Systematic Review/Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Continuous vs. intermittent terlipressin infusion for portal hypertension: a systematic review and meta-analysis

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Background: Portal hypertension, a major complication of chronic liver disease, often leads to life-threatening variceal bleeding, managed effectively with vasoactive drugs like terlipressin. However, the most optimal method of terlipressin administration, continuous versus intermittent infusion, remains a subject of debate, necessitating this systematic review and meta-analysis for evidence-based decision-making in managing this critical condition.

Methods: This systematic review and meta-analysis adhered to the PRISMA standards and explored multiple databases until 6 April 2023, such as MEDLINE through PubMed, Scopus, Web of Science, and CENTRAL. Independent reviewers selected randomized controlled trials (RCTs) that met specific inclusion criteria. After assessing study quality and extracting necessary data, statistical analysis was performed using Review Manager (RevMan), with results presented as risk ratios (RR) or mean differences.

Results: Five RCTs ($n = 395$ patients) were included. The continuous terlipressin group had a significantly lower risk of rebleeding (RR = 0.43, $P = 0.0004$) and treatment failure (RR = 0.22, $P = 0.02$) and fewer total adverse effects (RR = 0.52, $P < 0.00001$) compared to the intermittent group. However, there were no significant differences between the two groups in mean arterial pressure ($P = 0.26$), length of hospital stays ($P = 0.78$), and mortality rates ($P = 0.65$).

Conclusion: This study provides robust evidence suggesting that continuous terlipressin infusion may be superior to intermittent infusions in reducing the risk of rebleeding, treatment failure, and adverse effects in patients with portal hypertension. However, further large-scale, high-quality RCTs are required to confirm these findings and to investigate the potential benefits of continuous terlipressin infusion on mortality and hospital stays.

Keywords: continuous infusion, intermittent infusions, portal hypertension, rebleeding, terlipressin

Introduction

Portal hypertension, a significant complication of chronic liver disease, is characterized by increased pressure in the portal venous system and can develop varices in the esophagus and stomach[1]. Among the life-threatening complications of portal hypertension, variceal bleeding is considered the most severe, with a high mortality rate[2]. Therefore, the effective control of acute variceal bleeding is crucial in patients with portal hypertension.

Vasoactive drugs, such as terlipressin, are used as an immediate pharmacologic therapy to control variceal bleeding, and their administration has been associated with improved survival rates[3]. Terlipressin, a synthetic analog of vasopressin, has been shown to effectively reduce portal pressure and blood flow to the varices, thereby reducing bleeding[4,5]. Terlipressin causes vasoconstriction in both the splanchnic and peripheral regions when administered intravenously, which results in decreased portal blood flow and a reduction in portal venous pressure (PVP)[6–8].

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2023) 85:5001–5010

Received 27 May 2023; Accepted 23 August 2023

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 5 September 2023

http://dx.doi.org/10.1097/MS9.0000000000001261

Besides its role in managing portal hypertension, terlipressin is also utilized to treat septic shock and hepatorenal syndrome. It can elevate blood pressure in cases of septic shock and enhance renal blood flow in critically ill patients with cirrhosis[9].

The mode of terlipressin administration, however, remains a matter of debate. Continuous infusion and intermittent infusion are the two main methods that are commonly used, each having its advantages and potential drawbacks. While continuous infusion ensures a steady level of drug in the bloodstream, thereby possibly providing more consistent hemodynamic control, intermittent infusion allows for the adjustment of drug dose in response to patient response, potentially reducing side effects[5].

Despite the extensive use of terlipressin in the control of acute variceal bleeding, no systematic review and meta-analysis have been conducted to compare the efficacy and safety of continuous versus intermittent infusions of terlipressin. This lack of collective understanding limits our ability to make evidence-based decisions about the most optimal approach to managing this life-threatening condition. This systematic review and meta-analysis aimed to fill this gap in knowledge by comparing the efficacy and safety of continuous versus intermittent infusions of terlipressin for the control of acute variceal bleeding in patients with portal hypertension.

HIGHLIGHTS

- Our systematic review and meta-analysis, guided by PRISMA guidelines, compare the effectiveness and safety of continuous versus intermittent infusion of terlipressin, a vasoactive drug, in managing portal hypertension.
- The analysis included five randomized controlled trials, encompassing 395 patients, investigating the efficacy of terlipressin administered continuously versus intermittently.
- Continuous terlipressin infusion significantly reduced the risk of rebleeding (RR = 0.43, $P = 0.0004$), treatment failure (RR = 0.22, $P = 0.02$), and total adverse effects (RR = 0.52, $P < 0.00001$) in comparison to the intermittent group.
- No significant differences between the two groups regarding mean arterial pressure, length of hospital stays, and mortality rates, indicating that both administration methods have comparable impacts.
- While this research strongly suggests that continuous terlipressin infusion may be superior to intermittent infusions in certain aspects, further large-scale, high-quality, randomized controlled trials are necessary to reinforce these findings and explore potential benefits on mortality and hospital stays.

Methods

This systematic review and meta-analysis were conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplemental Digital Content 1, http://links.lww.com/MS9/A244) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) (Supplemental Digital Content 2, http://links.lww.com/MS9/A245) guidelines. Our work rigorously follows the PRISMA (Supplemental Digital Content 1, http://links.lww.com/MS9/A244) and AMSTAR (Supplemental Digital Content 2, http://links.lww.com/MS9/A245) criteria to ensure methodological integrity[10,11].

