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VAGINAL VERSUS RECTAL MISOPROSTOL BEFORE LAPAROTOMIC MYOMECTOMY

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Abstract
Background: Leiomyoma is benign, monoclonal tumor of the smooth muscle cells of the myometrium. It is much denser than normal myometrium. It affects mostly women during reproductive age; rarely found before menarche & usually regress after menopause.
Aim: to compare among vaginal & rectal misoprostol-as a preoperative medication-in controlling blood loss throughout myomectomy
Patients and methods: From January 2022 to January 2023, the Zagazig University Hospitals' department of obstetrics and gynecology hosted this randomized controlled experiment.
Results: There was no statistically significant difference in pre-operative mean hemoglobin, 24 hours postoperative hemoglobin content, pulse, need for blood transfusion, diastolic and systolic blood pressure among both groups (p-value>0.05). Regarding peri-operative complications & length of hospital stay in both groups, febrile morbidity and need for additional analgesics were statistically significantly higher in G2 than G1 (4.5% versus 31.8% and 9.1% versus 40.9% respectively) (p-value=0.04* & 0.01* respectively .However, no statistically significant difference among both groups with regard to hospital stay, need for hysterectomy& other complications as diarrhorea and abdominal cramps (p-value >0.05).
Key words: vaginal; rectal; Myomectomy.

Introduction

Leiomyoma is benign, monoclonal tumor of the smooth muscle cells of the myometrium. It is much denser than normal myometrium. It affects mostly women during reproductive age; rarely found before menarche & usually regress after menopause [1].

More leiomyomas grew intramurally than subserous or submucosally, while larger and medium-sized leiomyomas grew more than small ones. According to one study, MRI measurements of growth rates for various racial & ethnic groups were comparable [2].

Sonography can show symmetrical, well-defined, hypoechoic, & heterogeneous masses that are leiomyomas. Transvaginal sonography is a reasonably reliable method for uteri with a total volume of less than 375ml3 or those contain four or less leiomyomas [3].

Surgery is the mainstay of therapy for leiomyomas. Indications for surgical therapy are abnormal uterine bleeding, pressure symptoms, Infertility or recurrent pregnancy loss [4]. It includes; Laparotomy (hysterectomy and myomectomy), endoscopy (hysteroscopic myomectomy, laparoscopic myomectomy or hysterectomy or uterine artery occlusion or myolysis) [4].

The surgical excision of fibroids via a longitudinal or transverse abdominal incision is known as an abdominal myomectomy. It is a choice for women who want to keep their uterus or who have not finished having children [5].

Blood loss throughout myomectomy is related to the size & numbers of leiomyomas. There are several methods used to decrease blood loss throughout myomectomy including pharmacological and mechanical methods [6].

Pharmacological methods might provide benefits in decreasing blood flow during the operation, but they vary in effectiveness among individual patients, these agents include vasopressin injections and uterotonics (misoprostol) [6].

For the uterine incision, the conventional wisdom has been to make vertical incisions to stop the uterus' transversely running arcuate arteries from transposing. However, because leiomyoma alters normal vascular architecture, avoiding these veins is not practical[7].

Any leiomyoma or cluster of adjacent or surrounding leiomyomas may have an incision made over them all. With this method, the leiomyoma can be easily removed, and the myometrial flaws can be quickly closed to ensure haemostasis[8].

To remove leiomyoma, numerous surgeons use towel clamps or single tooth tenaculums to apply traction on the myometrial margins, exposing the leiomyoma. Usually, a sponge or the back of an empty knife handle is used to bluntly cut the plane among the myometrium & leiomyoma; it has been reported that each leiomyoma has a vascular pedicle at its base that, when ligated, allows for haemostasis throughout myomectomy[9].

Layers of sutures are used to close the uterine abnormalities. To reaproximate the tissue & accomplish haemostasis, 2 layers can be required if the defect is deep (>2cm)[10].

By constricting the smooth muscle in the walls of capillaries, tiny arterioles, & venules, intramyometrial vasopressin, injected into the planned uterine incision site for each fibroid, lowers blood loss. However, it has been linked to infrequent instances of bradycardia, heart failure, & even death[11].

Additionally useful in minimizing blood loss throughout myomectomy is epinephrine. An intramyometrial injection of bupivacaine with epinephrine (50ml of bupivacaine cloridrate 0.25% & 0.5ml of 1mg/ml epinephrine) decreased blood loss when compared to saline (69ml less), according to a randomized trial. Like vasopressin, intravascular injection of epinephrine can result in immediate cardiovascular adverse effects[12].

