SYSTEMATIC REVIEW AND META-ANALYSIS

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Vasoactive Agents for the Management of Acute Variceal Bleeding: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: Vasoactive agents with endoscopic therapy are used to treat acute variceal bleeding (AVB). There are two main groups of vasoactive agents: terlipressin and vasopressin (T-V), and octreotide and somatostatin (O-S). However, the benefit/harm balance is unclear. Our aim was to assess the efficacy and safety of T-V versus O-S for the management of AVB.

Methods: We performed a systematic search for randomized controlled trials (RCTs) in PubMed, Scopus, and CENTRAL. Our main outcomes were mortality and adverse events. Secondary outcomes were bleeding control, rebleeding, blood transfusion, hospital stay. We evaluated the certainty of evidence using GRADE methodology.

Results: We included 21 RCTs. The risk of mortality (RR: 1.01; 95%CI: 0.83-1.22), bleeding control (RR: 0.96; 95%CI: 0.91-1.02; I^2=53%), early rebleeding (RR: 0.91; 95%CI: 0.66-1.24: I^2=0%), late rebleeding (RR: 0.94; 95 CI: 0.56-1.60; I^2=0%), blood transfusion (MD: 0.04; 95%CI: -0.31-0.39; I^2=68%) and hospital stay (MD: -1.06; 95%CI: -2.80-0.69; I^2=0%) were similar between T-V and O-S groups. Only 15 studies reported adverse events, which were significantly higher in the T-V compared to the O-S group (RR 2.39; 95%CI: 1.58-3.63; I^2=57%). The certainty of evidence was moderate for the main outcomes, and low or very low for others.

Conclusions: In cirrhotic patients with AVB, those treated with T-V had similar mortality risk compared to O-S. However, the use of T-V showed an increased risk of adverse events compared to O-S.

Key words: liver cirrhosis – octreotide – somatostatin – terlipressin – vasopressin.

Abbreviations: AR: absolute risk reduction; AVB: acute variceal bleeding; CI: confidence interval; EIS: endoscopic injection sclerotherapy; EVL: endoscopic variceal ligation; MD: mean difference; NNTB: number needed to treat to benefit; NNTH: the number needed to harm; O: octreotide; RCT: randomized controlled trial; RR: relative risk; S: somatostatin; SR: systematic review; T: terlipressin; V: vasopressin.

INTRODUCTION

Acute variceal bleeding (AVB) is a common complication in cirrhotic patients.

Esophageal varices are present in approximately 30% of patients with compensated cirrhosis and almost 60% of patients with decompensated cirrhosis [1-3]. Although AVB-related mortality at 6 weeks has decreased to approximately 10-20% in the last decades, it is still significant [1, 2]. This reduction could be attributed to optimal management with vasoactive agents and endoscopic therapy, the cornerstone of treatment.

There are two main groups of vasoactive agents for the treatment of AVB: vasopressin (V) and its synthetic analog terlipressin (T), and somatostatin (S) and its synthetic analog octreotide (O) [4-7]. Vasopressin is a potent systemic vasopressor with splanchnic effects, and T has the same properties but with a longer half-life and apparently fewer adverse effects. Somatostatin is an oligopeptide that inhibits the secretion of several gastrointestinal hormones and has potent selective splanchnic vasoconstrictive effect. Likewise, O is characterized by the same S actions and has a longer half-life.

Previous randomized clinical trials (RCTs) and systematic reviews (SRs) found different results regarding mortality, bleeding control, and rebleeding related to these vasoactive agents [7-11]. Currently, the balance of benefits and harms for

each group of vasoactive agents remains unclear. Regarding efficacy, previous SRs have not evaluated all critical outcomes, nor have standardized definitions or assessed the risk of bias of primary studies [10, 11]. Moreover, there are safety doubts, with previous SRs describing it poorly. Finally, several clinical guidelines recommend the use of vasoactive agents, but do not recommend one agent over another [2, 3, 12]. Therefore, we conducted a SR and meta-analysis to compare the efficacy and safety of T-V versus O-S for the management of AVB in cirrhotic patients.

METHODS

We performed a SR of RCTs following guidance from the Cochrane Handbook for Systematic Reviews of Interventions [13] and following the reporting standards set by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [14]. The protocol was registered in PROSPERO (registration number: CRD42019139081).

Literature search and study selection

We performed a systematic search in PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) in June 2019 and updated the search in March 2020. Also, we searched for pertinent studies in clinical guidelines, Google Scholar, ClinicalTrial.gov, and in the references of previous SRs. The full search strategy is available in Supplementary File 1.

Eligibility criteria

We included RCTs that compared the benefits and/or harms of T or V versus O or S in cirrhotic patients with AVB aged 16 years and older. We included studies without restrictions of language, publication date, sample size, or length of follow-up. Trials published in another language were translated to English before data extraction.

We excluded studies that involved exclusively cirrhotic patients with gastrointestinal non-variceal bleeding or pregnancy. Other reasons for exclusion were lack of reporting of outcomes of interest, treatment with the combination of two vasoactive agents, or a treatment period less than one day. If different reports involved the same population, we included data from the most recent study.

Study selection

Two reviewers (M.H.R. and P.V.L.) independently carried out the study selection process. First, they screened the retrieved articles from database searches by title and abstract. When the title or abstract showed that the article did not meet the inclusion criteria, the study was excluded. If the inclusion criteria could not be assessed from the title/abstract, the article was evaluated in full text to determine inclusion. Then, M.H.R. and P.V.L. read the full text of selected articles to determine their inclusion. Disagreements were resolved by consensus among all the authors. We also included RCTs reported as abstracts, only if data of interest and risk of bias assessment was reported by other SRs. The reasons for exclusion of RCTs are shown in Supplementary File 1.

Data extraction and outcome measures

Two reviewers (A.B.C. and D.P.R.) independently extracted the following information from each of the included studies in Microsoft Excel: study characteristics (first author, year of publication, country, trial design, sample size, length of follow-up), participant characteristics (age, gender, Child-Pugh classification), intervention and comparator (type of vasoactive agent, dose, route of administration, frequency and duration of treatment), type of endoscopic therapy, and drug company sponsorship. If there were disagreements in some articles, they were reviewed again by the authors; If differences remained, a third reviewer resolved it (J.H.M.) (Supplementary File 1).

