

Coagulopathy and damage control resuscitation during transfer due to massive hemorrhage –a single-center retrospective study–

Hiroyuki Takahashi (✉ htakahashi1223@yahoo.co.jp)

Tokyo Joshi Ika Daigaku Higashi Iryo Center <https://orcid.org/0000-0003-0650-5088>

Tomohisa Shoko

Tokyo Joshi Ika Daigaku Higashi Iryo Center

Mitsuaki Kojima

Tokyo Joshi Ika Daigaku Higashi Iryo Center

Satoshi Nara

Teine Keijinkai Byoin

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Abstract

Background: To assess medical procedures, particularly damage control resuscitation, at the time of transfer between hospitals for the purpose of treating massive hemorrhage.

Methods: This study used a single-center retrospective observational design, enrolling patients referred to Teine Keijinkai Hospital from another hospital between April 2012 and March 2019 for the treatment of massive hemorrhage. We excluded patients who entered cardiac arrest before arriving at our center. Qualitative or categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Quantitative continuous variables were compared using Mann-Whitney nonparametric tests, as appropriate. Risk factors associated with coagulopathy from univariate analyses (fibrinogen level ≤ 150 mg/dl; prothrombin time-international normalized ratio ≥ 1.5) were entered into stepwise logistic regression analysis. Significance was defined for values of $p < 0.05$.

Results: Multiple logistic regression analysis revealed trauma (odds ratio (OR) 4.800; 95% confidence interval (CI) 2.016–11.433; $p < 0.001$) and volume of crystalloid solution (OR 1.001; 95%CI 1.000–1.001; $p = 0.008$) as independent factors associated with coagulopathy. Patients with coagulopathy showed higher 24-h mortality rates (10.9%) than patients without coagulopathy (1.2%; $p = 0.021$), and cause of death was hemorrhagic shock for all cases of death within 24 h.

Conclusion: In our area, withholding intravenous fluid to achieve permissive hypotension, early administration of fresh frozen plasma, and use of fibrinogen concentrate may improve the prognosis of patients with massive hemorrhage undergoing transfer between hospitals.

Trial registration: UMIN, UMIN000041201. Registered 24 July 2020 – Retrospectively registered, https://upload.umin.ac.jp/cgi-open-bin/icdr_e/ctr_view.cgi?recptno=R000047048

Background

Causes of hemorrhage vary widely and include trauma, maternal hemorrhage, gastrointestinal hemorrhage, and others [1]. Death from hemorrhage represents a substantial global problem, and individuals who survive the initial hemorrhagic insult display poor functional outcomes and significantly increased long-term mortality [1]. Although the treatment of bleeding with methods such as surgical exploration represents definitive hemostasis, damage control resuscitation (DCR) is recommended to minimize the amount of bleeding and coagulopathy before attempting definitive hemostasis, particularly in cases involving trauma [2–4]. DCR includes permissive hypotension to avoid exsanguination and dilutional coagulopathy, hemostatic resuscitation aimed at the control of coagulopathy, damage control surgery mainly for hemostatic operations, and so on [2, 3]. DCR must start in the prehospital environment or emergency room, and continues through the operating room and intensive care unit until resuscitation is complete [2, 5].

Our medical administration area of Hokkaido occupies a large area, accounting for about 22% of the country of Japan. On the other hand, Hokkaido shows problems in the uneven distribution of emergency room physicians and health resources. In areas of medical depopulation, patients are transferred from the scene to the nearest hospital for primary care, and may need to be transferred between hospitals for advanced

treatment. The time from the scene to a hospital that can provide definitive care can thus be quite long. Even if the patient is hospitalized, transfer to another hospital may be needed if the bleeding is beyond the capability of the receiving hospital to treat. Because the time from onset to definitive hemostasis is increased, DCR is likely to become even more important for patients transferred between hospitals.

This study was undertaken to assess medical procedures, particularly DCR, at the time of transfer between hospitals, for the purpose of treating massive hemorrhage in our medical administration area.

Methods

This study applied a single-center, retrospective, observational design. Patients referred to Teine Keijinkai Hospital from another hospital between April 2012 and March 2019 for the treatment of massive hemorrhage were enrolled. We excluded patients who had experienced cardiac arrest before arrival at our center. Patients with “bleeding”, “trauma”, or “shock” were extracted from the medical records, and patients with causes other than massive hemorrhage were excluded. Massive hemorrhage was defined as follows: 1) systolic blood pressure ≤ 90 mmHg at the referring hospital [6, 7]; 2) shock index (heart rate / systolic blood pressure) ≥ 1 at the referring hospital [8]; 3) in cases of maternal hemorrhage, cumulative blood loss $\geq 1,000$ ml or blood loss accompanied by signs or symptoms of hypovolemia [9]; and 4) the judgement of the doctor from the referring hospital (for example, when the amount of bleeding was unknown, measurement of blood pressure was difficult, and a description of massive hemorrhage or shock was present in the medical information).

