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Prostacyclin in trauma patients with hemorrhagic shock: A randomized clinical trial

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BACKGROUND: A main cause of trauma morbidity and mortality is multiple-organ failure, and endotheliopathy has been implicated. Pilot studies indicate that low-dose prostacyclin improves endothelial functionality in critically ill patients, suggesting that this intervention may improve trauma patient outcome.

METHODS: We conducted a multicenter, randomized, blinded, clinical investigator-initiated trial in 229 trauma patients with hemorrhagic shock who were randomized 1:1 to 72 hours infusion of the prostacyclin analog iloprost (1 ng/kg/min) or placebo. The primary outcome was the number of intensive care unit (ICU)–free days alive within 28 days of admission. Secondary outcomes included 28-day all-cause mortality and hospital length of stay.

RESULTS: The mean number of ICU-free days alive within 28 days was 15.64 days in the iloprost group versus 13.99 days in the placebo group (adjusted mean difference, −1.63 days [95% confidence interval (CI), −4.64 to 1.38 days]; $p = 0.28$). The 28-day mortality was 18.8% in the iloprost group versus 19.6% in the placebo group (odds ratio, 1.01 [95% CI, 0.51–2.0]; $p = 0.97$). The mean hospital length of stay was 19.96 days in the iloprost group versus 27.32 days in the placebo group (adjusted mean difference, 7.84 days [95% CI, 1.66–14.02 days], $p = 0.01$).

CONCLUSION: Iloprost did not result in a statistically significant increase in the number of ICU-free days alive within 28 days of admission, whereas it was safe and a statistically significant reduction in hospital length of stay was observed. Further research on prostacyclin in shocked trauma patients is warranted. (*J Trauma Acute Care Surg.* 2024;96: 476–481. Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Association for the Surgery of Trauma.)

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Traumatic injury is the fourth leading cause of death globally and the leading cause of death in patients younger than 45 years.[1] The main causes of death in trauma patients are exsanguination and multiple-organ failure including traumatic brain injury.[2]

Endothelial dysfunction and damage have been independently associated with development of multiple-organ failure and mortality in trauma patients, and furthermore, sympathetic activation has been reported to be independently associated with both endothelial dysfunction and mortality.[3–6] This pathophysiology has also been identified in patients suffering from other types of shock such as sepsis, myocardial infarction, and out-of-hospital cardiac arrest and is entitled shock-induced endotheliopathy.[7]

Prostacyclin (PGI_2) is an endogenous prostanoid formed and released by endothelial cells with paracrine function including dose-dependent vasodilation and platelet inhibition being the rationale for its use as a pharmacological therapy for patients with primary pulmonary hypertension and critical limb ischemia.[8,9] In the new millennium, multiple beneficial effects of prostacyclin on the endothelium were reported.[10–16] In clinical trials in critically ill patients in the intensive care unit (ICU), the use of low-dose (0.5–2.0 ng/kg/min) continuous infusion of prostacyclin as compared with placebo was safe.[17–20]

The aim of the present randomized controlled trial was, therefore, to investigate the safety and the efficacy of 72 hours infusion of the synthetic prostacyclin analog iloprost at a dose

of 1 ng/kg/min as compared with placebo on the number of ICU-free days alive within 28 days of admission in trauma patients with clinical signs of hemorrhagic shock.[21]

PATIENTS AND METHODS

Study Design and Patients

This is a Scandinavian multicenter, randomized, placebo-controlled, blinded, investigator initiated pilot trial of low-dose continuous infusion of iloprost versus placebo for 72 hours in trauma patients with clinical signs of hemorrhagic shock. The study was conducted at Copenhagen University Hospital—Rigshospitalet, Odense University Hospital, Odense and Skejby University Hospital, Aarhus, all in Denmark, and at Oslo University Hospital in Norway following CONSORT guidelines (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/D354).[22]

Inclusion criteria were adult (18 years or older) patients presenting with clinical signs of hemorrhagic shock (defined by systolic blood pressure of <90 mm Hg or prehospital blood transfusion), activation of the local massive transfusion protocol and initiation of the first transfusion after admission, randomization within 5 hours of injury and 3 hours of admission to the emergency department of the participating trial site, and consent provided on behalf of incapacitated patients by a scientific guardian.