The primary efficacy outcome was all-cause mortality (6-week mortality). Secondary efficacy outcomes were bleeding control (cessation of bleeding within the first 24 hours of starting treatment with a vasoactive agent with a period of at least 24 hours after ceasing of bleeding without evidence of rebleeding) early rebleeding (defined as any occurrence of bleeding after the successful control of bleeding, within 5 days after vasoactive agent administration), late rebleeding (rebleeding of alive participants 5 days after administration of the drug), blood transfusion (number of blood transfusions) and hospital stay. The primary safety outcome was overall adverse events (number of adverse events reported). Regarding adverse events, we compared them according to the drug dose used by the studies.

For this purpose, we defined recommended doses as stated in a previous guideline [2], any dose below these thresholds were classified as low dose. These outcomes were compiled based on the Baveno VI consensus [1] for key events related to the bleeding episode.

Risk of bias and certainty of the evidence

Two reviewers (D.U.I. and D.G.G.) independently assessed the risk of bias of the included studies using the Cochrane Collaboration's risk of bias tool 1.0 [15]. Each item was evaluated as having a low, unclear, or high risk of bias. Disagreements were resolved through consensus among all authors.

For assessing the certainty of the evidence, we employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [16]. GRADEpro was used to generate a "Summary of findings" table.

Data synthesis and analysis

We performed meta-analyses to summarize studies that evaluated similar outcomes. We used random-effects models because we anticipated that the included studies would have important differences in population, use of endoscopic therapy, vasoactive agent doses, follow-up time, and timing of outcome measurement. We preferred to use intention-to-treat values for efficacy outcomes and per-protocol values for safety outcomes. In studies that reported more than one measurement of the same outcome, we only considered the final measurement of each outcome to perform the meta-analyses, as suggested in the Cochrane Handbook [15]. Results measured in only one trial were reported narratively.

The pooled data of dichotomous outcomes were presented as relative risk (RR) with a 95% confidence interval (CI). The pooled data of continuous outcomes were presented as the mean difference (MD) with a 95%CI. A p-value < 0.05 was considered statistically significant. We also calculated the absolute risk reduction (AR), the number needed to treat to benefit (NNTB), and the number needed to harm (NNTH). We calculated the number needed to treat as 1/AR.

From the beginning, we assumed that there would be important clinical heterogeneity among the included studies. Due to the differences in therapy and population described in the studies, we decided to perform an analysis of subgroups. To examine whether the results of the studies were homogeneous, we used the Cochran Q test (significance level, p-value < 0.10). We also calculated the I^2 statistic, which describes the percentage variation across studies that is due to heterogeneity rather than chance. We used the following thresholds: 0-40%, 40-60%, 60-80%, and >80% to suggest low, moderate, substantial, and considerable heterogeneity, respectively.

We conducted a sensitivity analysis to determine the stability of the main efficacy outcome, excluding trials with a high risk of bias.

Publication bias was evaluated using funnel plots for the main outcomes. Small-study effect and publication bias were assessed by visual inspection of funnel plots and calculating the p-value of Egger's intercept.

Statistical analyses were performed using the Review Manager (RevMan) version 5.3 and Stata, version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Study selection

We identified a total of 2,692 articles through our systematic search strategy; 792 duplicate articles were excluded. After screening titles and abstracts, 1,869 articles were removed. Additionally, we selected 8 citations identified through other sources. In total, we retrieved 39 citations for full-text evaluation. Of these studies, 18 were excluded for different reasons (Supplementary File 1). Finally, 21 RCTs [7, 9, 17-35] were eligible for inclusion in the analysis (Fig. 1).

Characteristics of studies and patients

The 21 RCTs involved 2,431 patients. Twelve studies were conducted in Asia and nine in Europe. Six studies compared T and O (5 with endoscopic therapy and one without), 5 compared T and S (2 with endoscopic therapy and 3 without), 2 compared V and O (both without endoscopic therapy), 6 compared V and S (2 with endoscopic therapy and 4 without), and 2 compared T, S, and O (all with endoscopic therapy). In 11 studies endoscopic treatment was performed as the initial therapy, 2 studies utilized endoscopic injection sclerotherapy (EIS), 5 endoscopic variceal ligation (EVL), 2 either of therapies (EIS or EVL), and 2 studies did not specify which type of endoscopic therapy was employed. Until 1996, all RCTs were performed without endoscopic therapy (10 studies).

Not all included studies assessed or reported our outcomes of interest. Also, the included RCTs measured the outcomes at different time's points. Mortality was measured up to the 5th day or up to 6 weeks, and the secondary outcomes were also measured

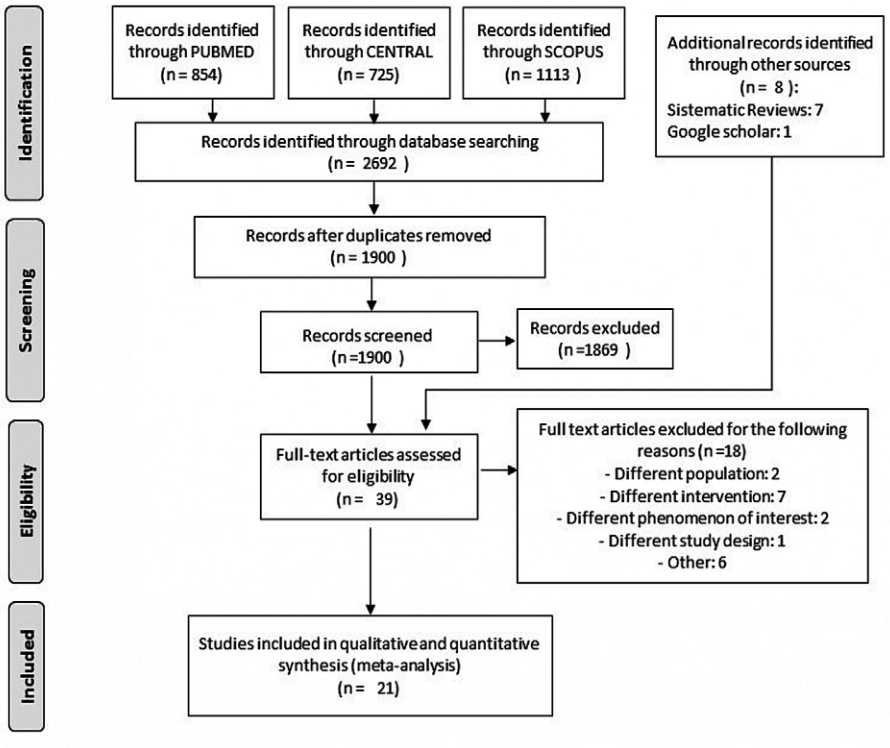

Fig. 1. Flow-Chart of search results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

at different times. Furthermore, only 15 studies reported adverse events, and these were reported differently between studies. Few of them classified the adverse events according to their severity and none of them according to Child-Pugh classification. We describe the main characteristics of the included RCTs, and their findings in Table I and Supplementary File 1, respectively.

