

Effect of systemic corticosteroids on serum apoptotic markers and quality of life in patients with asthma

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ABSTRACT

Despite corticosteroids being the first line drug treatment for asthma symptom control, the mechanisms of action of corticosteroids in asthma are still poorly understood. The current study aimed to evaluate the effect of systemic corticosteroids on serum level of apoptotic markers Survivin (for inflammatory cells) and M30 apoptosis (for bronchial epithelial cells) in patients of acute exacerbation of bronchial asthma. The study involved 60 patients with acute exacerbation of bronchial asthma who were prescribed systemic corticosteroids. Patients were evaluated for their serum levels of apoptotic markers (Survivin and M30 apoptosis) and their quality of life (QOL), before and after treatment with oral prednisolone. Paired t-test was used to compare the change in the serum values. The mean baseline serum Survivin and M30 apoptosis levels were 224.10 ± 42.76 and 123.00 ± 18.79 U/L, respectively, which decreased significantly ($p < 0.05$) to 111.20 ± 32.26 and 29.67 ± 7.53 U/L after seven days of oral prednisolone treatment. Systemic corticosteroids also significantly improved QOL scores and peak expiratory flow rate % (PEFR%) in the asthma patients. This improvement was seen irrespective of the initial severity score. Results from the study suggest that systemic corticosteroids administration decreases the survival of inflammatory cells and increases that of bronchial epithelial cells in patients with acute exacerbation of bronchial asthma.

The study has been registered with Clinical Trials Registry-India. Registry database number CTRI/2014/08/00483.

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Bronchial asthma is a major illness with profound morbidity and mortality outcomes. An estimated 300 million people worldwide suffer from asthma (which is maximum among all respiratory diseases), with 250,000 annual deaths attributed to the disease.¹

Although corticosteroids are among the first-line drug treatments for asthma symptom control, the mechanisms of action of corticosteroids in asthma are still poorly understood. However, their efficacy is most likely related to their antiinflammatory properties. Corticosteroids have widespread effects on gene transcription, increasing the transcription of several antiinflammatory genes, and suppressing transcription of many inflammatory genes.²

Recently, some studies have suggested possible role of apoptosis in asthma pathophysiology and severity. According to these, cellular pathophysiology of asthma is influenced by increasing apoptosis of airway epithelium and decreased apoptosis of inflammatory cells especially eosinophils. In the absence of any inflammatory survival-prolonging factors, eosinophils die by apoptosis in few days, but in inflamed airways,

eosinophil survival is thought to be prolonged due to the surrounding proinflammatory factors, such as interleukin-5, interleukin-3, and granulocyte monocyte-colony stimulating factor. Eosinophils release factors that damage the lung parenchyma and participate in the maintenance and exacerbation of inflammation. Resolution of eosinophilic inflammation is an important goal in the treatment of allergic asthma.^{3,4}

Many studies in the existing literature have already suggested role and mechanism of corticosteroids in induction of apoptosis of eosinophils and inhibition of lung epithelial cell apoptosis.^{5–7} Also, there is evidence supporting correlation of increased inflammatory cells survival with increasing asthma severity.⁸

In the last few years, it has been recognized that the unbalanced regulation of survival and apoptosis of bronchial inflammatory cells is a key component in the development of asthma.⁹

Baculoviral inhibitor of apoptosis (IAP) repeat containing 5 (also known as Survivin) is an important antiapoptotic protein that has been implicated in many cancer types, and recent studies provide evidence for its role in controlling inflammatory disorders, including bronchial asthma as well. It was found that induced sputum samples of patients with bronchial asthma contained elevated levels of baculoviral IAP repeat containing 5 mRNA compared with healthy subjects and its level was in correlation with sputum eosinophil percentages.¹⁰

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Likewise, M30 apoptosense is a unique tool for quantitative detection of apoptosis of keratin 18-positive cells. This cytokeratin 18 has been particularly identified as a bronchial epithelial antigen associated with nonallergic asthma.¹¹

This study aims to evaluate the effect of systemic corticosteroids on serum level of apoptotic markers, Survivin and M30 apoptosense, in patients of bronchial asthma and to correlate it with existing parameters of disease and symptom severity indicators like peak expiratory flow rate % (PEFR%) and quality-of-life (QOL) scores.

