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Effect of early use of noradrenaline on in-hospital mortality in haemorrhagic shock after major trauma: a propensity-score analysis

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Abstract

Background: The role of vasopressors in trauma-related haemorrhagic shock (HS) remains a matter of debate. They are part of the most recent European recommendations on the management of HS and are regularly used in France. We assessed the effect of early administration of noradrenaline in 24 h mortality of trauma patients in HS, using a propensity-score analysis.

Methods: The study included patients from a multicentre prospective regional trauma registry. HS was defined as transfusion of ≥4 erythrocyte-concentrate units during the first 6 h. Patients with a Glasgow coma scale=3 and pre-hospital traumatic cardiac arrest were excluded. The main outcome measure was in-hospital mortality. The explicative and adjustment variables for the outcome and treatment allocation were predetermined by a Delphi method. The in-hospital mortality of patients with and without early administration of noradrenaline was compared in a propensity-score model, including all predetermined variables.

Results: Of 7141 patients in the registry in the study period, 6353 were screened and 518 patients in HS (201 with early noradrenaline use and 317 without) were included and analysed. After propensity-score matching, 100 patients remained in each group, and the hazard-ratio mortality was 0.95 (95% confidence interval: 0.45–2.01; *P*=0.69).

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Conclusions: The results of the present study suggest that noradrenaline use in the early phase of traumatic HS does not seem to affect mortality adversely. This observation supports a rationale for equipoise in favour of a prospective trial of the use of vasopressors in HS after trauma.

Keywords: noradrenaline; propensity score; shock; trauma

Editor's key points

- Data on the use of vasopressors in the management of haemorrhagic shock are conflicting and opinions are divided.
- This retrospective study of a large multicentre database analysed the effect of early administration of noradrenaline on outcome in trauma-related haemorrhagic shock.
- The propensity-score-matching analysis showed no effect of early noradrenaline use on in-hospital mortality.
- Randomised prospective data are required to confirm these findings.

The most recent update of the European recommendations on the management of haemorrhagic shock (HS) suggests the use of vasopressors, noradrenaline in particular, when fluid expansion fails to maintain the target arterial blood pressure.[1] However, the usefulness of vasopressors in the management of trauma-related HS remains a matter of debate.[2]

From a pathophysiological standpoint, opponents highlight increased oxygen consumption, increased cardiac afterload, and a potentially detrimental effect on regional perfusion[3,4] as arguments against vasopressor therapy. Proponents point out that vasopressors mimic the initial response to blood loss; improve venous return, coronary perfusion, and myocardial contractility[5]; and compensate for sedation-induced vasodilation and uncontrolled vasoplegia after exhaustion of physiological response mechanisms.[6]

Generally, vasopressors are considered to have a negative impact on patient outcome in the management of HS, and the predominant strategy is based on permissive hypotension and low-volume resuscitation.[7] We lack a high level of evidence studies on vasopressor use in HS in humans. Observational retrospective studies in humans indicate a higher mortality with the use of catecholamines in traumatic shock.[8–10]

More recent experimental and animal data suggest a beneficial influence of vasopressor use in association to a balanced low-volume resuscitation to restore perfusion[11,12] and preserve intestinal perfusion.[13,14] One small prospective randomised human trial indicates a survival benefit.[15]

This conflicting body of evidence justified exploring the association of noradrenaline administration with mortality in HS in trauma patients using a large multicentre observational registry. Our hypothesis was that early pre-hospital administration of noradrenaline in HS is not associated with an increased mortality. As treatment allocation was not controlled because of the observational nature of the data, we used propensity score (PS) to estimate the potential causal effect.

Methods

This is an observational study using a prospective multicentre trauma registry, the TraumaBase©. The TraumaBase obtained approval from the Institutional Review Board (Pr Laurent Capelle, Paris Cedex 13, France) (Comité de Protection des Personnes, Paris VI), from the Advisory Committee on Information Processing in Health Research (CCTIRS, 11.305bis), and from the National Commission on Informatics and Liberties (CNIL, 911461). The structure of the database integrates algorithms for consistency and coherence. A central administrator assures the data monitoring.

