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Original Article

The effect of acute variceal bleeding interventions on reducing the requirement of blood transfusions in cirrhotic patients: a systematic review

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Abstract: Background: Blood transfusions are commonly used to treat variceal bleeding in cirrhotic patients. However, massive transfusions can worsen portal hypertension and increase mortality in these patients. Minimizing blood usage is rarely considered when treating cirrhotic patients with variceal bleeding. Thus, we performed a systematic review to assess the effect of different variceal bleeding management strategies on reducing the blood transfusion volume in cirrhotic patients. Methods: PubMed, Embase (from inception to August 2014), and the Cochrane Library (2014, Issue 8) were searched for eligible randomized controlled trials (RCTs). Data were extracted and assessed for quality by two independent reviewers. The primary outcome of interest was the blood volume requirement. Results: We identified thirty-three RCTs including 3129 patients related to management of acute variceal bleeding. There was a large variation in the treatment interventions used to treat acute variceal bleeding, including endoscopic therapy, shunt therapy, pharmacological therapy and combined therapies. Approximately 58% (19/33) of the studies reported a significant difference among the different interventions in the number of units transfused per patient. Endoscopic plus pharmacological therapies tended to have the smallest required blood volume (1.9 units) compared with other interventions. Conclusions: There are many varied interventions for treating acute variceal bleeding in cirrhotic patients. For patient blood management in variceal bleeding, the combinatorial approach of endoscopic and pharmacological therapies can promptly control acute variceal bleeding prior to transfusion and reduce the subsequent blood transfusion requirements in cirrhotic patients. Appropriately designed RCTs that assess the effect of specific interventions on reducing blood transfusion requirements are urgently needed.

Keywords: Variceal bleeding, transfusion, liver cirrhosis, systematic review

Introduction

Liver cirrhosis is a frequent outcome of the long clinical course of all chronic liver diseases and is histologically characterized by tissue fibrosis and diffuse nodular regeneration [1]. Portal hypertension is the most significant consequence of cirrhosis and underlies the majority of the clinical complications of the disease. Variceal hemorrhage is common and perhaps the most devastating complication of portal hypertension and is the leading cause of death in patients with cirrhosis [2, 3].

Blood transfusion can often be life saving for patients with cirrhosis and portal hypertension who also have active variceal bleeding. As blood is a precious resource, and blood shortages are a problem that requires more attention. In addition, transfusion-related risks, such as infectious agents (e.g., HIV and viral hepatitis), transfusion-related acute lung injury (TRALI), transfusion reactions, and circulatory overload, are serious complications that must be considered [4]. Most importantly, the presumed benefits of blood transfusion are being challenged by increasing evidence that massive transfusions are likely to worsen portal hypertension due to volume overload, which is associated with increased mortality and higher rebleeding [5-7]. Therefore, reducing the required blood transfusion volume in cirrhotic pa-

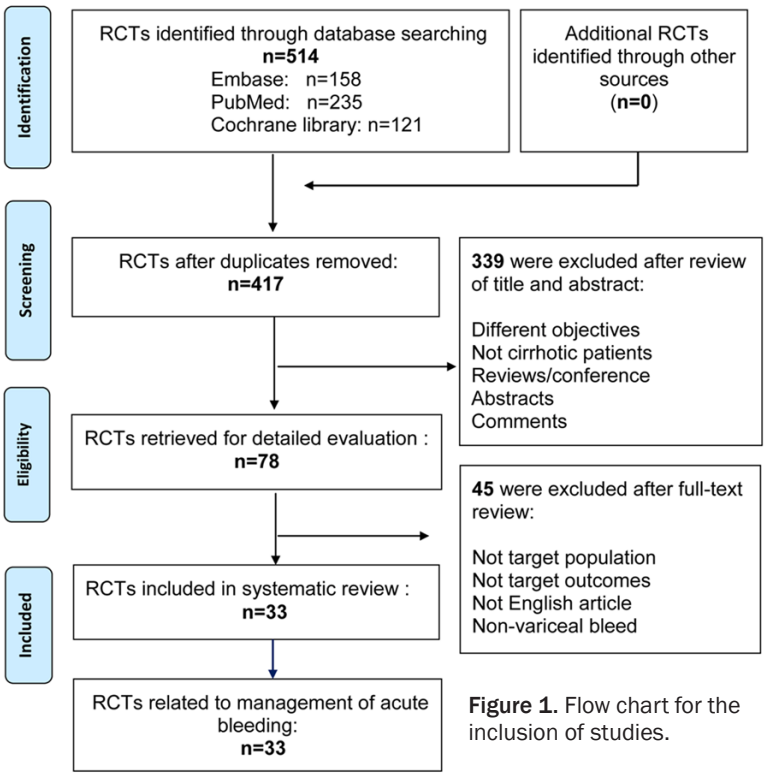

Figure 1. Flow chart for the inclusion of studies.

tients with active variceal hemorrhage can preserve our limited blood resources and potentially improve patient outcomes.

