CLINICAL EVALUATION OF NEBULISED BUDESONIDE IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE- A RANDOMISED STUDY

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ABSTRACT

BACKGROUND

Exacerbations in chronic obstructive pulmonary disease is common and frequent in nature. The present study was done to evaluate the clinical efficacy of nebulised budesonide over parenteral/oral steroids in patients with acute exacerbations of COPD.

MATERIALS AND METHODS

A randomised controlled study was conducted in a tertiary care teaching hospital. A total of 125 patients with acute exacerbations due to COPD were included in the study. The patients were randomised into study and control groups. The study group patients received inhaled budesonide along with the standard treatment for 5 days, while the control group received standard treatment for acute exacerbation of COPD. The primary outcome variables studied for the treatment efficacy were change in post bronchodilator FEV₁, FVC, FEV₁/FVC, PEFR. Secondary end points included the changes in dyspnoea score (MMRC grade, SPO₂ and SGRQ score).

RESULTS

A total of 125 patients were finally assessed. Sixty five patients belonged to study group and 60 in the control group. Baseline characteristics were similar and well matched in both the groups. Mean age was 64.20 ± 9.11 years while in control group it was 62.40 ± 11.31 years. There were no improvements in the lung functions (FEV₁, FVC, FEV₁/FVC, PEFR) at the end of 5 days of nebulised budesonide as compared to the standard therapy. As far as secondary outcome is concerned, it was observed that patients in study group showed better improvement in health related quality of life (HRQL) score as compared to control group at day 5 (p<0.01). Duration of hospitalisation also was lesser in the study group as compared to the control group. No serious adverse effects were observed during the course of the study.

CONCLUSION

Overall with the nebulised budesonide for the AECOPD, there was not much improvement in the lung functions, but there was improvement in the quality of life and the duration of hospitalisation in the study group. These findings should be confirmed by conducting a larger population based clinical study.

KEYWORDS

COPD, Acute Exacerbations, AECOPD, Nebulised Budesonide, Lung Functions, FEV₁, PEFR.

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BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. COPD is the 4th leading cause of death in the United States of America (USA) and Europe.¹ Currently, COPD is a costlier disease to treat than asthma and depending on country, 50% – 75% of the costs are for services associated with exacerbation. Tobacco smoke is by far the most important risk factor for COPD worldwide. An exacerbation is defined as an event in the natural course of the disease characterised by change in the patients

baseline dyspnoea, cough and/or, sputum that is beyond normal day-to-day variation, is acute in onset and may warrant a change in regular medication in a patient with COPD.² Systemic corticosteroids are used to treat acute exacerbation of COPD. This common clinical practice has been endorsed by various international guidelines. Compared with placebo, systemic corticosteroids accelerate the recovery of expiratory flow rates and reduce the length of hospital stays in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) receiving standard medical treatment with bronchodilators, antibiotics and oxygen. Despite proof of efficacy, some concerns remain about using systemic corticosteroids to treat all patients with AECOPD. This is mainly because the short-term advantages of corticosteroids may be outweighed by the occurrence of adverse effects such as hyperglycaemia, myopathy and osteoporosis.³ It has recently been reported that suppression of the adrenal response is common after short term, high dose corticosteroid treatment.⁴

In this context, the possibility of treating patients with AECOPD with inhaled corticosteroids, having less systemic adverse effects is of particular interest. Inhaled corticosteroids have a high level of topical anti-inflammatory

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activity and a low level of systemic activity.⁵ Preliminary data have demonstrated that nebulised budesonide to be as efficacious as parenteral corticosteroids in the treatment of acute severe asthma.⁶ Nebulised budesonide may also be sufficiently efficacious in the management of acute exacerbation of COPD, but only limited number of studies are available which have demonstrated that it might be an alternative agent in AECOPD, instead of the parenteral steroids. Hence, the present study was undertaken to know the clinical efficacy of nebulised budesonide with parenteral/oral steroids in patients with AECOPD.

MATERIALS AND METHODS

The present study was conducted in the Department of Pulmonary Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on adult patients diagnosed to have AECOPD. A total of 130 patients diagnosed to have AECOPD in one-year period were included in the study- 65 patients each in the control and study group.

