Review Article

The Effect of Inhaled Oxygen on Postpartum Hemorrhage: A Systematic Review and Meta-Analysis

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Abstract

Background: Postpartum Hemorrhage (PPH) is a significant problem that can increase the risk of maternal mortality. Previous studies investigated the effect of Inhaled Oxygen (IO) on PPH. They found some conflicting results. Thus, the current systematic review and meta-analysis aimed to determine the effect of IO on PPH. **Materials and Methods:** Randomized trials were searched according to the PRISMA framework until the end of November 2022 in Web of Science, PubMed, Scopus, and Cochrane Library databases. Statistical analyses were performed in the STATA v. 14 software. I^2 statistic was applied to assess heterogeneity between studies. The random effect model, sample size, and mean and standard deviation of each group were applied to report the pooled effect size. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to evaluate the risk of bias in the included studies. Finally, five articles were included in the meta-analysis. Two and three studies reported the mean of bleeding after vaginal delivery during one- and two-hours oxygen therapy, respectively. **Results:** Results showed that IO significantly reduced bleeding by 38.91 mL in the intervention group compared to routine care (WMD: −38.91, 95%CI: −60.18 to −17.64) after vaginal delivery. In addition, IO during one (WMD: −38.42, 95%CI: −71.62 to −5.22) and two (WMD: −41.93, 95%CI: −60.15 to − 23.71) hours significantly decreased bleeding in the intervention. **Conclusion:** According to the present study, IO can significantly reduce PPH in the intervention group compared to routine care. However, more rigorously randomized clinical trials are required to decide better about this issue.

Keywords: *Meta-analysis, oxygen inhalation therapy, postpartum hemorrhage, systematic review, uterine hemorrhage, vaginal bleeding*

Introduction

Postpartum Hemorrhage (PPH) is one of the five main causes of maternal mortality worldwide. It is considered responsible for more than 25% of direct maternal deaths.[1,2] PPH leads to long-term complications such as hysterectomy and kidney failure, which puts mothers' lives in life-threatening conditions.[3] These mothers' lives are overshadowed by this negative outcome, which is mostly irreversible; thus, timely management of PPH is very important.[4] Early PPH, which occurs in the first 24 hours after delivery, is responsible for the largest share of maternal mortality, which requires emergency interventions and active management to prevent avoidable cases.[5,6]

Timely diagnosis and treatment using appropriate strategies to prevent bleeding require planning and preparation of the healthcare system based on research based on clinical evidence.[7] So far, many strategies have been recommended to prevent uterine atony and maintain the contraction of the uterine muscles to respond appropriately.[8] These solutions consist of two categories. The first category is drugs such as oxytocin, methylergometrine, and misoprostol, which are prescribed intramuscularly, intravenously, and orally, independently, or together with each other in the first or second line of treatment.[8] In the second category, we can refer to herbal medicines such as Matricaria chamomile, edible dill extract, and Plantago.[9] In addition, some studies have considered Inhaled Oxygen (IO) as a method for the prevention of PPH.[10,11] Regarding the mechanism of action, several theories have been proposed regarding the effect of IO on reducing

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PPH.[12] First, increasing oxygen can prevent uterine atony by increasing uterine contractions.[10] Thus, based on the hemoglobin decomposition curve, the partial pressure of arterial blood oxygen during inhalation of room air is 100 mmHg, while this pressure increases to more than 200 mmHg by inhaling 40% oxygen. This increase in arterial blood oxygen partial pressure may on one hand cause contraction in the myometrium and on the other hand can cause an increase in muscle tone in the blood vessels, and as a result, reduce PPH.[10] In another theory, it is stated that dopamine causes vasodilation by stimulating dopamine-1 post-synaptic receptors in vascular smooth muscles. Increasing blood oxygen can prevent uterine atony by reducing serum dopamine.[10,13]

However, there are conflicting results regarding the effect of IO on PPH. In a number of studies, it has been stated that IO can be effective in reducing PPH,[10,11] but a study in Turkey stated that IO cannot significantly reduce PPH.[14] Considering the availability and ease of use of oxygen and the lack of systematic review research based on combining the results of literature review, through meta-analysis, the present study was conducted to determine the effect of IO on PPH through a systematic review and meta-analysis.

