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REVIEW ARTICLE

Damage-control resuscitation in obstetrics

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ABSTRACT

Severe obstetric hemorrhage is a catastrophic event and represents the main cause of maternal morbidity and mortality worldwide. The elevated mortality rate due to hemorrhage is associated with metabolic complications and organ hypoperfusion that may trigger a state of irreversible coagulopathy. Thus, the use of conventional measures to control bleeding frequently generates a vicious cycle in which the patient continues bleeding (prolonging surgical times). Damage-control surgery has proven to be feasible and effective in the context of obstetric hemorrhage. It combines surgical and resuscitative measures that generate successful results in the control of refractory bleeding, ultimately decreasing mortality in patients being in critical condition.

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Introduction

Obstetric hemorrhage is a catastrophic event and represents the main cause of maternal morbidity and mortality worldwide [1]. When the blood loss volume exceeds 40% of total blood volume, global hypoxia and multiple organ dysfunction develop, with metabolic damage because of hypothermia, coagulopathy, and metabolic acidosis [2]. Hemorrhagic shock is the most common form of shock in the obstetric practice [3] and although the term "severe postpartum hemorrhage (PPH)" is widely used in medical literature, there are inconsistencies regarding its definition. This has resulted in a lack of consensus on what constitutes this condition. Severe PPH has been defined as bleeding $\geq$1500 ml [4], considering only the blood loss, but not the metabolic decompensation state. Another term frequently used is massive hemorrhage, which can be defined as (i) blood loss exceeding circulating blood volume within a 24-h period, (ii) blood loss of 50% of circulating blood volume within a 3-h period, (iii) continuous blood loss exceeding 150 ml/min, or blood loss that requires red blood cells (RBCs), plasma, and platelet transfusion [4].

The objective of the initial phase of resuscitation is to aggressively optimize hemodynamic parameters by obtaining venous accesses to ensure resuscitation and blood products replacement that, in addition to the subsequent surgical management, will be the first step for the correction of systemic acidosis, hypothermia, and coagulopathy [2]. However, if medical and surgical therapeutic measures fail, the obstetrician encounters a dilemma of whether to attempt a primary definitive correction of the hemorrhage, or to perform alternative maneuvers in order to provide enough time to achieve patient survival by deferring her for a second definitive intervention in the following days [5,6]. The latter is the basis for damage-control surgery (DCS), concept derived from general surgery in which severely polytraumatized patients underwent surgery to control profuse bleeding [7].

Although maternal mortality due to hemorrhage has been reduced in developed countries, still some common errors in the approach to those cases have been identified [8]. Therefore, the pathophysiological conditions of patients with severe obstetric hemorrhage (including PPH), proper patient selection, indications for the approach, and an in-depth description of the damage-control resuscitation (DCR) concept will be presented in the following review.

Physiology of organ dysfunction during severe hemorrhage

Mortality due to hemorrhage is derived from metabolic complications and a general state of

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hypoperfusion, which can trigger an irreversible coagulopathy, prolongation of the hemorrhage and ultimately, multiple organ dysfunction and death [9]. DCS attempts to reverse organ dysfunction avoiding the trauma triad of death (hypothermia, acidosis, and coagulopathy), enabling a complete control of the hemorrhage. In situations of severe hemorrhage, the use of conventional measures to control bleeding is often ineffective and create a vicious cycle, wherein the patient continues to bleed. Prolonged surgical times, together with administration of intravenous cold fluids, worsen the hypothermia and abnormal coagulation states.

Hypothermia

Hypothermia in a severely injured patient with massive hemorrhage is associated with increased mortality and is likely caused by a combination of factors. In addition to the decreased metabolic activity in shock, hypothermia is exacerbated in the hospital by exposure and administration of cold intravenous fluids during resuscitation [10]. A series of simulations have shown that the exposed peritoneum is the dominant factor contributing to heat loss and bleeding rate [11]. Elevation of the operating room temperature and rapid abdominal closure are effective interventions available to the surgeon to modify the heat loss curve. It is important to know that during a "damage control" laparotomy for exsanguinating hemorrhage, the window of opportunity for salvage before the onset of an irreversible physiologic insult for hypothermia and coagulopathy is no longer than 60–90 min [11].

One of the most severe consequences of hypothermia is coagulopathy. The effect of hypothermia on the coagulation cascade has been proposed to result from inhibition of enzyme activity and platelet function. The inhibition of the enzyme activity has been estimated by the effect of cold on the prothrombin time (PT) and activated partial thromboplastin time (PTT) [10]. Prolonged PT has been found in hypothermic patients, experimental animals, and in plasma samples cooled *in vitro* [12]. Changes in platelet function under cold conditions are less consistent, but shear-induced platelet activation is markedly depressed at temperatures below 34 °C. Sheer-induced platelet aggregation is decreased in a swine model of hypothermia, causing a 57% increment in splenic bleeding time of this animal model, as well as a reduction of 17% in fibrinogen concentration (when combined with metabolic acidosis), delaying the onset of thrombin generation [13]. Effective platelet count is also decreased by hypothermia-related sequestration of platelets in the liver and the spleen [10]. Furthermore, enzyme kinetics is slowed with hypothermia. Johnston et al. found that at 35 °C, without dilution, there was a decrease in the function of several coagulation factors, such as factors XI and XII that are active only at 65% of the normal function, and at 33 °C, their activities dropped to 17 and 32% of the normal function, respectively [14].

Hypothermia is usually caused by a reduction in cellular heat generation secondary to severe tissue hypoperfusion. Frequently, it is compounded and exacerbated by the intraoperative heat loss, inadequate control measures such as no provision of thermal blankets, cold operating rooms, fluid resuscitation with cold crystalloids and, maybe the most important, an open abdominal cavity exposure during prolonged surgical periods. Patients with hypovolemic shock and body temperature below 34 °C for periods longer than 4 h are associated with a statistically significant increased mortality. Indeed, mortality rates rise up to 100% when the body temperature is below 32 °C [13]. Additionally, it increases the risk for cardiac arrhythmias, with a general decrease in cardiac output and an alteration in the hemoglobin–oxygen dissociation curve, resulting in an increased global oxygen debt.

