ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 5, Issue –2, March - 2020, Page No. : 150 - 160

A comparative study between vaginal misoprostol tablet versus intracervical dinoprostone gel for induction of labour in primi postdated pregnancy

[1]Dr. Abinash Moharana, Post Graduate student, Department of O&G, IMS and Sum Hospital, Bhubaneswar, Odisha
[2]Dr. Sibananda Nayak, Professor, Department of O&G, IMS and Sum Hospital, Bhubaneswar, Odisha,
Corresponding Author: Dr. Sibananda Nayak, Professor, Department of O&G, IMS and Sum Hospital, Bhubaneswar, Odisha,

Citation this Article: Dr. Abinash Moharana, Dr. Sibananda Nayak, "A comparative study between vaginal misoprostol tablet versus intracervical dinoprostone gel for induction of labour in primi postdated pregnancy", IJMSIR- March - 2020, Vol – 5, Issue -2, P. No. 150 – 160.
Type of Publication: Original Research Article
Conflicts of Interest: Nil

Abstract

Objective : The objective of this study was to compare the effectiveness of vaginally administered misoprostol tablet to that of vaginally administered dinoprostone gel in a well homogenized cohort of post-dated primi gravida patients with an unfavourable cervix without any pregnancy complications.

Background: My study was conducted in IMS and sum hospital during period 2018-2019 composed of 100 antenatal post-dated pregnant women randomized to undergo pre induction cervical ripening either with 25 µgm of misoprostol tablet vaginally every 4 hourly for maximum of 4 doses (Group 1) or 0.5mg of dinoprostone gel vaginally every 6 hourly for maximum of 3 doses (Group 2). The primary outcomes to be measured were change in Bishop's score, induction to vaginal delivery time, mode of delivery and neonatal outcomes. The secondary outcome variables were indications for caesarean section, maternal complications

Results: Cervical assessment was done at the end of 8 and 16 hours for cervical priming. At the end of 8 hours mean bishop score in misoprostol group is 6.64±1.4 and in dinoprostone group 6.68±1.2, (p = 0.4032). After 16 hours mean bishop score in misoprostol group is 7.96±2.2 and in dinoprostone group 8.02±2, (p=0.847). Mean change in bishop score after 8 hour in misoprostol group 2.52±1.6 and in dinoprostone group2.44±1, (p = 0.7833).Mean change in bishop score from 8th hour to 16th hour in misoprostol group was 1.32±1 and in dinoprostone group 1.16±1.2, (p =0.4654). Successful ripening after 8 hours in misoprostol group was 25 (50%) and in dinoprostone group 26 (52%), (p= 0.779) whereas after16 hours 31 (62%) in misoprostol group and 36 (72%) in dinoprostone group (P =0.1802). Both misoprostol and dinoprostone are equally effective for cervical ripening. Vaginal delivery in misoprostol group is 21 (42%) where as in dinoprostone group 24 (48%), statistically not significant (p= 0.3981). In misoprostol group 10(20%) patients in dinoprostone group 12(24%) had caesarean section for foetal distress, (p=0.4946). Mean intervention to delivery interval for vaginal delivery in both group didn't show any change, 1085±149.2 min vs

1046±177.6 min (p=0.6796). Maternal complications didn't show any difference in both the group. Neonatal parameters such as mean Apgar score at 1 min in misoprostol group was 7.82±.48 and in Dinoprostone group 7.84±05. APGAR score after 5 min in misoprostol group was 9.24±0.43 whereas in dinoprostone group it was 9.24±0.49, both values were statistically not significant (p > 0.05). Even rate of Neonatal Intensive care unit (NICU) admission in both the group didn't show any difference.

Conclusion: For cervical ripening with both vaginal misoprostol tablet and dinoprostone gel are equally effective in primi post-dated pregnancy with respect to induction to delivery time interval, mode of delivery, maternal and neonatal complication. Both the drugs are safe inducing agent.

