

ORIGINAL ARTICLE

External lumbar cerebrospinal fluid drainage in patients with aneurysmal subarachnoid haemorrhage: A systematic review and meta-analysis of controlled trials[☆]



G. Alcalá-Cerra^{a,b,*}, Á. Paternina-Caicedo^a, C. Díaz-Becerra^a, L.R. Moscote-Salazar^a, J.J. Gutiérrez-Paternina^a, L.M. Niño-Hernández^a, on behalf of Grupo de Investigación en Ciencias de la Salud y Neurociencias (CISNEURO)

^a Grupo de Investigación en Ciencias Neurológicas y Neurociencias, Cartagena de Indias, Colombia

^b Sección de Neurocirugía, Facultad de Medicina, Universidad de Cartagena, Cartagena de Indias, Colombia

Received 5 September 2013; accepted 16 January 2014

Available online 16 July 2016

KEYWORDS

Aneurysmal subarachnoid haemorrhage;
Cerebrospinal fluid drainage;
Delayed ischaemic neurological deficit;
External lumbar drainage;
Randomised controlled trial;
Vasospasm

Abstract

Introduction: External lumbar drainage is a promising measure for the prevention of delayed aneurysmal subarachnoid haemorrhage-related ischaemic complications.

Methods: Controlled studies evaluating the effects of external lumbar drainage in patients with aneurysmal subarachnoid haemorrhage were included. Primary outcomes were: new cerebral infarctions and severe disability. Secondary outcomes were: clinical deterioration due to delayed cerebral ischaemia, mortality, and the need of definitive ventricular shunting. Results were presented as pooled relative risks, with their 95% confidence intervals (95% CI).

Results: A total of 6 controlled studies were included. Pooled relative risks were: new cerebral infarctions, 0.48 (95% CI: 0.32–0.72); severe disability, 0.5 (95% CI: 0.29–0.85); delayed cerebral ischaemia-related clinical deterioration, 0.46 (95% CI: 0.34–0.63); mortality, 0.71 (95% CI: 0.24–2.06), and need of definitive ventricular shunting, 0.80 (95% CI: 0.51–1.24). Assessment of heterogeneity only revealed statistically significant indexes for the analysis of severe disability ($I^2 = 70\%$ and $P = .01$).

Conclusion: External lumbar drainage was associated with a statistically significant decrease in the risk of delayed cerebral ischaemia-related complications (cerebral infarctions and clinical deterioration), as well as the risk of severe disability; however, it was not translated in a lower

[☆] Please cite this article as: Alcalá-Cerra G, Paternina-Caicedo Á, Díaz-Becerra C, Moscote-Salazar LR, Gutiérrez-Paternina JJ, Niño-Hernández LM, et al. Drenaje lumbar externo de líquido cefalorraquídeo en pacientes con hemorragia subaracnoidea aneurismática: revisión sistemática y metaanálisis de estudios controlados. Neurología. 2016;31:431–444.

* Corresponding author.

E-mail addresses: cisneuro.investigacion@gmail.com, alcalag@egresado.uninorte.edu.co (G. Alcalá-Cerra).

PALABRAS CLAVE

Hemorragia subaracnoidea aneurismática; Drenaje de líquido cefalorraquídeo; Déficit neurológico isquémico tardío; Drenaje lumbar externo; Ensayo clínico aleatorizado; Vasoespasmo

mortality. Nevertheless, it is not prudent to provide definitive recommendations at this time because of the qualitative and quantitative heterogeneity among included studies. More randomised controlled trials with more homogeneous outcomes and definitions are needed to clarify its impact in patients with aneurysmal subarachnoid haemorrhage.

© 2013 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. All rights reserved.

Drenaje lumbar externo de líquido cefalorraquídeo en pacientes con hemorragia subaracnoidea aneurismática: revisión sistemática y metaanálisis de estudios controlados

Resumen

Introducción: El drenaje lumbar externo de líquido cefalorraquídeo es una medida promisorio para la prevención de las complicaciones de la isquemia cerebral tardía asociada a la hemorragia subaracnoidea espontánea de origen aneurismático.

Métodos: Se incluyeron los estudios controlados que evaluaran los efectos del drenaje lumbar externo en pacientes con hemorragia subaracnoidea aneurismática. Los desenlaces primarios fueron: nuevos infartos cerebrales y discapacidad grave. Los desenlaces secundarios fueron: deterioro clínico causado por isquemia cerebral tardía, mortalidad y necesidad de derivación ventricular definitiva. Los resultados se presentaron en riesgos relativos combinados, con un intervalo de confianza del 95% (IC 95%).

Resultados: Fueron incluidos un total de 6 estudios controlados. Los riesgos relativos combinados fueron: nuevos infartos cerebrales, 0,48 (IC 95%: 0,32-0,72); discapacidad grave, 0,5 (IC 95%: 0,29-0,85); deterioro clínico causado por isquemia cerebral tardía, 0,46 (IC 95%: 0,34-0,63); mortalidad, 0,71 (IC 95%: 0,24-2,06) y necesidad de derivación ventricular definitiva, 0,80 (IC 95%: 0,51-1,24). La evaluación de la heterogeneidad demostró índices estadísticamente significativos únicamente en el análisis de discapacidad grave ($I^2 = 70\%$ y $p = 0,01$).

Conclusión: El drenaje lumbar externo se asoció con una reducción estadísticamente significativa del riesgo de complicaciones causadas por la isquemia cerebral tardía (infartos cerebrales y deterioro clínico), así como del riesgo de discapacidad grave; sin embargo, esto no se tradujo en una menor mortalidad. No obstante, no es prudente emitir recomendaciones definitivas debido a la heterogeneidad cualitativa y cuantitativa entre los estudios. Son necesarios más ensayos clínicos con definiciones homogéneas de sus desenlaces para aclarar sus efectos en los pacientes con hemorragia subaracnoidea aneurismática.

