JNI Jurnal Neuroanestesi Indonesia

Original Article

Therapeutic Potential of Cilostazol in Aneurysmal Subarachnoid Hemorrhage: A Systematic Review

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Received: July 30, 2024; Accepted: December 27, 2024; Publish: June 21, 2025

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Abstract

Introduction: Vasospasm and delayed cerebral infarction (DCI) are factors that influence the prognosis and clinical outcomes in subarachnoid hemorrhage (SAH). Although several pharmacological therapies are considered potentially effective in reducing vasospasm and DCI, only a few have shown significant benefits. This systematic review aims to evaluate the therapeutic benefits of cilostazol in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Subject and Methods: A systematic search was conducted on studies from January 2009 to March 2024 across five databases, guided by PRISMA 2021. The outcomes evaluated may include angiographic vasospasm, symptomatic vasospasm, the severity of vasospasm, new cerebral infarctions, delayed cerebral ischemia, and functional outcomes.

Results: Following analysis, 9 studies were included in this systematic review, involving 627 patients in the cilostazol group and 631 patients in the control group. Most of these studies indicated that cilostazol administration in SAH yielded positive effects on cerebral vasospasm, new infarctions, and functional outcomes. However, there was no evidence to support the effectiveness of cilostazol in preventing DCI.

Conclusion: Overall, cilostazol appears to be a promising therapy for SAH. However, the impact of cilostazol on DCI warrants further investigation, possibly due to the complex mechanisms of DCI.

Keywords: Cerebral infarct, cilostazol, subarachnoid hemorrhage, vasospasm

J. neuroanestesi Indones 2025;14(2): 53–63

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) refers to bleeding into the subarachnoid space, the area between the arachnoid membrane and the pia mater resulting from the rupture of an intracranial aneurysm. This condition is a medical emergency, commonly presenting with a sudden and severe headache (often described as a thunderclap headache), nausea, vomiting, altered mental status, and neurological deficits.[1] The mortality rate for SAH ranges from 40-50%, with 30% of cases at risk of death within the first few days to weeks after the onset of hemorrhage.[2,3] Unlike ischemic stroke, which mainly affects individuals over the age of 65, SAH is more commonly observed in younger populations, particularly those aged 40–60 years.[4] Moreover, the majority of SAH survivors are expected to experience long-term disabilities, impairments, or cognitive deficits, resulting in significant societal losses due to the diminished productive workforce.[3] Cerebral vasospasm is a leading cause of morbidity and mortality in SAH. The incidence of vasospasm is reported to be as high as 75% in SAH cases, though clinical symptoms are observed in fewer than half of these cases.[5,6] 6 Cerebral vasospasm typically emerges 4–14 days after aneurysm rupture and might resolve spontaneously within 21 days.[6,7] More than 30% of these patients are estimated to develop neurological deficits due

doi: https://doi.org/10.24244/jni.v14i2.613
ISSN (Print): 2088-9674 ISSN (Online): 2460-2302
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JNI is accredited as Sinta 2 Journal: https://sinta.kemdikbud.go.id/journals/profile/796
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How to cite: Felicia, et al, "Therapeutic Potential of Cilostazol in Aneurysmal Subarachnoid Hemorrhage: A Systematic Review".

to Delayed Cerebral Ischemia (DCI), which may either improve or progress to permanent cerebral injury.[8,9] Vasospasm and DCI have a substantial impact on prognosis and outcomes in SAH. While several pharmacological therapies have been suggested to reduce these events, only a few have demonstrated significant efficacy. Even nimodipine, a calcium channel blocker used in the treatment of SAH, has not been proven effective in preventing vasospasm, although evidence indicates that it may improve functional outcomes.[6,9] Recent studies suggested that cilostazol, an antiplatelet agent, can mitigate the procoagulant effects triggered by SAH, thus preventing the formation of microthrombotic and microembolic within cerebral circulation.[8] Current SAH management guidelines, including those from the American Heart Association and the European Stroke Organization, suggested the use of calcium channel blockers (CCBs), specifically nimodipine, for all SAH patients. Beyond nimodipine, there are no established guidelines or recommendations that either support or oppose the use of other prophylactic agents, including cilostazol.[2,4,5]

This review focuses on adult patients aged ≥18 years with confirmed aSAH, analyzing outcomes such as angiographic vasospasm (aVS), symptomatic vasospasm (sVS), new cerebral infarction (NI), delayed cerebral ischemia (DCI), and functional recovery assessed using validated scales like the Modified Rankin Scale (mRS). The analysis encompasses diverse treatment groups, including patients undergoing surgical clipping and/or endovascular coiling, and evaluates the effects of cilostazol as an adjunctive therapy. Cilostazol, an antiplatelet agent, may counteract the procoagulant effects induced by SAH, potentially preventing microthrombosis and embolic events. By addressing these parameters, this systematic review aims to bridge gaps in clinical guidelines regarding the efficacy of cilostazol in aSAH management.