Inclusion Criteria

Patients with AECOPD

An exacerbation is defined as an event in the natural course of the disease characterised by change in the patients baseline dyspnoea, cough and/or, sputum that is beyond normal day-to-day variation, is acute in onset and may warrant a change in regular medication in a patient with COPD.

Exclusion Criteria

Patients with asthma, allergic rhinitis and atopy, specific cause for exacerbation such as pneumonia, pneumothorax, heart failure, etc., and patients with a risk of imminent respiratory failure requiring mechanical ventilator or direct admission to the ICU

Procedure

The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum. Patients fulfilling the inclusion criteria were included in the study. The selected patients were briefed about the nature of study and written informed consent was obtained. This was a hospital-based randomised study in patients with AECOPD done over a period of one year. These patients were grouped into two groups randomly consisting of 65 patients each in the control and study group. Randomisation was done by the lottery method for all the consecutive patients. The data like demography, history were recorded on predesigned and pretested proforma.

Group 1 (control group) received parenteral/oral steroids (IV hydrocortisone 200 mg t.d.s./40 mg of oral prednisolone) along with standard treatment that is; Salbutamol (2.5 mg) + Ipratropium bromide (500 µg) nebulisation every sixth hourly, supplemental oxygen inhalation, parenteral antibiotics, parenteral Deriphyllin and supportive therapy.

Group 2 (Study group) received budesonide nebulisation (2 mg diluted in 4 mL of normal saline every sixth hourly) along with standard treatment.

The patients were assessed for following parameters at different intervals: (i) Spirometry was carried out at baseline, 24 hours, 72 hours and on fifth day according to ATS standards³; (ii) Dyspnoea was assessed according to the

Modified Medical Research Council (MMRC) Grade; (iii) PEFR and SPO₂ were assessed at baseline, 24 hours, 72 hours and on fifth day; (iv) St. George Respiratory Questionnaire (SGRQ) was assessed at baseline, 24 hours and on fifth day.

Outcome Variables

The primary outcome variables studied for the treatment efficacy were change in post bronchodilator FEV₁, FVC, FEV₁/FVC, PEFR. Secondary end points included the changes in dyspnoea score (MMRC grade, SPO₂ and SGRQ score).

An adverse event is defined as any event reported by the patients from study entry to day 10 or discharge. Serious adverse events included life-threatening events and events resulting in prolongation of hospitalisation. Study discontinuation due to adverse events, including COPD deterioration or relapse was also monitored.

Deterioration of AECOPD while patients under study were defined as the need for treatment intensification according to the treating doctor, the development of confusion, lethargy, acute respiratory acidosis or need for mechanical ventilatory assistance.

Safety of study medication was assessed by monitoring occurrence of any adverse events during the acute and the followup phase of the study. Complete blood cell count including eosinophils obtained at admission.

Monitoring of Patients

Immediate (From Admission to 72 Hours of Hospitalisation)

Spirometry (FEV₁, FVC, FEV₁/FVC) at baseline, 24 hours, 48 hours and 72 hours; PEFR and SPO₂ at baseline, 24 hours, 48 hours and 72 hours; Dyspnoea (MMRC grade) was assessed at baseline, 24 hours, 48 hours and 72 hours; and SGRQ score at baseline and 24 hours.

After 72 Hours till Fifth Day and Discharge

Spirometry, PEFR, Dyspnoea grade and SGRQ score was monitored. The initial treatment was not changed for 10 days if the hospitalisation period exceeded 10 days. Both forms of corticosteroid preparations were tapered or discontinued according to the need. After discharge, all patients were advised combined form of inhaled salbutamol with ipratropium (transcaps q.i.d.), long acting β₂ agonist with inhaled corticosteroids, and methylprednisolone 16 mg twice daily for seven days orally.

In this study, the criteria to assess relapse of exacerbation of COPD was the number of unscheduled visits to any medical units due to increased symptoms of COPD requiring hospitalisation within one month after discharge.

