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The Role of Prehospital REBOA for Hemorrhage Control in Civilian and Military Austere Settings: A Systematic Review

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Abstract: Despite the success of prehospital resuscitative endovascular balloon occlusion of the aorta (REBOA) in combat and civilian settings, the prevalence of complications and the lack of conclusive evidence has led to uncertainty and controversy. Therefore, this systematic review aimed to evaluate the role of prehospital REBOA for hemorrhage control in trauma populations. We systematically searched Cochrane, Ovid MEDLINE, EMBASE and Google Scholar for all relevant studies that investigated the efficacy of prehospital REBOA on trauma patients with massive hemorrhage. Primary outcome was evaluated by blood pressure elevation and secondary outcome was measured by 30-day mortality and complications. Our search identified 546 studies, but only six studies met the inclusion and exclusion criteria. Included studies were low to moderate quality due to limitations within the studies. However, all of the studies reported significant elevation of blood pressure and survival, demonstrating the potential benefits of REBOA. For example, the 30-day mortality rate reduced significantly after REBOA, but studies lacked long-term outcome assessments across the continuum of care. Due to the heterogeneity of the results, a meta-analysis was not possible. We conclude that prehospital REBOA is a feasible and effective resuscitative adjunct for shock patients with lethal non-compressible torso hemorrhage. However, due to the unclear causes of complications and the lack of high quality and homogeneous data, the effects of prehospital REBOA were not truly reflected and comparison between groups was not feasible. Thus, further high-quality studies are required to attest the causality between prehospital REBOA and outcomes.

Keywords: prehospital; REBOA; aortic occlusion; hemorrhage; trauma



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1. Introduction

Traumatic hemorrhage is a global problem that accounts for up to 40% of trauma mortality, owing to violence, road traffic accidents and military conflicts [1–3]. More than one-fourth of these deaths were preventable, occurring before arrival at hospitals or definitive care. In both civilian and military settings, non-compressible torso hemorrhage (NCTH) represented the largest proportion of mortalities [1–4]. A large-scale study of the US Trauma registry postulated that the increase in prehospital time or the torso injury severity results in significantly higher mortality, where the first peak of death was identified in the first 30 min after significant torso trauma [2]. However, evacuation within the first 30 min is often infeasible or even unrealistic in austere settings. Despite the advent of novel hemostatic devices, NCTH are neither amenable to them nor to direct pressure. Therefore, efficient early proximal hemorrhage controls are imperative to temporize lethal conditions and to bridge patients to definitive care.

Due to the poor results of using resuscitative thoracotomy (RT) for aortic occlusion [5], resuscitative endovascular balloon occlusion of the aorta (REBOA) has been proposed to act instead in the setting of NCTH, since existing evidence suggests it significantly improves the overall survival rate (16.7% vs. 62.5%, $p < 0.001$) [5,6]. REBOA is a minimally invasive method that involves percutaneous insertion of a balloon catheter into the femoral artery and occlusion of the descending thoracic aorta (Zone I) or distal abdominal aorta (Zone III), depending on the indication. This aims to temporarily arrest the arterial inflow, restore circulating blood volume and preserve brain perfusion for patients with severe exsanguination [7]. The concept of aortic occlusion was first introduced in the Korean War by Carl Hughes despite its failure [8]. However, with advanced technology, the REBOA catheter has now emerged onto a variety of clinical scenarios, for instance, ruptured abdominal aortic aneurysm and post-partum hemorrhage and gastrointestinal tract bleeding [9–12]. The outcomes were found encouraging for both trauma and non-trauma patients in civilian and military settings, where it is also currently incorporated in the Joint Trauma System Clinical Practice [13]. This could be very beneficial to numerous military patients, as a surge in casualties sustaining NCTH has been underscored by the US Department of Defense, owing to increased improvised explosive device use [13–15].

Nonetheless, REBOA has potential devastating complications due to ischemic effects secondary to occlusion, for example, limb amputations, arterial dissection and balloon-related thromboembolic events [7]. A propensity score and sensitivity analysis on a large Japanese trauma population reported that the in-hospital mortality was significantly higher in the REBOA group than the non-REBOA group (61.8% vs. 45.3%) [16]. This could result from delayed definite hemostasis due to limited surgical capability, as the median door-to-primary surgery time was 97 min [17]. This revealed its time-dependent feature, requiring meticulous consideration about the risk and benefits based on available resources.

In the prehospital aspect, there is a paucity of inclusive data analysis about the best evidence-based practice of REBOA. Some statements and explanations of existing protocols are not clearly defined, and thus a systematic review on the effectiveness of prehospital REBOA use in traumatic hemorrhage has been attempted. This may help answer the questions of this literature gap by outlining conclusive evidence and providing a reliable basis for protocol enhancement to achieve the optimal clinical outcomes.