Search strategy

We conducted a comprehensive literature search using MEDLINE via PubMed, Cochrane CENTRAL, Web of Science, and Scopus databases. This systematic review and meta-analysis adhered to the PRISMA standards and explored multiple databases until 6 April 2023. The search strategy employed a combination of keywords and MeSH terms, including (terlipressin OR Glycylpressin OR TGLVP OR Terlypressin OR Triglycyl Lysine Vasopressin OR Triglycylvasopressin OR Glipressin OR Glypressin OR Remestyp) AND (Continuous terlipressin OR Intermittent terlipressin OR Intravenous terlipressin OR terlipressin Infusion OR Bolus infusion) AND (acute variceal bleeding OR portal hypertension). As indicated in the (Supplementary Tables, Supplemental Digital Content 3, http://links.lww.com/MS9/A246), the search strategy is demonstrated through various platforms, including PubMed, Cochrane CENTRAL, Web Science, and Scopus.

Selection process

Two independent reviewers screened the titles and abstracts of the identified studies against the inclusion criteria. Full-text articles were obtained for studies that potentially met the inclusion criteria or where there was uncertainty. Disagreements between reviewers during the study selection process were resolved through discussion or by consulting a third reviewer.

Inclusion and exclusion criteria

Our review included studies that met the following criteria.

Populations

Studies that included patients with portal hypertension confirmed by clinical, biochemical, ultrasound, and/or biopsy criteria.

Intervention and comparator

Studies that included patients who received continuous or intermittent terlipressin infusions.

Outcomes

Studies that assessed the efficacy of interventions on the rate of rebleeding, mean arterial pressure (MAP), hospital stay, and mortality, as well as the safety of these interventions.

Study Design

Randomized Controlled Trials (RCTs).

We excluded studies that were not RCTs, animal studies, and those not published in English.

Quality assessment

Two reviewers independently assessed the included studies using the revised Cochrane risk-of-bias tool for randomized trials (RoB-II)[12]. This tool evaluates five domains of bias, bias in the selection of the reported result, bias in the measurement of the outcome, bias due to missing outcome data, bias due to deviations from the intended interventions, and bias arising from the

randomization process. A discussion or consultation with a third reviewer was used to resolve any disagreements.

Data extraction

Two reviewers autonomously collected data from the included studies using a predefined extraction form. In cases where discrepancies arose, they were resolved through discussion or by seeking the input of a third reviewer. The extracted data encompassed various aspects, including study characteristics (e.g. author, year of publication, and country), patient demographics, details of the interventions and comparisons, as well as outcomes. The primary outcome focused on the rebleeding rate, while secondary outcomes comprised MAP, duration of hospital stay, mortality, and overall adverse events.

Statistical analysis

Data analysis was performed using Review Manager (RevMan) version 5.4. We used the random-effects model for meta-analysis, considering the potential clinical heterogeneity among the included studies. The presence of statistical heterogeneity among the included studies was evaluated using the χ^2test and the I^2 statistic. A P-value of less than 0.10 for the χ^2test or an I^2 value greater than 50% was considered indicative of substantial heterogeneity[13]. The results were reported in terms of risk ratios for dichotomous outcomes and mean differences for continuous outcomes, accompanied by 95% CIs. Statistical significance was defined as a P-value below 0.05. No subgroup analysis was planned due to the lack of data. Publication bias was not applicable due to the small number of included studies[14].

Results

Study selection

The initial database search yielded 1941 studies, comprised of 414 from PubMed, 154 from Cochrane CENTRAL, 985 from Scopus, and 388 from the Web of Science. After the removal of 561 duplicates, 1380 studies were screened for eligibility based on their title and abstract, leading to the exclusion of 1260 records. A full-text review of the remaining 120 articles resulted in the exclusion of 115 studies that did not meet the inclusion criteria. Ultimately, five studies were included in the systematic review and meta-analysis[15–19] (Figure 1).

Patients and studies characteristics

The five included studies were all RCTs conducted in China, India, and Italy, involving a total of 395 patients. The studies varied in terms of participant inclusion criteria, diagnostic criteria, and main findings. Each study compared the effects of continuous versus intermittent terlipressin infusions on outcomes related to portal hypertension, including portal venous pressure, heart rate, mean arterial pressure, treatment failure, adverse event rate, response to treatment, mean daily effective terlipressin dose, rebleeding rate, number of hospital days, and mortality rate, as shown in Table 1. The included studies showed a diverse range of baseline characteristics, with a considerable variation in mean age, sex distribution, heart rate, creatinine levels, bilirubin levels, hemoglobin levels, International Normalized Ratio (INR), Model for End-stage Liver Disease (MELD) scores, and Child-Turcotte-Pugh score (CTP) scores between the continuous and intermittent terlipressin groups. The variability in these baseline characteristics reflects the potential heterogeneity of the included study populations, as shown in Table 2.

Quality assessment

We could not evaluate the quality of the Palnati *et al.*[19] study as the full-text was not accessible. The remaining four trials demonstrated the use of appropriate methods for random sequence generation, such as web-based systems employing permuted blocks or computer-generated random sequences[15–18]. However, two of these four studies did not provide any information regarding allocation concealment, resulting in some concerns regarding bias[17,18]. Nevertheless, no significant differences in baseline characteristics were observed across all studies. Furthermore, all four trials employed appropriate analysis methods to evaluate the effect of intervention assignment and reported nearly complete outcome data. They also demonstrated appropriate outcome measurement, indicating a low risk of bias. Additionally, all studies reported their results in accordance with prespecified analysis plans and/or registered protocols. Further details and overall judgments are shown in Figure 2.

Meta-analysis

Rebleeding

Three studies encompassing 296 patients reported data on rebleeding rates[15,18,19]. The meta-analysis of these studies showed a significantly lower RR of rebleeding in the continuous terlipressin group compared to the intermittent group (RR = 0.43, 95% CI: 0.27–0.69; $P = 0.0004$), as shown in Figure 3A. There pooled data were homogenous ($I^2 = 3\%$; $P = 0.36$).