Statistical Analysis

For the various parameters mean and standard deviation (S.D.) were calculated. From baseline to three different time points comparison was made using student's paired 't' test. The comparison of the parameters in the study group and the control was done using student's unpaired 't' test. Chi-square test was used for comparing other characters between two groups. Fisher's Exact test was used to find out the level of significance between the intervals in the groups. A 'p' value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 130 patients were included in this study in 1:1 ratio. Five patients were excluded from the final analysis as they deteriorated during the study period and required intensification of the treatment. Thus, finally 125 patients were analysed- 63 patients in study group and 62 patients in control group. The mean age of the patients in study group was 64.20 ± 9.11 years while in control group it was 62.40 ± 11.31 years. The duration of disease in the control group was 6.60 ± 4.80 years while it was 6.90 ± 3.30 in the study group (Table 1). Overall male to female ratio was 3:1. In this study, majority of the patients belonged to age group of 51 to 60 years and 61 to 70 years.

The baseline FEV₁ was 0.45 ± 0.11 L/Sec in the study group and it was 0.51 ± 0.14 L/Sec in the control group (Table 2). The mean improvement in FEV₁ after 24 hours, 72 hours and at 5th day was 0.53 ± 0.15 L/Sec, 0.64 ± 0.18 L/Sec and 0.82 ± 0.19 L/Sec in study group, while it was 0.55 ± 0.15 L/Sec, 0.69 ± 0.15 L/Sec and 0.80 ± 0.16 L/Sec in control group respectively. It was observed that there was no statistical significance observed in FEV₁ improvement between the two groups at different intervals of the study period (Table 3). Baseline FVC observed in the study and the control group was 0.88 ± 0.19 L/Sec and 0.99 ± 0.30 L/Sec respectively. Applying ANOVA method, it was also observed that there was no statistical significance observed in FVC improvement between the two groups (Table 4). Similarly, there was no difference in FEV₁/FVC percent ratio between the study group and the control group at different time intervals after the use of the medications.

As far as PEFR is concerned, the baseline PEFR in both study and control groups were 141 ± 69.46 L/M and 139 ± 91.15 L/M respectively. When compared at different intervals, there was no statistically significant difference in PEFR values between the study group and the control group. The baseline oxygen saturation in both control and study group were $97\% \pm 1.65\%$ and $97\% \pm 1.67\%$ respectively. However, when compared at different intervals that is 24 hours, 72 hours and at fifth day, there was no statistical significant difference between the study group and the control group ($p > 0.05$).

Overall MMRC dyspnoea grade was 4 in both study and control groups at baseline. There was improvement in dyspnoea scale by one point in both the study group and the control group after 5 days of therapy (Table 5). Baseline SGRQ scores observed in study and control group were 88.76 ± 5.32 and 86.43 ± 4.75 respectively. SGRQ score improvement after 24 hours and at 5th day in study group was 82.55 ± 5.35 and 68.95 ± 6.75 while it was 82.36 ± 4.81 and 70.80 ± 7.09 in control group respectively. Patients in study group showed better improvement in health related quality of life (HRQL) score as compared to control group at day 5 ($p < 0.01$). In control group, HRQL score improved among 83.3% patients and remained same in 13.3% patients. In study group, 89.3% patients had improved HRQL score and while the score remained same among 10.7% patients (Table 6).

A total of 58 patients (89.2%) had total hospitalisation of less than 10 days in the study group. Twelve patients (20%) had more than 12 days of hospitalisation in the control group,

while it was 10.8% in the study group. Thus, it was observed more number of patients were discharged early in the study group as compared to control group (Table 7). A total of five patients (8.3%) in the control group were readmitted with relapse of AECOPD within 30 days of discharge from hospital. In the study group, two patients (3.0%) were readmitted for the relapse of exacerbation during the study period.

