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A prospective randomized controlled study to compare effectiveness of dexmedetomidine and lignocaine pre-treatment for prevention of etomidate induced myoclonus

Dr. Mitali Agrawal [1], Dr. Ranjeeta Tambey [2], Dr. Vijay Patil [3]

1. Dr. Mitali Agrawal, Junior Resident, Dept of Anaesthesia, Government Medical College, Nagpur.
2. Dr. Ranjeeta Tambey, Associate Professor, Dept of Anaesthesia, Government Medical College, Nagpur
3. Dr. Vijay Patil, Assistant Professor, Dept of Anaesthesia, Government Medical College, Nagpur

Corresponding Author: Dr Ranjeeta Tambey **E-mail:** drranjeetasakhare@yahoo.co.in

Introduction

Etomidate, an induction agent, was synthesized in 1964 and introduced in clinical practice in 1972 in Europe and 1983 in the United States [1]. However, the drug was reformulated using lipid emulsion and reintroduced in 2007 in India. Etomidate is a carboxylated imidazole, confers the advantage of better hemodynamic stability, minimal respiratory depression, cerebral protective effects, and less injection pain compared to propofol, when used for the induction of general anesthesia [2]. Its lack of effect on the sympathetic nervous system, baroreceptor reflex regulatory system, and its property of increased coronary perfusion even on patients with moderate cardiac dysfunction makes it an induction agent of choice in cardiac disease patients [3-5]. Despite the benefits, there are two major complications associated with etomidate use. The first one is pain on injection, which can be prevented to some extent with a new lipophilic combination. The second most certain and undesirable side effect of etomidate is myoclonus, which is still one of the difficulties of its use among anesthesiologists and the incidence has been reported as much as 50%–80% after induction [6]. The consequences of this side effect can be serious in nonfasted emergency patients, patients with open eye injuries, or patients with limited cardiovascular reserves [7].

Although the mechanism of etomidate-induced myoclonus (EM) is still not clear, a number of drugs like midazolam, opioids, dexmedetomidine, and lignocaine have been tried to reduce the occurrence of myoclonus induced by etomidate but each one has its own limitations [1]. Though few studies have confirmed the role of lignocaine in managing etomidate-induced myoclonus [8]. Lignocaine propensity to reduce the central nervous system excitability has been hypothesized as the mechanism behind its EM suppressing

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action [9]. The mechanism behind EM has also been postulated to be similar to convulsive seizures. Lignocaine anticonvulsant mechanism of action of suppressing the cortically induced facilitation of motor neurons might also result partially, though not completely for its myoclonus attenuating property. However, its supratherapeutic concentrations have been postulated to cause selective inhibition of cortical inhibitory pathways, the same mechanism proposed behind EM [10].

Dexmedetomidine is a highly selective α2 adrenoreceptor agonist. Its mechanism of action is at the locus ceruleus which shows one of the highest densities of α2A adrenoreceptors in the brain. Presynaptic activation of the α2A adrenoreceptors in the locus ceruleus inhibits the release of norepinephrine resulting in sedative and hypnotic effects. Other pharmacological properties include anxiolysis, analgesia, and sympatholysis with anesthetic sparing effects and absence of significant respiratory depression. An intravenous injection of the drug can significantly reduce the stress responses of laryngoscopy and endotracheal intubation and can reduce the dose of propofol and opioids. Therefore, the effect of dexmedetomidine in relieving myoclonus may be attributed to its sedative and analgesic effects [11].

The present study was conducted to ascertain an ideal pretreatment drug that can abolish or significantly reduce the incidence of etomidate-induced myoclonus and also confer the advantage of attenuation of stress response of laryngoscopy and intubation. A direct comparative study of dexmedetomidine and lignocaine has not been reported, however, so there is no evidence as to which agent is the better choice for reducing myoclonus after etomidate induction. Hence, the present study was undertaken to compare iv dexmedetomidine 1μg/kg with iv lignocaine 1.5mg/kg pre-treatment for prevention of etomidate induced myoclonus.

