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Research Article

New Protocols in the Management of Postpartum Hemorrhage

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Abstract

Objective: Identify the most effective uterotonic agents to prevent postpartum hemorrhage with the fewest side effects and to characterize women who respond best to one treatment or another.

Material And Method: A prospective study was carried out at Hospital Universitario Quironsalud Malaga in the period between December 2020 and March 2021, with included 60 pregnant women as participants. We have compare the estimation of blood loss using four different protocols with oxytocin in different moments, misoprostol or carbetocin to control postpartum bleeding.

Results: This study shows that the risk of bleeding with carbetocin first and with the combination of misoprostol and oxytocin in second place, is lower even with maternal risk factors, the results being statistically significant. Also, we have observed a strong and direct association between blood loss (difference in hemoglobin before delivery and after delivery) and the estimation of the lost blood Volume With The Visual Scale. With A Correlation Coefficient Of 0.86

Conclusions: After the results obtained, it is concluded that using carbetocin or oxytocin and misoprostol at prophylactic doses of 600 mcg, leads to a lower loss of bleeding, even in the case of having a maternal risk factor. In addition, postpartum bleeding can be quantified through the estimated volume lost using the visual scale.

Keywords: *Postpartum Hemorrhage; Misoprostol; Oxytocin; Carbetocin; Prevention*

Introduction

Around 1500 women die daily due to complications of pregnancy and childbirth in all the world. 99% of maternal deaths correspond to developing countries [1]. Postpartum hemorrhage is one of the more frequent causes of maternal deaths, along with infections and hypertension. it has been defined as a blood loss in excess of 500 mL in a vaginal delivery and more than 1 L in a cesarean delivery. For clinical purposes, any blood loss that may cause hemodynamic instability, should be considered [2].

Causes include uterine atony, birth canal injuries, product retention conception and coagulation disorders. Uterine atony is one of the most common causes of postpartum hemorrhage and consists of in loss of myometrial tone. Birth canal injuries include uterine rupture,

lacerations of the cervix and vagina. Another cause of postpartum hemorrhage is the retention of products of conception. Coagulation disorders can be congenital or acquired [3].

In relation to risk factors, different articles shows that postpartum bleeding is associated with hypertensive syndromes, uterine fibroids, macrosomia, polyhydramnios, multiparity, maternal age over 35 years, smoking and drugs, prolonged labor, placenta accreta, retained placenta, previous postpartum hemorrhage, instrumental delivery [3,4].

The diagnosis is mainly clinical by symptoms and / or signs of hypovolemia such as dyspnea, tachycardia, sweating, paleness, dizziness, confusion, weakness, decreased blood pressure, oliguria, anuria [5]. It can also be diagnosed by the amount of 0.5 liters blood loss after vaginal delivery or 1 liter if it is after cesarean section [6].

When postpartum hemorrhage is diagnosed, the first thing to do is notify health professionals involved. Second, the patient must be evaluated with the ABCDE system. Once the patient is stable, the cause must be diagnosed [7].

The most common uterotonic drugs are oxytocin, carbetocin and misoprostol. If drug treatment is not effective, we should start with the maneuvers such as intrauterine balloon or embolization of the uterine artery [8]. When mechanical methods and pharmacological treatment fail, we use the surgical treatment such as uterine compression sutures, vascular ligation or in the final case, obstetric hysterectomy [9].

The main therapeutic goals of the treatment of massive hemorrhage are maintain hemoglobin > 8 g / dl, platelet count > 75 x 100 / l, activated prothrombin 1.0 g / 14 l [10].

The blood transfusion protocol is activated when the estimated bleeding exceeds 2,000 ml or if the patient is hemodynamically unstable or presents alterations in the state of consciousness [11].

Among the pharmacological measures to prevent postpartum hemorrhages, various uterotonic drugs [12].

- Misoprostol: Prostaglandin E1 Analog. Different studies show that in communities with limited access to healthcare, could distribute misoprostol and teach women how to use it to reduce risk postpartum hemorrhage.
- Carbetocin is an oxytocin analog, so it binds selectively to oxytocin receptors. It is effective in reducing the need for additional uterotonics and blood transfusions. Is more cost-effective than oxytocin for the prevention of uterine bleeding.
- Oxytocin is the most standardized treatment. Used preventively in compared to placebo can reduce the risk of blood loss by 1000 ml.
- Various studies show that the binding of carbetocin plus oxytocin and the binding of Misoprostol and oxytocin is more effective than just oxytocin. However, they have not conducted quality clinical trials, so the effects remain to be assessed side effects that can be produced and the cost-effectiveness [13].
- There are different methods of quantifying bleeding associated with childbirth [14-16].
- Visual calculation is a subjective measure in which the professional scores the amount of blood lost by the patient. Although it is a test with little specificity and little sensitivity can be of great help when healthcare personnel are trained. A type of visual calculation is the visual estimation of blood loss (Figure 1).