2. Materials and Methods

2.1. Literature Search

The search and reporting of this review adhere to the protocols recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA), the Cochrane Handbook for Systematic Reviews of Interventions and the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis to enhance comprehensiveness and accuracy of this study [18–20]. After scoping searches, four electronic databases (Cochrane Library, Ovid MEDLINE, EMBASE, Google Scholar) were searched for relevant literatures from the inception to June 2021. The PICO strategy (Table 1) was adopted to identify the following keywords: “hemorrhage”, “trauma”, “prehospital”, “REBOA”, “resuscitative endovascular balloon occlusion of the aorta”, “aortic occlusion” and “balloon occlusion”. These terms were searched with different combinations in the title and abstract and against the exclusion criteria. Furthermore, the reference lists of all the literatures were also examined with the aim of being as inclusive as possible.

Table 1. PICO of the study.

Patient	Adults with traumatic haemorrhage
Intervention	Standard prehospital resuscitative interventions with REBOA
Comparison	Standard prehospital resuscitative interventions without REBOA
Outcome	Improved hemodynamic and reduced mortality

2.2. Data Collection

Two researchers (C.N.C. and Z.A.) independently performed the literature search and assessed the titles and abstracts for inclusion eligibility according to the inclusion and exclusion criteria (Table 2). The full texts of potentially eligible literatures were retrieved for further assessments.

Table 2. Inclusion and exclusion criteria.

Inclusion Criteria		Exclusion Criteria	
1.	The study design was RCT, observational study, prospective or retrospective case series and report	1.	Studies without a full text
2.	Adult trauma patients with haemorrhage	2.	Conference reports, reviews and quality assessment studies
3.	Patients treated with REBOA	3.	Animal studies and stimulation studies
4.	The study took place in prehospital settings (either civilian or military environment- equivalent to Role 1 MTF)	4.	The study took place in hospital settings
5.	The study was written in English	5.	Patients did not have trauma or bleeding pathology
		6.	The study was still ongoing

2.3. Data Extraction and Synthesis

Relevant data from the included studies were extracted and presented in tables where they were cross-checked and agreed upon by two researchers (C.N.C. and Z.A.). These extracted data were then divided into three parts: study characteristics, population characteristics and study results.

2.4. Quality Assessment

As all the studies included were case reports and case series, the JBI Critical Appraisal Tools for Systematic Reviews were used to evaluate the methodological quality of the included studies, in terms of the risk of bias in design, implementation, and analysis [20]. The appraisal checklists of case reports and case series have 8 and 10 questions, respectively. They focus on similar domains and allow responses with “Yes” for a low risk of bias, “No” for a high risk of bias and “Unclear” for an unclear risk of bias. Two reviewers (C.N.C. and Z.A.) assessed each article independently with the JBI tools and disagreement was solved through discussion.

2.5. Statistical Analysis

The included studies in this review were all retrospective descriptive studies where the clinical data (interventions, inclusion and exclusion criteria, outcome measurements), methodology (quality) and statistical significance were heterogeneous. These limited the eligibility of combination and integration of the extracted data. The available data was also analyzed by a medical statistician (B.K.), who agreed that there was a lack of statistical homogeneity for meta-analysis. Therefore, only a narrative synthesis could be carried out.

3. Results

3.1. Study Selection

A total of 546 articles were identified in Cochrane Library, Ovid MEDLINE, EMBASE and Google Scholar. After de-duplication, 533 studies were left for screening. Their titles and abstracts were examined for eligibility and were marked as 1, 2, 3, 4 and 5, which represented irrelevant studies, prehospital REBOA on animals, in-hospital REBOA on humans, prehospital REBOA on cadaver models and prehospital REBOA on humans, respectively. Seven potential studies were retained [21–27] and full text assessments were conducted. One study [27] was excluded because it was conducted in Role 2 MTF, where ‘prehospital care’ is defined as the medical care from the point of injury to Role 1 military Medical Treatment Facility (MTF), according to the North Atlantic Treaty Organization

Doctrine [28]. As a result, six articles were included in this systematic review. The PRISMA flow diagram is shown in Figure 1.