Exclusion criteria were withdrawal from active therapy, known hypersensitivity to iloprost, pregnancy (nonpregnancy confirmed in female patients by a negative urine or blood pregnancy test or age ≥60 years), known severe heart failure (New York Heart Association class IV), suspected acute coronary syndrome, and estimated weight of <40 kg.

Sample Size and Power

The power calculation was based on data from patients admitted to Copenhagen University Hospital—Rigshospitalet that were included in the iTACTIC (Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy) trial (NTC 02593877) having the same inclusion and exclusion criteria as the present trial.[21,23] A clinically relevant increase in the primary endpoint from 15 days to 19.5 days equaling 30% with $\alpha = 0.05$ and power of 0.85 required 107 patients in each 1:1 randomization group. The study was stopped when 110 patients had started the intervention in both groups.

Randomization and Masking

The randomization sequence was done in permuted blocks of variable sizes stratified per trial site using centralized, concealed allocation. The randomization sequence was generated 1:1 (active/placebo) using the online randomization software Sealed Envelope (https://www.sealedenvelope.com/). Once generated, the randomization sequence was formatted and uploaded into the electronic research database REDCap (http://projectredcap.org/) to facilitate centralized, web-based allocation according to local written instruction. The randomization sequence was printed and signed by two independent individuals and stored in a sealed envelope in the sponsor's trial master file.

The patient randomization at each site was conducted in REDCap, where each patient was given a unique study ID number. The randomization sequence was concealed from all clinicians, patients, investigators, and statisticians and first shown in REDCap after completion of all trial-related procedures, and statistical analyses were finalized.

To circumvent selection bias, researchers and health care personnel were blinded to the treatment assignment. Furthermore, to avoid investigator, health care staff, and patient performance and detection bias, patients were randomized to receive either iloprost or placebo similar in color, consistency, and volume. Blinded study and nonstudy personnel recorded clinical data and analyzed blood samples. All randomized patients continued to be included in the assessments of safety and efficacy. Also, all analyses of the endpoints were performed by blinded personnel.

Outcomes

The primary outcome was the number of ICU-free days alive within 28 days of admission (where death during the ICU stay gave the score of 0). Secondary outcomes included 28- and 90-day all-cause mortality, hospital length of stay, vasopressor-free days within 28 days, ventilator-free days within 28 days, renal replacement-free days within 28 days, and number of serious adverse reaction (SAR) and serious adverse event (SAE) (defined as ischemic events including intestinal or limb ischemia, myocardial infarction [ST elevation myocardial infarction], or cerebral ischemia [verified by computed tomography] within the first 4 days of admission [SAEs that were neither SAR, ischemic events, nor endpoints were not recorded]).

Treatment

Iloprost (Ilomedin; Bayer AG, Leverkusen, Germany) at a dose of 1 ng/kg/min or placebo (equal volume of saline) was administered as a continuous intravenous infusion for 72 hours.

Procedures

All patients were assessed from randomization (day 1) through day 90. Adverse events were recorded from time of signature of informed consent and graded according to the Common Terminology Criteria for Adverse Events, version 5.0. Causality[24] was assessed by the investigators for SAEs.

Statistical Analysis

The primary outcome was analyzed using linear regression adjusted for site. Effect size was summarized using adjusted mean differences with confidence intervals (CIs) based on robust standard errors because residuals were not expected to be normally distributed. The same analysis was used to continuous secondary outcomes. Binary outcomes were analyzed with logistic regression, and effects were reported as logistics regressions. G-computation–based conversions of effect measures to risk ratios and risk differences were conducted. All analyses were conducted following the intention to treat (ITT) principle (the primary analysis), and a per-protocol analysis was conducted for the primary endpoint. Analyses were conducted in the ITT population unless explicitly written otherwise. In all analyses, the iloprost group is the reference group. All CIs are 95% intervals.

Ethics

The protocol was approved by the National Ethics Committee (H-19014482), the National Data Protection Agency, and the National Medicines Agency. The study was registered

at ClinicalTrials.gov. The study was conducted at North European trauma centers in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent, in accordance with national legislation, was obtained from the patient's surrogate and confirmed by the patients who regained consciousness.

