Systematic Review and Meta-Analysis

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Terlipressin for the treatment of acute variceal bleeding

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background and aim: Acute variceal bleeding (AVB) is life-threatening. We aimed to systematically review the current evidence regarding the efficacy and safety of terlipressin for AVB in liver cirrhosis.

Methods: We searched the PubMed, EMBASE, and Cochrane Library databases. The reference list was also hand-searched. Using a random-effect model, we combined the data obtained according to the different time points when the events developed. Odds ratio (OR) and weighted mean difference (WMD) were calculated. Quality of evidence was evaluated by the GRADE methodology.

Results: Thirty randomized controlled trials with 3344 patients were included. Compared with no vasoactive drug, terlipressin significantly improved the control of bleeding within 48 hours (OR = 2.94, $P = .0008$) and decreased the in-hospital mortality (OR = 0.31, $P = .008$). Compared with somatostatin, terlipressin had a significantly higher risk of complications (OR = 2.44, $P = .04$). Compared with octreotide, terlipressin had a significantly inferior control of bleeding within 24 hours (OR = 0.37, $P = .007$). Compared with vasopressin, terlipressin had a significantly lower risk of complications (OR = 0.15, $P = .02$). Compared with terlipressin combined with endoscopic variceal ligation, terlipressin alone had significantly higher 5-day treatment failure (OR = 14.46, $P = .01$) and transfusion requirements within 49 to 120 hours (WMD = 1.20, $P = .002$). No outcome was significantly different between terlipressin and sclerotherapy. Compared with balloon tamponade, terlipressin significantly decreased the 30-day rebleeding (OR = 0.05, $P = .001$) and transfusion requirements (WMD = −2.70, $P = .02$). Quality of evidence was very low to moderate.

Conclusion: Our findings were in accordance with the current recommendations regarding terlipressin for the treatment of AVB in cirrhosis. However, due to low quality of evidence, further studies are recommended.

Abbreviations: AVB = acute variceal bleeding, CI = confidence interval, EVL = endoscopic variceal ligation, OR = odds ratio, RCT = randomized controlled trial, WMD = weighted mean difference.

Keywords: hemorrhage, liver cirrhosis, portal hypertension, terlipressin, variceal

1. Introduction

Acute variceal bleeding (AVB) is one of the major complications in cirrhosis.[1] Despite great progress in the diagnostic methods and treatment measures of AVB in cirrhosis, it remains the main cause of death with a mortality of 15% to 20% in advanced cirrhosis.[2,3] Major treatment options for AVB include vasoactive agents, endoscopic sclerotherapy, endoscopic variceal ligation (EVL), balloon tamponade, transjugular intrahepatic portosystemic shunt (TIPS), and surgery.[4–6]

Vasoactive agents are the first-line choice of therapy for AVB. Terlipressin is a synthetic analogue of vasopressin with potent vasoactive properties and less adverse effects. It mainly acts on the V1 receptors which are predominantly located in the arterial smooth muscle within the splanchnic circulation, thereby reducing the splanchnic blood flow and portal pressure and controlling AVB.[7,8]

Several meta-analyses about terlipressin for AVB have been published (Supplementary Table 1, http://links.lww.com/MD/C663). However, their potential limitations should be recognized. Wang et al[9] performed a systematic review and meta-analysis to compare the risk of rebleeding between vasopressin/terlipressin and somatostatin/octreotide groups. However, only the risk of rebleeding alone was explored, and not the other outcomes of interests, such as survival, transfusion requirements,

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and risk of complications. Furthermore, only control group was somatostatin/octreotide, but not endoscopic therapy or balloon tamponade. Wells et al[10] performed a meta-analysis to evaluate the efficacy of all vasoactive drugs for AVB. The potential limitations are that the efficacy of vasoactive drugs alone was evaluated, but not the safety; different vasoactive drugs (i.e., terlipressin, vasopressin, somatostatin, and octreotide) with different properties were assigned into a treatment groups; the control group did not include endoscopic therapy or balloon tamponade; and the data regarding outcomes obtained at different time points from each individual study was synthesized. Ioannou et al[11] performed a systematic review to evaluate the efficacy and safety of terlipressin in AVB. However, there were a relatively smaller number of studies and patients and the data regarding outcomes obtained at different time points from each individual study was synthesized.

This study aimed to systematically review the current evidence regarding efficacy and safety of terlipressin for AVB in liver cirrhosis and evaluated the quality of evidence.

2. Methods

We reported a systematic review and meta-analysis of randomized controlled trials (RCTs) according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[12] This work was registered in the PROSPERO on September 5, 2017 (registration number: CRD42017075990). Ethical approval is not necessary for this study, because it is only a systematic review and meta-analysis of published studies and synthesizes the published data, but not an original article in human or animals.

2.1. Search strategy

We searched the PubMed, EMBASE, and Cochrane Library databases. The search was performed using the following terms: ("terlipressin" [All Fields]) AND ("gastric or gastrointestinal or esophageal or esophagus" [All Fields]) AND ("bleed or bleeding or blood or hemorrhage or variceal or varices" [All Fields]). The reference list was also hand-searched. The last search was performed on September 1, 2017. There was no language restriction. The full texts of 7 old articles were obtained from the National Science and Technology Library of China.

2.2. Selection criteria

Inclusion criteria were as follows: RCTs, patients with liver cirrhosis, patients with AVB confirmed by endoscopy, studies comparing terlipressin with other interventions, and studies reporting the efficacy and/or safety of terlipressin. Exclusion criteria were as follows: non-randomized design, duplicated studies, case reports, reviews, editorials, letters, protocols, experimental studies, irrelevant articles, and non-variceal hemorrhage.

2.3. Data extraction

The following items were extracted: patient baseline characteristics including age, sex, etiology, Child-Pugh class, ascites, encephalopathy, previous variceal bleeding, active bleeding at endoscopy, and source of bleeding; study characteristics including first author, year of publication, country, and study design; outcomes including control of bleeding, treatment failure, rebleeding, mortality, duration of hospital stay, transfusion requirements, and complications.

2.4. Risk of bias assessment

We used the Cochrane Collaboration tool for assessing the risk of bias of included RCTs. The main domains included the following: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias. The risk of bias for each domain was divided into "low," "high," and "unclear." The risk of bias for each study was evaluated as follows.

(1) If ≥1 domains were judged to be at high risk, the study would be considered to have a high risk of bias.
(2) If all domains were judged to be at low risk, the study would be considered to have a low risk of bias.
(3) If ≥1 domains were judged to be at unclear risk, the study would be considered to have a low (if key domains were judged to be at low risk and the domains at unclear risk were unlikely to seriously alter the results) or unclear risk of bias (if key domains were judged to be at unclear risk of bias, raising some doubt about the results).[13]

2.5. Statistical analysis

Statistical analyses were performed using the Review Manager (RevMan) version 5.3 (Cochrane Collaboration, Oxford, UK) and Stata version 12.0 (StataCorp, College Station, TX 77845). The difference in dichotomous variables was expressed as odds ratio (OR) with 95% confidence interval (CI) and the difference in continuous variables was expressed as weighted mean difference (WMD) and 95% CI. $P < .05$ for the difference was statistically significant. Data were pooled using the random-effect model. The heterogeneity was analyzed by I^2 and χ^2 test. $I^2 < 50\%$ and/or $P > .10$ represents no statistical heterogeneity among studies. If only one study was included, the heterogeneity could not be calculated. Publication bias was assessed by Egger test and Begg test. If only one study was included, the publication bias could not be calculated. As for the meta-analysis with a statistically significant heterogeneity, sensitivity analyses were performed by omitting one study each time to assess the robustness of results.