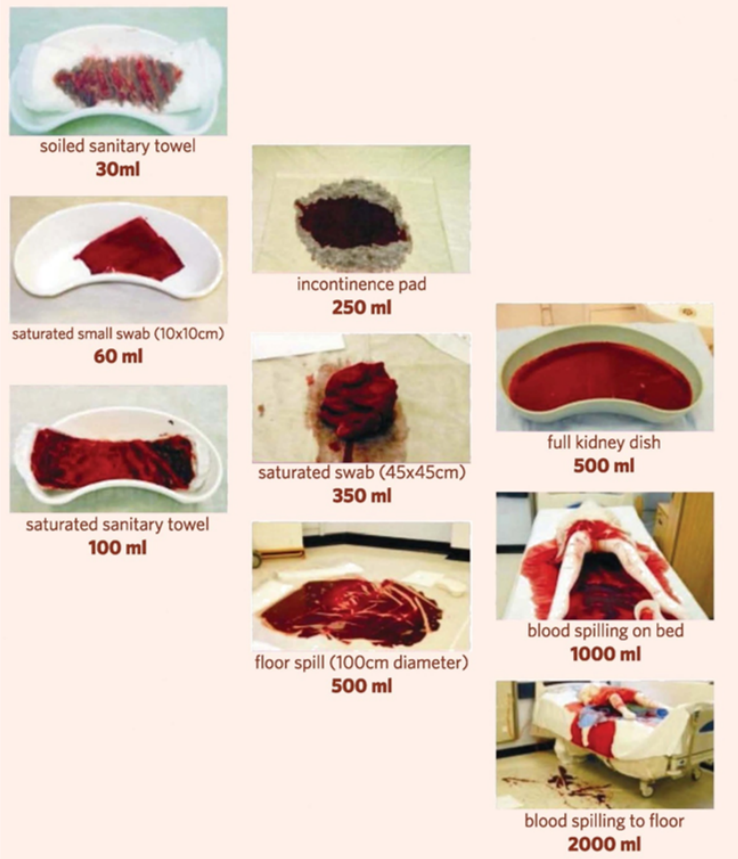


Figure 1: *Visual estimation of bloodloss [25].*

- Collection bag is an objective and easy method, which collects in a bag of marked the deposited volume. It is estimated that it has a sensitivity of 80%, specificity of 95.7%, positive predictive value of 88.9% and negative predictive value of the 91.8%.
- Gravimetric method is an objective method in which knowing the dry weight of the absorbent materials we can calculate the amount of blood loss. It is an easy to use, although bleeding tends to be overestimated as there may be other fluids
- Hemoglobin concentration can be found from a mathematical formula (from Brecher). It is based on easily measurable factors such as the blood volume of the patient, number and type of units of red blood cells transfused, hematocrit initial, the trigger for the transfusion, the volume of blood recovered after the transfusion and the amount of hemodilution performed.

Hemoglobin concentration can also be measured in blood by spectrometry, a non-invasive method and using nuclear medicine by introducing a radioactive marker that controls the concentration of hemoglobin.

These methods advanced measures could provide a better quantification of blood loss, but they are not accessible in most environments.

Objectives

Oxytocin, misoprostol, and carbetocin are uterotonic drugs used for prevention of postpartum hemorrhage.

The objectives of this retrospective study are compare the effectiveness of misoprostol plus oxitocin, cabetocin, and oxytocin after delivery or by targeted delivery, for prevention of hemorrhage postpartum.

As a secondary objective, we include the comparison of the visual method (subjective) with the comparison of pre and postpartum (target) hemoglobin for hematic loss estimation.

Material and Methods

We have carried out a prospective study at the Quirónsalud Universitary Hospital in Malaga in the period of time between December 2020 and June 2021.