Table I. Characteristics of the included studies.

Author Year	Number of patients	Vasoactive agent	Treatment	Source of bleeding	Endoscopic initial therapy†	Males (n%)	Age (mean ± SD)	Child-Pugh classification
Kravetz 1984 [21]	31	Vasopressin	Continuous iv infusion at an initial rate of 0.4 U per min.	Esophageal and gastric varices	None	25 (80.6)	54 ± 0.6	A/B/C: 10/9/12
	30	Somatostatin	Continuous iv infusion 250 μg per hr after a bolus of 50 μg.			22 (73.3)	56.9 ± 1.9	A/B/C: 6/11/13
Jenkins 1985 [19]	12	Vasopressin	0.4 U per min for 24hr	Esophageal varices	None	NR	NR	NR
	10	Somatostatin	250 μg bolus followed by a continuous infusion of 250 μg per hr for 24 hr			NR	NR	NR
Bagarani 1987 [27]	25	Vasopressin	0.1 U per min iv for 48 hrs	Esophageal varices	None	NR	NR	NR
	24	Somatostatin	250 μg per hr iv for 48 hrs			NR	NR	NR
Saari 1990 [25]	22	Vasopressin	0.4 IU per min for 72 hr	Esophageal varices	None	11 (50.0)	55 ± 14.4	NR
	32	Somatostatin	4.2 μg per min			16 (50.0)	54.6 ± 14.1	NR
Hwang 1992 [18]	24	Vasopressin	0.4 U per min for 24hr	Esophageal varices	None. After completion of drug infusion received EIS, surgery, or propranolol therapy.	23 (95.8)	63 ± 9	A/ B/C: 3/10/11
	24	Octreotide	Continuous infusion 25 μg per hr for 24 hr after an initial bolus 100 μg			22 (91.7)	59 ± 11	A/B/C : 2/7/15
Huang 1992 [35]	21	Vasopressin	0.4 U per min for 24hr	Esophageal varices	None	19 (90.5)	51.1 ± 12.1	NR
	20	Octreotide	100 μg bolus followed by 25 μg per hr infusion for 24hr			14 (70)	46.7 ± 12	NR
Pedretti 1994 [24]	30	Terlipressin	2 mg bolus every 4hr for 24hr	Esophageal and gastric varices	None. Patients still bleeding after 24hr underwent EIS	17 (56.7)	66.7 ± 10.6	A/B/C: 5/21/4
	30	Octreotide	100 μg bolus followed by continuous iv infusion of 25 μg per hr for 24hr			18 (60)	64.7 ± 10.7	A/B/C: 4/23/3
Pauwels 1994 [23]	17‡	Terlipressin	2 mg iv every 6 hr until bleeding stopped then 1 mg iv every 6 hr for 24hr	N//S	None	NR	NR	NR
	18‡	Somatostatin	250 μg iv bolus then 250 μg per hr infusion until 2 hr after bleeding arrest			NR	NR	NR
Feu 1996 [33]	80	Terlipressin	iv injections of 2 mg every 4hr	Esophageal and gastric varices	None	58 (72.5)	58 ± 12	A/B/C: 22/38/20
	81	Somatostatin	Continuous iv infusion of 250 μg per hr after an initial bolus injection of 250 μg			61 (75.3)	56 ± 12	A/B/C: 14/41/26
Walker 1996 [28]	53‡	Terlipressin	2mg iv initially and 1mg every 4 hr for 24 hr	Esophageal and gastric varices	No. After 24hr elective EIS was performed	28 (52.8)	51.8 ± 13	NR
	53‡	Somatostatin	250 μg as a bolus and continuous infusion of 250 μg per hr for 24 hr			31 (58.5)	52.7 ± 13.5	NR
Brunati 1996 [29]	28	Terlipressin	2mg iv every 6 hr for 2 days	Esophageal varices	Yes (EIS)	NR	NR	NR
	28	Octreotide	0.1mg iv every 8 hr for 2 days			NR	NR	NR
Chon 2000 [31]	13	Vasopressin	0.2 IU per min for 48 hr	Esophageal varices	Yes (N/S)	13 (100)	NR	A/B/C: 0/5/8

Table I (continued).

	15	Somatostatin	250 µg in bolus for the first 3 to 5 min, followed by 250 µg per hr for 48 hr			13 (86.7)	NR	A/B/C: 2/6/7
Ali Hafta 2001 [34]	17	Terlipressin	Bolus injection of 2 mg followed by a 2 mg iv infusion every 4 hr	Esophageal varices	Yes (EIS)	9 (52.9)	57.8 ± 12	A/B/C: 0/0/17
	17	Somatostatin	250 µg bolus injection followed by a 250 µg per hr infusion			11 (64.7)	55.6 ± 12	A/B/C: 0/0/17
Lee 2003 [22]	23	Vasopressin	Continuous iv infusion, at a rate of 0.4 IU per min for 48 hr	Esophageal and gastric varices	Yes (EVL or EIS).	17 (73.9)	54 ± 2.2	A/B/C: 5/14/4
	20	Somatostatin	Continuous iv infusion, following a 50 µg bolus, at a rate of 250 µg per hr			18 (90)	51.4 ± 2.2	A/B/C: 6/12/2
Kim 2005 [20]	36	Terlipressin	2 mg iv every 6 hr for 3 days	Esophageal varices	Yes (EVL)	31 (86.1)	NR	A/B/C: 5/21/10
	37	Octreotide	50 µg bolus IV then 25 µg per hr for 5 days			33 (89.1)	NR	A/B/C: 2/27/8
Cho 2006 [30]	43	Terlipressin	2 mg iv initially and 1 mg iv at every 4hr for 3 days	Esophageal varices	Yes (EVL)	36 (83.7)	53 ± 11	A/B/C: 8/21/14
	45	Octreotide	Continuous infusion of 25 µg per hr for 5 days			38 (84.4)	56 ± 11	A/B/C: 9/21/15
Seo 2006 [26]	48	Terlipressin	2 mg iv initially and 1 mg iv at every 8hr for 5 days	Esophageal and gastric varices	Yes (EVL in active bleeding)	43 (89.5)	54 .5 ± 9.9	A/B/C: 10/19/19
	50	Somatostatin	250 µg iv bolus followed by 250 µg per hr continuous infusion for 5 days			39 (78)	52.7 ± 9.3	A/B/C: 7/21/22
Abid 2009 [9]	163	Terlipressin	2 mg by iv bolus followed by 1 mg iv every 6h for 72hr	Esophageal varices	Yes (EVL)	NR	48.9 ± 10.4	A/B/C: 12/76/75
	161	Octreotide	100 µg iv bolus then 50 µg per hr as a continuous infusion for 72hr			NR	51.7 ± 11.4	A/B/C: 8/53/100
Adarsh 2011 [17]	69	Terlipressin	NR	Esophageal varices	Yes (N/E)	NR	NR	NR
	73	Somatostatin	NR			NR	NR	NR
	68	Octreotide	NR			NR	NR	NR
Seo 2014 [7]	261	Terlipressin	2 mg iv bolus followed by 1 mg iv every 6 hr for 5 days	Esophageal and gastric varices	Yes (EVL)	223 (85.4)	52.9 ± 9.2	A/B/C: 49/121/91
	259	Somatostatin	250 µg iv bolus followed by 250 µg per hr continuous infusion for 5 days			216 (83.4)	53.1 ± 9.7	A/B/C: 46/126/87
	260	Octreotide	50 µg iv bolus followed by 25 µg per hr continuous infusion for 5 days.			227 (87.3)	53.8 ± 10.0	A/B/C: 57/125/78
Fatima 2017 [32]	30	Terlipressin	1 mg iv 6 hourly for 48 hr	Esophageal varices	YES (EVL or EIS)	NR	51.4 ± 8.1	A/B/C: 4/19/7
	30	Octreotide	50 µg/hour iv infusion for 48 hr			NR	53.6 ± 7.7	A/B/C: 7/15/8