RESULTS

Study Participants

Between May 24, 2019, and August 14, 2021, 576 patients were screened and 242 were randomized, among whom 123 were allocated to iloprost and 119 to placebo (Fig. 1). A total of 119 patients in the iloprost group and 110 patients in the placebo group started the intervention and were included in the ITT analysis. Patient characteristics are presented in Table 1. Most patients (79%) were male suffering severe trauma (median ISS, 24) predominantly from blunt trauma (71%). They had syndecan-1 level indicative of severe endotheliopathy of the glycocalyx at admission to the hospital. They required a median of 4 U of red blood cells, 6 U of plasma, and 2 U of platelets in the first 24 hours from hospital admission.

Primary Outcome

In the ITT population, the mean number of ICU-free days alive within 28 days of admission was 15.64 days versus 13.99 days (adjusted mean difference, −1.63 days [95% CI, −4.64 to 1.38 days]; $p = 0.28$) in the iloprost group versus the placebo group, respectively (Table 2). Also, no statistically significant difference was found in the per-protocol population ($p = 0.23$).

Secondary Outcomes

The 28-day mortality was 18.8% in the iloprost group versus 19.6% in the placebo group (odds ratio, 1.01 [95% CI,

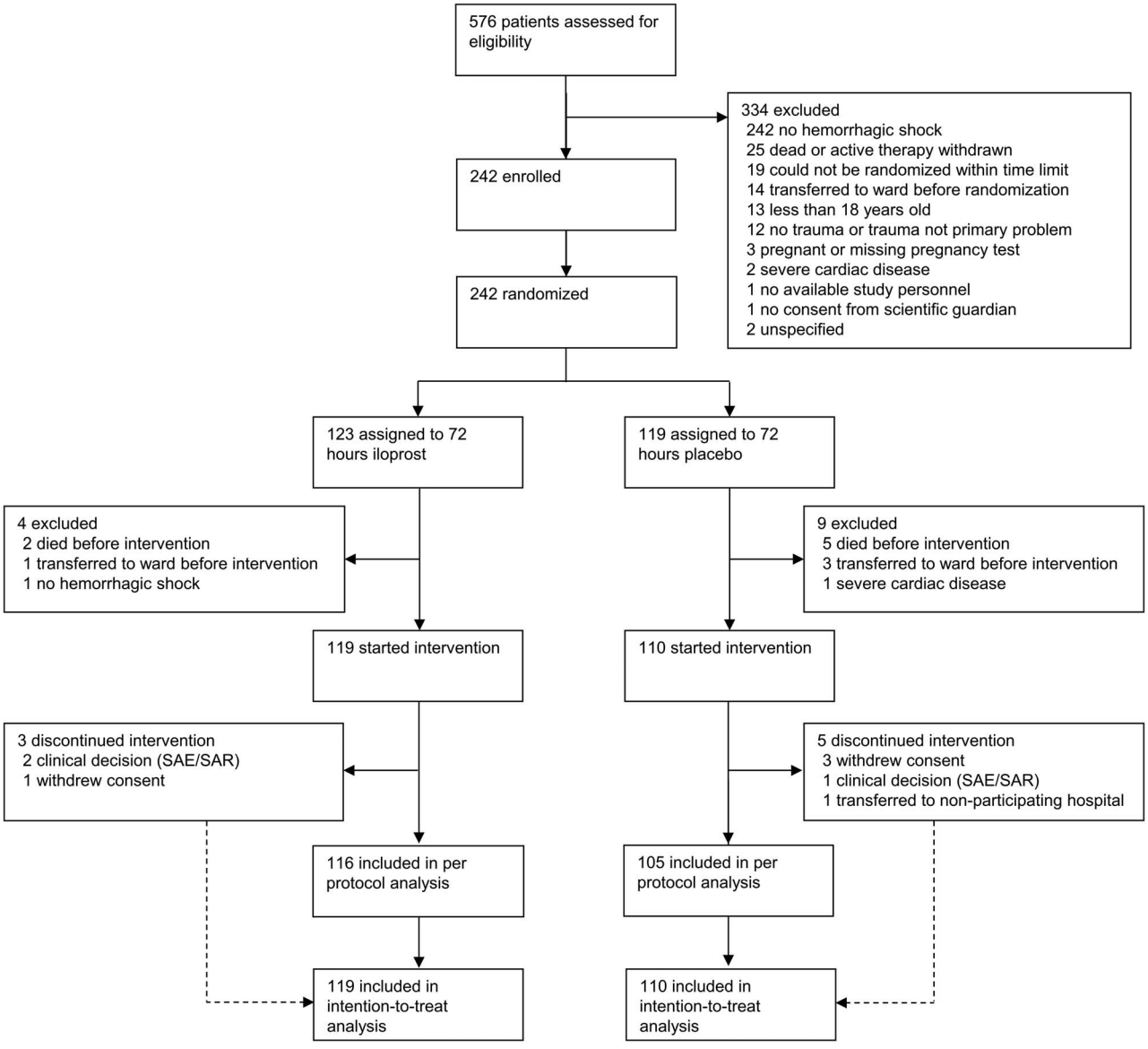

Figure 1. CONSORT diagram.

TABLE 1. Patient Characteristics

	Iloprost (n = 119)	Placebo (n = 110)
Age, y	50 (31–65)	46 (30–65)
Sex		
Male	96/119 (81%)	84/108 (78%)
Female	23/119 (19%)	24/108 (22%)
Cause of injury		
Traffic	56/119 (47%)	51/108 (47%)
Fall	21/119 (18%)	19/108 (18%)
Violence or self-harm	33/119 (28%)	30/108 (28%)
Other	9/119 (8%)	8/108 (7%)