Current recommendations, including those from the American Heart Association and the European Stroke Organization, advocate for the use of nimodipine but do not include other agents. This review assesses cilostazol's potential to improve critical outcomes in aSAH, providing a foundation for evidence-based updates to clinical practice.

Methods

This systematic review was conducted according to a predefined protocol following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for 2021. Literature searches were conducted from 20 th to 30th of March, 2024, across several databases including PubMed, Scopus, Cochrane Library, Proquest, and Google Scholar. The search strategy employed Boolean operators with keywords: Cilostazol AND ("Subarachnoid H(a)emorrhage" OR Aneurysm OR SAH). The articles included in this review were limited to human studies involving individuals aged ≥18 years, with full-text manuscripts written in Indonesian and/or English. Initial searches yielded a total of 231 articles across PubMed (n=67), Scopus (n=60), Cochrane Library (n=36), Proquest (n=21), and Google Scholar (n=47). Following the removal of duplicates, 95 articles were selected for further consideration. Subsequently, these articles underwent an initial screening based on their titles and abstracts, resulting in 67 articles proceeding to the next stage. A thorough full-text evaluation was then conducted according to predefined inclusion and exclusion criteria, leading to a total of 9 articles. The detailed search and screening procedure is illustrated in Figure 1.

Qualification Criteria

In this study, we conducted a review to evaluate the impact of cilostazol in SAH, comprising clinical trials and observational studies. The data extraction process was initiated with a thorough literature search and screening, conducted independently by two authors (F and MJ) to pinpoint relevant references. Articles that did not meet the inclusion criteria were excluded. The inclusion criteria for studies in this review were: (1) clinical trials (both randomized and non-randomized) or observational studies (OS), including pilot studies and preliminary reports; (2) studies involving a treatment group receiving

cilostazol and a control group, which could include placebo, standard therapy, supportive therapy, or other therapies not involving cilostazol; (3) studies reporting outcomes such as angiographic vasospasm (aVS), severity of vasospasm, symptomatic vasospasm (sVS), new cerebral infarction (NI), delayed cerebral ischemia (DCI), or functional outcomes measured by the Modified Rankin Score (mRS), Glasgow Outcome Scale (GOS), or Extended Glasgow Outcome Scale (eGOS); and (4) studies involving adult patients (aged ≥18 years). Exclusion criteria included manuscripts not written in Indonesian or English, publications older than 15 years (before 2009), unavailable full-texts or abstracts, animal studies, literature reviews, opinions, and expert comments. Information incorporated in this systematic review included authors, publication years, population demographics, sample sizes in the treatment group and protocols for cilostazol administration, sample sizes in the control group and the administration protocols, study outcomes, and study limitations.

Risk of Bias

Following the screening process, the authors will perform a critical appraisal, quality assessment, and evaluation of potential bias for each study reviewed. This will be done using the Modified Jadad Scale for randomized controlled trials (RCT), the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) for non-RCT, and the Newcastle-Ottawa Scale (NOS) for observational studies. On the Modified Jadad Scale, bias will be classified into several categories, resulting in a total score ranging from 0 to 7, with higher scores indicating better quality. The ROBINS-I tool assesses eight domains, with each domain rated as low, moderate, or high risk. For observational studies, the NOS will be used to evaluate risk in terms of selection, comparability, and outcome domains, with a score of ≥7 reflecting high study quality.

Results

After a thorough analysis of the complete manuscripts, a total of 9 studies were included in this review. These comprised four RCT, two non-RCT, two retrospective cohort studies, and one cross-sectional study. Summary data from each study are presented in Table 1.

