

Studying the Effectiveness of Various Treatment Methods Effective on Postpartum Hemorrhage

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Abstract

In developing countries, the first cause of maternal mortality is postpartum hemorrhage. Therefore, prevention and treatment of postpartum hemorrhage is an important step in the health of society, especially the health of women. So far, various studies have tried to suggest the best and most effective way to treat postpartum hemorrhage. The present study was conducted to review the studies conducted on medical and non-medical treatments effective on postpartum hemorrhage in Iran and the world. The information needed in this study was searched from IRCT, Scopus, SID, Google Scholar, Pubmed, and Science Direct databases with the keywords postpartum hemorrhage and clinical trial. Based on the reviews, the number of studies conducted in the field of herbal medicines was very few, but many in the field of chemical medicines. The results showed that oxytocin is used as the first line of treatment for postpartum hemorrhage due to fewer side effects, and the next drug is misoprostol. There is a need for more studies on the effect of other drugs, both medical and non-medical. There are various medical and surgical methods to control bleeding after childbirth, and if correct and timely measures are taken, the need for invasive methods, complications, and maternal mortality will be reduced.

Keywords: Herbal medicines, Chemical medicines, Postpartum hemorrhage, Treatment

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Introduction

Bleeding, blood pressure, and embolism are the three main causes of maternal mortality [1]. Today, due to the easy access to blood and its products, with the existence of new medical and surgical methods to control bleeding after childbirth, the death rate of mothers has decreased significantly, and the cause of death due to bleeding in developed countries is after embolism and hypertension

[2-7]. However, in Iran, the first cause of maternal death is bleeding [3].

As mentioned, one of the main causes of maternal death is postpartum hemorrhage, which can be greatly reduced by predicting the possibility of bleeding, prior preparation, and timely medical and surgical intervention. According to the reports, the main cause of maternal mortality was failure to perform standard treatments [6, 8, 9]. Bleeding from the place of replacement of the placenta in the lower part, uterine atony, damage to the birth canal and uterus,

and remaining products of pregnancy are among the causes of postpartum hemorrhage [10, 11].

Severe bleeding after childbirth leads to consequences such as hypovolemic shock, internal coagulation disorders vascular, liver disorders, acute respiratory distress syndrome, and renal failure [12-14]. Treatment should be in line with the causes of postpartum bleeding. Therefore, the use of uterine contractions plays a central role in the treatment. Intravenous oxytocin is the drug of choice. If intravenous oxytocin is not available, or if bleeding does not respond to oxytocin, intravenous ergometrine, oxytocin-ergometrine bistable, or a prostaglandin drug is recommended. The use of isotonic crystalloids, which is better than the use of colloids, is recommended for initial IV fluid maintenance in women with postpartum hemorrhage, and the use of tranexamic acid if oxytocin and other uterine contractions fail to stop bleeding. Uterine massage is also recommended to treat postpartum hemorrhage as soon as it is diagnosed. In case of non-response or lack of access to uterine contractions, the use of an intrauterine balloon is recommended to treat postpartum bleeding caused by uterine atony [15-18]. Other treatments include surgical interventions such as uterine artery ligation, uterine compression sutures, and internal iliac artery ligation [19-21].

Chemical drugs, with all their effectiveness, have undesirable side effects and high costs, which necessitate the existence of less dangerous drugs. Non-medical treatments including plants such as *Phoenix dactylifera*, and *Anethum graveolens dhi*, are effective in reducing bleeding after natural delivery [22]. Plants such as *Urtica Dioica* and *Capsella bursa pastoris* are effective in the treatment of severe bleeding [22, 23].

Considering that many studies have been conducted in the field of medical and non-medical treatments for postpartum hemorrhage in Iran and the world and different findings have been reported, the present study was conducted to investigate the types of effective treatment methods for postpartum hemorrhage in Iran and the world.