Primary injury mechanism		
Penetrating	35/119 (29%)	31/108 (29%)
Blunt	84/119 (71%)	77/108 (71%)
Time to treatment start		
From injury, median (IQR), h	3.0 (2.4–3.9)	2.7 (2.1–3.5)
From admission, median (IQR), h	1.7 (1.4–2.2)	1.6 (1.2–2.3)
Admission clinical characteristics		
HR, bpm	110 (89–130)	100 (79–120)
sBP, mm Hg	100 (80–120)	98 (80–120)
GCS score	14 (7.5–15)	13 (5.8–15)
ISS	22 (16–34)	25 (16–34)
Admission laboratory analyses		
pH	7.28 (7.19–7.34)	7.26 (7.15–7.31)
Calcium, mmol/L	1.09 (1.03–1.17)	1.08 (1.01–1.16)
Glucose, mmol/L	11 (8.9–14)	11 (8.8–15)
Lactate, mmol/L	4.5 (2.4–8.0)	4.3 (2.5–6.9)
Base excess, mmol/L	−5.7 (−10 to −3.2)	−5.7 (−9.6 to −3.3)
Hemoglobin, mmol/L	7.6 (7.0–8.4)	7.5 (6.7–8.6)
Leukocytes, 10^9/L	14 (11–19)	13 (9.3–18)
Platelet count, 10^9/L	223 (173–260)	229 (185–287)
Creatinine, mmol/L	96 (85–120)	99 (82–120)
PT-INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)
APTT, s	26 (23–31)	26 (23–30)
Syndecan-1, ng/mL	62.7 (29.4–149.8)	56.8 (33.1–138.1)
Prehospital blood products		
Plasma, U	1 (0–2)	0 (0–2)
RBC, U	0 (0–2)	0 (0–1)
Platelets, U	0 (0–0)	0 (0–0)
Total, U	2 (0–3)	0 (0–2)
Blood products at 24 h		
Plasma, U	7 (4–14)	6 (4–12)
RBCs, U	6 (3–10)	6 (2–9)
Platelets, U	2 (1–3)	2 (1–3)
Total, U	15 (9–25)	14 (7–24)
Blood products at 28 d		
Plasma, U	8 (5–15)	8 (4–17)
RBC, U	7 (4–15)	9 (4–16)
Platelets, U	2 (1–4)	2 (1–4)
Total, U	18 (10–34)	19 (10–35)

Data are median (IQR) or number (%).

APTT, activated partial thromboplastin time; GCS, Glasgow Coma Scale; HR, heart rate; IQR, interquartile range; ISS, injury severity score; PT-INR, prothrombin time international normalized ratio; RBC, red blood cell; sBP, systolic blood pressure.