Demographic Characteristics	Control Group (n=65)	Study Group (n=65)	p value Mean
	Mean $\pm$ SD	Mean $\pm$ SD	
Age (Years)	62.40 $\pm$ 11.31	64.20 $\pm$ 9.11	0.315
Duration (Years)	6.60 $\pm$ 4.80	6.90 $\pm$ 3.30	0.765
Pack years	10.40 $\pm$ 4.80	8.60 $\pm$ 4.50	0.019
Hb% (g%)	11.50 $\pm$ 1.55	12.03 $\pm$ 1.24	0.091
TLC (/mm ³)	13624.00 $\pm$ 1189.00	10589.00 $\pm$ 5513.00	0.062
B Urea (mg/dL)	47.00 $\pm$ 19.40	45.00 $\pm$ 19.15	0.700
Sr. Creatinine (mg/dL)	0.89 $\pm$ 0.31	0.83 $\pm$ 0.41	0.319

Table 1. Baseline Characteristics of the Patients

Variables		Control Group (n=62) Mean $\pm$ S.D.	Study Group (n=63) Mean $\pm$ S.D.
FEV ₁ (L/sec)	Baseline	0.51 $\pm$ 0.14	0.45 $\pm$ 0.11
	24 hours	0.55 $\pm$ 0.15	0.53 $\pm$ 0.15
	72 hours	0.69 $\pm$ 0.15	0.64 $\pm$ 0.17
	5 th day	0.80 $\pm$ 0.16	0.82 $\pm$ 0.19
FVC (L/sec)	Baseline	0.99 $\pm$ 0.33	0.88 $\pm$ 0.14
	24 hours	1.06 $\pm$ 0.31	0.99 $\pm$ 0.18
	72 hours	1.24 $\pm$ 0.33	1.13 $\pm$ 0.22
	5 th day	1.45 $\pm$ 0.37	1.36 $\pm$ 0.26
FEV ₁ /FVC%	Baseline	51.79 $\pm$ 12.38	50.66 $\pm$ 7.66
	24 hours	52.46 $\pm$ 12.96	53.05 $\pm$ 7.40
	72 hours	56.29 $\pm$ 11.33	55.76 $\pm$ 9.97
	5 th day	61.25 $\pm$ 10.27	59.21 $\pm$ 9.56
PEFR (L/min.)	Baseline	139.00 $\pm$ 91.15	141.00 $\pm$ 69.46
	24 hours	166.00 $\pm$ 98.99	159.00 $\pm$ 73.24
	72 hours	201.00 $\pm$ 93.44	187.00 $\pm$ 79.90
	5 th day	254.00 $\pm$ 87.72	226.00 $\pm$ 80.84
SpO ₂ (%)	Baseline	97.00 $\pm$ 1.76	97.00 $\pm$ 1.67
	24 hours	97.00 $\pm$ 1.52	97.00 $\pm$ 1.47
	72 hours	97.00 $\pm$ 1.48	98.00 $\pm$ 1.03
	5 th day	98.00 $\pm$ 1.05	98.00 $\pm$ 1.14
MMRC Grade	Baseline	4.00 $\pm$ 1.00	4.00 $\pm$ 1.00
	24 hours	4.00 $\pm$ 1.00	4.00 $\pm$ 1.00
	72 hours	4.00 $\pm$ 1.00	3.00 $\pm$ 1.00
	5 th day	3.00 $\pm$ 1.00	3.00 $\pm$ 1.00
SGRQ Score	Baseline	86.43 $\pm$ 4.75	88.76 $\pm$ 5.35
	24 hours	82.36 $\pm$ 4.81	82.55 $\pm$ 5.35
	5 th day	70.80 $\pm$ 7.09	68.95 $\pm$ 6.75

Table 2. Characteristics of the Patients During Hospitalisation

Interval	Control Group		Study Group		F value	p value
	% Predicted Mean $\pm$ S.D.	Actual Mean $\pm$ S.D.	% Predicted Mean $\pm$ S.D.	Actual Mean $\pm$ S.D.		
Baseline	27.48 $\pm$ 10.51	0.51 $\pm$ 0.14	50.57 $\pm$ 7.98	0.45 $\pm$ 0.11	1.11	0.253
24 Hours	29.86 $\pm$ 11.26	0.55 $\pm$ 0.15	30.22 $\pm$ 9.88	0.53 $\pm$ 0.15	1.21	0.942
72 Hours	37.24 $\pm$ 12.26	0.69 $\pm$ 0.15	36.63 $\pm$ 11.82	0.64 $\pm$ 0.17	1.08	0.749
5 th Day	47.19 $\pm$ 13.92	0.80 $\pm$ 0.16	46.63 $\pm$ 14.40	0.82 $\pm$ 0.19	1.00	0.798