Metabolic acidosis

Lactate comes from pyruvate, and the latter is produced in the glycolysis cascade [15]. When concentration of pyruvate exceeds its utilization by the mitochondria (mitochondrial aerobic oxidation *via* the Krebs cycle), the production of lactate increases [15,16]. Prolonged hypoperfusion causes hypoxia, which leads cellular metabolism to enter an anaerobic state, blocking normal functioning of the mitochondrial cellular system [15,16]. The inhibition in ATP synthesis and NADH reoxidation causes a pyruvate accumulation that, with alterations in the redox potential; increases the production of lactate. This allows the generation of some NAD^+ that in anaerobic glycolysis will originate two ATP molecules [15]. Besides, the adrenergic discharge and stress in shock patients leads to an accelerated glycolysis that continues promoting lactate formation. On the other hand, some shock patients have acute liver or renal dysfunctions which worsen the metabolic state, because of the decreased lactate clearance [16].

Increased blood lactate concentrations in shock, produces a drop in intracellular and extracellular pH, that consequently, leads to hemodynamic failure [16]. Although "severe lactic acidosis" definition remains

unclear, ICU physicians tend to consider that a pH <7.2 has harmful effects on the hemodynamic state of the patients; indeed, acidification causes dysfunction of coagulation system enzymes and the inactivation of clotting factors [13]. In addition, studies have shown the association between severe lactic acidosis and higher mortality rates (approximately 50%), with no survival reported in cases which pH <7.0 [16].

Experimental studies have demonstrated that severe metabolic acidosis worsens cardiovascular function through an increase in the amplitude of the systolic calcium transient and hence, the contraction pathway altering calcium binding to troponin C [16]. Another studied mechanism consists of the BNIP3 gene expression under hypoxic conditions. BNIP3 is one of the members of the Bcl-2 proapoptotic protein family and promotes cardiomyocyte death. It translocates to mitochondrial membrane and causes the release of another proapoptotic factors that produce nuclear translocation of DNase and finally, apoptosis [16].

Notwithstanding there is a lot of experimental studies, the prior effects and mechanisms have not fully demonstrated in humans. Lactic acidosis is one of the principal causes of metabolic acidosis in shock states, although others have also been reported [16].

Coagulopathy

While the mortality of trauma patients requiring massive transfusion exceeds 50%, at least 10% of those deaths are potentially preventable; many of these deaths occur within the first few hours of definitive care, with coagulopathy playing a crucial role. Indeed, coagulopathy is one of the most preventable causes of death in trauma and has been implicated as the cause of almost half of hemorrhagic deaths in trauma patients, being present at the time of admission to the emergency department in up to 25–35% of cases. Understanding the pathophysiology of trauma-induced coagulopathy is key, especially with respect to the critical issue of establishing therapeutic strategies for the management of patients. Reanimation based in crystalloids will lead to dilution of clotting factors, developing a dilutional coagulopathy. This mechanism has been studied and described in trauma, and is accepted that PPH may share some of these mechanisms [17]. Although no consensus has been reached regarding a definition of acute traumatic coagulopathy (ATC), there are different approaches to the classification and naming of trauma-associated coagulation impairment [18]. Trauma-induced coagulopathy (TIC) is a multifactorial, global failure of the coagulation system to sustain adequate hemostasis after major trauma, with acute coagulation alterations secondary to an early endogenous process. This acute traumatic coagulopathy (ATC) is driven by the combination of tissue trauma and systemic hypoperfusion, and characterized by global anticoagulation and hyperfibrinolysis [19].

It has been argued that activated protein C plays a central role in the mechanism of ATC. In initial observations in trauma patients with systemic hypoperfusion, defined by an elevated base deficit, a correlation was found between ATC and increased concentrations of activated protein C, reduced concentrations of protein C, and elevated soluble thrombomodulin [19]. The activation of the thrombomodulin-protein C system has been suggested as an important pathway mediating ATC, characterized as hyperfibrinolysis and a hypocoagulable state; this proposed mechanism is different from clotting factor consumption or dysfunction. Sustained tissue hypoperfusion is associated with elevated concentrations of soluble thrombomodulin secondary to endothelial damage, which can increase the availability of thrombomodulin to bound thrombin [17]. The result is the formation of a complex with thrombomodulin, and the role of thrombin can be diverted from procoagulant to anticoagulant by excess activation of protein C. These mechanisms may lead to the hyperfibrinolytic state in patients with ATC, which is reflected in increased tissue plasminogen activator (t-PA), decreased plasminogen activator inhibitor-1 (PAI-1), and increased D-dimer concentrations. This hypothetical condition has been named “acute coagulopathy of trauma-shock” [20].

Most coagulation assays (PT, PTT, and INR) frequently underestimate an state of coagulopathy in its initial stages; therefore, clinical judgment and a judicious intraoperative analysis based on viscoelastic coagulation tests as ROTEM (Rotational Thromboelastometry) and TEG (thromboelastography), and risk factors for bleeding and coagulopathy of each patient are crucial factors for survival in these cases [21].

Damage-control resuscitation

Resuscitation in a patient with hemorrhage has undergone significant changes in the last few decades, leading to the adoption of the novel concept of DCR or hemostatic resuscitation, moving the management from a definitive surgical approach to DCS. This method is used in patients with severe trauma and

massive hemorrhage, including women with severe obstetric hemorrhage related to shock and coagulopathy. DCR describes a systematic approach to minimize hemorrhage, prevent the deadly triad and maximize the oxygenation of tissues. The key principles of DCR are hypotensive and hemostatic resuscitation with limitation of crystalloid administration, the use of massive transfusion protocols, bleeding control [including DCS and damage-control interventional radiology (DCIR)], and physiological and biochemical stabilization in the ICU [10,22].