Misoprostol, an analogue of prostaglandin E1, is frequently used. Before a myomectomy, a single dosage of vaginal misoprostol would lessen blood loss & the requirement for postoperative blood transfusion in women who had myomectomy surgery[13].

Misoprostol decreases blood loss in the uterus through 2 different mechanisms: 1st, it strengthens myometrial contractions & influences the vascular structures that originate from the uterine artery & utero-ovarian anastomosis, resulting in decreased blood flow. 2nd, it could have a direct vasoconstrictive effect on the uterine arteries[14].

Misoprostol is a viscous liquid that dissolves in water. The therapeutic activity of misoprostol is attributed to its fast de-esterification to its free acid after broad absorption. Its 3 shortcomings have limited its clinical use: a short half-life due to chemical instability, several side effects, & a fast metabolism that prevents it from acting orally & prolongs its duration of action when administered parenterally[15].

In obstetric & gynaecological uses, additional routes of administration including vaginal, sublingual, & rectal have been widely utilized. The area under the serum concentration versus time curve (AUC, equivalent to bioavailability) indicates the total exposure to the drug, while the time to peak concentration (T max) indicates how quickly the drug can be absorbed and the peak concentration (C max) indicates how well the drug is being absorbed [16].

After taking 400mcg of oral misoprostol once, the plasma level rises quickly, peaks in around thirty minutes, then rapidly falls in 120minutes, & stays low for the rest of the time[17].

Rectal use is associated with a lower incidence of side effects, particularly shivering. It has the advantage of easy administration and rapid absorption [18].

When the impacts of misoprostol were studied on uterine contractility after various administration methods, it was discovered that uterine tonus increases more quickly & dramatically after oral & sublingual medication than it does after vaginal treatment[19].

Based on its strong stimulatory action on the myometrium and vascular effects, particularly on the uterine blood arteries, which cause vasoconstriction, misoprostol is thought to be involved in the treatment of heavy menstruation[20].

It can decrease blood loss during myomectomy as it induces vasoconstrictions in the most of human vascular beds such as limbs and kidneys and it is suggested that the impacts of oral misoprostol on uterine arteries are vasoconstrictive one hour after its administration [20].

Fever & chills are frequently seen when using misoprostol, but they are only temporary, especially whether taken orally or sublingually. Antipyretics & physical cooling help to relieve these symptoms[21].

The most frequent adverse effect is diarrhoea, which normally goes away on its own in a day or two. Usually, vomiting goes away in about six hours. After oral or sublingual intake, the adverse effects on the gastrointestinal tract are more prevalent[16].

Menstrual cramps, often known as abdominal cramps, can begin as soon as ten minutes after administration & typically appear during the 1st few hours[22].

The aim of the research was to compare among vaginal & rectal misoprostol-as a preoperative medication-in controlling blood loss throughout myomectomy& to compare the efficacy of preoperative vaginal and rectal misoprostol in controlling blood loss in laparotomic myomectomy.

Patients& methods

From January 2022 to January 2023, the Zagazig University Hospitals' department of obstetrics and gynecology hosted this randomized controlled experiment. The research complied with the Helsinki Declaration of 1964 & its subsequent revisions.

All studied cases gave a written informed consent before participation. An adequate number of patients were selected as per the inclusion and exclusion criteria. Forty-four premenopausal patients had been enrolled in this research. All studied cases had been scheduled for abdominal myomectomy due to symptomatic uterine leiomyoma. The study was a double blind randomized prospective study. The studied cases had been randomly allocated into 2 groups. Group A (n = 22) had been given 400µg of vaginal misoprostol (cytotec, 200µg**)** three hours before the operation, and group B (n = 22) were given 400 µg of rectal misoprostol three hours before the operation.

The inclusion criteria: married female patients, their ages ranged from 20 to 45 years. All of them were previously diagnosed with uterine leiomyoma by pelvic ultrasound. All patients were symptomatizing of pain and/or bleeding.

The exclusion criteria included virgin females, patients whose age was below20 or more than forty-five years, studied cases with body mass index more than 30, severely

anemic patients who needed preoperative blood transfusion for correction of anemia, patients with coagulation disorders, medical disorders like cardiac, pulmonary disease or endocrinal disorders. Patients with previous history of laparotomy or those who were given GnRH analogue before surgery had been excluded. Likewise, studied cases with known allergy to misoprostol were dropped out from the start.