Between January 2010 and December 2015, all consecutive trauma patients triaged to one of the six regional, designated Level 1, trauma centres in Paris (Beaujon, Bicêtre, Pitié-Salpétrière, Henri-Mondor, Hôpital Européen Georges Pompidou, and Hôpital d'Instruction des Armées Percy) were screened for inclusion. A detailed description of the French Emergency Medical Services (EMS) and trauma system in Paris has been provided elsewhere.[16] At any time, clinical management was left to the discretion of the responsible physician (pre- or in-hospital) according to existing guidelines.[1] Pre- or intra-hospital vasopressor use in the Paris EMS system is almost exclusively equivalent to the continuous i.v. administration of noradrenaline. Noradrenaline was only to be used after a fluid challenge of around 1000–1500 ml of crystalloid (normal saline or Ringer's lactate, exceptionally colloids) had failed to restore the target arterial pressure according to the type of injury (blunt *vs* penetrating) according to a national guideline.[17] Pre-hospital use of noradrenaline was considered as the treatment regimen. Pre-hospital arterial pressure (systolic and diastolic) was recorded twice; the first measurement on the arrival of the enhanced care team on the scene, and then the lowest systolic and diastolic arterial-pressure readings, both before noradrenaline administration.

All trauma patients with HS were included. HS was defined in the registry as transfusion of more than four erythrocyte concentrates in the first 6 h of admission.[18,19] This definition of HS was chosen because transfusion requirements in the first 6 h seem better correlated with mortality than transfusion of at least three packed red blood cells (RBCs) in 1 h[20] or five packed RBC in 4 h.[21] Patients with a Glasgow coma scale (GCS) score of 3 or with pre-hospital cardiac arrest and younger than 16 yr were excluded.

Supplementary Table S1 provides the complete list of clinical, physiological [trauma mechanism, haemodynamic status, GCS, and peripheral oxygen saturation (SpO_2)], and biological variables (lactate, haemoglobin, and variation between pre- and in-hospital haemoglobin measurements) that were recorded for each patient. Calculation of the following scores completed this information: simplified acute physiology score II[22] and the sequential organ failure assessment[23] after 24 h. Trauma injury assessment was performed with the calculation of the injury severity score (ISS).[24]

Statistical analysis

Data are expressed as median and quartiles (1; 3) for continuous variables, and numbers and percentages for nominal variables. The main outcome measure was in-hospital all-cause mortality. Actuarial survival was plotted using the Kaplan–Meier estimator. Given the observational nature of the data, treatment allocation was not randomly allocated in the study population. The risk of allocation bias caused by the presence of confounders was handled using PS matching.[25] Using PS matching, the causal effect of the exposure on the outcome could be more precisely estimated assuming a set of identifiable and causal assumptions. The PS was estimated from the observed data using a logistic-regression model, including a set of variables selected among available baseline variables based on an expert committee of 10 French critical care physicians with extensive experience in trauma that identified using the Delphi method[26] the variables both associated with treatment allocation and the outcome. The selection process is illustrated in the Supplementary Table S2.

Each patient treated with noradrenaline was matched to one untreated control with similar PS using the nearest-neighbour approach, with no replacement and a caliper size of 0.15. In this approach, each treated subject was matched to the nearest untreated subject within a specified maximum difference in the PS between two matched subjects (so-called caliper).[25] Covariate balance between the two groups before and after PS matching was assessed using the mean standardised differences (MSDs). An absolute MSD <10% was considered to support the assumption of balance between the groups.[27] A Cox proportional hazards regression model was then used to estimate the average treatment effect among the treated [i.e. the causal impact of the treatment regimen (pre-hospital noradrenaline administration)] on the main outcome measure in the PS-matched population. The estimate was expressed as a Hazard Ratio together with its 95% confidence interval (CI). All *P*-values were two-tailed, and $P<0.05$ was considered significant.

All statistical analyses were performed using R statistical software with the statistical package MatchIt for the matching process (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the 5 yr study period, 7141 patients were included in the registry, of these 788 were excluded according to the predefined criteria, as described in the flow chart (Fig 1); 6353 were screened for inclusion and 518 corresponded to the chosen definition of HS (≥4 RBC in the first 6 h). Table 1 provides the baseline data for both groups. Figure 2 illustrates the MSD diagram of all explicative and adjustment variables.