MATERIALS AND METHODS

Patients

Consecutive diagnosed patients of bronchial asthma, aged 18–55 years, presenting with exacerbations (as defined by breathlessness on slight walking/talking/at rest, ability to talk in only words/phrases/incomplete sentences without breathlessness, respiratory rate more than 20 per minute, presence of wheezing on chest auscultation) and undergoing treatment for the same, either on outpatient basis or admitted to a medicine unit of Smt. Sucheta Kriplani Hospital, New Delhi, India, between November 2012 and March 2014, were included in the study after taking informed written consent. As confirmed by the history, all the patients included in the study had allergic asthma. However, patients were not assessed (by serum sampling or pathological specimens) to classify them as having underlying eosinophilic inflammation. The patients with any other coexistent and active pulmonary or nonpulmonary pathology, on drug treatment for any other concomitant disease or disorder, with imminent respiratory arrest (as indicated by drowsy/confused state, paradoxical thoraco-abdominal movements with respiration, absent wheeze, bradycardia, *i.e.*, pulse less than 60 per minute), evidence of active infection on chest x ray, those who received systemic corticosteroid treatment in last four weeks and those who were contraindicated to receive systemic corticosteroids, were excluded from the study. Patients' profile, demography, and medical history were recorded. Asthma severity score at baseline was calculated for each patient using severity of asthma (SOA) scores.¹² This study has been approved by the Ethics Committee for Human Research-Lady Hardinge Medical College & Assoc. Hospitals.

Blood samples (approximately 5 mL) from patients ($n = 60$) were obtained to determine serum level of Survivin and M 30 apoptosense, before starting the corticosteroid treatment and at the time of its tapering/stopping. In partial responders after seven days of treatment, an additional third sampling was done at the time of discontinuation of corticosteroids after 21

days. The samples were centrifuged at 5000 rpm for 10 minutes and serum separated within one hour. Serum samples were stored at -20°C , until the estimation of markers, Survivin and M30 apoptosense, using commercial enzyme linked immunosorbent assay kits (BMASAY). Samples were thawed at room temperature for 30 minutes before the estimation of markers. The assay was performed at 450-nm wavelength under standard conditions. The optical density values of the standard solutions were plotted, and serum concentrations were determined using Prism (GraphPad Software, La Jolla, CA). At the time of serum sampling, patients were also evaluated for their QOL by QOLtech-AQLQ form¹³ and PEFR% using peak flow meter (Cipla, Mumbai, India), which was a standardized, portable, and easy to use device. In some of the previous studies,^{14,15} PEFR% has been shown as a reasonable alternative in terms of accuracy in diagnosing and evaluating clinical improvement after antiasthma treatment. Measured PEFR was compared with expected PEFR that was calculated using the formula:¹⁶ adult men, $\{[(\text{height} \times 5.48) + 1.58] - (\text{age} \times 0.041)\} \times 60$ and adult women, $\{[(\text{height} \times 3.72) + 2.24] - (\text{age} \times 0.03)\} \times 60$, as per the age, sex, and height of the patient. This PEFR% was used for diagnosis as well as evaluation of clinical improvement of the patients.

Treatment based upon Global Initiative for Asthma guidelines¹⁷ was started for every patient. Oral prednisolone was administered in doses of 1 mg/kg as single morning dose. Criteria for discontinuation of corticosteroids after seven days of treatment were more than 75% subjective improvement in symptoms, auscultatory findings of bilaterally clear chest with no/minimal wheeze, and PEFR more than or equal to 80% of predicted value (all three required). In partial responders, corticosteroid dose was tapered after seven days, which was continued up to 21 days. Criteria for tapering were an initial diagnosis of severe exacerbation of asthma, an audible wheeze on chest auscultation after seven days, less than 75% subjective improvement in symptoms after seven days, and PEFR less than 80% of predicted value after seven days (any one). All the patients right from the enrollment were also prescribed an inhalational bronchodilator SOS. This was either salbutamol (100–200 μg), terbutaline (250 μg), or a fixed dose combination of salbutamol + ipratropium bromide (100 + 20 μg). Patients who received any antibiotics during the study were excluded from the study analysis.

