

Title:

Optimal epinephrine injection volume in acute peptic ulcer bleeding. A systematic review and meta-analysis

Authors:

Alba Lira, Leticia Hernández, Myriam Martell, Eduard Brunet-Mas, Xavier Calvet, Sergio Lario, Alan Barkun

DOI: 10.17235/reed.2025.11726/2025

Link: [PubMed \(Epub ahead of print\)](#)

Please cite this article as:

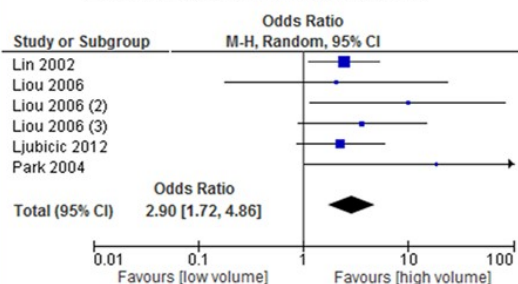
Lira Alba, Hernández Leticia, Martell Myriam, Brunet-Mas Eduard, Calvet Xavier, Lario Sergio, Barkun Alan.

Optimal epinephrine injection volume in acute peptic ulcer bleeding. A systematic review and meta-analysis. Rev Esp Enferm Dig 2025. doi: 10.17235/reed.2025.11726/2025.

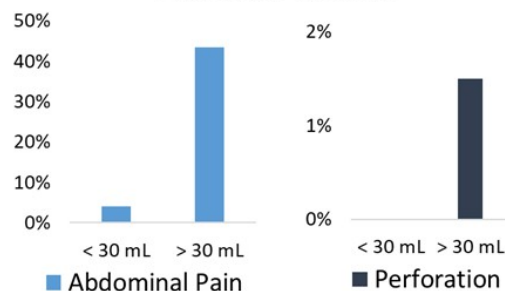
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Optimal epinephrine injection volume in acute peptic ulcer bleeding. A systematic review and meta-analysis.

Definitive hemostasis



Adverse Events



In patients with acute peptic ulcer bleeding, using larger endoscopic epinephrine injection volumes —up to 30 cc— seems to be safe and leads to higher rates of definitive hemostasis compared with smaller-volume injections.

Lira A, et al.

Revista Española de Enfermedades Digestivas (REED)
The Spanish Journal of Gastroenterology

Accepted

Optimal epinephrine injection volume in acute peptic ulcer bleeding. A systematic review and meta-analysis

Alba Lira^a; Leticia Hernández^a; Myriam Martel^d; Eduard Brunet-Mas^{a,c}; Xavier Calvet^{a,b,c}; Sergio Lario^{a,b,c,#}; Alan Barkun^{d,#}.

a) Gastroenterology department, Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA). Sabadell, Catalunya.

b) Departament de Medicina, Universitat Autònoma de Barcelona.

c) CIBERehd, Instituto de Salud Carlos III, Madrid, Spain.

d) Division of Gastroenterology, McGill University, Montreal, Canada.

Financial support: No external support was received.

Correspondence:

Xavier Calvet, MD, PhD

Servei de Digestiu. Hospital Universitari ParcTaulí.

Departament de Medicina. Universitat Autònoma de Barcelona.

Centro de Investigación Biomédica en Red de enfermedades hepáticas y digestivas (CIBERehd). Instituto de Salud Carlos III.

ParcTaulí, 1,

08208 SABADELL (BARCELONA)

e-mail: xcalvet@tauli.cat

ABSTRACT

Introduction: Endoscopic treatment improves the outcomes of patients with acute peptic ulcer bleeding (APUB). Epinephrine injection is a frequently used treatment. There is no consensus, however, on the optimal volume of epinephrine injection. Primary aim was to compare the efficacy and safety of endoscopic injection using different volumes of epinephrine for APUB treatment in a systematic review and meta-analysis.