All 518 patients in HS were included and analysed. Of these, 201 had received and 317 did not receive noradrenaline. The differences in patient baseline characteristics between these two groups of patients before and after PS matching are depicted in Table 2. In the original sample, the patients who

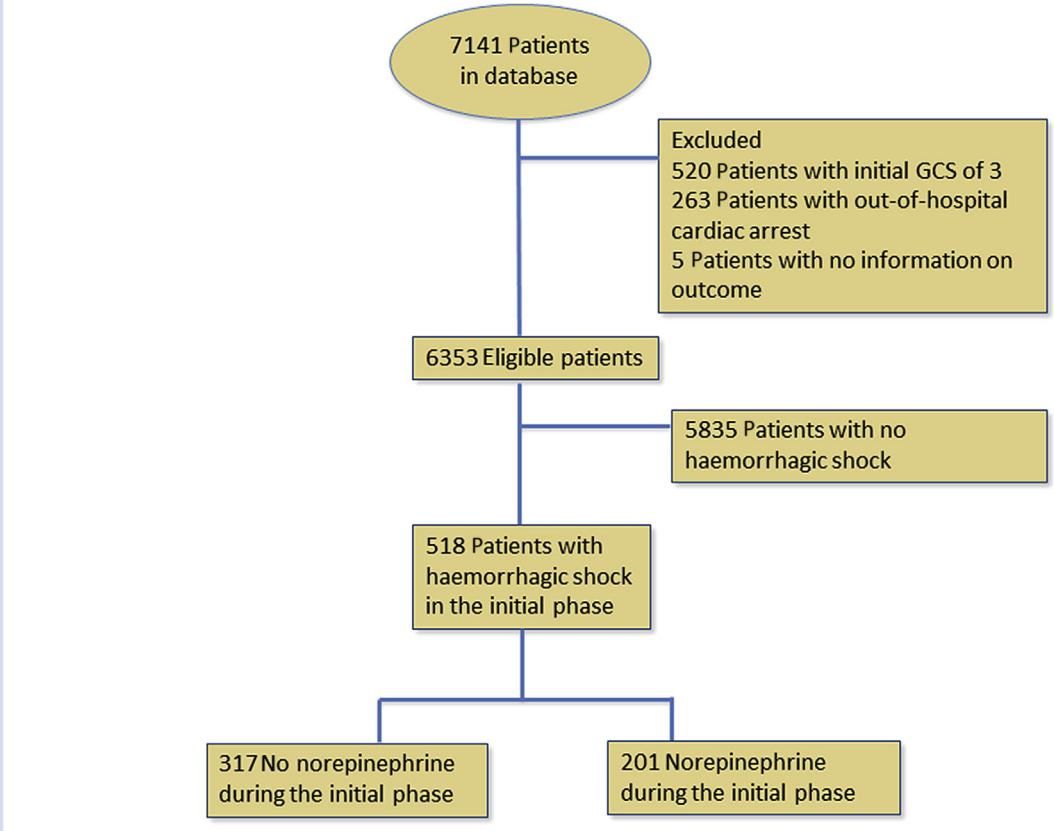

Fig 1. Flow chart of the study. GCS, Glasgow coma scale.

Table 1 Patient characteristics. Data are expressed as median (quartile 1; quartile 3) and *n* (%). AIS, abbreviated injury scale; GCS, Glasgow coma scale score; Hb, haemoglobin; HR, heart rate; ISS, injury severity score; MSD, mean standardised difference; SAPS II, simplified acute physiology score; SBP, systolic arterial blood pressure

	All patients (*n*=518)
Age (yr)	37 (25; 54)
Women	161 (31)
Blunt trauma	447 (86)
Penetrating trauma	71 (14)
Pre-hospital status	
Pre-hospital SBP (mm Hg)	87 (72; 103)
Pre-hospital SBP <85 mm Hg	236 (47)
Pre-hospital HR (beats min^{-1})	114 (95; 130)
Pre-hospital fluid expansion (ml)	1500 (1000; 2000)
Pre-hospital intubation	273 (53)
Initial pre-hospital GCS	15 (11; 15)
Pre-hospital capillary Hb (g dl^{-1})	13 (11.4; 14)
On-admission status	
On-admission SBP <85 mm Hg	179 (35)
On-admission HR (beats min^{-1})	105 (86; 124)
On-admission capillary Hb (g dl^{-1})	10 (8; 11.6)
Variation in capillary Hb (g dl^{-1})	−2.6 (−4; −1)
On-admission lactates (mmol $litre^{-1}$)	3.9 (2.3; 6.3)
Severity scores	
AIS head >3	82 (16)
SAPS II	42 (33; 57)
SOFA score at 24 h	9 (6; 11)
ISS	29 (18; 41)