Materials and Methods

This systematic review and meta-analysis was conducted according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol of the study was registered in PROSPERO (International Prospective Register of Systematic Reviews) under the code CRD42023408612, available from https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42023408612.

A comprehensive search was conducted in valid databases without time limits until the end of November 2022. The keywords of the medical subject title (mesh) included "Postpartum Hemorrhage," "Uterine Hemorrhage," "Vaginal Bleeding," and "Oxygen Inhalation Therapy" and formed the search strategy using Boolean operators "OR" and "AND." First, two researchers (EMG and TKh) independently searched external databases such as Web of Science, PubMed, Scopus, and Cochrane Library to find English clinical trial studies.

All RCT studies published in English with the aim of investigating the effect of IO on PPH in the postpartum period were included in the study. Lack of access to the full text of the article, articles such as letters to the editor, case reports, reviews, and articles in non-English languages were excluded from the study. The PICO framework was considered to retrieve relevant studies. The study population was women in the postpartum period who underwent oxygen therapy to investigate the outcome of PPH. The comparison group in this study was mothers who breathed room air.

Two researchers screened the literature by reviewing titles and abstracts primarily, and the selected articles were read in full. The differences and discrepancies were resolved by discussion and, when necessary, by consulting a third reviewer. The data extracted from each study includes the author's name, study location, year of publication, sample size, intervention, the stage in which the intervention took place, the control group, and the outcome (including the amount of bleeding in the postpartum period).

All statistical analyses were performed using STATA-14 software. The percentage of variability attributable to the heterogeneity of the studies was estimated by I^2 statistics, with a p-value of <0.10 and $I^2 \geq 50\%$ considered statistically significant. Otherwise, sensitivity analysis was performed to identify the heterogeneity. The random effect model was used for the studies with heterogeneity not being eliminated. The data of the numerical variables were expressed by Weighted Mean Difference (WMD) and Confidence Interval (CI) of 95%.

To assess the risk of bias, version 2 of the Cochrane Risk of Bias tool for randomized trials (RoB 2) was used. This tool examines the quality of articles in six areas, including selection bias, performance bias, detection bias, sample attrition, selective outcome reporting bias, and other biases. Each of the investigated cases in this tool is reported as low bias, medium bias, and ambiguous bias.[15]

Ethical considerations

The researchers tried to synthesize and report the data extracted from the mentioned studies honestly and without any bias. In addition, they declare that they have avoided any plagiarism and have cited all resources used. This study was approved by the Local Research Ethics Committee, Mashhad University of Medical Sciences, Mashhad, Iran (Code of ethics: IR.MUMS.NURSE.REC.1402.042).

Results

The characteristic and quality assessment

First, 387 articles were identified. Next, by removing duplicates and checking the abstract, title, and full text, according to the inclusion and exclusion criteria, six articles were included in the study. One article was excluded from the study due to the lack of access to the full text.[12] Finally, a systematic review and meta-analysis were performed on five articles [Figure 1]. The year of publication of the articles was from 2007 to 2020, and the total sample size was 764. Out of the five articles reviewed, two were from Iran,[10,11] one from India,[16] one from Sri Lanka,[17] and one from Turkey.[14] Regarding the parity of the studied women, only one study included primiparous women,[11] and four other studies were conducted on primiparous and multiparous women [Table 1].

In four studies, oxytocin with a dose of 10–20 units was prescribed as prophylaxis, while in one study,[16] no

medicine was used as prophylaxis. Bleeding measurement was done in four studies by weighing the scalp spread under the mother, and only one study used a pad.[16] In four reviewed articles, postpartum oxygen administration significantly reduced PPH in the intervention group compared to the usual care group.[10,11,16,17] In one study, the mean loss of blood in the third and fourth stages of labor was not significantly different between the control and intervention groups ($p > 0.05$).[14]

Risk of bias

The results of the risk of bias of the studies using the Rob 2 tool are shown in Figure 2.

Effect of IO on PPH

The results showed that IO in the intervention group reduced bleeding by 38.91 mL compared to usual care during 1 or 2 hours (WMD: −38.91, 95% confidence interval [CI]: −60.18 to − 17.64, Z = 3.59, $p > 0.001$, 90.8% I^2; Figure 3). In addition, sensitivity analysis showed that the overall effect size was not dependent on the outcome of a specific study (CI: −80.61 to −10.25).