Statistical Analysis

The serum concentration of apoptotic markers are expressed as mean $\pm$ standard error of mean and compared using Student's *t*-test (paired). PEFR% and QOL are compared using χ^2 test. Correlation between

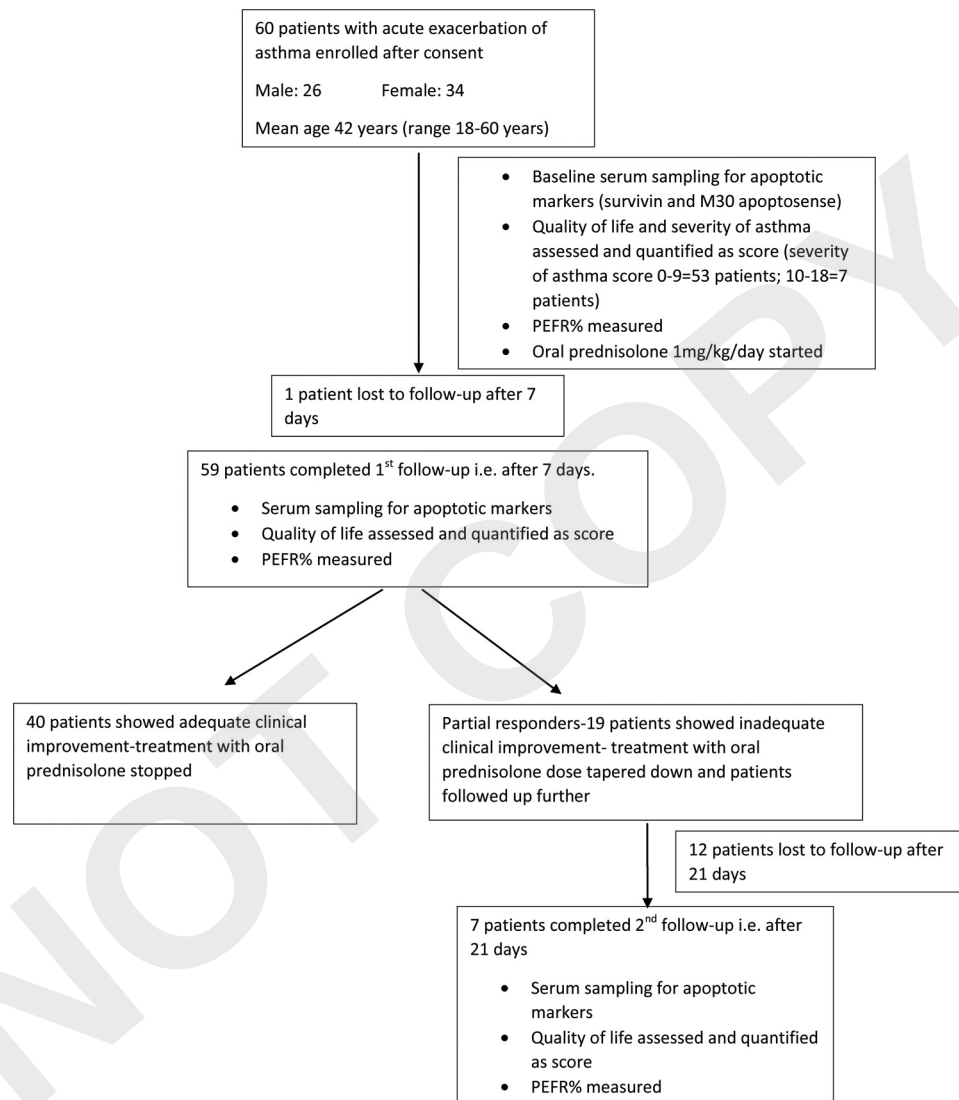


Figure 1. Flow diagram showing patient recruitment, demographics & study methodology.

each of the apoptotic marker level and scores of asthma severity and QOL done by Karl Pearson coefficient of correlation (r value). $p < 0.05$ was considered statistically significant.

RESULTS

A total of 60 patients with acute exacerbation of bronchial asthma were enrolled in the study. At baseline, majority of patients [53 (88.3%)] had a SOA score between 0 and 9, whereas only seven (11.7%) patients had a score between 10 and 18.

Out of these, 59 patients reported for the first follow-up after seven days. Of the 59 patients, 19 were considered as partial responders. Only seven out of these 19 patients completed the study for analysis after 21 days (second follow-up).

Patient recruitment, inclusions, exclusions, and demographics are shown in Fig. 1.

Effect of Systemic Corticosteroid Administration on Serum Apoptotic Markers

The mean baseline serum Survivin levels were 224.10 ± 42.76 U/L, which decreased significantly ($p < 0.05$) to 111.20 ± 32.26 after seven days (Fig. 2). The majority of the patients (75%) showed decrease in serum Survivin levels after seven and 21 days of systemic corticosteroid treatment.

