Journal of Trauma and Acute Care Surgery, Publish Ahead of Print
DOI: 10.1097/TA.0000000000002101

Massive Transfusion Protocols in Non-Trauma Patients:

A Systematic Review and Meta-Analysis

Nora Sommer, BM; Beat Schnüriger, MD; Daniel Candinas, MD; Tobias Haltmeier, MD

Department of Visceral Surgery and Medicine, Division of Acute Care Surgery, Inselspital, Bern University Hospital, Bern, Switzerland

Author’s email addresses:

Nora Sommer: nora_sommer@bluewin.ch

Beat Schnüriger: beat.schnuriger@gmail.com

Daniel Candinas: daniel.candinas@insel.ch

Tobias Haltmeier: tobias.haltmeier@icloud.com

Address of correspondence: Tobias Haltmeier, MD, FACS, Department of Visceral Surgery and Medicine, Division of Acute Care Surgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, Phone: +41 31 632 59 00, Fax: +41 31 632 59 99. E-mail: tobias.haltmeier@icloud.com

Disclosure: Nora Sommer, Beat Schnüriger, Daniel Candinas, and Tobias Haltmeier have no conflicts of interest or financial ties to disclose.

Abstract

Background

Massive bleeding is a major cause of death both in trauma and non-trauma patients. In trauma patients, the implementation of massive transfusion protocols (MTP) led to improved outcomes. However, the majority of patients with massive bleeding are non-trauma patients.

Objectives

To assess if the implementation MTP in non-trauma patients with massive bleeding leads to improved survival.

Data sources

National Library of Medicine's Medline database (PubMed).

Study eligibility criteria

Original research articles in English language investigating MTP in non-trauma patients.

Participants

Non-trauma patients with massive bleeding ≥ 18 years of age.

Intervention

Transfusion according to MTP versus off-protocol.

Study appraisal and synthesis methods

Systematic literature review using PubMed. Outcomes assessed were mortality and transfused blood products. Studies that compared mortality of MTP and non-MTP groups were included in meta-analysis using Mantel-Haenszel random effect models.

Results

A total of 252 abstracts were screened. Of these, 12 studies published 2007-2017 were found to be relevant to the topic, including 2,475 patients. All studies were retrospective and comprised different patient populations. Most frequent indications for massive transfusion were perioperative, obstetrical and gastrointestinal bleeding, as well as vascular emergencies. Four out of the five studies that compared the number of transfused blood products in MTP and non-MTP groups revealed no significant difference. Meta-analysis revealed no sigificant effect of MTP on the 24-hour mortality (OR 0.42, 95%CI 0.01-16.62, p=0.65) and a trend towards lower one-month mortality (OR 0.56, 95%CI 0.30-1.07, p=0.08).

Limitations

Heterogeneous patient populations and MTP in the studies included.

Conclusions and implications of key findings

There is limited evidence that the implementation of MTP may be associated with decreased mortality in non-trauma patients. However, patient characteristics, as well as the indication and definition of MTP were highly hetergenous in the available studies. Further prospective investigation into this topic is warranted.

Study type

Systematic review and meta-analysis

Level of evidence

Level III

Key words

Hemorrhage, non-trauma emergency, blood component transfusion, transfusion protocol, meta-analysis.

Background

In patients receiving massive transfusion a high mortality rate has been described, both in the trauma and non-trauma setting.(1-3) Rose et al. report an in-hospital mortality rate of 34% in a mixed patient population receiving massiv transfusion.(2) Halmin et al., in a nationwide cohort study assessing the epidemiology of massive transfusion in Sweden and Denmark, report a 30-day mortality of 24.8%.(1) Turan et al. investigated the mortality after massive transfusion in patients undergoing non-cardiac surgery using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. In this study, a postoperative 30-day mortality of 17% was found in patients undergoing massive transfusion.(3) Common causes for massive hemorrhage in non-trauma patients are gastrointestinal bleeding, ruptured abdominal aortic aneurisms, as well as surgical or obstetrical bleeding.(4-7) In the above-mentioned cohort study conducted in Sweden and Denmark, massive transfusion was reported with an incidence of 2.5 (Sweden) and 4.5 (Denmark) per 10,000 person years.(1) Turan et al. report massive transfusion in 7,485 out of 917,651 patients in NSQIP 2006-2009, corresponding to 0.8%.(3) Most recent studies investigating the pathophysiology and treatment of hemorrhage focused on trauma patients.(4, 6-11) However, major surgery for non-traumatic disease has been reported to be the most common cause of massive bleeding, followed by trauma and obstetric bleeding. Although the overall incidence of massive bleeding is relatively small, it remains an important source of mortality in non-trauma patients.(1, 3)

The goal of massive transfusion protocols (MTP) is to rapidly provide blood products to hemodynamically unstable bleeding patients and to treat coagulopathy. This includes the availability of blood products in predefined ratios and the rapid transport and transfusion of these products.(12) MTP have been successfully implemented in trauma patients and have been shown

to improve outcomes in this patient population(12), including lower mortality(13), a lower risk of multi-organ failure, higher rate of fascial closure(14), and decreased use of blood products(15). The current guidelines of the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP), support the implementation of MTP in the early care of trauma patients.(16)

In sumary, massive transfusion is rare but associated with a high mortality rate in non-trauma patients. Taking into account the above-mentioned improved outcomes related to MTP in trauma patients, non-trauma patients may benefit from MTP, too. The aim of this systematic review and meta-analysis was, therefore, to assess the use MTP and its effect on outomes in non-trauma patients. We hypothesized that the implementation MTP in non-trauma patients with massive bleeding leads to improved survival.

Methods

This is a systematic literature review and meta-analysis investigating the role of MTP in bleeding non-trauma patients. PRISMA guidelines(17, 18) were followed thoughout the literature search, meta-analysis, reporting of the data, and discussion. (*Table 5*)

Literature search

A systematic literature search was conducted using the National Library of Medicine's Medline database (PubMed)(19). The search strategy was based on the PICOS process.(20, 21) When possible, Medical Subject Headings (MeSH)(22) were used as search terms. The following

search terms were used for the PubMed search:

- massive AND transfusion AND protocol AND (surgical OR medical)
- massive AND transfusion AND protocol AND (surgical OR medical); Filters: review
- (((blood transfusion) AND exchange transfusion, whole blood) AND surgical procedures, operative) AND patient care
- (((blood transfusion[MeSH Terms]) AND exchange transfusion, whole blood[MeSH Terms]) AND surgical procedures, operative[MeSH Terms]) AND patient care[MeSH Terms]
- massive transfusion protocol AND (surgical procedures, operative OR patient care)

Only original research articles in english language were included. Exclusion criteria were articles including patients under 18 years of age and non-original research articles such as literature reviews and letters to the editor.

