Original Article

Retrospective Study on the Pattern of Off-label Use of Misoprostol in Tabuk, Saudi Arabia

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Introduction: Off-label drug use (OLDU) refers to the prescription of a currently available and marketed medication for a use that has never been approved by the Food and Drug Administration (FDA). Misoprostol is one of the drugs which is used off-label. This drug, authorized for the treatment or prevention of peptic ulcers and other stomach disorders, is commonly used off-label for inducing labor or intrauterine device insertion. This research focuses on identifying the percentage of morbidity and mortality by off-label use of misoprostol; classifying the most common off-label misoprostol use in Tabuk hospitals; and determining the availability of policy and procedures behind prescribing the off-label misoprostol.

Materials and Methods: Retrospective observational study was carried out. Data were collected from patients' files for those admitted to the maternity wards in Tabuk Hospitals from March 2019 until September 2019.

Results: Approximately 53% of cases were diagnosed with missed abortion. The mean time for abortion after administering misoprostol was 20.7 ± 28.2 h. About 76% of women had an indication of bleeding. Guidelines were not followed with respect to dosage regimen. The mean of hospital stay was 3 days. There were no significant complications associated with the administration of misoprostol.

Conclusion: There is no policy and procedure available in the hospital regarding off-label use of misoprostol. Moreover, physicians have low adherence to the guideline in terms of dosage, interval, and route of administration for each indication in obstetrics and gynecology.

Keywords: Induction of abortion, miscarriage, misoprostol, off-label use, postpartum hemorrhage

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INTRODUCTION

Off-label drug use (OLDU) refers to the prescription of a currently available and marketed medication for a use that has never been approved by the Food and Drug Administration (FDA).[1] Reasons for off-label prescriptions of a medication include—the medication used for a different indication than the ones registered, administered via a different route, given with a different dose, or given to a patient of a different age range than registered.[2] Adverse drug reactions (ADRs) of some off-label medications were still not been reported and documented, here comes the integral role of expert pharmacists in the medication review process, patient guidance, safety, and adverse drug issues.[3,4] Screening approved medications in order to identify therapeutics for drug repurposing is an effective tactic, and a deep research into OLDU is required as well as studies to monitor and evaluate the prevalence.

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The physician must ensure that no appropriate therapeutic alternative is available and inform the patient, fundamental principle of the right to respect for the will of the person. Off-label use of the prostaglandin-E1 analog misoprostol in obstetrics and gynecology is a good example. In fact, this drug obtained a marketing authorization for the treatment or prevention of peptic ulcers and other stomach disorders, is commonly used off-label when inducing labor or intrauterine device insertion.[6] The important role of misoprostol is endorsed by the World Health Organization (WHO) and it is included in the WHO model list of fundamental medicines for obstetric indications.[7] The WHO published a recent guideline that has detailed information about recommendations of use the misoprostol for obstetric and gynecologic indications. The Society of Obstetricians and Gynecologists of Canada and the American College of Obstetricians and Gynecologists also recommend misoprostol as an effective and safe method for labor induction. There is rising evidence that when compared the effect of low-dose of misoprostol taken vaginally or orally with the vaginal Dinoprostone, the effect will be better or at least the same. Several advantages of misoprostol over commercially available natural prostaglandin E2 (PGE2) preparations include: It can be used by oral and have rapid absorption, has little effect on blood vessels and bronchi, can be stocked at room temperature, and is inexpensive. Little is known about the reasons for using or not using misoprostol for labor induction and also the prevalence of off-label use of misoprostol.[8] Hence this study will be helpful to assess the use of misoprostol in various indications. The research focuses on identifying the percentage of morbidity and mortality by off-label use of misoprostol; classifying the most common off-label misoprostol use in Tabuk hospitals; determining the availability of policy and procedures behind prescribing the off-label misoprostol; and measuring the prevalence of adverse drug reactions associated with off-label prescribing.

**Materials and Methods**

Retrospective observational study was carried out. Data were collected from patients’ files for those admitted to the maternity wards in Tabuk Hospitals from March 2019 until September 2019. Study design does not include safety consideration, handling complication, sample disposal, or hazardous materials. Permission was obtained from the Research Ethics Committee (TU-077/019/019) for the conduct of study. The patient demographics, indications, dose, dosage form, dosage interval of misoprostol, duration of pregnancy, length of hospital stay were entered in a data entry form.