0.51–2.0]; $p = 0.97$). The 90-day mortality was 19.8% versus 20.2% (odds ratio, 0.98 [95% CI, 0.50–1.93]; $p = 0.96$) in the iloprost group versus the placebo group, respectively. The mean vasopressor-free days within 28 days was 19.86 days versus 18.07 days (adjusted mean difference, −1.75 days [95% CI, −4.44 to 0.94 days]; $p = 0.21$), the mean ventilator-free days within 28 days was 18.03 days versus 16.40 days (adjusted mean difference, −1.58 days [95% CI, −4.63 to 1.47 days]; $p = 0.31$), and the mean RRT-free days within 28 days was 23.11 days versus 22.99 days (adjusted mean difference, −0.03 days [95% CI, −2.49 to 2.54 days]; $p = 0.98$) in the iloprost group versus the placebo group, respectively. The mean hospital length of stay was 19.96 days versus 27.32 days (adjusted mean difference, 7.84 days [95% CI, 1.66–14.02 days]; $p = 0.01$) in the iloprost group versus the placebo group, respectively (Table 2). This difference was not a result of differences in the proportions of early deaths or early discharges between groups (Supplemental Digital Content, Supplementary Figure 1, http://links.lww.com/TA/D355). Furthermore, exploratory analyses of the potential impact of patient age (65 years or older vs. younger than 65 years), sex, ISS (25 or higher vs. <25) and trauma mechanism (blunt vs. penetrating) on the effect of iloprost versus placebo was conducted finding no significant differences. In patients with ISS at or higher than 25, however, the number of ICU free days at 28 days was 10.5 days versus 0 days ($p = 0.07$) in the iloprost versus the placebo group. Regarding hospital LOS at 90 days, in patients younger than 65 years, the number of days was 11 days versus 18 days ($p = 0.06$) in the ilopost and placebo groups, respectively, and in patients with ISS <25, it was 8 days versus 18 days ($p = 0.05$) in the ilopost and placebo groups, respectively. Similarly, in patients suffering blunt trauma, it was 19 days versus 21.5 days ($p = 0.08$) in the ilopost and placebo groups, respectively (Supplemental Digital Content, Supplementary Table S1, http://links.lww.com/TA/D356).

Safety Outcomes

No significant difference between groups was found regarding 24-hour and 28-day transfusion requirements (Table 1) or SAEs and reactions (Table 2), evaluated on the ITT and safety populations.

DISCUSSION

In this multicenter randomized trial, we did not find a statistically significant difference in the number of ICU-free days alive within 28 days of admission among trauma patients with clinical signs of hemorrhagic shock and severe endothelial glycocalyx damage allocated to iloprost or placebo for 72 hours. Apart from a significant reduction in the number of days in hospital in the iloprost group, no significant difference in any of the secondary outcomes was observed. The observed difference in hospital LOS between groups equals $25.900,00 per trauma patients suffering hemorrhagic shock and being treated with iloprost in saved hospital costs.

Endotheliopathy has been reported to be independently associated with poor outcome in patients suffering trauma and, in particular, shedding of the protective endothelial glycocalyx, as evidenced by increased levels of the circulating proteoglycan syndecan-1, which has consistently been reported.[4–6] The glycocalyx is composed of the membrane-spanning backbone molecules of proteoglycans, glycosaminoglycans, and glycoproteins. Together with associated plasma proteins, these molecules cover

TABLE 2. Primary and Secondary Outcomes (ITT Population)

	Iloprost (n = 119)	Placebo (n = 110)	Adjusted Difference of the Means (95% CI) or Risk Ratio (95% CI)	*p*
Mean days alive and free of intensive care at 28 d	15.64	13.99	−1.63 (−4.64 to 1.38)	0.28
Mean days alive and free of mechanical ventilation at 28 d	18.03	16.40	−1.58 (−4.63 to 1.47)	0.31
Mean days alive and free of vasopressor therapy at 28 d	19.86	18.07	−1.75 (−4.44 to 0.94)	0.21
Mean days alive and free of renal replacement therapy at 28 d	23.11	22.99	0.03 (−2.49 to 2.54)	0.98
Mean hospital length of stay at 90 d	19.96	27.32	7.84 (1.66–14.02)	0.01
Mortality at 28 d	22/117 (18.8%)	21/107 (19.6%)	1.01 (0.58–1.76)	0.97
Mortality at 90 d	23/116 (19.8%)	21/104 (20.2%)	0.99 (0.56–1.70)	0.96
Any serious adverse event(s) within 7 d	4/119 (3.4%)	5/108 (4.6%)	1.38 (0.29–8.46)	0.62
Any serious adverse reaction(s) within 7 d	1/119 (0.8%)	0/108 (0%)	0.00 (0.00–1.00)	0.26