Keywords: cervical ripening, Dinoprostone gel, Induction of labour, Misoprostol

Introduction

The process of childbirth has been regarded as the natural outcome of pregnancy. Sometimes, continuation of pregnancy to term or beyond term may accidentally be harmful for the health of the mother and fetus. Therefore an attempt has been made by the physicians to initiate the process of labour which is known as

Induction of Labour

Induction of labour is an intervention that artificially initiates uterine contractions leading to progressive dilatation and effacement of cervix and expulsion of fetus prior to spontaneous onset of labour.[1] In about 5-25% of pregnancies, the fetus and/or mother would be better off if delivery was conducted rather than to continue the pregnancy.[2] various prostaglandin analogue have been used for use in induction of labour. Prostaglandin alters the extracellular ground substance of the cervix and also increases the activity of collagenase in the cervix. They also allow for an increase in intracellular calcium levels, causing contraction of myometrial muscle.[3, 4.] Currently two prostaglandin analogs PGE1 (Misoprostol) and PGE2 (Dinoprostone gel) are available for the purpose of cervical ripening. Misoprostol is available as 25, 50, 100, 200 microgram tablets. PGE 2 gel is available in 2.5 ml syringe for an intracervical application of 0.5 mg of Dinoprostone.[5] Misoprostol can easily be given through various routs e.g. oral, vaginal, buccal or sublingual. Studies show that total systemic bioavailability of vaginally administered misoprostol is three folds higher than orally administered misoprostol. The additional benefits associated with misoprostol include its equivalency with respect to effectiveness with superior elements like oxytocin and dinoprostone, its stability at room temperature, economic availability and the case of oral administration. Thus, all these potential benefits have made it an ideal drug for inducing labor The American College of Obstetrics & Gynecology recommends the use of 25 microgram of misoprostol for labour induction, but their guidelines were developed in the absence of large well designed clinical studies. Misoprostol is proposed for induction in WHO model list of essential medicines for labour induction at term to be used in low dose (25-50 microgram).[6] There have been many studies to evaluate the efficacy of misoprostol for labour induction in various doses, routes and intervals of administration, suggesting that misoprostol is effective, but there is still a concern that misoprostol may increase the rates of tachysystole and hyperstimulation and a search for ideal dose and mode is still on.[7] Although, low-dose misoprostol is recommended by WHO,[8] SOGC[9],FIGO[10] but still not approved by FDA for this indication. The availability of low-dose

misoprostol tablet is restricted to a few countries. However it is available in India.

Dinoprostone (PGE2) drug is another effective agent used for cervical ripening by softening and stimulation of uterus contractions. In case of spontaneous labor disturbances or delay or among postdated women, Dinoprostone is recommended for effacement of cervix and labor pain[11] Dinoprostone gel has long been known as a useful and in most of the countries only licensed drug for the purpose of labor induction. Though, Dinoprostone is approved by FDA too, yet in most of the studies its efficacy has not been as remarkable as of Misoprostol.[12] A number of studies have established clearly higher effectiveness of vaginally administered misoprostol as compared to vaginal dinoprostone for both cervical ripening as well as labor induction. The Cochrane Pregnancy and Childbirth Group have concluded after critical review of 45 studies that Misoprostol, administrated vaginally shows better results as compared to both oxytocin and dinoprostone.[13-15]

However it is difficult to interpret previously published studies comparing misoprostol with dinoprostone for induction of labour as majority of studies were biased. They have included both complicated and uncomplicated pregnancies, nulliparous and multiparous women, different indications for induction, different gestational age (37 to 42weeks), different dose regimen in relation to time and dose. Hence this clinical study was conducted to compare the efficacy and safety of intravaginal 25 microgram misoprostol administered every 4 hourly for a maximum 4 doses with that of Dinoprostone gel containing 0.5 mg PGE2 every 6 hourly for maximum 3 doses for cervical ripening and labour induction at term.