Recently, DCR has been strengthened by the laboratory and pharmacological agents to improve the care of the patient with hemorrhage, such as thromboelastography as a detailed measure of the coagulation cascade, and the early use of tranexamic acid (TXA; an antifibrinolytic), as a strategy for hemostatic resuscitation [10].

Initial reanimation

Among the initial strategies for reanimation, the administration of crystalloids in boluses of 500 ml is recommended, looking for an improvement in signs and symptoms of shock resulting from blood loss. In hemorrhage state and according to the degree of shock, women could show diaphoresis, increased capillary refilling, cool extremities, tachycardia, tachypnea, hypotension and alterations in state of consciousness (agitation, confusion, or somnolence) [23]. It is important to recognize that symptoms like tachycardia and hypotension do not present until blood loss is substantial [24]. The shock index (SI) is the relation between heart rate/systolic blood pressure that can be done at the time of diagnosis of PPH, at 15 and 30 min and 24 h after the event to establish the degree of hemodynamic instability. Although the SI cut off points for action and to predict outcomes remains unclear and are not well established, and some limitations have been described in relation with its use, is an utility tool in clinical practice. Values above 0.9 have been considered abnormal. This index is directly related to the need for massive blood products transfusion and the development of coagulopathy in massive PPH [25,26], since SI values >1.7 have an odds ratio of 4.24 (95% CI 1.25–14.36) for blood transfusion [27]. On the other hand, Kohn et al. recently described delta-SI (difference between peak SI and SI at the last antenatal visit or at facility presentation) as a novel tool, which is the strongest predictor for PPH, transfusion and need for surgical intervention, although the peak SI is also, by itself, a strong predictor [28].

Moreover, the use of Non-Pneumatic Anti-Shock Garment (NASG) is one of the strategies that have proven effectiveness in the reanimation of patients with shock for PPH. Although the NASG by itself is not a therapeutic measure in patients with PPH, it is a cornerstone in the initial workup and resuscitation since it promotes the stabilization of patients by reducing bleeding and increasing perfusion to their core organs. Its main goal is to increase survival time in women with hypovolemic shock, extending the available timeframe to perform definite surgical interventions [29]. Additionally, it has shown that it favors the improvement of clinical shock parameters, such as SI and lactate clearance, and decreases the requirement for blood transfusions and intravenous fluids [30]. Also, the NASG allows performing surgical procedures, such as DCS, without the need to remove it [31].

Bleeding control

Effective DCR in PPH begins with the management of bleeding and its etiology. A range of interventions are used in obstetrics to control the bleeding, which include external aortic compression (as a temporary measure), intrauterine balloon tamponade (Bakri's or condom balloons), compressive hemostatic sutures, and resuscitative endovascular balloon occlusion of the aorta (REBOA) used in cases of severe pelvic trauma and placenta accreta protocols [22].

Recently, the use of endovascular balloons for vascular occlusion has become an important option for the management of massive PPH, especially in complicated cases such as patients with abnormally adherent and invasive placenta [32]. The REBOA is a novel endovascular intervention characterized by the insertion of an aortic balloon in order to have a proximal control of the hemorrhage. Ordoñez et al. reported their experience using REBOA in 12 patients that underwent cesarean section due to an abnormally adherent and invasive placenta [32]. The balloon was inflated after delivery of the fetus and umbilical cord clamping for all cases. The median time of aortic occlusion was 22 min (IQR 20–40 min), and there were no complications secondary to the use of REBOA. Moreover, a systematic review and meta-analysis of four studies including 441 patients demonstrated that the use of REBOA as prophylaxis for the prevention of major hemorrhage was associated with a lower amount of intraoperative hemorrhage and lower

requirements of blood products transfusions compared to patients without REBOA [32]. These findings demonstrate the feasibility of REBOA as a prophylactic intervention to improve the clinical outcomes of women at risk for severe PPH [32]. Recently, Morrison et al. conducted a systematic review including 41 studies about the use of REBOA for the management of resuscitation or bleeding control in patients with hemorrhagic shock. Among those studies, five were conducted in obstetric populations, and two of them were case-series of patients with massive bleeding due to uterine atony, placental remnants and vaginal trauma that required aggressive hemostatic resuscitation, bleeding control using REBOA and total abdominal hysterectomy, with no cases of maternal mortality [33].

Because of the solid body of evidence, the use of REBOA should be considered as a useful and efficient strategy for bleeding control in cases of massive bleeding, since it is associated with less blood loss and lower need for transfusion of blood products while definitive surgical interventions are conducted, being part of the DCR spectrum [32,33].

Novel hypotensive resuscitation

The aim of hypotensive resuscitation is to achieve a lower blood pressure until definitive hemostasis is performed in order to promote adequate tissue perfusion and hemostasis, avoiding further worsening of the coagulopathy. This approach is based on the concept that small crystalloid volumes are less likely to create dilutional coagulopathy, and lower blood pressure is less likely to break or fragment the already formed clots.

However, when given large fluid volumes, this may initiate dilution of clotting factors resulting in impairment of coagulation and coagulopathy [34]. Gillisen et al. performed a cohort study with the aim of describing the association between administration of different volumes of fluids and concentrations of coagulation parameters in women with PPH. In this cohort, women with the lowest fluid administration showed fewer signs of shock and less administration of blood products. Also, fibrinogen, hemoglobin, hematocrit, and platelets concentrations decreased over increasing fluid administration while PT and aPTT were longer [34]. On the other hand, Henriquez et al. used the same cohort of patients (TeMpOH-1) to demonstrate that resuscitation with >4-L fluids was associated with subsequent bleeding and more adverse maternal outcomes [35].

Sondeen et al. used a porcine aortic lesion model to quantify the upper limit of patient blood pressure after which fluid resuscitation becomes detrimental due to fragmentation of the clot. The authors determined an average mean arterial pressure (MAP) of 64 mmHg and a systolic blood pressure (SBP) of 94 mmHg after which further increases in BP resulted in new hemorrhages regardless of the size of the aortic structural injury [36]. Other noncontrolled hemorrhagic shock animal models have demonstrated a positive benefit in survival with mean arterial pressures (MAP) between 55 and 60 mmHg during active bleeding. According to current evidence, hypoperfusion can be tolerated for short periods of time and may decrease the volume of global hemorrhage [10,22].

