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Research Article

Intravenous Nicorandil Versus Adenosine for Fractional Flow Reserve Measurement to Assess Coronary Artery Stenosis: A Systematic Review and Meta-Analysis

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Abstract

Background: Fractional Flow Reserve (FFR) has become an increasingly accepted modality to assess coronary artery stenosis. Several clinical trials have been conducted to compare the effects of various pharmacologic agents, including nicorandil and adenosine, in achieving maximum coronary hyperemia.

Methods: We searched PubMed, Cochrane Library, Scopus, and Web of Science for randomized and observational studies comparing nicorandil with adenosine for measurement of FFR. Data were extracted from the eligible studies and pooled in a meta-analysis using the Revman software. Dichotomous data were pooled as Risk Ratio (RR) and continuous data were pooled as Standardized Mean Difference (SMD) with the corresponding 95% Confidence Intervals (CI). We aimed to evaluate the average FFR, hyperemia, duration of hyperemia, decrease in systolic blood pressure, and pain scores assessed by Visual Analog Scale (VAS).

Results: Five studies comprising a total of 595 patients met our inclusion criteria. The combined effect estimates favored nicorandil over adenosine for mean FFR (SMD = -0.17, 95% CI [-0.28, -0.06], P = 0.004). Nicorandil was more effective in achieving adequate hyperemia as compared to adenosine (SMD = -2.06, 95% CI [-4.36, -0.84], P=0.004). However, no significant differences were reported between nicorandil and adenosine in the duration of hyperemia, the decrease in systolic blood pressure, and VAS pain scores.

Conclusion: Nicorandil is associated with superior clinical outcomes and a similar safety profile as compared to adenosine and should therefore be considered as an alternative agent for FFR evaluation.

Keywords: Adenosine; Coronary artery stenosis; FFR; Fractional flow reserve; Nicorandil

Introduction

Fractional Flow Reserve (FFR) is a useful physiologic index to evaluate the severity of coronary artery stenosis. In most cases, coronary artery stenoses with greater than 80% diameter reduction on coronary angiography are associated with myocardial ischemia. When coronary angiogram demonstrates narrowing in the range of 40-80% diameter reduction, obtaining FFR can facilitate clinical decision making regarding the need for revascularization, particularly in individuals without noninvasive stress test documentation of myocardial ischemia.

Several studies have shown superior clinical outcomes with FFR-guided coronary artery revascularization strategies when compared to angiography-guided revascularization [1-3]. Since the ratio of the distal coronary artery pressure to the aortic pressure during hyperemia is used for calculation of the FFR [4], it is essential to achieve the maximum hyperemia to accurately measure FFR. Several agents and infusion methods have been suggested in clinical practice in order to obtain maximum hyperemia [3].

Intravenous infusion of adenosine is currently the standard technique for achieving hyperemia, however, adenosine is associated with significant adverse effects, increased infusion time, excessive costs, and several absolute contraindications; these have prompted investigators to search for alternative hyperemic agents [5,6].

Nicorandil is an anti-anginal agent that exhibits the dual properties of a nitrate and ATP-sensitive potassium channel agonist. This novel agent is known to induce coronary vasodilation of both the resistance and epicardial vessels [7,8]. The benefit of nicorandil administration over adenosine for FFR measurements – including decreased infusion time and fewer adverse effects – have been demonstrated in numerous recent studies [9,10].

In our systematic review and meta-analysis, we aimed to compare the efficacy and safety of nicorandil versus adenosine for FFR measurement.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions during the preparation of this systematic review [11,12].

Literature Search

We searched four electronic databases (PubMed, Cochrane Controlled Trials, Scopus, and ISI Web of Science) from their inception until March 2020. We used the following search strategy with no restrictions by language or year of publication; (nicorandil OR IV nicorandil) AND (adenosine OR IV adenosine) AND (Fractional Flow Reserve). We then manually searched references of included studies and published systematic reviews to retrieve studies that were not identified in the primary search.