Materials and Methods

In this review study, all the clinical trials conducted on various effective treatment methods for postpartum hemorrhage in Iran and the world from 2000 to 2023 were used. A time limit was used to conduct the electronic search. Based on this, all articles published from 2000 to 2023 were searched. To obtain the desired studies, the articles published in the internal journals of the databases of the Clinical Trials Registry, Medlib, Scopus, Google Scholar, Irandoc, SID, and the articles published in the Science Direct, Pubmed, and Cochrane databases were used.

The criteria for including articles in the study included: conducting the study as a clinical trial and treating

postpartum hemorrhage. The characteristics of the population participating in the study included women who gave birth naturally and by cesarean section. The investigated outcomes included the length of the third and fourth stages of labor, the amount of blood loss in the third and fourth stages of labor, the amount of hemoglobin and hematocrit drop after delivery, and the side effects of drugs.

Results and Discussion

Based on the types of intervention, the treatment methods were divided into two drug and non-drug groups. The first group included articles that examined medicinal plants and chemical treatments, and the second group included articles that used non-pharmacological methods. In medicinal methods, the effects of medicinal plants including *Cuminum cyminum L*, *Capsella bursa pastoris*, *Urtica Dioica*, *Anethum graveolens dhi*, and *Phoenix dactylifera* were investigated, and in the case of drugs, the effects of chemical drugs including Ergometrin, Oxytocin, Carbetocin, Tranexamic acid, and Misoprostol were investigated.

Pharmacological methods

Medicinal plants

Anethum graveolens dhi

The chemical composition of this plant includes tannin, a resinous substance, and an oily essential oil consisting of limonene, ketone, carvone, and a fatty substance. Tannins are often polyphenols that have astringent properties. The fruit of this plant is effective in reducing bleeding in dysmenorrhea. In the study of Mahdavian *et al.* the consumption of oral dill seed extract compared to the administration of intramuscular oxytocin caused a greater reduction in postpartum hemorrhage [24].

Phoenix dactylifera

Dates contain calcium, serotonin, tannin, linoleic acid, and peroxidase enzyme, which are very important in controlling bleeding [22]. 3 clinical trials have investigated the effectiveness of dates on postpartum bleeding. In one study, the use of dates was more effective in reducing postpartum bleeding compared to 10 units of intramuscular oxytocin [25]. In the study of Mujahid *et al.* the amount of bleeding in the group that consumed oxytocin and oxytocin at the end of two hours after delivery was less than in the group that was only prescribed oxytocin [22]. Other researchers also stated that dates are effective on postpartum bleeding [26].

Capsella bursa pastoris

This plant contains various substances such as tannin, choline, acetylcholine, flavonoids, amino acids, fatty

acids, sterols, thiamine, ascorbic acid, calcium, potassium, beta-carotene, vitamin K, and niacin-iron [14]. According to studies, this plant has oxytocin, anti-ulcer, and anti-inflammatory activities [27]. This plant has an effect on the smooth muscles of the uterus and increases its contraction and has a blood clotting effect [14]. This plant is useful for stopping bleeding after childbirth, stomach bleeding, intestinal bleeding, lung bleeding, nosebleeds, and bleeding hemorrhoids [14]. In the study of Naafe *et al.* the herb of the priest's bag was effective in women of reproductive age suffering from heavy menstrual bleeding [28].

Urtica dioica

This plant works by three mechanisms of anti-inflammatory and antioxidant effects, hormonal effects, and contraction of the smooth muscles of the uterus in reducing heavy menstrual bleeding or other uterine bleeding. In the study of Khadem *et al.* both nettle and mefenamic acid were effective in reducing heavy menstrual bleeding [29].

Cuminum cyminum L

This plant belongs to the umbelliferous family and has antispasmodic, carminative, diuretic, stomach tonic, laxative, and milk-enhancing properties. It also contains substances such as Simin, phalendron, caron, and cuminic alcohol in small amounts. This plant has tannin, resin oil, and essence [14]. In the study of Fazel *et al.* the effect of cumin juice and placebo on the amount of bleeding after delivery was the same [30].