Before surgery: All recruited studied cases had been subjected to complete history taking, combined general and abdominal & pelvic examination. Ultrasound examination (TAS and TVS) was done to all patients before surgery to exclude any other associated pathology and to record the uterine size, number of uterine myomas, site of myoma and the largest myoma diameter. Preoperative pulse, blood pressure, hemoglobin concentration was recorded.

Before the operation, studied cases had been randomly allocated (computer based) to group A (given vaginal misoprostol) or group B (given rectal misoprostol). Combined per vaginal and per rectal examinations were done with lubricant to all patients during the time of misoprostol insertion to mask the route of administration. So, the operative team did not know the route of misoprostol administration whether vaginally or rectally.

All cases were operated by the same team in general gynecology unit. Pfannenstiel incision was the incision of choice for all patients. The same hemostatic rules were followed during the operation for all patients. During the operation, average blood pressure and pulse were recorded. The intraoperative blood loss had been estimated by measuring the amount of blood in the suction bottle& by using the gravimetric method to calculate the amount of the absorbed blood by the surgical sponge and laparotomy pads. Postoperatively, the average pulse and blood pressure were recorded during the first 24 hours. Hemoglobin concentration was checked 24 hours after surgery. Post-operative febrile morbidity (body temperature ≥38 ˚C) and the need of postoperative blood transfusion were documented. Also, the need of postoperative additional analgesic and the total hospital stay were registered.

Statistical method

SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium) was used to analyzeall the data. The formula for continuous variables was mean plus standard deviation. Continuous variables were examined for normality using the Q-Q plot & the Shapiro-Wilk test (sig). For this regularly distributed quantitative data, 2 separate groups were compared using the T-test; for the qualitative data, 2 independent groups were compared using the Fischer Exact test, or chi square. Every test had 2 sides. The thresholds of significance were as follows: $p < 0.05$ meant statistical significance, $p < 0.001$ meant highly statistical significance, & $p \geq 0.05$ meant non-statistically significant.

Results

This study included 44 participants; they were classified into twogroups (22 each); 1st one received vaginal misoprostol (G1) and the 2nd group received rectal misoprostol (G2).

There was no statistically significant difference in demographic data (age, BMI, total number of myomas, largest myoma diameter (mm), number of uterine incision and parity) between both groups (p-value>0.05).**(table1)**

The difference in the mean operative time had statistically very high significance while the approximate average intraoperative blood loss had statistically high significance in G1 than G2 (p-value<0.001**) & (p-value<0.05*) respectively **(table2).**

There was no statistically significant difference in pre-operative mean hemoglobin, 24 hours postoperative hemoglobin content, pulse, need for blood transfusion, diastolic and systolic blood pressure among both groups (p-value>0.05).**(table 2).**

Regarding peri-operative complications & length of hospital stay in both groups, febrile morbidity and need for additional analgesics were statistically significantly higher in G2 than G1 (4.5% versus 31.8% and 9.1% versus 40.9% respectively) (p-value=0.04* & 0.01* respectively).**(table3).**

However, no statistically significant difference among both groups with regard to hospital stay, need for hysterectomy& other complications as diarrhorea and abdominal cramps (p-value >0.05).**(table3) & (figure1).**

Table (1): Comparing demographic data among the two studied groups:

Characteristic	Vaginal Misoprostol G1 (22) mean ± SD	Rectal misoprostol G2 (22) mean ± SD	P value
Age (year)	28.5±4.3	29.3±3.2	0.4
BMI	28.5±1.4	28.9±1.6	0.3
Total number of myomas	4.3±0.9	4.6±0.7	0.2
Largest myoma diameter (mm)	182±25.6	188±24.3	0.4

Number of uterine incision	2.2±0.3		2.4±0.5		0.11
Parity Nulliparous Multiparous	5 17	(22.7%) (77.3%)	6 16	(27.3%) (72.7%)	0.7

^;t-test, ^^; Chi square test, p-value>0.05 is non-significant.
In this table, there was no statistically significant difference in age, BMI, total number of myomas, largest myoma diameter (mm), number of uterine incision and parity between both groups.