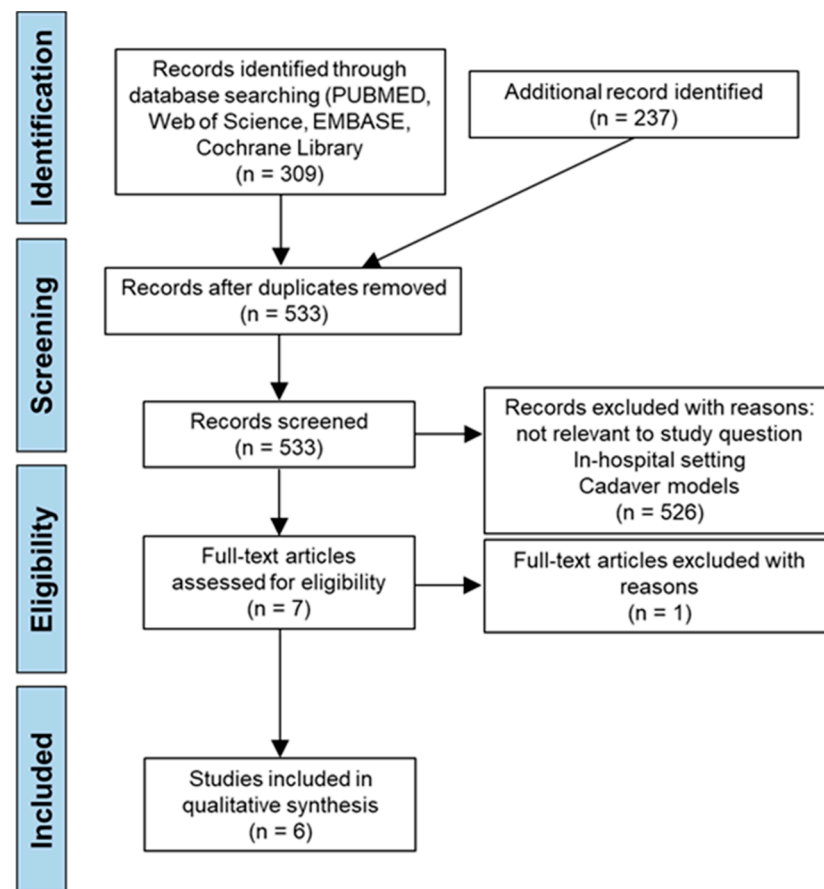


Figure 1. PRISMA flow diagram.

3.2. Study Characteristics

All six included studies were retrospective and descriptive in nature and were carried out in different western countries (the United Kingdom, the United States, France and Belgium) and published between 2016 and 2019 (Table 3). Three studies were conducted in civilian settings, while the other three were carried out in a far-forward unit of military medical care. Only three studies [21,25,26] clearly depicted inclusion criteria for REBOA utilization while the other three [22–24] did not. They shared comparable patient inclusion criteria, including non-compressible hemorrhage, blunt and penetrating injuries and shock (SBP < 90 mmHg).

Table 3. Characteristics of the included studies in chronological order.

Study	Design	Country	Setting	Inclusion and Exclusion Criteria	Intervention Protocol (Prehospital)	Outcomes Measures	Study Quality
Sadek et al., 2016 [21]	Case report	UK	Civilian	<ul style="list-style-type: none"> - Shocked adults with non-compressible exsanguinating haemorrhage from: <ol style="list-style-type: none"> 1. blunt or penetrating pelvic injury or 2. junctional vascular groin injury 	<ul style="list-style-type: none"> - REBOA only deployed in Zone Three - Blood transfusion - Rapid sequence intubation - Anaesthesia - 14 mm 7 Fr embolectomy balloon catheter 	<ul style="list-style-type: none"> - Blood pressure - Blood gas analysis - Blood product consumption - Length of ICU stay - Survival to discharge 	Low
Manley et al., 2017 [22]	Case series	FST operated by the US SOST	Military	Not specified	<ul style="list-style-type: none"> - Whole blood transfusion - Antibiotics - 1 g tranexamic acid - FAST examination with Vscan - 7 Fr Prytime ER-REBOA 	<ul style="list-style-type: none"> - Blood pressure - Survival to 2-h transfer to the next level of care - REBOA-related complications 	Moderate
Northern et al., 2018 [23]	Case series	FST operated by the US SOST	Military	Not specified	<ul style="list-style-type: none"> - FAST exam for abdominal and chest evaluation - Whole blood resuscitation - 7 Fr Prytime ER-REBOA 	<ul style="list-style-type: none"> - Blood pressure - REBOA access site complications - Survival to the next level of care 	Moderate
Lamhaut et al., 2018 [24]	Case report	France	Civilian	Not specified	<ul style="list-style-type: none"> - Intubation - IV fluid - Epinephrine - 7 Fr Prytime Medical, Boerne, TX, USA 	<ul style="list-style-type: none"> - Return to circulation (no objective data) - Survival to damage control surgery 	Low

Table 3. Cont.

Study	Design	Country	Setting	Inclusion and Exclusion Criteria	Intervention Protocol (Prehospital)	Outcomes Measures	Study Quality
de Schoutheete et al., 2018 [25]	Case series	FCCP operated by the Belgian SOST	Military	<p>Based on the MIST acronym:</p> <ul style="list-style-type: none"> - Mechanism of injury: high-energy trauma, penetrating trauma - Injury: exclude any bleeding injury above the diaphragm (e.g., cardiac tamponade and tension pneumothorax) - Signs: shock, SBP < 90 mmHg 	<ul style="list-style-type: none"> - FAST examination - IV fluid - Blood transfusion - Tranexamic acid - Antibiotics - Vasopressor - pREBOA strategy - 7 Fr ER-REBOA 	<ul style="list-style-type: none"> - Blood pressure - Survival to definite care - Complications - Blood product consumption 	Moderate
Lendrum et al., 2019 [26]	Case series	UK	Civilian	<ul style="list-style-type: none"> - Non-compressible exsanguinating haemorrhage from blunt or penetrating pelvic injury - Imminent hypovolemic cardiac arrest 	<ul style="list-style-type: none"> - Zone Three occlusion only - Standard trauma care protocol: Direct pressure, immobilisation of fractured site, intravenous access, Tranexamic acid, red cell transfusion - No surgical cutdown for CFA - Maximum 8Fr sheath 	<ul style="list-style-type: none"> - Blood pressure - Prehospital hypovolemic cardiac arrest - Lower limb amputation - Procedural complications - Survival to hospital discharge 	Moderate

Notes: FST, a far-forward surgical unit; SOST, Air Force Special Operations Surgical Teams; FCCP, far-forward casualty collection point; CFA, common femoral artery; Vscan, a handheld Ultrasound; pREBOA, a gradual deflation of the balloon after confirmation of hemodynamic stabilization and aims to keep systolic blood pressure > 90 mmHg [25].