Eligibility Criteria

We included prospective Randomized Controlled Trials (RCTs) that met the following inclusion criteria:

(1) Population: Patients undergoing FFR measurement; (2) Intervention: nicorandil (2 milligram dose); (3) Comparator: adenosine (140 milligram dose); and (4) Outcomes: mean FFR, the presence of hyperemia, duration of hyperemia, decrease in systolic blood pressure, and pain score based on Visual Analog Scale (VAS). Exclusion criteria included the following: (1) *in vitro* or animal studies; (2) non-randomized trials; (3) case reports; (4) studies that did not have abstracts; (5) studies consisting of only an abstract; and (5) studies that did not report data or measures for our selected outcomes. Two reviewers independently performed title and abstract screening for inclusion in the study. If titles and abstracts met criteria; the full texts were screened against the inclusion criteria. Discussion and consensus resolved any discrepancies between the reviewers for inclusion or exclusion of the studies.

Data Extraction

We extracted data using a standard data extraction table designed for this study. Extracted data included the baseline data of included patients, data required for risk of bias assessment, and outcome endpoints for analysis. Continuous outcomes were extracted as mean and standard deviation, while dichotomous outcomes were reported as risk ratio.

Risk of Bias Assessment

We evaluated the quality of the studies using the Cochrane Risk of Bias (ROB) assessment tool for the randomized studies which involve the following six domains: random sequence generation (selection bias); allocation sequence concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other potential sources of bias. Two reviewers independently rated the quality of the included studies as low risk, high risk, or unclear risk of bias. Regardless of risk of bias, all eligible studies were included in the meta-analysis [13]. We performed the risk of bias assessment of the observational studies using the New Castle-Ottawa Scale (NOS) [14]. The scale includes three domains: (1) selection, (2) comparability, and (3) outcome. A star rating of 0–9 was assigned based on the three parameters, as follows: Selection (S): 0-4; Comparability (C): 0-2;

Outcome (O): 0-3.

A study with 3 or 4 stars (★) in the selection (S) domain AND 1 or 2 stars in the comparability (C) domain AND 2 or 3 stars in the outcome (O) domain was deemed to be of good quality. Studies receiving six or more stars overall were also considered to be of good quality [15]. A study with 2 stars in the selection (S) domain AND 1 or 2 stars in the comparability (C) domain AND 2 or 3 stars in the outcome (O) domain was deemed to be of fair quality. A study with 0 or 1 stars the in selection (S) domain OR 0 stars in comparability (C) domain OR 0 or 1 stars in the outcome (O) domain was deemed to be of poor quality. Studies were judged as having either low, moderate, or high risk of bias.

Data Analysis

Risk Ratio (RR) with a 95% Confidence Interval (CI) was calculated for dichotomous outcomes using the Mantel-Haenszel method. Standardized Mean Difference (SMD) and relative 95% CI were used for the analysis of continuous outcomes. We used RevMan® software for statistical analysis (Review Manager Version 5.3; the Cochrane Collaboration, Copenhagen, Denmark). We assessed the statistical heterogeneity between studies using the chi-square test and I^2 statistics; values of ≥ 50% were indicative of moderate heterogeneity and ≥ 75% considered high heterogeneity. When heterogeneity was significant, a random-effects model was used for meta-analysis.

Publication Bias

According to Egger and colleagues [16,17], publication bias assessment is not reliable for less than 10 pooled studies. Therefore, in the present study, we could not assess the existence of publication bias by Egger's test for funnel plot asymmetry.

Results

Results of The Literature Search and Characteristics of Included Studies

A total of 1,263 articles were retrieved. Duplicates were removed using EndNote ® software. After screening, five studies with a total of 595 patients met inclusion criteria and were included in the meta-analysis. No new relevant studies were found on a manual search of previous studies or systematic reviews. The flow diagram of study selection is shown in Figure 1. Study characteristics are summarized in Table 1 and Table 2 and included: type of intervention, dose, risk factors, reference diameter (millimeters [mm]), minimum luminal diameter (mm), diameter stenosis (percent [%]), and lesion length (mm).