Material and Method

This prospective, randomized, controlled study was conducted in Department of obstetrics and gynecology, IMS and SUM Hospital from January 2018 to December 2019. Institutional ethical committee clearance of IMS and sum hospital was obtained via ref no- DMR/IMS.SH/SOA/180069 for the study. Sample size was calculated based on assumptions that the two groups are of same size and the standard deviations are the same. Keeping the power of test as 90% and level of significance as 99%, a sample size of 50 in each group was obtained. 100 primi gravida women admitted to labour ward with a single live foetus in cephalic presentation and period of gestation 40 weeks or more were included in study after obtaining an informed written consent after explaining the consequences. Exclusion criteria were multiparity, contraindications for vaginal delivery, malpresentation ,previous uterine surgery, antepartum haemorrhage, eclampsia, abnormal foetal heart rate pattern, multiple pregnancies, suspected chorioamnionitis and medical illness in mother contraindicating the use of prostaglandins. Detailed obstetric history, menstrual history, medical history and surgical history were obtained. General physical and systemic examination was done. Abdominal examination includes assessment of fundal height, lie, presentation, amount of liquor and normal foetal heart sounds. Vaginal examination was done to confirm presentation and to assess Bishop's score. Gestational age was confirmed by last menstrual period and/or Ultrasound. The enrolled women were randomly assigned into two study groups using computer generated random numbers. In Group A (n= 50), women received tab. Misoprostol 25 µgm vaginally at posterior fornix repeated every 4 hours for a maximum of 4 doses. In Group B (n= 50), women received 0.5

mg intracervical dinoprostone gel repeated every 6 hours for a maximum of 3 doses. Partogram was maintained in all patients. Foetal monitoring was done with CTG and modified Bishop's score was assessed at 0, 8 and 16 hrs. Need for any additional method of induction or augmentation was noted. Vaginal medications were continued till maximum dose is reached or patient gets adequate uterine contraction i.e. 3 per 10 minutes with each contraction lasting for 45 seconds, cervical dilatation of >3cm or fetal distress developed whichever occur earlier.

Progress of labour was observed and noted by per abdominal and vaginal examination. Tachysystole, hypertonus and hyperstimulation were noted. The patient was considered in the active phase when there was cervical dilatation of at least 3cm. Women in labour were cared for, according to current obstetric practices. When they entered into active phase, depending on the pattern of uterine contractility, syntocinon was used for augmentation. If women did not reach active phase within 24 hours of induction, caesarean section was done for failed induction. No augmentation was done when uterine contractions reached a frequency of 3 in 10 minutes with each contraction lasting for more than 45 seconds. Success of induction was defined as entry into active phase within 24 hours of the initial administration of the drugs. The primary outcomes to be measured were change in Bishop's score, induction to vaginal delivery time, mode of delivery and neonatal outcomes. The secondary outcome variables were indications for caesarean section, maternal complications.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square ($\chi 2$)/ Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with the unpaired t-test. If the p-value was < 0.05, then the results will be considered to be significant. Data were analyzed using SPSS software v.23

Results

The study comprised a total 100 women, 50 each in misoprostol and dinoprostone groups, both the groups had almost equal proportion of primi gravida women.

The distribution of patient age, parity and mean gestational age were similar in the two groups. (Table 1)

Table 1: Base line characteristic

Characteristic	Misoprostol(n=50)	Dinoprostone(n=50)	P Value
Mean age in years	25.6±2.7	26.2±2.6	0.3789(NS*)
Parity nullipara	50(100%)	50(100%)	1(NS)
Mean gestational age (Week)	40.44 ±0.43	40.35 ± 0.29	0.1902(NS)

*NS = not significant

Only primi gravida postdated women were included (statistically not significant). The cervix was considered unfavorable if the bishops score was <6.Table 2 shows distribution of bishops score among the groups at the time of recruitment.

Table 2: pre-ripening bishops score

Bishops score	Misoprostol(n=50)	Dinoprostone(n=50)	P value
2	3(6%)		
3	6(12%)	3(6%)	0.1362(NS)
4	23(46%)	23(46%)	1.0(NS)
5	18(36%)	24(48%)	0.0836(NS)

Total 23 (46%) patients in misoprostol group and 23 (46%) patients in dinoprost group has Bishop score 4,

statistically not significant, (P = 1). Total 18 (36%) patients in misoprostol group and 24 (48%) in Dinoprostone group has bishop score 5, statistically not significant, (p = 0.0836)

Table 3: Mean bishop score during induction

Mean bishops score	Misoprostol(n=50)	Dinoprostone(n=50)	P value
Pre ripening	4.12±0.8	4.42+_0.6	0.0424(S)
At 8 hours	6.64±1.4	6.86±1.2	0.4032(NS)
At 16 hours	7.96±2.2	8.02±2	0.847(NS)

Table3 is showing different changes in mean bishop score during induction of labour. Mean pre ripening bishop score before induction in misoprostol group is 4.12±0.8 and in dinoprostone group is 4.42±o.6 which is statistically significant, (P= 0.0424). At 8 hour mean bishop score in misoprostol group is 6.64±1.4 and in dinoprostone group is 6.68±1.2, both are statistically not significant. After16 hour mean bishop score in misoprostol group is 7.96±2.2 and in dinoprostone group is 8.02±2, statistically not significant (p = 0.847).