Moreover, the intervention protocols among six studies were diverse and were not clearly described. Four studies encompassed blood products use but they did not mention the types and the transfused volume [21–23,25,26]. Five studies mentioned medication uses, such as antibiotics, tranexamic acid and vasopressors without clear records of the dosage and the route of administration [21,22,24–26]. Regarding outcome measurements, most studies only evaluated the short-term efficacy of REBOA due to rapid evacuation and loss of follow-up, particularly in military settings. Primary outcomes were presented with blood pressure change and survival to the next MTF while secondary outcomes were measured by the incidence of complications, given that only two studies managed to measure long-term survival [21,26].

3.3. Risk of Bias

As the search was conducted using four English databases, publication and language bias were inherent. Using JBI appraisal tools for the scrutiny, the quality of included studies was determined to be low to moderate (Figures 2 and 3). Two case reports poorly presented cases as a timeline and lacked patients’ clinical details, such as history, pre- and post-intervention conditions and complications [21,24]. For the case series, although they demonstrated a comparatively higher quality, half of them obscurely describe the inclusion criteria, patients’ demographics and study site information, affecting the comparability. Paramount essential data were missing, namely, incomplete reporting of long-term outcomes due to the loss to follow up, resulting in bias in outcome measurements and information bias. Owing to the retrospective and descriptive nature, reporting bias, selection bias and allocation bias, bias due to confounding factors was inherent. The heterogeneity existed due to different study contexts and intervention protocols that could greatly influence outcomes and submerge the true effectiveness of prehospital REBOA. Nonetheless, since the procedure is rarely used, this review already encompassed the studies capturing the majority of the cases worldwide, regardless of the absence of high-quality evidence.

Additionally, two studies contained unmatched information in texts and graphs and corresponding authors were contacted for clarification [22,23]. However, there was no response received, which may subsequently affect the reliability of this review.

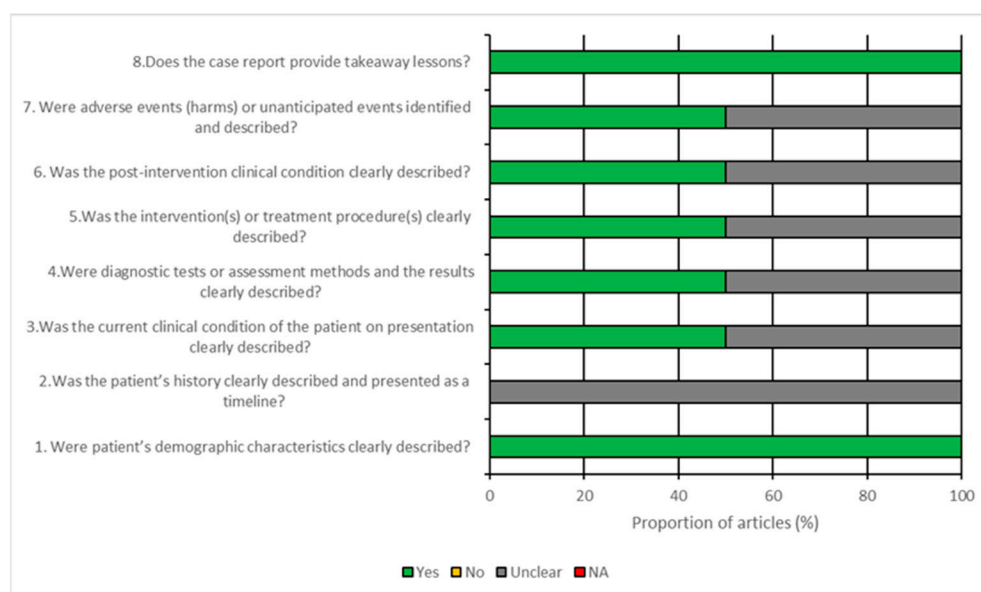


Figure 2. Quality assessment of 2 included case reports [21,24].