2.6. Quality of evidence

We graded the quality of evidence of the outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[14] The quality can be classified as high, moderate, low, and very low. The evidence from RCTs is categorized as high quality but can be downgraded by the limitations (i.e., risk of bias), inconsistency, indirectness, imprecision, and publication bias. The GRADEpro version 3.2 was used to produce the summary tables. The limitations were evaluated as follows:

(1) if a majority of patients were from the studies judged as low risk of bias, we would consider no serious limitations;
(2) if a majority of patients were from the studies judged as unclear risk of bias, we would consider serious limitations;
(3) if a majority of patients were from the studies judged as high risk of bias, we would consider very serious limitations.[15]

3. Results

3.1. Literature search and study characteristics

Our search strategy identified 1545 articles by computerized searches and additional 8 articles by hand-searching. We finally included 30 articles[16–45] with a total of 3344 patients (Fig. 1).

The number of patients in these studies ranged from 16 to 780. The patients' mean age ranged from 50 to 66 years old. The characteristics of included studies are listed in Table 1. The characteristics of patients are listed in Supplementary Table 2, http://links.lww.com/MD/C663. The outcomes are listed in Supplementary Table 3, http://links.lww.com/MD/C663. The definitions of outcomes are listed in Supplementary Table 4, http://links.lww.com/MD/C663. The specific type and number of complications reported among studies are listed in Supplementary Table 5, http://links.lww.com/MD/C663.

3.2. Risk of bias assessment

Risk of bias is shown in Supplementary Figure 1, http://links.lww.com/MD/C663. Eighteen and 12 studies were at high and unclear risk of bias, respectively. No study was at low risk of bias.

3.3. Meta-analyses

The results of meta-analyses regarding effect size, heterogeneity, and publication bias are shown in Table 2.

3.4. Terlipressin versus no vasoactive drug

Seven studies[20,31,34,36,37,42,44] with a total of 444 patients compared the outcomes of terlipressin with no vasoactive drug. Compared with no vasoactive drug, terlipressin significantly improved the control of bleeding within 48 hours (OR = 2.94, 95% CI = 1.57–5.51, $P = .0008$), with no significant effect on initial control of bleeding (OR = 2.50, 95% CI = 0.59–10.62, $P = .21$) or 5-day control of bleeding (OR = 1.86, 95% CI = 0.90–3.87, $P = .10$) (Fig. 2). Compared with no vasoactive drug, terlipressin significantly decreased the in-hospital mortality (OR = 0.31, 95% CI = 0.13–0.73, $P = .008$), with no significant effect on 5-day mortality (OR = 1.17, 95% CI = 0.52–2.62,

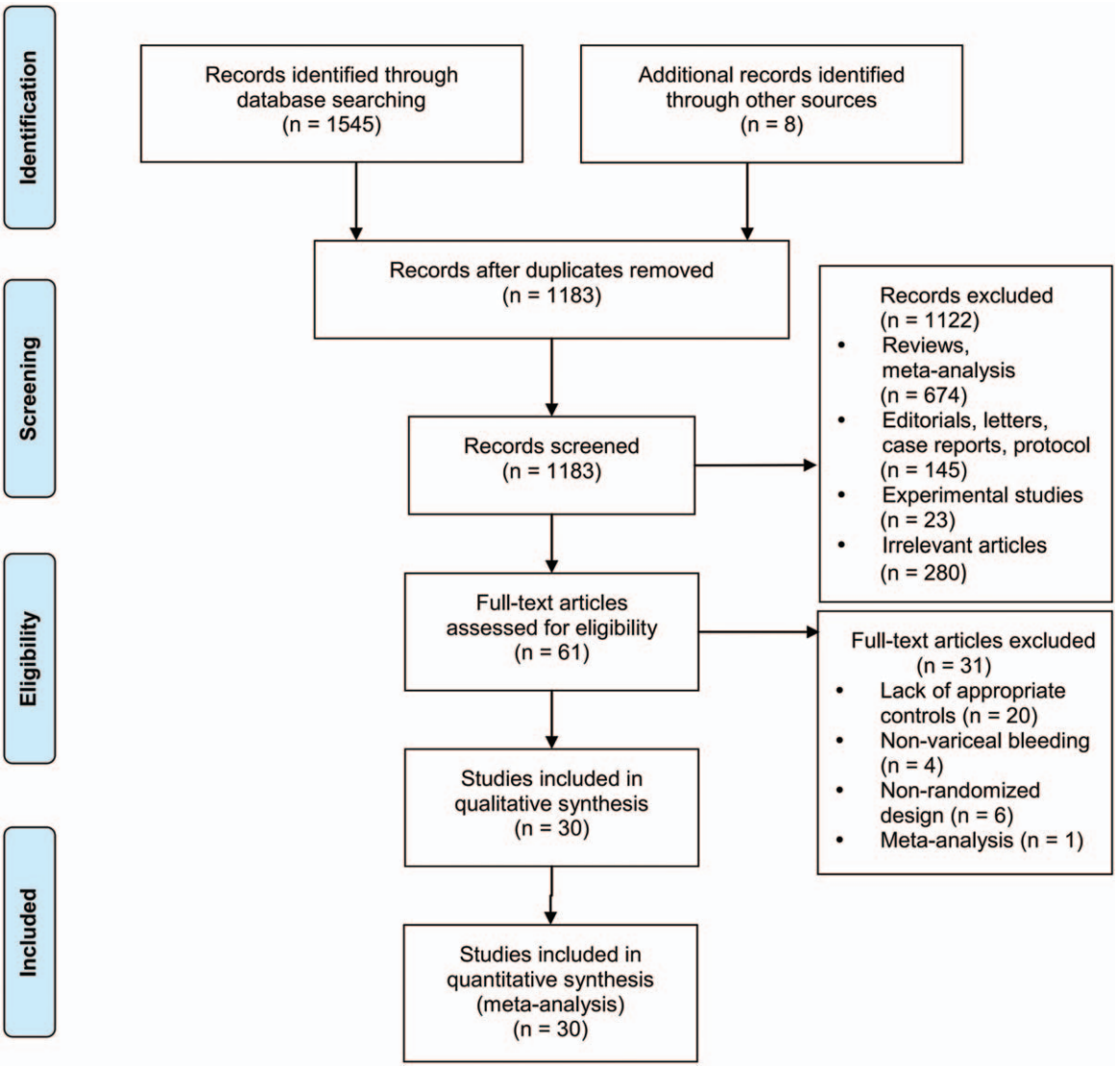

Figure 1. Flow chart of study selection.

Table 1

Characteristics of included studies.

