TRANSFUSION MEDICINE AND TRANSFUSION COMPLICATIONS

Review

The effect of massive transfusion protocol implementation on the survival of trauma patients: a systematic review and meta-analysis

Rafael Consunji[1], Alaa Elseed[1], Ayman El-Menyar[1,2,3], Brijesh Sathian[2], Sandro Rizoli[1], Hassan Al-Thani[1], Ruben Peralta[1,4]

[1]*Department of Surgery, Section of Trauma Surgery, Hamad General Hospital, Doha, Qatar;*
[2]*Department of Clinical Research, Hamad General Hospital, Doha, Qatar;*
[3]*Clinical Medicine, Weill Cornell Medical College, Doha, Qatar;*
[4]*Department of Surgery, Universidad Nacional Pedro Henriquez Urena, Santo Domingo, Dominican Republic*

Background - Massive transfusion protocol (MTP) has been widely adopted for the care of bleeding trauma patients but its actual effectiveness is unclear. An earlier meta-analysis on the implementation of MTP for injured patients from 1990 to 2013 reported that only 2 out of 8 studies showed statistical improvement in survival. This study aimed to conduct an updated systematic review and meta-analysis to evaluate the effect of implementing an MTP on the mortality of trauma patients.

Materials and methods - MEDLINE, PubMed, Cochrane Library and Google scholar databases were systematically searched for relevant studies published from 1st January 2008 to 30th September 2019 using a combination of keywords and additional manual searching of reference lists. Inclusion criteria were: original study in English, study population including trauma patients, and comparison of mortality outcomes before and after institutional implementation of an MTP. Primary outcomes were 24-hour, 30-day, and overall mortality.

Results - Fourteen studies met inclusion criteria, analysing outcomes from 3,201 trauma patients. There was a wide range of outcomes, patient populations, and process indicators utilised by the different authors. MTP significantly reduced the overall mortality for trauma patients (OR 0.71 [0.56-0.90]). No significant reduction was seen in either the 24-hour mortality (OR 0.81 [0.57-1.14]) or the 30-day mortality (OR 0.73 [0.46-1.16]). However, when mortality timing was unspecified, mortality was statistically reduced (OR 0.69 [0.55-0.86]).

Discussion - The present study found a significant reduction in mortality following MTP implementation and thus it should be recommended to all institutions managing acutely injured patients. To better identify which elements of an MTP contribute to this effect, we encourage the use of standard nomenclature, indicators, protocols and patient populations in all future MTP studies.

Keywords: *massive transfusion protocol, trauma, mortality, meta-analysis, systematic review.*

INTRODUCTION

Trauma accounts for a significant proportion of the annual global mortality. The World Health Organization (WHO) estimates that in 2016, 4.9 million people died worldwide from injuries[1]. In both civilian and military settings, the majority of potentially preventable

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Correspondence: Rafael Consunji
e-mail: RConsunji@hamad.qa

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deaths after trauma are related to uncontrolled haemorrhage and occur early after injury[2].

Haemorrhage control requires early definitive haemostasis, correction of coagulopathy, maintenance of critical tissue perfusion, and minimising harmful responses to shock and resuscitation fluids[3]. To address these goals, critically bleeding trauma patients most often require massive blood transfusion (MT) for haemostatic resuscitation. While there are various definitions of MT, it is still most-commonly defined as transfusion of ≥10 units of packed red blood cells (RBC) during a 24-hour (h) period[4].

While massive transfusion protocols (MTP) vary widely across the world, most direct the clinicians to initiate resuscitation of exsanguinating patients with blind transfusion of blood products, emphasising ratio and type of blood products. Optimal ratios and type of blood products are the subject of heated debate and have not yet been determined. Most MTPs, however, confirm that early access and initiation of blood transfusion and haemostatic procedures are linked to the survival of the exsanguinating patient. The prompt access to blood products in a balanced ratio is part of most MTP adopted across the world[5]. MTPs are developed to optimise specific component replacement in a setting of severe haemorrhage. They incorporate predefined volumes of different blood products and procoagulant agents to mitigate the hazards of excessive crystalloid administration and isolated RBC transfusion.

Despite the popularity of MTPs and directives mandating their use in trauma centres, their actual effectiveness has not been proven[5]. According to Mitra *et al.*, in an analysis of 8 studies that compared results before and after implementation of an MTP, it was associated with decreased mortality in only 2 studies[6]. However, with the rapid increase in the literature in this field, several observational studies have emerged since the publication of this analysis. We, therefore, aimed to conduct this systematic review and meta-analysis to update evidence on and evaluate the effect of implementing MTP on the mortality of trauma patients.

MATERIALS AND METHODS

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study was registered at the international prospective register of systematic reviews ('PROSPERO CRD42020157042').

Search strategy

MEDLINE, PubMed, Google Scholar and Cochrane Library databases were systematically searched for relevant studies published between January 1st 2008 and June 30th 2019. We used a combination of the following keywords: "Massive transfusion*", "Massive blood transfusion*", "blood component*", "blood component transfusion*", "massive transfusion protocol*", "massive transfusion guidelines", "massive transfusion protocol and compliance", "trauma*", "wound and injuries*", "haemorrhage*" and "hemorrhage*". Additional manual searching of reference lists was also conducted.

Selection criteria

To be eligible for inclusion, studies were required to meet all of the following criteria: 1) original study was published in English; 2) published within the period from January 1st 2008 through September 30th 2019; 3) study population included trauma patients who received or were anticipated to receive massive blood transfusion; and 4) described or compared mortality outcomes before and after institutional implementation of an MTP.