received noradrenaline presented with more severe circulatory insufficiency compromise and required more aggressive therapies compared with patients who did not. Patients with noradrenaline administration also received more i.v. fluids, suggesting the administration of noradrenaline after failure of fluid expansion to achieve a targeted perfusion pressure. Table 2 suggests that the administration of noradrenaline did not induce an excessive correction of systolic arterial blood pressure. Systolic arterial blood pressure remained beneath 85 mm Hg in 40% of patients in both groups. A total of 200 patients (100 in each group) were included in the PS-matched population. After PS matching, all major differences were appropriately balanced between groups (Table 2). Supplementary Table S1 provides details about the difference between the patient who could and those who could not be matched on the PS.

Before PS matching, noradrenaline administration was associated with an increased mortality [Hazard Ratio =2.16 (95% CI: 1.45–3.23); $P<0.001$]. After PS matching, the Hazard Ratio for in-hospital mortality was 0.95 (95% CI: 0.45–2.01; $P=0.69$). Figure 3 displays the survival curve before and after PS matching, and shows no significant difference between the groups in the PS-matched population.

Discussion

This study is, to our knowledge, the first to indicate in a large clinical cohort that noradrenaline use in the initial phase of traumatic HS is not associated with an increased mortality. After adjustment for treatment allocation and clinical factors, no significant mortality difference could be observed in

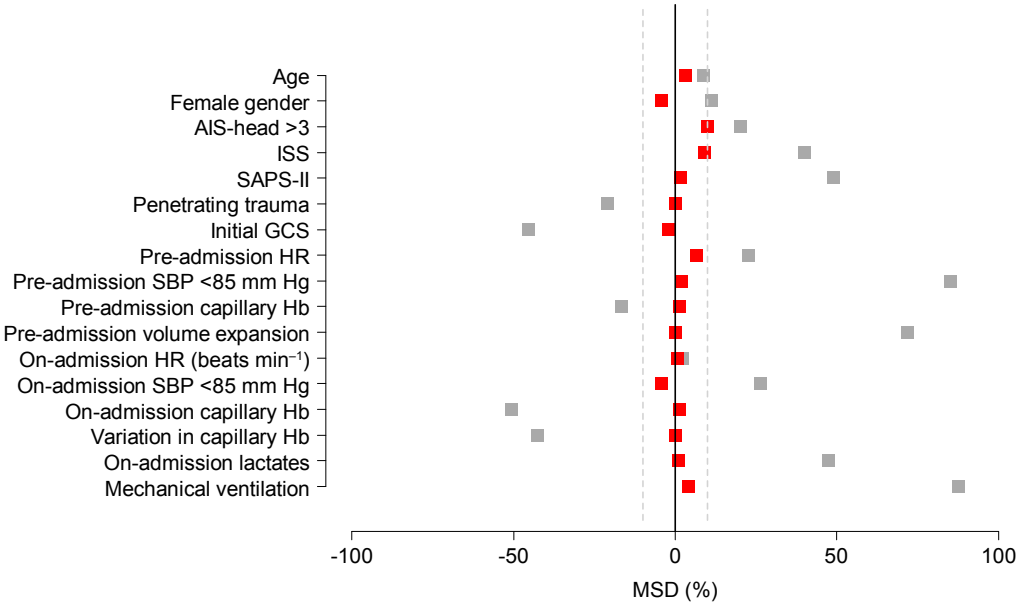

Fig 2. Imbalance in patient characteristics before and after propensity score (PS) matching. Grey squares represent imbalance before PS matching and red squares represent imbalance after PS matching. AIS, abbreviated injury scale; GCS, Glasgow coma scale; Hb, haemoglobin; HR, heart rate; ISS, injury severity score; MSD, mean standardised difference; SAPS II, simplified acute physiology score; SBP, systolic blood pressure.