The endothelial glycocalyx (EG) has recently been recognized as a complex of proteoglycans, glycosaminoglycans, and plasmatic proteins that are essential in maintaining the osmotic equilibrium and overall integrity of the endothelium. During hemorrhagic shock, the EG becomes thinner and the administration of crystalloids exacerbates this state, leading further fluid extravasation and overall volume depletion, worsening bleeding [17,22].

An excessive administration of crystalloids can also lead to cardiac dysfunction. The Frank–Starling curve demonstrates that an increase in cardiac volume results in a corresponding increase in cardiac output (through increased stroke volume) up to a certain threshold after which additional volume expansion results in decreased cardiac output. This decrease is secondary probably due to the deleterious effects of intracellular edema, which causes a dysfunction of intracellular metabolic processes and an improper cellular respiratory system while worsening the proinflammatory state of the hemorrhagic shock [22].

Massive transfusion protocols and hemostatic resuscitation

Massive transfusion means transfusion requirements of ≥4 PRBC units (some articles considered the need for ≥10 PRBC within 24 h), replacement of total blood volume within 24 h, or replacement of 50% of blood volume within 3 h [37–39]. Massive transfusion protocols involve the early utilization of blood products along with proportionate administration of PLT:FFP:PRBC, limiting the resuscitation based in large amounts of crystalloids. Therefore, it has been argued that with this approach the clotting factors dilution and third spacing formation is minimized [17,40].

It is widely accepted that a high PLT:FFP:PRBC ratio confers an advantage in patient survival. No significant differences between 1:1:1 or 1:1:2 ratios have been demonstrated in terms of patient mortality in 24 h and 30 days of follow-up. Nonetheless, the PROPPR study demonstrated that a greater proportion of patients in the 1:1:1 group achieved hemostasis and suffered less deaths due to exsanguination at 24 h [36]. Further analysis of the PROMTT study performed by Del Junco et al. revealed that early administration of plasma (within the first 3 h and within the first 3–6 units after transfused blood components) was associated with a decrease in mortality at 24 h and 30 days (OR = 0.47, $p = .009$; OR = 0.44, $p = .002$, respectively) [41].

Fibrinogen is the first clotting factor to decrease its concentrations, and values of <200 mg/dL are considered an indication for component replacement [42,43]. According to Pacheco et al., one unit of platelets will increase the platelet count by 5000–10,000/mm^3, and one unit of FFP contains all clotting factors and 2 g of fibrinogen for each 1000 ml; thus, a unit of FFP (200–250 ml) increases serum fibrinogen by 10 mg/dL [17].

Antifibrinolytic agents

The CRASH-2 trial provided evidence that an early administration of TXA reduces mortality secondary to bleeding in patients with trauma by approximately one-third. The current guidelines suggest a loading dose of 1 g for 10 min, and then an additional 1 g is infused for 8 h. TXA should be administered as soon as possible after the injury and within the first 3 h [44].

In the scenario of obstetric hemorrhage, the fibrinolytic activity in the immediate postpartum has led to an increased interest in TXA use [45]. The WOMAN trial studied the effect of early administration of TXA on maternal mortality after hysterectomy and other surgical morbidities in patients with PPH. In this randomized, double blind, placebo-controlled trial, patients of 16 years of age and older with a clinical diagnosis of postpartum hemorrhage after vaginal delivery or cesarean section in 193 hospitals throughout 21 different countries were included. A total of 20,060 women were included and were randomly assigned to receive 1 g of intravenous TXA or placebo, in addition to standard care for postpartum hemorrhage. If bleeding continued after 30 min, or stopped and resumed within 24 h of the first dose, a second dose of 1 g was administered (either TXA or placebo). Death due to hemorrhage was significantly reduced among women who received TXA (RR 0.81, 95% CI 0.65–1.00; $p = .045$), especially in women who received the treatment within 3 h after delivery (RR 0.69, 95% CI 0.52–0.91; $p = .008$), and additionally, thromboembolic events did not increase in patients receiving TXA [46]. Nowadays, the use of an antifibrinolytic agent such as TXA seems to be safe, effective, inexpensive and crucial in PPH management [45], because of the high chance of developing an acute coagulopathy secondary to a massive bleeding and trauma due to excessive fibrinolysis.

There is limited evidence about the use of fibrinogen concentrates in PPH; however, its use may reduce transfusion of blood products [42]. On the other hand, the use of prothrombin complex concentrates (concentrates of vitamin K-dependent clotting factors) is not recommended in the routine setting of PPH because of the lack of evidence to support it [42].

Point of care test (POCT)

POCT of viscoelastic coagulation such as ROTEM (Rotational Thromboelastometry) and TEG (thromboelastography) perform fast viscoelastic hemostatic analyses that provide a graphical evaluation of the kinetics of all stages of clot formation (initiation, propagation, strength, and dissolution) in whole blood, analyzing the enzyme kinetics of the entire coagulation process and facilitating targeted therapeutic interventions. Such tests allow for individualized treatment strategies and can reduce the requirement of blood products to be transfused [22].

Management of massive transfusion rests on simple, reliable and rapid diagnostic coagulation tests. Monitoring dynamic changes of hemostasis with TEG or ROTEM may enable: (i) distinction between a surgical cause of bleeding or coagulopathy; (ii) diagnosis of the specific type of coagulopathic impairment; and (iii) guidance in the choice of hemostatic treatment. This may reduce the use of blood products and bleeding, the need for reoperations, and the rate of complications associated with hypovolemic shock [47].

