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MISOPROSTOL USE PROFILE IN A PUBLIC HOSPITAL IN RIO DE JANEIRO/BRAZIL: FROM THE PERSPECTIVE OF A HOSPITAL PHARMACY DISPENSATION

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Abstract: **Objective:** In order to evaluate misoprostol (prostaglandin E1 analog) use profile in hospital unit in the scope of Brazilian Public Health through the Unified Health System (SUS), misoprostol is dispensed as a vaginal tablet. It is part of the basic component of Pharmaceutical Assistance and its dispensation is restricted to Brazilian hospitals**. Methods**: The study was observational, retrospective, descriptive and quantitative in which the aim was to describe the use of this drug in the hospital scenario and was performed in a medium-sized hospital in the Metropolitan Region II of Rio de Janeiro. The data (from July 2017 to July 2018) were obtained from the dispensation forms of misoprostol. The medical prescriptions or patient charts were not evaluated. All dispensations using misoprostol 25 μg or misoprostol 200 μg, regardless of indication, were included in the study. Meanwhile, these ones in which two presentations were prescribed, were excluded. **Results:** It was observed that the main indications of misoprostol 25 μg and misoprostol 200 μg were induction of labor (47.8%); induction of abortion (43,9%) and prevention of hemorrhage (5,5%), all of them is recommended by the International Federation of Obstetrics and Gynecology (FIGO). For induction of labor, in 46.2% of the cases were requested misoprostol 25 μg, against only 1.6% for misoprostol 200 μg. For induction of abortion and prevention of hemorrhage, respectively, misoprostol 25 μg and 200 μg were obtained: 4.4%; 35.7% and 0.5%; 4.9%. The use of misoprostol 200 μg for uterine hypertrophy and anembryonic gestation resulted in the lowest values in terms of indication, 0.5% and 1.1%, respectively. **Conclusion:** misoprostol use profile in a hospital unit was a crucial tool to understand the use of this drug in a Brazilian Hospital aiming at improving the quality of services provided by hospital pharmacy.

Keywords: Misoprostol; obstetrics; drug utilization, Hospital Pharmacy Service

INTRODUCTION

Misoprostol (15-deoxi-16-hydroxy-16-methyl prostaglandin E1) is a synthetic analog of prostaglandin used as a method to help induction of labor. Between the years 2003-2009, nearly 73% of all maternal deaths were due to direct obstetric causes.[1] Misoprostol has revolutionized the treatment of women in reproductive age, because its characteristics, as the low-cost, uterotonic and tablet form.[2,3] There are many reproductive health indications of this medicine as induced of abortion, uterine evacuation, labor and delivery, cervical priming and prevention & treatment of postpartum hemorrhage (PPH).[4]

This medicine has less adverse events due to the low doses that exist nowadays appropriate for induction of labor, like tablets of misoprostol 25 μg and misoprostol 200 μg. Besides that, this medicine is a cheaper alternative to surgery, as it is five times more inexpensive when it is compared to curettage procedure, with mild side effects. It is stable at room temperature, easy to administer and store and widely available.[4,5,6] According to the dosage form, it can be administered through vaginal, oral, oral and vaginal (in combination), rectally in single or multiple doses.[7-12]

The development of mechanisms for the safe dispensation of this medicine for abortive purposes, for example, requires continuing education of the pharmacy team, mainly of the pharmacist who should ensure the woman's right to survival, life, privacy, liberty, and security. One of the foundations of the use of misoprostol is in the knowledge of the new administration protocols in terms of clinical indication, dose, and dosage. The International Federation of Obstetrics and

Gynecology (FIGO) revised the chart with the recommended dosages of misoprostol when it is used alone.[13-15] In Brazil the sales of medicines based on the substance misoprostol is restricted to duly registered and accredited hospital establishments with the competent Sanitary Authority (The Brazilian Health Regulatory Agency - ANVISA). Thus, the knowledge of the profile of the use of misoprostol in Brazil which is restricted to hospital units [16] is an important tool to describe the use of this medicine in the scenario of Brazilian Public Health.[17]

This study is aimed to assess misoprostol profile use in a Hospital Unit in Brazil according to the last recommended regimes from FIGO.[15]

METHODS

This study is an observational, retrospective, descriptive and quantitative based on a survey performed by pharmacists in a medium-sized hospital in the Metropolitan Region II of Rio de Janeiro/Brazil and was carried out from the acquisition of data from the dispensing form of the medicine misoprostol, which is included in the standardization list of the Pharmacy Service. During the period of development of the study, that were from July 2017 to July 2018, the study size was arrived from data which were obtained and quantified from the dispensation forms of misoprostol.