Information on age, sex, diagnosis, past medical history (liver cirrhosis, blood disease, malignant tumor), oral medications (vitamin K antagonist, direct oral anticoagulants, and antiplatelet agents), vital signs in the referring hospital (Glasgow Coma Scale, systolic blood pressure, heart rate), tracheal intubation at the time of transfer, volume of crystalloid solution before arrival at our center, blood product administration before arrival at our center and dosage units when administered, Abbreviated Injury Scale in cases of trauma, catecholamine administration, tranexamic acid administration, time from onset to arrival at our center, vital signs on arrival at our center (Glasgow Coma Scale, systolic blood pressure, heart rate, body temperature), laboratory test data on arrival (pH, lactate, total bilirubin, creatinine, hemoglobin, platelet, prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time, fibrinogen), treatment (surgical exploration, angiography with embolization, endoscopic intervention), amount of blood transfused within 24 h of arrival, outcomes (24-h mortality, 30-day mortality), and adverse events of blood transfusion (transfusion-related acute lung injury, allergic reaction or transfusion related reaction) were obtained.

Qualitative and categorical variables were compared using the χ^2 or Fisher’s exact test, as appropriate. Quantitative continuous variables were compared using Mann-Whitney nonparametric tests where appropriate. Risk factors associated with coagulopathy according to univariate analyses were entered into stepwise logistic regression analysis, and results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Values of $p < 0.05$ were considered significant. SPSS Statistics version 25 software (SPSS, Chicago, IL) was used for all statistical analyses. Ethics approval was obtained from Teine Keijinkai Hospital, Hokkaido, Japan.

Results

Over the 7-year study period, a total of 1076 patients were transferred to our hospital for the treatment of bleeding, trauma, or shock (Fig. 1). Among these, 172 patients had shock or massive hemorrhage. After excluding 40 shock patients with other causes of shock, 132 patients with massive hemorrhage were included.

Table 1 shows the classification of the 132 cases, and Table 2 shows background characteristics of patients. Before arrival at our center, crystalloid solution had been administered to all cases, and median volume of infusion was particularly high with trauma (1,550 ml; interquartile range (IQR) 1,000–2,250 ml) and maternal hemorrhage (2,500 ml; IQR 1,000–3,000 ml). Blood products were administered to 26.5% of all patients, including 35.1% with trauma, and 30.3% with maternal hemorrhage. Red blood cell (RBC) transfusion was performed in 24.2% of all cases, including 35.1% with trauma, 24.2% with maternal hemorrhage, and 22% with gastrointestinal hemorrhage. Fresh frozen plasma (FFP) transfusion was performed in 7.6% of all cases, 8.1% of trauma cases, 15.2% of maternal hemorrhage cases, and 2.4% of gastrointestinal hemorrhage cases. Tranexamic acid administration was performed in 9.8% of all cases and in 13.5% of trauma cases. Mean systolic blood pressure at our center was 100 mmHg (IQR 80–117 mmHg) overall and 99 mmHg (IQR 84–120 mmHg) for trauma.

Table 1
Number of patients transferred from another hospital to our center for massive hemorrhage

| Cause of hemorrhage | n | % |
|-----------------------------|-----|------|
| Trauma | 37 | 28.0 |
| Maternal hemorrhage | 33 | 25.0 |
| Gastrointestinal hemorrhage | 41 | 31.1 |
| Intraabdominal bleeding | 11 | 8.3 |
| Ruptured aortic aneurysm | 10 | 7.6 |
| Total | 132 | 100 |