EIS: endoscopic injection sclerotherapy; EVL: endoscopic variceal ligation; NR: Not reported; N/S: Not specified. † Initial endoscopic therapy defined as endoscopy therapy (ES or EVL) performed within the first 24 hours after randomization or suggested as elective but finally performed in all participants with acute variceal bleeding; ‡ Episodes of bleeding.

Risk of bias within trials

Some RCTs were assessed as at unclear risk of bias on random sequence generation and allocation concealment. Other RCTs had a high risk of bias on blinding of participants, personnel, and blinded outcome assessment (Fig. 2).

Meta-analysis of outcomes

Due to the initial heterogeneity assumed, we performed the subgroup analysis according to the use of endoscopic therapy in all efficacy outcomes. Table II shows a summary of the meta-analyses of all the outcomes (More details are provided in Supplementary File 2).

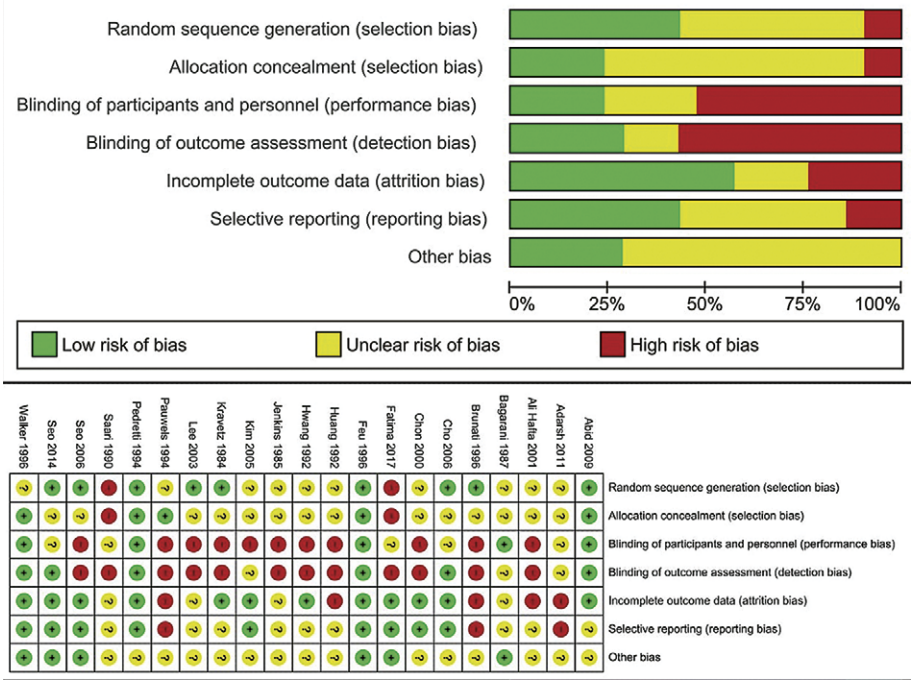

Fig. 2. Summary of Risk of bias assessment.

Table II. Summary of meta-analyses results.

	No. Studies	No. Pts	RR / MD (95% CI)	Overall effect p-value	Heterogeneity	
					I^2 (%)	p-value
1. Mortality (RR)						
1.1With Endoscopic Therapy	11	1794	0.88 (0.64 to 1.20)	0.41	0	0.87
1.2 Without Endoscopic Therapy	10	637	1.10 (0.85 to 1.41)	0.47	0	0.81
Total	21	2431	1.01 (0.83 to 1.22)	0.96	0	0.93
2. Bleeding control (RR)						
2.1 With Endoscopic Therapy	11	1794	1.00 (0.97 to 1.03)	0.93	0	0.56
2.2 Without Endoscopic Therapy	10	637	0.77 (0.64 to 0.93)	0.005	66	0.002
Total	21	2431	0.96 (0.91 to 1.02)	0.17	53	0.002
3. Rebleeding (RR)						
3.1 Early rebleeding						
3.2.1 With Endoscopic Therapy	7	1044	0.91 (0.55 to 1.50)	0.71	0	0.74
3.2.2 Without Endoscopic Therapy	6	322	0.88 (0.53 to 1.46)	0.62	20	0.28
Total	13	1366	0.91 (0.66 to 1.24)	0.54	0	0.66
3.2 Late rebleeding						
3.2.1 With Endoscopic Therapy	1	204	0.80 (0.43 to 1.51)	0.50	NA	NA
3.2.2 Without Endoscopic Therapy	2	211	1.35 (0.52 to 3.50)	0.54	0	0.75
Total	3	415	0.94 (0.56 to 1.60)	0.82	0	0.64
4. Blood Transfusion (MD)						
4.1 With Endoscopic Therapy	6	1082	-0.17 (-0.61 to 0.27)	0.44	30	0.21
4.2 Without Endoscopic Therapy	5	423	0.23 (-0.13 to 0.60)	0.21	48	0.10
Total	11	1505	0.04 (-0.31 to 0.39)	0.81	68	<0.001
5. Hospital stay (MD)						
5.1 With Endoscopic Therapy	3	214	-1.51 (-3.41 to 0.39)	0.12	0	0.58
5.2 Without Endoscopic Therapy	1	106	1.40 (-3.02 to 5.82)	0.53	NA	NA
Total	4	320	-1.06 (-2.80 to 0.69)	0.24	0	0.48
6. Adverse Events (RR)						
Total	15	1659	2.39 (1.58 to 3.62)	<0.0001	57	0.006