Blood conservation regarded as a means to promote the appropriate use of blood and minimizing their use, which can be implemented at different stages in the management of variceal bleeding [3, 9]. Though a restrictive transfusion strategy in patients with gastrointestinal bleeding may have a profound impact in blood product use, and may even result in reduced morbidity and mortality [9], if acute variceal bleeding is controlled promptly prior to transfusion, we can reduce the following blood requirements fundamentally. So various interventions for the management of variceal bleeding, including pharmacological therapy, endoscopic therapy and shunt therapy, are pre-emptive blood conservation strategies in cirrhotic patients. However, detailed information on the effect of these strategies for the management of variceal bleeding on blood usage in cirrhotic patients is unknown. We conducted a systematic review of randomized controlled trials (RCTs) to assess the effect of different intervention strategies on reducing blood transfusion volume in cirrhotic patients.

Materials and methods

Publication search and inclusion criteria

A comprehensive search of the PubMed, Embase (from inception to August, 2014), and Cochrane Library (2014, Issue 8) databases and a manual search were performed to identify all relevant RCTs on interventions for the management of variceal bleeding in patients with liver cirrhosis. The following words were used: "cirrhosis", "variceal bleeding", "blood transfusion", and "blood requirement".

Studies were included when the following criteria were fulfilled: (i) The participants were cirrhotic patients with acute variceal bleeding; (ii) The patients were over 18 years of age; (iii) The study addressed intervention or treatment measures for variceal bleeding; (iv) The number of units transfused was reported; and (v) The study was an RCT. Reviews, letters, abstracts, case reports and non-English language articles were excluded. We also excluded studies that reported patients with variceal bleeding due to non-cirrhotic portal hypertension and that included cirrhotic patients with non-variceal bleeding, such as bleeding due to portal hypertensive gastropathy. Disagreements for inclusion were resolved by Dr. Li and Dr. Wen.

Bias assessment

Guixiang Sun and Yao Lu independently assessed the risk of bias according to the Cochrane risk of bias tool [10]. The following six elements were used: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting, and free of other bias.

Data extraction

Guixiang Sun and Fang Teng independently extracted data from the included articles using

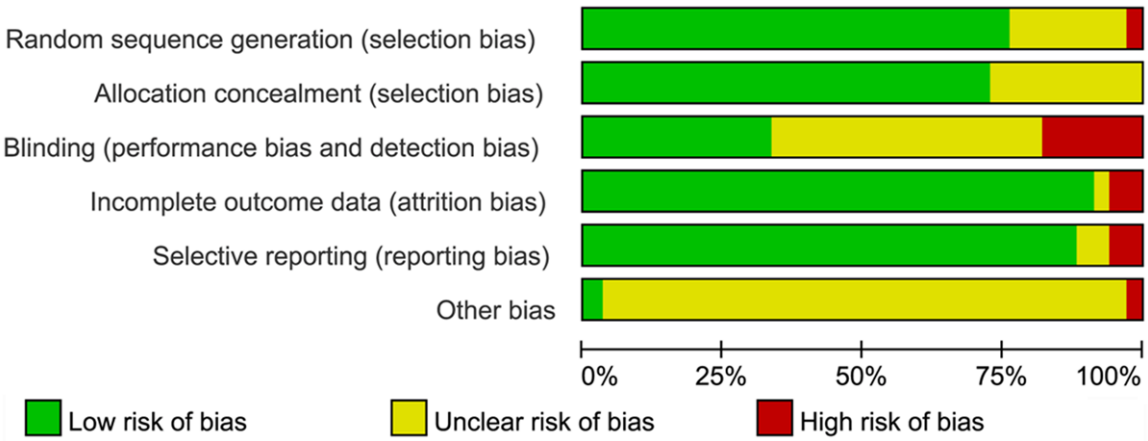

Figure 2. A review of the authors' judgments on each risk of bias item for each included study.

standardized forms. The recorded data included the following: 1) Study characteristics (author, publication year, study design, patient population, and interventions); 2) Outcome: blood requirements (number of blood units transfused while in respective timeframe); and 3) Quality of individual studies. Any necessary unpublished data were obtained by contacting the corresponding authors whenever possible.

Data analysis

Blood requirement was used to assess endpoint outcome. The studies were stratified according to the characteristics of their interventions. Meta-analysis was not conducted due to the considerable heterogeneity in the study interventions. We displayed the volume of blood transfusion both experimental and control groups as mean in a forest map. All analyses were done using Excel software.

Results

Literature search and selection

The search strategy identified 514 RCTs. A total of 97 articles were excluded because of duplication. After reviewing the titles and abstracts, an additional 339 studies were excluded. Seventy-eight references were retrieved for further assessment. Finally, 33 RCTs [11-43] fulfilled our inclusion criteria and were included in our systematic review. The details of study selection flow diagram were explicitly described in **Figure 1**.