Chemical drugs

Tranexamic acid

Tranexamic acid is an anti-fibrinolytic drug. When the bleeding is due to fibrinolysis, tranexamic acid acts as an effective inhibitor of fibrinolysis and promotes hemostasis, without increasing side effects such as thromboembolism. Probably, tranexamic acid neutralizes the effects of plasminogen and fibrin breakdown products that are released due to the separation of the placenta [31]. Tranexamic acid is widely used to treat heavy menstrual bleeding and reduces blood loss in elective surgeries and blood transfusions by approximately one-third [32].

Misoprostol

Misoprostol is a methyl ester of prostaglandin E1 and acts by changing the permeability of myometrial membrane cells by changing the calcium membrane receptors. Misoprostol acts on the selective stimulation of binding to prostanoid receptors EP-2/EP-3 of the myometrium. It is administered orally, sublingually, vaginally, or rectally [33]. It is effective for stimulating the myometrium of the pregnant uterus. Misoprostol is used in the medical evacuation of the uterus in spontaneous abortion and

cervical ripening and labor induction. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) and fever are the most common side effects of misoprostol, which are often mild and self-limiting. Unlike metrazine and carboprost, misoprostol can be prescribed in women with hypertension and asthma [34, 35].

Oxytocin

Oxytocin is an octapeptide whose six amino acids form a ring and the other three amino acids form a tail. Oxytocin is administered intravenously and intramuscularly and is also available as a nasal spray. The effect of oxytocin is uterine contraction. The sensitivity of the pregnant uterus to oxytocin is high and it causes strong muscle contraction [36]. The onset of the oxytocin effect is about two and a half minutes after intramuscular injection. This effect is intense for up to 15 minutes and ends after 30 minutes. Oxytocin rapidly contracts the uterus in uterine laxity after childbirth, but its effect is not as long as ergometrine [37].

Carbetocin

Carbetocin is a new drug for the prevention of uterine atony, an artificial analog of oxytocin, whose half-life is 4 to 10 times longer than oxytocin. Compared to oxytocin, instead of infusion, it is administered as a single dose intravenously or intramuscularly. The speed of its entry into the blood after intramuscular injection is 80% and its optimal dose in the third stage of labor is 100 micrograms. Patients receiving Carbetocin need fewer interventions than oxytocin, thus reducing the incidence of postpartum bleeding. Its half-life is 40 minutes and uterine contractions occur in less than 2 minutes after intravenous or intramuscular administration [38].

Ergometrin

Ergonoin is an alkaloid derived from ergot. Methylergonoin and ergonoin are similar alkaloids that are made from lysergic acid and have similar effects. These alkaloids are prepared in the form of maleate (metrazine) or as a solution for injectable use or as tablets for oral use, which are absorbed through digestion. Its amino type is absorbed from the rectum, it can also be used as a suppository.

This drug has an agonistic effect involving CNS dopamine and is a strong stimulant for uterine contraction, whose contraction effects are effective for controlling postpartum bleeding. The effect of these two drugs appears later than oxytocin, but it lasts longer. The administration of this drug should be after the removal of the placenta. Prescribing this drug to women prone to high blood pressure is dangerous [39].

Non-pharmacological methods

Uterine massage

In Meng *et al.*'s study, transverse abdominal uterine massage plus oxytocin after placental delivery did not reduce blood loss compared to oxytocin administration alone [40]. In the study of Abdul Alim *et al.* uterine massage was less effective than oxytocin in reducing blood loss after delivery [41].

Oxygen therapy

Uterine atony is the most common cause of postpartum hemorrhage. Hypoxia is an important etiology of postpartum uterine atony. Postpartum oxygen saturation may increase oxygen saturation and effective contraction of the myometrium and prevent postpartum hemorrhage caused by uterine atony [42]. In Jangerduk *et al.*'s study, oxygen inhalation after delivery was not effective in reducing vaginal blood loss during the third and fourth stages of labor [42].

Controlled cord traction

In Denox *et al.*'s study, controlled stretching of the umbilical cord to manage placental expulsion had no significant effect on the occurrence of postpartum hemorrhage and other markers of postpartum blood loss [43]. Also, in the study of Kashaniano colleagues [44], active management did not reduce blood loss in the third stage of labor, but it did reduce the duration of this stage. Active management was associated with increased blood loss during the fourth stage of labor.