In total, the studies included 627 patients in the cilostazol group and 631 patients in the control group, all diagnosed with aSAH. Among all of the studies, four involved patients were treated

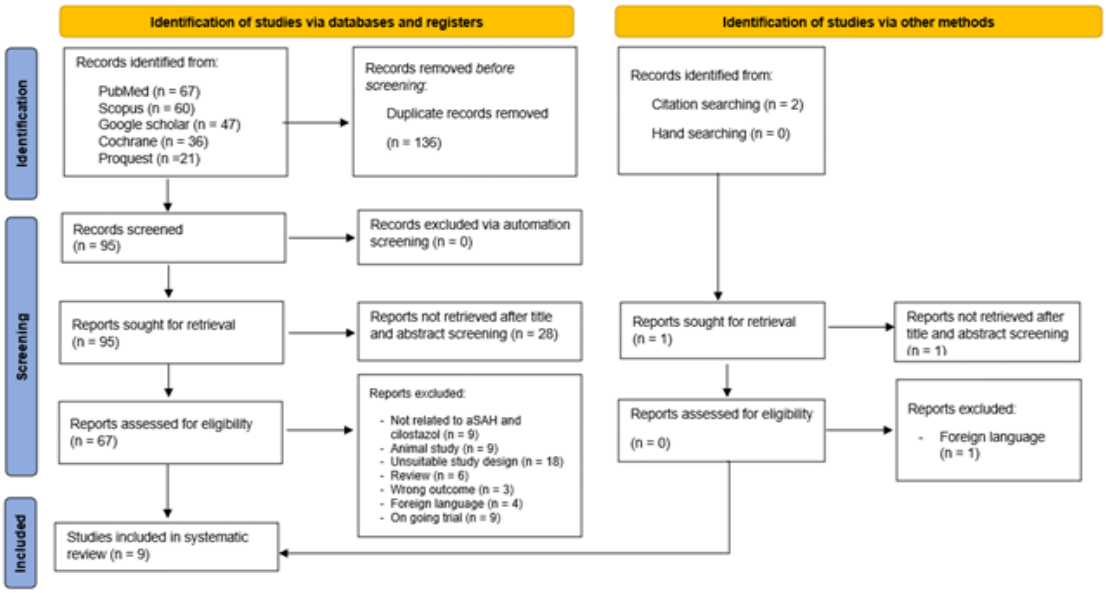


Figure 1. Article Search Method Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2021 Guidelines

solely with clipping for aneurysm, while the other five studies involved patients were treated with either coiling or clipping. Clipping involved the surgical closure of the aneurysm neck, whereas coiling was performed endovascularly by filling the aneurysm sac with titanium coils. This study evaluates the impacts of cilostazol on aSAH, focusing on several key outcomes: angiographic vasospasm, symptomatic vasospasm, vasospasm severity, new cerebral infarction, delayed cerebral ischemia, and functional outcomes. Angiographic vasospasm is defined as a reduction in diameter exceeding 50% as observed through digital subtraction angiography (DSA), magnetic resonance angiography (MRA), or computed tomography angiography (CTA).

Symptomatic vasospasm is defined as the emergence of new neurological deficits, either focal or global, or a decrease of at least 2 points on the Glasgow Coma Scale (GCS), where these changes are not attributable to other factors such as hydrocephalus, rebleeding, infection, brain edema, seizures, hypoxia, or electrolyte imbalances. Delayed cerebral ischemia (DCI) is defined as a persistent reduction in neurological function lasting more than one hour, suspected to be related to ischemic events after ruling out other potential causes, regardless of imaging findings.

New cerebral infarction (NI) is characterized by the presence of new infarcts observed on computed tomography (CT) or magnetic resonance imaging (MRI) during follow-up evaluations, provided that these infarcts are not attributable to procedural interventions or brain injury. Infarcts associated with procedural interventions or brain injury typically manifest within one day following the procedure or injury. In this study, favorable outcomes are defined as a Modified Rankin Scale (mRS) score of 0–2,7,15 a good recovery and moderate disability on the Glasgow Outcome Scale (GOS); or a score of 5–8 on the Extended Glasgow Outcome Scale (eGOS). Conversely, poor outcomes are characterized by an mRS score of 3-6, severe disability, a vegetative state, or death on the GOS; and an eGOS score of 1–4. Due to the variability in definitions and assessment across the studies, this review employs a qualitative approach to analyze the results.

Risk of Bias

The risk of bias using the Modified Jadad Scale for four RCT revealed that two studies exhibited good quality, while two studies were assessed as having moderate risk. For the non-RCT assessed with ROBINS-I, both demonstrated moderate risk. In the observational studies evaluated with the Newcastle-Ottawa Scale (NOS), the overall quality was rated as high, with two cohort studies scoring ≥8 (low risk) and one cross-sectional study showing moderate risk. Detailed information on the risk of bias is provided in Tables 2, 3, and 4.