First author (year)	Country	No. Pts	Terlipressin group Dose and duration	Control group Dose and duration	Initial therapeutic endoscopy at the time of diagnostic endoscopy	Length of follow-up
Terlipressin vs no vasoactive drug						
Walker (1986)	Germany	50	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 4 h for 36 h	No vasoactive drug	No	Discharge
Freeman (1989)	UK	31	Terlipressin 1–2 mg iv bolus every 4 h for 48 h	No vasoactive drug	No	Discharge
Söderlund (1990)	Sweden	60	Terlipressin 2 mg iv bolus every 4 h for 24–36 h	No vasoactive drug	No	Discharge
Pauwels (1994)	France	31	Terlipressin 2 mg iv bolus every 6 h until bleeding cessation; then 1 mg iv bolus every 6 h for 24 h	No vasoactive drug	No	30 d
Levacher (1995)	France	84	Terlipressin 2 mg iv bolus every 4 h for 48 h; then 1 mg iv bolus every 4 h for 72 h	No vasoactive drug	Yes (EIS)	42 d
Brunati (1996)	Italy	55	Terlipressin 2 mg iv bolus every 6 h for 48 h	No vasoactive drug	Yes (EIS)	5 d
Patch (1999)	UK	133	Terlipressin 2 mg iv bolus every 4 h for 48 h; then 1 mg iv bolus every 4 h for 72 h	No vasoactive drug	Yes (EIS)	42 d
Terlipressin vs somatostatin						
Pauwels (1994)	France	35	Terlipressin 2 mg iv bolus every 6 h until bleeding cessation; then 1 mg iv bolus every 6 h for 24 h	Somatostatin 250 μg iv bolus; then 250 μg/h infusion until 2 h after bleeding cessation	No	30 d
Walker (1996)	Germany	106	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 4 h for 24 h	Somatostatin 250 μg iv bolus; then 250 μg/h infusion for 24 h	No	30 d
Feu (1996)	Spain	161	Terlipressin 2 mg iv bolus every 4 h for 48 h	Somatostatin 250 μg iv bolus; then 250 μg/h infusion for 48 h	No	42 d
Ali (2001)	Turkey	34	Terlipressin 2 mg iv bolus; then 2 mg iv bolus every 4 h for 72 h	Somatostatin 250 μg iv bolus; then 250 μg/h infusion for 72 h	Yes (EIS)	Discharge
Chelarescu (2001)	Spain, France	59	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 4 h for 24 h	Somatostatin 50 μg iv bolus; then 50 μg/h infusion for 48 h	No	5 d
Seo (2006)	Korea	98	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 6 h for 5 days	Somatostatin 250 μg iv bolus; then 250 μg/h infusion for 5 d	No	42 d
Ck (2011)	India	142	Terlipressin, dose not specified, duration at least 48 h	Somatostatin, dose not specified, duration at least 48 h	Yes (Uncertain)	42 d
Seo (2014)	Korea	520	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 6 h for 5 d	Somatostatin 250 μg iv bolus; then 250 μg/h infusion for 5 d	Yes (EVL, EVO, EIS)	42 d
Terlipressin vs octreotide						
Silvain (1993)	France	87	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 4 h for 24 h	Octreotide 25 μg/h infusion for 12 h, 100 μg sc at 12 h and 18 h	No	30 d
Pedretti (1994)	Italy	60	Terlipressin 2 mg iv bolus every 4–6 h for 48 h; then 1 mg iv bolus every 6 h for 3–7 days	Octreotide 100 μg iv bolus; 25 μg/h infusion for 24 h; then 100 μg sc tid for 6 d	No	50 d
Brunati (1996)	Italy	56	Terlipressin 2 mg iv bolus every 6 h for 48 h	Octreotide 100 μg iv bolus every 8 h for 48 h	Yes (EIS)	5 d
Cho (2006)	Korea	88	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 4 h for 3 d	Octreotide 25 μg/h infusinon for 5 days	Yes (EVL)	42 d
Abid (2009)	Sweden	324	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 6 h for 72 h	Octreotide 100 μg iv bolus; then 50 μg/h infusion for 72 h	Yes (EVL)	Discharge
Ck (2011)	India	141	Terlipressin, dose not specified, duration at least 48 h	Octreotide, dose not specified, duration at least 48 h	Yes (Uncertain)	42 d
Seo (2014)	Korea	521	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 6 h for 5 days	Octreotide 50 μg iv bolus; then 25 μg/h infusion for 5 d	Yes (EVL, EVO, EIS)	42 d
Asad (2014)	Pakistan	80	Terlipressin, dose not specified, duration not specified	Octreotide, dose not specified, duration not specified	Yes (EVL)	30 d
Terlipressin vs vasopressin						
Freeman (1982)	UK	21	Terlipressin 2 mg iv bolus every 6 h until bleeding cessation; then 1 mg iv bolus every 6 h for another 18 h	Vasopressin 0.4 U/min infusion until bleeding cessation; then 0.2 U/min for another 18 h	No	Discharge
Desaint (1987)	Italy	16	Terlipressin 2 mg iv bolus every 6 h until bleeding cessation; then 1 mg iv bolus every 6 h for another 24 h	Vasopressin 0.3 U/kg/h infusion for 6 h	No	NA
Lee (1988)	Taiwan	45	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 6 h for 24 h	Vasopressin 0.66 U/h infusion for 6 h; then 0.33U/h up to 24 h	No	42 days
Chiu (1990)	Taiwan	54	Terlipressin 1–2 mg iv bolus every 4 h for 32 h	Vasopressin 0.2–0.4 U/min infusion for 32 h	No	Discharge
D'Amico (1994)	Italy	111	Terlipressin 2 mg iv bolus every 6 h	Vasopressin 0.4–0.8 U/min infusion	Yes (EIS)	30 d
Terlipressin vs terlipressin plus EVL						
Lo (2009)	Taiwan	93	Terlipressin 2 mg iv bolus; then 1 mg infusion every 6 h for 5 d	Terlipressin 2 mg iv bolus; then 1 mg infusion every 6 h for 48 h plus EVL	No	42 d
Terlipressin vs sclerotherapy						
Escorsell (2000)	France, Spain	219	Terlipressin 2 mg iv bolus every 4 h until bleeding cessation; then 1 mg iv bolus every 4 h for another 5 d	Sclerotherapy	NA	42 d
Terlipressin vs balloon tamponade						
Colin (1987)	France	81	Terlipressin 1–2 mg iv bolus every 6 h for 96 h	Sengstaken-Blakemore tube inflated until 24 h after bleeding cessation	No	Discharge
Fort (1990)	France	47	Terlipressin 2 mg iv bolus; then 1 mg iv bolus every 6 h for 30 h	Sengstaken-Blakemore tube for 24 h	No	Discharge
Blanc (1994)	France	40	Terlipressin 1–2 mg iv bolus every 4 h for 24 h	Linton-Michel tube for 24 h	No	30 d
Garcia- Compean (1997)	France	40	Terlipressin 1–2 mg iv bolus every 4 h for 24 h	Linton-Michel tube for 24 h	No	30 d

EIS = endoscopic injection sclerotherapy, EVL = endoscopic variceal ligation, EVO = endoscopic variceal obturation, iv = intravenous, NA = not applicable, sc = subcutaneous injection, tid = three times daily.

Table 2

Results of meta-analyses.