RR: Risk Ratio; MD: Mean Difference; NA: Not applicable

Mortality. We included 21 RCTs [7, 9, 17-35] with a total of 2,431 patients in this meta-analysis. The mortality risk was similar between the T-V and O-S groups (RR: 1.01; 95%CI: 0.83-1.22; I^2=0%). The use of endoscopic therapy did not affect the results (Fig. 3). When individual comparisons between all the vasoactive agents (terlipressin, vasopressin, octreotide, and somatostatin) were made, mortality risk was similar between all of them. There were also no differences in mortality between the two groups when the analysis was performed based on the Child-Pugh classification.

Bleeding control. Twenty-one RCTs [7, 9, 17-35] including 2,431 patients were included in this meta-analysis. The probability of bleeding control was similar between the T-V and O-S groups (RR: 0.96; 95%CI: 0.91-1.02; I^2=53%). However, in the subgroup of patients without endoscopic therapy, O-S showed a higher probability of bleeding control than T-V. In the subgroup analysis by a specific vasoactive agent, bleeding control was similar across all agents. Regarding the Child-Pugh classification, bleeding control was similar across each class treated with either T-V or O-S.

Rebleeding. We analyzed rebleeding in periods of less than 5 (early rebleeding) and more than 5 days (late rebleeding). For early rebleeding, we included 13 RCTs [7, 18, 20-22, 24-26, 30-33, 35] (n=1,366 patients). The probability of early rebleeding was similar between the T-V and O-S groups (RR: 0.91; 95%CI: 0.66-1.24: I^2=0%). When we compared every vasoactive agent against each other, no significant differences were found between them. For late rebleeding, we found 3 RCTs [17, 24, 33] (n=415 patients); the probability of late rebleeding was similar between T-V and O-S (RR: 0.94; 95%CI: 0.56-1.60; I^2=0%). In the subgroups analysis for both outcomes (early and late rebleeding), the use or not of endoscopic therapy or the type of vasoactive agent used did not change the results.

Blood transfusion. Blood transfusions were reported in 15 RCTs. We included 11 RCTs [7, 20-24, 26, 28, 31-33] (n=1,505 patients) for the meta-analysis of studies reporting the number of blood transfusions. There was no significant difference in the number of blood transfusions between T-V and O-S (MD: 0.04; 95%CI: -0.31-0.39; I^2=68%). Four RCT [9, 20, 30, 32] reported the number of packet blood transfusion, and the findings were similar between T-V and O-S (MD: -0.11; 95%CI: -0.45-0.22; I^2=0%). Regarding RCTs not included in the meta-analysis, Hwang et al. [18] reported blood transfusion requirements in milliliters and found no difference between V and O [18]; and Brunati et al. [29] found similar medians of blood transfusion between T and O.

Hospital stay. Four RCTs [26, 28, 30, 31] with a total of 320 patients were included in the meta-analysis. The hospital stay was similar between T-V and O-S groups (MD: -1.06; 95%CI: -2.80-0.69; I^2=0%).

Adverse events. Fifteen RCTs [7, 18-28, 31, 33, 35] reported adverse events in a total of 1,659 patients. T-V had a higher overall risk of adverse event (RR: 2.39; 95%CI: 1.58-3.62; I^2= 57%) compared to O-S (Fig. 4). The estimated NNTH was 6.85 with T-V (95%CI: 5.50-9.04) compared to O-S. In relation to major adverse events, patients who received T-V were more likely to present chest pain (RR: 3.97; 95%CI: 1.17-13.48; I^2=0%) and abdominal pain (RR: 2.01; 95%CI: 1.14-3.53;

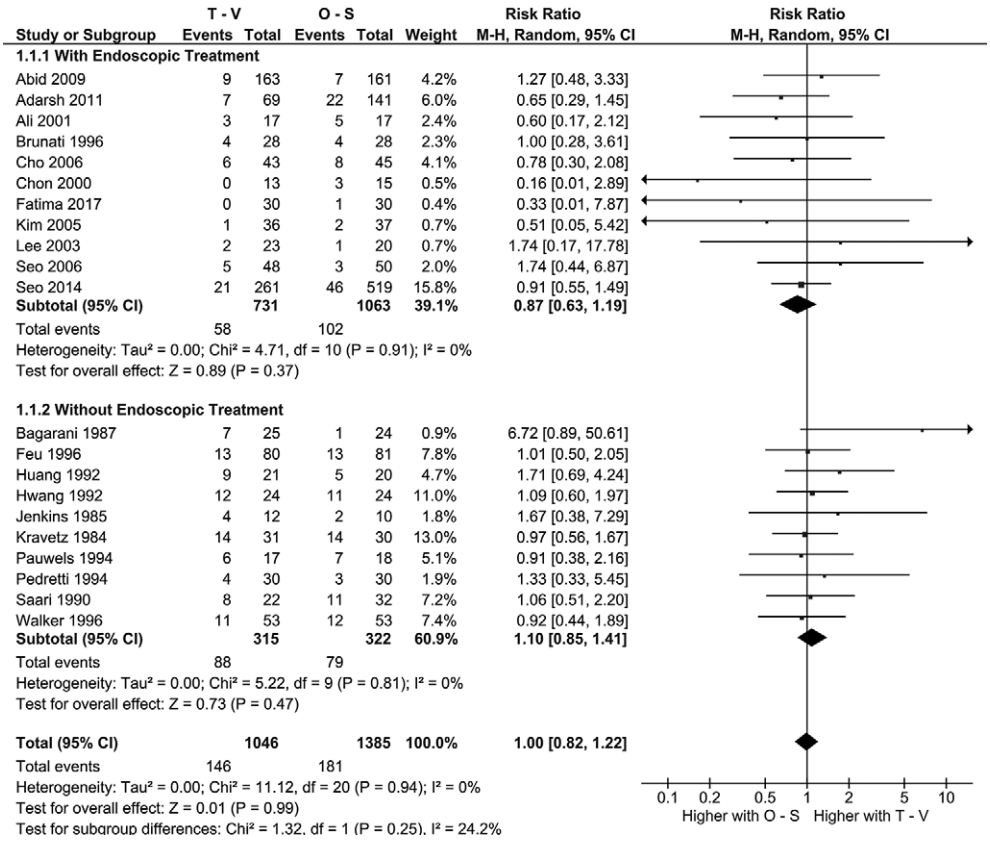

Fig. 3. Forest plot for mortality. T: terlipressin; V: vasopressin; O: octreotide, S: somatostatin; M-H: Mantel-Haenszel; CI: confidence interval.