Quality of included studies

The quality of the included studies was assessed using the Cochrane risk of bias tool (**Figure 2**). Only 12 (36%) trials reported adequate methods of randomization, allocation concealment, blinding, missing data, and most relevant outcome. Specifically, twenty-six (79%) trials reported the method of random sequence generation, twenty-four (73%) trials described allocation concealment, and seventeen (52%) trials reported blinding. There were no apparent losses to follow-up in 32 of the included trials (97%). Thirty-one (94%) trials reported the main relevant outcome. Other potential sources of bias were unclear in the majority of the trials. Each risk of bias item for all the included studies is shown in Figure S1.

Study characteristics

The 33 identified studies were published between 1984 and 2012 in 15 different countries (**Table 1**). All the included trials were related to the management of acute variceal bleeding in patients with cirrhosis. Approximately 67% (22/33) of the studies adopted a single intervention strategy to treat bleeding. We observed large variations in interventions involving sclerotherapy versus non-sclerotherapy (3 portacaval shunt [11, 14, 37], 1 sham sclerotherapy [23], 1 staple transection of the esophagus [16], 1 octreotide [24], and 1 standard medical therapy [13]); band ligation versus other interventions (2 endoscopic variceal obturation [27, 41], 1 somatostatin [31]); emergency portacaval shunt versus other interven-

Table 1. Study characteristics

Studies	Countries	Participants*	Intervention	Control	Outcome (Timeframe)	Study design
John P Cello [11] 1984	America	Cirrhosis, Child class C, bleeding, requiring at least six units of packed red cells or whole blood	Endoscopic sclerotherapy	Portacaval shunt	Blood requirement (Hospitalization)	RCT
John P Cello [14] 1987	America	Cirrhosis, Child class C, variceal hemorrhage, requiring six or more units of transfused blood	Endoscopic sclerotherapy	Portacaval shunt	Blood requirement (Hospitalization)	RCT
Marshall J Orloff [37] 2009	America	Cirrhosis, acute BEV, required transfusion of >2 U of blood	Endoscopic sclerotherapy	Portacaval shunt	Blood requirement (Hospitalization)	RCT
Pamela M Hartigan [23] 1997	America	Cirrhosis, male, bleeding from esophageal varices	Endoscopic sclerotherapy	Sham sclerotherapy	Blood requirement (Hospitalization)	Multicenter RCT
Andrew K Burroughs [16] 1989	United Kingdom	Cirrhosis, hematemesis or melena, a failure to control variceal bleeding, esophageal transection had not been performed previously, 16 years of age or older	Endoscopic sclerotherapy	Staple transection of the esophagus	Blood requirement (Hospitalization)	RCT
Bulent Sivri [24] 2000	Turkey	Cirrhosis, active bleeding from esophageal varices	Endoscopic sclerotherapy	Octreotide	Blood requirement (NR)	RCT
Alan W Larson [13] 1986	America	Cirrhosis, variceal hemorrhage	Endoscopic sclerotherapy	Standard medical therapy	Blood requirement (Two weeks)	RCT
Gin Ho Lo [27] 2001	Spain	Cirrhosis, 20 and 70 years of age, gastric variceal bleeding	Band ligation	Endoscopic obturation	Blood requirement (NR)	RCT
Neven Ljubicic [41] 2011	Croatia	Cirrhosis, acute gastrointestinal bleeding	Band ligation	N-butyl-2-cyanoacrylate injection	Blood requirement (NR)	RCT
Wen Chi Chen [31] 2006	Taiwan	Cirrhosis, acute EVB, admission within 12 hours after onset of the symptoms, no use of vasoactive drugs or endoscopic therapy before referral to our hospital, age between 20 and 75 years	Band ligation	Somatostatin	Blood requirement (NR)	RCT
Marshall J Orloff [43] 2012	America	Cirrhosis, acute BEV	Emergency portacaval shunt	TIPS	Blood requirement (NR)	RCT
Marshall J Orloff [20] 1994	America	Cirrhosis, bleeding esophageal varices	Emergency portacaval shunt	Emergency medical therapy: Intravenous vasopressin and esophageal balloon tamponade	Blood requirement (Hospitalization)	RCT
Marshall J Orloff [40] 2010	America	Cirrhosis, acute bleeding esophageal varices	Emergency portacaval shunt	Endoscopic sclerotherapy followed by rescue portacaval shunt	Blood requirement (NR)	RCT
Alberto Monescillo [30] 2004	Spain	Cirrhosis, age between 18 and 75 years, bleeding variceal	High risk +TIPS group: (High risk: Hepatic venous pressure gradient (HVPG)≥20 mmHg)	High risk +non-TIPS group	Blood requirement (Hospitalization)	RCT
Guo Shiou Liao [39] 2009	Taiwan	Cirrhosis, bleeding EGV, failed management with emergency endoscopy treatment or balloon tamponade with vasopressin infusion	Simplified surgical procedure	Modified surgical procedure	Blood requirement (Pre-operation/ during operation)	RCT
Shahab Abid [38] 2009	Sweden	Cirrhosis, upper gastrointestinal bleed	Octreotide	Terlipressin	Blood requirement (NR)	RCT
Christine Silvain [19] 1993	France	Cirrhosis, active variceal bleeding	Octreotide	Terlipressin + Nitroglycerin	Blood requirement (During treatment)	Multicenter RCT
J Pinto Correia [12] 1984	Portugal	Cirrhosis, actively bleeding esophageal or gastric varices	Vasopressin	Esophageal balloon tamponade	Blood requirement (During treatment)	RCT