© 2013 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Cerebral vasospasm and delayed cerebral ischaemia (DCI) are the most frequent and severe complications of aneurysmal subarachnoid haemorrhage (ASH), occurring in between 20% and 50% of all cases.¹⁻³ Vasospasm is characterised by a progressive reduction in arterial diameter in the circle of Willis, and it is usually observed between days 4 and 14 after symptom onset.⁴⁻⁶ DCI manifests clinically as neurological impairment which cannot be explained by such other conditions as hyponatraemia, hypoxaemia, infections, pulmonary oedema, drug intoxication, hydrocephalus, or rebleeding.⁷ Lesions secondary to DCI may cause cerebral infarctions irrespective of the development of cerebral vasospasm.^{8,9}

A great deal of the diagnostic and therapeutic resources required for managing patients with ASH are aimed at identifying, preventing, or treating vasospasms and DCI. Several studies have explored the use of glucocorticoids, endothelin-1 antagonists, statins, magnesium sulfate, acetylsalicylic acid, hypothermia, transdermal

nitroglycerin, ebselen, and thrombolytics. However, none of these treatments has been shown to be effective in clinical practice.^{1,10-12} In contrast, such other alternatives as oral nimodipine, haemodynamic therapy, intraarterial vasodilator therapy, and endovascular angioplasty have been proved useful for the prevention and treatment of vasospasm-related ischaemic neurological deficits. Their effectiveness, however, is limited.¹³

Although the pathophysiological mechanisms of vasospasm are yet to be fully understood, we currently know that breakdown products of haemoglobin play a major role in this process.^{14,15} Incidence of vasospasm and DCI shows a close correlation with volume, density, and persistence of clots in the subarachnoid space and ventricular cavities.^{4,14} In line with this idea, it has been suggested that early surgical removal of these clots may reduce the frequency and severity of vasospasms.¹⁶ Komotar et al.¹⁷ conducted a systematic review to assess the usefulness of cisternal drainage with microsurgical fenestration of the lamina terminalis, but concluded that this technique had no benefits.¹⁷

An external ventricular drain (EVD) also favours drainage of CSF containing breakdown products of haemoglobin; however, its clinical effectiveness has not been proved. In addition, this technique has been associated with an increased risk of developing posthaemorrhagic hydrocephalus.^{18–21}

Lumbar drainage (LD) is another alternative for extracting CSF; it has lower rates of haemorrhagic, obstructive, and infectious complications than ventricular drainage.²² Its use in patients with ASH is based on evidence provided by Macdonald²² and Hänggi et al.²³ These authors found that CSF drainage may reduce the incidence and potential consequences of vasospasms.

Some studies have revealed that the concentration of blood components in CSF in patients with ASH is greater when CSF is collected using an LD than with an EVD. This proves that blood products accumulate mainly in the lumbar and basal cisterns.^{24,25} These findings indicate that draining CSF from the lumbar cistern allows for more efficient clearance of breakdown products of haemoglobin from CSF and may therefore have detectable clinical benefits.

Some preliminary studies exploring the usefulness of LD in patients with ASH suggest that this technique reduces the risk of morbidity, mortality, and vasospasm-related ischaemic complications²⁶; however, no meta-analyses have been conducted to evaluate LD.

Methods

We conducted a systematic literature review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²⁷

Literature search

The online search took place in July 2013. We searched the following databases: MEDLINE/PubMed, EMBASE, Google Scholar, Cochrane Library, CINAHL, EBSCO, HINARI, and Scielo. We did not limit our search by language or dates of publication.

The search employed the following keywords: 'subarachnoid hemorrhage', 'hydrocephalus', 'lumbar drain', 'external ventricular drain', 'cerebral infarction', 'stroke', 'vasospasm', and 'delayed ischaemic neurologic deficit'.

Selection criteria

Inclusion criteria

Type of studies:

1. Observational studies or controlled clinical trials.
2. Studies with a prospective or retrospective design.

Type of participants:

1. Adults only (18 and older) with ASH.

2. Patients who underwent aneurysm occlusion with microsurgery or endovascular treatment.

Type of intervention:

1. LD placement during the acute phase of aneurysm rupture (first 7 days of bleeding).
2. LD for at least 3 consecutive days.

Type of outcome assessment. We included studies that analysed any of the following parameters:

1. New cerebral infarctions linked to DCI.
2. Disability, assessed with either the modified Rankin Scale (mRS) or the Glasgow Outcome Scale (GOS).^{28–30}

Exclusion criteria

1. Concomitant use of thrombolytics or other intrathecal drugs and LD.
2. Study population of fewer than 10 patients.
3. No control group.
4. Subarachnoid haemorrhage caused by anything other than intracranial aneurysm rupture (trauma, surgery, vasculitis, arteriovenous malformations, cavernous malformations, venous angiomas, capillary telangiectasias, etc.).
5. Aneurysms caused by trauma or infections.

Type of outcomes

Primary outcomes

1. New cerebral infarctions linked to DCI.
2. Severe disability.

Secondary outcomes

1. Clinical deterioration caused by DCI.
2. Mortality.
3. Need for a permanent shunt.

Definition of outcomes

- *New cerebral infarctions linked to DCI*: cerebral infarctions identified in CT or MRI scans performed during the first 6 weeks after ASH, or in pathology studies in autopsies. These infarctions may not be related to surgical or endovascular procedures (microsurgical or endovascular repair and/or ventricular drain placement).
- *Severe disability*: scores of 0, 1, or 2 on the mRS, or of 4 or 5 on the GOS.
- *Clinical deterioration caused by DCI*: focal neurological signs (including hemiparesis, aphasia, apraxia, hemianopsia, or hemispatial neglect) or a decrease of at least 2 points on the GOS, after ruling out other causes of clinical deterioration (metabolic or electrolyte changes, hydrocephalus, rebleeding, complications during aneurysm repair, etc.).
- *Mortality*: death during follow-up period (regardless of the cause).

- *Need for a permanent shunt*: permanent implantation of a ventricular shunt is required to treat posthaemorrhagic hydrocephalus.

Study selection

Article titles were evaluated by 2 independent reviewers who identified potentially relevant articles based on the abstracts. We subsequently gathered all the potentially relevant articles in full-text format and applied the inclusion and exclusion criteria mentioned above. The same reviewers collected data and assessed methodological quality. Discrepancies between reviewers were solved by consensus.

Data extraction

We gathered the following data: study design, sample size, method for repairing the aneurysm causing ASH, time of LD placement, duration of LD, CSF drainage speed with LD, definitions of the primary and secondary outcomes, and time elapsed from symptom onset to outcome assessment.