All abstracts of the articles found were screened. If the abstracts were relevant to the topic, the corresponding articles were included in the review. Articles relevant to the topic that were cited in articles found on PubMed using the above-named search terms were also included in the review, as well as articles that described MTP both trauma and non-trauma patients.

Quality assessment

The quality of the studies included in this systematic literature review and meta-analysis was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies (23) with mortality as outcome measure.

Outcomes

The primary outcome assessed was the 24-hour and one-month mortality. Secondary outcomes were the number of blood products transfused, including packed red blood cells (PRBC), fresh frozen plasma (FFP), and platetelts, as well as transfusion ratios.

Statistical analysis

Studies that compared the mortality rate of MTP and non-MTP groups in non-trauma patients specifically were included in the meta-analysis. The number of survivors and non-survivors in MTP and non-MTP groups reported in these studies was extracted for the meta-analysis.

Meta-analysis for the 24-hour and one-month mortality was performed using a Mantel-Haenszel random effect model. The estimated effect size for the 24-hour and one-month mortality was reported as odds ratio (OR) and 95% confidence interval (CI) for each study that compared MTP and non-MTP groups, as well as for the overall cohort. Heterogeneity of included studies was assessed using cochran's Q statistic and I^2.(24, 25) No funnel plots were created due to the small number of studies included in meta-analysis.

Statistical analysis was performed using Review Manager (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Articles included

The literature search and included articles are outlined in *Figure 1*. A total of 252 abstracts were screened. Twelve articles were found to be relevant to the topic.(4-11, 26-29) All articles were

published between 2007 and 2017. Included studies enrolled a total of 2,475 patients. Of these, 1,620 were non-trauma patients. (*Table 1)*

Seven studies included both trauma and non-trauma patients.(4-7, 9, 10, 29) The non-trauma groups in these studies were comprised of patients undergoing emergency or elective surgery(4-10, 29), as well as patients with gastrointestinal bleeding(4-7, 9, 29), obstetric hemorrhage(4, 5, 7, 10, 29), and vascular emergencies(4, 6, 7, 9, 29). In three of these seven studies, analysis was performed using a mixed trauma/non-trauma population, comprising 91%(10), 76%(29), and 38.2-100% (range, six hospitals included)(5) non-trauma patients. In four studies, trauma and non-trauma patients were analyzed separaterly.(4, 6, 7, 9) (*Table 1*)

Five studies investigated non-trauma patients only.(8, 11, 27) (26, 28) Three studies focused on patients with bleeding due to obstetric complications only(11, 26, 27), whereas Johansson et al. analyzed patients with massive bleeding after ruptured abdominal aortic aneurysm exclusively.(28) Martinez-Calle et al. included non-trauma patiens undergoing oncolocic surgery, cardiovascular surgery, other surgery, and non-surgical treatment for massive bleeding.(8)

Quality assessment

Table 4 shows the quality assessment of the studies included based on the NOS. None of the studies included used a matched study desing or adjusted for counfounders. Therefore, based on the criteria of the NOS, no study received stars for the comparability of the study groups. The studies by Chay(5), Gutierrez(27), and Goodnough(26) did not receive stars for the outcome categories, as mortality was not reported as an outcome measure in these studies. Furthermore,

the studies by Gutierrez and Goodnough did not include a controll group and consequently did not recieve a star in this category. In the studies by Chay(5) and Johanson(28) the number of survivors and death was not reported. These studies therefore did not receive stars for the adequacy of follow-up category.

Patient characteristics

The majority of the patients included were male, ranging from 64.4 to 87.1%.(4, 6-10, 28) Exceptions were the studies assessing obstetric patients only.(11, 26, 27) The age of included patients ranged from 29.9 to 73.0 years. (*Table 1*)

Three studies reported comorbidities of the patients included.(4, 10, 28) Balvers et al. showed that 26% of patients before the introduction of a MTP and 25% of the patients after the introduction had no known comorbidities. The remaining patients suffered from cardiovascular (57% in both groups) or pulmonary disease (8% and 7%), bleeding diathesis (4% and 3%), and other comorbidities (5% and 8%).(10) Johansson et al. found comorbidities in 74% and 73% of patients before and after the implementation of a MTP, respectively.(28) In the study by Baumann Kreuziger et al. the mean overall APACHE II score was 27, while it was significantly lower in trauma than in non-trauma patients (25 vs. 29, $p<0.05$).(4) The other studies did not report comorbidities of included patients.(5-9, 11, 26, 27, 29)

Definition of massive transfusion

The definition of massive transfusion was given in 9 articles. (4-11, 29) Massive transfusion was most commonly defined as the transfusion of 10 or more units of PRBC in the first 24 hours after hospital admission.(4-7, 9, 29) Other definitions were the transfusion of 5 or more units of PRBC

in the first twelve hours after hospital admission(10), the replacement of the whole blood volume (7% of ideal body weight in adults) in a 24 hour period (8), the replacement of 50% of the whole blood volume in a three hour period(8), the loss of ≥ 1500 ml blood in ten minutes(8), or the transfusion of 4 or more units of PRBC.(11)

Indications for massive transfusion

Indications for massive transfusion in non-trauma patients were bleeding during or after surgery (frequency reported as 11.2 to 82.2%)(4-10, 29), obstetrical bleeding (4.4 to 100%)(4, 5, 7, 10, 11, 26, 27, 29), gastrointestinal bleeding (20.0 to 66.7%)(4-7, 9, 29), vascular emergencies (2.7 to 100%)(4, 6, 7, 9, 28, 29), or other reasons (13.0 to 17.8%).(4, 8, 10)

Blood product transfusion

Transfused blood products are shown in *Table 2*. Of the five studies that compared the number of transfused units of blood products in non-trauma patients before and after the implementation of a MTP(6, 8, 10, 11, 28), four studies revealed no statistically significant difference of the number of transfused units of PRBC, FFP, and PLT.(6, 8, 10, 11) In the study investigating the implemantation of a transfusion protocol in patients with ruptured abdominal aortic aneurysms, a significantly higher number of FFP and PLT during surgery, but lower postoperative transfusion of PRBC, FFP and PLT were found after implementation of the protocol.(28)