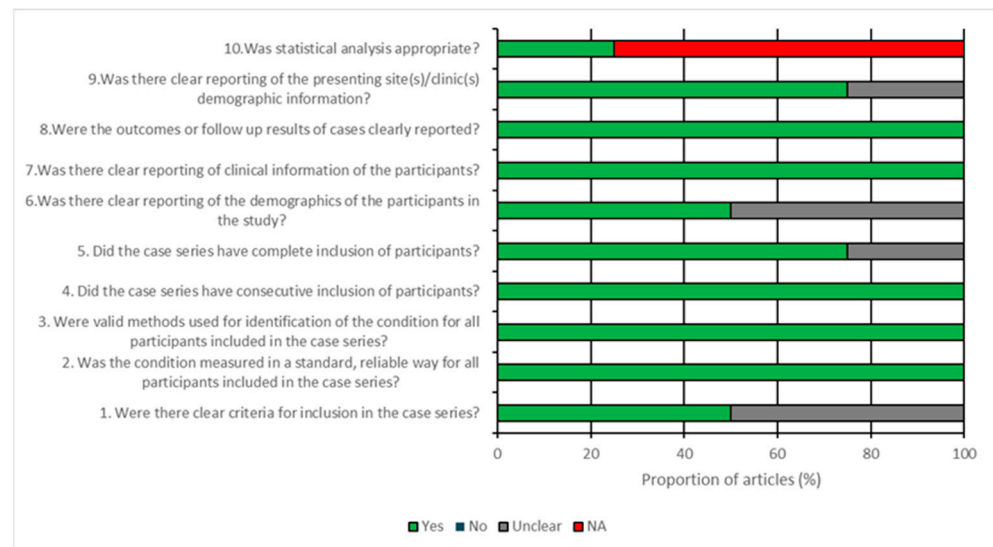


Figure 3. Quality assessment of 4 included case series studies [22,23,25,26].

3.4. Patient Characteristics

The patient characteristics of included studies were summarized in Table 4 and generally they had small sample sizes, ranging from 1 to 21 patients. Despite the great diversity, all patients sustained severe NCTH with shock or cardiac arrest. For military studies, patients were predominantly male combatants with a narrower age range (18–54 years old), while civilian studies included a wider age range of patients (22–79 years old). The studies used different tools to indicate injury severity, including Injury Severity Score (ISS) and Glasgow Coma Score (GCS). They suggested that most patients sustained a major and severe trauma with $ISS > 15$ or $GCS \leq 8$ [29]. Nevertheless, two studies [22,24] did not objectively present the patients' conditions. Regarding injury mechanism, high-energy trauma over torso and pelvic areas were predominant in these patients, regardless of the settings. Military cases were likely to be associated with penetrating gunshots and explosive devices, while civilian cases tended to involve fall and blunt trauma resulting from road traffic accidents.

3.5. Main Findings

In the summary of included studies (Table 5), 85% of the military patients received zone 1 REBOA while 93% civilian patients had zone 3 REBOA. Most of the studies allowed either percutaneous arterial access or surgical cutdown with a 100% success rate of catheter placement, while only a 68% success rate was reported in Lendrum's study due to forbidden cutdown [26].

Table 4. Patients' characteristics of included studies.

Study	Sample Size	Mean Age (Years)	Gender	Specific Characteristics of Interest	Injury Severity	Shock/ Cardiac Arrest *	Mechanism of Injury/Injury Patterns	Initial SBP, Mean (Range)
Sadek et al. [21]	1	32	Male	N/A	ISS: 45	Profound shock	Fell 15 m; pelvic haemorrhage	Not recordable
Manley et al. [22]	4	Not-mentioned	Male	Combat-related	Not mentioned	Shock	Significant NCTH penetrating injuries Gunshot wounds Diffuse fragmentation	78 mmHg (70–90 mmHg)
Northern et al. [23]	20 (19 successful AO, 1 failed)	18–30	Primarily male	Combatants	GCS: 7–15	Shock	NCTH Gunshot wounds Explosion injuries	71 mmHg (50–90 mmHg);
Lamhaut et al. [24]	1	49	Female	Diagnosed with advanced metastatic cancer in DCS	Not mentioned but patient had cardiac arrest at the scene; GCS should be 3	Cardiac arrest	Fall from 30 feet Blunt trauma with abdominal torso haemorrhage	Cardiac arrest
de Schoutheete et al. [25]	3	40 (25–54)	2 Male, 1 female	No known peripheral vascular disease.	Mean ISS:36 (20–66)	1 Shock, 2 Cardiac arrest	High-velocity penetrating trauma due to IEDs or gunshots	2 patients: non-measurable 1 patient: 60 mmHg
Lendrum et al. [26]	21 (19 trauma patients)	22–79	10 female, 9 male	N/A	Median ISS 34, IQR: 27–43	Profound shock	High-energy blunt trauma, pelvic haemorrhage due to fall, RTC	Median SBP: 57 mmHg (IQR: 40–68 mmHg)

Notes: * Systolic blood pressure (SBP) less than 90 mmHg is defined as shock in this review; N/A, not applicable; NCTH, non-compressible torso haemorrhage.

Table 5. Summary of main findings of included studies.