Table 4: Mean change in bishop score after ripening

Mean change in bishop score	Misoprostol(n=50)	Dinoprostone(n=50)	P value
0 to 8 hours	2.52±1.6	2.44±1.3	0.7833(NS)
8 to 16 hours	1.32±1	1.16±1.2	0.4654(NS)

This table 4 showing mean change in bishop score after 8 hour in misoprostol group2.52±1.6 and in dinoprostone group2.44±1.3,statistically not significant,(p = 0.7833).Mean change in bishop score after 16 hour in misoprostol group is 1.32±1 and in dinoprostone group it is 1.16±1.2, statistically not significant,(p = 0.4654).

Table 5: Successful cervical ripening

Total no of successful ripening	Misoprostol(n=50)	Dinoprostone(n=50)	P value
AFTER 8 HOURS	25 (50%)	26(52%)	0.779(NS)
AFTER 16 hours	31(62%)	36(72%)	0.1802(NS)

Table 5 showing successful cervical ripening following misoprostol and dinoprostone. Total no of successful ripening after 8 hours in misoprostol group is 25 (50%) and in dinoprostone is 26 (52%), statistically not significant, (p = 0.779). After16 hours 31 (62%) in misoprostol group and 36 (72%) in dinoprostone group shows favourable cervical ripening, statistically not significant, (P =0.1802).

Table 6: Delivery out come

Outcome	Misoprostol (n=50)	Dinoprostone(n=50)	P value
Vaginal delivery	21(42%)	24(48%)	0.3981(NS)
LSCS	29(58%)	26(52%)	0.3941 (NS)

Vaginal delivery in misoprostol group is 21 (42%) where as in dinoprostone group 24 (58%), statistically not significant, (p= 0.3981) (Table 6). LSCS rate in misoprostol group is 29 (58%) where as in dinoprostone group is 26 (52%), statistically not significant, (p= 0.3941).

Table 7: Indication for cesarean section

Indication	Misoprostol	Dinoprostone	P-Value
Fetal Distress	10(20%)	12(24%)	0.4946(Ns)
CPD	0(0%)	1 (2%)	
Failure Of Induction	10(20%)	5(10%)	0.0455(S)
Non Progress Of Labour	9(18%)	8(16%)	0.7069(Ns)

This table 7 showing different indications of caesarean section. Total 29 cases of LSCS from misoprostol group and 26 cases from dinoprostone group had Caesarean section for various indications.Fetal distress

and failure of induction are major indication for caesarean section in misoprostol group where as fetal distress and non progress of labour are important indication of cesarean section in Dinoprostone group.Total 10(20%) in misoprostol group and 12(24%) in Dinoprostone group had caesarean section for fetal distress,(P=0.4946) statistically not significant. Total 9(18%) in misoprostol group and 8(16%) in Dinoprostone group had caesarean section for non-progress of labour, P= 0.7069, statistically not significant. However 10 patients (20%) in misoprostol group and 5(10%) in Dinoprostone group had caesarean section for failure of induction, p = 0.0455, statistically significant.