Rey Heng Hu [33] 2008	Taiwan	Cirrhosis, esophageal varices with acute gastrointestinal bleeding	New brand of terlipressin: Haemopressin	Currently terlipressin: Glypressin	Blood requirement (NR)	RCT
Radan Bruha [35] 2009	Czech republic	Cirrhosis, Child-Pugh classification B or C, acute digestive tract bleeding, age between 18 and 70 years	5-day terlipressin	10-day terlipressin	Blood requirement (NR)	Multicenter RCT
C Soderlund [17] 1990	Sweden	Cirrhosis, extensive upper gastrointestinal tract bleeding	Terlipressin	Placebo	Blood requirement (36 hours)	RCT
Ibrahim Altraif [42] 2011	Saudi arabia	Cirrhosis, older than 18 years of age, hemodynamically stable	Erythromycin	Placebo	Blood requirement (24 hours)	RCT
Th Patsanas [29] 2002	France	Cirrhosis, esophageal varices	Sclerotherapy + Octreotide	Octreotide	Blood requirement (NR)	RCT
Isabelle Besson [21] 1995	France	Cirrhosis, acute variceal bleeding	Sclerotherapy + Octreotide	Sclerotherapy + Placebo	Blood requirement (24 hours/ 5 days)	Multicenter RCT
Bader Faiyaz [25] 2000	Pakistan	Cirrhosis, first episode of variceal bleeding from either esophageal or gastric junctional varices	Sclerotherapy + Octreotide	Sclerotherapy + Placebo	Blood requirement (NR)	RCT
GF Morales [32] 2007	Brazil	Cirrhosis, active variceal bleeding, nonbleeding varices with stigmata of recent bleeding, evidence of blood in the upper hemorrhage tract with no other potential source of hemorrhage	Sclerotherapy + Octreotide	Sclerotherapy + Placebo	Blood requirement (NR)	RCT
Paul Cales [28] 2001	France	Cirrhosis , 18 and 75 years of age, an interval of less than 24 hours between the initial episode of bleeding and enrollment, an interval of less than 6 hours between hospital admission and enrollment	Endoscopy + Vapreotide	Endoscopy + Placebo	Blood requirement (5 days/ 42 days)	Multicenter RCT
A Avgerinos [22] 1997	Greece	Cirrhosis, acute variceal bleeding	Sclerotherapy + Somatostatin	Sclerotherapy + Placebo	Blood requirement (NR)	Multicenter RCT
G H Lo [36] 2009	Taiwan	Cirrhosis, 18 and 75 years of age, acute inactive esophageal variceal bleeding	Banding ligation + Terlipressin	Terlipressin	Blood requirement (48 hours/ 2-5 days)	RCT
Liu Jin song [34] 2009	Taiwan	Cirrhosis, bleeding from esophageal varices, age from 20 to 70 years, hospitalized within 12 hours after onset of the symptoms, no use of vasoactive medicine or endoscopic therapy before referral to hospital	Endoscopic ligation + Octreotide	Octreotide	Blood requirement (NR)	RCT
F Junquera [26] 2000	Spain	Cirrhosis, gastrointestinal bleeding from esophageal or gastric varices	Somatostatin + Oral isosorbide-5-mononitrate	Somatostatin	Blood requirement (NR)	RCT
Jaime Bosch [15] 1989	Spain	Cirrhosis, acute variceal hemorrhage, no contraindications	Vasopressin + Nitroglycerin	Vasopressin + Placebo	Blood requirement (NR)	RCT
Roberto De Franchis [18] 1993	Italy	Cirrhosis, active variceal bleeding	Terlipressin + Desmopressin	Terlipressin + Placebo	Blood requirement (NR)	Multicenter RCT

Abbreviation: RCT, randomized controlled trial; EVB, esophageal variceal bleed; BEV, bleeding esophagogastric varices; EVS, endoscopic variceal sclerotherapy; NR, not reported. *Exclusion criteria not shown, and data are available in the original papers.