the lumen of the whole vasculature.[25] Given its central position between the bloodstream and the endothelium, the glycocalyx is the frontline regulator of numerous physiological functions, including shear stress, mechanotransduction, anti-inflammatory and anticoagulatory responses, and vascular permeability.[26] The shock-induced sympathetic activation with release of high levels of catecholamines secondary to hemorrhage is a pivotal driver of the shedding of the glycocalyx.[4]

Prostacyclin is an endogenous prostanoid formed and released by endothelial cells with paracrine function including dose-dependent vasodilation and platelet inhibition. Prostacyclin also has pleiotropic cytoprotective effects on the endothelium including synthesizing endothelial glycocalyx constituents (hyaluronic acid),[10,11] which we believe is particularly pivotal in shocked trauma patients with high glycocalyx shedding. Furthermore, it acts on prostaglandin I (IP_1) receptors on endothelial progenitor cells leading to re-endothelium formation in damaged vessels[13] upregulating VE-cadherin responsible for tight-junction integrity, that is, preventing capillary leakage[12]; inducing peroxisome PPAR attenuation of NF-kB and TNF activation in ischemia-reperfusion injury, which minimizes the inflammatory hit on the endothelium[14]; and protecting against ischemia-reperfusion injury through the PGI_2–PPARα–HEME oxygenase-1 signaling pathway that provides robust rejuvenation of the damaged endothelium.[15]

The finding of no beneficial effect of iloprost on the primary and secondary outcomes, apart from the clinically relevant reduction in number of hospital days, contrasts our recent finding of a beneficial effect of low-dose iloprost infusion for 72 hours on sequential organ failure assessment score in mechanically ventilated COVID-19 patients with severe endotheliopathy as compared with placebo.[27] A potential explanation for the observed difference may be that, as opposed to trauma, where glycocalyx shedding is reported to be the main cause of endotheliopathy,[3,6] in COVID-19 cleavage of thrombomodulin from the endothelial cell membrane, perturbing the protein C system anticoagulation dominates[28] and that this explains the observed differences. It could also be speculated that difference in the affected vital organs between the trauma and COVID-19 patients influences the beneficial effect of iloprost. It should be noted, however, that the significant 7-day shorter hospital stay in the iloprost group could not be explained by differences in early mortality or discharges in one of the groups. Therefore, it is tempting to speculate that the intervention with iloprost may be responsible for this difference by mitigating the endotheliopathy, but this needs further investigation.

In exploratory analyses, we found that, in patients with ISS at or higher than 25, those receiving iloprost had 10.5 ICU-free days within 28 days compared with none in the placebo group, suggesting a potential benefit in the most severely injured patients warranting further investigation. Similarly, concerning hospital LOS at 90 days, in patients younger than 65 years, or patients with an ISS lower than 25 or those suffering blunt trauma, there was a trend toward a shorter hospital stay in the iloprost groups. Since several different subgroups of trauma patients respond similarly, this finding suggests also a potential generalized beneficial effect of iloprost.

No significant difference in 24-hour and 28-day transfusion requirements between groups was observed, suggesting no adverse effect of iloprost on hemostasis. Also, no significant difference in SAE and SAR between groups was observed, indicating that iloprost at a dose of 1 ng/kg/min is safe in trauma patients with hemorrhagic shock.

The present study is limited by only including Scandinavian trauma centers. Furthermore, because of the known heterogeneity in trauma patients with hemorrhagic shock, the present study may have been underpowered to detect a clinically relevant effect of iloprost, further illustrated by the exploratory analyses. Furthermore, it cannot be excluded that a higher dose of iloprost and/or a longer treatment period may be more beneficial than what has been tested in the present study.