Cilostazol and Angiographic Vasospasm (aVS) Currently, nimodipine is the sole pharmacological agent approved by the U.S. Food and Drug Administration for the management of SAH. Its efficacy in preventing vasospasm is attributed to its mechanisms of action, which include the inhibition of platelet function, suppression of thromboxane B2 release, and cellular neuroprotection. However, recent studies have investigated the effectiveness of alternative agents in preventing vasospasm in SAH, including cilostazol. In this review, seven studies evaluated the effects of cilostazol on aVS. Among these, four studies reported a significant reduction in both the incidence and severity of aVS in the cilostazol group, for instance, cilostazol reduced aVS by 30–42% in two studies. Conversely, three studies found no statistically significant differences, although a trend toward reduced aVS was observed in the cilostazol group. Notably, two of the these studies also utilized imaging modalities such as Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA), in addition to Digital Subtraction Angiography (DSA), to assess vasospasm. Since DSA is considered the gold standard, the inclusion of alternative imaging methods may have introduced potential bias. Recent evidence suggested that aVS may not consistently correlated with sVS or poor outcomes, as demonstrated by Matsuda, who found that cilostazol improved sVS and functional outcomes

Table 1. Baseline Characteristics

Author (year)	Study Type	Sample size (F/M)	Age, mean ± SD		Sex (Female/Male)		Operation type (Clipping/coiling)		Grading of SAH		Treatment	Control
			Cilostazol	Control	Cilostazol	Control	Cilostazol	Control	Cilostazol	Control		
Yoshimoto[11] (2009)	Non-RCT	50 (26/24)	60.0	58.0	26	24	22/4	19/5	H&K: I-II: 15; III-IV:11	H&K: I-II: 16; III-IV:8	1x200 mg (14 days)	Standard therapy: Fasudil 60 mg/days
Suzuki[8] (2011)	RCT	100 (49/51)	62.0 ±13.0	64.0 ±14.0	49 (36/13)	51 (40/11)	49/0	51/0	HH: I-II: 29; III-IV: 20	HH: II: 25; III-IV: 26	2x100 mg	Standard therapy: Fasudil and/or Ozagrel Na
Senbokuya[6] (2013)	RCT	109 (54/55)	60.0 ±12.5	61.3 ±12.7	54 (35/19)	55 (33/22)	54/0	55/0	H&K: I-II: 26; III-IV:28	H&K: I-II: 23; III-IV: 32	2x100 mg (14 days)	Standard therapy: Fasudil 3x30 mg
Kimura[12] (2015)	Non-RCT	130 (62/68)	65.6 ±14.0	65.0 ±13.5	62 (44/18)	68 (54/12)	62/0	68/0	H&K I-II: 28; III-V:34	H&K I-II: 30; III-V: 38	2x100 mg (14 days) + Fasudil 3x30 mg + Nutrition	Standard therapy: Fasudil 3x30 mg + Nicardipin 2mg/hr
Matsuda[9] (2016)	RCT	148 (74/74)	58.0 ±12.0	59.0 ±12.0	74 (54/20)	74 (46/28)	61/13	65/9	HH: I-II: 42; III-IV:32	HH: I-II: 43; III-IV: 31	2x100 mg (14 days)	Standard therapy: Fasudil 3x30 mg + placebo
Sugimoto[10] (2018)	RCT	50 (23/27)	56.5 ±13.4	64.8 ±12.1	23 (15/8)	25 (19/6)	23/0	27/0	WFNS: I-II: 15; III-V:8	WFNS: I-II: 16; III-V: 9	2x100 mg (12 days)	Standard therapy: Fasudil 2x30 mg
Kim[14] (2023)	OS	321 (89/232)	55.37 (±14.2)	55.47 (±12.8)	89 (51/38)	232 (147/85)	16/73	169/63	HH: I-II:58; III-V:31	HH: I-II:127; III-V:105	Cilostazol + Nimodipin	Nimodipin only D1-D4: 2 mg/hrs then 360 mg/days

Baseline Characteristics (Nakajima) [13]

Author (year)	Study Type	Country	Age	Sex	Operation type		Grading of SAH		Prophylactic Agent					
				F/M (Total)	clipping	coiling	WFNS	MFS	Fasudil	Cilostazol	Ozagrel	Statin	EPA	Edaravon	Dextran
Nakajima[13] (2023)	OS	Japan	81.2 ±4.5	172/30 (202)	145	57	I-II : 83 III-V : 119	1-2 : 19 3-4 : 183	179	164	15	88	109	54	78

Baseline Characteristics (Nishikawa) [15]

Author (year)	Study Type	Country	Sample	Operation type clipping/coiling	DCI clipping/coiling	Prophylactic Agent								
						Fasudil	Cilostazol	Ozagrel	Statin	Nicardipin	EPA	Edaravon	Clazosentan	Steroid
Nishikawa[15] (2023)	OS (CS)	Japan	3093	1401/1692	165/116	150 (100)	86 (57)	83 (55.3)	49 (32.5)	37 (24.5)	16 (10)	25 (16.6)	7 (4.6)	5 (3.3)