Methods: Systematic searches were performed for full papers published from 1986 until January 2025 in multiple databases. We included randomized controlled trials (RCT) comparing different epinephrine volumes injection. Primary outcome was permanent haemostasis defined as achieved initial haemostasis and not rebleeding during admission. Secondary outcomes were adverse events, need for rescue treatment and mortality. We estimated the OR and 95%CI using random-effects models.

Results: Four RCT including 556 patients were analyzed. No studies comparing different doses of epinephrine in combination therapy were found. In studies comparing different doses of epinephrine alone, permanent haemostasis was more frequently achieved in the large-volume injection groups (91% vs 77%, OR:2.90; 95%CI:1.72-4.86, $p<0.0001$). Adverse events (AE) were also more frequent in the large-volume groups (33% vs 3%, OR: 21.02; 95%CI:6.51-67.87, $p<0.0001$). Abdominal pain was the most frequent AE. Bowel perforation appeared only when injection volumes exceeded 35 cc.

Conclusion: Endoscopic injection of large volumes of epinephrine up to 30cc appear safe and improve rates of permanent haemostasis when compared to lower injection volume in patients with APUB. Trials assessing the use of larger epinephrine volume in combination endoscopic hemostatic therapy are needed.

Keywords: Acute peptic ulcer bleeding. Epinephrine. Endoscopy. Permanent haemostasis.

(PROSPERO registration number: CRD42020112228)

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) due to acute peptic ulcer bleeding (APUB) results in significant morbidity and mortality. Endoscopic treatment improves outcomes, including a decrease in mortality in high-risk patients¹⁻³.

Endoscopic injection of epinephrine, often associated to a second hemostatic method, is one of the most used endoscopic hemostatic treatments⁴.

It is reasonable to expect a trade-off between safety and efficacy when using different epinephrine volumes. Individual studies suggest that larger volumes might be more efficacious but more dangerous⁵⁻⁸. The optimal volume of epinephrine injection, however, remains unclear and current consensus did not made recommendations on the optimal volume to be injected¹⁻³.

The primary aim of the study was to determine the optimal volume of epinephrine injection either alone or in combination for obtaining permanent endoscopic haemostasis in patients with APUB by performing a systematic review and meta-analysis. Secondary aims were to evaluate the safety of different volumes of epinephrine and to compare the need of surgery or radiological treatment, as well as the mortality.

METHODS

The meta-analysis protocol was registered in the Prospero database (CRD42020112228 registration number)⁹ and was performed in accordance with PRISMA statement recommendations¹⁰.

Search and Information sources

Systematic searches were performed for full papers published from 1986 until January 2025 using MEDLINE, EMBASE, and the ISI Web of knowledge. Citation selection used a

highly sensitive search strategy identifying randomized controlled trial using MeSH terms and controlled vocabulary for 1) gastrointestinal hemorrhage and 2) endoscopic therapy or endoscopic haemostasis (such as clips, thermal therapy, injection therapy or hemospray). Recursive searches and cross-referencing were also carried out using a “similar articles” function. Finally, natural language searches were performed using Open Evidence and ChatGPT to ensure that no RCT was missing and no study was included or excluded based solely on AI tools. The decision to include or exclude any trial was made separately by two independent researchers. Discordances were resolved by consulting a third reviewer.

Eligibility criteria: Randomized controlled trials (RCT) were searched for population inclusion criteria were a) patients >18 years old. b) patients treated for UGIB due to peptic ulcer, either gastric, duodenal or anastomotic ulcers c) results that displayed safety and efficacy of the endoscopic injection of different volumes and/or concentrations of saline epinephrine solution either alone or associated with a second treatment d) treatments that differed only according to the epinephrine volume injected.

Exclusion criteria: a) Observational studies, as well as abstracts, editorials, letters, reviews, expert opinions, case reports and duplicate publications, b) studies without outcome measures. c) results that did not allow the calculation of permanent haemostasis rates d) articles in languages other than English.

Data collection.