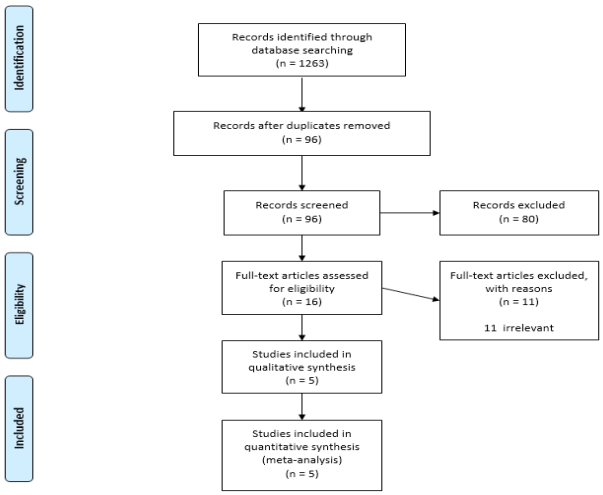

Figure 1: PRISMA flow diagram of the literature search.

Study Title	Intervention	Dose of Intervention	N	Study Design	Age	Gender (Male)	Body-Mass Index	Left Ventricular Ejection Fraction (%)	Left Ventricular Mass Index	Type Of Angina	
										Stable Angina	**Unstable Angina**
Nishi 2018	Nicorandil	2 mL (IV)	50	Crossover Randomized Single Blinded	69.7± 9.9	45 (88%)	23.8± 3.9	64.3± 9.5	97.4± 23.1	43 (86%)	7 (14%)
	Adenosine	150 mcg									
Kato 2015	Nicorandil	2 mL (IV)	124	Prospective	68.3 ± 9.6	78 (76.0)	23.7 ± 3.9	NR	NR	NR	NR
	Adenosine	150 mcg									

Ishi-buchi 2019	Nicorandil	2 mL (IV)	207	Prospective Observational	74 (67, 79)	147 (71)	25±3	NR	NR	144 (70)	63 (30)
	Adenosine	150 mcg									
Jang 2013	Nicorandil	2 mL (Iv)	194	Prospective	63.0 (56.3–70.0)	129 (66.5)	24.5 (23.1–26.7)	64.0 (58.0–68.0)	NR	122 (62.9	22 (11.3)
	Adenosine	150 mcg									
Maki Oi 2014	Nicorandil	2 mL (IV)	20	Prospective	69.6± 8.7	16 (80%)	24.3± 3.1	NR	NR	15 (75)	5(25)
	Adenosine	10 mcg									
Data are presented as mean ± SD, median (range), or number (%)											

Table 1: Baseline characteristics.

Study Title	HTN	DM	TOB	DLD	Evaluated Vessel Lesion			Reference Diameter, mm	Minimum Luminal Diameter (mm)	Diameter Stenosis (%)	Lesion Length (mm)	Newcastle-Ottawa Scale
					Left Anterior Descending Artery Lesion (LAD)	Left Circumflex Artery Lesion (LCS)	Right Coronary Artery (RCA)					
Nishi 2018	35 (70%)	18 (36%)	4 (8%)	35 (70%)	12 (24%)	25 (50%)	12 (24%)	2.7±0.6	1.4±0.4	47.3±11.9	13.4±6.8	NR
Kato 2015	84 (82.4)	49 (48.0)	38 (37.3	80 (78.4)	68 (54.8)	25 (20.2)	31 (25.0)	2.8 ± 0.6	1.3 ± 0.5	54.0 ± 11.9	17.1 ± 7.8	NR
Ishi-buchi 2019	148 (72)	72 (35)	56(27)	133 (64)	135 (64)	34 (16)	38 (18)	2.7 (2.3, 3.1)	1.6±0.4	40±13	NR	5 (S:3, C:0, O:2)
Jang 2013	121 (62.4)	53 (27.3)	35 (18.0)	137 (70.6)	152	19	23	3.0 (2.7–3.2)	1.6 (1.2–2.1)	54.3 (42.0–70.0)	NR	NR
Maki Oi 2014	9 (45)	4 (20)	NR	5 (25)	13 (65)	6 (30)	1 (5)	2.64 ± 0.62	1.15 ± 0.34	53.2 ± 12.2	NR	NR
Data are presented as mean ± SD, median (range), or number (%)												

*Abbreviations: DLD = Dyslipidemia; DM = Diabetes Mellitus; HTN = Hypertension; Mcg = Microgram; Ml = Milliliters; NR = Not Reported; TOB = Tobacco Use

Table 2: Disease history of patients and Newcastle-Ottawa Scale assessment.