CS: Cross sectional; EPA: Eicosapentaenoic acid; H&H: Hunt & Hess; H&K: Hunt & Kosnik; DCI: Delayed Cerebral Infarct; MFS: Modified Fisher Scale; mRS: Modified Rankin Score; non-RCT: Non-randomized controlled trial; OS: Observational Study; SAH: Subarachnoid Hemorrhage; RCT: Randomized controlled trial; WFNS: World Federation of Neurological Surgeons

Table 2. Risk of Bias of Randomized Controlled Trial using Modified Jadad Scale

Scale Items	Reference			
	Suzuki[8]	Senbokuya[6]	Matsuda[9]	Sugimoto[10]
Wa the study described as randomized?	1	1	1	1
Method used to generate the sequence of randomization are described and appropriate	0	1	1	1
Was the study described as double-blind?	0	1	1	0
The method of doble blinding is described and appropriate	0	1	1	0
The description of withdrawals and dropouts are present	1	1	1	1
Was there a clear description of the inclusion orexclusion criteria?	1	1	1	
Were the methods of statistic analysis described?	1	1	1	1
Total score	4(moderate risk)	7(good quality)	7(good quality)	5(moderate risk)

Table 3. Risk of Bias of non-randomized Clinical Trial using ROBINS-I

	Scale Item							
Reference	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	overall risk of bias judgement
Kimura[12]	Moderate risk	Moderate risk	Low risk	Moderate risk	No information	Low risk	Moderate risk	Moderate risk
Yoshimoto[11]	Low risk	Moderate risk	Low risk	Moderate risk	No information	Low risk	Moderate risk	Moderate risk

Table 4. Risk of Bias of Cohort and Cross Sectional Studies using New-Castle Ottawa Scale

Reference	Items								
	Selection				Comparability	Outcome			
Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of the study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough	Adequacy of follow up of cohorts	Total
Nakajima [13]	1	1	1	1	1	1	1	1	8/9 (low risk)
Kim [14]	1	1	1	1	2	1	1	1	9/9 (low risk)
	Selection				Comparability	Outcome			
Reference	Representativeness of the case	Sample size	Non-Response rate	Ascertainment of the exposure/ screening tool	Potential confounders were investigated by subgroup analysis or multivariable analysis	Assessment of outcome	Statistical test		
Nishikawa [15]	1	1	0	1	1	0	1		5/8 (moderate)