Data were extracted by two authors (AL and LH). Data collection was standardized and was independently performed from each study by the two authors. Data were revised in case of disagreement and, if necessary, the issue was resolved by consensus. Outcome variables compiled were permanent and initial haemostasis, rebleeding, need for transfusion, need for interventional procedure -arterial embolization or surgery- mortality rates and complications. Complications were classified as cardiovascular events, perforation, abdominal pain and other adverse events. Additional information collected included primary and secondary authors, publication year, sample size, country, participant characteristics, volume of epinephrine, and

hospital stay.

Risk of bias

Risk of bias was assessed independently by two reviewers (AL and XC) in accordance with the current recommendations from the Cochrane Collaboration for RCTs¹¹ and the PRISMA statement¹⁰ (annex 2). Discrepancies in interpretation were resolved by consensus.

Main outcomes

The definitions of outcomes used in the different studies are shown in table 1. Main outcome was permanent haemostasis, defined as the number of patients in whom initial haemostasis was achieved and rebleeding did not occur. Follow-up considered for rebleeding ranged from 7 days to 30 days depending on the study. Secondary outcomes included a) initial haemostasis, b) rebleeding, c) adverse events, including postprocedural abdominal pain, postprocedural perforation, and any cardiovascular events, d) Invasive treatment -surgical or radiological treatment post-endoscopic therapy- and e) Mortality as reported in the studies (either 14-day⁶ or 30-day^{5,7,8} assessment).

Statistical analysis:

Baseline characteristics were summarized using descriptive statistics. Results were grouped for comparison of outcomes between groups receiving high and low volumes of epinephrine. We calculated a pooled odds ratio (OR) and corresponding 95% confidence interval (CI) for all comparisons using random-effects models. A p -value <0.05 was considered statistically significant. Forest plots were created for each outcome. Publication bias was planned to be evaluated by the visual analysis of Funnel plots in the case that the analysis included more than 10 trials. Heterogeneity between studies was analyzed with the I-squared statistic (I^2). A I^2 of 0 to 40% is taken to reflect

low heterogeneity; 40% to 60%, moderate; and if 60% to 100% indicates that variability in the effect estimate is attributable to heterogeneity.

Data for initial haemostasis, rebleeding, invasive treatment and mortality were taken as described by the individual studies. Also, the threshold values for defining high and low-volume injection were considered according to the original data reported in the different studies. A *post-hoc* analysis was performed using a threshold cut-off value of 30mL. Pre-planned sensitivity analyses were attempted by: a) removing studies one-by-one, b) using only data from the studies at low risk of bias, c) separating patients according to the site of injection (gastric versus duodenal ulcers) and d) performing a fixed-effects model analysis for those comparisons showing non-significant heterogeneity. Analyses were performed using Review Manager (RevMan, version 5.3; the Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark) and SPSS 21(IBM,Chicago, ILL).

RESULTS

Study selection.

Recurrent searches identified 1617 studies. After reviewing the abstract of the selected studies, 4 RCTs comparing different volumes of epinephrine injection fulfilled all inclusion criteria ⁵⁻⁸. All studies evaluated the injection of epinephrine as the only treatment. No studies evaluating different doses associated with a second treatment - combination therapy- were found. The 4 articles selected, were included in the qualitative and quantitative analyses. The detailed flow diagram of our literature search is shown in Figure 1.

Risk of bias

An overview of the risk of bias is shown in Figure 2. All four studies had a low risk of bias.

Study characteristics:

The analysis included 4 RCT⁵⁻⁸ and 606 patients, of whom 556 were suitable for analysis. Characteristics of individual studies are shown in table 2. One of the studies was performed in Croatia, another in Korea, and 2 in China. Sample sizes ranged from 72 to 228 patients. All studies used a 1:10,000 epinephrine saline concentration. All were single-blinded, where the patient was blinded to the treatment provided. For the analysis, high and low-volume injections were defined as in the individual studies. The volumes varied from 5mL to 25mL in "low-volume" and from 12mL to 45mL in the "high volume" arms. One of the trials compared three different volumes of epinephrine⁵. For the comparisons in this study, we used the method recommended in the Cochrane Handbook and assigned half of the patients in each group to each of the one-to-one comparisons¹².