The use of misoprostol was compared with the guidelines to assess the appropriateness of usage.[9] Statistical Package for the Social Sciences SPSS database was used for the statistical analysis. Chi-square test was performed to assess the relationship between age of the patient and diagnosis and Kruskal–Wallis test was performed to find the relationship between age and abortion time, and length of hospital stay.

**Results**

Our study sample constituted of 150 patients, where 44% of them were from 31 to 40 years old, 29.3% from 26 to 30 years old, and the rest from 21 to 25 years, more than 40 years old, and 15 to 20 years old with 13.3%, 12.7%, and 0.7%, respectively.

The duration of pregnancy was distributed in three stages, where 42.7% were in the first 3 months of pregnancy, 30% were in 4 to 6 months, and 27.3% were in 7 to 9 months.

About 52.7% of cases were diagnosed with missed abortion, while 30% diagnosed with Postpartum hemorrhage (PPH), the rest distributed between different diagnosis such as Blighted ovum, complete abortion, fetal death, incomplete abortion, inevitable abortion, placenta removal, retained placenta, spontaneous abortion, and uterine atony.

With regard to indication, 64% of the women had induction of abortion, while 33.3% had bleeding, and the rest had removal of placenta residue, and termination of pregnancy with 1.3% for each of them.

Accordingly, misoprostol was given for the patients and dose concentration, hours of dose intervals, dosage forms and routes of administration were depicted in Table 1. The mean of misoprostol dose given was 450 ± 272 mcg; where most of the women were given 400 mcg dose followed by 200 mcg.

The mean of hours for dose interval was 13 ± 9, where majority of women (40%) were given the drug within 24h, and the rest were given the drug from 1 h up to 20h. Hundred percent of the women took the drug in tablet form. The route of administration was either oral (78%), oral/rectal (2.7%), or oral/vaginal (19.3%).

The mean time for abortion after administering misoprostol was 20.7 ± 28.2h. It showed that 15% of women were aborted within 6 h, while 12.9% were aborted after 24 h.

The length of hospital stay after administering misoprostol was shown in Table 2, where the mean of hospital stay was 3 days, where the majority stayed 1 day.
There was a statistically significant relationship between age of the patient and diagnosis as shown in Table 3. All age groups were diagnosed mostly with having missed abortion or PPH.

Table 4 does not show a statistically significant relationship between age and the abortion time, and length of hospital stay ($P > 0.05$). However, based on the results, the mean hours for patients with age 31 to 40 years, abortion was highest compared to other age groups. As well as, the mean of hospital stay was highest with patients more than 40 years age compared to other age groups.

Table 5 depicts the relationship between indication and adherence to guidelines, where statistically significant relationship existed ($P < 0.05$). As seen in the table, in 76% of women with bleeding, guidelines were not followed, as well as related to induction of abortion (94.8%), and removal of placenta residue (100%). However, with the cases related to termination of pregnancy, the guidelines were followed with 100%.

On the contrary, related to cases that followed the guideline properly, majority (63.2%) of cases were related to bleeding.

**DISCUSSION**

Many applications of misoprostol exist in the practice of obstetrics and gynecology. Efficacy and safety of misoprostol has good clinical evidence in uterine evacuation in termination of pregnancy and miscarriage. Researchers and providers must work continuously to increase the indications of misoprostol in numerous areas. The clinician must also be cautious to use an evidence-based regimen that would be facing medico-legal challenge in case of an adverse outcome. In our study, gestational age of women administered with misoprostol in PPH was high in 31–40 years but in another study, the percentage was higher in women aged 20–34 years. The frequency of using misoprostol in our study was high in induction of abortion (64%). It was inconsistent with the study conducted by Koch, in which the frequency of administration of misoprostol was higher in inducing delivery with a live fetus.\[^{10}\]

This difference may be due to difference in sample size. Regarding the time that the misoprostol give the complete abortion, in our study, mean ± STD was 20.7 ± 28.2 h which was very close to the systemic review conducted in 2017 by Wu \textit{et al.}\[^{11}\]. In 2011, a published study confirmed that the administration of misoprostol by the sublingual route is better than the oral and vaginal routes for cervical ripening.\[^{12}\]