Table (2): Comparing intraoperative blood loss & postoperative follow up data among the 2 studied groups:

Characteristic	Vaginal Misoprostol G1 (22) mean ± SD	Rectal misoprostol G2 (22) mean ± SD	P value^
Mean operative time (minutes)	68.5±0.8	58.1±0.5	0.001**
Approximate average intraoperative blood loss	510±23.7	458±21.5	0.03*
Mean hemoglobin Preoperative 24 hours postoperative	 12.1±2.5 9.9±0.7	 11.8±2.1 10.1±0.8	 0.6 0.08
Vital signs: Pulse rate: Average preoperative Average within 24 hours postoperative Systolic blood pressure : Average preoperative Average after 24 hours postoperative Diastolic blood pressure Average preoperative Average within 24 hours postoperative	 74.5±4.5 87.2±8.1 102.3±10.1 134.5±1.6 74.9±0.7 86.4±0.5	 76.1±3.6 85.6±5 99.7±12.6 133±1.7 75.1±0.6 87.1±0.8	 0.1 0.2 0.5 0.06 0.3 0.07
Need for transfusion (n.)	No. (%) 2 (9.1%)	No. (%) 1 (4.5%)	 0.5^^

* Statistically significant difference (P ≤ 0.05), * *Statistically highly significant difference (P ≤ 0.001), ^;t-test, ^^; Fischer Exact test. (p-value>0.05) non-significant

In this table, there was statistically very high significant difference among both groups in the mean operative time **, high significant difference in the approximate average intraoperative blood loss* & no statistically significant difference in pre-operative mean hemoglobin, 24 hours postoperative hemoglobin content, pulse, need for blood transfusion, diastolic and systolic blood pressure among both groups (p-value>0.05)

Table (3): Comparing peri-operative complications & length of hospital stay among the 2 studied groups:

Characteristic	Vaginal Misoprostol G1 (22) mean ± SD	Rectal misoprostol G2 (22) mean ± SD	P value^
Hospital stay (n days)	3.4±0.3	3.2±0.4	0.06
Need for hysterectomy (n)	0.00 (0.00%)	1.0 (4.5%)	0.5
Febrile morbidity	1.0 (4.5%)	7.0 (31.8%)	0.04*
Need for additional analgesics (n)	2.0 (9.1%)	9.0 (40.9%)	0.01*
Other complications eg Diarrhea, cramps	1.0 (4.5%)	2.0 (9.1%)	0.54

^^; Fischer Exact test, ^; T-test, * Statistically significant difference (P ≤ 0.05).

In this table, there was statistically significant difference between both groups in febrile morbidity and need for additional analgesics with higher rate in G2 than G1. But regarding Hospital stay, need for hysterectomy and other complications, there was no statistically significant difference among both groups.