The present research was submitted to the Research Ethics Committee of the University Hospital Gaffree and Guinle/HUGG UNIRIO for release of Voluntary Informed Consent Form (TCLE) and approved under Opinion n. 4.251.264 of 2020.

The medical prescriptions or patient charts were not evaluated. As insertion criteria, all dispensations using misoprostol 25 μg or misoprostol 200 μg, regardless of indication, were included (e.g., change of indication). All dispensations where the two medicine presentations were used during the medicine therapy were excluded from the study.

Under the Hospital's Pharmacist responsibility, misoprostol 25 μg and misoprostol 200 μg are dispensed through an individualized dispensation for the Maternity Sector of the Hospital Unit as the study was conducted. For the control of the dispensation a form must be filled for the assessment of the indications which consists in: 1. Induction of labor; 2. Legal abortion (1st gestational trimester); 3. Legal abortion (2nd trimester); 4. Legal abortion (3rd gestational trimester); 5. Fetal death (1st trimester); 6. Fetal death (13-17 gestational week); 7. Fetal death (18-26 gestational week); 8. Fetal death (3rd trimester); 9. Surgical abortion (prior to Manual Intrauterine Aspiration (MVA) or curettage) and 10. Postpartum hemorrhage.

All the data were managed in a Microsoft Office Excel 2010 spreadsheet for descriptive statistical analysis, in which the results were presented in tables, charts and descriptively

RESULTS

This section covers the results of the study. One hundred eighty-two forms (182) were addressed for the study from the strategy search (Figure 1). Among the main indications observed in the hospital unit (induction of labor, induction of abortion and prevention of postpartum hemorrhage), the use profile was verified in terms of presentation used.