MAP

Three studies ($n = 170$) reported data regarding the post-intervention MAP[16,17,19]. The random-effect size showed that MAP was comparable in both continuous and intermittent terlipressin groups (MD = −1.17 mmHg, 95% CI: −3.20–0.86; $P = 0.26$), as shown in Figure 3B. The pooled data were homogonous ($I^2 = 5\%$; $P = 0.35$).

Hospital stays

Three studies ($n = 236$) reported data regarding the length of hospital stays in both treatment groups[16,18,19]. The random-effect size showed that hospital stays were shorter in the continuous group compared to the intermittent group; however, the difference was not significant (MD = −0.22 days, 95% CI: −1.74–1.30; $P = 0.78$). The heterogeneity between the pooled studies was moderate ($I^2 = 43\%$; $P = 0.17$), as shown in Figure 4A.

Mortality

Four studies ($n = 346$) reported data regarding the mortality rate in both treatment groups[15,16,18,19]. The fixed-effect size showed that the mortality rate was lower in the continuous group compared to the intermittent group; however, the difference was not significant (RR = 0.89, 95% CI: 0.54–1.47; $P = 0.65$). The heterogeneity between the pooled studies was mild ($I^2 = 16\%$; $P = 0.31$), as shown in Figure 4B.

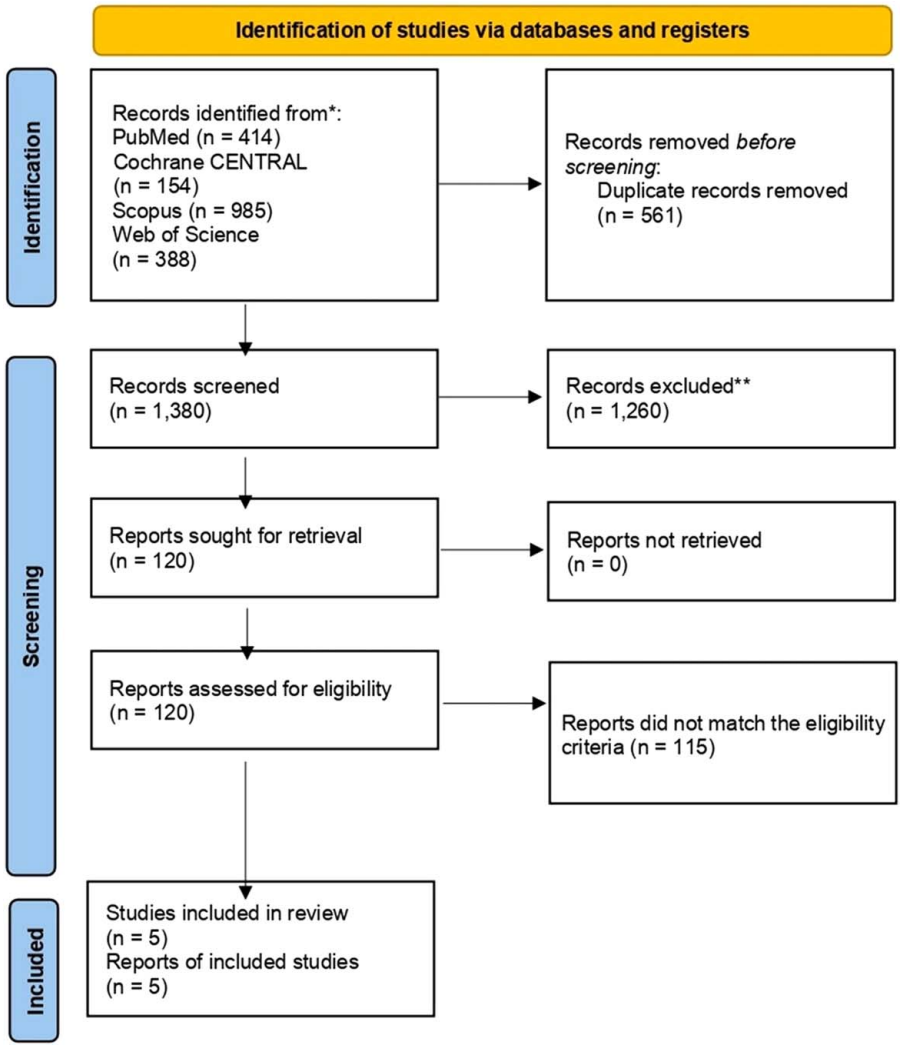

Figure 1. PRISMA Flow Diagram.

Treatment failure

Two studies ($n = 196$) reported data regarding treatment failure in both groups[15,18]. The fixed-effect size showed that the continuous group was associated with a significantly lower risk of treatment failure compared to the intermittent group (RR = 0.22, 95% CI: 0.06–0.82; $P = 0.02$), as shown in Figure 4C. The pooled data were homogenous ($I^2 = 0\%$; $P = 0.95$).

Adverse events

The fixed-effect model showed that the continuous group was associated with a significantly lower risk of the total number of adverse effects (RR = 0.52, 95% CI: 0.43–0.70; $P < 0.00001$) compared to the intermittent group. Moreover, the continuous group showed a lower risk of diarrhea (RR = 0.56, 95% CI: 0.29–1.09; $P = 0.09$), chest pain (RR = 0.60, 95% CI: 0.24–1.47; $P = 0.27$), cardiac arrhythmias (RR = 0.54, 95% CI: 0.18–1.60; $P = 0.26$), and acute abdomen (RR = 0.34, 95% CI: 0.08–1.40; $P = 0.14$), compared to the intermittent group; however, the difference was not statistically significant. On the other hand, both groups showed a comparable risk of arterial hypertension (RR = 1.01, 95% CI: 0.36–2.85; $P = 0.98$), as shown in Figure 5.