To assess disability, outcomes were dichotomised; we recorded the number of individuals with disability in the group treated with LD and in the control group. We used the equivalence between the mRS and the GOS established by Wong et al.³¹; according to these authors, favourable outcomes correspond to scores of 0, 1, or 2 on the mRS and to scores of 4 or 5 on the GOS. This equivalence is routinely used in meta-analyses evaluating the effectiveness of pharmacological interventions in patients with ASH and shows good concordance between scales.^{7,31–33}

When the data necessary for analysis and quality assessment were not published in the full-text article, we requested this information from the main authors via e-mail. This approach to obtaining the data necessary for our analysis had to be employed in the case of only one study.³⁴

Assessment of methodological quality

Observational studies were assessed with the Newcastle–Ottawa Scale, which is recommended by the Cochrane Non-Randomised Studies Methods Group³⁵; randomised studies were assessed on the Jadad scale, also known as the Oxford quality scoring system.^{36,37}

Synthesis, data analysis, and assessment of heterogeneity

Therapeutic effects were analysed by estimating the relative risk (RR) using a random-effects model and 95% confidence intervals (95% CI) for all dichotomous analyses.^{9,33}

Statistical heterogeneity was assessed using the I^2 statistic and the chi-square test. For purposes of data interpretation, I^2 values > 50% and $P < .1$ in the chi-square test were considered statistically significant.³⁸

Statistical analysis was performed using Review Manager statistical software, version 5 (The Cochrane Collaboration, Oxford, UK).

We assessed potential publication bias using funnel plots.

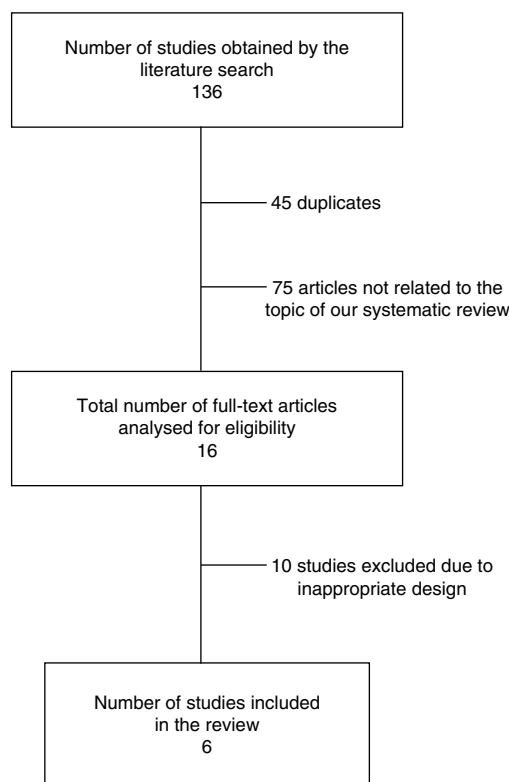


Figure 1 Flow chart showing the literature search and study selection process.

In addition, we conducted a subgroup analysis to determine the magnitude of the therapeutic effect according to the methodology of the studies (controlled observational studies and clinical trials).

Results

Search results

Our literature search identified 136 articles. After evaluating the abstract, reading the full-text article, and applying the inclusion and exclusion criteria, we selected a total of 6 controlled studies (635 individuals) evaluating at least one of the primary or secondary outcomes of our meta-analysis (Table 1). Three of these studies randomly assigned participants to treatment or control groups (randomised clinical trials).^{34,39,40}

The results of our literature review are shown in Fig. 1, and the main characteristics of the studies are summarised in Table 1.

Quality of the studies

Observational studies

The Newcastle–Ottawa Scale demonstrated that all the observational studies included appropriate definitions of patients and outcomes. Likewise, all studies included a representative sample from the population potentially able to benefit from this treatment (patients with ASH). Control

Table 1 Characteristics of the included studies.

Author	Design	P/C	Severity	Repair	Period of drainage	Drainage speed
Klimo et al., ²⁴ 2004	Retrospective observational study	81/86	Patients ^a : I: 7; II: 30; III: 25; IV: 15; V: 4. Controls: I: 5; II: 25; III: 22; IV: 28; V: 6.	Mixed	From surgery until no blood was seen in CSF and the risk period for experiencing a vasospasm had ended	5-10 mL/h
Kwon et al., ⁴⁰ 2008	RCT	47/60	Patients ^a : II: 12; III: 27; IV: 7; V: 1. Controls: II: 14; III: 25; IV: 11; V: 10.	EV	From embolisation until no blood was present in CSF or at 14 days after haemorrhage	5-10 mL/h
Hänggi et al., ²³ 2008	Prospective observational study	20/20	Patients ^a : II: 3; III: 2; IV: 6; V: 9. Controls: II: 5; III: 6; IV: 8; V: 1.	Mixed	5 days, starting immediately after aneurysm occlusion	Not specified
Al-Tamimi et al., ³⁹ 2012	RCT	105/105	Patients ^a : I: 67; II: 33; III: 5. Controls: I: 72; II: 27; III: 6.	Mixed	Time of placement is not specified. LD was used until CSF was visibly clear or until day 10 after placement	5 mL/h
Maeda et al., ²⁵ 2013	Retrospective observational study	34/17	Patients ^a : I: 12; II: 11; III: 3; IV: 4; V: 4. Controls: I: 0; II: 1; III: 1; IV: 3; V: 12.	EV	From the day of aneurysm repair until day 14 after haemorrhage	5-10 mL/h
Borkar, ³⁴ 2013	RCT	30/30	Patients ^b : II: 11; III: 14; IV: 5. Controls: II: 15; III: 11; IV: 4.	MSC	72 hours, starting on the day of aneurysm repair	Not specified

C: controls; MSC: microsurgical clipping; LD: lumbar drain; P: patients; RCT: randomised controlled trial; EV: endovascular; CSF: cerebrospinal fluid.

^a According to the World Federation of Neurological Surgeons scale.

^b According to Hunt and Hess scale.

Table 2 Quality assessment of the included observational studies, using the Newcastle–Ottawa Scale.

Study	Selection	Comparability	Exposure
Klimo et al., ²⁴ 2004	****	**	***
Hänggi et al., ²³ 2008	****	*	*
Maeda et al., ²⁵ 2013	****	*	**

groups in each of the studies consisted of series of patients who were not selected because they had a condition other than ASH. Results were assessed using blind interviews and by reviewing medical histories to ensure that data had an acceptable level of reliability. The results of each study are summarised in [Table 2](#).

Randomised controlled trials

We included 3 controlled studies in which patients were randomised to the study groups.^{34,39,40} In one of them, however, the randomisation method is not explicitly described.⁴⁰ Given that LD is an intervention, patients will know whether or not they have received this treatment. As a result, none of the studies was double-blind. The study by Al-Tamimi et al.³⁹ was the only one in which outcomes were assessed by blinded interviewers. Finally, after applying the Jadad scale, only the studies by Borkar and Al-Tamimi et al. were considered to show high methodological quality.^{34,39} A detailed assessment of each of these studies is shown in [Table 3](#).