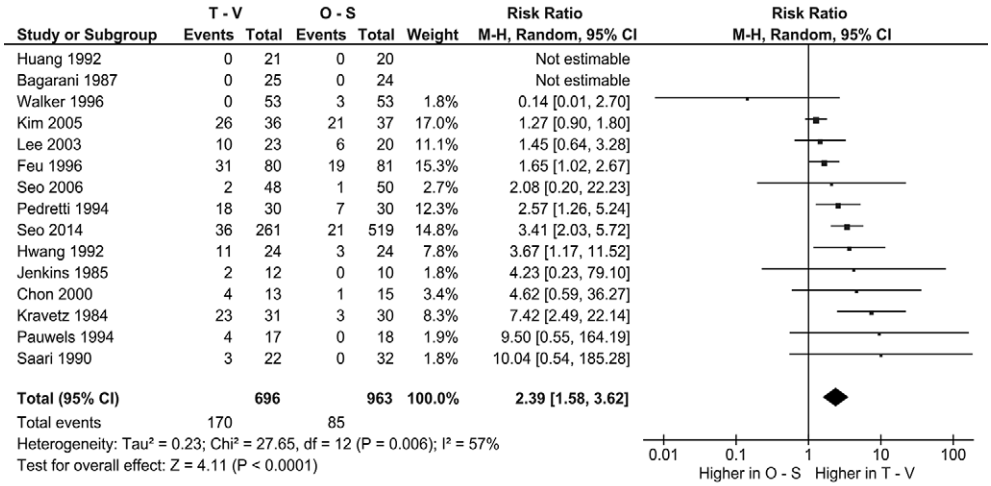

Fig. 4. Forest plot for adverse events. T: terlipressin; V: vasopressin; O: octreotide; S: somatostatin; M-H: Mantel-Haenszel; CI: confidence interval.

I^2=0%) compared to O-S; but the risk of presenting bradycardia, electrocardiogram changes and high blood pressure was similar in both groups. Regarding minor adverse effects, patients who received T-V were more likely to have diarrhea (RR: 3.16; 95%CI: 1.17-8.56; I^2=0%) or hyponatremia (RR: 4.29; 95%CI: 1.28-14.29; I^2=50%) compared to O-S, while the probability of having hyperglycemia or headache was similar in both groups. Table III summarizes the meta-analyses of each adverse event. In addition, adverse events were significantly more frequent with T compared to O (RR: 2.09; 95%CI: 1.01-4.30; I^2=80%), with T compared to S (RR: 2.11; 95%CI: 1.06-4.17; I^2=43%), with V compared to O (RR: 3.67; 95%CI: 1.17-11.52), and with V compared to S (RR: 3.71; 95% CI: 1.42 to 9.70; I^2= 45%).

Adverse events were more frequent with low-dose terlipressin compared with recommended-dose somatostatin (RR: 3.31; 95%CI: 1.16-6.13; I^2=0%), with low-dose T compared with low-dose O (RR: 2.07; 95%CI: 0.64-6.75; I^2=90%); with recommended-dose T compared to recommended-dose O (RR: 2.25; 95%CI: 1.16-4.36). Adverse events were also more frequent with recommended-dose V compared to recommended-dose S (RR: 3.71; 95%CI: 1.42-9.70); with low-dose V compared to low-dose S (RR: 3.40; 95%CI: 1.18-9.77; I^2=53%); and with recomended-dose vasopressin compared to low-dose octreotide (RR: 3.67; 95%CI: 1.17-11.52).

Publication bias

For mortality, visual inspection of the funnel plot did not show significant publication bias. Besides, the estimated overall effect of this outcome did not appear to be undermined by publication bias and a small study effect, as revealed by a non-significant p-value for Egger's intercept (p=0.645). For adverse events, visual inspection of the funnel plot did not show significant publication bias, and the Egger test also suggested a similar conclusion. Regarding secondary outcomes, we found publication bias in the bleeding control observed in the funnel plot and in the Egger's test (Supplementary File 2).

The certainty of the evidence

According to GRADE methodology, the certainty of the evidence was moderate for mortality and total adverse events. Regarding secondary outcomes, the certainty of the evidence was low for bleeding control, early rebleeding, blood transfusion, and hospital stay; and very low for late rebleeding. More details are shown in Table IV.

Table III. Summary of the meta-analyses of each adverse event

Outcomes	N° of studies included	T-V (Events/ Total)	O-S (Events/ Total)	Effect Size RR (95% CI)	Overall effect p-value	Heterogeneity	
						p	I^2 (%)
Abdominal pain	8	33/533	15/791	2.01 (1.14 to 3.53)	0.02	0.84	0
Electrocardiogram changes	7	14/510	8/771	2.12 (0.84 to 5.37)	0.11	0.68	0
Chest pain	6	12/369	1/625	3.97 (1.17 to 13.48)	0.03	0.88	0
Bradycardia	5	26/200	11/198	1.73 (0.87 to 3.44)	0.12	0.46	0
Hyperglycemia	5	5/201	13/202	0.44(0.17 to 1.15)	0.10	0.62	0
Diarrhea	4	17/358	6/616	3.16 (1.17 to 8.56)	0.02	0.5	0
High blood pressure	4	18/152	10/153	1.65(0.63 to 4.35)	0.31	0.27	24
Headache	4	4/103	2/106	1.44(0.31 to 6.64)	0.64	0.42	0
Hyponatremia	3	36/354	10/615	4.29 (1.28 to 14.29)	0.02	0.14	50

N°: Number, RR: Risk Ratio, T: terlipressin, V: vasopressin; O: octreotide, S: somatostatin.

Table IV. Summary of the findings of main outcomes: GRADE.