Materials and Methods

A prospective, randomized, double-blind comparative study was carried out in the Department of Anesthesiology, at a tertiary care hospital of India between January 2020 to November 2021 after obtaining approval from Institutional Ethical Committee and written informed consent from the patients. A total of 106 patients of either sex, ASA grade I & II, age between 18 to 60 years, weight 40 to 80 kg, scheduled for elective surgery under general anesthesia were included in the study. Patients who refused to give consent, having allergy history to dexmedetomidine, lignocaine, or etomidate, anticipated difficult airway, impaired renal, hepatic functions or cardiorespiratory functions, known adrenal cortical dysfunction, psychiatric or neurological disorders, pregnant or lactating mothers, patients with significant

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bradycardia, beta-blockers, antiarrhythmic medications, sedatives or chronic opioids therapy and with pacemakers were excluded from the study. A thorough history, clinical examination, and relevant investigations were done. The pre-anesthetic check-ups of the patients were done a day before surgery. The hemodynamic parameters e.g., blood pressure and pulse rate were noted. The details of the study, blood investigations, pros & cons of the present study were explained and informed to patients and their relatives. Patients were given Tab Alprazolam 0.25mg HS night before surgery to alley the anxiety. Patients were instructed to remain nil by mouth for 6 hours before the surgery.

Inside the OT, baseline parameters like pulse rate, blood pressure, SpO2, and ECG were recorded on a multipara monitor. After recording vitals, premedication was done with Inj. Pantoprazole 40mg and Inj. Glycopyrrolate 4mcg/kg body weight. The study population was divided randomly into two groups of 53 patients each. Group L was given inj. lignocaine (1.5mg/kg) diluted in 10ml normal saline over 10 min. Group D was given inj. dexmedetomidine (1mcg/kg) diluted in 10 ml saline slowly over 10 minutes. Simultaneously, patients were pre-oxygenated with 100% Oxygen for 3 minutes. Two minutes after administering the study drug, inj. etomidate 0.3mg/kg IV was administered over the 30s or till the abolition of eyelash reflex whichever was earlier, and the patients were monitored for myoclonus after the end of etomidate injection over the next 2 min. The study was a double-blind study where the investigator cum observer of myoclonus and hemodynamic parameters and patients were blind, and they did not know about the anesthetic drug used for pre-treatment before induction of anesthesia with etomidate. The anesthesia colleague of the operation room was requested to prepare/ load the anesthetic drug in the syringe and then was instructed to induce the patient. Myoclonus was defined as ‘involuntary short muscle contractions leading to short observable movements in parts of the body and its severity was assessed using the four-point intensity scoring such as- (0): No myoclonus; (1): Mild myoclonus (mild movements of a body segment, e.g., finger or a wrist only); (2): Moderate myoclonus (mild movements of two different muscles e.g., face and leg); (3): Severe myoclonus (intense tonic movements in two or more muscle groups e.g., fast adduction of a limb). Depending on the time of onset, the presence or absence of myoclonus at 1 min (EM1) and 2 min (EM2) was recorded.

After recording myoclonus, inj. fentanyl 2mcg/kg iv and inj. midazolam 0.03mg/kg iv was administered and inj. vecuronium bromide 0.1mg/kg iv was administered after the 2 min observation period, and intubation done. The general anesthesia was maintained with nitrous oxide: oxygen (50%:50%), sevoflurane, and inj. vecuronium 0.02mg/kg as maintenance dose

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and controlled ventilation. All the hemodynamic parameters were recorded at the various intervals- TB-baseline after study drug infusion (dexmedetomidine/lignocaine); TA- after etomidate injection; T0-3min after induction and at time of intubation; T1-1 min after intubation; T3-3 min after intubation; T5-5 min after intubation; 15 min after intubation; 30 min after intubation; 60 min after intubation; TE- At time of extubation