The mean length of hospital stay for women who took misoprostol in our study was 3.0 ± 2.9 h. A study compared between the oral and vaginal misoprostol regarding length of hospital stay and they found no statistical significant difference between two mean (hours).\[^{13}\]

In our study, majority of patients were given oral therapy (78%) and it was found to be effective. It was contradictory to other study which reported that vaginal misoprostol results in a higher rate of complete abortion than oral misoprostol.\[^{14}\]

In this study, the mean time for abortion after administering misoprostol was 20.7 ± 28.2 h. Other study reported that the abortion was nearly 70% within

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**Table 1: Drug dose concentration, hours for dose intervals, dosage forms, and routes of administration of misoprostol**

| Dose (mcg) | $n = 150$ | % |
|------------|-----------|----|
| 100        | 3         | 2.0|
| 200        | 45        | 30.0|
| 400        | 61        | 40.7|
| 500        | 2         | 1.3|
| 600        | 6         | 4.0|
| 800        | 26        | 17.3|
| 1000       | 3         | 2.0|
| 1200       | 2         | 1.3|
| 1440       | 1         | 0.7|
| 1600       | 1         | 0.7|

| Hours for dose interval | $n = 150$ | % |
|-------------------------|-----------|----|
| 1                       | 1         | 0.7|
| 2                       | 17        | 11.3|
| 3                       | 10        | 6.7|
| 4                       | 2         | 1.3|
| 5                       | 2         | 1.3|
| 6                       | 20        | 13.3|
| 7                       | 3         | 2.0|
| 8                       | 17        | 11.3|
| 9                       | 4         | 2.7|
| 10                      | 1         | 0.7|
| 12                      | 12        | 8.0|
| 20                      | 1         | 0.7|
| 24                      | 60        | 40.0|

| Dosage form | $n = 150$ | % |
|-------------|-----------|----|
| Tablet      | 150       | 100|

**Table 2: Length of hospital stay after administering misoprostol**

| Length of hospital stay (days) | $n = 150$ | % |
|-------------------------------|-----------|----|
| 0                             | 3         | 2.0|
| 0.5                           | 3         | 2.0|
| 1.0                           | 48        | 32.0|
| 2.0                           | 27        | 18.0|
| 3.0                           | 25        | 16.7|
| 4.0                           | 17        | 11.3|
| 5.0                           | 10        | 6.7|
| 6.0                           | 6         | 4.0|
| 7.0                           | 4         | 2.7|
| 8.0                           | 1         | 0.7|
| 9.0                           | 1         | 0.7|
| 10.0                          | 1         | 0.7|
| 11.0                          | 1         | 0.7|
| 13.0                          | 1         | 0.7|
| 20.0                          | 2         | 1.3|
Table 3: Relationship between age of the patient and diagnosis

| Diagnosis                | Age of patient (years) | Total | P-value |
|--------------------------|------------------------|-------|---------|
|                          | 15–20 | 21–25 | 26–30 | 31–40 | >40 | |
| Blighted ovum            | Count | 0 | 2 | 0 | 1 | 0 | 3 | 0.012 |
|                          | %     | 0.0 | 10.0 | 0.0 | 1.5 | 0.0 | 2.0 |
| Complete abortion        | Count | 0 | 0 | 0 | 1 | 1 | 1 | |
|                          | %     | 0.0 | 0.0 | 0.0 | 0.0 | 5.3 | 0.7 |
| Fetal death              | Count | 0 | 1 | 1 | 0 | 0 | 2 | 1.3 |
|                          | %     | 0.0 | 5.0 | 2.3 | 0.0 | 0.0 | 1.3 |
| Incomplete abortion      | Count | 0 | 0 | 0 | 9.1 | 9.1 | 0.0 | 6.7 |
|                          | %     | 0.0 | 0.0 | 9.1 | 9.1 | 0.0 | 6.7 |
| Inevitable abortion      | Count | 0 | 0 | 0 | 3 | 0 | 0 | 3 |
|                          | %     | 0.0 | 0.0 | 6.8 | 0.0 | 0.0 | 3 |
| Missed abortion          | Count | 0 | 7 | 20 | 41 | 11 | 79 | |
|                          | %     | 0.0 | 35.0 | 45.5 | 62.1 | 57.9 | 52.7 |
| Placenta removal         | Count | 0 | 0 | 0 | 2.3 | 0.0 | 0.0 | 1 |
|                          | %     | 0.0 | 0.0 | 2.3 | 0.0 | 0.0 | 1 |
| PPH                      | Count | 1 | 7 | 13 | 17 | 7 | 45 | |
|                          | %     | 100.0 | 35.0 | 29.5 | 25.8 | 36.8 | 30.0 |
| Retained placenta        | Count | 0 | 0 | 0 | 2 | 0 | 2 | |
|                          | %     | 0.0 | 0.0 | 4.5 | 0.0 | 0.0 | 1.3 |
| Spontaneous abortion     | Count | 0 | 0 | 0 | 1 | 0 | 1 | |
|                          | %     | 0.0 | 0.0 | 4.5 | 0.0 | 0.0 | 1.3 |
| Uterine atony            | Count | 0 | 3 | 0 | 0 | 0 | 3 | |
|                          | %     | 0.0 | 15.0 | 0.0 | 0.0 | 0.0 | 2.0 |