Study	Zone of Balloon Deployment	Success Rate in Catheter Placement	Time of Occlusion (Mean)	Primary Outcomes (Change in BP)	Secondary Outcomes		
					Survival to the Next Higher Level of MTF	30 day Mortality Rate	Complications
Sadek et al. [21]	Zone 3 (n = 1)	100% (Femoral arterial access-percutaneous)	>30 min no exact value	(Non-measurable -> 88/46 mmHg)	100%	0%	Not mentioned
Manley et al. [22]	Zone One (n = 3); Zone 3 (n = 1)	100% (Femoral arterial access-3 percutaneous, 1 cutdown)	Zone One: 25 min Zone Three: 65 min	51% (Mean SBP 78 mmHg ->118 mmHg)	100%	N/A	No access-related site complication in open cut-down patients One patient had femoral sheath hematoma, exploration and arteriotomy repair done uneventfully One patient had distal migration of the balloon
Northern et al. [23]	Zone One (n = 17); Zone 3 (n = 3) *	100% (Femoral arterial access 13 percutaneous, 6 cut down)	Zone One: 21 min * Zone Three: 9 min	79%; (Mean SBP 71 mmHg ->127 mmHg)	100%	N/A	No access-related site complication One patient had failed zone 3 REBOA with no pressure change, suspected balloon rupture due to overinflation, Shunting and ligation were done uneventfully to temporise the wound
Lamhaut et al. [24]	Zone One (n = 1)	100% (Modified cutdown technique)	Zone One: 36 min	Asystole -> return of circulation	100%	N/A—palliative care after diagnosis of advanced cancer in DCS	Not mentioned
de Schoutheete et al. [25]	Zone One (n = 3)	100% (1 percutaneous, 2 cutdown)	Zone One: 31 min	Non-measurable & cardiac arrest & SBP 60 -> Mean SBP: 77 mmHg (70–90 mmHg)	100%	N/A	Two patients developed thrombosis (One before surgical closure without clear cause, one after due to a technical error)
Lendrum et al. [26]	Zone Three (n = 13)	68% (6/19 failed attempts in trauma patients due to inability to obtain arterial access resulting from poor US visualisation of CFA or failure to pass a guidewire)	Zone Three: 80 min median (IQR 75–115).	100% (SBP 57 mmHg -> 114 mmHg (Median of differences 66, 95% CI: 25–74 mmHg; $p < 0.001$))	100%	38% (Non-REBOA: 67%, $p = 0.035$)	77% (10/13) patients developed distal arterial thrombus, requiring embolectomy or thrombectomy, (6/10 were directly related to a traumatic vascular injury) Lower limb amputation: REBOA group 31%, non REBOA 50%, $p = 0.617$)

Notes: * Two patients had complete and partial occlusion in Zone One for 18 + 8 min and 30 + 5 min, respectively [3]; SBP, systolic blood pressure.

In these studies, the average occlusion time for zone 1 REBOA was 21 min to 36 min, which is generally shorter compared to the zone 3 REBOA time of 9 min to 80 min. All patients in this review demonstrated positive effects of REBOA, showing a significant increase in blood pressure (>51%), except in the study by Lamhaut et al. [24] due to unavailable data. Despite the lack of objective data, the patient returning to spontaneous circulation after REBOA could still be seen as proof of a positive effect. All the patients managed to survive the transport to definite care; however, the secondary outcome measurements such as 30-day mortality were only available in two civilian studies. Their results suggested that prehospital REBOA groups were more likely to survive, with considerably lower 30-day mortality compared to non-REBOA group (38% vs. 67%) [21,26]. The incidence of prehospital cardiac arrest and bleeding-related mortality was also significantly lower in prehospital REBOA patients (50% vs. 0%, $p = 0.031$) (67% vs. 0%, $p = 0.007$) [26].

Moreover, post-REBOA complications were common in the included patients: thromboembolic events were predominant and reached as high as 77% among REBOA patients, who required thrombectomy [26].

3.6. Narrative Synthesis

A total of 48 patients were enrolled in this review; they all sustained profound shock or cardiac arrest after severe blunt and penetrating trauma. Generally, patients who received prehospital REBOA showed a significant increase in blood pressure (>50%) and survived the transport to the next MTF without en route cardiac arrest. Despite the secondary outcome measurements such as 30-day mortality only being available in two civilian studies [21,26], the results suggested REBOA patients were more likely to survive, with a lower mortality rate of 38% compared to that of 67% for non-REBOA patients [26]. However, this can only elucidate the association between REBOA and immediate blood pressure elevation, and early hemorrhage control and decreased short-term mortality.

Apart from aortic occlusion, other resuscitative interventions were concurrently used for hemostasis. For instance, blood products and tranexamic acid promoted clotting and prevented fibrinolysis. Other resources, such as surgical capacity, rapid evacuation and responsible personnel's competency along the chain of care were also indispensable. Interestingly, it not only temporized lethal hemorrhage, but also treated the bleeding site in some instances. Six patients stopped bleeding spontaneously with prehospital REBOA alone in Lendrum's study [26]. Also, the benefits were magnified in massive casualties, as it extended the survival window to definite care in the absence of other resources.

Nevertheless, thromboembolic events were prevalent among REBOA patients. The causes were not clearly investigated but attributed to blood transfusion, pro-thrombotic medication uses and traumatic vascular injury instead of REBOA itself. A group of emergency and trauma experts suggested that zone 3 REBOA would minimize visceral ischemic effects if prolonged occlusion time (>30 min) was expected [26]. 93% of civilian REBOA cases in this review were deployed in zone 3 while 85% of military patients received zone 1 REBOA. In general, the transport time between the points of care in military settings is longer than in civilian settings. Due to vaguely described protocols and, paradoxically, zone 1 REBOA with longer occlusion time, the effects of occlusion duration on the outcomes between two different zones were not comparable.