Transfusion ratios (FFP:PRBC, PLT:PRBC) were reported in 9 studies.(4-11, 29) Of these, five studies compared transfusion ratios in MTP and non-MTP groups.(6, 8, 10, 11, 29) Sinha et al. reported significantly higher FFP:PRBC and PLT:PRBC transfusion ratios in the MTP group

compared to the Pre-MTP group.(29) In the study by Balvers et al. a significantly higher proportion of patients in the MTP-group received PRBC:FFP transfusion ratios ≤ 1.1 compared to the Pre-MTP group.(10) In the other 3 studies, no statistically significant difference of the transfusion ratios in the MTP and non-MTP groups was found.(6, 8, 11) (*Table 2)*

Overactivation of MTP, defined as the proportion of patients with MTP activation that received ≤ 10 units of PRBC, was reported in four studies. The rate of MTP overactivation found in these studies was high, ranging from 53.8% to 65%.(4, 6, 7, 9) (*Table 2*)

McDaniel et al. analyzed the wasted units of blood products before and after the implementation of a MTP. A significantly increased waste of platelets was observed in patients with MTP activation compared to patients without MTP activation (12.8% vs. 8.1%, p=0.046).(6)

Impact of MTP on mortality

Four studies compared the one-month mortality in patients with and without MTP activation(6, 8, 10, 28) Of these four studies, two studies found a significantly lower 30-day mortality in the MTP group compared to the non-MTP group (Martinez-Calle et al.: 18.1% and 13.0% vs. 30.2%. [two MTP groups], p=0.010(8); Johansson et al.: 34% vs. 56%, p=0.02(28)). In contrast, McDaniel et al. found no significant difference of the 30-day mortality in the MTP group and non-MTP group (50.0% vs. 42.1%, p=0.207).(6) Likewise, the study by Balvers et al. revealed no significant difference of the 28-day mortality after the implementation of a MTP (35% vs. 34%, p=0.801).(10) (*Table 3*)

Three studies compared the 24-hour mortality in MTP and non-MTP groups. In two of these three studies, the 24-hour mortality was not significantly different between the MTP and non-

MTP group (McDaniel et al.: 30.8% vs. 15.8%, p=0.155(6); Balvers et al.: 15% vs. 12%, p=0.386(10)). On the other hand, Martinez-Calle et al. found a significantly lower 24-hour mortality in the MTP group compared to the non-MTP group (0.0% and 1.1% vs. 7.3% [two MTP groups], p=0.002).(8) (*Table 3*)

Meta-analysis included four studies that reported mortality of MTP and non-MTP groups in non-trauma patients specifically.(6, 8, 11, 28) Meta-analysis revealed no statistically sigificant effect of MTP on the 24-hour mortality rate (OR 0.42, 95%CI 0.01-16.62, p=0.65) and one-month mortality (OR 0.56, 95%CI 0.30-1.07, p=0.08). (*Figure 2*)

Discussion

The aim of this systematic literature review and meta-analysis was to find scientific evidence for the use of MTP in bleeding non-trauma patients. Twelve studies including patients with perioperative, gastrointestinal, and obstetrical bleeding, as well as bleeding from vascular emergencies, were assessed. (*Figure 1*)

Two studies found a significantly lower mortality associated with the introduction of a MTP in bleeding non-trauma patients.(8, 28) In two other studies that analyzed mortality before and after implementation of a MTP, no statistically significant effect of the introduction of a MTP on mortality was found.(6, 10) Furthermore, one study that found a lower mortality in the MTP group included patients with ruptured aortic aneurysm only, which is a distinct group of patients with a very high mortality and morbidity.(30, 31) On the other hand, meta-analysis including the same studies showed a trend towards a lower one-month mortality rate. Based on these results it is possible that MTP may lower the mortality rate in bleeding non-trauma patients. Taking into

account the small number of studies eligible for inclusion in meta-analysis, more statistical power is needed to confirm this hypothesis.

Another reason for the non-significant effect of MTP on mortality found in the current meta-analysis may be delayed MTP activation in the studies included. In major trauma patients, severe bleeding is anticipated and MTP are readily activated according to clearly defined criteria.(16) In non-trauma patients, the onset of bleeding may be more subtle, delaying the activation of MTP. Furthermore, well-defined criterial for massive transfusion in non-trauma patients are lacking. Martinez et al. report proactive triggering of MTP in only 20% in non-trauma patients. In the other 80%, MTP was automatically activated by the blood bank after the transfusion of more than 8 PRBC.(8) In the study by McDaniel et al. MTP activation accelerated the delivery of of FFP and platelets. However, MTP activation was not associated with improved survival in this study.(6)

Although one of the goals of MTP is to achieve higher plasma and platelets to PRBC transfusion ratios, FFP:PRBC and/or PLT:PRBC transfusion ratios did not meet the currently recommended ratios of 1:1:1 or 1:1:2(32) in four studies.(8, 9, 11, 29) (*Table 2*) This finding is surprising, as with the introduction of a MTP, predefined ratios of blood products should be available for transfusion.(12, 15, 33-35) A possible explantation for the lower than recommended transfusion ratios in these studies may be a delayed MTP activation with unbalanced PRBC transfusion prior to the activation of the protocol.(8)

A high rate of MTP overactivation was found in four studies.(4, 6, 7, 9) The identification of non-trauma patients that require MTP activation may be challenging as specific criteria are still lacking. In trauma patients, on the contrary, there are well established criteria for massive transfusion and MTP activation, such as the ACS TQIP Best Practice Guidelines(16), the

Assessment of Blood Consumption (ABC) score(36-38), the Trauma Associated Severe Hemorrhage (TASH) score(39), the algorithm developped for combat casualty patients by McLaughlin and collegues(40), the Revised Assessment of Bleeding and Transfusion (RABT) score(41), and the Massive Transfusion Score (MTS)(42). The absence of defined criteria for massive transfusion in non-trauma patients most likely explains the high overactivation rate in this patient population.