Risk of Bias Assessment

The included studies showed high quality in most criteria except for blinding of the outcome, attrition, and selective outcome reporting domains, which were of high or unclear risk of bias according to the Cochrane ROB tool. The risk of bias summary is reported in Supplementary File 1.

Outcomes

Mean FFR

Five studies including a total of 595 patients reported mean FFR. The combined effect estimate favored the nicorandil group over adenosine groups in terms of average FFR (SMD = -0.17, 95% CI [-0.28, -0.06], P = 0.004). The combined studies showed substantial heterogeneity (I^2 = 76%, P = 0.002). Heterogeneity was best solved by excluding Ishibuchi et al. Homogeneous results did not reveal any significant difference (SMD = 0.00, 95% CI [-0.14, 0.14], P = 1) (Figure 2).

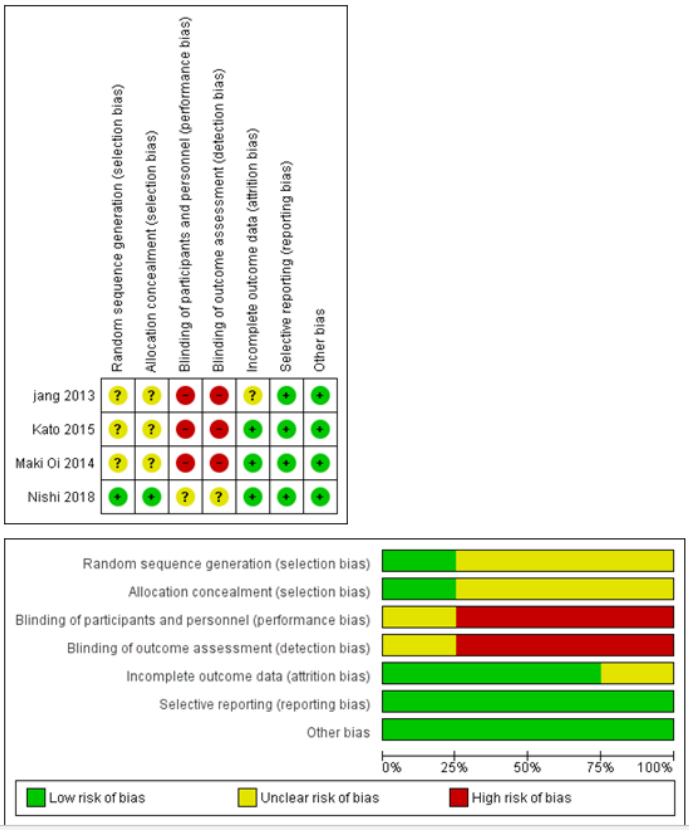

Figure 2: Risk of Bias (ROB) assessment of included studies.

Hyperemia

Two studies including a total of 174 patients reported hyperemia. The combined effect estimate favored the nicorandil group over the adenosine group in terms of the presence of hyperemia (SMD = -2.06, 95% CI [-4.36, -0.84], P = 0.004). The combined studies showed high heterogeneity (I^2 = 97%, P = 0.001) (Figure 3).

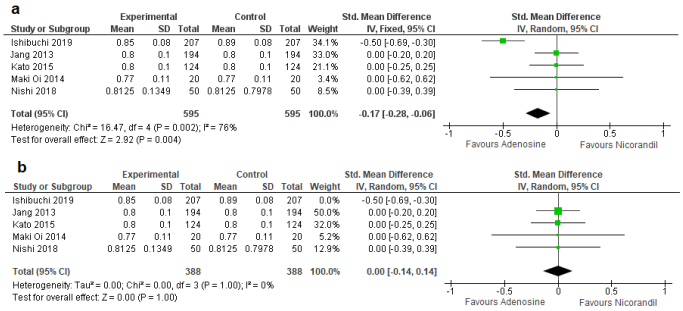

Figure 3 (a and b): Forest plot for analysis of FFR outcome (a = heterogeneous results; b = homogenous results after the leave-one-out method).