Results of individual studies

Hemodynamic changes

Ding *et al*. investigated the effects of continuous and intermittent infusion of terlipressin on PVP following the transjugular intrahepatic portosystemic shunt procedure. While both methods reduced PVP, the continuous infusion group maintained a more consistent decrease (– 24.88% on average) over 24 h compared to the intermittent infusion group, whose PVP levels fluctuated and tended to restore to baseline during 6 h intervals. Additionally, heart rate (HR) decreased significantly ($P < 0.005$) in both groups after terlipressin use, with no significant difference between both groups ($P = 0.57$)[17].

Predictors of early bleeding

Jha *et al*. showed that factors such as the active bleeding during endoscopy ($P = 0.005$), larger esophageal varices ($P = 0.04$),

Table 1

Summary table of the included studies.

References	Country	Study design	*N*	From	To	Inclusion criteria	Criteria of diagnosis	Main findings
Ding *et al.*[17]	China	RCT	21	June 2011	June 2012	Patients with BCS or recurrent variceal hemorrhage variceal bleeding did not occur in the latest two weeks preceding the hospitalization, and vasoactive drugs had not been taken in the latest week. TIPS was planned for these patients for treatment of BCS or rebleeding prevention.	The diagnosis of portal hypertension was made based on ultrasonographic or medical history or computed tomography scan findings	At a 1 h time point, PVP dropped rapidly in both groups and was reduced by 16.46 and 28.22%, respectively. HR decreased significantly, 1 h after the start of drug administration, in both groups (84.1 (12.8) vs. 73.8 (12.6) in the intermittent group and 86.7 (11.5) vs. 77.1 (13.6) in the continuous group, $P < 0.005$), and the MAP increased in both groups, although no statistical differences were found.
Jha[18]	India	RCT	86	February 2016	November 2017	Patients with portal hypertension with AEVB were included.	Diagnosis of portal hypertension was made by biomedical, clinical, ultrasound, and/or biopsy criteria. The criteria for diagnosis of esophageal variceal bleeding were one of the following: (a) visualization of actively bleeding esophageal varices, (b) fibrin clot attached to esophageal varix, (c) presence of fresh blood in the stomach in patients with esophageal varices in the absence of any other lesion in the upper digestive tract that can explain bleeding.	Patients in group A had a lower rate of treatment failure (4.7%) as compared to patients in the other group (20.7%) ($P = 0.02$). Four and eight patients died within 6 weeks in groups A and B, respectively ($P = 0.21$). MELD-Na score and continuous infusion of terlipressin showed a significant relationship with treatment failure on multivariate analysis.
Cavallin *et al.*[16]	Italy	RCT	78	2007	2014	Patients aged more than 18 years with cirrhosis as diagnosed by liver biopsy or clinical, ultrasound, biomedical, and/or endoscopic findings.	Diagnosis of type 1 HRS as defined by the criteria of the International Club of Ascites, which are: Cirrhosis with ascites. Rapid progressive renal failure. No improvement of sCr (decrease to a level of 133 lmol/l) after at least two days with diuretic withdrawal and volume expansion with albumin. Absence of shock. (5) No current or recent treatment with nephrotoxic drugs. (6) Parenchymal kidney disease absence.	The adverse events rate was lower in the TERLI-INF group (35.29%) than in the TERLI-BOL group (62.16%, $P < 0.025$). Response to treatment rate, including both complete and partial response, was not significantly different between the two groups (76.47 versus 64.85%). The mean daily effective terlipressin dose was lower in the TERLI-INF group than in the TERLI-BOL group (2.23 6 0.65 versus 3.51 6 1.77 mg/day; $P < 0.05$).
Palnati[19]	India	RCT	100	NR		Patients with endoscopically diagnosed acute variceal bleeds were included.	NR	MAP was significantly lower in the continuous group (83.98 (4.03) vs 85.62 (3.65)). Also, Rebleeding was lower in the continuous group (25 vs 47.92%). There was no significant difference in the number of hospital days (7.94 (1.35) vs 8.14 (1.4)). Adverse events like AKI (3.8 vs. 18.8%), Diarrhea (7.69 vs. 18.75%), and chest pain (3.85 vs. 12.5%) were higher in the intermittent group. The mortality rate within 28 days was lower in the continuous group (7.69 vs 12.5%).
Arora *et al.*[15]	India	RCT	110	May 2016	January 2018	Patients with a diagnosis of cirrhosis, based on imaging/histology or endoscopic criteria and aged between 18 and 70 years with acute esophageal variceal bleeding.	Acute variceal bleed was defined as per the APASL criteria	HVPG response at 24 h was achieved in significantly more patients in CONI than the other group {47/55(85.4%) vs. 32/55(58.2%), $P = 0.002$}. Also, early HVPG response at 12 h was also higher in the CONI group (71.5 vs. 49.1%). Median terlipressin dose was significantly lower {4.25 $\pm$ 1.26 mg vs. 7.42 $\pm$ 1.42 mg/24 h). and adverse events were fewer {20/55(36.3%) vs. 31/55(56.4%) in the CONI than the other group. Very early rebleed was significantly higher in the BOL group {8/55 (14.5%) vs. 1/55 (1.8%)}.

AEVB, acute esophageal variceal bleeding; APASL, Asian Pacific Association for the Study of Liver; BCS, Budd–Chiari syndrome; HR, heart rate; HRS, Hepatorenal syndrome; HVPG, hepatic venous pressure gradient; MELD-Na, model for end-stage liver disease-sodium; PVP, portal venous pressure; sCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic shunt.