Quantitative analysis of the literature and results of the meta-analysis

According to the analysis of primary outcomes, LD was associated with a lower risk of new cerebral infarctions visible by CT or MRI. The combined RR of the 5 studies evaluating this outcome was 0.48 (95% CI, 0.32–0.72) and met criteria for statistical significance ($P < .001$). Analyses revealed no statistically significant heterogeneity ($I^2 = 23\%$, $P = .27$).^{23–25,34,39} Five studies were included in the analysis of severe disability; combined results showed that LD is associated with a lower risk of this outcome (RR, 0.50; 95% CI, 0.29–0.85; $P = .01$). However, results were statistically heterogeneous ($I^2 = 70\%$; $P = .01$) ([Fig. 2](#)).^{23–25,34,39,40}

Regarding secondary outcomes, results were more homogeneous in the analyses corresponding to clinical deterioration caused by DCI, mortality, and need for a permanent shunt. The risk of clinical deterioration caused by DCI was

lower in the patients treated with LD than in controls (RR, 0.46; 95% CI, 0.34–0.63; $P < .001$). Results were consistent among studies included in the analysis ($I^2 = 26\%$; $P = .24$).^{23–25,34,39,40} Five studies evaluated the effects of LD on the risk of mortality. The analysis yielded a combined RR of 0.77 (95% CI, 0.33–1.80), which demonstrates the lack of either positive or negative effects ($I^2 = 44\%$; $P = .25$).^{23,24,39,40} Similarly, the results of the 6 studies examining the influence of LD on the need for surgery for posthaemorrhagic hydrocephalus demonstrated that this treatment has no effect on the need for a permanent shunt (RR, 0.82; 95% CI, 0.55–1.21; $P = .31$) ([Fig. 3](#)).^{23–25,34,39,40}

Analysis by subgroups

Studies were divided according to their methodology: observational studies and clinical trials were analysed separately. Estimations of the effects of this treatment and heterogeneity are shown in [Table 4](#).

Risk of bias

Broadly speaking, the included studies were considered to have a high risk of bias since full-text articles did not offer explanations of the methods used to assess final outcomes, especially with regard to evaluator blinding. Funnel plots showed no asymmetries potentially indicative of publication bias for any of the outcomes. However, the reliability of these analyses is low since fewer than 10 studies were available ([Fig. 4](#)) ([Appendix A](#)).³⁵

Discussion

The results of the present meta-analysis show that LD is useful for preventing cerebral infarctions linked to DCI; these results correspond to the combined analysis and the

Table 3 Quality assessment of the randomised controlled clinical trials included in our study, using the Jadad scale.

Criterion	Kwon et al., ⁴⁰ 2008	Al-Tamimi et al., ³⁹ 2012	Borkar, ³⁴ 2013
1. Randomisation	Yes	Yes	Yes
2. Description and appropriateness of the randomisation method	No	Yes	Yes
3. Double-blind	No	No	No
4. Description and appropriateness of the blinding method	No	Yes	No
5. Description of withdrawals and drop-outs	Yes	Yes	Yes
Total score	2	4	3

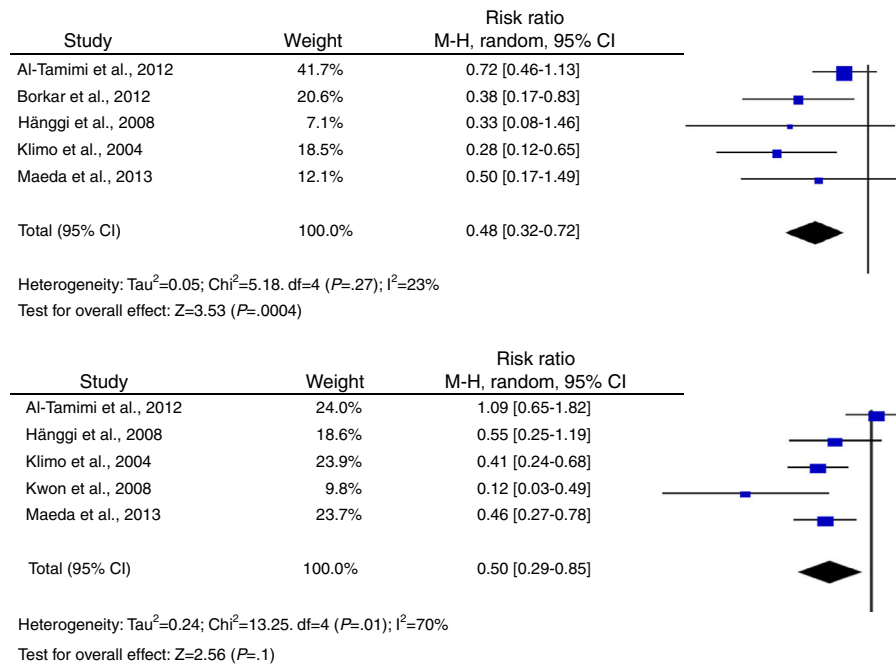


Figure 2 Random-effects model of risk ratios for new cerebral infarctions. Above: new cerebral infarctions. Below: severe disability.

Table 4 Subgroup analysis by study design.

Outcomes of interest	n	Effect		Heterogeneity			
		RR (95% CI)	P	Chi ²	df	I ²	P
<i>New cerebral infarctions linked to DCI</i>							
Observational studies	3	0.34 (0.19-0.63)	<.001	0.72	2	0%	.70
RCT	2	0.56 (0.30-1.04)	.07	1.95	1	49%	.16
<i>Severe disability</i>							
Observational studies	3	0.45 (0.32-0.63)	<.001	0.39	2	0%	.82
RCT	2	0.40 (0.04-3.91)	.43	9.47	1	89%	.002
<i>Clinical deterioration caused by DCI</i>							
Observational studies	3	0.51 (0.17-1.56)	.24	4.54	2	56%	.10
RCT	3	0.49 (0.36-0.66)	<.001	1.72	2	0%	.42
<i>Mortality</i>							
Observational studies	2	1.20 (0.26-5.47)	.81	1.81	1	45%	.18
RCT	3	0.56 (0.19-1.66)	.29	2.56	2	22%	.28
<i>Need for a permanent shunt</i>							
Observational studies	3	0.67 (0.45-1.02)	.06	1.39	2	0%	.50
RCT	3	1.26 (0.64-2.47)	.50	1.84	2	0%	.40

RCT: randomised controlled trial; DCI: delayed cerebral ischaemia; 95% CI: 95% confidence interval; RR: relative risk. A random-effects model was used for all the analyses. Statistically significant values are shown in bold.

subgroup analysis for observational studies. However, the analysis of the 2 high-quality randomised trials showed no differences in RR, probably due to the statistical power of the data.^{34,39} These findings are especially relevant for patients with ASH: some studies have demonstrated a strong association between DCI and poor functional recovery in the medium and long term.⁴¹ In addition, we found a decrease in risk of severe disability associated with LD, which is another primary outcome recommended for evaluating interventions

aimed at preventing vasospasm and DCI.^{8,9} Nevertheless, the heterogeneity of functional outcomes was statistically significant, which does not allow us to establish firm recommendations.