Serum M30 apoptosense levels also decreased after systemic corticosteroids administration. The majority of the study patients showed decrease after seven days (83%) as well as after 21 days (75%). The mean M30 apoptosense levels at baseline were 123.00 ± 18.79 U/L, which decreased significantly ($p < 0.01$) to 29.67 ± 7.53 U/L after seven days (Fig. 2).

In the partial responders, mean serum Survivin levels at baseline, seven days, and at 21 days were 82.04 ± 19.65 , 76.60 ± 43.56 , and 23.78 ± 13.75 , respectively. Similarly, in these patients, mean serum M30 apop-

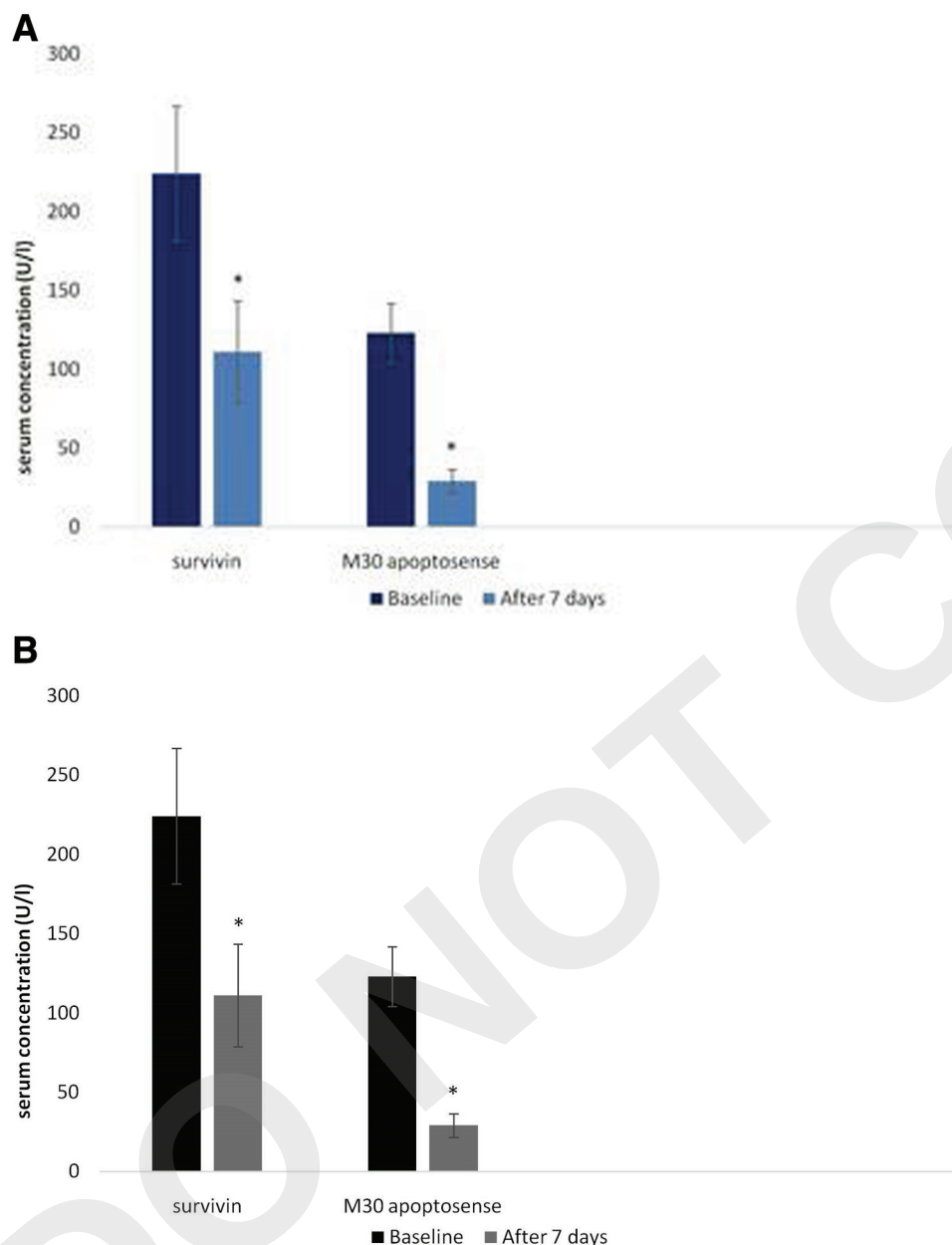


Figure 2. Changes in serum Survivin and M30 apoptosense levels after 7 days of systemic corticosteroid treatment in patients with acute exacerbation of asthma ($n = 59$). Values are expressed as mean $\pm$ SEM. Paired t -test for comparing pre and post corticosteroid treatment values. * $P < 0.05$ significant in comparison to baseline.