Table 2
Patient characteristics, vital signs, and treatments before arrival at our center

| | All (N = 132) | Trauma (n = 37) | Maternal hemorrhage (n = 33) | Gastrointestinal hemorrhage (n = 41) | Intraabdominal bleeding (n = 11) | Ruptured aortic aneurysm (n = 10) |
|--|----------------------|----------------------|------------------------------------|--|--|--|
| Age, years | 67 [38–8] | 71 [46–78] | 33 [28–39] | 71 [63–80] | 60 [40–83] | 83 [76–86] |
| Male sex | 57 (43.2) | 23 (62.2) | 0 (0) | 27 (65.9) | 2 (18.2) | 5 (50) |
| Time from onset to arrival at our center, min | 210 [143– 317] | 238 [170– 310] | 243 [121– 360] | 195 [129–334] | 203 [147–279] | 134 [111– 184] |
| Past medical history | | | | | | |
| Liver cirrhosis | 5 (3.8) | 0 (0) | 0 (0) | 4 (9.8) | 1 (9.1) | 0 (0) |
| Blood disease | 2 (1.5) | 0 (0) | 1 (0) | 1 (2.4) | 0 (0) | 0 (0) |
| Malignant tumor | 14 (10.6) | 1 (2.7) | 0 (0) | 9 (22.0) | 4 (36.4) | 0 (0) |
| Oral medication | | | | | | |
| Vitamin K antagonist | 9 (6.8) | 4 (10.8) | 0 (0) | 4 (9.8) | 1 (9.1) | 0 (0) |
| DOAC | 7 (5.3) | 2 (5.4) | 0 (0) | 5 (12.2) | 0 (0) | 0 (0) |
| Antiplatelet agents | 21 (15.9) | 5 (13.5) | 0 (0) | 10 (24.4) | 2 (18.2) | 4 (40) |
| Vital signs at referring hospitals | | | | | | |
| GCS score | 15 [14– 15] | 15 [14– 15] | 15 [15–15] | 15 [14–15] | 15 [15–15] | 15 [14– 15] |
| Systolic blood pressure, mmHg | 80 [69– 100] | 78 [61– 92] | 99 [72– 118] | 76 [63–88] | 86 [65–102] | 84 [70– 111] |
| Heart rate, beats/min | 98 [84– 116] | 90 [85– 108] | 109 [86– 129] | 98 [79–116] | 92 [84–115] | 87 [76– 95] |
| Treatments before arrival at our center | | | | | | |
| Intubation | 11 (8.3) | 5 (13.5) | 0 (0) | 5 (12.2) | 1 (9.1) | 0 (0) |

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).

Abbreviations: IQR, interquartile range; GCS, Glasgow coma scale; RBC, red blood cell; FFP, fresh frozen plasma; DOAC, direct oral anticoagulant

| | All (N = 132) | Trauma (n = 37) | Maternal hemorrhage (n = 33) | Gastrointestinal hemorrhage (n = 41) | Intraabdominal bleeding (n = 11) | Ruptured aortic aneurysm (n = 10) |
|--|------------------|--------------------|------------------------------------|--|--|--|
| Volume of crystalloid solution, ml | 1000 [500–2000] | 1550 [1000–2250] | 2500 [1000–3000] | 650 [500–1500] | 1000 [700–1600] | 500 [500–1075] |
| RBC transfusion | 32 (24.2) | 13 (35.1) | 8 (24.2) | 9 (22.0) | 2 (18.2) | 0 (0) |
| FFP transfusion | 10 (7.6) | 3 (8.1) | 5 (15.2) | 1 (2.4) | 1 (9.1) | 0 (0) |
| Catecholamines | 20 (15.2) | 7 (18.9) | 2 (6.1) | 9 (22.0) | 1 (9.1) | 1 (10) |
| Tranexamic acid | 13 (9.8) | 5 (13.5) | 2 (6.1) | 6 (14.6) | 0 (0) | 0 (0) |
| Vital signs at our center | | | | | | |
| GCS score | 15 [14–15] | 14 [9–15] | 15 [15–15] | 15 [13–15] | 15 [14–15] | 15 [14–15] |
| Systolic blood pressure, mmHg | 100 [80–117] | 99 [84–120] | 100 [80–119] | 96 [80–108] | 104 [90–110] | 93 [72–104] |
| Heart rate – beats/min | 100 [82–120] | 93 [80–110] | 110 [95–130] | 100 [82–119] | 93 [80–119] | 89 [81–96] |
| Body temperature – °C | 36.6 [36.1–37.2] | 36.6 [35.9–37.0] | 37.0 [36.5–37.2] | 36.6 [36.0–37.4] | 36.6 [35.2–37.2] | 36.2 [35.6–37.5] |
| Continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%). | | | | | | |
| Abbreviations: IQR, interquartile range; GCS, Glasgow coma scale; RBC, red blood cell; FFP, fresh frozen plasma; DOAC, direct oral anticoagulant | | | | | | |

Table 3 shows the results of blood examination on arrival at our center. Median hemoglobin concentration was 7.5 g/dl (IQR 5.7–9.1 g/dl) in the overall study cohort, which was particularly low for maternal hemorrhage (5.9 g/dl; IQR 5.4–7.8 g/dl) and gastrointestinal hemorrhage (6.8 g/dl; IQR 5.5–8.9 g/dl). Median overall fibrinogen level was 180 mg/dl (IQR 127–241 mg/dl), and was especially low for trauma (128 mg/dl; IQR 97–179 mg/dl) and maternal hemorrhage (170 mg/dl; IQR 109–223 mg/dl). Median fibrinogen level in gastrointestinal hemorrhage was not low, at 224 mg/dl (IQR 168–307 mg/dl).