Despite the beneficial effects of draining CSF with an LD in patients with DCI, this technique had no statistically significant effect on the risk of mortality. Again, this finding points to a lack of association between incidence of complications linked to DCI and clinical outcomes in

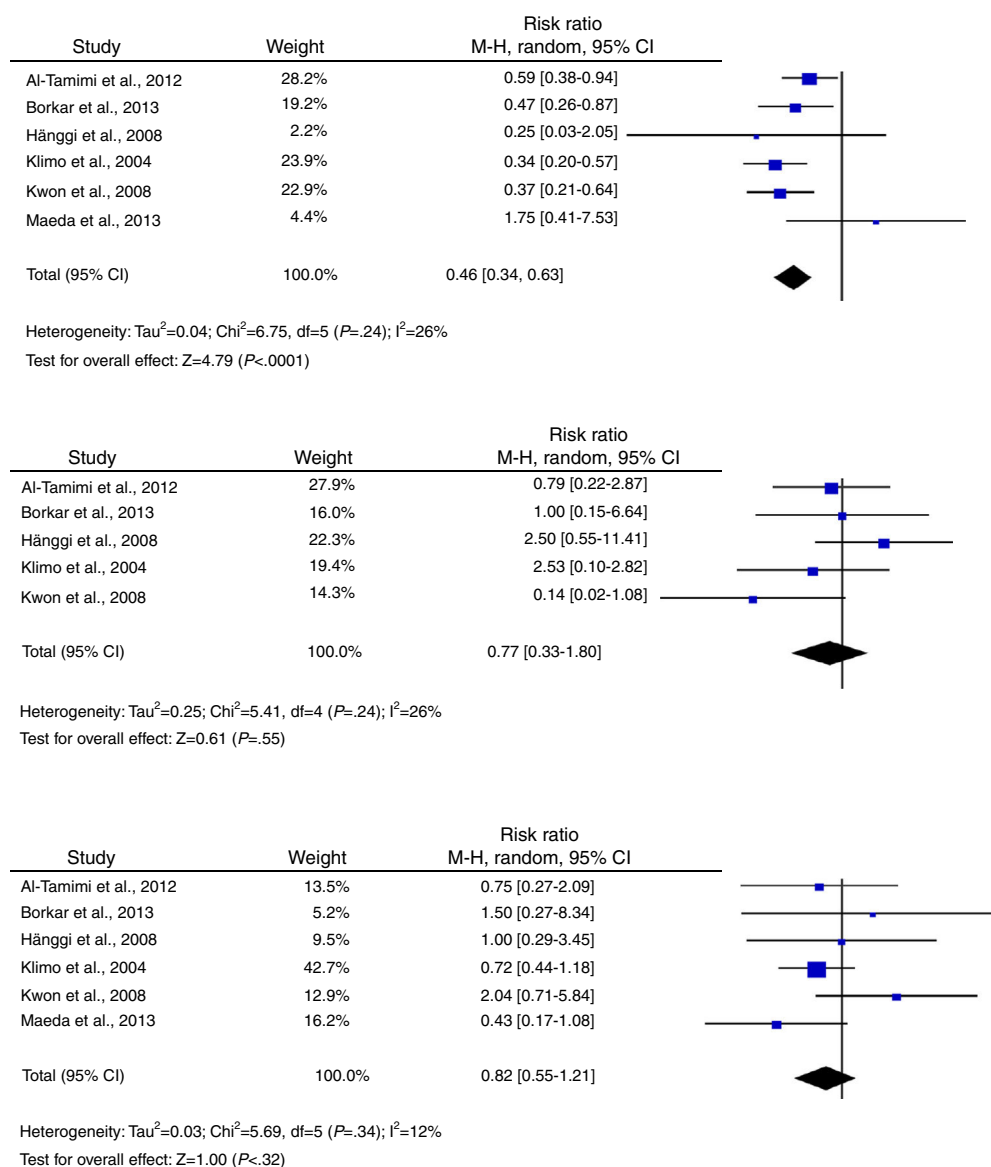


Figure 3 Random-effects model of risk ratios. Above: clinical deterioration caused by DCI. Centre: mortality. Below: need for a permanent shunt due to haemorrhagic hydrocephalus.

patients with SAH. Some authors have pointed out that this discrepancy may be due to the appearance of adverse events and complications that may counteract the benefits of certain treatments.¹³ This hypothesis was supported by a meta-analysis on the effectiveness of clazosentan, an endothelin receptor antagonist, which was found to be effective for preventing ischaemic neurological deficit and cerebral infarctions.¹³ However, mortality and disability rates in patients were no lower than in controls, since pulmonary, haemodynamic, and haematological complications associated with this drug negated its benefits.^{42–44}

Although complications associated with LD may have had an influence on the similarities in mortality risk between groups, this hypothesis may be refuted based on several studies proving that LD has a good safety profile in patients with ASH, since it does not increase the risk of rebleeding or mortality.^{45–47} Brain herniation is another potential

complication of LD in patients with ASH, and especially in those with intracranial hypertension. For this reason, the studies in the present meta-analysis excluded all patients with compression of the basal cisterns and those who were not good candidates for LD according to the neurosurgeon. Likewise, preliminary studies have proved the safety of LD, even in patients with intracranial hypertension, provided that an EVD is placed and an adequate pressure gradient is maintained.⁴⁶ This evidence shows that complications associated with lumbar catheter placement are not sufficient to explain the lack of an effect on the risk of mortality; future research should explore other possible mechanisms.