60 pregnant women between 18 and 45 years old have been included, with the criteria of no family history of congenital malformations, which have been correctly followed during pregnancy, do not take any treatment that may affect the study and with vaginal birthing. The patients included in the study were randomized.

For the calculation of postpartum bleeding we have used the visual scale of estimation of blood loss that is carried out using gauze that is equivalent to a quantity of 25 ml of blood, compresses equivalent to 75ml, 200ml soaker, 800ml caesarean section and blood in the legs 1000ml.

Variables included were type of delivery, age, weight, height, body mass index, race, maternal risk factors obstetric history, gestational age, induction of labor, type of pregnancy, intrapartum anesthesia, type of delivery, episiotomy, perineal tear, estimation of the volume lost, hemoglobin before delivery, hemoglobin after delivery, side effects, fetal weight, rescue drugs.

The statistical study was carried out with SPSS, obtaining a statistical significance for the value of $p < 0.05$.

Protocols

- Protocol 1: Infusion of 20 IU of oxytocin diluted in 500 ml of fluid, at a speed 200 mL / hour after delivery of the placenta.
- Protocol 2: Targeted delivery, IV infusion of 10 IU of oxytocin in 9 ml of crystalloid administered after the anterior part of the shoulder has come out. It continues with 15 IU at 200 ml / h.
- Protocol 3: Oxytocin + PGE1 (misoprostol): Infusion of 20 IU of oxytocin diluted in 500 ml of fluid with 3 rectal misoprostol tablets (600 mcg).
- Protocol 4: Carbetocin, 100 ml bolus in slow infusion.

Results

Of the 60 patients included in the study, 15 were assigned to each of the four protocols.

The mean age of the women who gave birth was 34.089 years with a 95% CI [32.76 - 35.42]. The minimum age of was 22 years and the maximum age was 43 years.

The mean body mass index of all women was 25.36 with a 95% CI [24.5 - 26.22].

76.7% do not present maternal risk factors. However, 33.3% if they present risk factor's.

The mean gestational age was 39.31 weeks with a 95% CI [38.84 - 39.78].

100% of the women had a single pregnancy, 93.33% received epidurals and the 7.67% did not receive any type of anesthesia.

75.56% had a eutocic delivery, 8.89% had a forceps delivery, and 15.56% they had a vacuum delivery.

28.89% required episiotomy. 42.22% had a type I perineal tear, 32.33% had a type II perineal tear, 4.44% had a type IIIa perineal tear and 20% of the women did not have a perineal tear. The mean weight of the newborns was 3312 grams with a 95% CI [3055.67 - 3568.55].

Homogeneity in the population was demonstrated between the different criteria studied and analyzed between the different protocols.

In relation to protocol 1, the average estimated lost volume was 391.73 ml with a 95% CI [279.77 - 503.69]. In protocol 2 the average of the volume lost estimated was 225.47 ml with a 95% CI [170.04 - 280.9]. In protocol 3 the average of the estimated lost volume was 212.2 ml with a 95% CI [92.34 - 332.06]. At protocol 4 the mean estimated lost volume was 173.5 ml with a 95% CI [80.72 - 224.16].

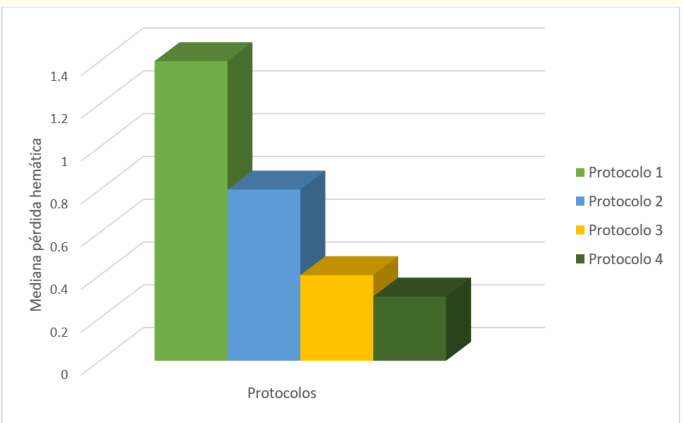
In relation to blood loss, the previous mean hemoglobin decrease and postpartum, in protocol 1 it was 1.58 with a 95% CI [1.11 - 2.05], in protocol 2, that of 0.9067 95% CI [0.74 - 1.08], in protocol 3 of 0.88 with a 95% CI [0.20 - 1.53], and in protocol 4 of 0.34 with a 95% CI [0.11 - 0.86].