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with O-S	Risk difference with T-V
General mortality: T-V vs O-S (With and without endoscopic treatment)	2431 (21 RCTs)	☑☑☑☐MODERATE[a]	RR 1.01 (0.83 to 1.22)	131 per 1000	1 more per 1000 (22 fewer to 29 more)
Bleeding Control: T-V vs O-S (With and without endoscopic treatment)	2431 (21 RCTs)	☑☑☐☐LOW [b,c,e]	RR 0.96 (0.91 to 1.02)	861 per 1000	34 fewer per 1000 (78 fewer to 17 more)
Early rebleeding: T-V vs O-S (With and without endoscopic treatment)	1366 (13 RCTs)	☑☑☐☐LOW [b,c]	RR 0.91 (0.66 to 1.24)	102 per 1000	9 fewer per 1000 (35 fewer to 24 more)
Late rebleeding: T-V vs O-S (With and without endoscopic treatment)	415 (3 RCTs)	☑☐☐☐VERY LOW[b,c,f]	RR 0.94 (0.56 to 1.60)	143 per 1000	9 fewer per 1000 (63 fewer to 86 more)
Blood transfusion: T-V vs O-S (With and without endoscopic treatment)	1505 (11 RCTs)	☑☑☐☐LOW [b,g]	-	MD 0.04 U more (0.31 fewer to 0.39 more)	
Hospital stay: T-V vs O-S (With and without endoscopic treatment)	320 (4 RCTs)	☑☑☐☐LOW [b,c]	-	MD 1.06 days lower (2.8 lower to 0.69 higher)	
Total adverse events: T-V vs O-S (With and without endoscopic treatment)	1659 (15 RCTs)	☑☑☑☐MODERATE[b,h]	RR 2.39 (1.58 to 3.62)	88 per 1000	123 more per 1000 (51 more to 231 more)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; MD: mean difference. Explanations: a. Some studies had a high risk of bias in the generation of random sequences. Blinding was uncertain in almost half of the studies; b. Some studies have a high risk of bias in the generation of random sequences. Concealment of the random sequence was not adequate in some studies. Blinding of outcome assessment was unclear in some studies; c. The optimal information size criterion was not met, and the total sample size was not large; d. The funnel plot is asymmetry, there is a gap probably due to publication bias. Furthermore, the Egger test shows a low p-value (p: 0.013); e. Point estimates vary across studies, confidence intervals show minimal overlap, the statistical test for heterogeneity show a very low p-value. However, we note that the inconsistency is mainly explained by the use of endoscopic therapy; f. The optimal information size criterion was not met, and the total sample size was not large. Confidence intervals are wide; g. Point estimates vary across studies, confidence intervals show moderate overlap, the statistical test for heterogeneity show a very low p-value. Also, I^2 is moderate; h. The statistical test for heterogeneity shows a low p-value and I2 is high, but point estimates are on the left side of the no-effect line, and confidence intervals show overlap. We decided did not rate down for inconsistency.

DISCUSSION

Summary of the results

In this meta-analysis of RCTs, we provide strong evidence that the risk of all-cause mortality in cirrhotic patients with AVB is similar for both vasoactive agent groups (T-V vs. O-S), and this is not influenced by the use of endoscopic therapy, the type of vasoactive agent used, or the Child-Pugh classification. Additionally, the sensitivity analysis performed for the risk of bias showed the same results. According to GRADE the certainty of the evidence was moderate for this outcome, thereby ensuring that the estimated effect is close to the true effect.

Regarding harm (adverse events), there was a significant increase in the risk of adverse events associated with the use of T-V compared to O-S. Although we found moderate statistical heterogeneity, almost all the primary studies reported more adverse events in the T-V group, and most of them showed statistically significant results. These findings could be attributed to the mode of administration and its ischemic effects since it has powerful systemic vasoconstrictive action [2]. The most frequent adverse events reported were bradycardia, high blood pressure, hyponatremia, and abdominal pain. Also, the certainty of the body of evidence was moderate indicating that our findings are reliable.

No significant differences were found in the secondary outcomes of bleeding control, early rebleeding, late rebleeding, blood transfusion, and hospital stay for which the certainty of the evidence was low or very low.

Comparison with other studies

Previous SRs [6, 11, 35-37] have compared the efficacy of vasoactive agents with placebo, other vasoactive agents, or other non-pharmacological therapy. Few SRs have attempted to directly compare vasoactive agents used in AVB [10, 38], and others have compared different therapies for AVB by network meta-analysis [39-41]. However, many of these SRs are outdated, did not include RCTs from Asia, only evaluated the efficacy and non-safety outcomes, did not adequately assess risk of bias or methodological quality, and finally, did not pool all the studies and only presented by subgroups assuming that certain characteristics influence outcomes [11, 37].

Concerning mortality, our findings agree with those reported in other SRs. Ioannou et al. [37] found lower mortality in patients treated with T compared to placebo, but no difference versus other vasoactive agents. This review, however, included only a few studies with low quality. Gotzsche et al. [38] evaluated S analogs versus placebo or no treatment and found no significant difference for mortality risk; however, their findings were inconsistent because they did find a significant difference for failed initial hemostasis and number of transfusions which favored S analogs over placebo. Besides, their search and selection of studies were not exhaustive, assessment of the risk of bias was inadequate, and they omitted to summarize some outcomes. Wells et al. [11] found no differences between terlipressin, vasopressin, octreotide, and somatostatin for mortality. Regarding our SR, we included all studies reported in previous SRs, except when

one vasoactive agent was combined with another. Furthermore, we performed a sensitivity analysis excluding studies with a high risk of bias. Our results were similar to the estimated overall effect. Taking these findings into account, we believe that our results are reliable.

On the other hand, we also looked for safety outcomes. Adverse events were often poorly reported in some trials and almost none classified these events as severe or causing treatment discontinuation. We found strong evidence of an increased risk of adverse effects with T-V compared to O-S, which was similar to the findings of Zhou et al. [6], who described a higher risk of complications with Terlipressin compared to Somatostatin. Corley et al. [36] reported a 47% lower risk of complications with Octreotide than Terlipressin or Vasopressin, and a 69% lower risk of presenting major complications. Zou et al. [40] also found Somatostatin and Octreotide had fewer adverse events and non-serious adverse events than V and T. Our findings were consistent with most primary studies that reported adverse events. Furthermore, these findings remained the same despite the different doses of vasoactive agents. However, all the included studies evaluated bolus-applied T; studies evaluating its use in continuous infusion are needed given the findings of lower incidence of adverse events in other complications of cirrhotic patients [42].