Table 3. Comparison of Forced Expiratory Volume in One Second (FEV₁) at Different Intervals

Interval	Control Group		Study Group		F value	p value
	% Predicted Mean $\pm$ S.D.	Actual Mean $\pm$ S.D.	% Predicted Mean $\pm$ S.D.	Actual Mean $\pm$ S.D.		
Baseline	40.00 $\pm$ 13.82	0.99 $\pm$ 0.33	37.79 $\pm$ 8.56	0.88 $\pm$ 0.14	1.33	0.150
24 Hours	42.94 $\pm$ 14.43	1.06 $\pm$ 0.31	42.67 $\pm$ 10.37	0.99 $\pm$ 0.18	1.06	0.650
72 Hours	50.35 $\pm$ 16.17	1.24 $\pm$ 0.33	48.35 $\pm$ 12.08	1.13 $\pm$ 0.22	1.23	0.415
5 th Day	58.68 $\pm$ 18.89	1.45 $\pm$ 0.37	58.09 $\pm$ 15.16	1.36 $\pm$ 0.26	2.01	0.803

Table 4. Comparison of Forced Vital Capacity (FVC) at Different Intervals

Intervals	Control Group (n=62)	Study Group (n = 63)
	Mean $\pm$ SD	Mean $\pm$ SD
Baseline	4 $\pm$ 0	4 $\pm$ 0
24 Hours	4 $\pm$ 0	4 $\pm$ 0
72 Hours	4 $\pm$ 0	3 $\pm$ 0
5 th Day	3 $\pm$ 0	3 $\pm$ 0

Table 5. Comparison of MMRC Grading at Different Intervals

Intervals	Control Group (n = 62)		Study Group (n = 63)		p value
	Mean ± S.D.		Mean ± S.D.		
Baseline	86.43 ± 4.75		88.76 ± 5.32		0.377
24 hours	82.36 ± 4.81		82.55 ± 5.35		0.164
5 th day	70.80 ± 7.09		68.95 ± 6.75		0.013
Improvement in SGRQ score (Number of patients and percentage)					
Improved	50	83.34%	58	89.30%	
Same	08	13.33%	07	10.70%	
Worsen	02	3.33%	-	-	
Table 6. St. George Respiratory Questionnaire (SGRQ) Score					

Duration	Control Group (n=62)		Study Group (n=63)	
	No.	Percentage	No.	Percentage
5 days	13	21.7%	25	38.4%
6 to 10 days	35	58.3%	33	50.8%
> 10 days	12	20.0%	07	10.8%
Total	60	100%	65	100%

Table 7. Duration of Hospitalisation (Days)