In protocol 1, 53.33% had no side effects derived from the loss hematic, 40% had anemia and 6.66% had anemia and hypotension. In protocol 2 66.67% had no side effects of blood loss, 26.67% had anemia and 6.67% had anemia and hypotension. With respect to protocol 3, 60% had no effects secondary effects derived from blood loss and 40% had anemia.

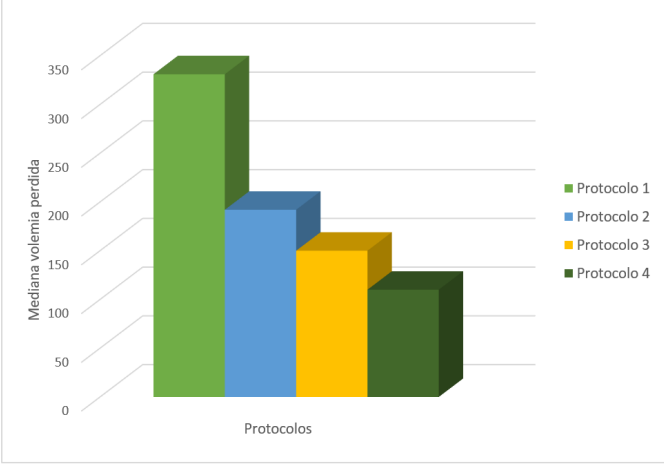
Protocol 3, have been described in the data collected low-grade fever by 42% of the patients without reaching her at a demonstrated fever with a temperature above 38 ° C. In protocol 4, 47.26% had no side effects derived from the loss hematic, 32% had anemia.

In protocol 1, 60% did not need rescue drugs, 13.33% needed methergin and 26.67% needed other drugs. In protocol 2 they did not need rescue drugs 66.67%, 20% needed methergin, 6.67% amchafibrin and others drugs 6.67%. In protocol 3 they did not need rescue drugs in 100% of women who gave birth. In protocol 4, one patient required Amchafibrin from subtract yourself.

Graphs 1 and 2 represent the median estimate of blood loss as well as of the volume lost between the different treatments used, showing better results with carbetocin, later with misoprostol + oxytcin, and finally with oxytocin.

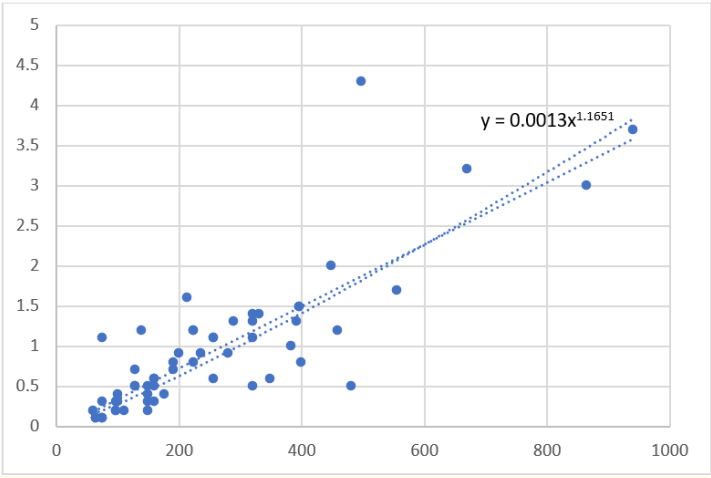


Graph 1: *Median of estimated blood los.*



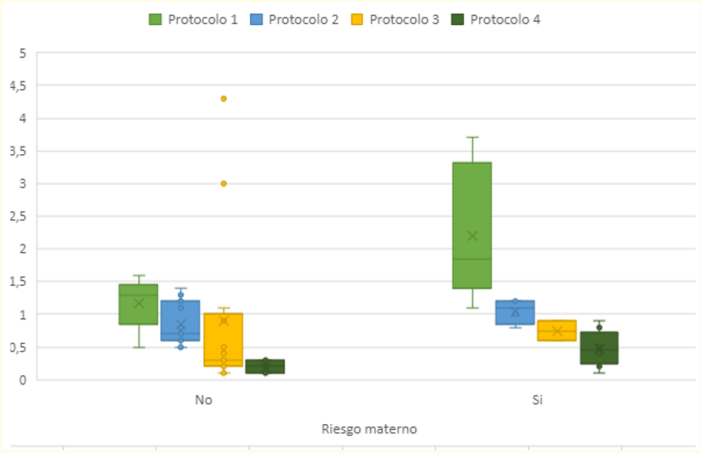
Graph 2: *Median of pre-postpartum lostvolume.*

In graph 3, we observe a strong and direct association between blood loss (difference in hemoglobin before delivery and after delivery) and the estimate of the lost blood volume with a correlation coefficient of 0.86, which means that the visual scale of blood loss in a trained team, is valid and correct for the estimation of intrapartum bleeding.