Table 2. Characteristics of study participants

Number	Study (yr)	No. of patients (A/C)	Age (mean or mean ± SD) (yr) (A/C)	Males (%) (A/C)	Alcoholic etiology (%) (A/C)	Child-Pugh class n (%) (A; C)
1	John P Cello [11] 1984	28/24	45±2/44±2	89.3/87.5	82.1/100	C 28 (100); C 24 (100)
2	J Pinto Correia [12] 1984	17/20	50.1/47.7	41.2/30	70.6/85	A 7 (41)/B 8 (47)/C 2 (12); A 6 (30)/B 11 (55)/C 3 (15)
3	Alan W Larson [13] 1986	44/38	45.8±11.5/45±10.3	75/78.9	81.8/73.7	A 7 (16)/B 13 (30)/C 24 (54); A 6 (16)/B 9 (24)/C 23 (60)
4	John P Cello [14] 1987	32/32	44±2/44±2	90.6/81.3	84.4/100	C 32 (100); C 32 (100)
5	Jaime Bosch [15] 1989	30/35	53±11/52±11	80/74.3	60/62.9	A 5 (17)/B 11 (37)/C 14 (46); A 4 (11)/B 12 (34)/C 19 (55)
6	Andrew K Burroughs [16] 1989	50/51	55/53	72/52.9	48/52.9	A 5 (10)/B 17 (34)/C 28 (56); A 5 (10)/B 18 (35)/C 28 (55)
7	C Soderlund [17] 1990	31/29	57±11/60±13	64.5/72.4	77.4/86.2	A+B 20 (65)/C 11 (35); A+B 20 (69)/C 9 (31)
8	Roberto De Franchis [18] 1993	24/22	56/59	75/63.6	66.6/45	A 9 (37)/B 12 (50)/C 3 (13); A 8 (36)/B 8 (36)/C 6 (28)
9	Christine Silvain [19] 1993	41/46	58 (37-77)/57 (37-76)	82.9/76.1	90/91	A 5 (12)/B 16 (39)/C 20 (49); A 9 (19)/B 16 (35)/C 21 (46)
10	Marshall J Orloff [20] 1994	21/22	<40 y: 1, 40-49 y: 5, 50-59 y: 11, >60 y: 4; <40 y: 2, 40-49 y: 3, 50-59 y: 10, >60 y: 7	100/100	95/95	A 2(10)/B 8(38)/C 11 (52) A 10(45)/B 5(23)/C 7 (32)
11	Isabelle Besson [21] 1995	98/101	56/56	73.5/79.2	90.8/92.1	A 26 (26)/B 46 (47)/C 26 (27); A 17 (17)/B 37 (37)/C 47 (46)
12	A Avgerinos [22] 1997	101/104	58.7±1.2/58.4±1.3	71.3/70.2	58.4/58.6	A 18 (18)/B 46 (46)/C 25 (25); A 20 (19)/B 52 (50)/C 29 (28)
13	Pamela M Hartigan [23] 1997	44/43	Total: 53	100/100	Total: 83% (over 15 yr)	A 8 (18)/B 24 (55)/C 12 (27); A 13 (30)/B 12 (28)/C 18 (42)
14	Bulent Sivri [24] 2000	28/24	48±9.4/46±10.4	47.4/29.2	25/20.8	A 3 (11)/B 10 (36)/C 15 (53); A 2 (8)/B 9 (38)/C 13 (54)
15	Bader Faiyaz [25] 2000	35/35	38.7±7.8/38.2±9.4	Total: 80% (56/70)	8.6/5.7	Child score 5.7 ±0.8; Child score 5.9 ±0.6
16	F Junquera [26] 2000	30/30	64±8/60±10	66.7/76.7	43.3/36.7	A+B 24 (80)/C 6 (20); A+B 28 (93)/C 2 (7)
17	Gin Ho Lo [27] 2001	31/29	58±17/55±13	77.4/75.9	32.2/20.7	A 8 (26)/B 16 (52)/C 7 (22); A 5 (18)/B 17 (58)/C 7(24)
18	Paul Cales [28] 2001	98/98	55±11/55±11	68/83	84/86	A 14 (14)/B 42 (43)/C 36 (37); A 14 (14)/B 41 (42)/C 39 (40)
19	Th Patsanas [29] 2002	15/15	50 (24-75)/52 (27-76)	78.5/66.7	53/53	A 2 (13)/B 4 (27)/C 9 (60); A 4 (27)/B 3 (20)/C 8 (53)