Tabel 5. Summary of all nine studies examining the impact of cilostazol on aSAH

Author (years)	Type of Design	Treatment	Outcomes	Results	Limitation
Yoshimoto[11] (2009)	Non-RCT (Quasi-experimental)	1x200 mg (14 days)	- sVS, NI - Vasospasm severity - mRS discharge/30 d	- Moderate and severe vasospasm, as well as persistent sVS, were significantly lower in the cilostazol group - No significant differences in transient sVS, NI, or FO	- This study has a limitation of a small sample size (50)
Suzuki[8] (2011)	RCT	2x100 mg	- sVS - NI - mRS (discharge)	- Cilostazol improve FO significantly - No significant differences in sVS and NI - Better FO were noted in H&H grade ≤ 2, aged ≤65, aSAH without hydrocephalus, and those with cilostazol	- The relatively small sample size makes it difficult to conduct subgroup analyses - This study is an open-label trial, which may lead to bias.
Senbokuya[6] (2013)	RCT	2x100 mg (14 days)	-aVS, sVS, NI - Vasospasm severity -mRS (month-1,3,6)	- Incidence of aVS, sVS, severity of vasospasm, and DCI were significantly lower in the cilostazol group -FO were improved in the cilostazol group, but not statistically significant. - No significant differences in hospital length of stay	- Open-label trial without a placebo; the sample is confined to patients treated with clipping - NI was assessed using CT (lower sensitivity to MRI) - Evaluation of vasospasm was performed using CTA (less sensitive than DSA)
Kimura[12] (2015)	Non-RCT (Quasi-experimental)	2x100 mg (14 days)	-aVS, sVS, NI -mRS (discharge)	- Incidence of sVS and DCI were significantly lower in the combination group (cilostazol + nutrition) - Combination therapy improved FO - No significant difference in aVS	- Retrospective study; This study aimed to assess the efficacy of combining nutritional therapy with cilostazol. However, prior studies have shown that cilostazol alone is effective in reducing SVS and NI in aSAH
Matsuda[9] (2016)	RCT	2x100 mg (14 days)	-aVS, sVS, NI -GOS (3 months)	- Cilostazol reduce the incidence of sVS and poor outcome - Poor outcomes in the cilostazol group was significantly lower compared to the control -No significant differences in aVS and DCI	- Age>80, severe clinical conditions at admission, and thin local aSAH were not included; sample was relatively small - NI was assessed using CT (lower sensitivity to MRI)
Sugimoto[10] (2018)	RCT	2x100 mg (12 days)	-aVS, NI, DCI - eGOS (6 months)	- No significant differences in aVS, DCI, NI, and FO - There was a trend toward decreased DCI and improved FO in the cilostazol group, but not statistically significant	- NI was assessed using CT (lower sensitivity to MRI) - The study used fasudil hydrochloride as standard therapy, which has not been adopted in other countries
Kim[14] (2023)	OS (RCS)	Cilostazol + Nimodipin	- aVS, NI	- Incidence of aVS and NI was significantly lower in the combination group of cilostazol and nimodipine (cilonimo). - Multivariate analysis revealed an OR of 0.556 (p=0.012) for new infarctions in the cilonimo group	-The average aneurysm size in the cilonimo group is significantly larger compared to the control group - In the cilonimo group, coiling is used more frequently, whereas clipping is more common in the control group
Nishikawa[15] (2023)	OS (CS)	Depends on each centre	- Prophylactic agents for vasospasm - NI	- Cilostazol can significantly reduce the incidence of NI - The combination of cilostazol, fasudil, and statins has proven to be the most effective prophylaxis in reducing NI	- Survey was conducted in multicentre, leading to variability in imaging modalities for infarct evaluation. - The response rate for the survey was relatively low (30%)
Nakajima[13] (2023)	OS (RCS)	Depends on each centre	- aVS, NI, DCI - mRS (3 months)	- Cilostazol can reduce the incidence of NI and improve FO in elderly, but does not prevent aVS or DCI - Cilostazol remains an independent factor associated with favorable FO in patients with aSAH over 75 years old	- Survey was conducted in multicentre -The assessment of vasospasm, infarction, and cilostazol administration was determined by local physicians - The sample size in the non-cilostazol group was smaller and unbalanced compared to the cilostazol group

ngiographic vasospasm; sVS: symptomatic vasospasm; Cilonimo: cilostazol and nimodipin; CS: cross sectional; CT: Computed Tomography; CTA: computed tomography angiography DCI: delayed al ischemia; DSA: Digital Substraction Angiography; eGOS: Extended Glasgow Outcome Scale; FO: Functional Outcomes OR: Odds Ratio; OS: Observational Study; GOS: Glasgow Outcome Scale; Hunt & Hess; NI: New Infarct; MRI: Magnetic Resonance Imaging; mRS: Modified Rankin Score; non-RCT: non-randomized controlled trial;aSAH: aneurysmal subarachnoid hemorrhage; RCS: pective cohort study; RCT: Randomized controlled trial.

without significantly reducing aVS. Cilostazol and Symptomatic Vasospasm (sVS) Five studies investigated cilostazol's effects on sVS. Three of these studies reported a significant reduction in the incidence of sVS in the cilostazol group, with reductions ranging from 17% to 19% (Odds Ratio [OR]: 0.22; 95% Confidence Interval [CI]: 0.09–0.55; p=0.001). Factors associated with sVS include thick and diffuse aSAH, intraventricular hemorrhage (IVH), and higher Hunt and Kosnik grade. Regression analysis in one study identified cilostazol as the only independent factor associated with reduced sVS (OR:0.293; 95% CI: 0.099–0.568; p=0.027). However, two other studies did not observe statistically significant differences, potentially due to their smaller sample sizes (n=50 and n=100). Despite this, one of these studies noted that persistent symptoms were significantly higher in the control group compared to the cilostazol group (p<0.01).