The results also showed that IO significantly reduced bleeding in the intervention group by 38.42 mL compared to usual care during 1 hour (WMD: −38.42, 95% CI: −71.62 to − 5.22, Z = 2.27, $p = 0.02$, $I^{2:}$ 88.4%).

The results showed that the IO significantly reduced postpartum bleeding by 38.91 mL in the intervention group compared to the usual care during 2 hours (WMD: −41.93, 95% CI: −60.15 to −23.71, Z = 4.51, $p > 0.001$, $I^{2:}$ 82.0%).

Discussion

The present study is a systematic review and meta-analysis regarding the effect of IO on PPH. The results of the present study showed that IO after delivery can prevent uterine atony and PPH and significantly reduce bleeding in the first and second hours after delivery. Among the studies included in the meta-analysis, only the study by Güngördük *et al*.[14] had somewhat inconsistent results with the other four studies. According to this study, oxygen therapy has no significant effect on reducing PPH. Although this study had a larger sample size compared to other studies, which can increase the validity of the findings of this study, one of its limitations is the lack of blinding of the participants and personnel, as well as the blinding of the outcome, which can have a negative impact on the findings. This issue led to the widening of the confidence interval and a reduction in the impact of this study in the results of the present meta-analysis; thus, the lowest weight percentage (15.94%) was assigned to this study. On the contrary, the study by Sekhavat *et al*.[11] had the greatest impact on the results of the present study (weight = 24%), which indicates the higher accuracy of the study.

Among other differences between the studied studies, the measurement of the outcome was the amount of bleeding at different times. Banupriya's study examined the amount of bleeding in 1 and 2 hours after the intervention and showed that the amount of bleeding in both times decreased significantly after IO, but this amount was higher in the first

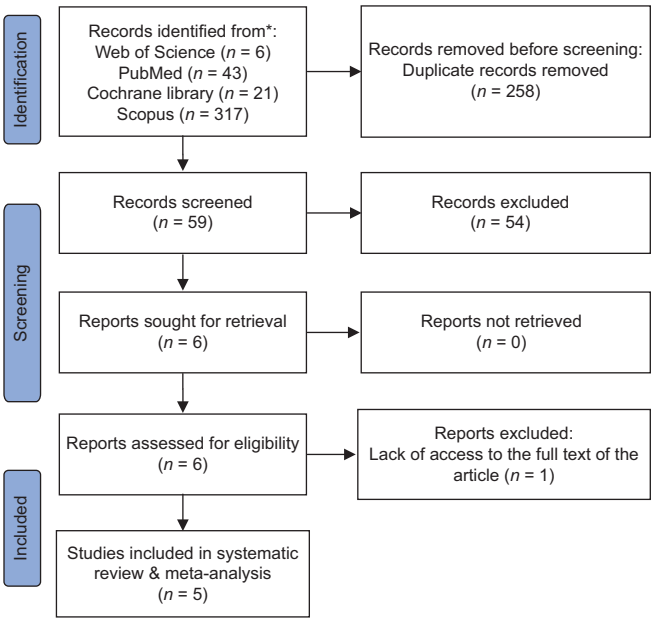

Figure 1: PRISMA 2020 Flow diagram of study selection

Tools name	Rob II						
Items / Author name	Random sequence generation	Allocation concealment	Blinding of participation and personal	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Yatawatta *et al*., 2007	?	?	?	?	?	+	+
Sekhavat *et al*., 2009	+	?	?	?	+	+	+
Gungorduk *et al*., 2011	+	+	-	?	+	+	+
Sohrabi *et al*., 2015	+	?	?	?	+	+	+
Banupriya *et al*., 2020	+	+	-	?	+	+	+

?: Unclear/ +: Low risk/ -: High risk/ 0: not reported/ 1: reported but incomplete/ 2: reported completely/ N/A: Not Applicable