Table 3
Blood examination results at our center

| | All (N = 132) | Trauma (n = 37) | Maternal hemorrhage (n = 33) | Gastrointestinal hemorrhage (n = 41) | Intraabdominal bleeding (n = 11) | Ruptured aortic aneurysm (n = 10) |
|---|-------------------------|-------------------------|------------------------------------|--|--|--|
| pH | 7.38 [7.33– 7.43] | 7.36 [7.25– 7.41] | 7.39 [7.37– 7.45] | 7.39 [7.35– 7.44] | 7.34 [7.26– 7.43] | |
| Lactate, mg/dl | 29 [21– 55] | 40 [24– 67] | 23 [17–44] | 29 [18–73] | 31 [20–47] | |
| Hb, g/dl | 7.5 [5.7– 9.1] | 8.1 [7.1– 10.3] | 5.9 [5.4– 7.8] | 6.8 [5.5–8.9] | 8.1 [7.5–10.4] | 8.5 [6.8– 10.3] |
| Plt, ·10 ⁴ /μl | 15.3 [11.3– 19.0] | 14.4 [10.1– 16.7] | 15.2 [10.3– 18.8] | 17.2 [14.0– 22.8] | 14.9 [13.3– 22.5] | 14.1 [11.5– 17.9] |
| PT-INR | 1.22 [1.12– 1.42] | 1.26 [1.15– 1.59] | 1.19 [1.10– 1.33] | 1.26 [1.15– 1.46] | 1.12 [1.09– 1.18] | 1.15 [1.09– 1.19] |
| APTT, s | 30.8 [27.3– 38.7] | 32.0 [27.7– 42.4] | 32.6 [29.2– 47.4] | 30.0 [26.8– 38.4] | 26.5 [24.5– 29.1] | 28.8 [27.2– 30.6] |
| Fibrinogen, mg/dl | 180 [127– 241] | 128 [97– 179] | 170 [109– 223] | 224 [168–307] | 229 [154–285] | 236 [117– 298] |
| Variables are presented as median [interquartile range] | | | | | | |
| Abbreviations: Hb, hemoglobin; Plt, platelets; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time | | | | | | |

Table 4 shows treatments and outcomes. The 24-h mortality rate was 4.5% in the overall study cohort, and all patients who died within 24 h died due to hemorrhagic shock. The 30-day mortality rate was 9.1%. Deaths among patients who survived > 24 h but died within 30 days were attributed to complications such as end-stage pancreatic cancer, myocardial infarction, acute kidney injury, or chronic disease such as exacerbation of interstitial pneumonia or chronic heart failure.

Table 4
Treatments and outcomes

| | All (N = 132) | Trauma (n = 37) | Maternal hemorrhage (n = 33) | Gastrointestinal hemorrhage (n = 41) | Intraabdominal bleeding (n = 11) | Ruptured aortic aneurysm (n = 10) |
|-----------------------------------|------------------------------|----------------------------|---|---|---|--|
| Surgical exploration | 54 (40.9) | 16 (43.2) | 19 (57.6) | 4 (9.8) | 7 (63.6) | 8 (80) |
| Angiography with embolization | 26 (19.7) | 18 (48.6) | 1 (3.0) | 1 (2.4) | 5 (45.5) | 1 (10) |
| Endoscopic intervention | 34 (25.8) | 1 (2.7) | 0 (0) | 33 (80.5) | 0 (11) | 0 (0) |
| 24-h mortality | 6 (4.5) | 4 (10.8) | 0 (0) | 1 (2.4) | 1 (9.1) | 0 (0) |
| 30-day mortality | 12 (9.1) | 5 (13.5) | 0 (0) | 5 (12.2) | 2 (18.2) | 0 (0) |
| Variables are presented as n (%). | | | | | | |

Subsequently, the background characteristics of patients showing coagulopathy at our center were examined. Coagulopathy was defined as fibrinogen ≤ 150 mg/dl, or PT-INR ≥ 1.5 [4, 10, 11]. Table 5 shows the results. According to univariate analyses, patients with coagulopathy were characterized by trauma, lack of gastrointestinal hemorrhage, and administration of a large volume of crystalloid solution before arrival at our center. Multiple logistic regression analysis was performed using trauma, gastrointestinal hemorrhage, and volume (ml) of crystalloid solution administered before arrival at our center as independent variables, revealing trauma (OR 4.800; 95%CI 2.016–11.433; $p < 0.001$) and volume of crystalloid solution (OR 1.001; 95%CI 1.000–1.001; $p = 0.008$) as independent factors.