20	Alberto Monescillo [30] 2004	26/26	56±12/59±11	84.6/73.1	80.7/61.5	A 11 (42)/B 3 (12)/C 12 (46); A 4 (16)/B 10 (38)/C 12 (46)
21	Wen Chi Chen [31] 2006	62/63	54.5±12.8/51.8±15.2	69.3/82.5	38.7/46	A 13 (21)/B 31 (50)/C 18 (29); A 18 (29)/B 27 (43)/C 18 (28)
22	GF Morales [32] 2007	40/28	52.15/51.41	67.5/64.2	22.5/7.1	A+B 16 (40)/C 24 (60); A+B 18 (64)/C 10 (36)
23	Rey Heng Hu [33] 2008	19/22	58.16±11.74/54.82±12.14	63.2/72.7	Viral: 68.4/72.7	A 6 (31)/B 6 (31)/C 7 (38); A 6 (27)/B 11 (50)/C 4 (18)
24	Liu Jin song [34] 2009	51/50	42±11/40±15	78.4/84	NR	B 23 (45)/C 28 (55); B 26 (52)/C 24 (48)
25	Radan Bruha [35] 2009	15/10	49.4±12/56.3±13.5	46.7/100	93.3/100	B 9 (60)/C 6(40); B 8 (80)/C 2(20)
26	G H Lo [36] 2009	46/47	50±12/52±11	89.1/76.6	37/32	A 14 (30)/B 25 (54)/C 7 (15); A 13 (27)/B 20 (43)/C 14 (30)
27	Shahab Abid [37] 2009	163/161	48.9±10.4/51.7±11.4	Total: 71% (230/324)	HCV 70/66	A 12 (7)/B 76 (47)/C 75 (46); A 8 (5)/B 53 (33)/C 100 (62)
28	Guo Shiou Liao [38] 2009	26/25	52.5/54	80.8/64	23.1/28	A 3 (12)/B 18 (69)/C 5 (19); A 2 (8)/B 17 (68)/C 6 (24)
29	Marshall J Orloff [39] 2009	106/105	47.8/49.8	76.4/77.1	55/51	A 32 (30)/B 46 (43)/C 28 (26) A 26 (25)/B 49 (47)/C 30 (28)
30	Marshall J Orloff [40] 2010	105/50	49.9/ 47.7	78/78	51/54	A 26(25)/B 49 (47)/C 30 (28) A 14(28)/B 26 (52)/C 10 (20)
31	Neven Ljubicic [41] 2011	22/21	57±11.9/59±9.3	72.7/71.4	86% (37/43)	A 4 (18)/B 9 (41)/C 9 (41); A 8 (38)/B 9 (43)/C 4 (19)
32	Ibrahim Altraif [42] 2011	47/43	62.3±9.8/62.7±14.7	68.1/72.1	NR	Child score 7.9±2.5; Child score 8.1±2.3
33	Marshall J Orloff [43] 2012	76/78	49.1/49	78.9/71.8	32/37	A 15 (20)/B 37 (49)/C 24 (31) A 16 (21)/B 39 (50)/C 23 (29)

Abbreviations: A/C: active/control; NR, not reported; HCV, hepatitis C virus.