tosense level at baseline, seven days, and at 21 days were 140.60 ± 39.99 , 49.41 ± 17.93 , and 5.10 ± 1.37 , respectively (Fig. 3).

Effect of Systemic Corticosteroids Administration on QOL Scores and PEFr%

Systemic corticosteroids significantly improved QOL scores as well as PEFr% in the asthma patients. Because the design of QOL questionnaire was such that QOL scoring was inversely related to actual clinical benefits in terms of disease symptoms and disability, our analysis showed a decrease in QOL score. The improvement in QOL and PEFr% were statistically significant ($p < 0.05$) after seven days of systemic corticosteroids treatment as well as after 21 days (Fig. 4).

This improvement was seen irrespective of initial severity score (Fig. 5).

DISCUSSION

In our study, it was observed that the serum levels of apoptotic markers Survivin and M30 apoptosense decrease progressively after treatment with systemic corticosteroids.

As per the GINA guidelines¹⁷ for the treatment of acute exacerbation of bronchial asthma, systemic corticosteroids were continued for minimum seven days, after which depending upon clinical evaluation they were either stopped or their dose was tapered down over a period of two weeks. Patients enrolled in this study also included patients of asthma with high SOA

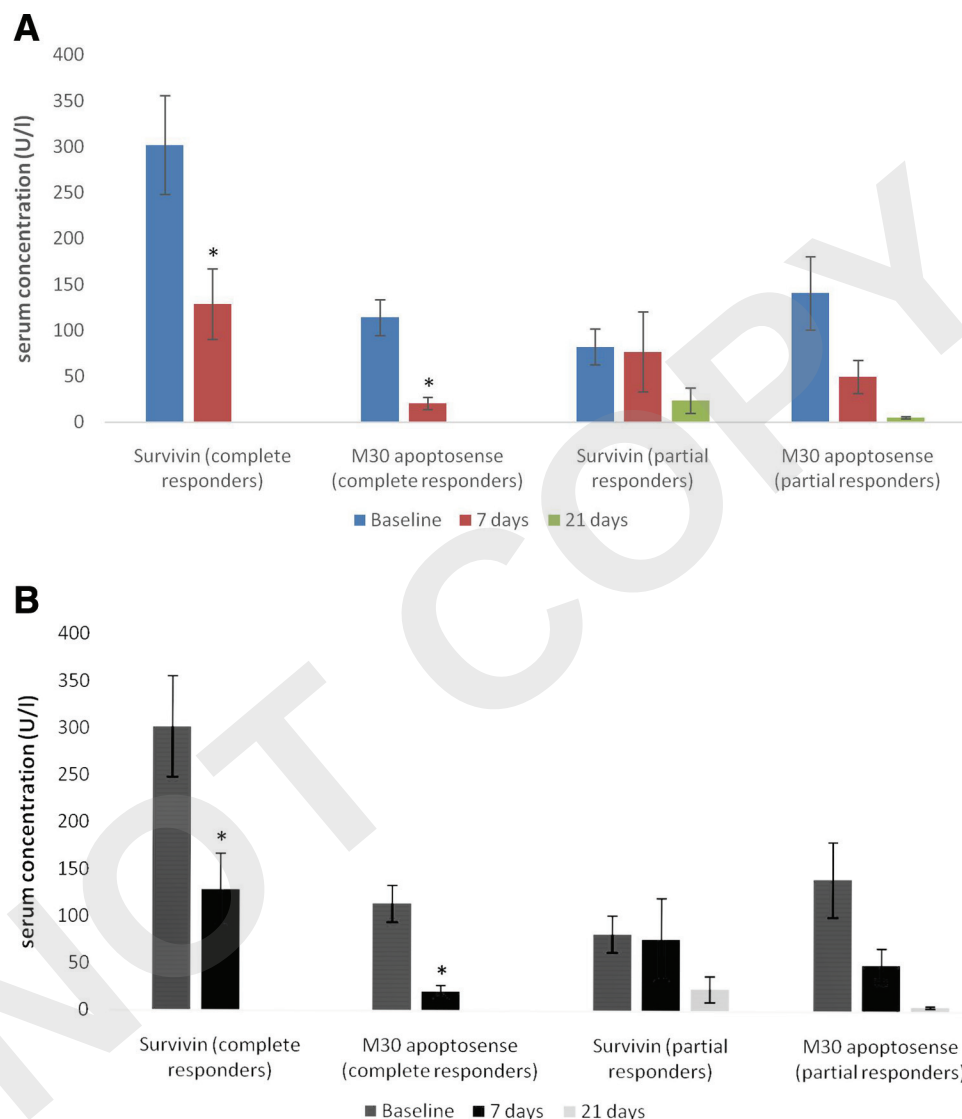


Figure 3. Changes in serum Survivin and M30 apoptosense levels in patients with acute exacerbation of asthma whose symptoms were controlled ($n = 40$) and those who showed partial response ($n = 19$) after 7 days of systemic corticosteroid treatment. Values are expressed as mean $\pm$ SEM. Paired t -test for comparing pre and post corticosteroid treatment values. * $P < 0.05$ significant in comparison to baseline.

