International Journal of Medical Toxicology & Legal Medicine Volume 27, No. 2S, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Review refractory postpartum hemorrhage severity and therapeutic approaches

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Received: 15.08.2024 Revised: 17.09.2024 Accepted: 24.10.2024

ABSTRACT
Refractory postpartum hemorrhage (PPH) occurs in 10–20% of individuals who inadequately respond to first-line interventions. These patients necessitate second-line interventions, comprising three or more uterotonics, supplementary drugs, transfusions, non-surgical treatments, and/or surgical procedures. Numerous studies indicate that patients with resistant PPH exhibit distinct clinical characteristics and etiologies of PPH in contrast to those who respond to first-line treatments. This review emphasizes contemporary perspectives on therapeutic strategies for managing refractory PPH. The first therapy of refractory postpartum hemorrhage necessitates hypovolemic resuscitation and hemostatic control, prioritizing prompt blood product replacement and adherence to large transfusion procedures. Point-of-care assays, such as thromboelastography, can facilitate the swift and precise identification of transfusion requirements. Medical interventions for refractory postpartum hemorrhage (PPH) encompass the management of uterine atony and the associated coagulopathy, including tranexamic acid and supplementary therapy such factor replacement. The concepts governing the management of refractory postpartum hemorrhage (PPH) involve the restoration of normal uterine and pelvic anatomy through the assessment and treatment of retained products of conception, uterine inversion, and obstetric lacerations. Intrauterine vacuum-induced hemorrhage control devices represent innovative approaches for managing refractory postpartum bleeding due to uterine atony, among other uterine-sparing surgical techniques now under examination. Resuscitative endovascular balloon occlusion of the aorta may be utilized in instances of critical refractory postpartum hemorrhage to mitigate or reduce persistent blood loss during definitive surgical procedures.

INTRODUCTION

Obstetric hemorrhage continues to be the primary cause of maternal mortality globally, representing 27% of maternal fatalities. Present in 5% of all live deliveries, postpartum hemorrhage (PPH) is a primary contributor to severe maternal morbidity, leading to considerable short-term and long-term implications for mother health.Three The repercussions encompass the immediate effects of hemorrhagic shock, including multiorgan failure, transfusion-associated morbidity, exacerbation of chronic anemia, and admission to the critical care unit. Moreover, the incidence of postpartum hemorrhage (PPH) has consistently increased worldwide during the past ten years [1,2]. From 2010 to 2014, postpartum hemorrhage rates in the United States rose by 13%, with uterine atony responsible for 79% of the cases. Alongside various patient characteristics that independently elevate the risk of postpartum hemorrhage (PPH), research has investigated the mode of delivery and labor induction as

potential contributors to the notable rise in PPH rates; nevertheless, alterations in established risk factors during this timeframe have not entirely elucidated this trend [3]. The early identification and therapy of refractory postpartum hemorrhage (PPH) depend on recognizing antenatal risk factors, with continuous clinical risk evaluations during labor, delivery, and the postpartum period. Various risk assessment instruments and protocols, including the Safe Motherhood Initiative Risk Assessment Checklist, the California Maternal Quality Care Collaborative Obstetric Hemorrhage Risk Assessment Guide, and the Association of Women's Health, Obstetric and Neonatal Nurses PPH Risk Assessment Table, can be employed upon labor unit admission to identify patients at elevated risk for severe postpartum hemorrhage, based on obstetric history and antepartum risk factors [4,5].Patients identified as at elevated risk for postpartum hemorrhage due to antenatal risk factors can be recognized prenatally, assigned to an appropriate level of care during labor and delivery, and preparations can be made with cross-matched blood and bleeding kits readily available. Individuals at elevated bleeding risk from suspected morbidly adherent placenta may be preemptively booked for surgery in a facility equipped with necessary resources, with consulting teams and blood bank preparations for prompt support [6].

Review

Patients with refractory postpartum hemorrhage exhibit distinct clinical characteristics and risk factors compared to those who respond to first-line treatments for postpartum hemorrhage. Prevalent risk factors for postpartum hemorrhage (PPH) encompass advanced age, multiple pregnancies, polyhydramnios, uterine fibroids, coagulation problems, antepartum hemorrhage, chorioamnionitis, operative delivery, previous instances of PPH, aberrant placentation, and extended labor, among others. Widmer et al. discovered that patients experiencing refractory postpartum hemorrhage (PPH) who underwent labor induction or augmentation, had episiotomies or perineal lacerations necessitating suturing, and had neonatal birthweights of 3500g or greater were at a markedly elevated risk for refractory PPH compared to those with PPH responsive to first-line treatments [7].