Studies were excluded if the patient population consisted exclusively of obstetric, paediatric or non-trauma surgical patients. Studies that included heterogeneous populations (trauma and non-trauma patients) were also excluded if the authors were unable to distinguish trauma patients from the larger study population. When multiple publications from the same institution representing the same population were presented, all publications presenting unique outcomes were included. Any definition of MT was accepted.

Characteristics of selected studies

- ***Participants*** - trauma patients.
- ***Intervention*** - implementation of an MTP, as defined by the study institution(s).
- ***Control*** - patients in the same institution in a period prior to the implementation of an MTP.
- ***Outcomes*** - overall mortality, 24-hour mortality and 30-day mortality.

Study selection

After duplicates were removed, three authors (RC, AE and BS) independently screened the titles and/or abstracts of the identified studies for potential inclusion. Eligible studies then underwent full- text assessment. Finally, only

those studies approved by the authors were included in this review. Agreement between the authors on the quality of the studies ranged between 90 and 100%. All disagreements were resolved by consensus among the authors.

Data collection

Two reviewers independently extracted data from each included study. Extracted data were: first author's name, year of publication, study design (retrospective/prospective), study settings and duration, study size and number of patients in each study arm, injury severity scores (ISS) of included patients, study-specific definitions of MT, details of the implemented MTPs, and mortality outcomes. Any disagreements in extracted data were resolved by a third author. We contacted the corresponding authors of the included studies to obtain additional details about missing or incomplete data.

Quality assessment

We used the "Grading quality of evidence and strength of recommendations" (GRADE criteria) to assess the quality of the included studies and rate the level of evidence[7]. The methodological quality of the selected studies was assessed based on certainty assessment (study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations) by Cochrane Grade pro software. We evaluated the quality of the proposed outcome, i.e. mortality.

Data analysis and synthesis

Odds ratios (OR) were calculated for categorical variables. The decision to select either a fixed effect or random effects model depended on results of statistical tests for heterogeneity. Data heterogeneity was assessed using the Cochrane Q homogeneity test; $p<0.10$ was considered statistically significant. If the studies were statistically homogeneous, fixed effect model was selected. A random effects model was used when studies were statistically heterogeneous. The Higgin's I^2 test is the ratio of true heterogeneity to the total variation in observed effects. A rough guide to interpretation of the I^2 test is: 0-25%: "might not be important"; 25-50%: "may represent moderate heterogeneity"; 50-75%: "may represent substantial heterogeneity"; >75%: "considerable heterogeneity"[7].

Publication bias was visually estimated by assessing funnel plots. Pooled estimates of mortality were calculated using R 3.5.1 and R Studio. GRADEpro GDT was used for study grading[7].

RESULTS

The literature search identified a total of 4,174 studies of which 2,075 were duplicates and were excluded. Of the remaining 2,099, 23 full-text studies were selected and further assessed. Of these, 6 were excluded: 3 because of duplicate publication[8-10] and another 3 due to the lack of differentiation between the population of interest (trauma patients) and the entire study population[11-13]. Therefore, 17 original studies met all inclusion criteria and were considered for the systematic review[14-30]. Subsequently, another 3 studies consisting of subgroup analysis were excluded[21,23,28], and the remaining 14 studies were included in the final meta-analysis[14-20,22,24-27,29,30]. Searching the references of included studies did not identify any additional studies (**Table I**, **Figure 1** and *Online Supplementary Content*, **Table SI**).

Description of included studies

No randomised controlled trial was identified. Thirteen studies were retrospective cohort studies[14,15,17,18,22-30] and 4 were prospective studies with historical controls[16,19-21]. The total number of patients included in the present analysis was 3,201 with a median of 195.5 (83-263) patients in each study. The mean ISS for pre- and post-MTP implementation were 30.6 and 32, respectively. The mean age was 38.1 years for pre- and 39.1 years for post-implementation populations. The median duration of patient enrolment was 6.5 years with an interquartile range (IQR) of 4-7 years. Two studies reported an interim period during initial MTP implementation. For the present analysis, the interim period population was combined with the post-MTP population[15,25].

The majority of studies were conducted in the United States (n=9)[16,17,19-22,24,27,28]. Only one study included patients from multiple trauma centres[26]. Thirteen studies focused exclusively on patients with haemorrhage requiring MT[14-22,24,28-30] while 4 considered all transfused patients[23,25-27]. Simmons *et al.* exclusively analysed injured military personnel, whereas all others only included civilian patients[17]. Sinha *et al.* was the only study to include both trauma and non-trauma patients; however, the mortality of trauma patients was reported separately[29]. Regarding age of inclusion, one study restricted inclusion to patients aged ≥15 years[15], three studies included only individuals aged >15 years[19,23,29], while 2 other studies included patients aged >16 years[25,30]. The remaining

