in methylergometrine maleate group all had expelled the placenta within 9 minutes. Similar duration of third stage of labor was observed by Surbek, *et al.* and Ng, *et al.*, who used oral misoprostol and syntometrine in third stage of labor. However, longer duration was observed by Devi, *et al.* and Bhattacharya, *et al.* while using methylergometrine maleate 0.2 mg intravenously [3-6]. In the present study, shivering was observed in 30% cases in misoprostol group compared to 6% cases in methylergometrine group which is statistically significant. In the study conducted by F Amant, *et al.* the incidence of shivering in misoprostol and methylergometine group was 42% v/s 8.5% [12]. Refaey, *et al.* has reported as high as 72% v/s 37%, $p<0.001$ incidence of shivering in misoprostol group [17]. In the study conducted by Zachariah, *et al.* shivering was reported in misoprostol group compared to other oxytocics as 7.4%, 2.1%, 3.7% [18]. Lumbinganon, *et al.* observed shivering in 19% and pyrexia in 7.5% of the cases in 400 µg oral misoprostol vs 19% and 7.5% in 600 µg misoprostol group. Thus most of the side effects are dose related [19]. Hofmeyr, *et al*. noted shivering in 19% of the cases in misoprostol group as against only 5% in the placebo group [20]. Although shivering is the major side-effect overall in all the studies, it is self-limiting and lasts for 20 -30mins. In some patients handling and feeding the neonate is problem which can be the reason for no acceptance of misoprostol.

Conclusion

Although efficacy of both the drugs are comparable, even in presence of shivering which is a serious side effect but self-limiting with oral misoprostol offers. The use of oral misoprostol (400 µg) following delivery of anterior shoulder of baby reduced postpartum blood loss as estimated by reduction in the fall of hemoglobin level. Oral misoprostol administration proves to be simple, non-invasive, easy to administer, safe and an acceptable alternative to existing available other uterotonics in use for the third stage management of labor. It is also useful in patients at high risk for post partum hemorrhage and where intravenous access is limited or difficult to achieve. It is the simplest route desirable in developing countries where many of the deliveries are still being conducted at home especially in the rural areas, not attended by medically trained staff.

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