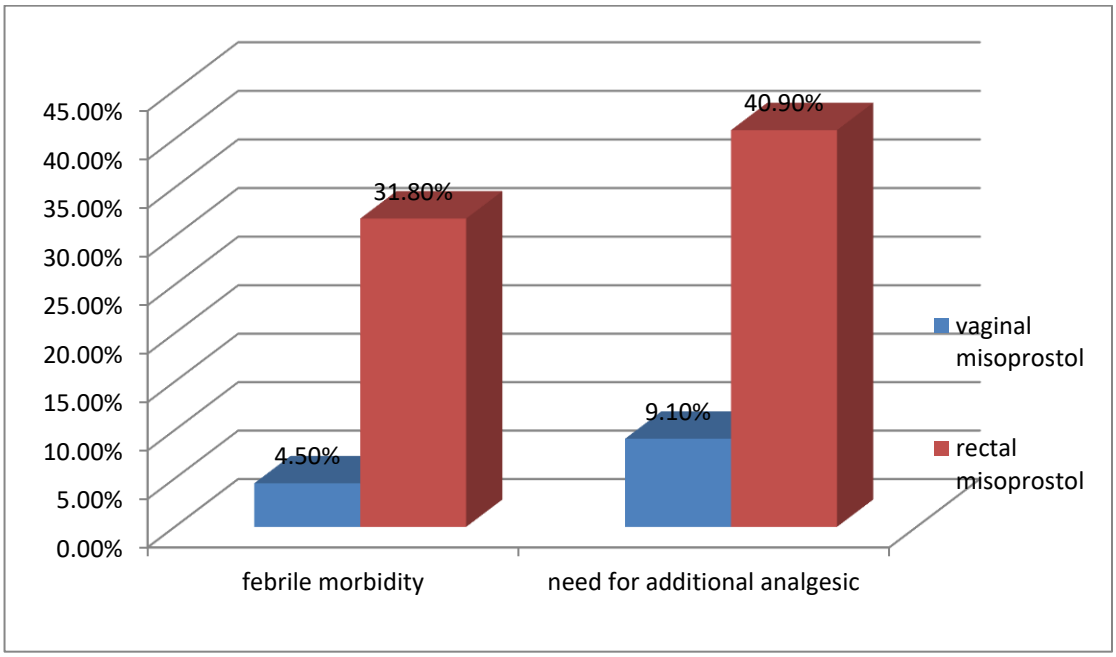

Fig (1): the significance difference in febrile morbidity and need for additional analgesics between vaginal and rectal misoprostol groups.

Disscusion

The surgical excision of fibroids via a longitudinal or transverse abdominal incision is known as an abdominal myomectomy. It is a choice for women who want to keep their uterus or who have not finished having children [5].

There are several methods used to decrease blood loss throughout myomectomy including pharmacological and mechanical methods [6].

Pharmacological methods might provide benefits in decreasing blood flow during the operation, but they vary in effectiveness among individual patients, these agents include vasopressin & other injections and uterotonics (misoprostol) [6].

Misoprostol reduces blood loss in the uterus by increasing myometrial contractions & by the direct vasoconstrictive impact on uterine arteries [14].

In this double-blind randomized trial study, 44 participants were classified into two groups (22 each); 1st one received vaginal misoprostol (G1) and the 2nd group received rectal misoprostol (G2) 400 µg each 3 hours before myomectomy. There was no statistically significant difference in demographic data (age, BMI, total number of myomas, largest myoma diameter (mm), number of uterine incision and parity) between both groups which coincides with the outcomes of research described by **Ragab et al., (14) & (Abdel-Hafeez etal., (23).**

No statistically significant difference in pre-operative mean hemoglobin, 24 hours postoperative hemoglobin content, pulse, need for blood transfusion, diastolic and systolic blood pressure between both groups which coincides with the outcomes of research described by **Ragab et al., (14) & (Abdel-Hafeez etal., (23).**

The average blood loss in G1 was (510±23.7) ml & in G2 was (458±21.5) ml, according to this study, which agrees with **Chiang et al, (24)** who reported that the average blood loss volume during an abdominal myomectomy range from about 200 to 800ml depending on their study.

This agreed with another research done by **Niroomand et al., (25)** in which 40 studied cases with leiomyoma scheduled for myomectomy received a preoperative single dose of intravaginal misoprostol and the amount of blood loss was (485 ± 287).

Data from the current study stated that transrectal route was found to decrease the amount of hemoglobin loss intra and postoperatively which agreed with the study of **(Irum Batool er al., (26)** in which they compared results of 400 µg misoprostol 1 hour preoperatively. The results were comparable with the current study results but it differs in the interval time (1 hour vs 3 h) and number of the participants (100 vs 44) **(Irum Batool er al., (26).**

The study of **Maneerat P et al., (27)** observed that there was no significant benefit in blood loss decrease after using preoperative rectal misoprostol & this is not agreed with the current study results which can be attributed to the time interval, dose of drug & route and myoma size and type.etc

The difference in the mean operative time had statistically very high significance in favor with G2 (58.1±0.5) min than G1 (68.5±0.8) min. which also was matching with study by **Iavazzo C et al., (28)** which was a meta-analysis & discovered that the characteristics that make misoprostol helpful in the realization of myomectomy, regardless of the surgical technique used & after use of both transvaginal & transrectal administration route, are its ease of use, minor or no side effects, & good clinical outcomes.

There was statistically significant difference among both groups in febrile morbidity and need for additional analgesics with higher rate in G2 than G1, but as regarding Hospital stay, need for hysterectomy and other complications; there was no statistically significant difference among both groups. These results agreed with the results from **Maneerat P et al., (27)** in which there was statistically significant difference in the side effects after rectal misoprostol use as abdominal cramps, fever, vomiting and diarhorrhea.

Celik and Spamaz (29) noted in their study that there was a statistically significant decrease in the demand for blood transfusion; however, in the present research, blood transfusion requirements were lower in G2 than in G1, although they did not reach statistically significant values. Further research with a larger sample size may be necessary to validate the results & allow significant values to emerge.

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