The use of protocols for massive transfusion is considered a useful tool for the emergency team, since it helps standardizing the management of these patients and improves the response to a massive hemorrhage. In a systematic review, Wikkelsø et al. evaluated the hemostatic management of an algorithm using TEG or ROTEM among patients with a severe hemorrhage, and compared this management with other algorithms based on clinical judgement, usual treatment or standard laboratory tests. The primary outcome was overall

mortality, and the secondary outcomes were bleeding events, blood loss, proportion of patients in need of transfusion and amount of blood products transfused, complications probably related to underlying conditions, incidence of surgical intervention and reoperation due to bleeding, and complications probably related to transfusion, among others. The authors included 17 trials (1493 participants), most of them involving cardiac surgery. Thromboelastography or rotational thromboelastometry seemed to reduce overall mortality compared to usual treatment based in laboratory test (3.9 versus 7.4%, RR (95% CI) 0.52 (0.28–0.95); $I^2 = 0\%$, 8 trials, 717 participants). However, the quality of evidence is graded as low due to the high risk of bias, heterogeneity, imprecision and low event rate. TEG or ROTEM significantly reduced the proportion of patients transfused with red blood cells (RR (95% CI) 0.86 (0.79–0.94); $I^2 = 0\%$, 10 trials, 832 participants), fresh frozen plasma (RR (95% CI) 0.57 (0.33–0.96); $I^2 = 86\%$, 10 trials, 832 participants) and platelets (RR (95% CI) 0.73 (0.60–0.88); $I^2 = 0\%$, 10 studies, 832 participants) [47].

On the other hand, it has been suggested that reanimation with blood products should be individualized and adjusted according to the results of the point of care viscoelastic testing (PCVT). Snegovskikh et al. conducted a retrospective cohort study comparing two groups of patients with severe postpartum hemorrhage: (i) those with blood transfusion guided by PCVT, and (ii) those managed using a standardized massive hemorrhage transfusion protocol, either because PCVT was not yet available, or because no PCVT credentialed providers were on site [48]. There was no statistically significant difference between the PCVT and non-PCVT groups regarding the amount of crystalloids, colloids, albumin, and cryoprecipitate administered. However, patients in the PCVT group received significantly fewer transfusions of PRBCs ($p < .0001$), FFP ($p < .0001$), and platelets ($p < .0001$). Estimated blood loss was also significantly lower in the PCVT group (median [IQR] 2000 ml [1600–2500] versus 3000 ml [2000–4000], $p < .001$). Similarly, the incidence of puerperal hysterectomy (25% [7/28] versus 54% [31/58], $p = .013$) and postoperative ICU admission (4% [1/28] versus 43% [25/58], $p < .001$) were significantly lower in the PCVT group [48].

The evidence provided above shows that the use of TEG and ROTEM as bedside tests may improve the clinical outcomes and reduce the cost by considering clinically efficient decisions for the management of blood and blood products transfusions in patients with severe postpartum hemorrhage.

Damage-control surgery (DCS)

DCS is the term used to describe a series of surgical procedures performed in stages during a period of patient hemodynamic instability. These procedures have applicability in traumatic and nontraumatic scenarios in General Surgery, Orthopedics, as well as Gynecology and Obstetrics. DCS consists of performing limited surgical interventions to swiftly counteract life-threatening conditions, with the definitive surgical procedure deferred until a period of stabilization has been achieved in the Intensive Care Unit (ICU). DCS is usually reserved for the severely injured patient that may not survive the surgical efforts to achieve primary repair in the operating room. Frequently, the hemorrhage in these patients may not be able to be controlled surgically, mainly due to a combination of hypothermia, acidosis, coagulopathy and hypocalcemia [49].

The most common indications for DCS in the setting of hemorrhage include the following: difficult surgical access to the bleeding site, venous bleeding not suitable for mechanical control, need of blood products and intravenous fluids in nonarterial bleeding scenarios, hemodynamic instability despite use of vasopressors, and coagulopathy. This is explained in Tables 1 and 2. Other indications are exsanguination and impossibility of abdominal closure by regular methods [49].

Typically, these patients present with diffuse bleeding in the absence of clot formation despite maximum surgical efforts. Like DCS in other surgical specialties, packing is the cornerstone in the damage control of obstetric patients [49].

Decision of DCS: a critical point

The decision to perform a DCS must be taken as early as possible; time is a factor that plays against survival [50]. Several patient markers, both physiological and metabolic, have been proposed to identify patients that could benefit from DCS (Tables 1 and 2). These indicators are explained in Figure 1, and along with sound clinical judgment, are the prime determinants whether the patient is eligible for DCS.

Table 1. Indicators for damage-control surgery (prior to entering the operating room).

Systolic blood pressure <70 mmHg
Body temperature <34 °C
Maternal blood pH <7.1

Adapted from: Pacheco et al. [49].

Damage-control surgery technique

After identifying candidate patients, a sequential approach has been documented that can serve as a general guideline for DCS:

1. initial laparotomy: fast control of bleeding and/or contamination, including hysterectomy
2. resuscitation in intensive care or High Dependency Unit
3. definitive surgery
4. definitive closure

Table 2. Intraoperative indications for damage-control surgery secondary to hemorrhage.

Venous bleeding not suitable for surgical control
Persistent bleeding despite several transfusions of blood products (>10 units of PRBC)
Massive transfusion – 6 units of Red Blood Cells (during the first 4 h)
Increasing and continuous need for fluids due to an active nonarterial bleeding
Hemodynamic instability, requiring persistent vasopressor support or that results in the development of ventricular arrhythmias
Coagulopathy resulting from a combination of hypothermia (temperature <35 °C), acidosis (pH <7.3) and loss of coagulation factors
Duration of surgery >90 min

Adapted from: Pacheco et al. [49].