Figure 2: The risk of bias included studies

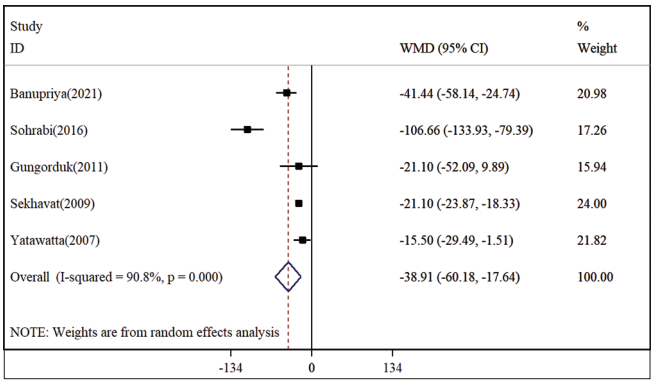

Figure 3: Effect of oxygen inhalation on the mean of blood loss after delivery

Table 1: Characteristics of the included studies

Authors/Year	Country	Design	Sample size	Intervention Group: -oxygen concentration -duration -Device	Delivery Phase of intervention	Control Group	Outcome
Yatawatta *et al*. (2007)[17]	Sri Lanka	Clinical trial	60 Women (30 women in Intervention group/30 women in Control group)	Receiving 40% oxygen via facemask for 6 hours	After the third stage of labor	Breathing in room air	In the intervention group, the average volume of vaginal bleeding was significantly reduced in the first hour after the intervention and during 6 hours after the intervention.
Sekhavat *et al*. (2009)[11]	Iran	Randomized trial	104 women (52 women in the intervention group/52 women in the control group)	Receiving 8 L/min oxygen via a facemask for 2 hours	After the third stage of labor	Breathing in room air	In the intervention group, the average volume of vaginal bleeding was significantly reduced in the 2 hours after the intervention
Güngördük *et al*. (2011)[14]	Turkey	Randomized trial	430 women (214 women in the intervention group/216 women in the control group)	Receiving 8 L/min oxygen via a facemask for 2 hours	After delivery	Breathing in room air	The mean estimated blood loss at the third and fourth stages of labor did not significantly differ between the control and intervention.
Sohrabi *et al*. (2015)[10]	Iran	Clinical trial	120 women (60 women in the intervention group/60 women in the control group)	Receiving 8 L/min oxygen via a facemask for 2 hours	After delivery	Breathing in room air	In the intervention group, the average volume of vaginal bleeding was significantly reduced in the 2 hours after the intervention
Banupriya (2020)[16]	India	Experimental design	50 women (25 women in the intervention group/25 women in the control group)	Receiving 8 L/min oxygen via a facemask for 2 hours	After delivery	Breathing in room air	In the intervention group, the average volume of vaginal bleeding was significantly reduced in the 1 and 2 hours after the intervention

hour of the intervention than in the second hour.[16] Sohrabi *et al*. study[16] also measured the PPH level 1 hour after the intervention, and Sekhavat *et al*.[11] and Güngördük *et al*.[14] measured the PPH level 2 hours after the intervention.

In comparing the reviewed studies, only in the study of Yatawatta *et al*.,[17] the percentage of oxygen used was mentioned. Although the duration of oxygen administration in this study was 6 hours, which is longer than other studies, it does not seem that IO has a greater effect on reducing PPH. This can raise the issue that a longer duration of oxygen administration does not have a greater benefit; however, this requires further study in the form of a three-group clinical trial study, considering the control group, and two groups with different IO periods. In four other studies, the amount of oxygen used (8 L/min) was precisely mentioned.

In Ani Grace's study,[12] a randomized controlled trial was conducted at the obstetric ward in Kundrathur over a period of 12 months. Women with normal vaginal delivery were alternatively allocated into either experimental group (who received 4 L/min oxygen with a nasal canulla for 2 hours after the third stage of labor) or control group (who inhaled room air in addition to routine care). Consistent with the present meta-analysis, this study concluded that oxygen inhalation reduced PPH in normal delivery during the first and second hours significantly (p = 0.000). They also showed that the partial pressure of oxygen in the experimental group's arterial blood was much greater than the control group. As we could not access Kalaimathi's[12] full text as a required criterion to perform a meta-analysis, we had to exclude it from the present meta-analysis.