	No. studies	No. pts	Pooled OR [95% CI]	Pooled WMD [95% CI]	*P* value	Heterogeneity I^2	Heterogeneity χ^2 *P* value	Publication bias P_{Begg}	Publication bias P_{Egger}
1. Terlipressin vs no vasoactive drug									
1.1 Control of bleeding									
1.1.1 Initial control of bleeding	1	31	2.50 [0.59, 10.62]	–	.21	–	–	–	–
1.1.2 ≤48 hours control of bleeding	4	225	2.94 [1.57, 5.51]	–	.0008	10%	.34	1.000	.991
1.1.3 5-day control of bleeding	3	217	1.86 [0.90, 3.87]	–	.10	28%	.25	.296	.016
1.2 Rebleeding									
1.2.1 In-hospital rebleeding	2	81	0.74 [0.22, 2.47]	–	.63	0%	.4	1.000	–
1.2.2 48-hour rebleeding	1	31	2.64 [0.10, 69.88]	–	.56	–	–	–	–
1.2.3 42-day rebleeding	1	84	1.08 [0.44, 2.63]	–	.87	–	–	–	–
1.3 Mortality									
1.3.1 In-hospital mortality	3	141	0.31 [0.13, 0.73]	–	.008	0%	.43	.296	.097
1.3.2 5-day mortality	2	187	1.17 [0.52, 2.62]	–	.70	0%	.76	1.000	–
1.3.3 ≤42 days mortality	3	247	0.63 [0.37, 1.06]	–	.08	0%	.68	1.000	.723
1.4 Transfusion requirements	2	81	–	−0.62 [−1.75, 0.50]	.28	20%	.26	1.000	–
1.5 Complications	3	194	3.52 [0.97, 12.71]	–	.06	47%	.15	1.000	.65
2. Terlipressin vs somatostatin									
2.1 Control of bleeding									
2.1.1 Initial control of bleeding	3	768	1.35 [0.88, 2.07]	–	.17	0%	.65	.296	.335
2.1.2 48-hour control of bleeding	3	230	0.79 [0.41, 1.50]	–	.47	0%	.38	1.000	.868
2.2 Treatment failure									
2.2.1 24-hour treatment failure	1	106	0.52 [0.20, 1.32]	–	.17	–	–	–	–
2.2.2 5-day treatment failure	3	677	0.92 [0.61, 1.41]	–	.71	2%	.36	.296	.465
2.3 Rebleeding									
2.3.1 In-hospital rebleeding	1	106	1.76 [0.74, 4.15]	–	.20	–	–	–	–
2.3.2 ≤48 hours rebleeding	2	141	0.86 [0.27, 2.74]	–	.80	0%	.63	1.000	–
2.3.3 5-day rebleeding	2	618	1.10 [0.37, 3.26]	–	.87	41%	.19	1.000	–
2.3.4 42-day rebleeding	2	303	0.99 [0.57, 1.71]	–	.97	0%	.66	1.000	–
2.4 Mortality									
2.4.1 In-hospital mortality	2	140	0.85 [0.38, 1.91]	–	.69	0%	.49	1.000	–
2.4.2 5-day mortality	3	677	1.01 [0.59, 1.71]	–	.98	0%	.69	.296	.375
2.4.3 ≤42 days mortality	4	858	1.12 [0.76, 1.66]	–	.57	0%	.94	.734	.737
2.5 Transfusion requirements	6	954	–	0.59 [−0.19, 1.37]	.14	81%	.0001	.260	.144
2.6 Duration of hospital stay	2	204	–	−0.24 [−2.60, 2.12]	.84	0%	.39	1.000	–
2.7 Complications	4	822	2.44 [1.03, 5.80]	–	.04	51%	.11	1.000	.734
3. Terlipressin vs octreotide									
3.1 Control of bleeding									
3.1.1 Initial control of bleeding	5	1154	1.26 [0.74, 2.14]	–	.39	26%	.25	.806	.503
3.1.2 ≤24 hours control of bleeding	2	147	0.37 [0.18, 0.76]	–	.007	0%	.87	1.000	–
3.1.3 5-day control of bleeding	1	56	1.22 [0.35, 4.24]	–	.75	–	–	–	–
3.2 5-day treatment failure	1	521	0.83 [0.51, 1.35]	–	.45	–	–	–	–
3.3 Rebleeding									
3.3.1 ≤48 hours rebleeding	1	60	0.68 [0.20, 2.33]	–	.54	–	–	–	–
3.3.2 5-day rebleeding	3	689	0.84 [0.41, 1.71]	–	.63	0%	.65	1.000	.876
3.3.3 ≤42 days rebleeding	4	369	0.96 [0.35, 2.63]	–	.93	68%	.02	.308	.307
3.3.4 60-day rebleeding	1	60	1.00 [0.13, 7.60]	–	1.00	–	–	–	–
3.4. Mortality									
3.4.1 In-hospital mortality	1	324	1.29 [0.47, 3.54]	–	.63	–	–	–	–
3.4.2 5-day mortality	3	657	0.89 [0.51, 1.53]	–	.67	0%	.93	1.000	.705
3.4.3 ≤60 days mortality	6	977	1.03 [0.71, 1.48]	–	.88	0%	.91	1.000	.534
3.5 Transfusion requirements	4	993	–	0.02 [−0.29, 0.34]	.90	0%	.74	.734	.878
3.6 Duration of hospital stay	2	412	–	−1.25 [−3.04, 0.54]	.17	38%	.20	1.000	–
3.7 Complications	3	668	2.50 [0.83, 7.56]	–	.10	74%	.02	.296	.654
4. Terlipressin vs vasopressin									
4.1 24-hour control of bleeding	5	247	1.60 [0.53, 4.88]	–	.41	62%	.03	.806	.638
4.2 Rebleeding									
4.2.1 In-hospital rebleeding	2	34	3.27 [0.24, 45.29]	–	.38	53%	.15	1.000	–
4.2.2 7-day rebleeding	1	28	1.78 [0.32, 10.01]	–	.51	–	–	–	–
4.3 Mortality									
4.3.1 In-hospital mortality	3	91	1.20 [0.50, 2.89]	–	.69	0%	.74	1.000	.186
4.3.2 42-day mortality	1	45	1.82 [0.54, 6.07]	–	.33	–	–	–	–
4.4 Transfusion requirements	1	45	–	0.80 [−1.46, 3.06]	.49	–	–	–	–

(*continued*)

Table 2

(continued).