Moreover, the results showed that the restriction-of-arterial-access approach could lower the success rate of catheter placement and subsequently lead to higher mortality. Most of the studies allowed either percutaneous arterial access or surgical cutdown, demonstrating 100% successful balloon catheter placement, whereas Lendrum et al. [26] had only a 68% success rate due to forbidden cutdown, having a significantly higher 30-day mortality of 67% [26].

Due to the substantial heterogeneity across included studies and the missing data, the true effects of prehospital REBOA were still unclear. The causality between REBOA and its effectiveness was not illustrated and conclusions cannot be generalized.

4. Discussion

This systematic review evaluated current evidence regarding the effectiveness of pre-hospital REBOA in traumatic hemorrhage. Of those included studies, they are determined to have low to moderate quality due to profound limitations. They reported primary outcomes of significant blood pressure elevation and survival to the next MTF, concordantly showing the potential benefits of prehospital REBOA to temporize or even stop lethal bleeding [21–26]. They are consistent with another systematic review's results that REBOA can cause an average 50 mmHg blood pressure increase on patients with severe traumatic exsanguination [30]. However, secondary outcome measurements were heterogeneous. Only [26] reported 30-day mortality with statistical significance, while the remaining studies lacked long-term outcome assessment across the continuum of care. Historically, the peak of deaths occurred within the first 6 h after arrival at hospitals; therefore, survival to hospitals does not equate to survival to discharge [31–33]. Trauma patients are at high risk of trauma-induced coagulopathy and brain injury, leading to rapid deterioration. The concept of golden hour in trauma care should be applied for early initiation of REBOA [2]. Proactive use was proposed because early access was found to be associated with a significantly higher 30-day survival rate, preventing hypovolemic cardiac arrest and facilitating hemodynamic monitoring [16].

REBOA is extraordinarily useful in the context of a mass casualty, as major surgical interventions may not be readily available. Also, proximal aortic occlusion allows a relatively dry field for rapid identification of bleeding sources afterwards [23]. Moreover, it could be a feasible alternative to open thoracotomy for patients requiring aortic cross-clamping with significantly improved overall survival and decreased complication rate, especially in prehospital settings [22,26,34]. Not only useful as a resuscitative adjunct, REBOA could also be therapeutic, since 46% patients who underwent prehospital REBOA stopped bleeding spontaneously without angio-embolization [26]. This procedure can be achieved by non-specialist physicians, as advanced endovascular techniques are not compulsory. Training for REBOA skillsets is still necessary for safe and effective implementation.

On the other hand, the outcomes of REBOA could greatly depend on patient selection, resource availability, trauma system integrity and the total balloon occlusion time [21–26]. Although the MIST acronym [25] was used to rapidly identify eligible patients, challenges still exist due to variances among different trauma systems. A customized protocol for an individual system is essential for an efficient procedure. Patient selection requires careful consideration because REBOA may increase the rate of bleeding for patients with contraindications such as cardiac tamponade or bleeding inferior to the balloon. Manley et al. [22] suggested that portable ultrasound machines (V-scan) could offer better diagnostic assessment to exclude patients with contraindications, facilitate REBOA placement and confirm balloon position in a prehospital environment, despite the fact that some studies accomplished the same procedure without its assistance [21,24,26].

Moreover, resource availability and coordination within the trauma system are the keys to success because definitive surgical capability (operating rooms, REBOA operators, etc.) needs to be available expeditiously followed by REBOA, and blood transfusion is regarded inherent in trauma resuscitation. Three of the included US military studies emphasized the advantages of whole blood transfusion [22,23,25], as advocated by previous military surgeons' experience and incorporated into the 2018 United States Tactical Combat Casualty Care guidelines [35]. In the setting of coagulopathy, the pressure of REBOA alone may be inadequate, so active infusion of blood products and medication uses are necessary to control exsanguination. Whole blood is seen as the optimal balanced resuscitation product with small volume but superior hemostatic effects, compared with balanced component therapy that reconstitutes whole blood with platelets, plasma and red cells [36,37]. The function of reconstituted platelets is reduced and the larger volume could result in dilutional coagulopathy [36]. Nonetheless, whole blood is currently unavailable in many western countries and some studies in this review did not specify the types of blood products they

used, as they may be limited to component therapy. Without adequate data, comparison between the outcomes of REBOA upon transfusion protocols are infeasible.

Other factors such as rapid evacuation and the competency of involved personnel along the chain of care are essential. If the personnel are competent to handle REBOA, the catheter could be retained during transport to facilitate blood pressure monitoring, keep patients stable and potentially allow straight evacuation to Role 3 MTF; thus, patients can reach definite care faster.