Table 2

Shows the baseline characteristics of the included studies' populations.

References	Number		Age Mean (SD)		Sex (male) (*N*, %)		Heart rate		Creatinine level		Bilirubin level		Hemoglobin level		INR		MELD		CTP	
	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group
Chao Ding[17]	10	10	43.9 (17.5)	47.4 (12.4)	5 (50%)	6 (60%)	86.7 (11.5)	84.1 (12.8)	64.3 (10.8)	59 (12.2)	23.1 (13.5)	22.3 (10.0)	107.4 (23.6)	91.5 (22.3)	1.28 (0.24)	1.29 (0.12)		NR		NR
Jha[18]	43	43	41.74 (12.72)	43.53 (14.91)	31 (72.1%)	35 (85.4%)	–		0.92 (0.29)	0.92 (0.29)	7.6 (15.7)	6.2 (12.5)	7.43 (1.81)	7.08 (2.11)	1.39 (0.51)	1.52 (0.44)		NR	7.92 (2.00)	8.56 (1.98)
Cavallin[16]	34	37	57.41 (10.48)	59.41 (8.87)	24 (70.5%)	24 (64.8)	73.69 (13.44)	78.18 (10.57)	296.59 (117.09)	275.14 (90.15)	150.77 (173.44)	157.83 (160.04)	NR		1.88 (0.74)	1.93 (0.58)	29.26 (7.76)	29.81 (6.40)	10.79 (2.12)	10.78 (1.74)
Paina[19]	50	50	NR		NR		NR		NR		NR		NR		NR		NR		NR	
Arora[15]	55	55	48.29 (11.66)	49.22 (11.25)	41 (74.5%)	42 (76.4%)	103.6 (12.2)	105.13 (10.20)	1.10 (0.39)	1.07 (0.54)	4.16 (3.15)	4.02 (3.07)	8.05 (1.98)	7.82 (1.62)	NR		18.80 (7.31)	18.49 (6.87)	9.5 (2.1)	9.37 (1.7)

NR, Not reported.

serum sodium level ($P = 0.03$), serum albumin ($P = 0.02$), INR ($P = 0.001$), creatinine ($P = 0.001$), serum bilirubin ($P = 0.003$), hepatic encephalopathy ($P = 0.03$), presence of ascites ($P = 0.03$), MELD-Na score ($P = 0.001$), and CTP score ($P = 0.001$) were significantly associated with early bleeding. Upon multivariate analysis, the MELD-Na score was associated with an increased risk of early bleeding [Odds ratio (OR) = 1.37, 95% CI: 1.16–1.62; $P < 0.001$), whereas continuous infusion of terlipressin was associated with a significantly reduced risk of early bleeding (OR = 0.18, 95% CI: 0.037–0.91; $P = 0.04$)[18]. Similarly, Arora1 *et al.* conducted a multivariate analysis to determine the predictors of rebleeding. Their findings demonstrated that hepatic venous pressure gradient (HVPG; OR = 1.90, 95% CI: 1.25–2.89; $P = 0.002$) and MELD (OR 1.18, 95% CI: 0.99–1.41; $P = 0.05$) were significant predictors of rebleeding[15].

Predictors of survival

Cavallin *et al.* showed that the response to treatment (Hazard ratio [HR] = 3.07, 95% CI: 1.35–7.01; $P = 0.008$) and chronic liver failure consortium score (HR = 1.10, 95% CI: 1.05–1.16; $P < 0.001$), age (HR = 1.06, 95% CI: 1.02–1.11; $P = 0.006$), baseline serum creatinine (HR = 1.004, 95% CI: 1.000–1.008; $P = 0.048$), and serum bilirubin (HR = 1.004, 95% CI: 1.001–1.006; $P = 0.002$) were found to be independent predictors of survival[16].

Discussion

The present systematic review and meta-analysis aggregated data from five RCTs to compare the effects of continuous versus intermittent terlipressin infusions in patients with portal hypertension. The results of this meta-analysis indicated that continuous terlipressin infusion could be a more efficacious treatment option than intermittent infusions in certain aspects. In particular, continuous terlipressin infusion was associated with a significantly lower risk of rebleeding, treatment failure, and overall adverse effects. Moreover, the continuous terlipressin infusion group exhibited a non-significant trend towards lower mortality rates and shorter hospital stays, albeit these differences did not reach statistical significance. This nonsignificant trend could be due to a lack of power, suggesting that larger studies might be needed to definitively ascertain the effects of continuous versus intermittent terlipressin infusions on these outcomes.

Rebleeding is a critical concern in the management of portal hypertension, with substantial implications for patient morbidity and mortality[1]. Our findings align with previous research indicating the benefits of continuous vasoactive drug infusion in preventing variceal rebleeding[20]. A previous meta-analysis of 13 RCTs showed that terlipressin significantly improved bleeding control within 48 h compared to no treatment (OR = 2.94, $P = 0.0008$)[21]. The potential mechanism could be the sustained reduction of PVP achieved with continuous infusion, as highlighted by Ding *et al.*[17], which may contribute to better hemostasis and a lower risk of rebleeding.