Table 8: Time duration for delivery

Parameter	Misoprostol(n=21)	Dinoprostone(n=24)	P value
Mean intervention to delivery interval(min)	1085.43±149.2	1046.67±177.6	0.6796(NS)

Mean intervention to vaginal delivery interval in misoprostol group was 1085±149.2 minutes and in Dinoprostone group 1046±177.6 minutes (p =0.6796). (Table 8)

Table 9: Side effects

	Misoprostol	Dinoprostone	p value
PPH	1 (2%)	3(6%)	0.3173(NS)
Uterine hyperstimulation	1(2%)	1(2%)	1 (NS)
Meconium stained liquor	1 (2%)	3 (6%)	0.3173 (NS)
Vomiting	3(6%)	3(6%)	1 (NS)

This table 9 showing side effects of the drug which includes vomiting during labour, Hyperstimulation and PPH after delivery. Vomiting and Hyperstimulation incidence are same in both misoprostol and dinoprostone group i.e. 1 (2%). Incidence of meconium stained liquor and PPH following delivery is more in dinoprostone group than misoprostol group i.e. 3 (6%) vs 1 (2%), but not statistically significant, (p= 0.3173)

Table10: Perinatal outcome

	Misoprostol	Dinoprostone	P Value	Significance
Birth weight (Kg)	3.02±0.4	3.14±0.33	0.1236	NS
APGAR 1 min	7.82±0.48	7.84±0.50	0.8384	NS
APGAR 5 min	9.24±0.43	9.24±0.49	0.8357	NS
MSL	1(2%)	3(6%)	0.1474	NS
NICU ADM	7(14%)	6(12%)	0.6745	NS

Neonatal parameters such as mean APGAR score at 1 min in misoprostol group is7.82±.48 and in Dinoprostone 7.84±0.5, statistically not significant (p =0.8384) (Table 10). APGAR score after 5 min in misoprostol group is 9.24±0.43 whereas in dinoprostone group it is 9.24±0.49 statistically not significant (p= 0.8357). Rate of NICU admission in misoprostol group is 14% and in Dinoprostone group 12%, statistically not significant, (p = 0.6745).

Discussion

Labour induction at term gestation is the most common obstetric intervention of our times. Shorter induction to delivery time and quicker cervical priming is the need of hour in order to decrease the period of anxiety and discomfort for the patient and increased workload in hospitals. Almost 20% of the deliveries around the world require artificial labor induction. [16]

"The present study is designed to compare and accesses the efficacy of misoprostol and dinoprostone as a cervical ripening agents". Different studies [17 -19] have used different proportion of primigravida to multigravida for the induction of labour which lead to bias in induction of labour. Hence we chose to include only primigravida for the induction. Moreover many studies have used different criteria like term,

hypertension, IUGR, diabetes, oligohydramnios for induction of labour.

These indications for induction leads to bias as the above indications induces more chances for stopping the induction and preference is given for earlier caesarean section. Hence in our study we have used only postdated primi gravida pregnancy as the only indication for induction and excluded all high risk groups. As per the base line characteristics mean age and mean gestational age of the patients were similar and statistically not significant.

In our study mean initial Bishop score was 4.12±0.8 for misoprostol group, and 4.42±0.6 for dinoprostone group. Mean change in Bishops score after 8hrs for misoprostol was 2.52±1.6 and for Dinoprostone was 2.44±1.3.Mean change in bishop score after 16 hour from 8th hour onwards was 1.32±1 for misoprostol and1.16±1.2 for Dinoprostone. It is found that change in bishop's score after 8 hours and 16 hours were not statistically different. This indicates that rate of cervical ripening occurs equally with both misoprostol and dinoprostone over 8 hours and 16 hours. Successful ripening after 8 hours i.e. bishop's score > 6 in misoprostol group was 50% (table 5) and 52 % in dinoprostone group, statistically not significant. Even after 16 hours bishop's score was improved to 62% and 72% in misoprostol group and dinoprostone group respectively, statistically not significant. This indicate both agents are equally effective as cervical ripening agent over equal interval of time when misoprostol is used 25 µg 4 hourly and dinoprostone 0.5 mg 6hourly. Similar result was seen as per the study conducted by Sobha Mukherjee et al [20]

In various studies [21-28], the rate of successful vaginal delivery varies from 31 - 98% with misoprostol and 32 - 98% with dinoprostone. In our study 42% patients in misoprostol group and 48% in dinoprostone group had vaginal delivery, statistically not significant. (Table 6)

As seen in table 7 rates of caesarean section due to foetal distress in misoprostol group and in dinoprostone group are not statistically different (p= 0.4946). Foetal distress incident was 20% vs 24%. Similar indication was found by Ramya D et al. [29]

LSCS due to failure of induction in misoprostol group is 10(20%) whereas in dinoprostone group 5(10%), p value-0.0455(S). These patients didn't reach up to active stage of labour. This implies probably 4 doses of misoprostol is not as effective as three doses of dinoprostone to reach at active stage of labour. But misoprostol doesn't cause more foetal distress as compared to dinoprostone as the number of foetal distress in both groups is not statistically significant. However once the patient goes into active stage of labour the progress of labour is equal in both group as shown by the rate of LSCS due to nonprogress of labour, 9(18%) in misoprostol group and 8(16%) in dinoprostone group(p= 0.7069(NS).