Patients with refractory PPH exhibit distinct underlying risk factors and etiologies compared to those with responsive PPH. A subsequent analysis of the WHO CHAMPION trial revealed that uterine atony was the sole reason in 31.5% of refractory PPH cases, while it accounted for 53.2% of PPH cases that responded to first-line treatments. Additional research has similarly shown that uterine atony is responsible for up to 80% of all instances of postpartum hemorrhage (PPH), yet only about 33–50% of refractory PPH cases. Widmer et al. established that obstetric lacerations accounted for 28% of refractory PPH patients in their study, in contrast to 12.8% of PPH-responsive cases, while aberrant placentation was present in 11% of refractory PPH cases, compared to 5.6% of PPH-responsive cases [12].

Numerous types of cognitive bias have been documented in the literature.11 In the management of PPH, numerous factors might negatively impact patient care and lead to deviations from ideal medical and collaborative management. Anchoring bias may lead physicians to fixate on a single etiology for postpartum hemorrhage (e.g., atony), while hindering the exploration of other etiologies (e.g., laceration or retained products of conception). Normalcy bias causes individuals to dismiss or downplay hazard alerts, resulting in an inability to see indicators of danger as atypical (for instance, excessive bleeding is deemed "normal" or tachycardia is attributed to "anxiety"). Availability bias denotes the propensity of individuals to assign disproportionate significance to recent experiences when assessing a novel situation (e.g., a recent instance of amniotic fluid embolism may lead a provider to more frequently suspect this condition in subsequent patients, despite the likelihood of alternative explanations for hemorrhage being greater). Implicit biases manifest when attitudes and prejudices unconsciously influence our comprehension, behaviors, and decisions, resulting in unintentional discrimination. Implicit bias is a recognized contributor to healthcare inequities, resulting in racial and ethnic disparities in health outcomes. It is suspected that this bias may influence variations in responses to postpartum hemorrhage (PPH), thereby contributing to the established disparity in severe maternal morbidity (SMM) rates associated with PPH [13].

To respond rapidly and effectively to severe postpartum hemorrhage, the implementation of obstetric hemorrhage bundles has been suggested to enhance patient outcomes. Systematic PPH guidelines have led to expedited cessation of hemorrhaging, reduced transfusion rates, and diminished necessity for invasive interventions such as uterine artery embolization and cesarean hysterectomy. In 2015, the Council on Patient Safety in Women's Health Care and the SMI established obstetric bundles to address critical areas for enhancing maternal morbidity and death outcomes [14,15]. The obstetric hemorrhage bundles emphasized the necessity of system and unit preparedness, encompassing prompt availability of hemorrhage medications and supplies, established protocols for massive transfusion and blood banking, unit education, and the formation of a hemorrhage response team, which may include consult teams such as gynecologic oncology surgery and interventional radiology as required.

Nonetheless, research suggests that the simple implementation of a stage-based procedure may not diminish the incidence of postpartum hemorrhage (PPH) or the rate of severe maternal morbidity (SMM) associated with PPH. Advocates of PPH bundles contend that this issue pertains to the absence of protocol implementation,

referred to as the "implementation gap," in several different scenarios.14, 15 Hospital systems and state perinatal quality collaboratives (PQCs) that emphasize implementation have demonstrated a decrease in morbidity among patients suffering from postpartum hemorrhage (PPH). California investigators analyzed the rates of severe hemorrhage-related morbidity during hospital deliveries before and after the introduction of a state PQC targeting PPH, discovering that involvement in the collaborative correlated with a 20.8% decrease in hemorrhage-related morbidity. While the California Maternal Quality Care Collaborative offers comprehensive guidelines on PPH treatment, local leaders tailored their procedures to address facility-specific requirements and possibilities [16,17].

Management approches

In 2012 and 2017, the WHO issued recommendations for the primary treatment of PPH, categorized into care bundles for the initial response to PPH and for managing refractory PPH [17]. The initial reaction PPH bundle comprises the administration of intravenous crystalloids, uterotonics, tranexamic acid, and uterine massage. To manage PPH unresponsive to first-line treatment, it is advisable to administer supplementary uterotonics, a second dose of tranexamic acid, and implement compressive measures such as intrauterine balloon tamponade, aortic compression, or bimanual uterine compression. Additionally, the utilization of non-pneumatic antishock garments (NASG), if accessible, is recommended to reduce persistent blood loss before or during preparations for invasive surgical interventions [18].