Furthermore, the lower risk of treatment failure associated with continuous terlipressin infusion highlights its potential role in improving patient outcomes. Treatment failure in portal hypertension is often linked to a poor prognosis and increased

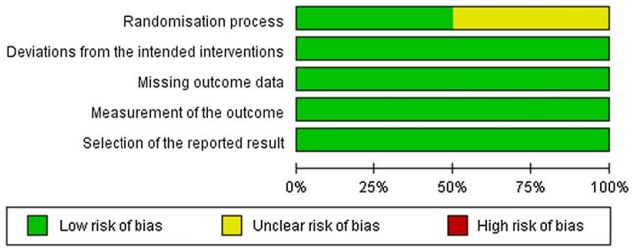

Figure 2. The risk of bias summary using the ROB-II tool.

mortality[22]. The significant reduction in treatment failure risk observed in our analysis could translate into improved patient survival and reduced healthcare burden. A study investigating the pharmacokinetics of terlipressin in healthy individuals found that terlipressin is metabolized in the body through a first-rate process. This means that the elimination rate of the drug increases as its concentration in the plasma rises. Consequently, the therapeutic effect of terlipressin weakened rapidly after each intermittent infusion[23]. Additionally, when plasma levels of terlipressin are high, it stimulates V1 receptors in the smooth muscle cells of blood vessels. However, excessive stimulation of these receptors may trigger a downregulation response as a feedback mechanism. This phenomenon could partially explain why the subsequent injections of terlipressin have a much weaker portal hypotensive effect compared to the initial injection[17].

The decreased incidence of adverse effects with continuous terlipressin infusion compared to intermittent infusion also merits attention. The tolerability of a treatment regimen is crucial to ensure patient compliance and minimize treatment discontinuation. Considering the common adverse effects of terlipressin, such as abdominal pain, diarrhea, and arrhythmias[24], the observed reduction in overall adverse effects with continuous infusion could enhance treatment acceptability and patient adherence, thereby maximizing the therapeutic benefits of terlipressin.

The analysis of individual studies highlighted that both continuous and intermittent terlipressin infusions effectively decreased PVP and heart rate, with the continuous infusion group maintaining a more consistent decrease over 24 h. This could be particularly advantageous in the management of patients with portal hypertension, where a consistent reduction in PVP could potentially reduce the risk of variceal bleeding and other serious complications. Similar to this finding, several studies reported that terlipressin significantly reduced PVP in different clinical settings. Li and his colleagues showed that the administration of continuous terlipressin (2 mg/day for 4 days) in patients who underwent hepatectomy was associated with a significant reduction in the PVP ($P < 0.001$)[25]. In addition, those who showed a positive response to terlipressin had significantly lower median postoperative abdominal drainage ($P = 0.004$) and lower incidence of posthepatectomy liver failure (26 vs. 53%; $P = 0.04$) compared to nonresponders. These findings suggest that terlipressin can effectively reduce posthepatectomy PVP, potentially reducing the occurrence of posthepatectomy liver failure and postoperative abdominal drainage[25].

We could not find a significant difference between the two groups in terms of hospital stays and mortality rate, which could be explained by the small number of included studies and patients. However, a previous meta-analysis demonstrated that vasoactive agents, including terlipressin, were linked to a decrease in 7-day mortality, better management of bleeding, reduced transfusion needs, and shorter hospital stays compared to placebo[26]. Further well-structured RCTs with large sample sizes and long follow-up periods are required to investigate the effect of continuous and intermittent terlipressin on mortality rate and hospital stays.

Several studies included in this review also identified various predictors of early bleeding and survival, with the MELD score emerging as a significant predictor in multiple analyses. These findings highlight the importance of comprehensive clinical evaluation and risk stratification in patients with portal hypertension, which can inform personalized treatment strategies and improve patient outcomes[27].

While the promising results of this meta-analysis suggest a potential paradigm shift in the management of portal hypertension, it is crucial to underline that patient individuality must be

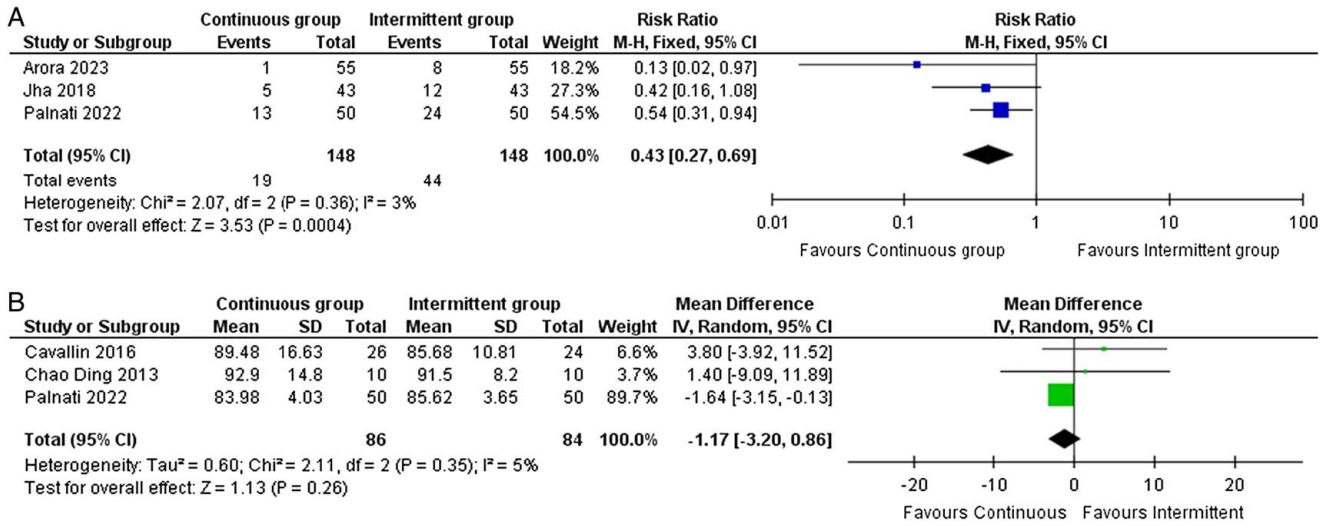

Figure 3. Forest plot shows the difference between continuous infusion and intermittent infusion in terms of (A) Rebleeding and (B) MAP.