This finding suggests that cilostazol may exert subtle benefits not fully captured in smaller cohorts and that a larger sample size might reveal a significant effect of cilostazol on vasospasm. Cilostazol and Delayed Cerebral Ischemia (DCI) Two studies evaluated cilostazol's relationship with delayed cerebral ischemia (DCI), and both found that cilostazol was not effective in preventing DCI. DCI remains a significant cause of mortality and morbidity in patients with SAH. Historically, DCI was primarily attributed to persistent narrowing of the major cerebral arteries. However, recent research suggested that its pathogenesis involved multiple factors, including microcirculatory dysfunction, early brain injury, impaired autoregulation, microthrombosis, and cortical spreading depression. Predictors of DCI include poor condition at admission, extensive extravasation (diffuse and thick SAH in cisternal and intraventricular), age between 65 and 74 years, and the presence of elevated intracranial pressure and hydrocephalus. Variability in patient populations may account for differences in study outcomes. For instance, one study included only patients over 75 years old, while another study predominantly involved lower-risk patients, as indicated by a higher proportion of WFNS grades I and II compared to grades III-V, with ratios of 15:8 in the cilostazol group and 16:9 in the control group. These differences in baseline characteristics may have influenced the observed lack of efficacy

Cilostazol and New Cerebral Infarct (NI)

Nine studies examined cilostazol's effects on new cerebral infarction (NI), with five demonstrating significant reductions in its incidence. Notably, a cross-sectional study by Nishikawa reported that cilostazol reduced NI (OR: 0.43– 0.50; p<0.05), with benefits observed even in patients over 75 years of age. Among the nine prophylactic agents evaluated for NI prevention, cilostazol was the only one to show a significant reduction in the frequency of NI (OR 0.48; 95% CI 0.27–0.82). Kim's study highlighted that the combination of cilostazol and nimodipine was more effective in reducing the incidence of NI and aVS compared to nimodipine alone (OR: 0.556; 95% CI: 0.351–0.879; p=0.012). However, the protective effect of this combination was less pronounced than that observed in other studies where cilostazol was used alone. This discrepancy may be attributed to variations in control treatments between the studies; Kim's study was conducted in Korea,

whereas most prior studies were conducted in Japan. In Japan, nimodipine has not been approved for aSAH treatment, and fasudil has been used as the standard therapy instead. In contrast, four studies found no significant difference in NI reduction. These findings may be related to methodological limitations, such as the use of CT instead of MRI for detecting infarctions, which is less sensitive; this limitation was acknowledged in the studies.

Cilostazol and Functional Outcomes (FO)

Six studies assessed FO in aSAH, with four showing significant improvement in the cilostazol group compared to controls. A study by Kimura found that cilostazol significantly improved FO (OR: 2.25, 95% CI: 1.09–4.63, p=0.031) and reduced mortality, though the latter was not statistically significant (p=0.064). This benefit was also observed in patients over 75 years old, with favorable outcomes reflected in mRS scores

at 90 days. Propensity score analysis further identified cilostazol as an independent predictor of favorable outcomes (adjusted OR: 0.305; 95% CI: 0.097–0.955). Conversely, two other studies found no significant difference, although cilostazol groups generally showed better FO. Senbokuya reported that cilostazol significantly reduced the incidence of NI, aVS, sVS, and the severity of vasospasm, but did not demonstrate a significant improvement in FO for aSAH. These findings suggest that FO are influenced not only by cerebral vasospasm but also by other factors, including EBI, clinical condition at admission, complications from surgical interventions, and systemic complications. Similar results were observed in the Matsuda's study, where multiple logistic regression analysis indicated that higher Hunt & Hess grade ($\geq$ 3) was an independent predictor of poor outcomes (OR: 5.721; 95% CI: 1.367–23.946; p=0.017), whereas cilostazol independently reduced the risk of poor outcomes (OR: 0.221; 95% CI: 0.054–0.903; p=0.035). A summary of these findings is presented in Table 5.

Adverse Effects

Among five studies reported on the side effects related to cilostazol, four of them found no adverse effects or hemorrhagic events in the cilostazol group. However, elevated liver enzymes, headaches, diarrhea, and mild tachycardia were observed. The percentage of adverse effects ranged from 2–5%, with elevated liver enzymes and diarrhea also noted in the control group. Senbokuya identified hemorrhagic events in 3 patients from the cilostazol group and 2 patients from the control group, including gastrointestinal bleeding, epidural hematoma, and intracerebral hemorrhage. Additionally, a total of 3 cases of cardiac issues were reported, all of which resolved within 96 hours after cilostazol was discontinued. However, after analysis, it was concluded that the cardiac issues and hemorrhagic events were not statistically significant.