Table I - *Summary of the included studies*

Study name, year	Timing of mortality	Protocol pRBC:FFP: PLT	Age Pre/Post-MTP	Male (%) Pre/Post-MTP	Study design	Study duration	Mortality in Post-MTP group	Mortality in Pre-MTP group	Survival in post-MTP group	Survival in pre-MTP group
van der Meij *et al.*[14], 2019	Overall/ In- hospital	6: 4: 4	39±18 43±20	83.3 76.6	R	8 yrs	20	21	27	33
Hwang *et al.*[15], 2018	Overall/ In- hospital	1: 1: 1	Pre-MTP: 5±15 *Interim*: 47±18 Post-MTP: 49±17	Pre: 81.3 *Interim*: 70.3 Post: 79.0	R	7 yrs	46	35	80	29
Söderlund *et al.*[23], 2017	Overall	pRBC: FFP=1: 1	36.3±16.6 41.0±21	69.6 56.5	R	8 yrs	12	20	34	36
Nunn *et al.*[24], 2017	Overall	1: 1: 1	38.7±15.64 39.5±16.05	79.9 72.1	R	9 yrs	85	113	123	126
Brinck *et al.*[25], 2016	Overall/ 30 days	1: 1: 1	Pre-MTP: 39.0±17.7 *Interim*: 41.9±22.1 Post-MTP: 2.2±20.5	Pre-MTP: 76.9 *Interim*: 66.3 Post-MTP: 69.4	R	7 yrs	35	39	172	108
Noorman *et al.*[26], 2016	Overall/ In- hospital	4: 3: 1	_	_	R	4 yrs + 2 m	10	13	134	44
Maciel et al.[27], 2015	Overall	pRBC: FFP=1.5: 1	31±19 34±15	93 94	R	12 yrs+ 9 m	9	24	8	5
Ball *et al.*[28], 2013	Overall	6: 6: 8-10	_	_	R	4 yrs + 1 m	17	14	18	11
Sinha *et al.*[29], 2013	Overall/ In- hospital	5: 2-4: 5	_	_	R	7 yrs	3	6	11	17
Sisak *et al.*[30], 2012	Overall	1: 1: 1	46.0±17.7 42.6±18.8	77 71	R	7 yrs + 4 m	13	12	15	18
Shaz *et al.*[16], 2010	Overall/ 30 days	pRBC: FFP=6: 6 pRBC: PLT=10: 6-7	38±16 35±15	83 82	R/P	4 yrs	63	42	69	42
Simmons *et al.*[17], 2010	Overall	1: 1: 1	25±6 25±6	Not reported	R	5 yrs + 6 m	81	84	345	267
Dirks *et al.*[18], 2010	Overall/ 30 days	5: 5: 4	Median 40 [28-55] 43 [27-59]	74 72	R	6 yrs	47	24	109	73
Riskin *et al.*[19], 2009	Overall	6: 4: 6	42.0 45.0	73 62	R/P	4 yrs	7	18	30	22
Cotton *et al.*[20], 2009	Overall/ 30 days	10: 4: 10	38.5 ±17.8 35.6 ±15.5	86 94	R/P	3 yrs + 5 m	54	88	71	53
Zaydfudim *et al.*[21], 2009	Overall/ 30 days	10: 6: 10	36±15 34±13	74 64	R/P	2 yrs	17	27	19	12
O'Keeffe *et al.*[22], 2008	Overall	5: 2: 6	34.6±16.1 34.9±16.1	73.9 81.8	R	3 yrs	69	23	63	23

MPT: massive transfusion protocol; pRBC: packed red blood cells; FFP: fresh frozen plasma; PLT: platets; R: retrospective; P: prospective; yrs: years; m: month.

studies had no restriction on age and included all patients[14,16-18,20-22,24,26-28].

Five studies included only severely injured patients defined by ISS >15[14,15,23,25,30]. In 4 of the 17 studies included in the systematic review, analysis was carried out exclusively in either blunt or penetrating trauma[21,23,27,28]. Both Ball *et al.* and Zaydfudim *et al.* analysed only patients with intra-abdominal haemorrhage due to high-grade (III-V) liver injury[21,28]. Maciel *et al.* analysed patients with abdominal aortic injury[27], whereas Söderlund *et al.* only studied patients with pelvic fractures[23].

Effect of MTP on mortality among trauma patients

Overall mortality

Fourteen studies reported the effect of MTP implementation on overall mortality[14-20,22,24-27,29,30]; this included the mortality rates reported at the conclusion of patient follow-up or termination of the study. In 5 of these studies, the overall mortality was significantly lower in the post-implementation compared to pre-MTP patients: Hwang *et al.*[15]: 36.5 *vs* 54.7% (p=0.007); Riskin *et al.*[19]: 19 *vs* 45% (p=0.02); Brinck *et al.*[25]: 16.9 *vs* 26.5% (p=0.032); Noorman *et al.*[26]: 7 *vs* 23% (p=0.002); Maciel *et al.*[27]: 53 *vs* 83% (p=0.03). The remaining studies found no