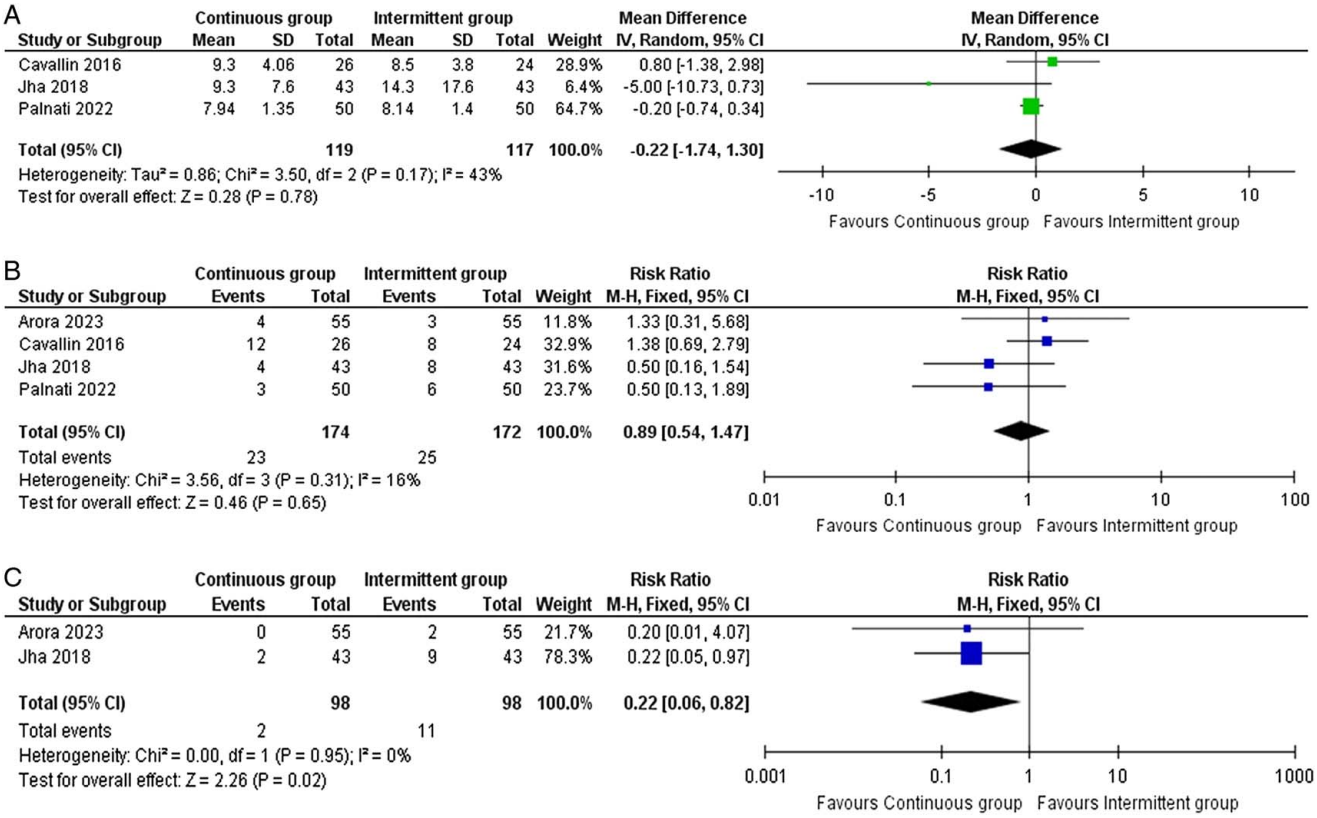

Figure 4. Forest plot shows the difference between continuous infusion and intermittent infusion in terms of (A) Hospital stays, (B) Mortality, and (C) Treatment failure.

considered in determining the optimal treatment approach. Indeed, the choice between continuous and intermittent terlipressin infusion should be made considering not only the potential benefits and risks but also the patient's overall health status, comorbidities, lifestyle, and preferences[28]. Additionally, it would be interesting to explore further the cost-effectiveness of continuous versus intermittent terlipressin infusion. While our analysis did not directly address this aspect, the reduced rates of rebleeding and treatment failure associated with continuous infusion could potentially translate into lower healthcare costs through reduced hospitalizations and interventions[29].

It is important to highlight that most of the studies included were of high-quality. However, two of them lacked adequate details on allocation concealment. The limited number of studies and participants could affect the broader applicability of our results. Nonetheless, the low heterogeneity among the studies strengthens the credibility of our findings and the conclusions drawn from this meta-analysis.

In conclusion, this systematic review and meta-analysis provide robust evidence suggesting that continuous terlipressin infusion may be superior to intermittent infusions in reducing the risk of rebleeding, treatment failure, and adverse effects in patients with portal hypertension. However, further large-scale, high-quality RCTs are required to confirm these findings and to investigate the potential benefits of continuous terlipressin infusion on mortality and hospital stays.

Ethical approval

Ethical committee permission is not required for our meta-analysis research study. Meta-analysis involves systematically reviewing and statistically synthesizing existing studies on a specific topic, aiming to draw overall conclusions and provide a comprehensive understanding. There are several reasons why ethical committee permission is not needed for meta-analyses. Firstly, no primary data collection is involved, as the analysis relies on previously published research that has already undergone ethical review. Secondly, the data used is publicly available and has undergone ethical scrutiny. Thirdly, the anonymity of participants is ensured as the data is aggregated and anonymized. Lastly, since there is no direct interaction with participants, there is no risk of physical or psychological harm.