The study of McDaniel et al. was the only one that analyzed the waste of blood products. An increased waste of platelets was found after the introduction of a MTP.(6) The waste of blood products associated with MTP could potentially be prevented, as unused blood products may be provided to other patients if they are returned promptly to the blood bank.(6) Furthermore, timely termination of the MTP once the endpoints of transfusion are achieved may reduce the waste of blood products. The ACS TQIP lists several criteria for the termination of MTP, including downgrading to goal-directed transfusion if bleeding has been controlled by surgery or angioembolization, further resuscitation is futile, and - in patients with no active bleeding - laboratory findings indicate adequate blood coagulation.(16) Although the ACS TQIP criteria for the termination of MTP were elaborated for trauma patients, they may also be useful in non-trauma patients. Further studies will need to evaluate the criteria for MTP termination in non-trauma patients specifically.

Non-trauma patients included in the current review had many comorbidities, especially from cardiovascular origin.(4, 10, 28, 29) (*Table 1*) Trauma patients are typically younger and have less comorbidities than the non-trauma patients included in the current review. Furthermore, polytrauma patients may bleed from multiple injuries, whereas bleeding is often localized in non-trauma patients, e.g. in patients with gastrointestinal bleeding or bleeding during cardio-vascular

surgery. Both trauma and non-trauma patients may suffer from profuse bleeding due to coagulopathy. However, due to the above-mentioned cardiovascular comorbidities, drug-induced coagulopathy is more likely in non-trauma than in trauma patients.(43) When extrapolating indications and goals of MTP from trauma to non-trauma patients, the different characteristics of these two patient populations need to be considered.

This systematic literature review and meta-analysis has several limitations. First, all studies were retrospective. Second, three studies analyzed mixed cohorts of non-trauma and trauma patients(5, 10, 29), while others focused on a specific group of patients(11, 26-28). Third, the total number of patients that were included in meta-analysis was relatively small, limiting the validity of the results. Fourth, the quality of the studies included varied and was poor in some studies. (*Table 4*) Fifth, massive transfusion protocols, including the indication for MTP activation and predefined transfusion ratios, differed between the studies included. In order to take into account the heterogeneity of the studies included, only studies reporting outcomes of MTP- and non-MTP groups in non-trauma patients specifically were included in the quantitative analysis. Furthermore, a radom-effects model was chosen for meta-analysis.

Conclusion

Based on the current literature review and meta-analysis, there is limited evidence that the implementation of MTP may be associated with decreased mortality in non-trauma patients. Both, overactivation and an increased waste of blood products have been reported with the introduction of MTP. However, patient characteristics, as well as the indication and definition of MTP were highly hetergenous in the available studies. Further prospective investigation into this topic is warranted.

Author contribution statement

Literature search: NS and TH. Study design: TH and BS. Data collection: NS and TH. Data analysis: TH and BS. Data interpretation: TH, NS, BS, and DC. Writing: NS, TH, and BS. Critical revision: TH, BS, and DC.

References

1. Halmin M, Chiesa F, Vasan SK, Wikman A, Norda R, Rostgaard K, Vesterager Pedersen OB, Erikstrup C, Nielsen KR, Titlestad K, et al. Epidemiology of Massive Transfusion: A Binational Study From Sweden and Denmark. *Crit Care Med*. 2016;44(3):468-77.

2. Rose AH, Kotze A, Doolan D, Norfolk DR, Bellamy MC. Massive transfusion - evaluation of current clinical practice and outcome in two large teaching hospital trusts in Northern England. *Vox Sang*. 2009;97(3):247-53.

3. Turan A, Yang D, Bonilla A, Shiba A, Sessler DI, Saager L, Kurz A. Morbidity and mortality after massive transfusion in patients undergoing non-cardiac surgery. *Can J Anaesth*. 2013;60(8):761-70.

4. Baumann Kreuziger LM, Morton CT, Subramanian AT, Anderson CP, Dries DJ. Not only in trauma patients: hospital-wide implementation of a massive transfusion protocol. *Transfus Med*. 2014;24(3):162-8.

5. Chay J, Koh M, Tan HH, Ng J, Ng HJ, Chia N, Kuperan P, Tan J, Lew E, Tan LK, et al. A national common massive transfusion protocol (MTP) is a feasible and advantageous option for centralized blood services and hospitals. *Vox Sang*. 2016;110(1):36-50.

6. McDaniel LM, Neal MD, Sperry JL, Alarcon LH, Forsythe RM, Triulzi D, Peitzman AB, Raval JS. Use of a massive transfusion protocol in nontrauma patients: activate away. *J Am Coll Surg*. 2013;216(6):1103-9.

7. Morse BC, Dente CJ, Hodgman EI, Shaz BH, Winkler A, Nicholas JM, Wyrzykowski AD, Rozycki GS, Feliciano DV. Outcomes after massive transfusion in nontrauma patients in the era of damage control resuscitation. *Am Surg*. 2012;78(6):679-84.

8. Martinez-Calle N, Hidalgo F, Alfonso A, Munoz M, Hernandez M, Lecumberri R, Paramo JA. Implementation of a management protocol for massive bleeding reduces mortality in non-trauma patients: Results from a single centre audit. *Med Intensiva*. 2016;40(9):550-9.

9. Wijaya R, Cheng HM, Chong CK. The use of massive transfusion protocol for trauma and non-trauma patients in a civilian setting: what can be done better? *Singapore Med J*. 2016;57(5):238-41.

10. Balvers K, Coppens M, van Dieren S, van Rooyen-Schreurs IH, Klinkspoor HJ, Zeerleder SS, Baumann HM, Goslings JC, Juffermans NP. Effects of a hospital-wide introduction of a massive transfusion protocol on blood product ratio and blood product waste. *J Emerg Trauma Shock*. 2015;8(4):199-204.

11. Dutta EH, Poole AT, Behnia F, Dunn HE, Clark SM, Pacheco LD, Saade GR, Hankins GD. Hemostatic Resuscitation in Peripartum Hysterectomy Pre- and Postmassive Transfusion Protocol Initiation. *Am J Perinatol*. 2017;34(9):861-6.

12. Nunez TC, Young PP, Holcomb JB, Cotton BA. Creation, implementation, and maturation of a massive transfusion protocol for the exsanguinating trauma patient. *J Trauma*. 2010;68(6):1498-505.

13. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, Spain DA, Brundage SI. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg*. 2009;209(2):198-205.

14. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma*. 2009;66(1):41-8; discussion 8-9.

15. O'Keeffe T, Refaai M, Tchorz K, Forestner JE, Sarode R. A massive transfusion protocol to decrease blood component use and costs. *Arch Surg*. 2008;143(7):686-90; discussion 90-1.