Another potential benefit of LD is the decreased risk of posthaemorrhagic hydrocephalus: this procedure helps remove breakdown products of haemoglobin which accumulate in the subarachnoid space, blocking arachnoid villi.^{48,49} However, the combined analysis demonstrated that there

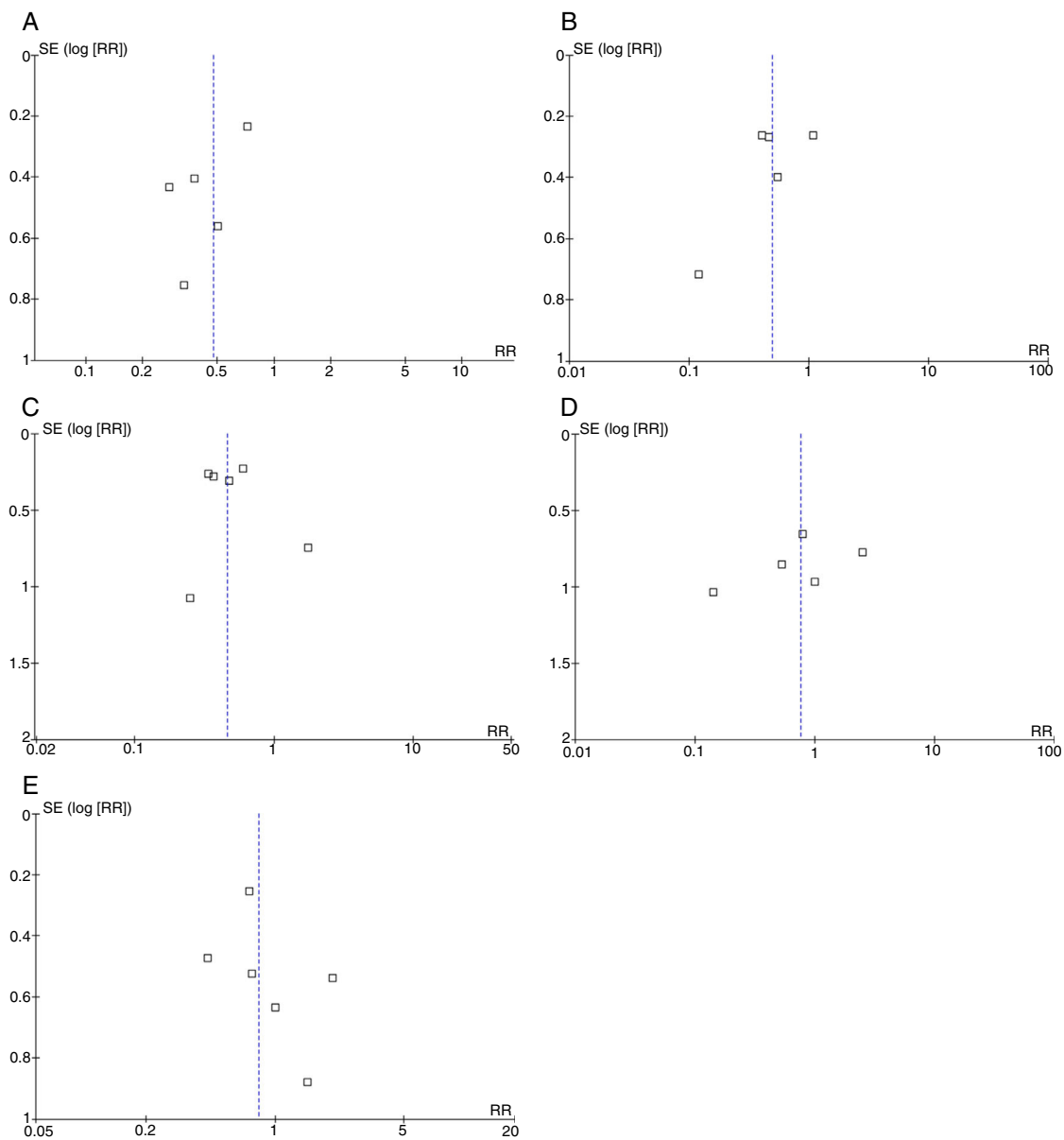


Figure 4 Funnel plots. (A) New cerebral infarctions linked to DCI. (B) Severe disability. (C) Clinical deterioration linked to DCI. (D) Mortality. (E) Need for permanent ventricular shunt.

were no differences in the risk of needing a permanent shunt for posthaemorrhagic hydrocephalus. This is probably due to the fact that a small amount of blood products may impede CSF reabsorption, and LD may be insufficient to remove these products.⁴⁹

Limitations

Our study has a number of limitations inherent to its methodology and to the studies included in the meta-analysis. The most relevant limitation concerns the combined analysis of randomised and observational studies, which may result in differences between intervention groups (selection bias). Another issue is that some studies did not explicitly indicate that they had followed a strict research protocol

(reporting bias). Although combined analyses of randomised and observational studies are frequently conducted in systematic reviews to increase accuracy of the results, they are not recommended by the Cochrane Non-Randomised Studies Methods Group as this may lead to bias.⁵⁰ With this in mind, we conducted a subgroup analysis based on study methodology. The analysis of clinical trials showed benefits of LD limited to a reduced risk of clinical deterioration caused by DCI; this finding may indicate a bias in the results of the combined analysis.

We should also point out that the funnel plots drawn for the purpose of detecting any publication biases have a low reliability since only a small number of studies were analysed.³⁵

In conclusion, the results of our meta-analysis show that LD may reduce the risk of complications caused by DCI (cerebral infarctions and clinical deterioration), and risk of severe

disability, but it has no effect on the risk of mortality. However, due to the quantitative and qualitative heterogeneity of the included studies, these findings are not conclusive and should be updated using the results of forthcoming clinical trials with homogeneous definitions of outcomes. These additional findings will provide a better understanding of the effects of LD in patients with ASH.^{51,52}

Funding

This study was funded by the Neuroscience and Neurological Science Research Group, Cartagena de Indias, Colombia.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to thank Dr Sachin A. Borkar from the department of neurosurgery at the All India Institute of Medical Sciences (New Delhi, India), for providing us with additional data from his study.

We also wish to thank Dr Keith Suárez-Jaramillo from the department of internal medicine at the University of Texas Health Science Centre (San Antonio, Texas), for his invaluable assistance with the English version of the abstract.