Consent

Patient consent was not required or obtained for the Systematic Review and Metanalysis research study. This was because the study involved secondary data analysis, specifically a meta-analysis, which utilized pre-existing data from previously published studies. The participants in the original studies had already provided consent for their data to be collected. Furthermore, the data used in a meta-analysis is anonymized and aggregated, ensuring the privacy and confidentiality of individual participants.

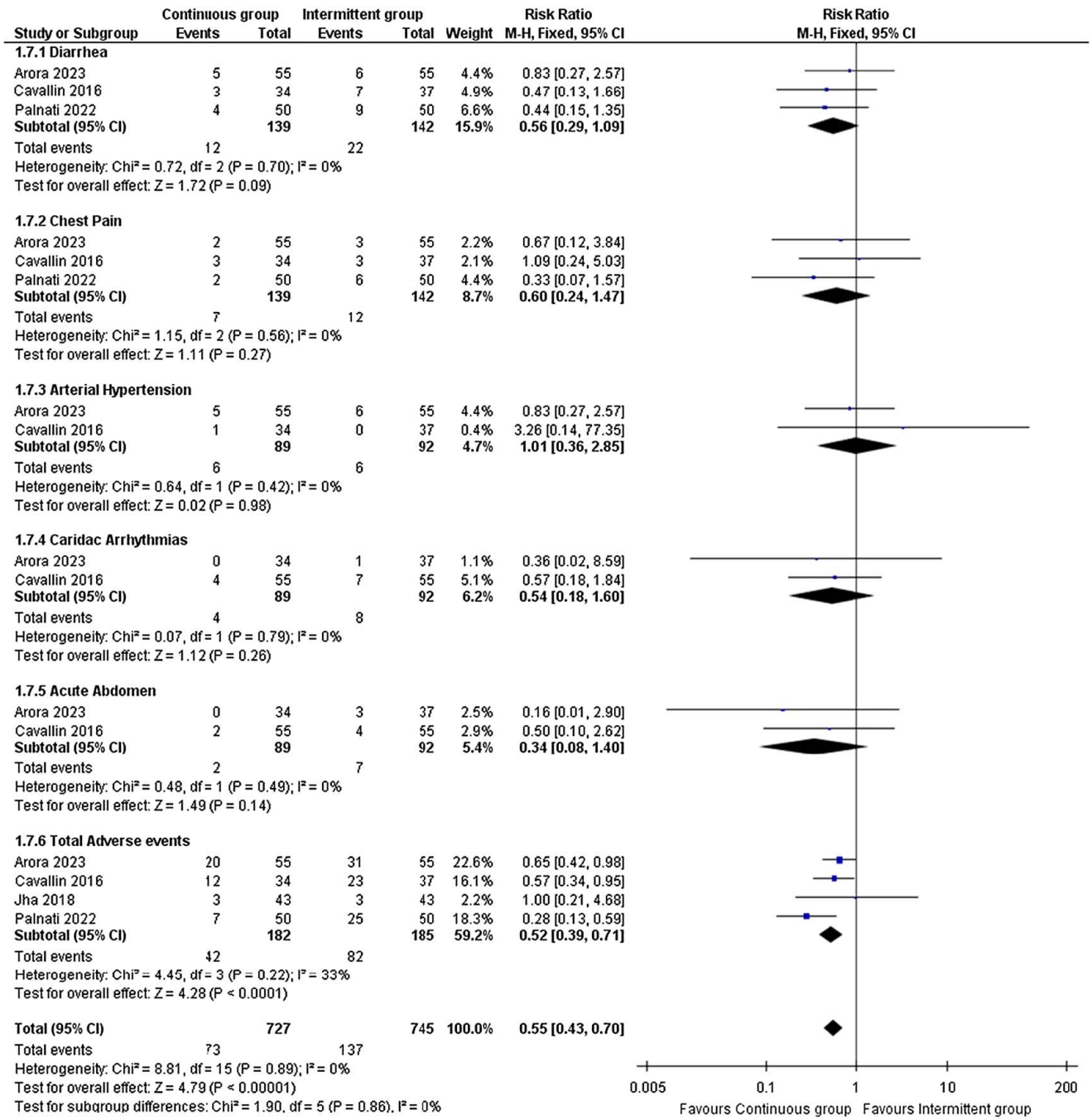

Figure 5. Forest plot shows the difference between continuous infusion and intermittent infusion in terms of adverse events.

Additionally, the data used in a meta-analysis is often sourced from publicly available articles, databases, or other ethically reviewed and approved sources. Since the study did not involve direct interaction with participants or collecting new primary data, obtaining consent from individuals involved in the original studies was unnecessary.

Sources of funding

No source of funding.

Author contribution

E.I.B., Z.A., S.E.D.M.E,S., N.M., A.A.-H., M.A.A., S.D., D.S.D., Y.N., and A.K.: manuscript writing, an overview of the previously published works on a topic, database extraction, results, and statistics; M.H., and D.S.D.: manuscript preparation and editing; E.I.B., N.M.: data collection, manuscript preparation, and editing content; E.I.B., A.A.-H., Y.N., M.A.A., D.S.D., M.H., and E.I.B.: drafting and approval of final version, manuscript review, critical revision of the manuscript for important intellectual content.

Conflicts of interest disclosure

No conflicts of interest to declare.

Research registration unique identification number (UIN)

Our submitted research manuscript has been duly registered with the Research Registry (www.researchregistry.com), ensuring its transparency and adherence to recognized research protocols.

Guarantor

Eshak I. Bahbah.

Data availability statement

The data supporting the findings of this meta-analysis are available upon request from the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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