Initial laparotomy

The initial surgical period, where obstetric patients can present in different scenarios, is an important factor to take into account. This period can be regarded as the moment where the hemorrhage was generated (e.g. C-section with severe hemorrhage), an intermediate point of bleeding control after a B-Lynch procedure, or after a postpartum hysterectomy in which there is persistent bleeding. Hence, due to the possible variations in the initial surgical period, it is recommended that the obstetrician must be in constant communication with the surgical team in order to assess the condition of the patient to determine if she is a candidate

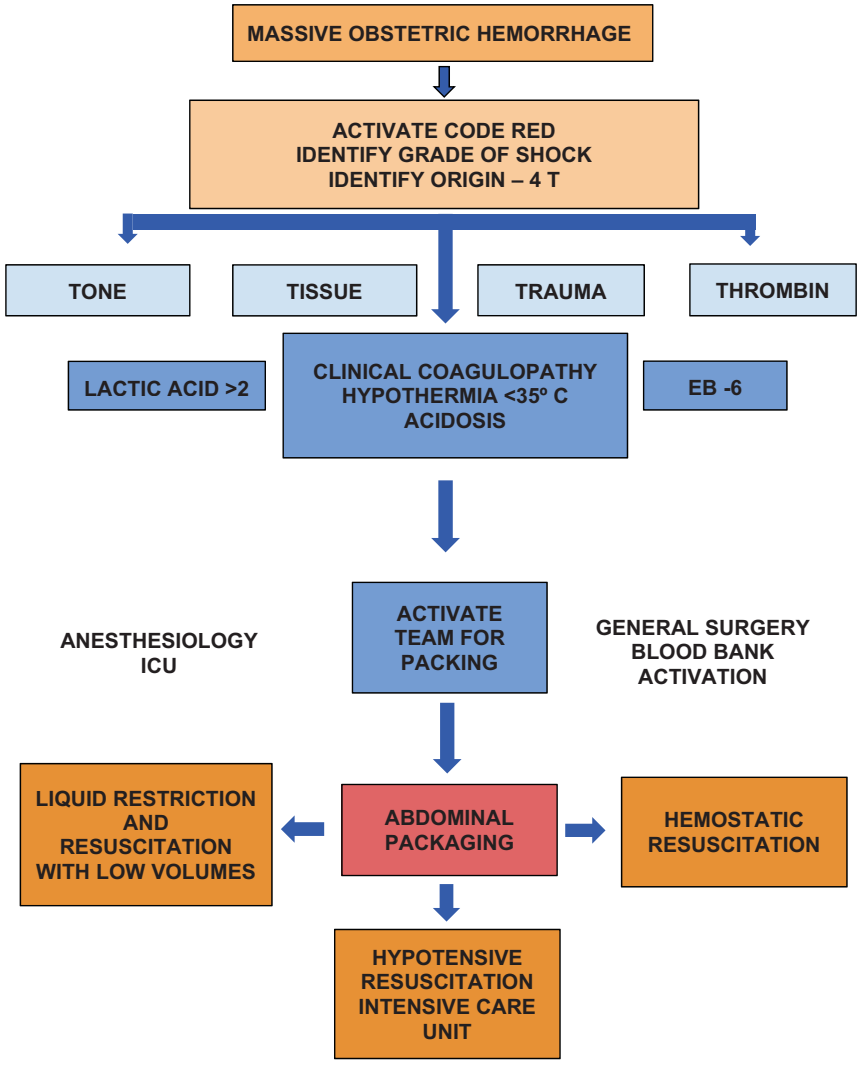

Figure 1. Algorithm of management.

for DCS. A constant report and interpretation of arterial blood gas values, patient body temperature, surgical time and number of blood units transfused is of paramount importance.

The objective of this initial approach is to achieve rapid control of bleeding. It is recommended that at this stage the obstetrician performs an abdominal hysterectomy. The type of hysterectomy to be performed has to be chosen depending on the preference and expertise of the operator, the clinical condition of the patient, and considering other factors like age, cause of hemorrhage, hemodynamic stability and pelvic anatomy [51]. A few studies [51–53] have demonstrated that there is no statistical differences between the two techniques in terms of complications, blood transfusions, and ICU admission; nevertheless, faster bleeding control and shorter surgical times corresponds to subtotal hysterectomy (STH), which are the reasons why it is preferred over total hysterectomy (TH) [51,53]. If the origin of the hemorrhage is from the lower uterine segment, cervix or vaginal fornices, then a STH may not be effective controlling bleeding since the arterial circulation of the cervix has a high blood flow rate and could cause bleeding persistence. In those cases, a TH should be performed [51,52].

Surgical time is a determining factor in patient survival, and is recommended to be less than 90 min, since longer operating times should be considered a predictor of adverse outcomes, because of the onset of an irreversible physiologic insult demonstrated in computer simulation models [11,54]. Hemorrhage control of the pelvic cavity is frequently carried out through the means of packing [55], which can be achieved with either separated smaller compresses or a large single compress. Based on our reported experience on two case series with 28 and 108 critical patients with obstetric hemorrhage, we recommend that pelvic packing should be done with at least 7–10 compresses [2,56]. In these case series, the mean number of applied compresses was 14, with a range from 8 to 22. Importantly, 73% of the patients were intervened with DCS within the first hour of the diagnosis of massive hemorrhage, and 88% had a total abdominal hysterectomy at the time of DCS.

In DCS, abdominal closure is temporary. The ideal method should be easy to perform and remove. The method chosen should be able to adequately protect the abdominal content from evisceration, prevent the development of fistulas and the lateral retraction of the fascia, since the latter can result in an inability to complete a final closure of the abdominal wall [49]. Compresses should be complemented with a temporary abdominal wall closure using a negative pressure system like Vacuum-Pack or partial closure with a Viaflex bag (Bogota Bag) without the need for negative pressure [2,56].

The most widespread open abdomen with negative pressure technique was described by Barker et al., in which after performing pelvic packing, the intestines are protected with a cover of fenestrated polyethylene, over which a layer of compresses is placed at the midline and two silicone drains are placed, being exposed outwards to the skin by additional incisions [57]. New layers of compresses are placed over the drains and are sealed with a cover of adherent polyester. When the Vacuum Pack has been assembled, the drains are connected to a source of negative pressure with a reservoir of 100–125 mmHg. If commercial VAC® systems are available, an intestinal covering must be made with polyurethane over which the flexible polyurethane foam included in the system must be applied. It is not necessary to perform additional drainage incisions. Subsequently, the foam is coated with adherent polyester and an orifice is made on the plastic coating where the negative pressure commercial drainage system is connected.