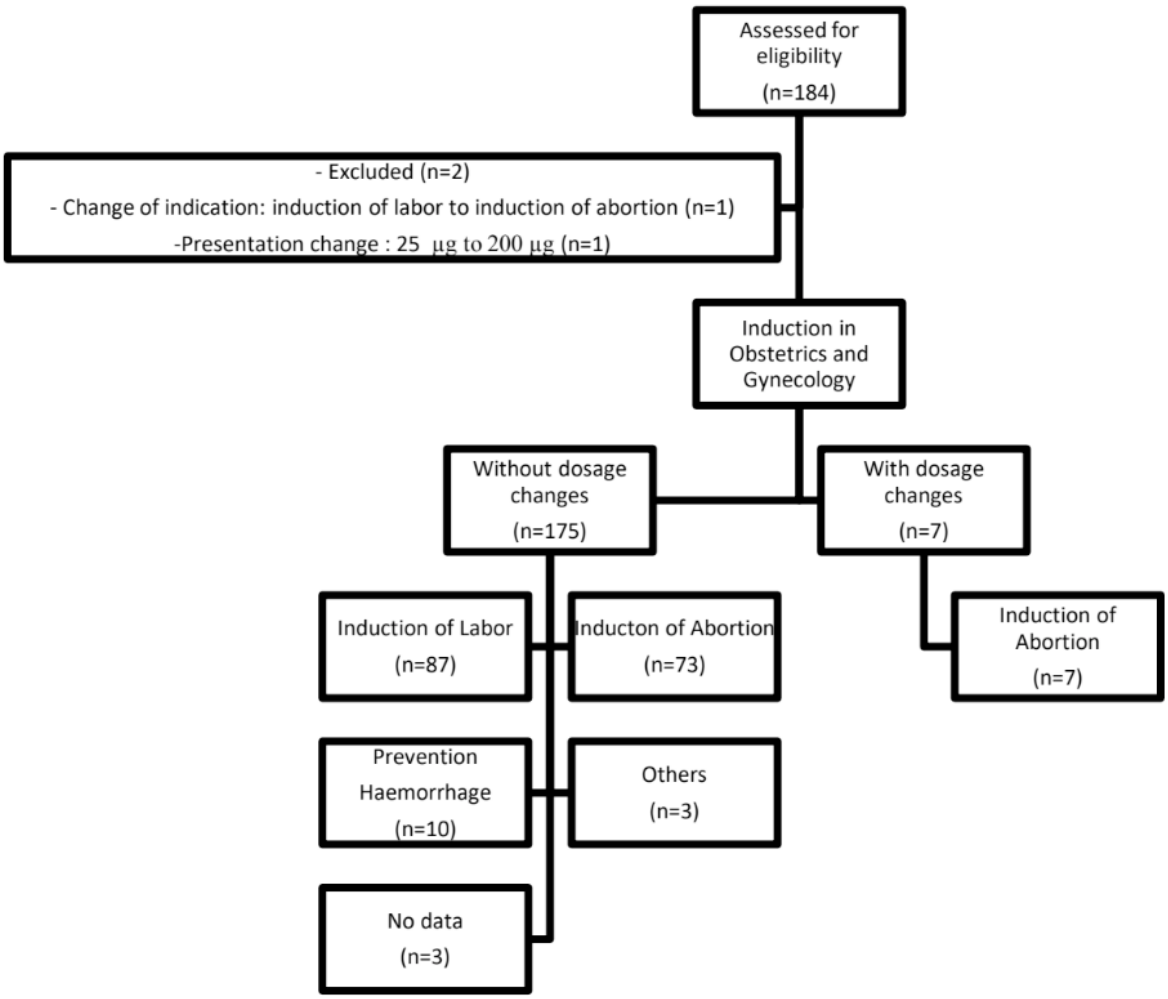

Figure 1. Flowchart of forms of patients enrolled in the study.

The analysis of the dosages provides a scenario of adequacy when it comes to the use of misoprostol for what is set up by FIGO (Table 1). Dispensations of misoprostol 25 µg and misoprostol 200 µg have been seen with the main indications found. For labor induction, 46.2% of the forms were requested misoprostol 25 µg, against only 1.6% for misoprostol of 200 µg. Within the same reasoning, for induction of abortion and prevention of hemorrhage, respectively, misoprostol 25 µg and 200 µg were obtained: 4.4%; 35.7% and 0.5%; 4.9%. The use of misoprostol 200 µg for uterine hypertrophy and anembryonic gestation resulted in the lowest values in terms of indication, 0.5% and 1.1%, respectively.

Time of gestation / postpartum	< 13 weeks gestation	13-26 weeks gestation	> 26 weeks gestation	Postpartum use
Indication (Posology)	**Pregnancy Termination** 800 µg every 3-12 hours (2-3 doses)	**Pregnancy Termination** 13-24 weeks: 400 µg every 3 hours 25-26 weeks: 200 µg every 4 hours	**Pregnancy Termination** 27-28 weeks: 200 µg every 4 hours >26 weeks: 100 µg every 6 hours	**Pregnancy Termination Postpartum Hemorrhage Prophylaxis (PPH)** There is no regimen to vaginal administration
	Missed abortion 800 µg every 3 hours (2 doses)	**Fetal death** 200 µg every 4-6 hours	**Fetal death** 27-28 weeks: 100 µg every 4 hours >28 weeks: 25 µg every 6 hours	**PPH treatment** There is no regimen to vaginal administration
	Incomplete abortion 400 µg - 800 µg	**Inevitable abortion** 200 µg every 6 hours	**Induction of Labor** 25 µg every 4-6 hours	-
	Cervical Preparation for Surgical Abortion 400 µg 3 hours before procedure	**Cervical Preparation for Surgical Abortion** 13-19 weeks: 400 µg 3-4 hours before procedure >19 weeks needs combinations with other procedures	-	-

Table 1. Misoprostol-only recommended regimen 2017 by FIGO to vaginal route of administration

Source: Elaborated by the authors from FIGO recommendation[15]

Two (2) patients were excluded, one of them (1) had the misoprostol indication changed from induction of labor to induction of abortion and one (1) had the misoprostol presentation changed from 25 µg (6/6 h) to 200 µg (single dose). From 182 patients, one hundred seventy-five (175) did not have changes in the dosages of misoprostol. From them eighty-seven (87) had the indication to induction of labor, seventy-three (73) to induction of abortion, ten (10) to prevention of PPH. Other indications were noted in three (3) patients with uterine hypertrophy (1) and anembryonic gestation (2). Both of them from using misoprostol 200 µg in single dose. For two (2) patients no data were observed. From the total patients of the study (182), it was observed changing the dosage of misoprostol in seven (7) patients to induction of abortion (Table 2).