score (seven patients had score between 10 and 18 out of 28) at the time of enrollment. It is very likely that these patients and some other patients with naturally inherent resistance to OCS did not respond to it. Also, the 19 patients that were partial responders did show improvement in some of the criterion for clinical evaluation after seven days. In fact, there were no completely nonresponders in this study.

Increased inflammatory cells activity, both in terms of survival as well as functioning, is a well-accepted part of pathology in bronchial asthma. de Souza and Lindsay¹⁸ in their study on asthmatic patients have shown that infiltrating inflammatory cells in bronchial asthma are resistant to cell death. Similarly, because bronchial asthma ultimately affects airways, evidences of altered survival of bronchial epithelial cells have been also seen in some of the recent studies. Zhou *et al.*¹⁹ found that bronchial epithelial apoptosis increases in asthma. Further, Cohen *et al.*²⁰ observed that the

epithelial cell apoptosis increases with asthma severity. In a study on apoptosis of eosinophils in asthmatics, Kankaanranta *et al.*²¹ found that rate of apoptosis of eosinophils in patients taking corticosteroids is more than those not taking corticosteroids. Similarly, Abdulmir *et al.*²² in their study on blood lymphocytes of asthmatic patients concluded that with increasing asthma severity, levels of antiapoptotic factors nuclear factor- κ B, B-cell lymphoma-2 (Bcl-2), and Bcl-2/Bcl-2 associated $\times$ protein (Bcl-2/Bax) increase, whereas those of Bax (proapoptotic) decrease progressively. In the current study, we observed that after systemic corticosteroid administration, there is a reduction in serum M30 apoptosense and serum Survivin levels, the serum markers for bronchial epithelial cells apoptosis and inflammatory cells survival, respectively. This indicates that systemic corticosteroids do increase bronchial epithelial cell survival and decrease that of inflammatory cells in asthma patients. However, it is