	No. studies	No. pts	Pooled OR [95% CI]	Pooled WMD [95% CI]	*P* value	Heterogeneity I^2	Heterogeneity χ^2 *P* value	Publication bias P_{Begg}	Publication bias P_{Egger}
4.5 Complications	1	25	0.15 [0.03, 0.78]	–	.02	–	–	–	–
5. Terlipressin vs terlipressin plus EVL									
5.1 48-hour control of bleeding	1	93	0.23 [0.02, 2.12]	–	.19	–	–	–	–
5.2 5-day treatment failure	1	93	14.46 [1.78, 117.33]	–	.01	–	–	–	–
5.3 48–120 hours rebleeding	1	93	18.04 [1.00, 325.75]	–	.05	–	–	–	–
5.4 42-day mortality	1	93	3.21 [0.32, 32.04]	–	.32	–	–		
5.5 Transfusion requirements									
5.5.1 ⩽48 hours transfusion requirements	1	93	–	0.60 [0.00, 1.20]	.05	–	–	–	–
5.5.2 49–120 hours transfusion requirements	1	93	–	1.20 [0.43, 1.97]	.002	–	–	–	–
5.6 Duration of hospital stay	1	93	–	1.30 [−0.94, 3.54]	.25	–	–	–	–
5.7 Complications	1	93	1.13 [0.50, 2.57]	–	.76	–	–	–	–
6. Terlipressin vs sclerotherapy									
6.1 48-hour control of bleeding	1	219	0.90 [0.46, 1.80]	–	.77	–	–	–	–
6.2 5-day treatment failure	1	219	1.08 [0.61, 1.91]	–	.78	–	–	–	–
6.3 Rebleeding									
6.3.1 5-day rebleeding	1	219	1.02 [0.48, 2.18]	–	.96	–	–	–	–
6.3.2 42-day rebleeding	1	219	0.96 [0.52, 1.78]	–	.91	–	–	–	–
6.4 42-day mortality	1	219	1.65 [0.85, 3.19]	–	.14	–	–	–	–
6.5 Transfusion requirements	1	219	–	0.20 [−1.01, 1.41]	.75	–	–	–	–
6.6 Duration of hospital stay	1	219	–	−1.00 [−3.65, 1.65]	.46	–	–	–	–
6.7 Complications	1	219	0.59 [0.32, 1.10]	–	.10	–	–	–	–
7. Terlipressin vs balloon tamponade									
7.1 ⩽48 hours control of bleeding	4	177	0.44 [0.14, 1.37]	–	.16	35%	.20	.174	.073
7.2 Rebleeding									
7.2.1 ⩽48 hours rebleeding	1	37	2.67 [0.55, 12.88]	–	.22	–	–	–	–
7.2.2 ⩽7 days rebleeding	2	77	0.51 [0.16, 1.57]	–	.24	0%	.41	1.000	–
7.2.3 30-day rebleeding	1	33	0.05 [0.01, 0.30]	–	.001	–	–	–	–
7.3 Mortality									
7.3.1 In-hospital mortality	2	101	0.72 [0.23, 2.29]	–	.58	0%	.67	1.000	–
7.3.2 7-day mortality	1	40	0.58 [0.14, 2.50]	–	.47	–	–	–	–
7.3.3 30-day mortality	2	80	1.00 [0.40, 2.51]	–	1.00	0%	1.00	1.000	–
7.4 Transfusion requirements	1	40	–	−2.70 [−4.98, −0.42]	.02	–	–	–	–
7.5 Complications	3	141	0.41 [0.10, 1.66]	–	.21	65%	.06	1.000	.614

CI = confidence interval, EVL = endoscopic variceal ligation, OR = odds ratio, WMD = weighted mean difference.

P = .70) or mortality within 42 days (OR = 0.63, 95% CI = 0.37–1.06, P = .08) (Fig. 3). There was no significant difference in the in-hospital (OR = 0.74, 95% CI = 0.22–2.47, P = .63), 48-hour (OR = 2.64, 95% CI = 0.10–69.88, P = .56), or 42-day rebleeding (OR = 1.08, 95% CI = 0.44–2.63, P = .87) between them. There was no significant difference in the transfusion requirements (WMD = −0.62, 95% CI = −1.75–0.50, P = .28) or incidence of complications (OR = 3.52, 95% CI = 0.97–12.71, P = .06) between them. The heterogeneity was not statistically significant in these above-mentioned meta-analyses. Thus, the sensitivity analysis was not performed. The publication bias was statistically significant in the meta-analysis regarding terlipressin versus no vasoactive drug for 5-day control of bleeding (P_{Begg} = .296, P_{Egger} = .016). However, no significant publication bias was observed in other meta-analyses. Quality of evidence was very low to moderate (Supplementary Table 6, http://links.lww.com/MD/C663).

3.5. Terlipressin versus somatostatin

Eight studies[17,23,28,37,39,40,43,45] with a total of 1155 patients compared the outcomes of terlipressin with somatostatin. There was no significant difference in the initial (OR = 1.35, 95% CI = 0.88–2.07, *P* = .17) or 48-hour control of bleeding (OR = 0.79, 95% CI = 0.41–1.50, *P* = .47) between them. There was no significant difference in the 24-hour (OR = 0.52, 95% CI = 0.20–1.32, *P* = .17) or 5-day treatment failure (OR = 0.92, 95% CI = 0.61–1.41, *P* = .71) between them. There was no significant difference in the in-hospital rebleeding (OR = 1.76, 95% CI = 0.74–4.15, *P* = .20), 5-day rebleeding (OR = 1.10, 95% CI = 0.37–3.26, *P* = .87), 42-day rebleeding (OR = 0.99, 95% CI = 0.57–1.71, *P* = .97), or rebleeding within 48 hours (OR = 0.86, 95% CI = 0.27–2.74, *P* = .80) between them. There was no significant difference in the in-hospital mortality (OR = 0.85, 95% CI = 0.38–1.91, *P* = 0.69), 5-day mortality (OR = 1.01, 95% CI = 0.59–1.71, *P* = .98), or mortality within 42 days (OR = 1.12, 95% CI = 0.76–1.66, *P* = .57) between them. There was no significant difference in the transfusion requirements (WMD = 0.59, 95% CI = −0.19–1.37, *P* = .14) or duration of hospital stay (WMD = −0.24, 95% CI = −2.60–2.12, *P* = .84) between them. Compared with somatostatin, terlipressin had a significantly higher risk of complications (OR = 2.44, 95% CI = 1.03–5.80, *P* = .04) (Supplementary Figure 2, http://links.lww.com/MD/C663). The heterogeneity was statistically significant in the meta-analysis regarding transfusion requirement (I^2 = 81%, *P* = .0001) and complications (I^2 = 51%, *P* = .11). However, no significant

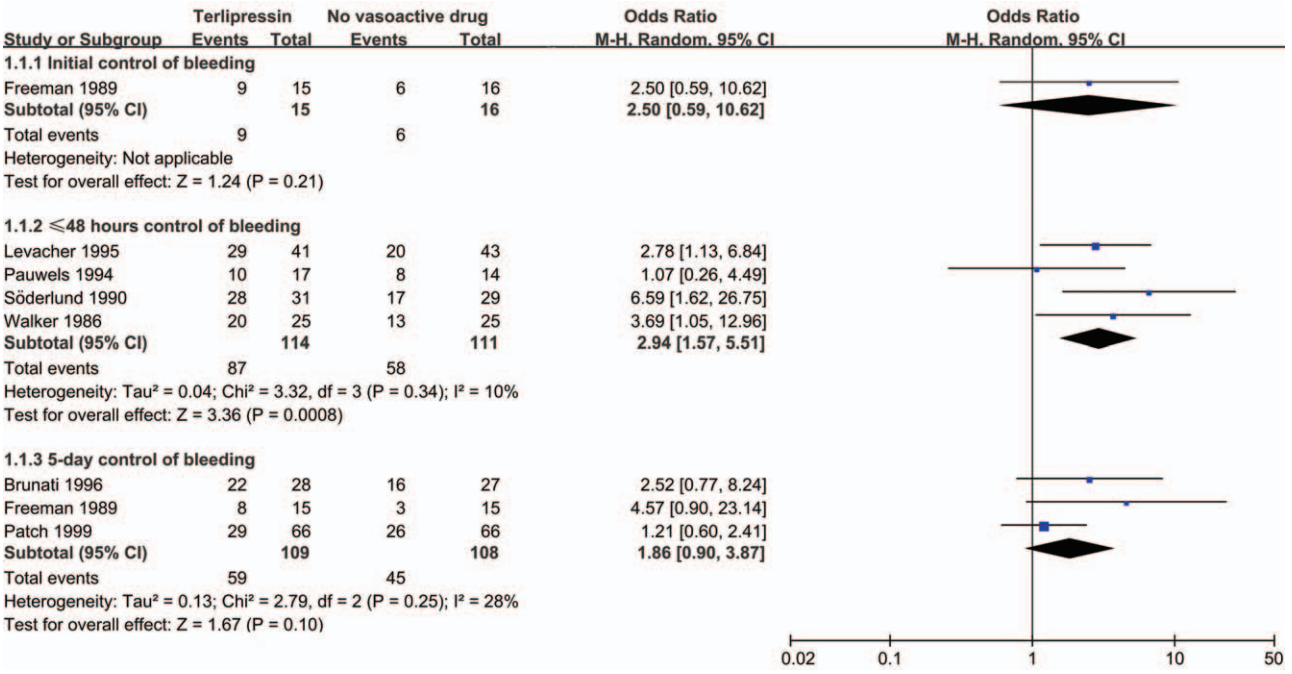

Figure 2. Forest plot showing the difference in the control of bleeding in patients treated with terlipressin compared with no vasoactive drugs.

heterogeneity was observed in other meta-analyses. The sensitivity analyses regarding transfusion requirements and complications suggested the results of meta-analyses were stable (Supplementary Figure 3A–B, http://links.lww.com/MD/C663). The publication bias was not statistically significant in these above-mentioned meta-analyses. Quality of evidence was very low to moderate (Supplementary Table 7, http://links.lww.com/MD/C663).