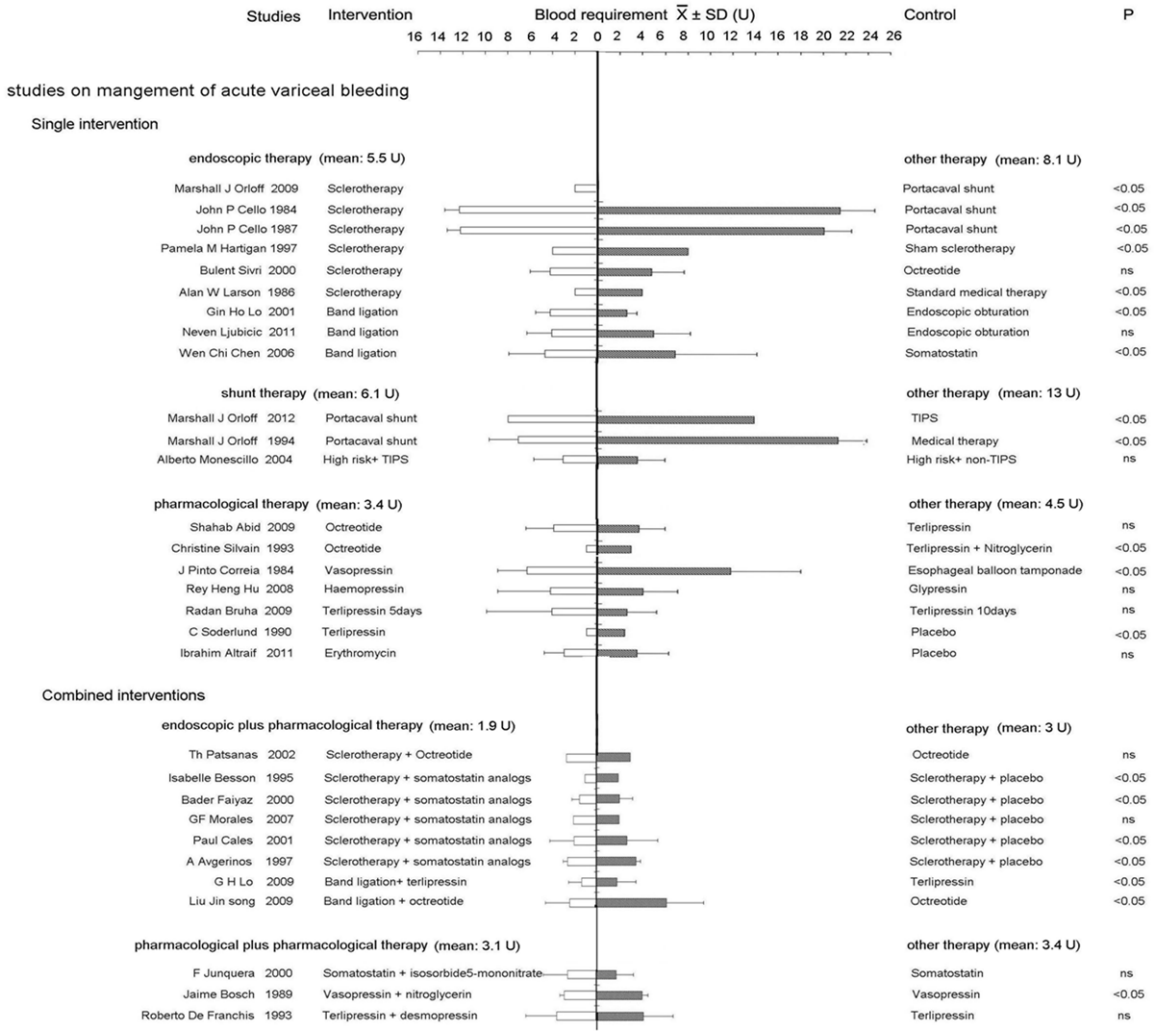

Figure 3. Effects of different interventions for the treatment of acute variceal bleeding on blood requirements in cirrhotic patients. Studies describing the management of acute variceal bleeding, which were stratified according to the characteristics of their interventions, including single intervention and combined interventions. The mean volume of blood transfused in each subgroup was calculated. The *P* value is derived from original article. TIPS: transjugular intrahepatic portosystemic shunt.

tions (1 TIPS [43], 1 emergency medical therapy [20], 1 sclerotherapy plus rescue portacaval shunt [40]); and other pharmacological therapies (2 octreotide [19, 38], 3 terlipressin [17, 33, 35], 1 vasopressin [12], 1 erythromycin [42]). The remaining 33% (11/33) used either a combination of endoscopic and pharmacological therapies [21, 22, 25, 28, 29, 32, 34, 36] or a combination of different pharmacological therapies [15, 18, 26] to treat acute variceal bleeding. All the trials reported blood requirements, but the timeframe in these studies was varied, and 52% (17/33) did not report the timeframe for blood requirements.

Characteristics of study participants

Table 2 shows the patient characteristics from the selected studies. A total of 3129 participants were enrolled in the 33 trials, and the mean sample size was 54 patients (range 10-163 patients). The mean patient age was 52 years, and the majority of the patients were male (mean proportion 75%, range 29% to 100%). Alcohol was the etiology of cirrhosis in more than half of the patients (mean 59%; range 6%-100%). The percentages of Child-Pugh A, B, and C patients were 18%, 42%, and 40%, respectively. Child-Pugh B and C patients

formed the predominant patient population (82%).

Outcome

We observed a large variation in interventions among trials. Thus, the majority of the data could not be pooled and were analyzed descriptively (**Figure 3**). Thirty trials reported the number of units transfused per patient as mean ± SD, and 3 studies [17, 34, 36] reported the total number of units transfused, which are not shown in **Figure 3**. A total of 19 (58%) of the studies reported a significant difference in the number of units transfused per patient with acute variceal bleeding among the different interventions.

For the management of acute bleeding, studies were stratified according to the characteristics of their interventions, including single and combined interventions. Single intervention for the treatment of acute bleeding included endoscopic therapy (e.g., sclerotherapy, band ligation and endoscopic obturation), shunt therapy (e.g., portacaval shunt and TIPS), and pharmacological therapy (e.g., vasopressin, terlipressin, somatostatin and its analogues, and prophylactic antibiotics). Combined interventions included endoscopic plus pharmacological therapies and combined pharmacotherapies. The mean volume of blood transfusion caused by the endoscopic and pharmacological combinatorial therapy was 1.9 units, which suggested that this approach required the lowest blood volume compared to other interventions (**Figure 3**).

Discussion

This systematic review described the effect of various interventions on the use of blood in cirrhotic patients with acute variceal bleeding from 33 RCTs. We observed that interventions on treatment of acute variceal bleeding in cirrhotic patients were varied. Approximately 58% (19/33) of the studies reported a significant reduction in the number of units transfused per patient. A combination of endoscopic and pharmacological therapies in the treatment of acute variceal bleeding resulted in the lowest blood transfusion volume when compared to other interventions. These findings of our study are similar with the results in a meta-analysis of RCTs [44].

Acute upper gastrointestinal bleeding in cirrhosis is the most common reason for emergency hospital admission and is also the leading indication for red blood cell transfusion [45]. The quantity of blood transfused is likely one of the indicator of the efficacy of blood management strategies to variceal bleeding [46]. For the purpose of patients blood management in variceal bleeding, on the one hand we can promptly control acute variceal bleeding prio to transfusion, on the other hand the strategies of blood transfusion and bleeding prophylaxis in patients with acute variceal bleeding need to be considered [47]. This systematic review demonstrated that more than half of the included studies showed a tendency to significantly control bleeding and reduce the utilization of blood in many different interventions, some of which should be preferred to treat acute variceal bleeding. However, in this review, we can't conclude which intervention is best for blood management and blood conservation in cirrhotic patients with acute variceal bleeding, because of the heterogeneity of interventions among the included trials. Nonetheless we found that a combination of pharmacological and endoscopic therapies appeared to be the preferred approach for reducing the utilization of blood volume required in the treatment of variceal bleeding, which was in accordance with current recommendations [48].