		Dosage						
Indications	**Dose**	**Single Dose**	**12/12 h**	**8/8 h**	**6/6 h**	**4/4 h**	**Dosage Changes**	**Total n (%)**
Induction of Labor	25 µg	25	00	01	58	00	-	84 (46.2)
	200 µg	02	00	00	01	00	-	03 (1.6)
Induction of Abortion	25 µg	04	01	00	03	00	-	08 (4.4)
	200 µg	55	07	00	02	01	-	65 (35.7)
	Dosage Changes	-	-	-	-	-	07	07 (3.8)
Prevention Haemorrhage	25 µg	00	00	00	01	00	-	01 (0.5)
	200 µg	07	02	00	00	00	-	09 (4.9)
Hypertrophy of the Uterus	200 µg	01	00	00	00	00	-	01 (0.5)
Anembryonic Pregnancy	200 µg	02	00	00	00	00	-	02 (1.1)
No Data	25 µg	00	00	00	02	00	-	02 (1.1)
Total n (%)	-	-	-	-	-	-	-	182 (100)

n. Number of patients

Table 2. Dosage of misoprostol to obstetric indications.

The main indications were: 1. Induction of labor (47.8%); 2. Induction of abortion (43,9%) and 3. PPH (5,5%) (Figure 2).

Figure 2 illustrates the main indications for the use of misoprostol in obstetrics and gynecology in the hospital in which the study was performed.

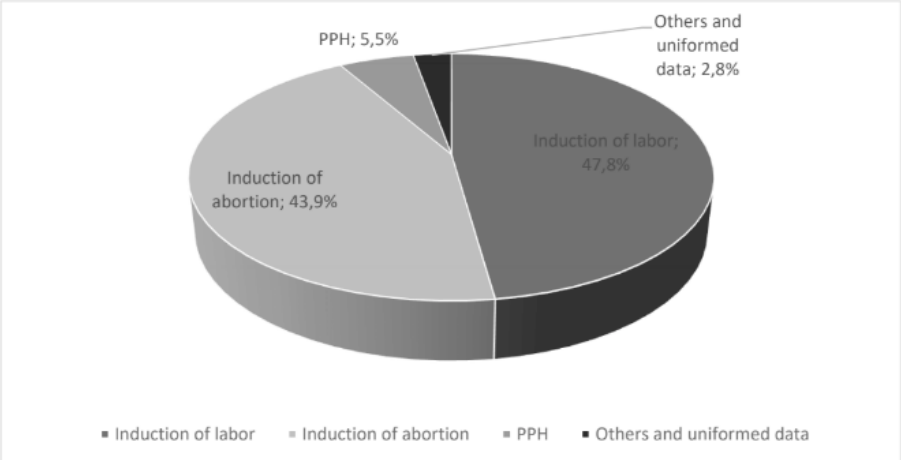

Figure 2. The indications for the use of misoprostol in a hospital unit.

DISCUSSION

Misoprostol is a medicine for hospital utilization, whose understanding about the drug use profile is capable of generating data for using in a safer and more effective way.

This is the key force of the present research that lies with the fact that the acquisition and analysis of data are instruments for research/ clinical evaluations.

Misoprostol is available in the Unified Health System (SUS) in Brazil. It is part of the National Medicine List of the Basic Component of Pharmaceutical Assistance in the form of a vaginal tablet.[18] The documentation of the experience in different countries is important to target the necessary interventions in order to reduce maternal mortality.[19] The use of misoprostol in Brazil is not only medical but also legal. Its use in different obstetric procedures registered by Hebron Pharmaceuticals (induced abortion, labor induction and intra-uterine fetal death) has been restricted to hospitals since 1998. [14] As in the present Hospital Unit the dosage form of misoprostol is the tablet to vaginal administration from Hebron Laboratory (Prostokos™), in the present study there are only the recommendations by FIGO applied to this method of administration of misoprostol alone, i. e., vaginal one. [15]