4.1. Complications

Despite the positive effects of prehospital REBOA, most studies reported high thrombotic incidence, reaching as high as 77% where balloon migration and failure due to balloon rupture were also mentioned [22,23,26]. This contradicts other authors claiming that no procedural related complication was observed [38,39]. The rate of procedural morbidity & mortality is proposed to be associated with occlusion time and sheath size [38–40]. Prolonged total occlusion time with REBOA strongly correlated with increased lactate concentration ($p = 0.02$) and visceral ischemic injury, particularly for Zone 1 REBOA [41]. To minimize the procedural risk, the included studies adopted small sheath size catheters (<8 Fr) and some of them were restricted to zone 3 REBOA because theoretically zone 1 REBOA had a stricter time limit due to the ischemic effects on more sensitive renal tissues. Paradoxically, 85% of military cases had zone 1 REBOA with supposing longer evacuation time compared to civilian settings (Table 5).

Moreover, complete balloon deflation at once after prolonged AO may cause washout of metabolic by-products and reperfusion injury. To avoid refractory hemodynamic collapse, a dynamic approach or early partial REBOA (pREBOA) was adopted to allow titrated blood flow to distal tissues [23,25,26]. de Schoutheete [25] defined the dynamic approach as using a partial occlusion and manual operating method on the aortic compliance to keep systolic blood pressure not higher than 90mmHg. Small and gradual deflation of balloon and the idea of causing hypotension were introduced to tackle the reperfusion injury [25]. A Japanese multicenter retrospective study showed that pREBOA significantly improved patients' hemodynamics and stability, better than complete REBOA (cREBOA) ($p < 0.05$) [42]. Regardless of significantly longer occlusion in the pREBOA group, it had similar 30-day survival to cREBOA. Therefore, pREBOA may be superior to cREBOA, allowing extended occlusion duration without increased risk.

Nevertheless, most studies did not ascertain the causes of complications and relate lower limb amputations to primary amputation or non-salvageable mangled injuries [26]. After trauma, the pathology of hypercoagulation and coagulopathy with concurrent administration of procoagulant blood products and anti-fibrinolytics interfered with the clotting mechanism, potentially prompting thrombosis [26]. Two included studies [21,24] did not report REBOA-related complications, possibly due to single-case inclusion. Since the baseline characteristics were completely different, the outcomes were not comparable, considering that the patient's age and pre-morbidity could affect physical reserve and the response to trauma.

4.2. Surgical Cutdown versus Percutaneous Access

Although there was no comparison between the surgical cutdown or percutaneous access in the included studies to determine their superiority, limited percutaneous insertion was found to prohibit the catheter placement, leading to failure of REBOA and reduced survival rate. Since obtaining arterial access is deemed as the most challenging part in prehospital resuscitation for hypovolemic patients, the success rate of catheter placement has become a concern. The civilian studies limited their protocols to percutaneous arterial cannulation, possibly due to current evidence of several randomized control trials that suggest percutaneous femoral access is less invasive and has more favorable outcomes than the cutdown cohort [43]. Also, it shows significantly fewer wound complications, deep vein thrombosis and reduced length of hospital stay. On the contrary, the included

studies of this review did not report any access-related complication in the open cutdown population. Supported by other authors, surgical cutdown could rapidly expose the anterior vessel wall and no significant difference was seen in access-related complications between two methods [44,45]. Although a new REBOA catheter allows manual compression after removal, open common femoral artery closure is still recommended in case of uncontrolled exsanguination during unexpected duration of evacuation. The two insertion approaches should be considered complementary to each other and their availability could enhance the success rate of balloon deployment and subsequent survival.

4.3. Limitations

The biggest limitation of this review is the lack of high-quality studies, depreciating its generalizability. The mediocre data quality resulted from the retrospective and descriptive nature of included studies. Restrictions in English databases and patient survival caused publication bias, small sample size caused decreased statistical power and loss of long-term follow-up caused reporting bias and missing data. With uncontrolled variables, causality cannot be established and the included evidence cannot show explicit correlation between occlusion time, zone of balloon deployment and outcomes. Thus, it is difficult to clearly define the time limit for balloon occlusion in different regions. Moreover, the success of prehospital REBOA is setting-dependent and involves the entire trauma system and the competence of medical personnel, so it is unfair to compare the outcomes of studies having heterogeneous contexts. Since the medical personnel in this review were recruited in developed countries and were highly trained and adhered to institutional protocol within mature trauma systems, the results may not be transferrable to other developing countries. These limitations affect the detecting power and reliability of this review, as the treatment efficacy could be under or overestimated.

However, these limitations are to be expected because REBOA is rarely used in pre-hospital settings. This review has already captured the majority of the prehospital REBOA operations performed worldwide; hence, the findings attained can serve as a steppingstone for any future studies. Consistently, studies supported the fact that for patients who arrive at a trauma center, death from hemorrhage occurs within approximately 2 h of being in the hospital.

5. Conclusions

Our study demonstrated that prehospital REBOA is a feasible and effective resuscitative adjunct for shock patients with lethal traumatic NCTH. This could be safely and effectively performed by non-specialist physicians with appropriate REBOA training. However, the quality of evidence presented was low to moderate and thus conclusions from the study should be interpreted with care. Larger, high-quality studies are therefore warranted to improve the evidence base for the use of REBOA in hemorrhage control in the prehospital environment.

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