Table 2 Imbalance in patients' characteristics before and after PS matching. Results are expressed as median with inter-quartile range and *n* (%). AIS, abbreviated injury severity; GCS, Glasgow coma scale score; Hb, haemoglobin; HR, heart rate; ISS, injury severity score; PS, propensity score; SAPS, simplified acute physiology score; SBP, systolic blood pressure; SOFA, sequential organ failure assessment. *Variation in capillary haemoglobin concentration is the difference between pre-hospital and admission capillary haemoglobin concentrations

	Before PS matching			After PS matching		
	No noradrenaline (*n*=317)	Noradrenaline (*n*=201)	MSD	No vasopressor (*n*=100)	Vasopressor (*n*=100)	MSD
Age (yr)	36 (25; 53)	38 (26; 57)	8.9	36.5 (26.8; 54)	39 (25; 55)	3.3
Women	92 (29)	69 (34)	11.2	35 (35)	33 (33)	−4.2
Penetrating trauma	52 (17)	19 (10)	−20.9	11 (11)	11 (11)	0
Pre-hospital status						
Pre-hospital SBP <85 mm Hg	97 (32)	139 (71)	85.4	53 (53)	54 (54)	2
Pre-hospital HR (beats min^{-1})	110 (92; 128)	120 (100; 130)	22.6	118 (99; 130)	120 (98; 134)	6.7
Pre-hospital fluid expansion (ml)	1000 (700; 1500)	1500 (1225; 2500)	71.8	1500 (1000; 2000)	1500 (1000; 2000)	0.1
Pre-hospital intubation	118 (37)	155 (77)	87.6	66 (66)	68 (68)	4.2
Initial GCS	15 (13; 15)	14 (8; 15)	−45.4	14 (10; 15)	14 (9.8; 15)	−2.2
Pre-hospital capillary Hb (g dl^{-1})	13 (11.7; 14)	12.8 (11; 14)	−16.7	12.1 (11; 14)	12.8 (11; 14)	1.4
On-admission status						
Admission SBP <85 mm Hg	94 (30)	85 (42)	26.3	37 (37)	35 (35)	−4.1
Admission HR (beats min^{-1})	103 (86; 122)	110 (87; 129)	2.3	109 (94; 124)	111 (88; 130)	0.6
Admission capillary Hb (g dl^{-1})	10 (9; 12)	9 (7.8; 10.9)	−50.9	9.2 (8.5; 10.7)	10 (8; 11)	1.4
Variation in capillary Hb (g dl^{-1})*	−2 (−4; −1)	−3.5 (−5; −2)	−42.5	−3 (−4; −1.8)	−3 (−4.7; −1.6)	0
Admission lactates (mmol $litre^{-1}$)	3.2 (2.1; 5.1)	4.9 (3.2; 7.9)	47.3	3.8 (2.2; 5.9)	4.2 (2.6; 6.1)	0.9
Severity scores						
AIS head >3	41 (13)	41 (20)	20.1	18 (18)	22 (22)	10
SAPS II	40 (31; 52)	49 (38; 63)	49	43.5 (34; 58.2)	44.5 (35.8; 56.2)	1.7
ISS	27 (17; 38)	34 (24; 45)	40	31.5 (22; 41)	34 (21.8; 43)	9.1