Evidence regarding the addition of local hemostatic agents, whether applied directly on the tissue or immersed in sterile compresses, is limited. In some series, the addition of these agents like thrombin spray or fibrin glue has proven to be a useful coadjuvant when packing with compresses is applied to limit continuous bleeding [49].

Currently, there is neither consensus nor sufficient evidence regarding the use of prophylactic antibiotics in patients undergoing DCS with abdominal packing. Several surgical guidelines recommend the administration of a single preoperative dose of broad-spectrum antibiotics that, in theory, should provide sufficient coverage for aerobic and anaerobic microorganisms. Furthermore, these guidelines suggest that preoperative antibiotic prophylaxis should be extended to 24 h post injury in patients who have suffered hollow viscous injuries [58,59]. Nevertheless, the former is not applicable in the context of obstetric patients (as no hollow viscous injury occurs); consequently, it could be inferred that antibiotic use is not required. Other experts recommend prophylactic doses of broad-spectrum antibiotics every 6–8 h until the abdominal packing is removed. However, further studies are needed to provide evidence-based recommendations in the obstetric population [49].

Interestingly, DCS can also be performed vaginally in cases of associated vaginal tears and combined

with other surgical techniques for effective bleeding control. In our series, 8% of the patients required vaginal packing and 4% associated vascular ligatures.

Resuscitation – intensive care, high dependency unit

During this stage, the patient must be transferred to the Intensive Care Unit where coagulation disorders and metabolic abnormalities should be corrected [22]. These patients require a significant investment of hospital resources as demonstrated in our series of 108 cases: 100% required massive transfusion protocols with an average of 5 units of RBC, 6 units of plasma, 4.5 units of platelets and 10 units of cryoprecipitate. In addition, 34% received vasoactives, 14% tranexamic acid, 8% specific coagulation factors, 5% topical thrombin, and 2% renal replacement therapy [2].

The obstetrician must keep strict clinical vigilance and perform care alongside the intensive care specialist since complications could arise at any time. Significant problems that must be recognized in order to take prompt actions during this period are the following:

Abdominal compartment syndrome (ACS)

Due to the mechanical effect of packing and progressive edema of the abdominal tissues during the resuscitation process, there is an increase of the intra-abdominal pressure (IAP), which is a common complication after pelvic packing. This increase in the IAP may result in Abdominal Compartment Syndrome (ACS), a common complication that is associated to decreased venous return of the inferior vena cava, producing a subsequent decrease in cardiac output and renal perfusion (evidenced by oliguria or anuria), as well as abnormalities in mechanical ventilation [60,61].

Pregnancy is a state of chronically elevated intra-abdominal pressure. The median intra-abdominal pressure during the last stage of pregnancy is reported to range between 15 and 29 mmHg. It decreases to a median pressure of 16 mmHg at 24 h after delivery. Hence, during pregnancy or the postpartum period, patients will have a higher intra-abdominal baseline pressure and should not be treated based on an isolated measurement of IAP in the absence of clinical findings consistent with ACS, such as hypotension, oliguria that does not respond to fluid therapy, abdominal distension, and high airway pressures seen on mechanical ventilation [49]. All patients under post-packing management should receive continuous measurement of IAP; values greater than 16 mmHg can be associated with hemodynamic repercussion and can indicate the need for early surgical intervention [62].

Once a diagnosis of ACS is confirmed, definitive treatment involves opening the abdominal cavity (if closed) to allow decompression. In the scenario of DCS with open fascia, if the opening is too small, an extension of the incision may decrease the IAP. On the other hand, if the packing of the cavity is too tight, repacking should be considered using a lower number of compresses and applying less pressure when placing them. Certain medical interventions can decrease IAP, such as the use of nasogastric tubes, rectal tubes, gastrointestinal prokinetic agents, diuretics, and the use of muscle relaxants. However, these interventions should not replace surgical management when indicated [56].

Persistent bleeding of abdominal cavity

It is very important to accurately quantify the production of fluid of the abdominal cavity; the most recommended device to measure it after partial abdominal closure is the use of Vacuum Pack, which allows more precise quantification of bleeding during the postoperative period. It is considered that production higher than 400 cc/hrs, in a patient in whom all the coagulation disorders have been corrected, is an early indicator for laparotomy.

Definitive surgery

After stabilization of the physiological variables of the patient, it is considered safe to review the abdominal cavity. Ideally, this should be performed 48–72 h after the first surgical procedure. The plan and the surgical team should be determined based on the findings of the first intervention, since at this time issues that were partially solved should be corrected, such as the case of ureteral ligation, bladder injury or bowel perforation. Depending on intraoperative findings, this may be the final surgery or the moment to define whether the patient will need additional interventions for definite control. If further interventions are needed, it is recommended to continue with techniques of temporary closure of the abdominal cavity [60]. In our largest case series, the mean reintervention time was 48 h, with a standard deviation of 42–72 h, and in 65% of the patients total control of bleeding was achieved in the first DCS [2].

Definitive closure of abdominal wall and cavity

The final stage is the definitive closure of the abdominal wall, which is performed after all surgeries have been successfully completed and all additional damage has been repaired. It is important to take into account that the number of reinterventions is directly related to a higher percentage of infectious complications, wound dehiscence and abdominal wall closure problems [62].

Complications derived from damage control surgery

The majority of complications derived from DCS are dependent on when the closure of the abdominal fascia occurs. The most frequent complications are infections and intra-abdominal collections. It is recommended to initiate broad-spectrum antibiotic treatment early, targeting the polybacterial flora present in the female genital tract. Complications derived from injured organs during the initial laparotomy such as urinomas, intestinal perforations, and fistulas may require an interdisciplinary approach [61]. In our cohort, the main complications included infection of the surgical wound in 28% of the cases, presence of intra-abdominal collections in 20%, and evisceration in 10% of the patients [2].