Synthesis of results

Primary outcomes

Overall, 556 patients with UGIB due to peptic ulcer were included. Permanent haemostasis was found to be significantly more frequent after large-volume injection (91% vs 77%, OR=2.90; 95%CI:1.72-4.86, $p<0.0001$, $I^2 = 0\%$, $p=0.61$) (Figure 3). The sensitivity analyses yielded similar results.

Secondary outcomes

The overall rate of initial haemostasis was more than 95% with no between-groups differences (high volume 100% vs low volume 98%), OR: 1.97, 95% CI:0.33-11.59, $p=0.45$, $I^2 = 0\%$, $p=0.82$) (Figure 3). Rebleeding occurred in 9% of large-volume and 22% of low-volume patients (OR 0.35, 95% CI:0.20-0.59, $p<0.0001$, $I^2= 0\%$, $p=0.65$).

The adverse events rates (mainly perforation and abdominal pain) were significantly greater in the large-volume group (33% vs 3%, OR: 21.02; 95%CI: 6.51-67.87, $p<0.0001$, with moderate heterogeneity: $I^2=47\%$) (figure 4). The risk of abdominal pain was especially greater in patients receiving large volumes, (31% vs 3%, OR: 22.9; 95% CI:7.48-70.07, $p<0.0001$, moderate heterogeneity, $I^2=42\%$). Perforation was rare, but

numerically greater in the large-volume group (2% vs. 0%) (OR:4.08; 95%CI:0.85-19.68, $p < 0.08$, $I^2 = 0\%$, $p = 0.99$). No cardiovascular adverse events were recorded.

Rates of a subsequent invasive procedure -arteriography or surgery- were not significantly different when comparing high and low-volume patients (5% vs 4%, OR:1.25; 95%CI:0.56-2.80, $p = 0.58$, $I^2 = 0\%$, $p = 0.92$). Mortality rates did not differ (2% vs 3% in the high vs low-volume groups respectively, OR: 0.75; 95%CI:0.24-2.39, $p = 0.63$, $I^2 = 0\%$; $p = 0.67$).

When compared to the main set of analyses, the sensitivity analyses did not observe significant differences.

Two studies provided transfusion volume but without standard deviations,^{6,8} and the other two provided transfusions as mean numbers of blood units^{5,7}, not allowing for a pooled analysis. Regarding hospital stay, data were insufficient to perform a pooled analysis.

Additional analysis

Regarding the post-hoc exploratory analysis, we compared the efficacy in terms of permanent haemostasis, morbidity and mortality and the adverse event rate comparing arms where epinephrine volume was less than 30 mL vs those where 30 mL or more were administered. Only three of the four studies used epinephrine volumes of 30mL or more. Lin et al. used lower volumes and was excluded from this additional analysis. Permanent haemostasis was significantly greater in patients assigned to receive 30mL or more of epinephrine (94% vs 80%; OR:3.31; 95CI:1.66-6.61; $p = 0.0007$; with an $I^2 = 0\%$; $p = 0.51$).

Regarding adverse events, abdominal pain appeared in 87 cases (43.5%) in the 30mL or more groups compared to only 8 cases (4%) in the less than 30mL group ($p < 0.0001$). Moreover, all six perforations were observed in the groups receiving more than 30mL of epinephrine. All perforations occurred when the volume injected was above 35mL whereas no perforation was reported with less than 35 mL (0% vs 3% $p = 0.1$). No

differences in mortality were observed.

DISCUSSION

The main finding of our review is that the use of high-volume epinephrine increases the rate of permanent hemostasis. However, when the volume exceeds 35 mL, injection is associated to adverse events, including perforation.