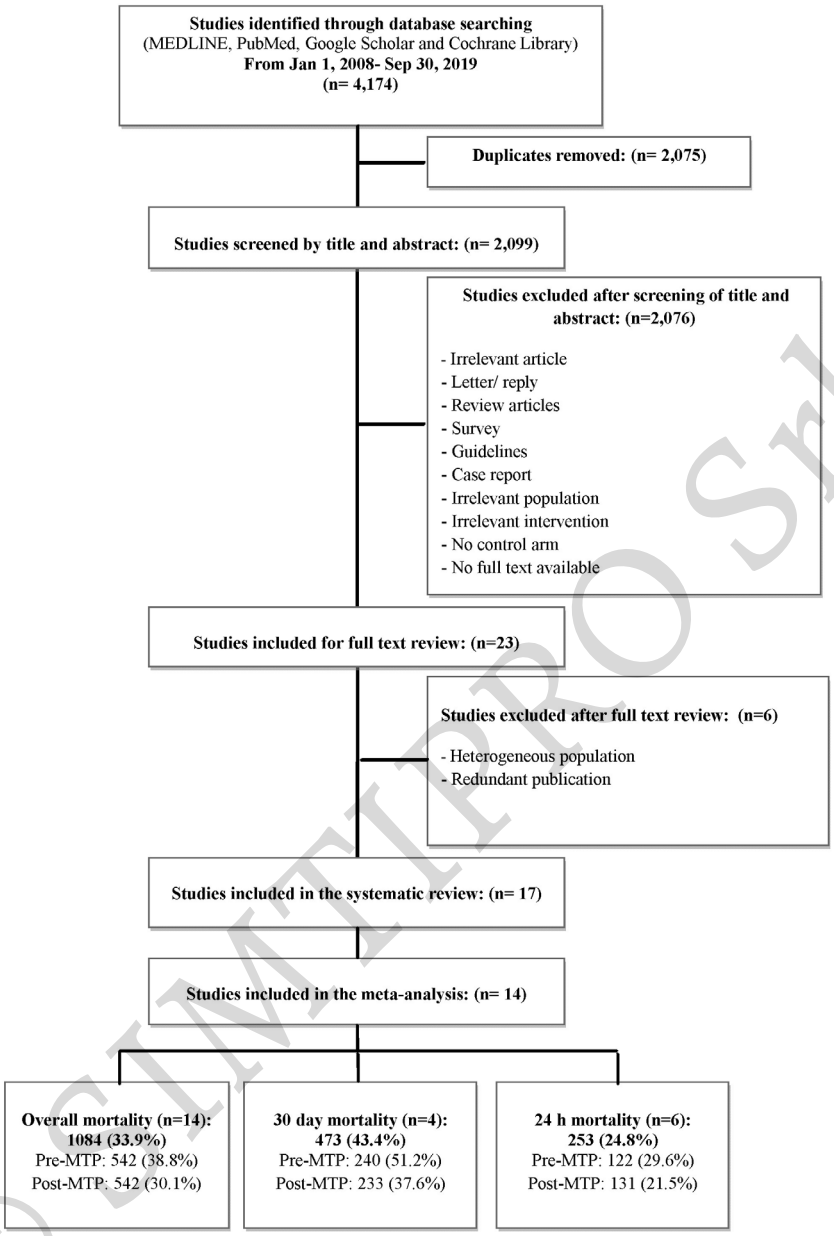

Figure 1 - Flow diagram of study selection process for the systematic review and meta-analysis
MTP: massive transfusion protocol.

significant difference in overall mortality between post- and pre-MTP implementation[14,16-18,20,22,24,29,30].

30-day mortality

Five studies reported the effect of the MTP implementation on 30-day mortality[16,18,20,21,25]. In 3 of these studies, the 30-day mortality was significantly lower in the post-implementation compared to pre-MTP patients: Brinck *et al.*[25]: 16.9 *vs* 26.5% (p=0.032); Cotton *et al.*[20]: 43.2 *vs* 62.4% (p=0.001); and Zaydfudim *et al.*[21]: 47 *vs* 69% (p =0.05). The remaining studies found no significant difference in the 30-day mortality between post- and pre-MTP implementation: Dirks *et al.*[18]: 30.1 *vs* 24.7% (p=0.382); and Shaz *et al.*[16]: 52 *vs* 50% (p=0.47).

24-hour mortality

Seven studies compared the 24-hour mortality rates between post- and pre-MTP groups[14,16,20-22,26,30]. Except for

the study by Noorman *et al.*, all others found no change in 24-hour mortality. Noorman *et al.* reported a significant reduction in mortality from 11% pre-MTP implementation to 2% after (p=0.004)[26]. For Meij *et al.*[14]: 29.8 *vs* 29.6% (p=0.99); Sisak *et al.*[30]: 35.7 *vs* 30% (p=1.00); Zaydfudim *et al.*[21]: 36 *vs* 49% (p=0.27); O'Keeffe *et al.*[22]: 20.5 *vs* 19.6% (p > 0.05); Shaz *et al.*[16]: 29 *vs* 32% (p=0.28); and Cotton *et al.*[20]: 31 *vs* 39% (p=0.185) there was no significant difference in 24-hour mortality between post- and pre-MTP groups.

Unspecified mortality timing

Six studies compared the mortality rates between post- and pre-MTP groups[15,17,19,24,27,29] without specifying the timing of their reported mortality. Only one of these studies reported a significant reduction in unspecified mortality. Riskin *et al.* reported a significant reduction in mortality from 45% pre-MTP implementation to 19% after (p=0.02)[19]. The remaining studies found no significant difference in the unspecified mortality between post- and pre-MTP implementation[15,17,24,27,29].

Patients with specific organ injury

Two studies on the effect of MTP implementation on patients with specific organ injuries reported a significant reduction in mortality. Maciel *et al.* only included patients with abdominal aortic injury and the overall mortality dropped from 83 to 53% after MTP implementation (p=0.03)[27]. Zaydfudim *et al.* conducted a subgroup analysis from the patient cohort studied by Cotton *et al.*, limiting the analysis to patients undergoing immediate surgery due to grade III-V liver injury. While there was no difference in 24-hour mortality (p=0.27), the 30-day mortality rate in the post-MTP implementation group was significantly lower than in the pre-MTP cohort (47 *vs* 69%, p=0.05)[21].