16. ACS TQIP Best Practice Guidelines. Accessed 08-20-2018. Available from: https://www.facs.org/quality-programs/trauma/tqip/best-practice.

17. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-84.

18. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Accessed 08-20-2018. Available from: http://prisma-statement.org/Default.aspx.

19. PubMed - US National Library of Medicine. Accessed 08-20-2018. Available from: https://www.ncbi.nlm.nih.gov/mesh.

20. Cochrane Handbook for Systematic Reviews of Interventions. Accessed 08-20-2018. Available from: http://training.cochrane.org/handbook.

21. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res*. 2014;14:579.

22. Medical Subject Headings (MeSH). Accessed 08-20-2018. Available from: https://www.ncbi.nlm.nih.gov/mesh.

23. Newcastle-Ottawa Scale (NOS). Accessed 08-20-2018. Available from: http://www.ohri.ca/Programs/clinical_epidemiology/oxford.asp.

24. Sedgwick P. Meta-analyses: what is heterogeneity? *Bmj*. 2015;350:h1435.

25. Hak T, Rhee Hv, Suurmond R. How to interpret results of meta-analysis (Version 1.3). Accessed 08-20-2018. Available from: https://repub.eur.nl/pub/80102.

26. Goodnough LT, Daniels K, Wong AE, Viele M, Fontaine MF, Butwick AJ. How we treat: transfusion medicine support of obstetric services. *Transfusion*. 2011;51(12):2540-8.

27. Gutierrez MC, Goodnough LT, Druzin M, Butwick AJ. Postpartum hemorrhage treated with a massive transfusion protocol at a tertiary obstetric center: a retrospective study. *Int J Obstet Anesth*. 2012;21(3):230-5.

28. Johansson PI, Stensballe J, Rosenberg I, Hilslov TL, Jorgensen L, Secher NH. Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice. *Transfusion*. 2007;47(4):593-8.

29. Sinha R, Roxby D, Bersten A. Experience with a massive transfusion protocol in the management of massive haemorrhage. *Transfus Med*. 2013;23(2):108-13.

30. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. *Br J Surg*. 2002;89(6):714-30.

31. Rayt HS, Sutton AJ, London NJ, Sayers RD, Bown MJ. A systematic review and meta-analysis of endovascular repair (EVAR) for ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg*. 2008;36(5):536-44.

32. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-82.

33. Cotton BA, Gunter OL, Isbell J, Au BK, Robertson AM, Morris JA, Jr., St Jacques P, Young PP. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma*. 2008;64(5):1177-82; discussion 82-3.

34. Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, Cocanour CS, Balldin BC, McKinley BA. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma*. 2007;62(1):112-9.

35. Repine TB, Perkins JG, Kauvar DS, Blackborne L. The use of fresh whole blood in massive transfusion. *J Trauma*. 2006;60(6 Suppl):S59-69.

36. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma*. 2009;66(2):346-52.

37. Cotton BA, Dossett LA, Haut ER, Shafi S, Nunez TC, Au BK, Zaydfudim V, Johnston M, Arbogast P, Young PP. Multicenter validation of a simplified score to predict massive transfusion in trauma. *J Trauma*. 2010;69 Suppl 1:S33-9.

38. Cantle PM, Cotton BA. Prediction of Massive Transfusion in Trauma. *Crit Care Clin*. 2017;33(1):71-84.

39. Yucel N, Lefering R, Maegele M, Vorweg M, Tjardes T, Ruchholtz S, Neugebauer EA, Wappler F, Bouillon B, Rixen D. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma*. 2006;60(6):1228-36; discussion 36-7.

40. McLaughlin DF, Niles SE, Salinas J, Perkins JG, Cox ED, Wade CE, Holcomb JB. A predictive model for massive transfusion in combat casualty patients. *J Trauma*. 2008;64(2 Suppl):S57-63; discussion S.

41. Joseph B, Khan M, Truitt M, Jehan F, Kulvatunyou N, Azim A, Jain A, Zeeshan M, Tang A, O'Keeffe T. Massive Transfusion: The Revised Assessment of Bleeding and Transfusion (RABT) Score. *World J Surg*. 2018.

42. Callcut RA, Cotton BA, Muskat P, Fox EE, Wade CE, Holcomb JB, Schreiber MA, Rahbar MH, Cohen MJ, Knudson MM, et al. Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. *J Trauma Acute Care Surg*. 2013;74(1):59-65, 7-8; discussion 6-7.

43. Kreuziger LMB, Salzman J, Subramanian AT, Morton CT, Dries DJ. Massive Transfusion in Non-Trauma Patients. *Blood*. 2011;118(21):3376.

Figures and Tables Legend

Figure 1. *Records relevant to the topic that were cited in articles identified by the literature search

Figure 2. MTP: massive transfusion protocol, CI: confidence interval, M-H: Mantel–Haenszel statistics.