Patients were monitored for perioperative complications such as nausea, vomiting, bradycardia, tachycardia, hypotension, hypertension, or any other adverse events. A decrease in systolic blood pressure and mean blood pressure by >20% of baseline value was considered significant hypotension and was treated with intravenous fluids and decreasing the depth of anesthesia. Pulse rate less than 50 per minute was considered as significant bradycardia and was treated with inj. atropine injection 0.6mg iv, repeated if required and total dose noted. At the end of the surgery, the patient was reversed with inj. neostigmine 0.05mg/kg & inj. glycopyrrolate 8μg/kg intravenously slowly. The patient was extubated after through oropharyngeal suction. The postoperative blood pressure (systolic, diastolic & mean) and heart rate were noted. After reversal of anesthesia and extubation, patients were shifted to Post Anaesthesia Care Unit (PACU) and monitored for a period of 2 hours. Patients were kept fasting for 4-6 hours postoperatively and monitored for any postoperative complications. Ramsay's sedation score was used for the assessment of sedation in the postoperative period.

Statistical analysis

Continuous variables (Demographic and hemodynamic parameters) were presented as Mean ± SD. Categorical variables were expressed in frequency and Percentages. Categorical variables were compared between 2 groups by performing a chi-square test. For small numbers, Fisher exact test was used wherever applicable. Hemodynamic parameters were compared at different time points in each group by performing one-way repeated measure ANOVA test. An Independent t-test was used to compare hemodynamic parameters between 2 groups at different time points. $P<0.05$ was considered as statistical significance. Statistical software STATA version 14.0 was used for data analysis.

Observations and Result

A total of 106 patients were enrolled in the study and divided randomly into two groups of 53 patients each. Both the groups were comparable and found no significant difference in regard to demographic profile of the patients as shown in table 1.

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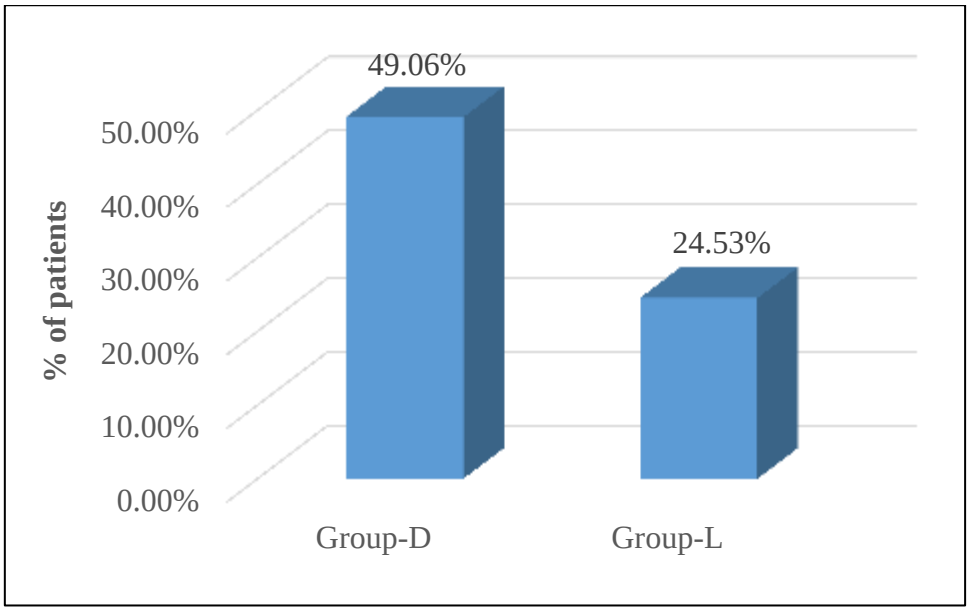
Table 1: Demographic profile of patients

Demographic data	Group-D	Group-L	P value
Mean Age (Years)	39.50±12.72	36.83±13.86	0.3023
Mean weight (kgs)	58.68±9.24	58.07±8.24	0.7234
Mean BMI (kg/m^2)	23.14±2.80	23.08±2.66	0.9249
Male	29 (54.72%)	28 (52.83%)	0.846
Female	24 (45.28%)	25 (47.17%)	

Lignocaine shows more reduction in myoclonus incidence (75.47%) as compared to dexmedetomidine (50.94%) and proves to be more effective than dexmedetomidine in reducing myoclonus with a highly significant p-value of 0.009 as depicted in figure 1.