Duration of hyperemia

Two studies, including a total of 214 patients, reported the duration of hyperemia. The combined effect showed no significant difference between the nicorandil and adenosine groups in terms of the duration of hyperemia (SMD = -1.81, 95% CI [-5.44, 1.81], P = 0.33). The combined studies also showed high heterogeneity (I^2 = 98%, P = 0.001) (Figure 4).

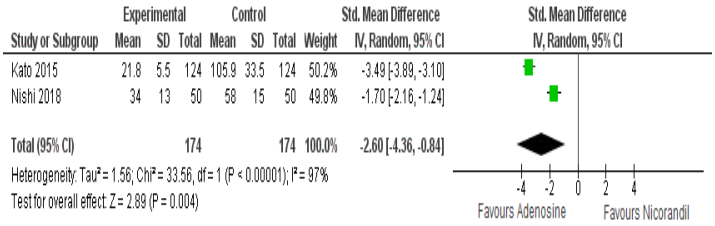

Figure 4: Forest plot for analysis of the presence of hyperemia.

Decrease of systolic blood pressure

Four studies, including a total of 401 patients, reported change in systolic blood pressure. The combined SMD favored neither the nicorandil nor adenosine groups in terms of decrease in systolic blood pressure (SMD = -0.11, 95% CI [-0.71, 0.49], P = 0.72). The combined studies showed high heterogeneity (I^2 = 93%, P = 0.001) (Figure 5).

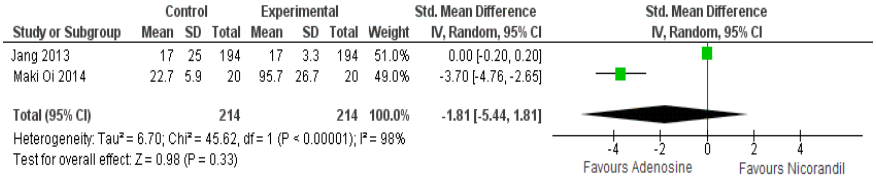

Figure 5: Forest plot for analysis of the duration of hyperemia outcome.

VAS pain score

Two studies, including a total of 214 patients, reported VAS score for pain. The overall SMD favored neither the nicorandil nor adenosine groups in terms of pain score with these agents (SMD = 1.54, 95% CI [-0.97, 4.04], P = 0.33). The combined studies showed high heterogeneity (I^2 = 97%, P = 0.001) (Figures 6,7).

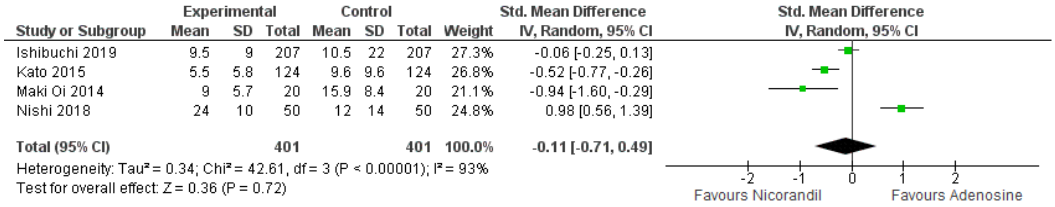

Figure 6: Forest plot for analysis of decrease in systolic blood pressure outcome.

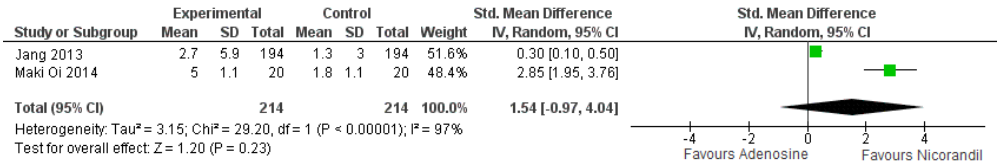

Figure 7: Forest plot for analysis of VAS score for pain outcome.

Discussion

Our meta-analysis revealed a significant improvement in the FFR measurement and hyperemia with nicorandil administration as compared to adenosine, however, there was no significant difference between nicorandil and adenosine in duration of hyperemia, decrease in systolic blood pressure, or VAS pain score.