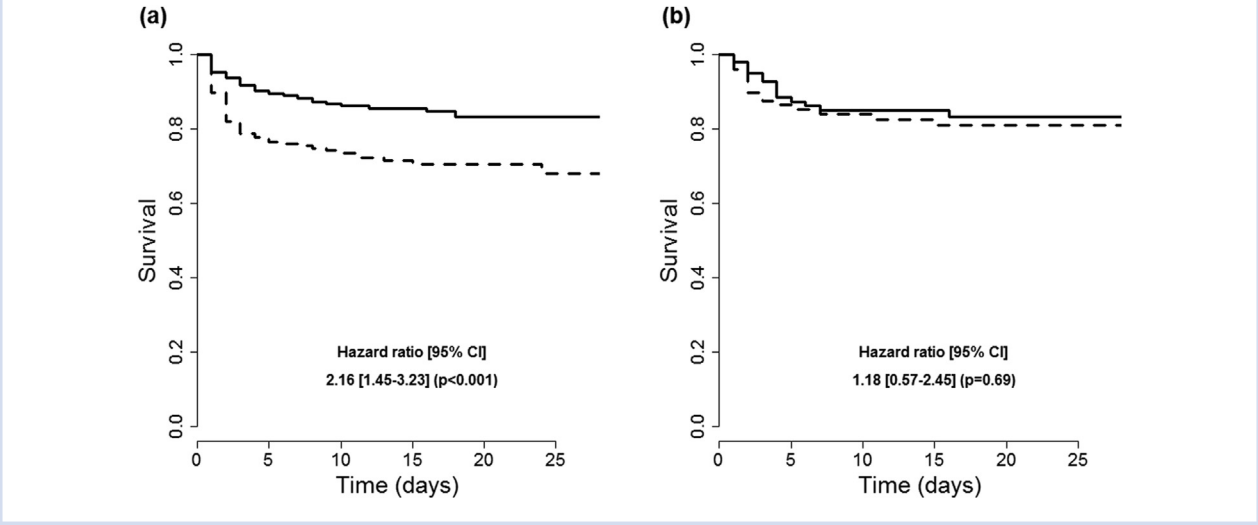

Fig 3. Kaplan–Meier survival curves: bold line (—), without noradrenaline; dashed line (—), with noradrenaline; *n*=100 in each group. (a) Survival of both groups before propensity score (PS) matching, whilst (b) represents the difference in survival between the two groups after PS matching. CI, confidence interval.

patients with pre-hospital noradrenaline administration *vs* those without.

The rationale in favour of noradrenaline use in HS is actually stronger than conventionally conceived. Initial experimental studies administered noradrenaline or other vasopressors without concurrent fluid expansion,[3,28,29] a strategy in contrast to clinical practice. In models that administered vasopressors or noradrenaline sequentially or concurrently to fluids, this strategy appeared to be beneficial, including increased survival.[11,12,30,31] One explanation of the beneficial influence of noradrenaline in these models is to consider it as the effector of a complex neurohormonal response that supports and mimics the overburdened physiological adaptation to shock.[6] It is, however, beyond the scope

of this work to discuss extensively the physiopathology and pharmacology of noradrenaline in HS.

The combination of judicious fluid expansion followed by early noradrenaline administration corresponds to the use of noradrenaline in the present study. Trauma patients received noradrenaline support only after a significant amount of fluid expansion had failed to restore the desired perfusion-pressure level. A strategy associating limited fluid expansion with low-dose noradrenaline administration may stand in contrast to the dominating dogma and invite conceptual critique. The strategy remains, however, in accordance with the current European guidelines.

Data on vasopressor or noradrenaline use in traumatic HS in humans are not abundant. The results presented in this study stand in contrast with two retrospective studies that suggest a higher mortality after vasopressor and inotrope use during the initial care of trauma patients in shock.[8,9] This contrast can be explained. First, in the preceding studies, different types of vasopressor and inotropes were administered. Second, the studies concerned the first 24 h with a wide range of timings from early in resuscitation to very late in organ failure or systemic inflammatory reaction syndrome, and none were administered in the pre-hospital phase. Third, the studies report a wide range of indications for vasoactive agent initiation. Fourth, in the preceding studies, the resuscitation strategies, such as amount of fluid expansion, haemorrhage controls, and indication for vasopressor use, were heterogeneous. Finally, the aforementioned studies excluded patients who did not survive the first 24 h, which may generate a survival bias. In contrast, the present study focused on one type of vasopressor (i.e. noradrenaline) and on administration in the initial resuscitation phase. The study included patients who did not survive the first 24 h, as they are a potential target group for a beneficial impact of early noradrenaline administration and to reduce survival bias. As shown, and as expected, patients that received noradrenaline had lower initial arterial blood pressures, received more fluids, had higher ISS and abbreviated-injury-scale head scores, and were more often mechanically ventilated. The advantage of the present study is to adjust for the influence of these factors and to attempt control of treatment allocation using PS matching. After adjustment, the results suggest that the cumulative effect of these factors accounts for the differences in mortality observed in preceding studies and not the noradrenaline treatment itself. Blood lactate concentrations were higher on admission in patients on noradrenaline. This can reflect shock severity,[32] but also noradrenaline-induced Na^+/K^+ ATPase pump activation. However, the effect of noradrenaline on blood lactate levels is far less pronounced than the effect of adrenaline.[6] The observed difference can thus be attributed to shock severity and to a lesser extent to noradrenaline administration.