Figure 1: Incidence of myoclonus in both study groups



The severity of myoclonus was significantly decreased in both study groups at 1 and 2 minutes, but group L shows a highly significant decrease in severity as compared to group D. At 2 min, group D shows no grade 3 myoclonus and group L was having less grade 1 myoclonus as compared to group D, (Table 2).

Table 2: Comparison of myoclonus grade in both study groups at 1 and 2 min

At 1 and 2 min	Grade	Group-D	Group-L	P value
At 1 min	0	29 (54.72%)	44 (83.02%)	0.002

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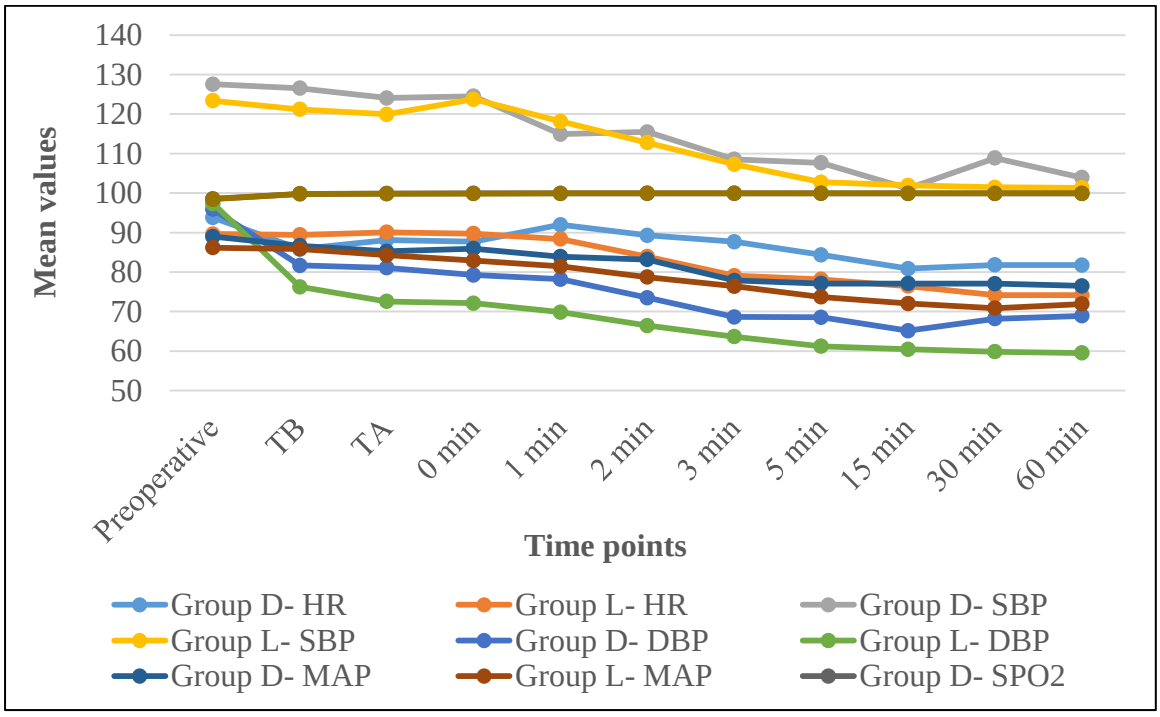
	1	20 (37.74%)	04 (7.55%)	
	2	03 (5.66%)	02 (3.77%)	
	3	01 (1.89%)	03 (5.66%)	
At 2 min	0	37 (69.81%)	45 (84.91%)	0.019
	1	12 (22.64%)	02 (3.77%)	
	2	04 (7.55%)	04 (7.55%)	
	3	00 (0.0%)	02 (3.77%)	

Mean heart rate, systolic, diastolic and mean arterial blood pressure as well as SPO2 was found to be within normal limits at all the intervals and no significant difference was found to be present. Hence the hemodynamic parameters were found to be comparable in both the groups at various time point as depicted in figure 2.

Figure 2: Haemodynamic parameters and SPO2



There were no significant side effects were observed in either group during the study period as shown in figure 3.