Graph 3: *Relationship between volume and blood los.*

Graph 4 lists the maternal risk factors in relation to the loss blood pressure, observing that in protocol 1 there are more risk factors in the population that in protocols 2, 3 and 4 thus increasing the loss, this may be due to the sample size collected and influences the results. In protocols 2 and 3 having a risk factor is not so significant.



Graph 4: *Relationship between risk factors and blood los.*

After performing the Kruskal-Wallis test, it is obtained that the difference in blood loss both with the subjective assessment with the visual scale, and with the objective one with the difference in pre and postpartum hemoglobin values are statistically significant between the different protocols, with p = 0.0006 (< 0.05), therefore, the management of the carbetocin, has been shown to be superior to oxytocin + misoprostol, as well as oxytocin in targeted labor, versus treatment with oxytocin after fetal expulsion without increasing the complications associated with it.

Discussion

Frederick., *et al.* [17] conducted a study with 1736 women, 1238 were matched and compared. Women who received oxytocin-misoprostol were less likely to to have Postpartum Hemorrhage compared to those who received only oxytocin.

Naadem., *et al*. [18] analyzed 66 patients and although they could not measure significance statistics of any of the main criteria, if they observed that adding misoprostol sublingual to standard Postpartum Hemorrhage treatments such as oxytocin there was a trend for reduction in postpartum blood loss, a decrease lower postpartum hemoglobin and the need for fewer additional interventions.

Another clinical trial conducted by Thibaud Quibel., *et al.* [19] had to be suspended after that the analysis including 1,721 patients showed that misoprostol administered routine prophylactic oxytocin did not reduce the risk rate of postpartum hemorrhage and was significantly associated with more adverse effects. However, this happened due to the dose of misoprostol used, since the patients received 400 micrograms of misoprostol orally and the action occurs more quickly causing adverse effects. Therefore, in our essay we will use the rectal route which results in greater bioavailability and a prolonged activity [20].

Cimona Lyn Saldanha., *et al.* [21] Conducted a study to determine the efficacy of the misoprostol and oxytocin in the prevention of postpartum haemorrhage in patients with high risk. Patients at high risk of bleeding were randomized into two groups with 110 patients in each group. It was found that the group that received misoprostol along with oxytocin had significantly decreased the mean total (545 ± 110) blood compared to the other group that received only oxytocin (630 ± 108).

Emmanuel Numforet., *et al*. [22] studied the obstetric records of 1,778 pregnant women. 857 in group A and 879 in group B. Both groups were comparable in several baseline sociodemographic and clinical characteristics. The prevalence of bleeding postpartum was

2.7%. The risk of postpartum hemorrhage in the oxytocin group was approximately 1.5 times higher than in the oxytocin plus misoprostol group.

All these data are consistent with the results of this study [23, 24], that is, using carbetocine or misoprostol and oxythicin at appropriate doses significantly reduces bleeding postpartum (mean hematic estimate was 0.867) compared to treatment of oxytocin after delivery and with oxytocin treatment after delivery the descent of the anterior shoulder (the average estimate of the blood loss was 1.58 and 0.9067 respectively).

Conclusions

The use of carbetocin or oxytocin + misoprostol at prophylactic doses of 600 mcg improves the results of bleeding even in the case of having a maternal risk factor. Also, the management of the delivery directed with oxytocin improves results in related to obstetric hemorrhage, in relation to oxytocin after fetal expulsion.

We can observe that postpartum bleeding can be quantified through the estimated blood volume loss by visual scale with a high correlation with the estimate Blood loss due to pre and postpartum hemoglobin difference.

For last, the results of our study reflect what is interpreted in the scientific literature more current and endorse the new indication in the technical data sheet of carbetocin for prevention of postpartum obstetric hemorrhage.

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