Manual removal of placenta

In Jan *et al.*'s study [45], there was no relationship between the placenta removal method and blood loss after cesarean section [14].

Results and Discussion

Examining the results of various studies on the effectiveness of dates on postpartum hemorrhage showed that dates have a positive effect on reducing postpartum hemorrhage. In these trials, the existence of a tannin substance has been pointed out, which due to its astringent property causes contraction in the uterine and myometrid muscles and reduces the amount of bleeding after childbirth [22, 25, 29]. Dill seed plant has a positive effect on postpartum bleeding [24], the cumin plant reduces postpartum bleeding [30], and the nettle plant and priest's bag were effective on menorrhagia [26, 28]. Studies conducted in the field of herbal medicines and date fruit showed that plants containing tannins can be effective on bleeding. Tannin is one of the polyphenols that have a contractile effect on the smooth muscles of the uterus. A review of the studies conducted in the field of herbal medicines showed that the effects of limited herbs on bleeding have been investigated, which cannot be used clinically due to the very small number of studies. In

addition, no systematic studies were found to examine the effects of these herbs on bleeding.

According to the studies conducted, various studies investigated the effect of misoprostol on postpartum hemorrhage, although in these studies misoprostol was compared in various pharmaceutical forms with different doses and different drugs. In some of these studies, misoprostol was more effective than oxytocin [46], and in some studies, sublingual misoprostol was equivalent to oxytocin [33, 47], and in one study, sublingual misoprostol plus oxytocin infusion was the same as intravenous carbetocin [35]. In the study of Tewatia *et al.*, 10 units of intravenous oxytocin were more effective than sublingual misoprostol [48]. Therefore, it is recommended to conduct a study with a larger sample size and measure the amount of bleeding at least 3 hours after delivery. In a clinical trial comparing the effects of tranexamic acid and misoprostol, misoprostol had no superiority over tranexamic acid [49]. In all the studies that investigated the effect of Carbetocin, the results showed a reduction in blood loss when using Carbetocin [38]. It seems that Carbetocin is more effective than oxytocin because of its half-life and its high speed to enter the blood and lower dose. Due to the limited number of studies in this field, it is recommended to carry out wider research for the application of this drug.

Various studies have investigated the effect of oxytocin infusion after childbirth. Although the method of using oxytocin in these studies has been different, in 4 trials it has been directly mentioned that oxytocin is effective in reducing postpartum bleeding. In these studies, oxytocin was effective in reducing postpartum bleeding by stimulating contractions [50]. However, in the study of Jackson *et al.* who compared the infusion of 20 units of intravenous oxytocin before and after placental discharge, they concluded that the prophylactic administration of oxytocin before placental discharge does not reduce the incidence of postpartum hemorrhage [51]. In the study of Tita *et al.* who compared different doses of oxytocin, it was stated that higher doses of oxytocin did not affect reducing postpartum bleeding loss [52]. Higher doses of oxytocin are used in cesarean surgery, where bleeding is more likely [53]. Examining the results of different studies shows that more studies are needed to reach the effective dose, time, and way of prescribing oxytocin. Regarding the effects of methylergonovine, due to the small number of studies, more studies are needed [39, 54].

Conclusion

A review of the clinical trials conducted on medical and non-medical treatments shows that there are many chemical treatments in the field of postpartum bleeding. Most of the studies conducted were in the field of misoprostol, and in most of these studies, it has been mentioned that it is effective on postpartum bleeding,

although more studies are needed to find the form, dosage, and method of its use. Waller's fever is also mentioned as its most common complication. However, the drug that has been mentioned in most of the review studies as being effective and uncomplicated is oxytocin. Due to the known effectiveness of oxytocin for the treatment of postpartum hemorrhage, the use of misoprostol is not recommended due to its side effects. Regarding other chemical drugs, the number of studies for their application is limited. In all the studies, the effectiveness of date fruit in the treatment of bleeding has been mentioned, but more studies are needed for its application. In the case of other plants, it is necessary to conduct more and wider studies.

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