Table 5
Patient characteristics in the coagulopathy^a group and no coagulopathy group

| | Coagulopathy group (n = 46) | No coagulopathy group (n = 84) | p |
|---|--------------------------------|-----------------------------------|-------|
| Cause of hemorrhage | | | |
| Trauma | 23 (50.0) | 14 (16.7) | 0.000 |
| Maternal hemorrhage | 11 (23.9) | 22 (26.2) | 0.775 |
| Gastrointestinal hemorrhage | 7 (15.2) | 32 (38.1) | 0.006 |
| Intraabdominal bleeding | 2 (4.3) | 9 (10.7) | 0.181 |
| Ruptured aortic aneurysm | 3 (6.5) | 7 (8.3) | 0.501 |
| Age, years | 66 [36–77] | 67 [39–79] | 0.511 |
| Male sex | 19 (41.3) | 37 (44.0) | 0.763 |
| Vital signs at referring hospital | | | |
| GCS score | 15 [14–15] | 15 [14–15] | 0.780 |
| Systolic blood pressure, mmHg | 79 [64–98] | 80 [70–108] | 0.371 |
| Heart rate, beats/min | 96 [80–116] | 98 [84–114] | 0.896 |
| Treatments before arrival at our center | | | |
| Volume of crystalloid solution, ml | 1850 [1000–2500] | 1000 [500–2000] | 0.001 |
| RBC transfusion | 13 (28.3) | 18 (21.4) | 0.382 |
| FFP transfusion | 4 (8.7) | 6 (7.1) | 0.499 |
| Tranexamic acid | 5 (10.9) | 8 (9.5) | 0.514 |
| Vital signs at our center | | | |
| GCS score | 15 [14–15] | 15 [14–15] | 0.823 |
| Systolic blood pressure, mmHg | 91 [79–117] | 100 [80–118] | 0.334 |
| Heart rate, beats/min | 101 [81–119] | 97 [82–120] | 0.695 |
| Body temperature, °C | 36.4 [35.6–36.9] | 36.7 [36.2–37.2] | 0.039 |

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%).

Abbreviations: GCS, Glasgow coma scale; RBC, red blood cell; FFP, fresh frozen plasma; Hb, hemoglobin; Plt, platelets; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time

^a Coagulopathy is defined as fibrinogen < 150 mg/dl or PT-INR > 1.5.

| | Coagulopathy group (n = 46) | No coagulopathy group (n = 84) | p |
|---|--------------------------------|-----------------------------------|-------|
| Blood examination results at our center | | | |
| pH | 7.37 [7.27–7.42] | 7.38 [7.34–7.44] | 0.209 |
| Lactate, mg/dl | 29 [23–60] | 30 [17–52] | 0.215 |
| Hb, g/dl | 7.5 [5.5–8.9] | 7.6 [5.7–9.3] | 0.582 |
| Plt, $\cdot 10^4/\mu\text{l}$ | 12.9 [8.7–15.8] | 17.0 [13.4–21.4] | 0.000 |
| PT-INR | 1.31 [1.22–1.59] | 1.16 [1.10–1.31] | 0.000 |
| APTT, s | 35.2 [30.5–50.2] | 29.0 [25.9–32.8] | 0.000 |
| Fibrinogen, mg/dl | 108 [75–131] | 223 [183–288] | 0.000 |
| Continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%). | | | |
| Abbreviations: GCS, Glasgow coma scale; RBC, red blood cell; FFP, fresh frozen plasma; Hb, hemoglobin; Plt, platelets; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time | | | |
| ^a Coagulopathy is defined as fibrinogen < 150 mg/dl or PT-INR > 1.5. | | | |

Patients with coagulopathy displayed a significantly higher 24-h mortality rate than patients without coagulopathy, and cause of death was hemorrhagic shock in all cases of death within 24 h (Table 6). Considering the cause of hemorrhage, coagulopathy due to trauma tended to be associated with 24-h mortality, but no significant difference was observed (21.7% in the coagulopathy group; 0% in the no coagulopathy group, $p = 0.077$). No significant difference in 30-day mortality was identified. Patients with coagulopathy received more blood transfusions within 24 h. No differences were noted in rates of transfusion-related acute lung injury, allergic reaction or transfusion-related reaction.