Discussion

A total of 9 studies were included in this review which comprised of four RCT,[7,10–12] two non-RCT,[13,14] two retrospective cohort studies,[15,16] and one cross-sectional study.[17] The findings of this systematic review suggest that cilostazol is a promising agent for preventing and reducing the severity of both angiographic and symptomatic vasospasm in aSAH. As a selective phosphodiesterase 3 (PDE 3) inhibitor, cilostazol enhances intracellular cyclic AMP (cAMP) levels and activates protein kinase A. Therefore, in addition to its antiplatelet properties, cilostazol also improves endothelial function, inhibits vascular smooth muscle proliferation, and induces peripheral vasodilation. A significant reduction in the incidence of angiographic and symptomatic vasospasm observed in several studies indicates that cilostazol has a positive effect on vasospasm-related outcomes. However, its effectiveness in preventing delayed cerebral ischemia (DCI) remains debated due to the complex pathophysiology of DCI, which involves more than just vasospasm. Previous studies suggested that DCI might arise not only from cerebral vasospasm but also from other brain injury processes initiated by aneurysm rupture and early brain injury (EBI).[20] EBI occurred during the initial period of aSAH, specifically within the first 24–72 hours following the onset of hemorrhage. EBI can be attributed to several factors, including sudden elevations in intracranial pressure, blood extravasation, acute vasospasm, reduced cerebral blood flow, disturbances in cerebral autoregulation, and cerebral edema.

The reduction of new cerebral infarction in the cilostazol group is evident in the majority of studies. This finding is particularly noted in studies that use MRI for infarct evaluation, given MRI's superior sensitivity compared to CT scans for detecting new infarction.[7] The potential mechanism of cilostazol in preventing NI is likely due to its antiplatelet effects and vasodilatory properties, which help reduce microthrombosis and enhance cerebral microcirculation. Moreover, factors such as arteriolar constriction, spreading depolarization, damage to the blood-brain barrier, disruptions in cerebral autoregulation, and variability in capillary transit times are also believed to contribute to the pathophysiology of DCI and NI.[20] Several studies have reported that

clipping was linked to a higher risk of DCI and NI compared to coiling.[6,14] These finding align with Nishikawa's study, which found that in aSAH, coiling is associated with a lower incidence of infarct related to vasospasm compared to clipping. (OR: 0.90; 95% CI: 0.84–0.96; p=0.007).[17]

In several studies, the cilostazol group has shown greater improvements in functional outcomes, as measured by mRS, GOS, and eGOS. Cilostazol may enhance recovery and long-term prognosis in aSAH. Nonetheless, it is important to recognize that outcomes in aSAH are influenced by various factors. Previous studies indicated that mechanisms occurring within the first 72 hours of aSAH not only contribute to the development of EBI but also affect secondary complications and overall clinical outcomes.[20] These findings align with other studies indicating that poor condition at admission (H&H $\geq$ 3), older age (65–74 years), and the presence of intraventricular or intracerebral hemorrhage (MFS $\geq$ 4) are linked to poor outcomes in aSAH.[11,15] In contrast, cilostazol administration identified as an independent factor associated with favorable outcomes (OR: 0.305; 95% CI: 0.097-0.955).[15] Cilostazol has been proven safe with minimal side effects. Five studies reported no significant difference in hemorrhagic events in the cilostazol group compared to the control. Side effects were noted in a small percentage of samples (2–5%), including cardiac issues, diarrhea, elevated liver enzymes, and hemorrhagic events. Furthermore, clinical trials on ischemic stroke prevention have demonstrated that the incidence of hemorrhagic events with cilostazol is significantly lower compared to aspirin, suggesting that short-term use of cilostazol in aSAH is generally considered safe. The typical duration of cilostazol administration in aSAH is 10–14 days.[7,18]

Conclusion

In summary, cilostazol appears to be a promising therapeutic option for aSAH. It shows potential benefits in preventing both angiographic and symptomatic vasospasm, reducing new cerebral infarctions, and improving overall outcomes. However, the impact of cilostazol on delayed cerebral ischemia remains controversial, likely due to the complex nature of DCI. Cilostazol has been demonstrated to be safe when administered for up to 14 days. Further research through large-scale RCT is needed to confirm and evaluate the role of cilostazol in aSAH, particularly its effectiveness in preventing vasospasm, delayed cerebral ischemia, new cerebral infarction, and its impact on functional outcomes.

Limitation

In this systematic review, there were several limitations: 1) Research on cilostazol and aSAH has predominantly been conducted in China, Japan, and Korea. However, our review was restricted to articles in English and Indonesian, which led to the exclusion of relevant studies from these regions; 2) The overall sample size was relatively small, as most of the studies included had limited sample; 3) Not all studies used randomized controlled trial designs; 4) There was considerable variability in patient characteristics, treatment modalities (clipping/coiling), and cilostazol administration, including differences in duration, follow-up, and dosing regimens (some studies administered cilostazol alone, while others combined it with fasudil or nimodipine); 5) Inconsistent definitions and assessments regarding outcomes such as vasospasm, DCI, NI, and functional outcomes.

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