Fluid resuscitation for significant blood loss due to postpartum hemorrhage has conventionally emphasized vigorous volume replacement, adhering to the notion that 1 liter of blood loss necessitates 4–5 liters of fluid replacement. The objective of vigorous fluid resuscitation is to swiftly restore circulating blood volume and regulate blood pressure through the infusion of a substantial amount of crystalloid fluid. Recent investigations have suggested a hypotensive fluid resuscitation strategy, referred to as permissive hypotension, in the initial phases of hemorrhagic shock [19]. Hypotensive resuscitation emphasizes prompt, vigorous administration of blood products over extensive crystalloid infusion. Restrictive intravenous fluid resuscitation involves administering small 500mL boluses of fluid to mitigate the danger of dilutional coagulopathy, the disruption of pre-existing blood clots due to elevated intravascular hydrostatic pressures, and hypothermia. Small-volume boluses mitigate the danger of third spacing and fluid extravasation, which may lead to deteriorating hemodynamics, cardiac dysfunction, and reduced renal perfusion due to elevated intra-abdominal pressure. A study indicated that elevated intravenous fluid administration correlated with reduced fibrinogen and hemoglobin levels; individuals receiving over 4 liters of fluid for acute blood loss encountered heightened future bleeding and unfavorable maternal outcomes. Permissive hypotension is advised for patients aiming for a mean arterial pressure (MAP) of 50–60 mmHg or a systolic blood pressure of 80–90 mmHg until hemorrhage control is achieved. Balanced crystalloids, such as lactated Ringer's solution, are favored over saline solutions due to the potential for hyperchloremic acidosis and compromised renal function.

Hemostatic resuscitation seeks to minimize fluid resuscitation while emphasizing the prompt replenishment of blood products and the implementation of massive transfusion procedures (MTP). Massive transfusion is characterized by the administration of more than 10 units of red blood cells within 24 hours, the replacement of whole blood volume within 24 hours, or the replacement of 50% of total blood volume within 3 hours. Massive transfusion methods entail the automatic issuance of red blood cells, fresh frozen plasma, and platelets. This is often distributed in a specified 1:1:1 ratio of 1 unit of RBCs to 1 unit of FFP to 1 unit of pooled platelets (6 packs). Cryoprecipitate is a crucial element of MTP, offering a concentrated source of fibrinogen, and should be supplied to patients with disseminated intravascular coagulation (DIC) or fibrinogen levels below 200–300 mg/dL [21].

The MTP may be initiated by a physician or nurse, contingent upon institutional protocols, and blood products must be consistently dispensed by the blood bank until the MTP is terminated. Extensive transfusion has demonstrated a reduction in overall hemorrhage-related mortality by means of vigorous coagulopathy treatment. The PROMTT trial in trauma literature indicated that elevated transfusion ratios correlated with reduced mortality within the initial 6 hours of transfusion, and that prompt plasma administration within the first 3 hours was linked to lower mortality rates at 24 hours and 30 days [22]. The PROPPR experiment indicated that a 1:1:1 transfusion ratio was linked to sufficient hemostasis and reduced mortality from exsanguination after 24 hours. Consequently, although conventional initiation thresholds for massive transfusion protocols differ among institutions, several facilities commence massive transfusion with an estimated blood loss of 1500 mL accompanied by persistent hemorrhage. MTP must be promptly initiated for clinically substantial and fast hemorrhaging to mitigate maternal morbidity and mortality [23].

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are essential non-invasive diagnostic instruments for assessing and rectifying coagulopathy during active hemorrhage. These expedited point-of-care assessments are now progressively employed in obstetric intensive care units and labor and delivery departments to inform transfusion requirements in refractory postpartum hemorrhage [23].

Conventional coagulation assays are inadequate for evaluating clinically relevant coagulopathy resulting from persistent blood loss, as well as specific coagulation factors including factor XIII, platelet functionality, and the efficacy of the fibrinolytic system. Standard coagulation assays are conducted on plasma, but TEG is executed on whole blood, allowing for the assessment of specific cellular components, including platelet functionality, along with the timing and magnitude of fibrinolysis. This facilitates prompt and precise evaluation of coagulopathy to inform real-time blood component transfusion needs for patients experiencing active bleeding [23]. TEG has demonstrated a reduction in transfusion needs, transfusion-related mortality, postoperative ICU admissions, and hospital duration of stay [24].