3.6. Terlipressin versus octreotide

Eight studies[16,18,20,22,23,38,39,41] with a total of 1357 patients compared the outcomes of terlipressin with octreotide. The control of bleeding within 24 hours was significantly inferior in terlipressin group than octreotide group (OR = 0.37, 95% CI = 0.18–0.76, $P = .007$), but there was no significant difference in the initial (OR = 1.26, 95% CI = 0.74–2.14, $P = .39$) or 5-day control of bleeding (OR = 1.22, 95% CI = 0.35–4.24, $P = .75$) between

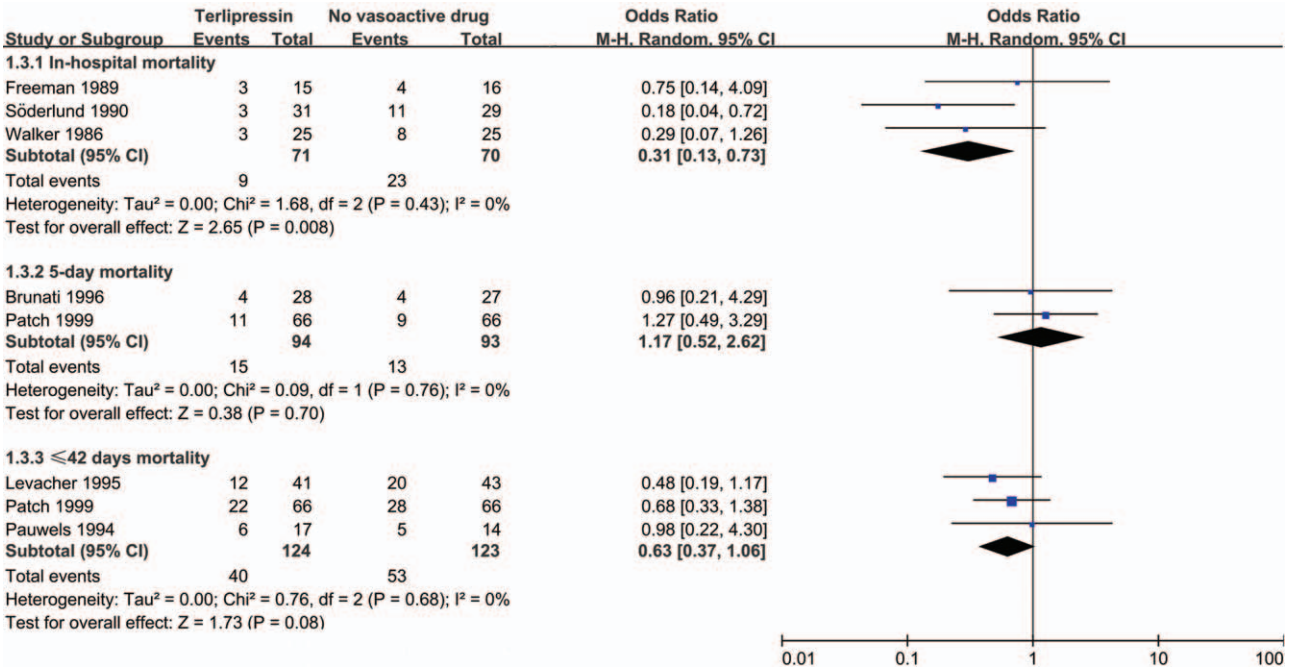

Figure 3. Forest plot showing the difference in the mortality in patients treated with terlipressin compared with no vasoactive drugs.

them (Supplementary Figure 4, http://links.lww.com/MD/C663). There was no significant difference in the 5-day treatment failure (OR = 0.83, 95% CI = 0.51–1.35, $P = .45$) between them. There was no significant difference in the rebleeding within 48 hours (OR = 0.68, 95% CI = 0.20–2.33, $P = .54$), 5-day rebleeding (OR = 0.84, 95% CI = 0.41–1.71, $P = .63$), rebleeding within 42 days (OR = 0.96, 95% CI = 0.35–2.63, $P = .93$), or 60-day rebleeding (OR = 1.00, 95% CI = 0.13–7.60, $P = 1.00$) between them. There was no significant difference in the in-hospital mortality (OR = 1.29, 95% CI = 0.47–3.54, $P = .63$), 5-day mortality (OR = 0.89, 95% CI = 0.51–1.53, $P = .67$), or mortality within 60 days (OR = 1.03, 95% CI = 0.71–1.48, $P = .88$) between them. There was no significant difference in the transfusion requirements (WMD = 0.02, 95% CI = −0.29–0.34, $P = .90$), duration of hospital stay (WMD = −1.25, 95% CI = −3.04–0.54, $P = .17$), or incidence of complications (OR = 2.50, 95% CI = 0.83–7.56, $P = .10$) between them. The heterogeneity was statistically significant in the meta-analyses regarding rebleeding within 42 days ($I^2 = 68\%$, $P = .02$) and complications ($I^2 = 74\%$, $P = .02$). However, no significant heterogeneity was observed in other meta-analyses. The sensitivity analyses regarding rebleeding within 42 days and complications suggested that the results of meta-analyses were stable (Supplementary Figure 3 C–D, http://links.lww.com/MD/C663). The publication bias was not statistically significant in these above-mentioned meta-analyses. Quality of evidence was very low to moderate (Supplementary Table 8, http://links.lww.com/MD/C663).

3.7. Terlipressin versus vasopressin

Five studies[21,25,26,30,33] with a total of 247 patients compared the outcomes of terlipressin with vasopressin. There was no significant difference in the 24-hour control of bleeding (OR = 1.60, 95% CI = 0.53–4.88, $P = .41$) between them. There was no significant difference in the in-hospital (OR = 3.27, 95% CI = 0.24–45.29, $P = .38$) or 7-day rebleeding (OR = 1.78, 95% CI = 0.32–10.01, $P = .51$) between them. There was no significant difference in the in-hospital (OR = 1.20, 95% CI = 0.50–2.89, $P = .69$) or 42-day mortality (OR = 1.82, 95% CI = 0.54–6.07, $P = .33$) between them. There was no significant difference in the transfusion requirements (WMD = 0.80, 95% CI = −1.46–3.06, $P = .49$) between them. Compared with vasopressin, terlipressin had a significantly lower risk of complications (OR = 0.15, 95% CI = 0.03–0.78, $P = .02$) (Supplementary Figure 5, http://links.lww.com/MD/C663). The heterogeneity was statistically significant in the meta-analysis regarding 24-hour control of bleeding ($I^2 = 62\%$, $P = .03$) and in-hospital rebleeding ($I^2 = 53\%$, $P = .15$). However, no significant heterogeneity was observed in other meta-analyses. The sensitivity analyses regarding 24-hour control of bleeding and in-hospital rebleeding suggested that the results of meta-analyses were stable (Supplementary Figure 3E–F, http://links.lww.com/MD/C663). The publication bias was not statistically significant in these above-mentioned meta-analyses. Quality of evidence was very low (Supplementary Table 9, http://links.lww.com/MD/C663).