We found a similar probability of bleeding control with O-S or T-V. However, there was an important heterogeneity, possibly attributed to endoscopic therapy. In the subgroup analysis, patients treated with endoscopic therapy had a similar probability of bleeding control whether they received T-V or O-S; however, in patients who did not undergo endoscopic therapy, those who received O-S were more likely to control bleeding than those who received T-V. Previous SRs found that in patients treated with a vasoactive agent and endoscopic therapy bleeding control was more likely than in patients treated with a vasoactive agent without endoscopic therapy [11, 36, 38]. Therefore, this suggests that patients treated with a vasoactive agent but without endoscopic therapy have a higher baseline risk to fail bleeding control; and they were more likely to control bleeding with O-S than T-V. Nonetheless, further studies are needed to corroborate these findings.

Regarding rebleeding, primary studies reported different classifications of rebleeding, and different times of measuring rebleeding. We found that patients treated with T-V or O-S had the same risk of early rebleeding. Few studies reported late rebleeding, similar findings were noted between them. Previous SRs found similar results in both outcomes [10, 11, 37, 43].

Primary studies evaluated blood transfusion in different ways. Some reported total transfused blood units, while others reported globular package, fresh frozen plasma, or platelet units. Also, the criteria for transfusing blood product units were different in the studies that reported this outcome. We found no differences between T-V and O-S. However, there was a high heterogeneity, which was probably due to different protocols, volumes, and types of units transfused. Moreover, we found that the use of endoscopic therapy influenced the number of blood transfusions. Our findings were similar to the results of previous SRs [37, 38].

The hospital stay was similar in patients treated with T-V or O-S. We also noted that hospital stay was longer in patients who were treated with a vasoactive agent without endoscopic therapy. The heterogeneity among the studies was important, probably due to changes in management approaches over the last years.

Few included RCTs assessed outcomes based on the severity of cirrhosis. Thus, more studies are needed to compare the effect of T-V versus O-S on bleeding control, rebleeding, hospital stay, and blood transfusions, according to the severity of cirrhosis. A specific approach would be interesting in more severe cases because of their worse prognosis.

The certainty of evidence and implications for clinical practice

The certainty of the body of evidence was moderate for the main outcomes, due to the risk of bias in most studies. Generation of the random sequence and allocation concealment were unclear or high in some studies, and other studies were not blinded or there was a high probability that the blinding was broken. Concerning mortality, we performed a sensitivity analysis and found similar results; the CI was narrow, the results of the primary studies were consistent with the estimated overall effect, and there was no evidence of publication bias. Therefore, it can be stated that patients with AVB treated with T-V or O-S have a similar probability of mortality. Concerning adverse events, the results of primary studies were consistent with our estimated overall effect; the CI did not show imprecision, and publication bias was not detected. Furthermore, we are confident that the use of T-V is more likely to develop adverse events than O-S.

For secondary outcomes, the certainty of the evidence was low or very low. This was due to the risk of bias, imprecision, and inconsistency. Also, most of the studies had small sample sizes, which made the estimated overall effect imprecise. Moreover, bleeding control, rebleeding, and blood transfusions are subjective outcomes that could be affected by improper blinding. Finally, we assumed an important heterogeneity, mainly due to different population characteristics, different doses, and times of administration of vasoactive agents, different comparators, and different times of evaluation of the outcomes.

Regarding the balance of desirable and undesirable effects of each group of interventions, O-S showed the best balance. While T-V showed a similar mortality risk than O-S, T-V presented a significantly higher probability of developing adverse events compared to O-S. Besides, if therapeutic endoscopy were not possible, the use of O-S would be more likely to control acute variceal bleeding. Choosing between O or S would depend on drug availability. Terlipressin remains an option with careful consideration of adverse events. Similarly, V could be used but close monitoring of adverse events. We believe that T-V could be a good option for cirrhotic patients with AVB and other complications as a hepatorenal syndrome or hypotension [44], but further studies are needed.

For some patients or physicians T could be more convenient due to its bolus administration or familiarity with the drug. Conversely, O-S could be more user-friendly because of its safety profile or its current experience. However, in medical practice, the decision of the vasoactive agent would depend on availability and cost. These factors vary by country and region.

In summary, our results showed a similar mortality risk between T-V and O-S but a significantly higher risk of adverse events with T-V. The certainty of the body of evidence was moderate for the main outcomes. However, there was uncertainty regarding bleeding control, rebleeding, hospital stay, and blood transfusion.

Limitations and strengths

The current study has some limitations. First, we included some abstracts with no full-text studies, but the results of these abstracts had been used in previous SRs, and assessment of the domains of risk of bias had been performed. Second, the average duration of follow-up was variable between trials. Third, most of the trials had a small sample size, but we found 21 trials totaling 2,431 participants. Fourth, most of the trials had a high or unclear risk of bias; however, sensitivity analyses excluding high-risk bias showed consistency in results for the main outcome. Fifth, the included studies had considerable heterogeneity, which, after analysis, did not significantly affect our main outcomes.

Our study includes the largest amount of RCTs that compare T-V versus O-S, it includes a rigorous and extensive literature search without language restriction and a robust methodology that includes the assessment of efficacy and safety, analysis by intention to treat for efficacy outcomes and analysis protocol for safety outcomes, as well as detailed analysis of adverse events. Besides, we performed an assessment of the risk of bias, interpretation of the results considering the heterogeneity of the studies, determination of the certainty of the evidence with GRADE methodology, a sensitivity analysis that showed consistency in our findings, and evaluation of the benefit/harm balance.

CONCLUSIONS

Octreotide or Somatostatin should be preferred over other vasoactive agents in cirrhotic patients with acute variable bleeding. Terlipressin or Vasopressin remains an option, but close monitoring of adverse events is necessary. The choice between one of them would depend on availability and cost. An important part of analyzed studies suffer mainly from selection, performance, and detection bias. Better designed RCTs are needed, and also there is a need for RCTs, to resolve some questions in patients with more advanced disease, evaluate other critical and important outcomes such as control of bleeding or rebleeding, as well as the effect of continuous infusion of Terlipressin.

Conflicts of interest: None to declare.

Authors' contribution: J.H.M., M.R.H, A.B.C., P.V.L., and D.F.P.R. participated in the conception and design of the study. J.H.M., M.R.H., A.B.C., P.V.L., and D.F.P.R. acquired the data. J.H.M., M.R.H., A.B.C., P.V.L., and D.F.P.R. participated in the analysis and interpretation of data. All authors participated in drafting or revising the manuscript.

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