To our knowledge, there is only one prospective, randomised trial of early infusion of low-dose vasopressin (2.4 IU h^{-1} for 5 h on arrival at the emergency department) *vs* placebo in trauma patients. It showed a significantly lower requirement of total fluids at 24 h. The study was underpowered to show a significant difference in mortality in favour of the vasopressin group; mortality at 5 days was reduced by 12%.[33] Data from the European Vasopressin for therapy of persistent traumatic hemorrhagic shock (VITRIS) trial studying the use of vasopressin in traumatic shock are not yet available. However, the physiological effects of vasopressin and noradrenaline are not totally identical; to attempt an analogy may, therefore, be misleading.

The study is characterised by limitations inherent to its observational design. The use of a well-structured PS allowed control for some of the intrinsic limitations and sources of bias. However, these results apply only to the patients in each group that were similar enough in terms of the propensity to receive noradrenaline. We cannot exclude a potential impact of noradrenaline administration in patients that were discarded by the matching procedure. Hence, as Supplementary Table S1 suggests, matched patients were more acutely ill than those not matched. The causal relationship between noradrenaline administration and the outcome relies on the assumption of absence of unmeasured confounding. This assumption is untestable from the observed data; therefore, we cannot firmly rule out a certain degree of bias related to unmeasured confounding. Finally, the necessary matching also reduced the power of the study. The definition of HS may appear arbitrary. However, there is currently no consensus definition of HS, as again demonstrated by two recent major trials.[34,35] The definition used in this work has already been applied in the literature,[18,19] and correlates well with mortality and is less selective than the more frequently used definition of >10 RBC in the first 24 h.

The database contains only two data points for the pre-hospital arterial pressure: the first one, pre-hospital systolic pressure, and the worst, pre-hospital recorded systolic arterial pressure, and it is therefore impossible to provide more detailed data about the arterial pressure or a response to treatment. The database also does not contain information on the amount of pre-hospital administered noradrenaline.

Most included patients were in shock from blunt trauma; the findings might not apply to penetrating trauma or paediatric patients. The study was performed in a specific system: the physician-staffed EMS in the region of Paris. This system has a specific structure and standardised operational procedures, and makes the extensive use of noradrenaline in early management of HS. Some of these aspects may be difficult to transpose to a non-physician-staffed EMS or with differing protocols, and thus limit external validity. Several other European countries also operate physician-staffed EMS (Germany, Austria, Scandinavia, Belgium, Hungary, and parts of the UK) and use vasopressors.[36] External validity inside physician-staffed EMS is strengthened by the fact that patients were recruited from a large cohort constituted by patients from all EMS of several administrative departments and trauma centres in a densely populated region. Finally, the choice of variables to explain the outcome and to adjust for noradrenaline treatment attribution may appear arbitrary, but was based on expert consultation to make them as consensual and rational as possible.

Based on observational data with a more robust control of confounding bias than previous studies,[37] the results of the present study suggest that noradrenaline administration in the early phase of traumatic HS is not associated with an increased in-hospital mortality rate. This observation contributes to the growing evidence that supports a rationale for equipoise in favour of a prospective clinical trial of the administration of noradrenaline in trauma-related HS.

Authors' contributions

Study concept: T.G., S.H.
Study design: T.G., E.G., S.H.
Data acquisition: T.G., E.G., A.H., A.F., J.-L.D., S.H.
Data analysis: T.G., S.H.
Statistical analysis: E.G.

Data interpretation: T.G., E.G., A.H., S.H.
Drafting of manuscript: all authors.
Important intellectual content: T.G., E.G., A.H., F.C., S.H.

Declaration of interest

None of the authors has any conflict of interest to declare.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.02.032.

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