3.8. Terlipressin alone versus terlipressin plus EVL

Only one study[35] with a total of 93 patients compared the outcomes of terlipressin alone versus in combination with EVL. The 5-day treatment failure was significantly higher in terlipressin alone group than terlipressin in combination with EVL group (OR = 14.46, 95% CI = 1.78–117.33, $P = .01$). The transfusion requirements within 49–120 hours was significantly higher in terlipressin alone group than terlipressin in combination with EVL group (WMD = 1.20, 95% CI = 0.43–1.97, $P = .002$). There was no significant difference in the 48-hour control of bleeding (OR = 0.23, 95% CI = 0.02–2.12, $P = .19$), rebleeding within 48 to 120 hours (OR = 18.04, 95% CI = 1.00–325.75, $P = .05$), 42-day mortality (OR = 3.21, 95% CI = 0.32–32.04, $P = .32$), transfusion requirements within 48 hours (WMD = 0.60, 95% CI = 0.00–1.20, $P = .05$), duration of hospital stay (WMD = 1.30, 95% CI = −0.94–3.54, $P = .25$), or incidence of complications (OR = 1.13, 95% CI = 0.50–2.57, $P = .76$) between them. Neither heterogeneity nor publication bias could be calculated due to only one study included in this analysis. The sensitivity analysis was not performed. Quality of evidence was low (Supplementary Table 10, http://links.lww.com/MD/C663).

3.9. Terlipressin versus sclerotherapy

Only one study[27] with a total of 219 patients compared the outcomes of terlipressin with sclerotherapy. There was no significant difference in the 48-hour control of bleeding (OR = 0.90, 95% CI = 0.46–1.80, $P = .77$), 5-day treatment failure (OR = 1.08, 95% CI = 0.61–1.91, $P = .78$), 5-day rebleeding (OR = 1.02, 95% CI = 0.48–2.18, $P = .96$), 42-day rebleeding (OR = 0.96, 95% CI = 0.52–1.78, $P = .91$), 42-day mortality (OR = 1.65, 95% CI = 0.85–3.19, $P = .14$), transfusion requirements (WMD = 0.20, 95% CI = −1.01–1.41, $P = .75$), duration of hospital stay (WMD = −1.00, 95% CI = −3.65–1.65, $P = .46$), or incidence of complications (OR = 0.59, 95% CI = 0.32–1.10, $P = .10$) between them. Neither heterogeneity nor publication bias could be calculated due to only one study included in this analysis. The sensitivity analysis was not performed. Quality of evidence was very low (Supplementary Table 11, http://links.lww.com/MD/C663).

3.10. Terlipressin versus balloon tamponade

Four studies[19,24,29,32] with a total of 208 patients compared the outcomes of terlipressin with balloon tamponade. Compared with balloon tamponade, terlipressin significantly decreased the 30-day rebleeding (OR = 0.05, 95% CI = 0.01–0.30, $P = .001$), with no significant effect on rebleeding within 48 hours (OR = 2.67, 95% CI = 0.55–12.88, $P = .22$) or within 7 days (OR = 0.51, 95% CI = 0.16–1.57, $P = .24$) (Fig. 4). Compared with balloon tamponade, terlipressin significantly decreased the transfusion requirements (WMD = −2.70, 95% CI = −4.98–−0.42, $P = .02$). There was no significant difference in the control of bleeding within 48 hours (OR = 0.44, 95% CI = 0.14–1.37, $P = .16$) between them. There was no significant difference in the in-hospital (OR = 0.72, 95% CI = 0.23–2.29, $P = .58$), 7-day (OR = 0.58, 95% CI = 0.14–2.50, $P = .47$), or 30-day mortality (OR = 1.00, 95% CI = 0.40–2.51, $P = 1.00$) between them. There was no significant difference in the incidence of complications (OR = 0.41, 95% CI = 0.10–1.66, $P = .21$) between them. The heterogeneity was statistically significant in the meta-analysis regarding complications ($I^2 = 65\%$, $P = .06$). However, no significant heterogeneity was observed in other meta-analyses. The sensitivity analyses regarding complications suggested that the result of meta-analysis was stable (Supplementary Figure 3 G, http://links.lww.com/MD/C663). The publication bias was not statistically significant in these above-mentioned meta-analyses. Quality of evidence was very low (Supplementary Table 12, http://links.lww.com/MD/C663).

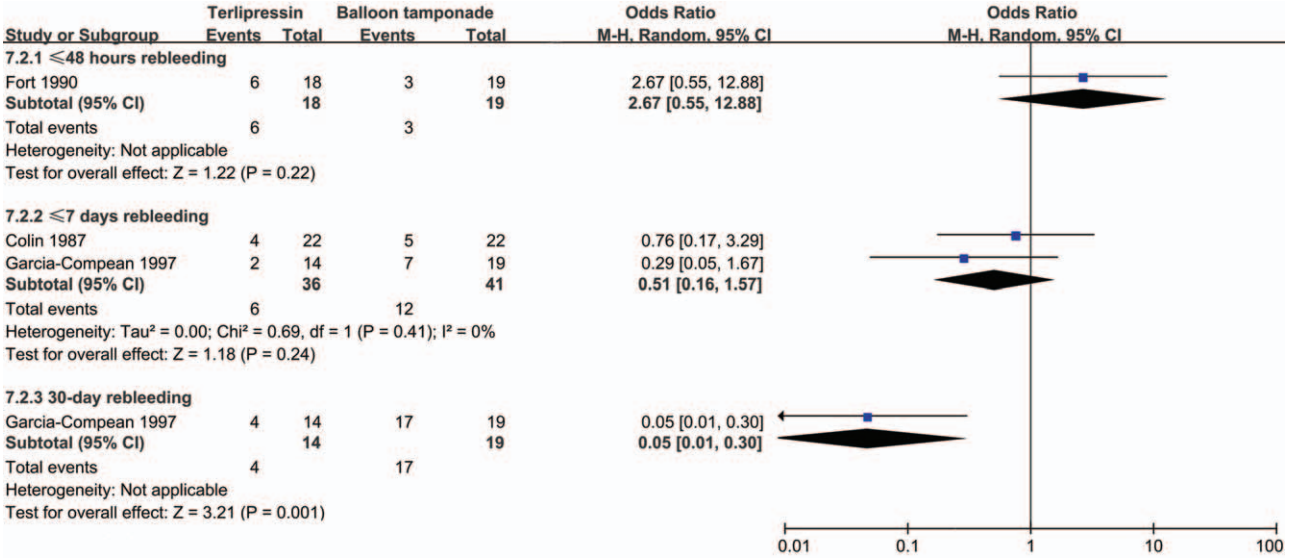

Figure 4. Forest plot showing the difference in the rebleeding in patients treated with terlipressin compared with balloon tamponade.