There are other available synthetic prostaglandin analogues. Although, misoprostol is not permitted worldwide or approved in some countries for use in obstetrics and gynecology, it is a low-cost and availability medicine and easy to storage with improved quality of life for women.[20] Thus, it is necessary that clinical protocols to be worked out so that pharmacological management provides the safe use, for the correct indication, dose, and time of treatment. All observed indications in the hospital unit are in accordance with the main guidelines. According to World Health Organization (WHO) recommendations, the indications of misoprostol for obstetrics and gynecology indications are mainly: 1. Induction of labor; 2. Prevention and treatment of PPH (when? oxytocin is not available); 3. Management of incomplete and spontaneous abortion with medical supervision and 4. Pregnancy termination in combination with mifepristone.[5] The initial use of misoprostol to stimulation of labor in term pregnancy was an off-label one. Nowadays, this medicine is part of the protocol of usage and vaginal administration is the preferred method used by gynaecologits.[15,21,22] It was noticed that, for induction of labor, misoprostol 25 μg was requested for 84 (46.2%) patients and for misoprostol 200 μg for 3 (1.6%) patients. For induction of labor, as it is recommended by FIGO, misoprostol 25 μg every 6 hours to vaginal administration alone. This dosage was examined in 58 dispensations forms. Other dispensations were also noticed: single dose (25) and three times a day (01). Despite there was no indication for misoprostol 200 μg to induction of labor by FIGO, it was seen in two dispensations forms a single dose of misoprostol 200 μg and in one form, it was administered 4 times a day (Table 2).

A key finding to highlight is that for induction of abortion, regardless of gestational age, as it was not reported, 10 (5.5%) patients used misoprostol 25 μg and 70 (38.5%) patients used misoprostol 200 μg from them, it was observed dosage changes for 7 patients (3.8%). It was also observed that the main dosage for misoprostol 25 μg (4) and misoprostol 200 μg (55) was single dose. Knowledge of gestational age is required. This information is not obtained at the time of dispensing the medicine. However, single dose administration of misoprostol 25 μg or 200 μg for discontinuation of pregnancy is not recommended by FIGO.[11] However, misoprostol in single dose 800 μg vaginally is a safe and effective choice for the curettage

for interrupted gestation in the period between 7 and 12 weeks of pregnancy.[15] The using of misoprostol when compared to other methods for induction of abortion according to the gestational age brings benefits when compared to other methods. It was demonstrated that patients who used other methods to have an abortion were more prone to have peritonitis, intra-abdominal abscesses, and more injuries in the genital tract.[16] The discussion of these data is reduced, since the gestational period does not exist in the dispensation form. Although, misoprostol 25 μg is not recommended vaginally by FIGO regardless of the period of gestation.[16]

There are obstetric causes of maternal death as unsafe abortion, obstructed labor, eclampsia, sepsis and PPH - blood loss of 500 ml or more within 24 hours after birth. PPH causes woman mortality, and the deaths are associated to PPH event during the first 24 hours after birth.[23] Its treatment must be improved with the use of uterotonics in the third stage of labor. Misoprostol is used orally, sublingually, rectally, and vaginally as a prophylactic uterotonic and it is used to prevent, to manage and to decrease the incidence of PPH. And it is a cheaper alternative to intravenous oxytocin.[10,24-26.] To PPH prevention a single dose of misoprostol 600 μg orally can be used. And to the PPH treatment, it can be administered misoprostol 800 μg sublingually if blood loss exceeds 500mL. The Worldwide hemorrhage represents the principal direct cause of maternal deaths and PPH leads the two thirds of reported hemorrhage deaths.[1]

In the present study, off-label usage of misoprostol was effective: to prevents PPH, it was observed that 1 (0.5%) patient managed misoprostol 25 μg and 9 (4.9%) patients taken misoprostol 200 μg, mainly in single dose regimen by the intravaginal via. According to FIGO, there is no procedure to vaginal administration to prevent PPH and there is no available data for off-label use of misoprostol 200 μg in the dispensing forms.[15] However, misoprostol works to prevent and to manage the PPH must be implemented and continuously sustained to improve the maternal indicators.[25]

It is important to highlight that this study was carried out by data acquisition from the dispensing form of the medicine misoprostol, so clinical data were not available for the researchers, what had been a limitation of the present research.

CONCLUSION

Obtaining data from a Brazilian Hospital on the misoprostol use profile was an important and useful tool for the Brazilian Public Health System, since it is a medicine restricted to hospital use.

This study discusses the use of misoprostol in Brazil in comparison with the indications of international protocols that aim to improve the provision of care by the Hospital Pharmacy.

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COLLABORATORS

When collaborated in the conception, data analysis and in article writing, LG collaborated in data acquisition and RE collaborated in the final critical review of the intellectual content.

DECLARATION OF CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding this article.

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