A second finding of the systematic review is that there are not studies analyzing the role of high-volume epinephrine when combined with a second endoscopic method. This is a limitation of the study as combined therapy is more effective than epinephrine alone⁴ and so, combination therapy is the current standard treatment¹⁻³.

Even without data on combined therapy, our study may be useful for modifying clinical practice. First of all, it shows that the epinephrine volume injection could be increased safely up to 30 mL in the patients with active bleeding. This may allow higher rates of initial hemostasis and a clear operation field allowing to precisely place a second endoscopic method. Second, in high-risk ulcers -those showing a large visible vessel or placed in the duodenal posterior wall- large-volume epinephrine injection might be used with the aim of increase the chance of permanent therapy.

In contrast, volumes over 30 mL were associated with high rates of adverse events, especially abdominal pain and an increased risk of perforation. Although all perforations in our review occurred when the injected volume exceeded 35 mL, in our opinion, 30 mL should be considered a safety ceiling, and doses above this threshold should be avoided due to the increased risk of perforation. A methodological point regarding our study is that the primary endpoint generally used has been rebleeding. However, combining initial haemostasis and rebleeding may be a better primary outcome from a clinical point of view¹³. For this reason, we grouped both in a combined endpoint under the term permanent haemostasis. This approach has

already been used in other publications³.

The number of patients included in the meta-analysis was adequate for the primary endpoint analysis. Another strength of the study is the high quality of all the included works and the low heterogeneity of results in evaluating the primary endpoint and most of the secondary outcomes.

As stated, a major limitation of the present study is that the meta-analysis did not provide data on the effect of large-volume injection in the efficacy of combination treatment, as no articles on the topic were found. In this sense, it will be important to monitor the safety and efficacy of large volumes of epinephrine alone in this setting. Another limitation of the study is that the number of patients did not allow the evaluation of infrequent events as further intervention, or mortality. Finally, an additional limitation is that the follow-up window for permanent haemostasis was different for each study (7, 14, and 30 days) and was not reported in the remaining study. However, this is unlikely to have significantly affected the results of the meta-analysis, as most rebleeding episodes occur during the first three days after the index bleeding. Additionally, rebleeding after seven days is extremely rare. In conclusion, large epinephrine volumes seem to achieve better results in terms of permanent haemostasis than lower volumes and do not seem to increase the adverse events rate if limited to 30mL. In contrast, greater volumes result in high rates of abdominal pain and may lead to greater risk of perforation.

Funding

No external funding was received.