Ball *et al.* conducted a subgroup analysis on the patients analyzed by Shaz *et al.* but limited the analysis to those with intra-abdominal haemorrhage due to liver injury. The overall survival rate was not affected by MTP implementation (51.4 *vs* 44% pre-MTP (p=0.61)[28]. Similarly, Söderlund *et al.* used the same data set as Brinck *et al.* to evaluate the effect of MTP implementation among patients with pelvic fractures; this analysis reported no statistically significant difference in mortality between post- and pre-MTP groups (26.1 *vs* 35.7%, respectively)[23].

Methodological quality of included studies

Table I, **Appendix A** and *Online Supplementary* **Table SI** show the details of the quality assessment based on GRADE criteria of the fourteen selected studies. All studies were of moderate quality. **Table II** demonstrates the quality assessment of the included studies which shows the moderate level of evidence based on GRADE criteria.

Outcome measures

Effect of MTP on mortality among trauma patients

- ***Overall mortality*** - The mortality outcome was reported in all studies. After eliminating 3 subgroup analyses, the results of 14 (out of 17) studies were used for the meta-analysis[14-20,22,24-27,29,30]. The total number of pooled patients was 3,201. The *post-hoc* statistical power was 100%. Overall mortality in the MTP and control groups was 542 of 1,799 patients (30.1%) and 542 of 1,402 patients (38.7%), respectively (**Figure 2A**). The pooled result showed a statistically significant decrease in overall mortality in the post-MTP group, with a pooled odds ratio (OR) of 0.71 (95% CI: 0.56-0.90).
- ***30-day mortality*** - Four of the 5 studies that reported 30-day mortality were included in this analysis[16,18,20,25]. The total number of pooled patients was 1,089. The *post-hoc* statistical power was 86.5%. Overall mortality in the MTP and control groups was 199 of 620 (32.1%) and 193 of 469 (41.1%), respectively (**Figure 2B**). The pooled result showed a non-statistically significant decrease in the 30-day mortality in the post-MTP group compared to the pre-MTP group (OR 0.73 [95% CI: 0.46-1.16]).
- ***24-hour mortality*** - Of the seven studies that evaluated the 24-hour mortality rate, we used 6 for this analysis[14,16,20,22,26,30]. The total number of pooled patients was 1,020. The *post-hoc* statistical power was 83.3%. Overall mortality in the MTP and control groups was 131 of 608 (21.5%) and 122 of 412 (29.6%), respectively (**Figure 2C**). The pooled result showed a non-statistically significant decrease in the 24-hour mortality of the post-MTP group compared to the pre-MTP group (OR 0.81 [95% CI: 0.57-1.14]).
- ***Unspecific mortality timing*** - Six studies did not specify the time of mortality[15,17,19,24,27,29]. The total number of pooled patients was 1,574. The *post-hoc* statistical power was 98.2%. Overall mortality in the MTP and control groups was 231 of 826 (27.9%) and 280 of 746 (37.5%), respectively (**Figure 2D**). The pooled result showed a

Table II - *GRADE rating of quality of evidence (post-MTP compared to pre-MTP)*

Certainty assessment							Summary of findings				
N. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Pre-MTP	With Post-MTP		Risk with Pre-MTP	Risk difference with Post-MTP
Mortality among trauma patients (assessed with: Overall)											
3,201 (14 observational studies)	Not serious	Serious	Not serious	Not serious	Strong association all plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕O MODERATE	542/1,402 (38.7%)	542/1,799 (30.1%)	OR 0.71 (0.56 to 0.90)	**Study population**	
										387 per 1,000	77 fewer per 1,000 (from 126 fewer to 25 fewer)
										Low	
										0 per 1,000	0 fewer per 1,000 (from 0 fewer to 0 fewer)
										High	
										435 per 1,000	82 fewer per 1,000 (from 134 fewer to 26 fewer)
Mortality among trauma patients (assessed with: 30 days)											
1,089 (6 observational studies)	Not serious	Serious	Not serious	Not serious	Strong association all plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕O MODERATE	193/469 (51.2%)	199/620 (37.6%)	OR 0.73 (0.46 to 1.16)	**Study population**	
										512 per 1,000	78 fewer per 1,000 (from 186 fewer to 37 more)
										Low	
										0 per 1,000	0 fewer per 1,000 (from 0 fewer to 0 fewer)
										High	
										417 per 1,000	74 fewer per 1,000 (from 169 fewer to 36 more)
Mortality among trauma patients (assessed with: 24 hours)											
1,020 (6 observational studies)	Not serious	Serious	Not serious	Not serious	Strong association all plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕O MODERATE	122/412 (29.6%)	131/608 (21.5%)	OR 0.81 (0.57 to 1.14)	**Study population**	
										296 per 1,000	42 fewer per 1,000 (from 103 fewer to 28 more)
										Low	
										0 per 1,000	0 fewer per 1,000 (from 0 fewer to 0 fewer)
										High	
										102 per 1,000	18 fewer per 1,000 (from 41 fewer to 13 more)