Table 6
Patient outcomes in the coagulopathy^a group and no coagulopathy group

| | Coagulopathy group (n = 46) | No coagulopathy group (n = 84) | p |
|---|--------------------------------|-----------------------------------|-------|
| 24-h mortality | 5 (10.9) | 1 (1.2) | 0.021 |
| 30-day mortality | 6 (13.0) | 6 (7.1) | 0.211 |
| 24-h volume of RBCs transfused, units | 6 [4–6] | 4 [2–6] | 0.006 |
| 24-h volume of FFP transfused, units | 9 [4–16] | 0 [0–6] | 0.000 |
| 24-h volume of platelets transfused, units | 0 [0–20] | 0 [0–0] | 0.001 |
| Continuous variables are presented as median [interquartile range]. Categorical variables are presented as n (%). | | | |
| Abbreviations: RBC, red blood cell; FFP, fresh frozen plasma | | | |
| ^a Coagulopathy is defined as fibrinogen < 150 mg/dl or PT-INR > 1.5. | | | |

Discussion

According to this survey, many patients with massive hemorrhage who were transferred to our center had coagulopathy, especially due to trauma and maternal hemorrhage. Trauma and volume of crystalloid solution were factors independently associated with coagulopathy. Patients with coagulopathy had higher 24-h mortality, and required more blood transfusions within 24 h.

In trauma patients without brain injury, permissive hypotension to achieve a target systolic blood pressure of 80–90 mmHg is recommended until major bleeding has been stopped in the initial phase following trauma [4, 12]. In prehospital settings, intravenous fluid administration is recommended to be titrated for a palpable radial pulse using small boluses of fluid (250 ml) rather than fixed volumes or continuous administration [13]. In this survey, median systolic blood pressure at the time of arrival to our center was 100 mmHg (IQR 80–117 mmHg) overall and 99 mmHg (IQR 84–120 mmHg) for trauma, all of which were within standard values, but were high from the perspective of permissive hypotension. Both trauma and maternal hemorrhage cases received large volumes of crystalloid infusion before reaching our center and many showed coagulopathy at the time of visit, so there was considered to be some room to limit infusion volumes before arrival at our center.

Regarding prehospital administration of blood products, both RBCs and FFP have been reported to show improvements in mortality and coagulopathy among trauma cases [5–7, 14]. This study targeted transfer cases from hospitals that can administer blood products, not direct transport from the field. However, the rate of blood product administration was 23.5% for RBCs and 7.6% for FFP in all cases, and 32.4% for RBCs and 8.1% for FFP in trauma cases. In Europe, viscoelastic methods (VEMs), like thromboelastography and rotational thromboelastometry, are recommended for the diagnosis of trauma-induced coagulopathy because of the ability to provide rapid assessment of hemostasis to support clinical decision-making [4]. In Japan,

VEM is usually restricted to experimental and research settings in academic hospitals, and VEM equipment is rarely present in most primary-care hospitals. Coagulopathy due to trauma occurs early after trauma [15, 16], and in severe trauma such as multiple injuries, the frequency of established coagulopathy on emergency room admission is high [11, 17]. In patients with massive hemorrhage, early administration of FFP is rational to prevent coagulopathy. In fact, early administration [18] and high-ratio administration [19, 20] of FFP are recommended. In our area, even in environments in which testing for coagulopathy is not possible, blood products including FFP should be administered more often at the time of transfer to a hospital.

On the other hand, patients experiencing massive hemorrhage are under severe time constraints, because transfer to a hospital that can achieve definitive hemostasis is required as soon as possible. One of the reasons why the rate of FFP administration was low may be that a longer time is needed to thaw the product. In that respect, fibrinogen concentrate does not require thawing or cross-matching and allows rapid administration [21], and is useful in prehospital settings [22]. Furthermore, because fibrinogen levels decrease earlier than any other hemostatic factors in the case of massive hemorrhage [23], supplementation of fibrinogen is required from early in trauma. Conversely, FFP requires high volumes to maintain fibrinogen levels [24], so fibrinogen concentrate can be supplemented with fibrinogen even in small amounts [21]. This is also advantageous from the perspective of restricted volume replacement for permissive hypotension and prevention of hypocalcemia resulting from the citrate chelation of serum Ca^{2+} . Fibrinogen concentrate reportedly carries lower risks of massive transfusion or multiple organ failure than FFP [25]. Fibrinogen concentrate has also been reported to reduce blood loss and total amount of FFP when treating coagulopathy from postpartum hemorrhage [26]. At present, although fibrinogen concentrate is only approved for bleeding episodes in patients with congenital fibrinogen deficiency in Japan, due to the above-mentioned advantages, some facilities use fibrinogen concentrate for trauma and obstetric bleeding with the approval of the hospital ethics committee. If administration of fibrinogen concentrate for patients with bleeding becomes approved in Japan as in many European countries, early correction of coagulopathy should be possible.