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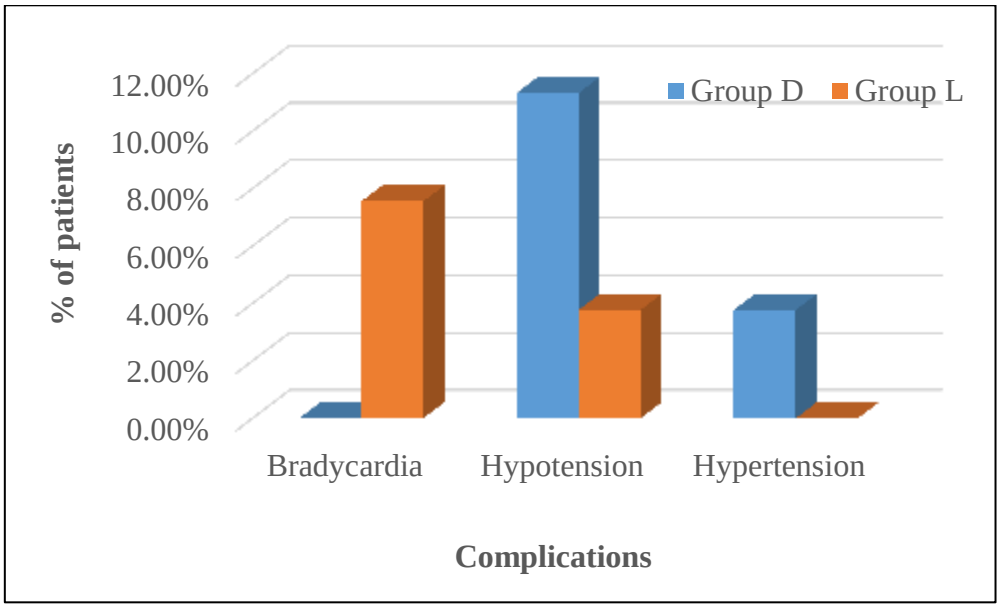
Figure 3: Perioperative complications in group D and group L



Degree of Sedation scored on the Ramsay sedation scale at various time intervals throughout the study duration showed no clinically significant difference in the two groups at any time interval as shown in table 3.

Table 3: Comparison of postoperative Ramsay sedation score between group D and group L

Timepoint		Group-D	Group-L	P value
0 min	1	15 ± 28.30	6 ± 11.32	0.027
	2	26 ± 49.06	39 ± 73.58	
	3	12 ± 22.64	8 ± 15.09	
15 min	1	44 ± 83.02	45 ± 84.91	0.791
	2	09 ± 16.98	08 ± 15.09	
30 min	1	44 ± 83.02	51 ± 96.23	0.026
	2	09 ± 16.98	02 ± 3.77	
60 min	1	50 ± 94.34	53 ± 100	0.079
	2	03 ± 5.66	00 ± 0.0	
120 min	1	53 ± 100	53 ± 100	-

Discussion

In the present study there was no statistically significant difference among both the groups concerning their demographic profile in terms of age, weight, BMI, and sex, and this

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finding did not have any clinical implications on the study as similar to previous studies [10, 12-15]. Intravenous dexmedetomidine has been used as a premedication in different doses, ranging from 0.2 to 2.5 μg /kg body weight. We chose the dose of dexmedetomidine to be 1μg/kg body weight, as it is the standard loading dose, and the literature supports [13, 15] no significant bradycardia. The literatures [10, 12] evaluating the efficacy of lignocaine for myoclonus prevention is scarce. We chose the dose of 1.5mg/kg based on the study conducted by Gupta P et al [10]