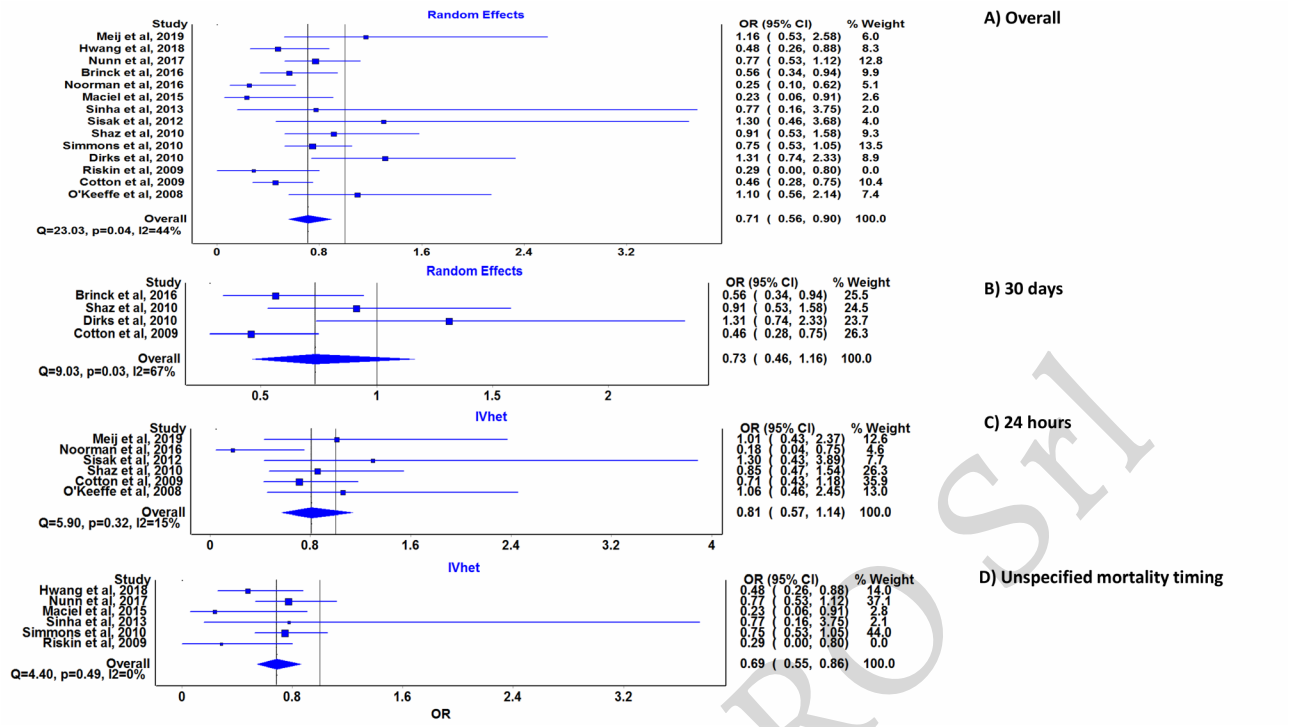

Figure 2 - Forest plot representing the effect of massive transfusion protocol (MTP) on mortality (24-hour, 30-day, and overall survivals and unspecific timing)