Table 1. Definitions of variables in each study

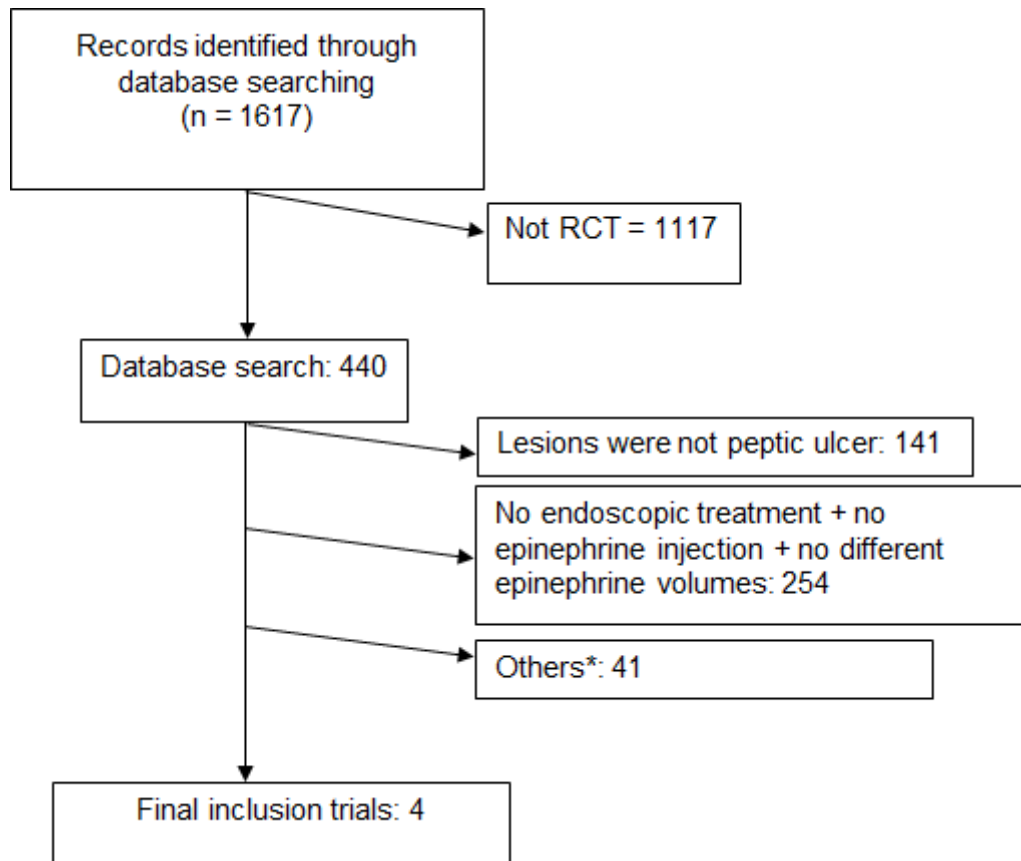
Study	Countr y	Cessation of bleeding time to consider initial haemostasis	Permanent haemostasis	Recurrent bleeding	Invasive procedure	Mortality evaluation (days)
Lin 2002	China	≥5'	14days	Fresh blood in stomach 6h after entry Hemodynamic Instability Continued melena or bloody stool Hematemesis	surgery or embolization	14
Liou2006	China	≥5'	Initial haemostasis + no rebleeding*	Subsequent ulcer bleeding after initial haemostasis	surgery or embolization	30
Ljubicic2012	Croatia	≥10'	30 days	One or more: - Fresh hematemesis or melena - Hematochezia - Aspiration of fresh blood - Instability - Reduction Hb > 2g/dL	surgery	30
Park 2004	Korea	≥10'	7 days	One or more: - fresh hematemesis - hematochezia - aspiration of fresh blood - instability - reduction of Hb > 2g/dL within 24h	surgery or embolization	30

*follow-up period not stated

Table 2. Characteristics of the studies.

Study	Ulcer/high-risk stigmata	Dose of epinephrine (mL)	n	Initial haemostasis	Rebleeding	Permanent haemostasis	Further treatment	transfusion	Hospital stay (days)	mortality	Pain/perforation (n/n)	Excluded
Ljubicic 2012	Gastric, duodenal/ Forrest IIa	15-25	50	50	15/50	35	6	1041 mL**	7.5	3	3/0	11
		30-40	50	50	8/50	42	3	912 mL**	7.6	0	34/0	
Liou 2006	Gastric, duodenal, stoma/ Forrest Ia-Ib	20	76	74	15/74	59	4	4.7BU ±3.4	10.8 ±3.3	3	2/0	56
		30	76	75	4/75	71	2	4.5BU ±3.2	9.7 ±3.5	2	5/0	
		40	76	76	2/76	74	5	4.2BU ±3.1	10.2 ±3.1	4	51/4	
Park 2004	Gastric, duodenal, stoma/ Forrest Ia, Ib, IIa+IIb	15-25	36	35	6/35	29	1	4.4BU**	11.6	1	0/0	211
		35-45	36	36	0/35	36	0	4.6BU**	13.3	0	0/1	
Lin 2002	Gastric, duodenal, stoma/ Forrest Ia, Ib or IIa +high-risk*	5-10	78	78	24/78	54	2	885mL**	9	0	0/0	12
		13-20	78	78	12/78	66	2	734mL**	8	0	0/0	

* Presence of “coffe ground” material in the stomach, blood in the stomach/duodenum, shock or an initial hemoglobin level of less than 10g/dL. **SD not provided



* Languages different from English, trials on animals.