DISCUSSION

A total of 125 patients were included into the study. Sixty-three patients were in the study group and another sixty-two patients were in control group. In the study by Morice et al,⁷ the mean baseline FEV₁ was similar in both groups (1.8 L/sec and 1.9 L/sec for prednisolone and budesonide, respectively). There was no significant difference in response to treatments. In the present study, baseline FEV₁ was 0.45 $\pm$ 0.11 L/Sec in study group and 0.51 $\pm$ 0.14 L/Sec in control group. In the study group, mean improvement in FEV₁ after 24 hours, 72 hours and at 5th day were 0.53 $\pm$ 0.15 L/Sec, 0.64 $\pm$ 0.18 L/Sec and 0.82 $\pm$ 0.19 L/Sec respectively while in the control group the mean improvement in FEV₁ was 0.55 $\pm$ 0.15 L/Sec, 0.69 $\pm$ 0.15 L/Sec and 0.80 $\pm$ 0.16 L/Sec respectively. It was observed that there was no statistical significance observed in FEV₁ improvement between the two groups. Similar results were observed by Matais et al,⁸ Gunen et al⁹ and Wei et al.¹⁰ In a study by Gunen et al⁹ when comparison was made between groups treated with placebo, systemic steroids and nebulised budesonide, the baseline FVC was 64.5 $\pm$ 21.5 L/Sec, 57.5 $\pm$ 17.5 L/Sec and 64.3 $\pm$ 20.4 L/Sec in group 1, group 2 and group 3 respectively. Improvement observed in FVC at 24 hours, 72 hours, 7 days and at 10th day was significantly higher in group 2 and group 3 when compared to group 1. There was no statistical significance as comparison was made between group 2 and group 3. In the present study, the baseline FVC observed in study and control group was 0.88 $\pm$ 0.19 L/Sec and 0.99 $\pm$ 0.30 L/Sec respectively. FVC improvement observed after 24 hours, 72 hours and at 5th day in study group was 0.99 $\pm$ 0.18 L/Sec, 1.13 $\pm$ 0.22 L/Sec and 1.36 $\pm$ 0.26 L/Sec respectively. FVC improvement in control group was 1.06 $\pm$ 0.31, 1.24 $\pm$ 0.33 & 1.45 $\pm$ 0.37 L/Sec respectively. The results of the present study were similar to those observed by Gunnen et al⁹ and Morris et al.⁷ In a study by Mirici et al,¹¹ the improvement in PEFR at different intervals in both parenteral steroid and nebulised budesonide group were similar and it was observed that there was no statistical difference between two groups. In the present study, baseline PEFR in both study and control groups were 141 $\pm$ 69.46 L/M and 139 $\pm$ 91.15 L/M respectively. Similarly, no statistical difference was observed among the two groups.

In the present study, the MMRC grades of dyspnoea at baseline, 24 hours, 72 hours and at 5th day were 4, 4, 3, and 3 in study group; while it was 4, 4, 4 and 3 in control group respectively. Compared to control group there were early improvements in severity of dyspnoea in study group. But statistically this was negligible. Similar improvement in the dyspnoea index has been observed by Morrice et al⁷ and Wei et al.⁹ Maltais et al¹² observed reduction in Borg Dyspnoea Scale between the nebulised budesonide group and the control group. In the present study, the baseline SGRQ score observed in study and control group were 88.76 $\pm$ 5.32 and 86.43 $\pm$ 4.75 respectively. SGRQ score improvement after 24 hours and at 5th day in study group was 82.55 $\pm$ 5.35 and 68.95 $\pm$ 6.75 while it was 82.36 $\pm$ 4.81 and 70.80 $\pm$ 7.09 in control group. Patients in study group showed better improvement in HQRL score as compared to control group. Mirici et al¹¹ also observed similar improvement in SGRQ score after nebulised budesonide in AECOPD patients.

In the study by Gunen et al,⁸ proportions of the patients with early (relatively) and delayed discharges did not yield any statistically significant results, between the control and study groups. In the present study, mean duration of hospitalisation was 7 ± 2.9 days in study group while in control group it was 7.25 ± 2.8 days. More number of patients discharged early in study group as compared to control group. The overall reduction in duration of hospitalisation was similar as those observed by Maltais et al¹² and Guozhong et al.¹⁰ In the present study, deterioration of AECOPD while patients under study was defined as the need for treatment intensification according to the treating doctor, the development of confusion, lethargy, acute respiratory acidosis or necessity for mechanical ventilator assistance. One patient each in the study and control group deteriorated and they required mechanical ventilation. Maltais et al¹² and Wei et al⁹ observed that budesonide group had less systemic side effects than the groups treated with systemic steroids. In the present study, the side effect profile of nebulised budesonide was excellent. No patient had any side effect due to nebulised budesonide including oral candidiasis. Thus, there was no discontinuation of the patients in the study group due to side effects. Marcus et al¹³ also observed that inhaled budesonide was well tolerated in AECOPD.

Gunen et al⁸ showed exacerbation rates within one month of discharge were 14, eight and nine in placebo, parenteral and nebulised budesonide groups respectively. In the present study, it was observed that two patients in study group and 5 patients in control group had relapse of AECOPD. Marcus et al¹³ showed there was 70% reduction in relapse of AECOPD over a period of one year.

CONCLUSION

In conclusion, with the nebulised budesonide for the AECOPD, there was not much improvement in the lung functions, but there was improvement in the quality of life and the duration of hospitalisation in the study group.

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