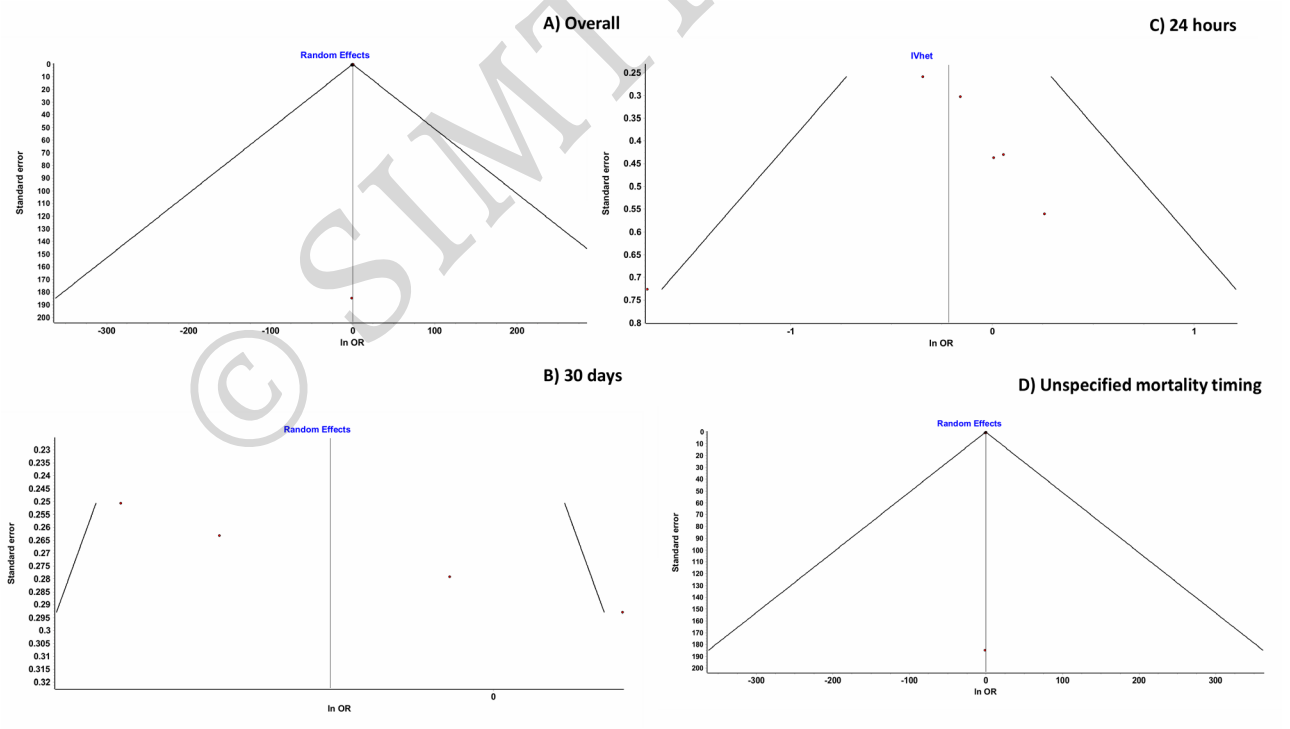

Figure 3 - Funnel plot representing the absence of publication bias

statistically significant decrease in the mortality of the post-MTP group compared to the pre-MTP group (OR 0.69 [95% CI: 0.55-0.86]).

Heterogeneity among included studies

The results for the test of heterogeneity for the meta-analysis of the effect of MTP activation on mortality are displayed towards the bottom of the forest plot in the line: for overall mortality studies Q [χ^2]=23.03, p=0.04, I^2=44%, τ^2=0.076 (**Figure 2A**), for 30-day mortality Q [χ^2]=9.03, p=0.03, I^2=67%, τ^2=0.147 (**Figure 2B**), for 24-hour mortality Q [χ^2]=5.90, p=0.32, I^2=15%, τ^2=0.028 (**Figure 2C**), for unspecified mortality timing Q [χ^2]=4.40, p=0.49, I^2=0%, τ^2=0.01 (**Figure 2D**). If I^2 was>25%, a random effects model was considered (applied). τ^2 reflects the amount of true heterogeneity among the studies, which was less in the overall and 24-hour mortality groups compared to the 30-day mortality group.

Publication bias and funnel plots

For all of the above analyses, sensitivity analysis yielded consistent results. Based on a visual inspection of the funnel plot, there was no evidence of publication bias for the included studies (**Figure 3A-D**).

DISCUSSION

This meta-analysis included 14 original studies that reported the effect of the implementation of an MTP on trauma patients. It shows that MTP implementation improves overall survival, with a statistically significant 29% reduction in the pooled OR of overall mortality. The key findings from the systematic review of 17 studies are the marked inconsistency and/or opaqueness in the reporting of mortality outcomes and selecting the age of the study population. These variations affected the ability to identify and compare studies that are similar and subject them to pooled statistical analyses and make stronger conclusions.

To date, this meta-analysis has the distinction of having the largest study population; it analysed data on the effect of an MTP on more than 3,000 patients, from more trauma centres and included the most recent studies. It has focused on 3 clinically pertinent mortality outcomes, evaluated the studies for quality, heterogeneity and publication bias, and produced an analysis of studies on a critically injured and homogenous trauma population. The study period is inclusive of the most recent advances and trends in the implementation of MTPs, i.e. tranexamic acid, point-of-care-testing, and is reflective of results from civilian trauma populations. In contrast to older studies that focused on the effect of MTP implementation on military trauma, this analysis had a majority (75.7%) of civilian or mixed patient populations.

The absence of standard indicators for evaluating MTPs was evidenced by the variety in reporting and defining the mortality outcome. Not all studies reported 24-hour mortality (only 7 out of 14) or 30-day mortality (only 5 out of 14), and there was considerable variation in the definition of overall mortality. Out of 14 studies, 6 did not specify the timing of death but showed a significant reduction in mortality post-MTP implementation. We found inconsistencies in the studies included in this analysis: the indications for, delivery of and evaluation of MTP to the inclusion criteria, and patient selection. Additionally, it has been shown that there is a great variability in the details of the MTPs that were used **(***Online Supplementary Content*, **Table SII).**

Not all studies reported the full age range of the patients included and there were at least 3 definitions of "adult trauma patients": >15, ≥15, and >16 years. This is despite the globally accepted WHO definition of "adult"[31]. These inconsistencies constrained our ability to make more definite recommendations on the effect of MTP implementation on adult trauma patients.

The patient enrolment periods of the included studies ranged widely from 2 years to 12 years and these periods (2000-2016) saw many developments and advances on the delivery of trauma and critical care, i.e. increased use of interventional radiology, preperitoneal pelvic packing, tranexamic acid, point-of-care-testing; these may act as confounders to the effects we are attributing to the implementation of the MTPs. However, testing the effect of "MTP only" implementation is not a realistic objective and no trauma centre will delay applying recently developed haemostatic adjuncts and/or procedures solely for the purpose of evaluating MTP implementation outcomes.

Survival bias was evident in most studies in which only survivors receiving massive blood transfusion were included in the analysis. Although some of these studies attempted to account for this bias, any inference is inherently limited by the fact that the most severely injured and bleeding trauma patients often do not survive

long enough to benefit from the full implementation of an MTP.

We identified 3 previous pooled analyses of the effect of an MTP on trauma patient mortality (2 full papers[6,32], and one published abstract[33]). The pooled OR from the 2 full papers ranged from 0.69 to 0.73 but only one showed a statistically significant mortality reduction. The abstract reported non-significantly improved odds of survival following the introduction of an MTP with a pooled OR of 1.33. The results from the present study show a statistically significant reduction in mortality, with a pooled OR of 0.71, and it also included considerably more studies and patients. There is no significant difference in pooled results between the 3 full analyses, and all reported reduced mortality with the implementation of an MTP for trauma patients. All the 3 analyses are affected by moderate heterogeneity between the included studies, and the possibility of publication and survival bias cannot be overstated.