Figure 1. PRISMA 2009 Flow Diagram

Author	Type of study	Randomization present?	Randomization method is described?	Randomization method is adequate?	Double blinded study?	Blinding method is described?	Blinding method is adequate?	Concealment method is adequate?	Withdrawals and dropouts?
Lin HJ. 2002	RCT								
Park CH 2004	RCT								
Liou TC 2006	RCT								
Ljubicic N 2012	RCT								

Green:Low risk, Yelow:not reported, Red:high risk

Figure 2. Risk of bias.

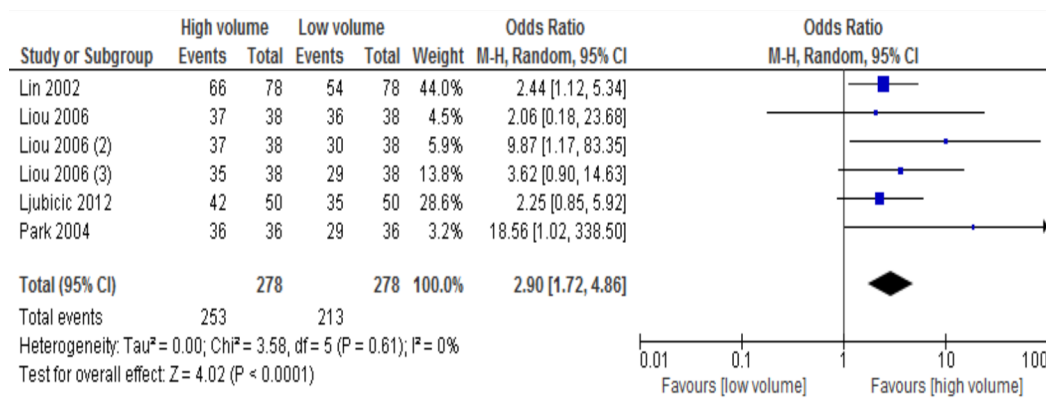


Figure 3. Permanent haemostasis pooled analysis favoured high-dose epinephrine (OR: 2.9, 95%CI:1.72-4.86, $p < 0.0001$): Heterogeneity was low ($I^2 = 0\%$)

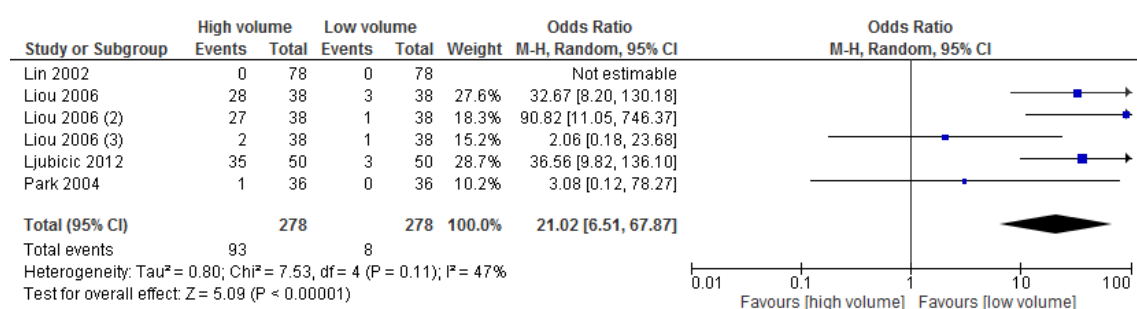


Figure 4 Adverse events pooled analysis showed a significant increase of adverse events in the high-volume group (OR = 21.02; 95%CI 6.51-67.87, $p < 0.00001$); heterogeneity was moderate ($I^2 = 47\%$)

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