In conclusion, low-dose iloprost did not result in a significant increase in the number of ICU-free days within 28 days in trauma patients with hemorrhagic shock. However, a significant reduction in hospital length of stay was observed in the iloprost group. No safety concerns related to iloprost were observed. Further research is needed to fully understand the effect of prostacyclin in trauma patients with shock-induced endotheliopathy,[29] and the exploratory analyses suggest that the most severely injured patients with ISS at or higher than 25 should be investigated first.

AUTHORSHIP

P.I.J., C.F.E., C.G., M.P., T.L., P.A.N., H.K., and J.S. contributed in the study design. P.I.J., C.F.E., P.E.B., C.G., M.P., H.H.H., K.H.P., M.V., P.A.N., M.S.A., and J.S. contributed in the data collection. P.I.J., T.L., and J.S. contributed in the data analysis. P.I.J., C.F.E., P.E.B., C.G., M.P., T.L., P.A.N., M.S.A., H.K., and J.S. contributed in the data interpretation. P.I.J., C.F.E., P.E.B., C.G., M.P., H.H.H., K.H.P., M.V., T.L., P.A.N., M.S.A., H.K., and

J.S. contributed in the writing of the article. P.I.J., C.F.E., P.E.B., C.G., M.P., H.H.H., K.H.P., M.V., T.L., P.A.N., M.S.A., H.K., and J.S. contributed in the critical revisions.

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DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D357).
Regulatory Approvals: Danish Ethics Committee (H-19014482), the Danish Data Protection Agency (P-2019-85), and the Danish Medicines Agency (EudraCT number 2019-000936-24).