Mean intervention to delivery interval for vaginal delivery in misoprostol group is 1085±149.2 minutes and in Dinoprostone group is 1046±177.6 minutes which is not statistically significant (Table 8). Mean induction to delivery interval in various studies ranged from 10.2 to 24.9 hours in misoprostol group versus 14.8 to 28.7 hours in dinoprostone group.[18-28]Though, most studies showed misoprostol give shorter induction to delivery interval compared to dinoprostone, the protocols used were different. Most of the studies used 6 doses of misoprostol whereas we used 4 doses. We find no difference in mean intervention-delivery interval between both the groups. This indicates that both are equally effective in the context of induction to delivery interval.

Side effects during induction such as vomiting, hyperstimulation, meconium staining liquor or PPH following delivery were not statistically significant in both the group (Table 9). These finding are similar to the findings of Ramsey et al and Neelu[16] and Puja et al[30]

Mean birth weight of the newborn in misoprostol group was 3.02± 0.4 kg and in Dinoprostone group 3.14± 0.33 kg, statistically not significant (Table 10). This indicate that during induction of labour antenatal weight was not measured and were not biased as per weight of the foetus.

Apgar score both in 1 min and 5 min didn't show any difference. Rate of NICU admission in misoprostol group was 14% and in dinoprostone group was 12%, statistically not significant. As we have seen the indication for caesarean section in misoprostol and dinoprostone group as foetal distress were equal, hence probably equal number of fetuses were admitted to NICU. Moreover as shown in table 10 the side effects like meconium stained liquor was not statically significant which reflect the neonatal outcome in terms of APGAR score both at 1 and 5 minute and NICU admission. Similar results were seen as per study of snigdha kumari et al, Pandis et al, Paul Bernstein and Marjorie et al [31-34] in terms of APGAR score and NICU admission. However Papanikolaou et al. [35] noticed high rate of abnormal FHR tracings during induction with misoprostol and these findings, in agreement with the previous Cochrane meta analysis[36] which demonstrated that with misoprostol there was an increased possibility of meconium staining of amniotic fluid in addition to of uterine tachysystole and of abnormal FHR tracings. Harms et al [37] who showed no differences either in tachysystole and uterine hyper stimulation. Hence probably 4 doses of misoprostol do not cause more foetal abnormality and safe dose for induction of labour.

Conclusion

My study was conducted in IMS and sum during period 2018-2019 composed of 100 antenatal primi gravida women for induction of labour for pre induction cervical ripening comprising of 50 patients in misoprostol group and 50 patients in the dinoprostone group. All patients were randomized to either 25 µgm of misoprostol every 4 hourly for maximum of 4 doses or 0.5mg of dinoprostone every 6 hourly for maximum 3 doses. With this dose regimen it is found that both misoprostol and dinoprostone are equally effective for cervical ripening. Hence total number of vaginal delivery, induction to vaginal delivery interval and maternal side effects are comparable in both groups. Even perinatal outcome is comparable in both the group. Mean APGAR score at 1 minute, 5 minute and NICU admission are not affected by above regimen of misoprostol and dinoprostone. It was found to have similar maternal and fetal safety profile. This drug was well tolerated. Therefore its use is recommended for cervical ripening and labour induction in developing countries.

Our recommendation; that it is essential to achieve more clinical studies to weigh misoprostol against dinoprostone at the doses utilized here, and to embrace more outcomes like pregnancy satisfaction.

Acknowledgements

The authors would like to thank all of the patients who participated in the trial, the doctor and nurses of labour ward and neonatal intensive care unit, whose involvement made this study possible.

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