Table 4: Relationship between age and abortion time, and length of hospital stay

| When was it aborted after drug administration or stop bleeding in case of PPH (hours) | Age of patient | n | Mean rank | Mean | P-value |
|----------------------------------------------------------------------------------|----------------|---|-----------|------|---------|
| 15–20 years                                                                      | 1              | 1 | 102.50    | 20.0 | 0.932   |
| 21–25 years                                                                      | 20             | 20| 72.25     | 13.5 |         |
| 26–30 years                                                                      | 44             | 44| 76.10     | 16.7 |         |
| 31–40 years                                                                      | 64             | 64| 71.82     | 26.1 |         |
| more than 40 years                                                               | 18             | 18| 76.97     | 19.2 |         |
| Length of hospital stay (days)                                                   |                |   |           |      |         |
| 15–20 years                                                                      | 1              | 1 | 115.00    | 4.0  | 0.105   |
| 21–25 years                                                                      | 20             | 20| 68.45     | 2.8  |         |
| 26–30 years                                                                      | 44             | 44| 63.60     | 2.1  |         |
| 31–40 years                                                                      | 66             | 66| 81.63     | 3.3  |         |
| more than 40 years                                                               | 19             | 19| 87.11     | 4.4  |         |

Table 5: Relationship between indication and adherence to guidelines

| Indication and following guidelines | Guidelines followed | Total | P-value |
|------------------------------------|---------------------|-------|---------|
|                                    | Yes | No |       |       |
| Bleeding                           | 12  | 38 | 50    | 0.000 |
| % within indication                | 24.0| 76.0| 100.0|       |
| % within following guidelines      | 63.2| 29.0| 33.3|       |
| Induction of abortion              | 5   | 91 | 96    | 96.0 |
| % within indication                | 5.2 | 94.8| 100.0|       |
| % within following guidelines      | 26.3| 69.5| 64.0|       |
| Removal of placenta residue        | 0   | 2  | 2     | 2     |
| % within indication                | 0.0 | 100.0| 100.0|       |
| % within following guidelines      | 0.0 | 1.5 | 1.3   |       |
| Termination of pregnancy           | 2   | 0  | 2     | 2     |
| % within indication                | 100.0| 0.0| 100.0|       |
| % within following guidelines      | 10.5| 0.0| 1.3   |       |
first 12 h, 80% in 24 h and 95% in 48 h. The expulsion of products of conception increases until 72 h.\textsuperscript{[12]} In our study, majority of women (40%) were given the drug within 24 h, and the rest were given the drug from 1 h up to 20 h. It was inconsistent with another study which depicted that the dose was administered over the interval of more than 48 h.\textsuperscript{[16]} There were no significant complications associated with the administration of misoprostol.

The physicians use misoprostol off-label without following policies or guidelines. Moreover, the hospital does not have specific guidelines for off-label use of drug. There must be a unified guideline in the hospital for the physicians to follow unified pattern of prescribing misoprostol.

Limitations

There were very less studies conducted with regard to off-label use of misoprostol. Hence, there was a main limitation of comparing with other studies.

CONCLUSION

There is no policy and procedure available in the hospital regarding off-label use of misoprostol. Moreover, physicians have low adherence to the guideline in terms of dosage, interval, and route of administration for each indication in obstetrics and gynecology.

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Conflicts of interest
There are no conflicts of interest.

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