Figure 1 PRISMA Flow Diagram

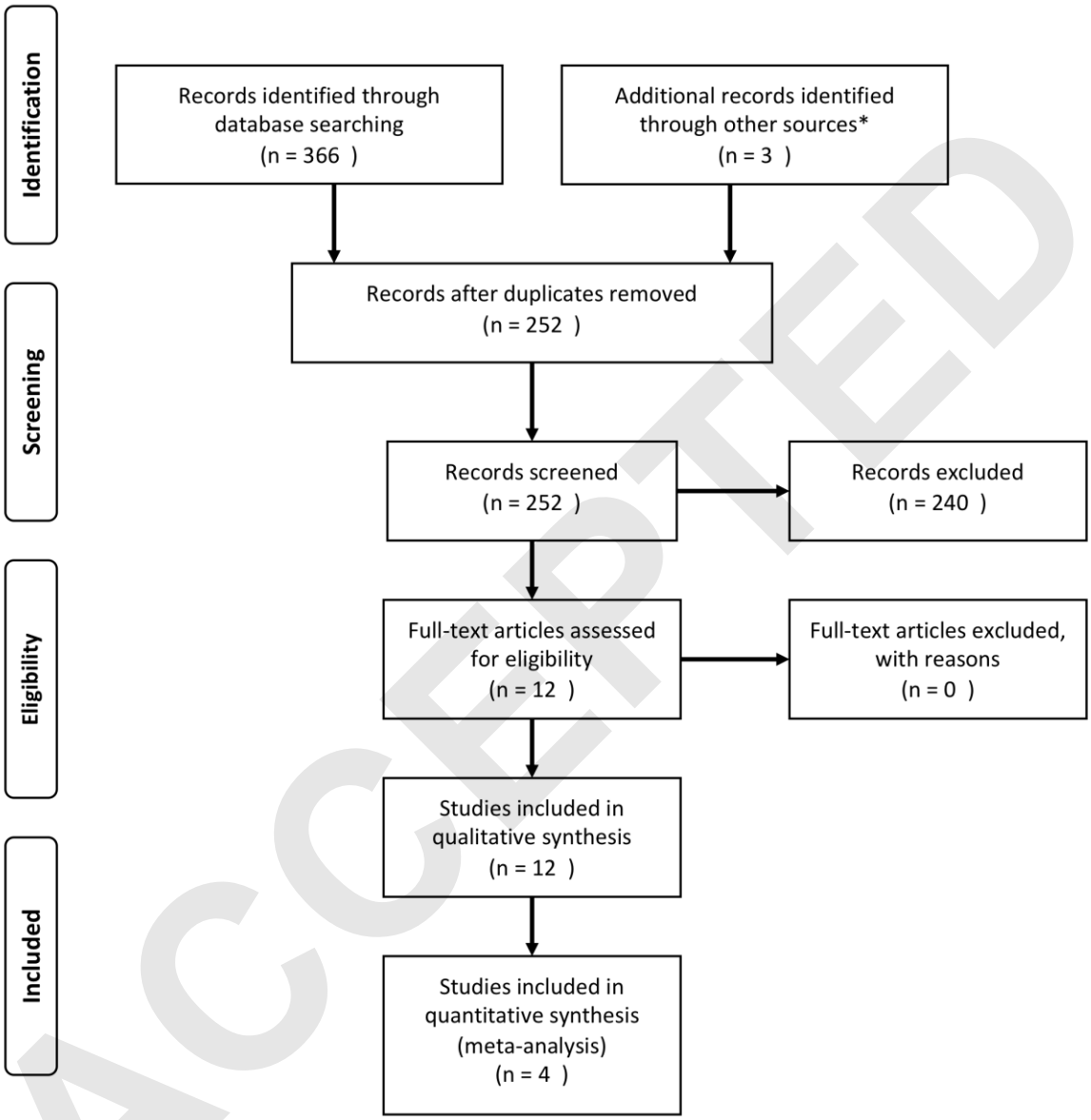

Figure 2 Effect of MTP on mortality

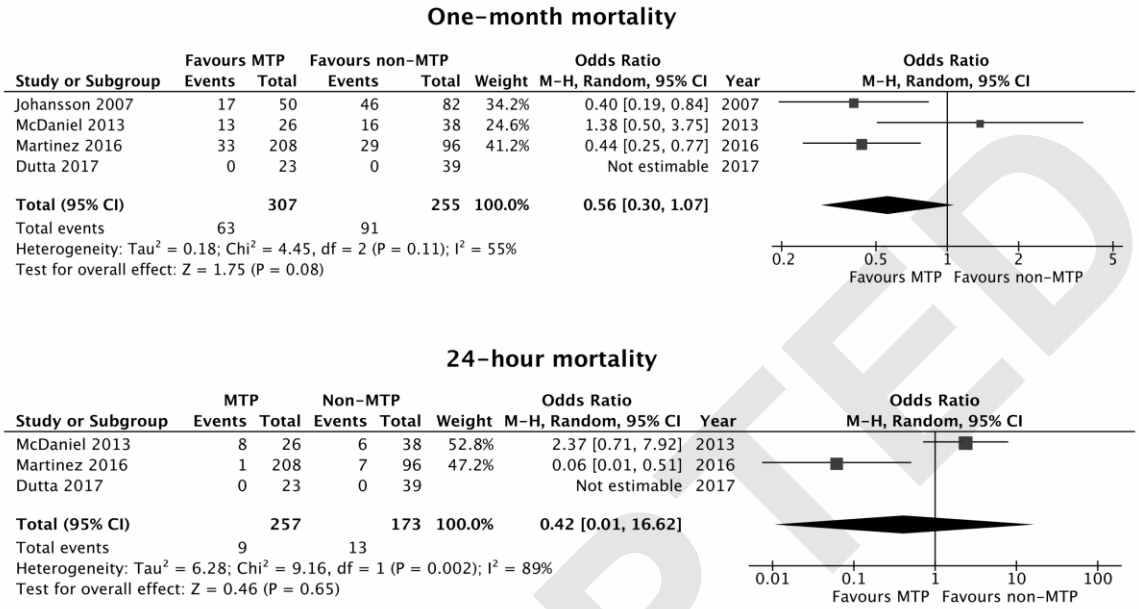

Table 1. Studies included

Author, *Journal,* Year	Study type	Study size* (n=)	Patient characteristics*	Age (Years)	Indication for MTP activation	MTP/Non-MTP*
Dutta et al., *Am J Perinatol,* 2017	Retrospective single center	62	Obstetric: 62 (100)	Pre-MTP: 29.9±1.0[‡] Post-MTP: 32.7±1.2[‡]	Clinical judgement	6/56
Chay et al., *Vox Sang,* 2016	Retrospective multicenter	434	Major surgery: 130 (30), gastrointestinal bleeding: 109 (25), obstetric: 26 (6), trauma: 169 (39)	-	Clinical judgement	434/0
Martinez-Calle et al., *Med Intensiva,* 2016	Retrospective single center	304	Oncologic surgery: 88 (28.9), cardiovascular surgery: 105 (34.5), other surgery: 57 (18.8), non-surgical bleeding: 54 (17.8)	Pre-MTP: 62 (52-74)[+] MTP: 62 (50-71)[+]	Replacement of whole blood volume in 24h/Replacement of 50% of blood volume in 3h/Blood loss > 1500ml in 10min/Triggered by blood bank if > 8 PRBC used	208/96
Wijaya et al., *Singapore Med J,* 2016	Retrospective single center	46	GIT bleeding: 12 (26.1), ruptured AAA: 3 (6.5), ruptured splenic artery aneurysm: 1 (2.2), intraoperative bleeding: 1 (2.2), postoperative bleeding: 1 (2.2), trauma: 28 (60.9)	55.67±19.36[‡]	Clinical judgement	46/0
Balvers et al., *J Emerg Trauma Shock,* 2015	Retrospective single center	547	Trauma: 48 (8.8), surgery: 348 (63.1), obstetric: 22 (4.0), internal Medicine: 69 (12.6), other: 60 (11.0)	Pre-MTP: 65 (51-76)[+] MTP: 65 (52-73)[+]	SBP <90mmHg with no response to fluid administration and suspicion of massive bleeding	115/432
Baumann Kreuziger et al., *Transfus Med,* 2014	Retrospective single center	133[a]	Vascular rupture: 23 (18.4), GIT bleeding: 16 (12.8), cardiothoracic surgery: 11 (8.8), obstetric: 5 (4.0), thrombosis: 2 (1.6), orthopedic: 1 (0.8), trauma: 62 (49.6), other: 5 (4.0)	53±18.6[‡]	Clinical judgement	125/8
McDaniel et al., *J Am Coll Surg,* 2013	Retrospective single center	164	GIT bleeding: 21 (12.8), medical bleeding for other reasons: 6 (3.7), postsurgical/procedural complications: 18 (11.0), vascular emergencies: 18 (11.0), cerebral hemorrhage: 1 (0.6), trauma: 100 (61.0)	MTP: 57.9±19.8[‡] nMTP: 64.6±16.4[‡]	Clinical judgement	52/112
Sinha et al., *Transfus Med,* 2013	Retrospective single center	152	Ruptured AAA: 31 (20), cardiac surgery: 12 (8), other surgery: 29 (19), GIT bleeding: 23 (15), obstetric: 16 (11), liver transplantation: 4 (3), trauma: 37 (24)	61 (40-78)[+]	Clinical judgement	83/69

Morse et al., *Am Surg,* 2012	Retrospective single center	439	GIT bleeding: 18 (4.1), intraopoerative bleeding: 13 (3.0), obstetric: 5 (1.1), ruptured AAA: 1 (0.2), trauma: 402 (91.6)	37.5±0.74[#]	Clinical judgement	439/0