REFERENCES

1. World Health Organization. (2008). The global burden of disease: 2004 update. Geneva, Switzerland: World Health Organization.
2. Brohi K, Gruen RL, Holcomb JB. Why are bleeding trauma patients still dying? *Intensive Care Med*. 2019;45:709–711.
3. Johansson PI, Stensballe J, Rasmussen L, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis and increased mortality in trauma patients. *Ann Surg*. 2011;254:194–200.
4. Johansson PI, Stensballe J, Rasmussen L, Ostrowski SR. High circulating adrenaline levels at admission predict increased mortality after trauma. *J Trauma Acute Care Surg*. 2012;72:428–436.
5. Johansson PI, Henriksen HH, Stensballe J, Gybel-Brask M, Cardenas JC, Baer LA, et al. Traumatic endotheliopathy: a prospective observational study of 424 severely injured patients. *Ann Surg*. 2017;265:597–603.
6. Gonzalez E, Ostrowski SR, Cardenes JC, Baer LA, Tomasek JS, Henriksen HH, et al. Syndecan-1: a quantitative marker for the Endotheliopathy of trauma. *Journal Am Coll Surg*. 2017;225:419–427.
7. Johansson PI, Stensballe J, Ostrowski SR. Shock induced endotheliopathy (SHINE) in acute critical illness — a unifying pathophysiologic mechanism. *Crit Care*. 2017;21:187.
8. Robbins SL, Kumar V, Cotran RS. *Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: Saunders; 2010.
9. Mitchell JA, Kirkby NS. Eicosanoids, prostacyclin and cyclooxygenase in the cardiovascular system. *Br J Pharmacol*. 2019;176:1038–1050.
10. Bruggerman LA, Pellicoro JA, Horigan EA, Klotman PE. Thromboxane and prostacyclin differentially regulate murine extracellular matrix gene expression. *Kidney Inter*. 1993;43:1219–1225.
11. Sussmann M, Sarbia M, Meyer-Kirschrat J, Nüsing RM, Schrör K, Fischer JW. Induction of hyaluronic acid synthase 2 (HAS2) in human vascular smooth muscle cells by vasodilatory prostaglandins. *Circ Res*. 2004;94:592–600.
12. Birukova AA, Tian Y, Dubrovskyi O, Zebda N, Sarich N, Tian X, et al. VE-cadherin trans-interactions modulate Rac activation and enhancement of lung endothelial barrier by iloprost. *J Cell Physiol*. 2012;227:3405–3416.
13. Kawabe J, Yuhki K, Okada M, Kanno T, Yamauchi A. Tashiro net al. Prostaglandin I2 promotes recruitment of endothelial progenitor cells and limits vascular remodeling. *Arterioscler Thromb Vasc Biol*. 2010;30:464–470.
14. Chen HH, Chen TW, Lin H. Prostacyclin-induced peroxisome proliferator-activated receptor-alpha translocation attenuates NF-kappaB and TNF-alpha activation after renal ischemia-reperfusion injury. *Am J Physiol Renal Physiol*. 2009;297:F1109–F1118.
15. Cheng CF, Lian WS, Chen SH, Lai PF, Li HF, Lan YF, et al. Protective effects of adiponectin against renal ischemia-reperfusion injury via prostacyclin-PPARα-heme oxygenase-1 signaling pathway. *J Cell Physiol*. 2012;227:239–249.
16. Zardi EM, Zardi DM, Cacciapaglia F, Dobrina A, Amoroso A, Picardi A, et al. Endothelial dysfunction and activation as an expression of disease: role of prostacyclin analogs. *Int Immunopharmacol*. 2005;5:437–549.
17. Bärthel E, Rauchfuss F, Hoyer H, Halbrecht O, Jandt K, Götz M, et al. Impact of stable PGI_2 analog iloprost on early graft viability after liver transplantation: a pilot study. *Clin Transplant*. 2011;26:E38–E47.
18. Beirne C, Hynes N, Sultan S. Six years' experience with prostaglandin I2 infusion in elective open repair of abdominal aortic aneurysm: a parallel group observational study in a tertiary referral vascular center. *Ann Vasc Surg*. 2008;221:750–755.
19. Berthelsen RE, Ostrowski SR, Bestle MH, Johansson PI. Co-administration of iloprost and eptifibatide in septic shock (CO-ILEPSS)—a randomised, controlled, double-blind investigator-initiated trial investigating safety and efficacy. *Crit Care*. 2019;23:301.
20. Johansson PI, Mortensen CR, Nielsen T, Tollund C, Stensballe J, Hansen CP, et al. The effect of intra- and six hour postoperative i.v. administration of low-dose prostacyclin on the endothelium, hemostasis and hemodynamics in patients undergoing pancreaticoduodenoctemy — a randomized controlled pilot study. *Eur J Gastroent & Hepatol*. 2017;29:400–406.
21. Johansson PI, Fenger Eriksen C, Schmal H, Gaarder C, Pall M, Henriksen HH, et al. Efficacy and safety of iloprost in trauma patients with haemorrhagic shock-induced endotheliopathy—protocol for the multicentre randomized, placebo-controlled, blinded, investigator-initiated shine-trauma trial. *Acta Anaesthesiol Scand*. 2021;65:551–557.
22. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869.
23. Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, et al. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. *Intensive Care Med*. 2021;4:49–59.
24. Liu L, Suo T, Shen Y, Geng C, Song Z, Liu F, et al. Clinicians versus patients subjective adverse events assessment: based on patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Qual Life Res*. 2020;29:3009–3015.
25. Weinbaum S, Cancel LM, Fu BM, Tarbel JM. The Glycocalyx and its role in vascular physiology and vascular related diseases. *Cardiovasc Eng Technol*. 2021;12:37–71.
26. Becker BF, Chappell D, Jacob M. Endothelial glycocalyx and coronary vascular permeability: the fringe benefit. *Basic Res Cardiol*. 2010;105:687–701.
27. Johansson PI, Søe-Jensen P, Bestle MH, Clausen NE, Kristiansen KT, Lange T, et al. Prostacyclin in intubated patients with COVID-19 and severe endotheliopathy: a multicenter randomized clinical trial. *Am J Respir Crit Care Med*. 2022;205:324–329.
28. Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-Centre, cross-sectional study. *Lancet Haematol*. 2020;7:e575–e582.
29. Bunch CM, Chang E, Moore EE, Moore HB, Kwaan HC, Miller JB, et al. SHock-INduced Endotheliopathy (SHINE): a mechanistic justification for viscoelastography-guided resuscitation of traumatic and non-traumatic shock. *Front Physiol*. 2023;14:1094845.