Appendix A. Appendix Assessment methods for each of the primary outcomes in the included studies

Author	Definition of clinical deterioration linked to DCI	Definition of new cerebral infarction	Assessment of neurological recovery	Final assessment
Klimo et al., ²⁴ 2004	1) Appearance of new neurological deficits, including confusion, disorientation, altered level of consciousness, or focal motor deficits, 4 to 14 days after the haemorrhage; 2) negative findings in a CT scan performed to rule out other causes of neurological deterioration (haemorrhage, cerebral oedema, hydrocephalus, etc.); 3) no other identifiable causes of neurological deterioration, such as hyponatraemia (sodium levels < 132 mEq/L), hypoxia, drug intoxication, infection, or epileptic seizures; and 4) evidence of vasospasm in transcranial Doppler or cerebral angiography studies, revealing vascular narrowing in a territory in which neurological changes are suspected to originate.	The region of cerebral infarction in neuroimaging has a vascular distribution consistent with the vasospasm	GOS	3 months
Kwon et al., ⁴⁰ 2008	1) New neurological deficits, including confusion, disorientation, somnolence, focal motor deficits, language impairment, or changes in pupillary reflexes; 2) there is no other cause for neurological deficits, including hyponatraemia, hypoxaemia, infection, pulmonary oedema, or drug intoxication; and 3) brain CT scan shows no findings compatible with secondary haemorrhage, cerebral oedema, or hydrocephalus.	Not listed among the outcomes in this study	GOS	6 months
Hänggi et al., ²³ 2008	Not specified	Ischaemic lesions in CT which were not linked to either the initial lesion or surgery	mRS and GOS	6 months

Author	Definition of clinical deterioration linked to DCI	Definition of new cerebral infarction	Assessment of neurological recovery	Final assessment
Al-Tamimi et al., ³⁹ 2012	A drop in consciousness (grade 1 on motor response or 2 on eye/verbal response on the Glasgow Coma Scale) or a new focal neurological deficit at least 96 hours after the haemorrhage not present immediately after aneurysm treatment and after exclusion of other causes. Angiographic vasospasm was not a prerequisite for diagnosis in noncomatose patients with a good grade on the World Federation of Neurological Surgeons scale.	Established cerebral infarction confirmed by CT or MRI	mRS	6 months
Maeda et al., ²⁵ 2013	1) Worsening of neurological state, including focal deficits, decreased level of consciousness, and paresis; 2) no other causes of neurological impairment are identified (intracranial disorders, systemic complications); and 3) vasospasm confirmed by medical assessment, including evidence of cerebral vasospasm in cerebral angiography, 3D CT angiography, or MR angiography; a new low-density area in CT associated with cerebral vasospasm; reduced cerebral blood flow; and increased mean flow velocity in cerebral arteries as shown by transcranial Doppler ultrasonography.	New low-density area in CT images associated with vasospasm, appearing between 4 and 30 days after bleeding, not seen during the immediate post-operative period, and not due to causes other than vasospasm	mRS	1 month
Borkar, ³⁴ 2013	1) Confusion, disorientation, somnolence, or focal neurological deficits 4 to 14 days after the haemorrhage; 2) negative findings in CT scans performed to rule out such other causes of neurological impairment as haemorrhage, cerebral oedema, or hydrocephalus; 3) absence of other causes of neurological impairment, including hyponatraemia (sodium level < 132 mEq/L), hypoxia, drug intoxication, infection, or epileptic seizures; and 4) evidence of vasospasm in transcranial Doppler ultrasonography.	Delayed ischaemic neurological deficits beyond the period of vasospasm, or if neuroimaging studies revealed a region of cerebral infarction in the vascular territory of the vasospasm	GOS	3 months

GOS: Glasgow Outcome Scale; mRS: modified Rankin Scale.

References

- Muñoz-Sánchez MA, Murillo-Cabezas F, Egea-Guerrero JJ, Gascón-Castillo ML, Cancela P, Amaya-Villar R, et al. Ultrasonografía doppler transcraneal urgente: utilidad predictiva del vasoespasmio sintomático en la hemorragia subaracnoidea espontánea en pacientes con buena situación neurológica. *Med Intensiva*. 2012;36:611–8.
- Muñoz-Sánchez MA, Cayuela-Domínguez A, Murillo-Cabezas F, Navarrete-Navarro P, Muñoz-López A, Guerrero-López F, et al. Mejora de los resultados en la hemorragia subaracnoidea espontánea: proyecto EHSA. *Rev Neurol*. 2009;49:399–404.
- Solenski NJ, Haley EC Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, et al. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med*. 1995;23:1007–17.
- Macdonald LR. Management of cerebral vasospasm. *Neurosurg Focus*. 2006;29:179–93.
- Rodríguez-García PL, Rodríguez-Pupo LR, Rodríguez-García D. Diagnóstico de la isquemia cerebral tardía y el vasoespasmio cerebral en la hemorragia subaracnoidea. *Neurología*. 2010;25:322–30.
- Valencia-Calderón C, Gabarros-Canals A, Calderón-Valdiviezo AI. Diagnóstico de la isquemia cerebral tardía y el vasoespasmio en la hemorragia subaracnoidea: ¿hasta cuándo monitorizar? *Neurología*. 2011;26:377–9.
- Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke*. 2008;39:3015–21.
- Vergouwen MD. Vasospasm versus delayed cerebral ischemia as an outcome event in clinical trials and observational studies. *Neurocrit Care*. 2011;15:308–11.
- Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391–5.
- Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–37.
- Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35:93–112.
- Alcalá-Cerra G, Gutiérrez Paternina JJ, Buendía de Ávila ME, Preciado Mesa EI, Barrios RS, Niño-Hernández LM, et al. Treatment of aneurysmal subarachnoid hemorrhage and unruptured intracranial aneurysms by neurosurgeons in Colombia: a survey. *Surg Neurol Int*. 2011;2:125.
- Shen J, Pan JW, Fan ZX, Xiong XX, Zhan RY. Dissociation of vasospasm-related morbidity and outcomes in patients with aneurysmal subarachnoid hemorrhage treated with clazosentan: a meta-analysis of randomized controlled trials. *J Neurosurg*. 2013;119:180–9.
- Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke*. 2001;32:2012–20.
- Muñoz-Guillén NM, León-López R, Túnez-Fiñana I, Cano-Sánchez A. Del vasoespasmio a la lesión cerebral precoz: una nueva frontera en la investigación de la hemorragia subaracnoidea. *Neurología*. 2013;28:309–16.
- De Aguiar PH, Barros I, Paiva BL, Simm RF. Removal of clots in subarachnoid space could reduce the vasospasm after subarachnoid hemorrhage. *Acta Neurochir Suppl*. 2013;115:91–3.
- Komotar RJ, Hahn DK, Kim GH, Starke RM, Garrett MC, Merkow MB, et al. Efficacy of lamina terminalis fenestration in reducing shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhage: a systematic review. *J Neurosurg*. 2009;111:147–54.
- Kasuya H, Shimizu T, Kagawa M. The effect of continuous drainage of cerebrospinal fluid in patients with subarachnoid hemorrhage: a retrospective analysis of 108 patients. *Neurosurgery*. 1991;28:56–9.
- Ohwaki K, Yano E, Nakagomi T, Tamura A. Relationship between shunt-dependent hydrocephalus after subarachnoid haemorrhage and duration of cerebrospinal fluid drainage. *Br J Neurosurg*. 2004;18:130–4.
- Klopfenstein JD, Kim LJ, Feiz-Erfan I, Hott JS, Goslar P, Zabramski JM, et al. Comparison of rapid and gradual weaning from external ventricular drainage in patients with aneurysmal subarachnoid hemorrhage: a prospective randomized trial. *J Neurosurg*. 2004;100:225–9.
- Hirashima Y, Hamada H, Hayashi N, Kuwayama N, Origasa H, Endo S. Independent predictors of late hydrocephalus in patients with aneurysmal subarachnoid hemorrhage – analysis by multivariate logistic regression model. *Cerebrovasc Dis*. 2003;16:205–10.
- Macdonald RL. Lumbar drainage after subarachnoid hemorrhage: does it reduce vasospasm and delayed hydrocephalus? *Neurocrit Care*. 2007;7:1–2.
- Hänggi D, Liersch J, Turowski B, Yong M, Steiger HJ. The effect of lumboventricular lavage and simultaneous low-frequency head-motion therapy after severe subarachnoid hemorrhage: results of a single center prospective Phase II trial. *J Neurosurg*. 2008;108:1192–9.
- Klimo P Jr, Kestle JR, MacDonald JD, Schmidt RH. Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. *J Neurosurg*. 2004;100:215–24.
- Maeda Y, Shirao S, Yoneda H, Ishihara H, Shinoyama M, Oka F, et al. Comparison of lumbar drainage and external ventricular drainage for clearance of subarachnoid clots after Guglielmi detachable coil embolization for aneurysmal subarachnoid hemorrhage. *Clin Neurol Neurosurg*. 2013;115:965–70.
- Staykov D, Schwab S. Clearing bloody cerebrospinal fluid: clot lysis, neuroendoscopy and lumbar drainage. *Curr Opin Crit Care*. 2013;19:92–100.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
- Quinn TJ, Dawson J, Walters MR, Lees KR. Exploring the reliability of the modified rankin scale. *Stroke*. 2009;40:762–6.
- Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry*. 1981;44:285–93.
- Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–7.
- Wong GK, Boet R, Poon WS, Chan MT, Gin T, Ng SC, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage: an updated systemic review and meta-analysis. *Crit Care*. 2011;15:R52.
- Etminan N, Vergouwen MD, Ilodigwe D, Macdonald RL. Effect of pharmaceutical treatment on vasospasm, delayed cerebral ischemia, and clinical outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Cereb Blood Flow Metab*. 2011;31:1443–51.
- Vergouwen MD, de Haan RJ, Vermeulen M, Roos YB. Effect of statin treatment on vasospasm, delayed cerebral ischemia, and