Gutierrez et al., *Int J of Obstet Anesth,* 2012	Retrospective single center	31	Obstetric: 31 (100)	33.5±6.1[‡]	Clinical judgement	31/0
Goodnough et al., *Transfusion,* 2011	Retrospective single center	31	Obstetric: 31 (100)	-	Emergent need for blood products (not further specified)	31/0
Johansson et al., *Transfusion,* 2007	Retrospective single center	132	Ruptured AAA: 132 (100)	Pre-MTP: 73 (51-84)[+] MTP: 71 (48-89)[+]	Massive bleeding (not further specified)	50/82

*Values are numbers (percentages). [+]Median (IQR). [#]Mean±SEM. [‡]Mean±SD. [a]Including 8 patients that were transfused off-protocol and were not included in the analysis.

MTP: massive transfusion protocol, PRBC: packed red blood cells, GIT: gastrointestinal tract, AAA: abdominal aortic aneurism, SBP: systolic blood pressure.

Table 2. Blood products, transfusion ratios, and overactivation

Author, Year, Journal	Units transfused per patient			Transfusion ratios	Over-activation
	PRBC	*FFP*	*Platelets*		
Dutta, E. H., et al., 2017, *Am J Perinatol*	Pre-MTP: 6 (5-8)[+] MTP: 7 (5-9)[+] p=0.85	Pre-MTP: 4 (1-5)[+] MTP: 2 (0-4)[+] p=0.28	Pre-MTP: 0 (0.0-0.6)[+] MTP: 0 (0.0-0.6)[+] p=0.63	*FFP:PRBC* Pre-MTP: 0.5 (0.1-0.6)[+], MTP: 0.3 (0.0-0.5)[+], p=0.31 *PLT:PRBC* Pre-MTP: 0.0 (0.0-0.6)[+], MTP: 0.0 (0.0-0.7)[+], p=0.42	-
Chay et al., 2016, *Vox Sang*	Range 5-12[†]	Range 4-8[†]	Range 3- 8[†]	*FFP:PRBC* Range 0.6-0.8[†] *PLT:PRBC* Range 0.6-0.8[†]	-
Martinez-Calle et al., 2016, *Med Intensiva (two MTP groups)*	Pre-MTP: 9 (6)[+] MTP: 19 (9)[+] p=0.688	Pre-MTP: 5 (6)[+] MTP: 77 (37)[+] p=0.238	Pre-MTP: 1 (2)[+] MTP: 5 (2)[+] p=0.751	*FFP:PRBC* Pre-MTP: 0.44 (0.30-0.67)[+], MTP: 0.57 (0.33-0.77)[+] and 0.55 (0.33-0.79)[+], p=0.053 *PLT:PRBC* Pre-MTP: 0.10 (0.0- 0.15)[+], MTP: 0.11 (0.0-0.18)[+] and 0.1 (0.0-0.17)[+], p=0.429	-
Wijaya et al., 2016, *Singapore Med J*	-	-	-	FFP:PRBC: 0.655±0.192[‡] PLT:PRBC: 0.141±0.072[‡]	11 (61.1)
Balvers et al., 2015, *J Emerg Trauma Shock*	Pre-MTP: 8 (6-12)[+] MTP: 8 (7-13)[+] p=0.279	Pre-MTP: 6 (3-9)[+] MTP: 6 (4-11)[+] p=0.224	Pre-MTP: 2 (1-3)[+] MTP: 2 (0-4)[+] p=0.139	*PRBC:FFP ≤ 1.1* Pre-MTP: 70 (37)*, MTP: 168 (47)*, p=0.014 *PRBC:PLT ≤ 1.1* Pre-MTP: 119 (62)*, MTP: 230 (65)*, p=0.514	-
Baumann Kreuziger et al., 2014, *Transfus Med*	8.7±7.0[‡]	6.2±5.7[‡]	1.5±1.3[‡]	*Plasma:PRBC* <1:4: 7 (11.1)* 1:4-1:2: 11 (17.5)* 1:2-1:1: 37 (58.7)* >1:1: 8 (12.7)*	41 (65)
McDaniel et al., 2013, *J Am Coll Surg*	Non-MTP: 12.2±9.0[‡] MTP: 12.6±11.5[‡] p=0.864	Non-MTP: 8.9±8.7[‡] MTP: 9.2±8.0[‡] p=0.631	Non-MTP: 6.5±8.6[‡] MTP: 7.2±6.7[‡] p=0.183	*FFP:PRBC* MTP: 0.79:1±0.34:1[‡], Non-MTP: 0.65:1±0.39:1, p=0.282 *PLT:PRBC* MTP: 0.61:1±0.42:1[‡], Non-MTP: 0.53:1±0.54:1, p=0.476	14 (53.8)