Tranexamic acid should be given to bleeding trauma patients as early as possible [27, 28], but administration at the referring hospital was limited to 13.5% in our region. In the obstetric setting, tranexamic acid has been shown to be effective, particularly when given early after bleeding onset [29], but administration was limited to 6.1%. On the other hand, routine use of tranexamic acid is not recommended for upper gastrointestinal bleeding [30], and tranexamic acid was used in 14.6% of gastrointestinal bleeding cases. Early treatment with tranexamic acid for trauma and maternal hemorrhage should thus be promoted in our region.

The mechanisms of coagulopathy following trauma are considered to involve tissue hypoperfusion and hypoxia, which in turn induce endothelial damage and activation [31–33], and an iatrogenic factor that occurs secondary to uncritical volume therapy leading to acidosis, hypothermia, and hemodilution [33]. Maternal hemorrhage is also associated with a high risk of early coagulopathy, because loss of clotting factors by placental separation and atonic bleeding causes early progression, so dilute coagulopathy is more likely to occur with a small amount of bleeding compared to intraoperative bleeding in other diseases, and obstetric disseminated intravascular coagulation with premature separation of the placenta and amniotic fluid embolism shows a very high bleeding tendency [34]. Both trauma and maternal hemorrhage are prone to

a high degree of coagulopathy, since the properties cause coagulopathy as well as consequences of bleeding and dilution. In the present study, many coagulopathies were observed due to trauma and maternal hemorrhage.

On the other hand, coagulopathy due to gastrointestinal hemorrhage was not observed. Although many facilities use massive transfusion protocols for early replacement of coagulation factors in cases other than trauma [35, 36], the results of this study suggest that administration of a high ratio of FFP to RBCs for gastrointestinal bleeding may not be effective. Many reports have described restriction of blood transfusion as showing better prognosis for gastrointestinal bleeding [37–39]. However, since many reports exclude massive bleeding or do not consider severity, transfusion strategies for severe gastrointestinal hemorrhage warrant closer consideration.

This study showed several limitations that merit consideration when interpreting the results. First, this study was a single-center, retrospective study, and the number of subjects was limited, so our results cannot be generalized. However, the results that a large infusion volume of crystalloid solution is associated with coagulopathy and that the presence of early coagulopathy is associated with poor prognosis were the same as reported elsewhere. Few reports have examined whether DCR is performed in prehospital settings, so the result of low compliance with DCR seems to be a problem that is not exclusive to our region. Second, the judgement of the doctor from the referring hospital was adopted in the definition of massive hemorrhage, because blood pressure or estimated blood loss is difficult to determine due to intra- or retroperitoneal hemorrhage in some cases. Although this involved the inclusion of subjective judgments from doctors at the referring hospital, there was not considered to be any difference in treatment content or prognosis after transfer, because this study did not identify the doctor from the referring hospital or the doctor in charge at that time. Third, this study involved a review of medical records, so if the details of treatment by the doctor from the referring hospital remain unclear, missing values may occur, and results may differ. Fourth, the 30-day mortality rate was 9.1% in the overall study cohort and 13.5% in trauma cases. No deaths due to ruptured aortic aneurysm were identified. Mortality rates in studies of massive hemorrhage due to trauma reportedly vary from 8.4–37.5% [5, 7, 12], but were generally higher than the mortality rates in this survey. This was thought to be due to the exclusion of more severe patients, such as those who experienced cardiac arrest before arrival at our center or those in an unstable condition and could not be transferred to the hospital. Preventing coagulopathy may stabilize the patient into a transferable condition, which does not change the conclusion that early response to coagulopathy is warranted.