Any centre that treats trauma patients of a sufficient number and severity should have an MTP in place. Whether the survival benefit is due to the MTP itself or due to the attendant or accompanying changes that come with an MTP, the findings of this analysis cannot be ignored. The increase in implementation of an MTP for trauma patients is shown to have a clinically and statistically significant survival benefit for this target population. Future research must focus on elucidating which specific element(s) provide the most benefit for bleeding trauma patients.

This report of significant intra-study variation in the evaluation and reporting of methods and results of studies on the effect of MTPs represent an obstacle to the next step. The potential to conduct these deeper analyses will be greatly enhanced if academic trauma centres and scientific journals are able to arrive at a consensus towards which outcomes should be consistently evaluated and identify specific target trauma populations.

Arriving at a consensus and achieving greater homogeneity in the inclusion criteria, protocol reporting, study populations and outcomes (24-hour mortality, haemorrhagic shock) will help future researchers to conduct more in-depth analyses and identify specific components of the MTP that contribute to survival and/or identify specific patient populations that will benefit most from the implementation of an MTP. The authors provide an example of "standard" indicators and characteristics of an MTP as a starting point for discussion and consensus (**Appendix A**).

Only one study reported haemorrhagic death rates (33-88% depending on the grade of liver injury[28]), and this is an oversight that must be addressed globally. Failing to record, report and evaluate this primary outcome that MTPs are supposed to directly impact suggests the lack of a collective understanding of the pathophysiology of the coagulopathy of trauma and the reasons for MTP implementation; this is essential for initial management of bleeding trauma patients. In a similar vein, acknowledging that paediatric and adult trauma patients do not share many common characteristics and, as such, analyses of impacts on these populations should be carried out separately utilising a globally accepted definition of "child", i.e. ≤19 years, is another necessary step forward. The recent study from Schauer *et al.* is an example of the importance of this distinction[34].

The authors strongly encourage all who conduct clinical research in this field to become conversant, if not deeply fluent, in the methodology and reporting of the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Study Group. The PROPPR trial was the first multicentre randomised trial using approved blood products to compare 2 transfusion ratios with mortality as the primary end point[35]. This landmark paper demonstrated that a massive transfusion strategy targeting a balanced delivery of plasma-platelet-RBC in a ratio of 1: 1: 1 results in improved survival of patients with severe trauma at 3 hours and a reduction in deaths due to exsanguination in the first 24 hours compared to a 1: 1: 2 ratio. It should be used as a template on how to completely define the study population, measure clinically pertinent clinical outcomes, and fully describe each step and element of an MTP.

The PROPPR trial also showed that, from admission, the median time to haemorrhagic death was 2.4 hours (IQR: 1.2-4.0) and the median time to haemostasis was 2.3 hours (IQR: 1.6-3.6). This prompted a further statement on behalf of the PROPPR Study Group that "Primary endpoints should be congruent with the timing of the disease process. Therefore, if a resuscitation/haemorrhage control intervention is under study, a primary end point of all-cause mortality evaluated within the first 6 hours is

appropriate"[36].

Limitations

This meta-analysis and systematic review is limited by the inherent characteristics of MTPs, i.e. lack of equipoise, emergency consent, etc., that render them intractable to testing or evaluation through prospective randomised clinical trials. Likewise, the heterogeneity of trauma patient populations, centre-specificity of MTPs, and lack of "standard" reporting and measurement of outcomes all constrain the ability of researchers to conduct more optimal analysis of MTPs and their clinical effect.

CONCLUSIONS

The implementation of an MTP is shown to provide a statistically and clinically significant reduction in the overall mortality of trauma patients. We recommend that all centres that provide care for severely injured bleeding patients must have an MTP in place. All future studies that evaluate the effect of MTP on trauma patients should have clear and globally consistent definitions of their protocols, study populations, and outcomes.

AUTHORSHIP CONTRIBUTIONS

RC conceptualised the study, and led the analysis and discussion of the results of the analyses. AE, BS and RC reviewed and selected the studies included in the final analysis. AEl-M and BS provided methodological and statistical oversight. All authors made significant contributions to the Discussion section and the content of the final manuscript.

The Authors declare no conflicts of interest.

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APPENDIX A

Recommended minimal data set for reporting the effect of an MTP on bleeding trauma patients	
Indicator/data element	Recommended Indicator/data element
Mortality	4 hour mortality
	24 hour mortality
	30 day mortality
	Mortality associated with blunt and penetrating injuries
Cause of death	Hemorrhagic
	Non-Hemorrhagic
Study population	Adults >19 years
	Children ≤19 years
	Civilian
	Military
Patient characteristics	Associated major organs injured
	Recipient of MT
	ISS score [severity adjustment]
Indications	Scoring system used to trigger MTP use
Protocol elements/ components ratios	PLt: pRBC during first 24-hrs (intended and attained) FFP: pRBC during first 24-hrs (intended and attained)
	Adjuvant use: rFVIIa TXA PCC

MTP: massive transfusion protocol; ISS: injury severity score; PLT: platelet unit; pRBC: packed red blood cell unit; Hrs: hours; FFP: fresh frozen plasma unit; rFVIIa: recombinant factor seven; TXA: tranexamic acid; PCC: prothrombin complex concentrate.