Sinha et al., 2013, *Transfus Med*	Pre-MTP: 16 (12-20)[+] MTP: 14 (11-21)[+]	Pre-MTP: 6 (5-10)[+] MTP: 10 (7-17)[+]	Pre-MTP: 2 (1-3)[+] MTP: 3 (2-4)[+]	*FFP:PRBC* Pre-MTP: 1:2.4 (1:1.8-1:3.4)[+], MTP: 1:1.4 (1:1.2-1:2.0)[+], p<0.001 *PLT:PRBC* Pre-MTP: 1:10 (1:6.0-1:14.0)[+], MTP: 1:6 (1:4.1-1:8.0)[+], p<0.001	-
Morse et al., 2012, *Am Surg*	12.5±2.0[#]	7.9±1.3[#]	8.6±1.4[#]	PRBC:FFP: 1:2.2±0.3[#] PRBC:PLT: 1:2.3±0.4[#]	20 (54)
Gutierrez et al., 2012, *Int J of Obstet Anesth*	3.0 (1.8-7.0)[+]	3.0 (1.5-5.5)[+]	1.0 (0.0-2.5)[+]	-	-
Goodnough et al., 2011, *Transfusion*	5.0 (4.0-7.5)[+]	2.0 (0.0-4.0)[+]	1.0 (0.0-1.0)[+]	-	-
Johansson et al., 2007, *Transfusion*	*OR:* no difference *ICU:* Pre-MTP: 6 (0-54)[+], MTP: 2 (0-30)[+], p<0.05	*OR:* Pre-MTP: 0 (0-3)[+], MTP: 4 (2-16)[+], p<0.05 *ICU:* Pre-MTP: 1 (0-6)[+], MTP: 0 (0-4)[+], p<0.05	*OR:* Pre-MTP: 7 (0-46)[+], MTP: 11 (2-42)[+], p<0.05 *ICU:* Pre-MTP: 4 (0-32)[+], MTP: 2 (0-12)[+], p<0.05	-	-

*Numbers (percentage). [+]Median (IQR). [†]Median. [‡]Mean ± SD. [#]Mean ± SEM.

MTP: massive transfusion protocol. PRBC: packed red blood cells. FFP: fresh frozen plasma. PLT: platelets. AAA: abdominal aortic aneurysm. OR: operating room. ICU: intensive care unit.

Overactivation: < 10 units of PRBC transfused for patients with activated MTP.

Table 3. 24-hour and one-month mortality

Author, Year, *Journal*	**24-hour mortality** n (%)	**One-month mortality*** n (%)
Dutta, E. H., et al., 2017, *Am J Perinatol*	Pre-MTP: 0 (0) MTP: 0 (0)	Pre-MTP: 0 (0) MTP: 0 (0)
Chay et al., 2016, *Vox Sang*	-	-
Martinez-Calle et al., 2016, *Med Intensiva*	Pre-MTP: 7 (7.3) MTP: 0 (0.0) and 1 (1.1) (2 MTP groups) p=0.002	Pre-MTP: 29 (30.2) MTP: 21 (18.1) and 12 (13.0) (2 MTP groups) p=0.010
Wijaya et al., 2016, *Singapore Med J*	-	-
Balvers et al., 2015, *J Emerg Trauma Shock*	Pre-MTP: 23 (12.0) MTP: 52 (15.0) p=0.386	Pre-MTP: 65 (34) MTP: 124 (35) p=0.801
Baumann Kreuziger et al., 2014, *Transfus Med*	-	-
McDaniel et al., 2013, *J Am Coll Surg*	Non-MTP: 6 (15.8) MTP: 8 (30.8) p=0.155	Non-MTP: 16 (42.1) MTP: 13 (50.0) p=0.207
Sinha et al., 2013, *Transfus Med*	-	-
Morse et al., 2012, *Am Surg*	MTP: 15 (41.0)	MTP: 18 (49.0)
Gutierrez et al., 2012, *Int J of Obstet Anesth*	-	-
Goodnough et al., 2011, *Transfusion*	-	-
Johansson et al., 2007, *Transfusion*	-	Pre-MTP: 46 (56) MTP: 17 (34) p=0.02 (death in OR excluded)

*Fisher's exact test, studies that reported mortality in non-trauma patients specifically.

MTP: massive transfusion protocol, OR: operating room, CI: confidence interval.

Table 4. Quality assessment using the Newcastle-Ottawa Scale for cohort studies

Author, *Journal,* Year	Selection				Comparability	Outcome			Total
	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Dutta et al., *Am J Perinatol,* 2017	✻	✻	✻	✻		✻	✻	✻	7
Chay et al., *Vox Sang,* 2016	✻	✻	✻	✻					4
Martinez-Calle et al., *Med Intensiva,* 2016	✻	✻	✻	✻		✻	✻	✻	7
Wijaya et al., *Singapore Med J,* 2016	✻	✻	✻	✻		✻	✻	✻	7
Balvers et al., *J Emerg Trauma Shock,* 2015	✻	✻	✻	✻		✻	✻	✻	7
Baumann Kreuziger et al., *Transfus Med,* 2014	✻	✻	✻	✻		✻	✻	✻	7
McDaniel et al., *J Am Coll Surg,* 2013	✻	✻	✻	✻		✻	✻	✻	7
Sinha et al., *Transfus Med,* 2013	✻	✻	✻	✻		✻	✻	✻	7
Morse et al., *Am Surg,* 2012	✻	✻	✻	✻		✻	✻	✻	7
Gutierrez et al., *Int J of Obstet Anesth,* 2012	✻		✻	✻					3
Goodnough et al.,	✻		✻	✻					3

Transfusion, 2011								
Johansson et al., *Transfusion,* 2007	✻	✻	✻	✻		✻	✻	6

Quality assessment with mortality as outcome.

Table 5. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1, 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3, 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3, 4

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3, 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3, 4, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4, 14, 15
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4, 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4, 5

Table 5. PRISMA 2009 Checklist (cont.)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, 7, Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10, 11, Table 3, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10, 11, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4, 5, 14, 15, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12, 13, 14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14, 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A