Conclusion

Many patients transferred to our center with massive hemorrhage showed coagulopathy at the time of visit. Risk factors for coagulopathy at the time of transfer were trauma and volume of crystalloid solution before arrival. Patients with coagulopathy at the time of visit showed a higher 24-h mortality rate. In our area, withholding intravenous fluid for permissive hypotension, early administration of FFP, and use of fibrinogen concentrate were suggested to improve the prognosis of patients with massive hemorrhage.

List Of Abbreviations

DCR, damage control resuscitation; PT-INR, prothrombin time-international normalized ratio; OR, odds ratio; CI, confidence interval; IQR, interquartile range; RBC, red blood cell, FFP, fresh frozen plasma; VEM, viscoelastic method

Declarations

Ethics approval and consent to participate

This study was approved by our institutional review board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Figures

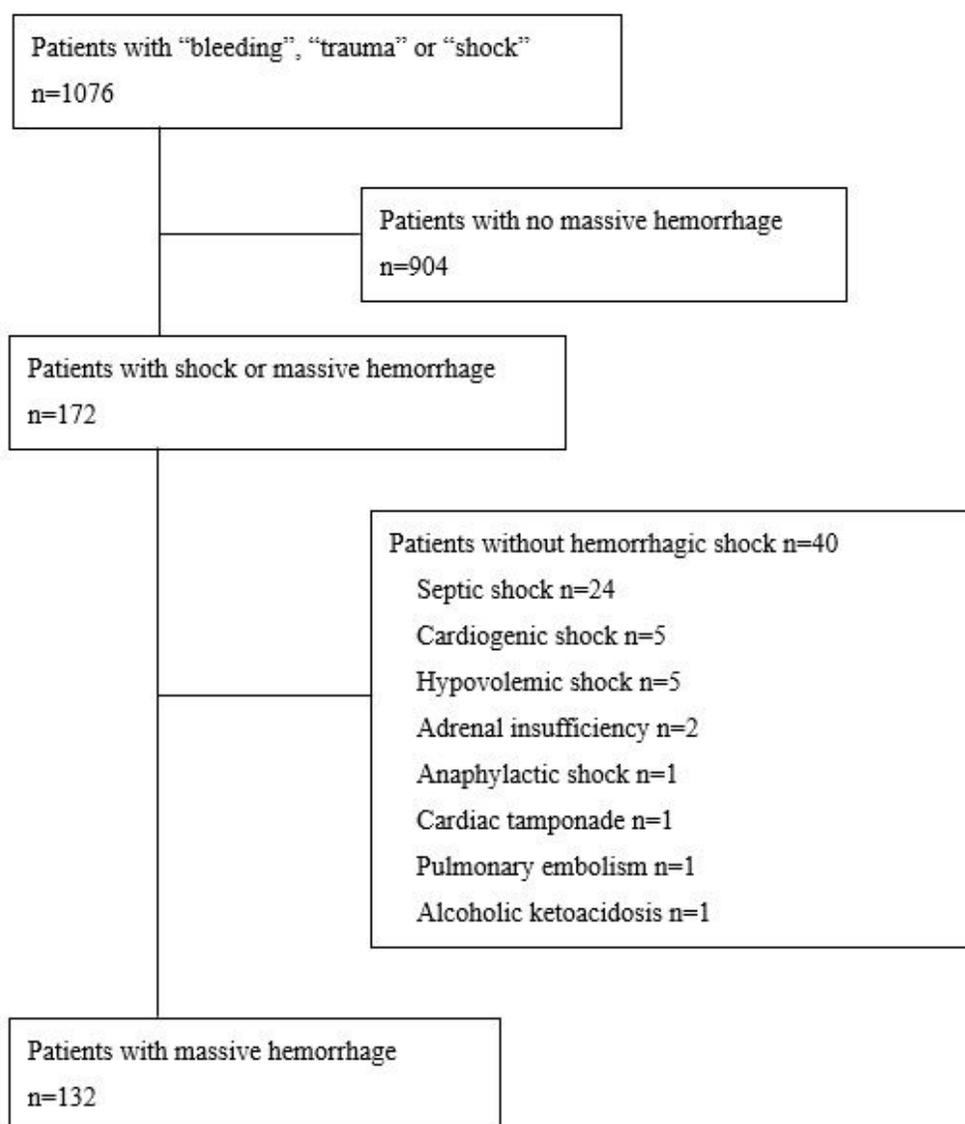


Figure 1

Screening process for study patients Over the 7-year study period, a total of 1076 patients were transferred to our hospital for treatment of bleeding, trauma, or shock. Among these, 172 patients had shock or massive hemorrhage. After excluding 40 shock patients with other causes of shock, 132 patients with massive hemorrhage were included.