Due to the novelty of the subject under investigation in the field of gynecology and obstetrics and the lack of studies conducted in this field, the results of this study were compared with more studies that were similar to the present study only in terms of the use of oxygen. However, the oxygen used in the studies mentioned below is hyperbaric oxygen, which is different from the oxygen used in our studies. Hyperbaric oxygen is the use of pure oxygen in a specially designed chamber. Preclinical research has shown that hyperbaric oxygen has a neuroprotective effect against hemorrhagic brain injuries.[18] Wright *et al*. (2002)[19] investigated the effects of hyperbaric oxygen on bleeding in rabbits. They showed that in the intervention group compared to the control group, the amount of bleeding (29% vs. 37%) and the time to reach the baseline level of hemoglobin (11 days in the intervention group and 14 days in the control group) ($p < 0.001$)) were significantly

reduced. The results of the study by Wright *et al*.[19] are in line with the results of the present study. In both studies, the use of oxygen reduced the bleeding volume, with the difference that in Wright *et al*. study,[19] hyperbaric oxygen (oxygen with 100% purity) was used on animals and the source of bleeding was from the femoral vein, while in the studies reviewed in the present systematic review and meta-analysis, the effect of oxygen with a concentration of 30%–60% on uterine bleeding in the period after normal delivery in humans was investigated.The mechanisms of oxygen effects were different in the two studies. In Wright *et al*.'s study,[19] the possible reason for the reduction of bleeding in the group receiving hyperbaric oxygen was cytokine suppression after acute bleeding or the hemodynamic effects of vasoconstriction following hyperbaric oxygen consumption.

In the case presented by Sun *et al*. (2010),[20] the effects of hyperbaric oxygen (HBO) and normobaric hyperoxia (NBO) on secondary hemorrhage after thrombolysis in thromboembolic middle cerebral artery occlusion (MCAO) (tMCAO) were assessed. One hour after beginning tMCAO, spontaneously hypertensive rats (n = 96) received either 100% oxygen at 3 bar (HBO) or 100% oxygen (NBO), for 1 hour. They found that NBO and HBO reduced post thrombolytic intracerebral hemorrhage. The results of Sun *et al*.'s study[20] are consistent with the present study. However, there are considerable differences between Sun *et al*.'s study[20] and the present review and meta-analysis, including the type of oxygen used (HBO or NBO in Sun *et al*.'s study[20] vs. oxygen 30%–60% in the present meta-analysis), its duration (only 1 hour in Sun *et al*.'s study[20] vs. 1 and 2 hours in the present meta-analysis), and the source of bleeding (secondary hemorrhage after thrombolysis in tMCAO in Sun *et al*.'s study[20] vs. PPH in the present meta-analysis). Moreover, this study was performed on animals, while the participants entered in the present meta-analysis are human.

This meta-analysis study was conducted to investigate the effect of IO on reducing PPH. The results of this meta-analysis indicate the effect of IO in reducing PPH, which can be used as a guide in clinical care and a way to prevent maternal mortality and morbidity and can save the lives of millions of women in the postpartum phase around the world. Oxygen is a safe, non-toxic, cheap, and available drug that has not been reported to have any contraindications or side effects in its short-term use.[10] However, the number of available studies in this field is limited and sometimes they do not have the necessary quality. Thus, further studies in this field, taking into account a larger sample size and following the principles of clinical trial studies, can confirm the present results.

One of the strengths of the present study is the comprehensive search in reliable databases, regardless of time and place limitations. Among its other strengths, we can mention the search and review of articles by two researchers independently, which increased the quality of the obtained data. However, there are some limitations in the present study. Some studied works, such as allocation of concealment and especially blinding, which is one of the pillars of clinical trial studies, have not been mentioned. In addition, the studies reviewed were in English, which limits access to articles in other languages. The high heterogeneity of the current study is another weakness; due to the limited number of studies, sensitivity analysis was not conducted to reduce it. All these factors can affect the final result of the report. Due to the lack of previous systematic review articles in this field, the comparison of the results of the present study with other studies was limited.

Conclusion

According to the present study, postpartum oxygen therapy significantly reduces PPH. It is recommended to consider IO as one of the necessary plans in bleeding control in severe postpartum bleeding that occurs due to atony.

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Conflicts of interest

Nothing to declare.

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