- functional outcome in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis update. *Stroke*. 2010;41:e47–52.
34. Borkar SA. Spinal cerebrospinal fluid drainage for prevention of vasospasm in aneurysmal subarachnoid haemorrhage: a prospective randomized controlled study. *Neurosurgery*. 2013;60 Suppl 1:180–1.
 35. The Cochrane Non-Randomised Studies Methods Group. *Manual Cochrane*. Oxford: John Wiley & Sons; 2012.
 36. Clark HD, Wells GA, Huet C, McAlister FA, Salmi LR, Fergusson D, et al. Assessing the quality of randomized trials: Reliability of the Jadad scale. *Control Clin Trials*. 1999;20:448–52.
 37. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
 38. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index. *Psychol Methods*. 2006;11:193–206.
 39. Al-Tamimi YZ, Bhargava D, Feltbower RG, Hall G, Goddard AJ, Quinn AC, et al. Lumbar drainage of cerebrospinal fluid after aneurysmal subarachnoid hemorrhage: a prospective, randomized, controlled trial (LUMAS). *Stroke*. 2012;43:677–82.
 40. Kwon OY, Kim YJ, Cho CS, Lee SK, Cho MK. The utility and benefits of external lumbar CSF drainage after endovascular coiling on aneurysmal subarachnoid hemorrhage. *J Korean Neurosurg Soc*. 2008;43:281–7.
 41. Frontera JA, Fernández A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? *Stroke*. 2009;40:1963–8.
 42. Rosenberg NF, Koht A, Naidech AM. Anemia and transfusion after aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 2013;25:66–74.
 43. Ortega-Gutiérrez S, Thomas J, Reccius A, Agarwal S, Lantigua H, Li M, et al. Effectiveness and safety of nicardipine and labetalol infusion for blood pressure management in patients with intracerebral and subarachnoid hemorrhage. *Neurocrit Care*. 2013;18:13–9.
 44. Bruder N, Rabinstein A. Cardiovascular and pulmonary complications of aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2011;15:257–69.
 45. Ochiai H, Yamakawa Y. Continuous lumbar drainage for the preoperative management of patients with aneurysmal subarachnoid hemorrhage. *Neurol Med Chir (Tokyo)*. 2001;41:576–80.
 46. Murad A, Ghostine S, Colohan AR. Role of controlled lumbar CSF drainage for ICP control in aneurysmal SAH. *Acta Neurochir Suppl*. 2011;110:183–7.
 47. Ruijs AC, Dirven CM, Algra A, Beijer I, Vandertop WP, Rinkel G. The risk of rebleeding after external lumbar drainage in patients with untreated ruptured cerebral aneurysms. *Acta Neurochir (Wien)*. 2005;147:1157–61.
 48. Ormond DR, Dressler A, Kim S, Ronecker J, Murali R. Lumbar drains may reduce the need for permanent CSF diversion in spontaneous subarachnoid haemorrhage. *Br J Neurosurg*. 2013;27:171–4.
 49. Yong CI, Hwang SK, Kim SH. The role of lumbar drainage to prevent shunt-dependent hydrocephalus after coil embolization for aneurysmal subarachnoid hemorrhage in good-grade patients. *J Korean Neurosurg Soc*. 2010;48:480–4.
 50. The Cochrane Collaboration. *Cochrane Collaboration open learning material for reviewers*. Oxford: The Cochrane Collaboration; 2002.
 51. Alcalá-Cerra G, Paternina-Caicedo A, Gutiérrez-Paternina J. Lumbar drainage of cerebrospinal fluid after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis of randomized controlled trials. *PROSPERO*. 2013. CRD42013005279.
 52. Bardutzky J, Witsch J, Juttler E, Schwab S, Vajkoczy P, Wolf S. EARLYDRAIN-outcome after early lumbar CSF-drainage in aneurysmal subarachnoid hemorrhage: study protocol for a randomized controlled trial. *Trials*. 2011;12:203.