3.11. Subgroup analysis

The results of subgroup meta-analyses according to the Child-Pugh classifications are shown in Supplementary Table 13, http://links.lww.com/MD/C663. The results of the subgroup analyses are not different from those of the overall analyses.

4. Discussion

The findings of our meta-analyses were summarized as follows. Compared with no vasoactive drug, terlipressin significantly improved the control of bleeding within 48 hours and significantly decreased the in-hospital mortality in cirrhosis with AVB. The benefit of terlipressin on the short-term outcomes of AVB patients has established the foundation on the use of terlipressin as the first-line choice of therapy for AVB. Compared with somatostatin, terlipressin had a significantly higher incidence of complications. However, the incidence of severe adverse events was not significantly different between terlipressin and somatostatin.[28] Additionally, most of adverse events related to terlipressin, such as bradycardia, arterial hypertension, ventricular fibrillation, abdominal cramps, diarrhea, and hyponatremia, were mild and could be pharmacologically reversed. By contrast, the incidence of severe adverse reactions related to terlipressin was low.[25,31,42] Compared with octreotide, terlipressin had a significantly inferior control of bleeding within 24 hours. However, only 2 studies,[38,41] which were published >20 years ago with a relatively small number of patients, were included in the meta-analysis regarding control of bleeding within 24 hours. Therefore, this finding should be interpreted cautiously. Compared with vasopressin, terlipressin had a significantly lower risk of complications. This finding may be readily explained by the fact that terlipressin has a slower drug release and a milder effect on systemic hemodynamics than vasopressin.[25,30] Compared with terlipressin alone, terlipressin in combination with EVL significantly decreased the 5-day treatment failure or transfusion requirements within 49 to 120 hours without any increased risk of complications. This is consistent with the current recommendation from practice guideline regarding the use of vasoactive drugs combined with endoscopic treatment for AVB.[46] No significant difference in any outcome was demonstrated between terlipressin and sclerotherapy groups. This finding was based on only one study. Similarly, another study also found that octreotide was as effective as sclerotherapy for the control of AVB with fewer complications.[47] Compared with balloon tamponade, terlipressin significantly decreased the 30-day rebleeding or transfusion requirements. Thus, balloon tamponade should only considered as temporary therapy if terlipressin is not effective. Additionally, it should be noted that the use of balloon tamponade is often unpleasant for the patients and the rate of rebleeding is about 50% after the balloon is deflated.[48] A recent nationwide study also suggested that balloon tamponade might be negatively associated with the survival of patients with AVB.[49]

Compared with previously published meta-analyses,[9–11] our study has some strengths: we focused on the use of terlipressin; we compared terlipressin with all available other interventions; our literature search was extensive and rigorous and the number of included studies was larger; and because the duration of follow-up or observation was heterogeneous among studies, we combined the data obtained according to the different time points when the events developed, such as in-hospital mortality, 5-day mortality, and mortality within 42 days.

Our study has limitations. First, the publication year was broad from 1984 to 2014. The prognosis of AVB patients has been improved with time. The definitions of outcomes and the dosage and duration of drugs and procedures varied among studies. Second, only one RCT each compared the efficacy and safety of terlipressin versus sclerotherapy and terlipressin alone versus terlipressin in combination with EVL. Third, only few studies reported the results according to the Child-Pugh classifications. Fourth, some included studies had a high risk of bias. The quality of evidence was unsatisfied according to the GRADE methodology.

In conclusion, the findings of the present meta-analyses are consistent from the current recommendation from consensus and practice guideline that terlipressin should be an effective choice of therapy for AVB in liver cirrhosis.[4,5] Additionally, it is important for us to select the optimal type of vasoactive drugs. Our study suggested a disadvantage of terlipressin compared

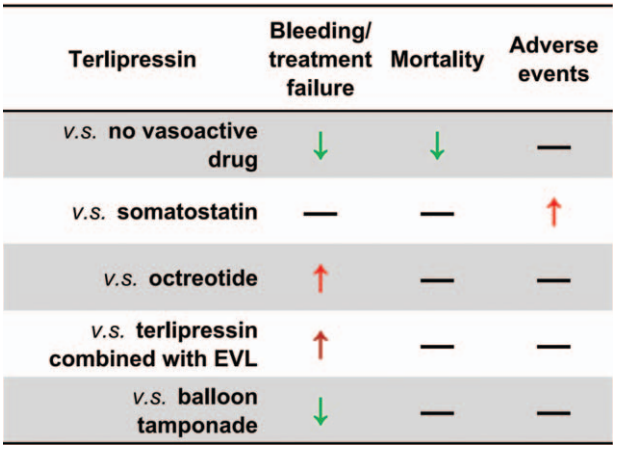

Figure 5. An overview of our findings.

with somatostatin in term of adverse events and with octreotide in term of control of bleeding with 24 hours. However, the relevant data were obtained from earlier low-quality studies. Further trials should explore the difference in the efficacy and safety of different vasoactive drugs. Since the mechanisms of terlipressin are different from those of somatostatin and octreotide, future trials should also explore the role of terlipressin combined with somatostatin or octreotide versus terlipressin alone.

5. Perspectives

Based on the current findings, we have several perspectives regarding use of terlipressin for management of AVB (Fig. 5). First, in the contemporary era, terlipressin or other vasoactive drugs must be initiated as soon as AVB is suspected. This point has been supported by the advantages of terlipressin over no vasoactive drug in terms of controlling the bleeding and improving the survival. Second, terlipressin may not be the preferred first-line choice of vasoactive drug for the treatment of AVB. This point has been indicated by the disadvantage of terlipressin over somatostatin in term of adverse events or octreotide in term of controlling the bleeding with 24 hours. Third, terlipressin should be combined with endoscopic treatment, if any. This point has been supported by the advantages of terlipressin combined with EVL over terlipressin alone in terms of treatment failure and transfusion requirement. Fourth, balloon tamponade may be abandoned, if terlipressin is available. This point has been supported by the disadvantage of balloon tamponade over terlipressin in terms of 30-day rebleeding and transfusion requirements without any benefit.

Author contributions

Xinmiao Zhou: reviewed and searched the literature, wrote the protocol, collected the data, performed the statistical analysis and quality assessment, interpreted the data, and drafted the manuscript.
Dhiraj Tripathi: interpreted the data, gave critical comments, and revised the manuscript.
Tingxue Song: searched the literature, wrote the protocol, collected the data, and performed the statistical analysis and quality assessment.
Lichun Shao: checked the data and gave critical comments.
Bing Han: searched the literature and checked the data.
Jia Zhu: checked the data and gave critical comments.
Dan Han: performed the quality assessment and gave critical comments.
Fufang Liu: searched the literature and gave critical comments.
Xingshun Qi: conceived the work, reviewed and searched the literature, wrote the protocol, performed the statistical analysis, interpreted the data, and revised the manuscript.
All authors have made an intellectual contribution to the manuscript and approved the submission.
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Methodology: Xinmiao Zhou, Tingxue Song, Lichun Shao, Bing Han, Jia Zhu, Dan Han, Fufang Liu, Xingshun Qi.
Software: Xinmiao Zhou, Tingxue Song, Lichun Shao, Bing Han, Jia Zhu, Dan Han, Fufang Liu, Xingshun Qi.
Supervision: Xingshun Qi.
Writing – original draft: Xinmiao Zhou, Xingshun Qi.
Writing – review & editing: Dhiraj Tripathi, Xingshun Qi.

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