Final objectives in resuscitation and damage control surgery

Perhaps the greatest challenge when applying DCR is to determine when to stop this therapeutic modality. Clearly, it should be sustained as long as there are signs of bleeding and coagulopathy. A continuous assessment of the hemodynamic and physiological status of the patient is required. There is consensus that pursuing not only one but several resuscitation parameters are essential until tissue hypoxia has been resolved. These parameters include the following:

- pH
- base deficit
- lactate
- hematocrit
- coagulation: ideally evaluated with conventional laboratory tests and POCT (ROTEM/TEG)

In patients with a clinical trend toward improvement, the decision to perform definitive surgery is appropriate. On the other hand, in those patients with compromised micro- and macrohemodynamics, a minimal surgical intervention that provides stability should be considered until the pathophysiological conditions of the patient are more favorable [18].

Extension of the concept of damage control

Hemostatic resuscitation should begin as soon as the patient arrives, allowing for improvement of perioperative physiological conditions without delaying surgical procedures. The adoption of this integrated approach combines surgical and resuscitative measures which results in an overall increased survival of patients with PPH. This approach should be applied during the initial management of the injured patient by ambulance personnel, performing hemorrhage control and hemostatic resuscitation as soon as possible; this extension of DCR to the first response team is termed remote DCR (RDCR) [63], and is explained in Figure 2. This extension of damage control is also valid in the setting of critical obstetrics. The resuscitation of patients with life-threatening obstetric hemorrhages should begin at the site of the obstetric event (even if it is a level I of attention), applying strategies of the obstetric red code and performing interventions for bleeding control. DC should be given continuously during the transfer of the patient to the highest possible complexity care center for comprehensive and interdisciplinary care, with a medicalized ambulance and trained personnel to ensure clinical monitoring and proper resuscitation maneuvers. DCR incorporates the concept of damage control radiology (DCRad) for diagnostic and therapeutic aspects. Diagnostic DCRad (dDCRad) employs multidetector computed tomography (MDCT) to rapidly find life-threatening injuries and sources of bleeding, facilitating decision-making for other treatment options.

The notion that critical patients should be withheld transfer to the imaging service has been challenged by evidence that demonstrates that this subset of patients receive the highest benefit of diagnostic imaging procedures. Experienced radiologists can quickly discern and deliver a primary report to expedite team decision making, including transfer of the patient to the operating room, angiography room or ICU [22]. The therapeutic DCRad (tDCRad) is based on having a rapidly available service (typically $<$60 min). However, this is not yet possible in the main obstetric care centers in many countries. Minimally invasive techniques such as balloon arterial occlusion, occlusive embolization and vascular stents are feasible in the context of tDCRad and have become important tools in treating obstetric complications, including pelvic

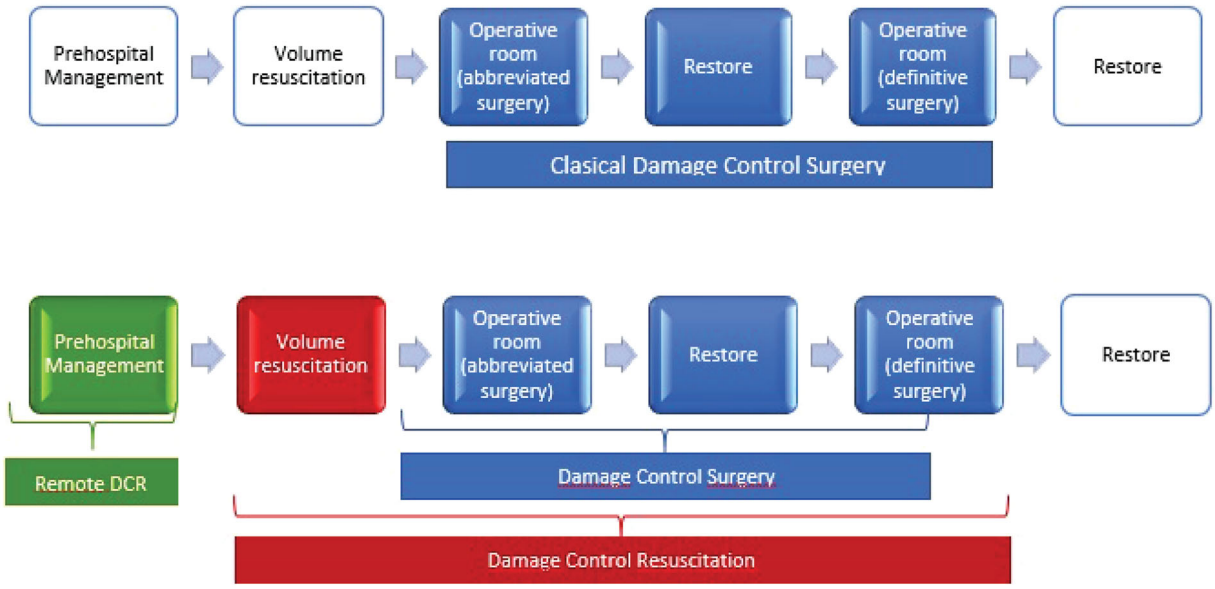

Figure 2. Evolution and extension of the concept of damage-control.

arterial hemorrhage with a difficult surgical approach and vaginal and perineal trauma [22].

Impact on maternal mortality for major obstetric hemorrhage

DCS has proven to be applicable in the context of obstetric hemorrhage, with successful results in the control of refractory obstetric hemorrhage and an overall decreased mortality of patients in severely critical conditions. This is especially true in those patients in whom the use of conventional measurements is associated with a high probability of failure. In a study published by Escobar et al. [2], currently the largest registry of DCS in obstetrics, an adequate control of hemostasis was achieved in 60% of the cases in the first surgical intervention, with subsequent control of hemorrhage in 98% of the cases. The study also showed a reduction in the expected mortality (Apache II score average of 14) from 40 to 7%. We consider that this strategy should be implemented in the management algorithms of major obstetric hemorrhage. It is paramount for obstetrician and gynecologists to familiarize themselves in depth with this approach, the technique, and indications. We emphasize that proper training in the concept of DCS must be widespread, because it is an available technique to manage severe PPH in obstetric patients with severe and life-threatening conditions.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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