Both the dexmedetomidine and lignocaine significantly reduced the incidence of myoclonus. However, lignocaine showed more reduction in myoclonus incidence (75.47%) as compared to dexmedetomidine (50.94%) and proves to be more effective than dexmedetomidine in reducing myoclonus with a highly significant p-value of 0.009. These results are corroborated with the earlier studies [11-13, 15-18]. At 1 min, group D had no myoclonus in 29 (54.72%) patients, grade 1 myoclonus in 20 patients (37.74%), grade 2 myoclonus in 3 patients (5.66%) and grade 3 myoclonus in 1 patient (1.89%) at 1 min. Group L had no myoclonus in 44 (83.02%) patients, grade 1 myoclonus in 4 patients (7.55%), grade 2 myoclonus in 2 patients (3.77%), grade 3 myoclonus in 3 patients (5.66%). The severity of myoclonus was significantly decreased in both study groups at 1 minute, however group L shows highly significant decrease in severity as compared to group D. These results are correlated with the study done by Singh KA et al [12] and Dixit P et al [13]. Similarly, at 2 min group D had no myoclonus in 37 (69.81%) patients, grade 1 myoclonus in 12 patients (22.64%), and grade 2 myoclonus in 4 patients (5.66%). Group L had no myoclonus in 45 (84.91%) patients, grade 1 myoclonus in 2 patients (3.77%) grade 2 myoclonus in 4 patients (7.55%) and grade 3 myoclonus in 2 patients (3.77%). The severity of myoclonus was significantly decreased in both study groups at 2 minutes. These findings are in concordance with the other studies [10, 11, 14] which find dexmedetomidine and lignocaine efficacious in suppressing etomidate-induced myoclonus. The differences in our results from those of previous authors may be related to differences in the dosage and timing of administration of pre-treatment agents, the rate of administration of etomidate. The incidence of EM has been shown to increase with the speed of etomidate administration and the period of observation. We, therefore, employed a standard protocol to minimize these confounding variables. The reported incidence of myoclonus with etomidate injection over 30s and an observation period of 1 min has been found to vary widely. The majority of myoclonic episodes occur within two minutes of etomidate administration and approximately 50% of the episodes occur after the first minutes as reported by Sidighinejad A et al [19]. An observation period of 2 min was

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therefore chosen to capture the true incidence of myoclonus both in the dexmedetomidine and lignocaine groups.

The mean HR, systolic, diastolic, and mean arterial blood pressure was found to be within normal limits at all the intervals and no significant difference was found to be present. Thus, SBP, DBP, and MAP were stable in both groups which may also attribute to the hemodynamic stability of etomidate. The hemodynamic stability seen with Etomidate may be due to its lack of effect on the sympathetic nervous system, baroreceptor function, and capacity to bind & stimulate peripheral α2B adrenergic receptor with subsequent vasoconstriction [2]. Among the dose-dependent hemodynamic changes caused by dexmedetomidine, hypotension and bradycardia are the two common adverse effects. In present study, six patients experienced hypotension and no patients experienced bradycardia in the dexmedetomidine group. However, these hemodynamic changes were not significantly different between the two groups. Besides, no patient was reported to experience dizziness, respiratory depression, or nausea/vomiting. Accordingly, the pre-treatment with dexmedetomidine 1 μg/kg was safe and did not increase the incidence of adverse effects. Intraoperative hypotension was noted in 3.77% of patients in group L. Two patients in group D had hypertension. This transient rise in blood pressure is caused by the vasoconstricting property of dexmedetomidine due to the stimulation of the peripherally situated α2 receptors [20]. No incidence of respiratory depression was observed in any patient intra or postoperatively in the two groups correlated with the study done by Miao et al [18].

Both groups were comparable with respect to postoperative sedation with a majority of patients showing level 1 or 2 sedation after extubation suggesting that patients were awake, anxious, cooperative, and oriented. We found no study in the literature comparing postoperative sedation scores after giving study drugs for the prevention of etomidate-induced myoclonus

Limitations

As we did not have a control group or placebo group for estimating the actual incidence of myoclonus caused by etomidate, so we need to compare the efficacy of both the drugs based on the incidence quoted by previously published studies. Also, we only studied the incidence and severity of etomidate-induced myoclonus and not the duration of myoclonus which may also have an adverse effect.

Conclusion

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The present study found that the incidence of myoclonus was more in the dexmedetomidine group as compared to the lignocaine group. The hemodynamic parameters were found to be comparable in both the groups and no significant side effects were observed in either group during the study. Hence, we are of opinion that IV Lignocaine 1.5mg/kg proves to be a more effective pre-treatment as compared to IV dexmedetomidine 1µg/kg in preventing etomidate induced myoclonus.

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