The medical care of postpartum hemorrhage (PPH) has been focused on uterine atony and involves the use of uterotonics, including oxytocin (Pitocin), methylergonovine (Methergine), 15-methylprostaglandin F2α (Hemabate), and misoprostol (Cytotec). This technique fails to treat the coagulopathy frequently observed in severe PPH cases.

Medical treatments aimed at rectifying coagulopathy in persistent postpartum hemorrhage (PPH) encompass tranexamic acid (TXA), fibrinogen concentrates, prothrombin complex concentrates, desmopressin, and, in infrequent specific cases, recombinant factor VII [25].

Tranexamic acid (TXA) is an antifibrinolytic drug that obstructs plasmin activation and slows the degradation of fibrinogen and fibrin. Given that heightened fibrinolysis occurs during early hemorrhage, tranexamic acid (TXA) has been suggested to mitigate perioperative bleeding [21,25]. The WOMAN experiment demonstrated that patients with postpartum hemorrhage (PPH) who were administered tranexamic acid (TXA) within three hours after delivery experienced a 31% reduction in maternal death due to hemorrhage and a 36% reduction in the necessity for laparotomy to manage bleeding, relative to those who did not receive TXA. The administration of TXA beyond this 3-hour timeframe was deemed ineffective. Patients administered TXA did not exhibit an elevated risk of thrombosis. Consequently, the World Health Organization (WHO) has advised the simultaneous use of TXA as a primary treatment with uterotonics for the management of postpartum hemorrhage (PPH) [26]. TXA is often administered intravenously at a dosage of 1g over 10 minutes, with an extra dose permissible for ongoing bleeding after 30 minutes or for recurrent bleeding after 24 hours, irrespective of the etiology of PPH. Although the current dosage employed in obstetrics poses minimal thrombotic risk, TXA should be administered judiciously in patients with an elevated risk of thrombosis. TXA is contraindicated in patients with renal impairment because to its renal clearance.

After excluding other sources of postpartum hemorrhage, such as lacerations, retained products of conception, or uterine inversion, mechanical tamponade remains recommended by the Safe Motherhood Initiative and in most hemorrhage protocols for managing refractory postpartum hemorrhage due to uterine atony. The predominant intrauterine balloon tamponade system is the Bakri balloon, which reduces uterine blood flow by compressing the uterine vasculature inwardly [27]. Research indicates that mechanical tamponade reduces the necessity for more invasive interventions and effectively manages postpartum hemorrhage due to atony in up to 80% of instances. The success rate nears 100% when uterine balloon tamponade is administered promptly before the onset of hemorrhagic shock. A recent meta-analysis conducted by Suarez et al. investigated the application and effectiveness of uterine balloon tamponade for managing postpartum hemorrhage across 91 trials. The aggregated success rate of balloon tamponade for the therapy of postpartum hemorrhage (PPH) was 85.9%, exhibiting the maximum efficacy in cases of uterine atony and placenta previa. Some trials indicated no difference in the risk of invasive surgical interventions or mortality, while others shown a considerable reduction in the necessity for uterine artery embolization and invasive operations [28].

CONCLUSION

Refractory postpartum hemorrhage constitutes the predominant cause of morbidity and mortality associated with postpartum hemorrhage, despite the fact that most instances are avoidable and manageable with adequate access to resources and care. The implementation of obstetric hemorrhage bundles, as recommended by the Safe Motherhood Initiative, the WHO, and the Alliance for Innovation on Maternal Health (AIM), is essential for the prompt and effective management of refractory postpartum hemorrhage through system and unit preparedness. The efficient management of refractory PPH necessitates a comprehensive and systematic assessment of the bleeding's underlying cause to implement the most efficacious therapies, aiming to reduce maternal morbidity and mortality.Hospital systems and state perinatal quality collaboratives have determined that a comprehensive, interdisciplinary approach to postpartum hemorrhage management enhances patient outcomes and, in certain cases, mitigates racial inequities. An essential aspect of this emphasis is the execution of stage-based hemorrhage protocols for the management of postpartum hemorrhage. Stage-based bleeding guidelines aim to minimize delays in diagnosis and therapy while circumventing cognitive biases. These protocols are intricate, and their efficacy is contingent upon the quality of their execution. The systematic benchmarking and establishment of quality indicators for compliance with postpartum hemorrhage protocols are anticipated to enhance clinical outcomes; however, the literature provides minimal information regarding the efficacy of this practice.

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