FFR is the gold standard for assessing the hemodynamic significance of coronary artery lesions. Indeed, superior clinical outcomes have been achieved with FFR-guided percutaneous coronary intervention (PCI) as compared to angiography-guided PCI [1,2]. However, despite increasing evidence of cost-effectiveness and strong recommendations in current practice guidelines [6], FFR is still seldom used in the clinical setting. It is conceivable that adverse effects represent a significant deterrent to the administration of hyperemic agents. Adenosine, for example, causes chest discomfort, hypotension, dyspnea, and arrhythmias in up to 38% of patients [18]. Papaverine is another hyperemic agent that is occasionally favored over adenosine for its ability to induce extremely rapid coronary vasodilatation, however, its use is limited due to serious adverse events, including ventricular tachycardia and ventricular fibrillation [19,20].

The drawbacks of these hyperemic agents have prompted a search for alternatives with fewer side effects. Recently, Intravenous (IV) or Intracoronary (IC) administration of nicorandil has been proposed for invasive coronary physiological assessment. Nicorandil acts as a 2-nicotinamidoethyl-nitrate ester – a nitric oxide donor – and is considered a hybrid compound derived from an ATP-sensitive potassium channel. The drug has been reported to induce vasodilatory effects on both the coronary microvasculature and the epicardial coronary artery and thus increases blood flow to the coronary arteries [8,21,22].

Ishibuchi et al. found that IC nicorandil created more pronounced hyperemia than continuous IV adenosine; the rate of achieving maximum hyperemia was 92% with IC nicorandil versus 54% with IV adenosine [23]. They also reported that the incidence of chest discomfort, transient Atrioventricular (AV) block, and systolic aortic pressure drop increased in a dose-dependent manner with IV adenosine infusion whereas no adverse

effects were observed among the IC nicorandil group. Nishi et al. also conducted a randomized crossover study to compare IV nicorandil and adenosine for the measurement of FFR [24]. The authors concluded that IV nicorandil can be used to obtain maximal hyperemia and therefore offers acceptable diagnostic performance for assessment of FFR [24]. Notably, a decrease in systolic blood pressure and a wide range of variations in the hyperemic plateau were observed.

Nicorandil is not without adverse effects. Indeed, administration of an ATP-sensitive potassium channel opener has been associated with a risk of ventricular arrhythmia. Animal studies have demonstrated that the use of high dose nicorandil in ischemic myocardium may produce arrhythmias [25]. Conversely, other animal and human studies of long QT syndrome have shown that nicorandil may function as an anti-arrhythmic agent [26,27]. Previous studies in humans using IC nicorandil at clinical doses have shown no serious electrical adverse events [28,29].

In addition to arrhythmias, hyperemia-associated AV block has been reported. Recent data suggests that this is less common with nicorandil as compared to other agents. In a study of 210 patients undergoing FFR measurement, Jang, et al. reported transient AV block in 16 patients receiving adenosine as compared to zero patients receiving nicorandil [10]. In addition, effects on heart rate, systemic blood pressure, and PR interval duration were less significant with nicorandil as compared to adenosine. The authors concluded that nicorandil is a simple, safe, and effective way to induce steady-state hyperemia with fewer adverse effects than adenosine. Our findings support this conclusion.

Limitations

The main strength of our study was adherence to the PRISMA guidelines and checklist. In addition, all steps were performed in following with the Cochrane Handbook of Systematic Reviews for Interventions. Limitations of this study include the small number of the included studies, small sample size, heterogeneity reported in most of our selected outcomes, and differences in doses and times of administration of both nicorandil and adenosine. We were unable to perform subgroup analysis comparing IC and IV administration of the hyperemic agents due to lack of reporting in the included studies. Lastly, due to limited data, we could not assess the incidence of the adverse events in both groups. Nevertheless, we believe that this comparison of nicorandil and adenosine offers valuable insight to help guide physicians in selecting the most appropriate hyperemic agent for FFR measurement.

Conclusion

The preponderance of the evidence suggests that nicorandil is superior to adenosine for FFR measurement and should therefore be considered the hyperemic agent of choice for most patients.

Author Contributions

NN conceived the study hypothesis. NN, KRB, and DA designed the study and performed the systematic search, study selection, and data extraction. NN analyzed the data. All authors contributed to the interpretation of the data, writing and critical editing of the manuscript.

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