For the strategy of blood transfusion, RCTs indicate that a restrictive transfusion strategy (hemoglobin drops below 7 g/dL) saves blood without worsening, and in some cases even improving, the mortality observed with a liberal transfusion strategy (hemoglobin drops below 9 g/dL) [9, 49]. Two large observational studies have also indicated a strong correlation between RBC transfusion after acute upper gastrointestinal bleeding and the risk of further bleeding, with a trend towards increased mortality [50, 51].

In this review, although we cannot definitively determine which intervention is superior, we expect clinicians to become more aware of minimizing blood transfusion volumes in cirrhotic patients with variceal bleeding. Well-designed and adequately powered RCTs are needed to assess the effect of different interventions for variceal bleeding on reducing blood transfusion volumes. These studies would unify the criteria for both blood transfusion and transfusion

thresholds and should include the number of units transfused per patient and the adverse events associated with blood transfusion.

Limitations

Our study has several limitations. First, only 5 trials reported the criteria for blood transfusions, and only 7 trials reported the final outcome of maintaining hematocrit or hemoglobin levels. Therefore, the criteria for the transfusions likely differed. Second, the results of the individual studies were not combined because of the variability among the applied interventions. Instead, the descriptive data were presented for individual studies. Unfortunately, we cannot determine which intervention or combination of interventions is better at reducing the blood transfusion volume.

Conclusions

In this study, there is a significant variation in the effectiveness of interventions on the treatment of acute variceal bleeding in cirrhotic patients. For the purpose of patients' blood management in variceal bleeding, the combination of endoscopic and pharmacological therapies can promptly control acute variceal bleeding prio to transfusion and reduce the subsequent blood transfusion requirements in cirrhotic patients with acute variceal bleeding. Well-designed, high-quality RCTs are also needed to assess the effect of the specific interventions on the treatment of acute variceal bleeding in cirrhotic patients with regard to reducing blood transfusion volumes.

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Disclosure of conflict of interest

None.

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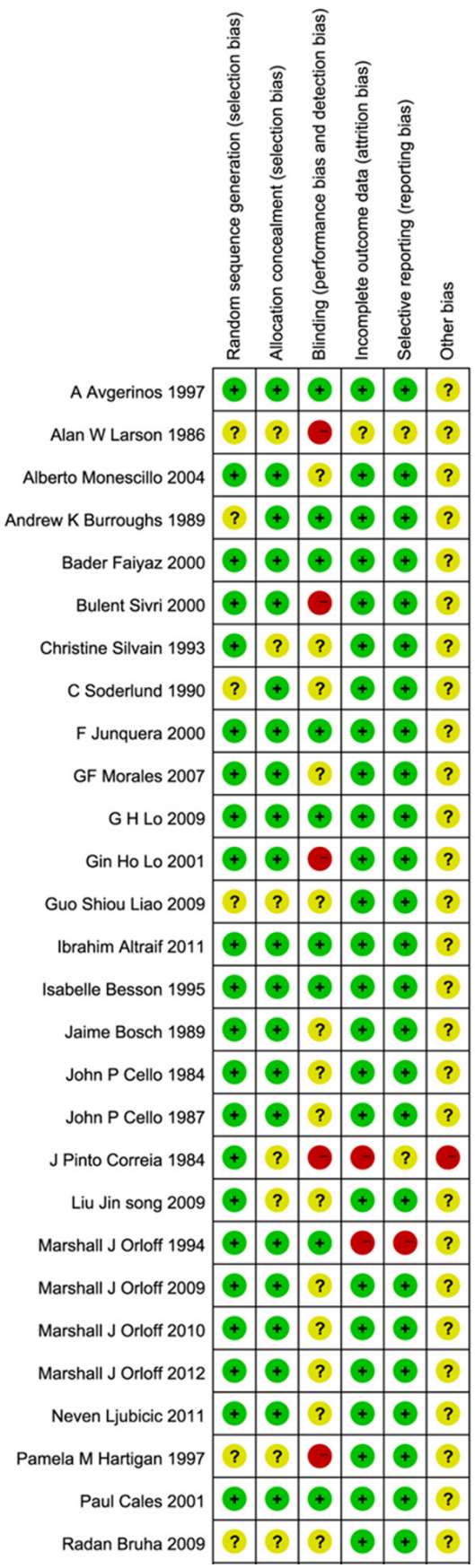
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding (performance bias and detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
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Alan W Larson 1986
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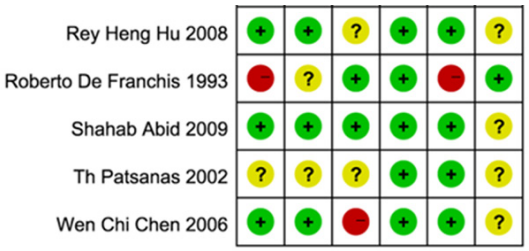

Figure S1. Each risk of bias item for each included study.