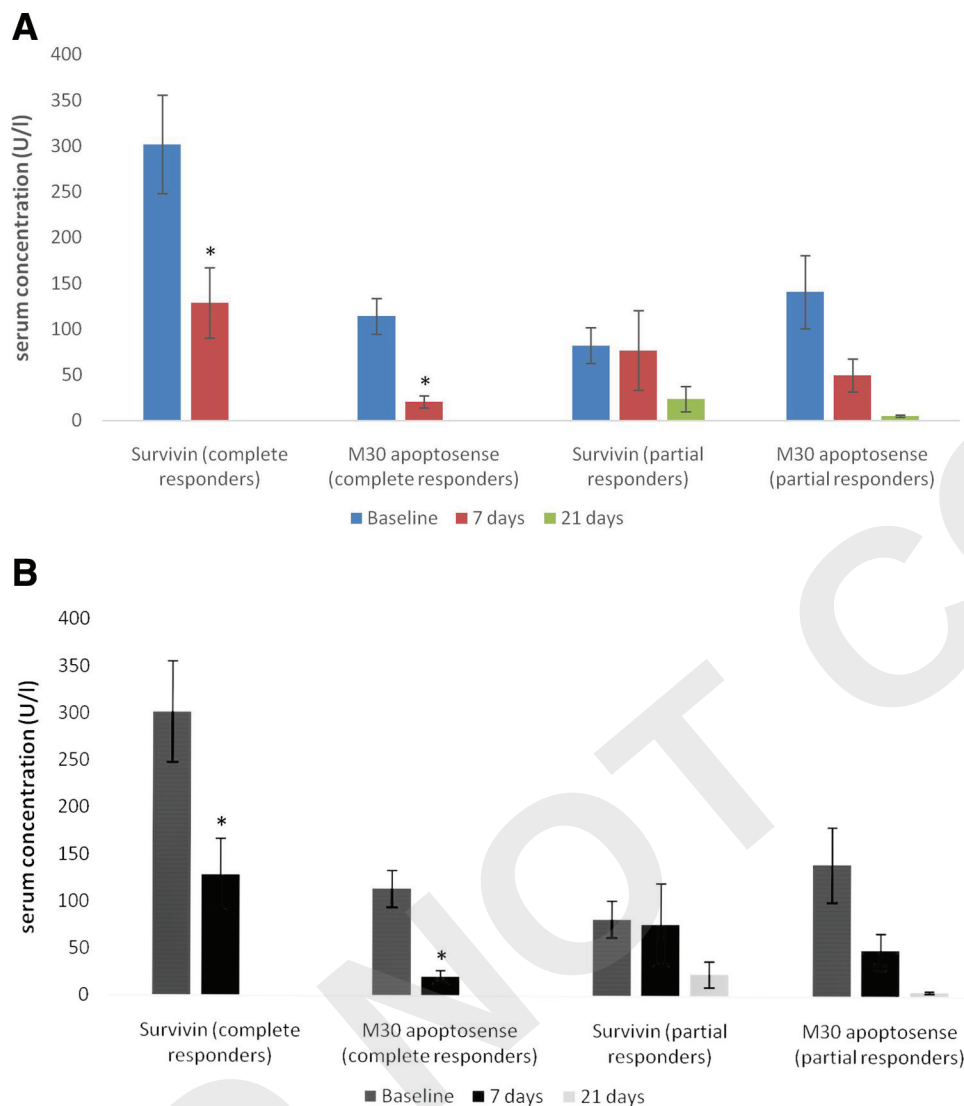


Figure 4. Changes in mean peak expiratory flow rate (PEFR) % & quality of life (QOL) score after 7 days and 21 days of systemic corticosteroid treatment in patients with acute exacerbation of asthma. χ^2 test for comparing pre and post corticosteroid treatment values. * $P < 0.05$ significant in comparison to baseline.

pertinent to mention that our results show baseline Survivin levels are not indicative of asthma severity. Baseline Survivin level in partial responders was much lower than that of whole group. Further, it is possible that the rate of decline of serum Survivin level corresponds with asthma symptom improvement.

Although only seven out of 19 patients completed the second follow-up after 21 days of systemic corticosteroids treatment, an important finding in our study was that the reduction in the mean serum values was statistically significant only until first follow-up (after seven days). However, the mean values of serum Survivin and M30 apoptosense did show decreasing trend even after seven days of systemic corticosteroids administration (with tapered dosing).

Pelaia *et al.*²³ suggested a possible role of MAPK activation as a mechanism of apoptosis regulation of airway epithelium by corticosteroids. On the other hand, Wen *et al.*²⁴ found that dexamethasone, acting *via* up-regulation of cellular inhibitor of apoptosis 2, was a

potent IAP induced by interferon- γ and Fas ligation in A549 lung epithelial cells. Similarly, animal studies also suggest apoptosis induction of eosinophils by dexamethasone in infant asthmatic rats.²⁵

Tumes *et al.*²⁶ observed increased expression of Survivin mRNA (a member of the IAP family) in lung eosinophils in a mouse model of allergic asthma. Ungvári *et al.*¹⁰ had studied Survivin mRNA in induced sputum samples of patients with bronchial asthma, and the level was found to be increased as compared with healthy subjects, and it was in correlation with the sputum eosinophil percentage. In the current study, we have used serum Survivin as a marker for inflammatory cells survival. The decrease in serum Survivin is indicative of the possible mechanism how corticosteroids brings about clinical benefit at cellular level, *i.e.*, by decreasing the survival of inflammatory cells, particularly eosinophils.

Interestingly, M30 apoptosense showed statistically significant reduction between seven and 21 days in

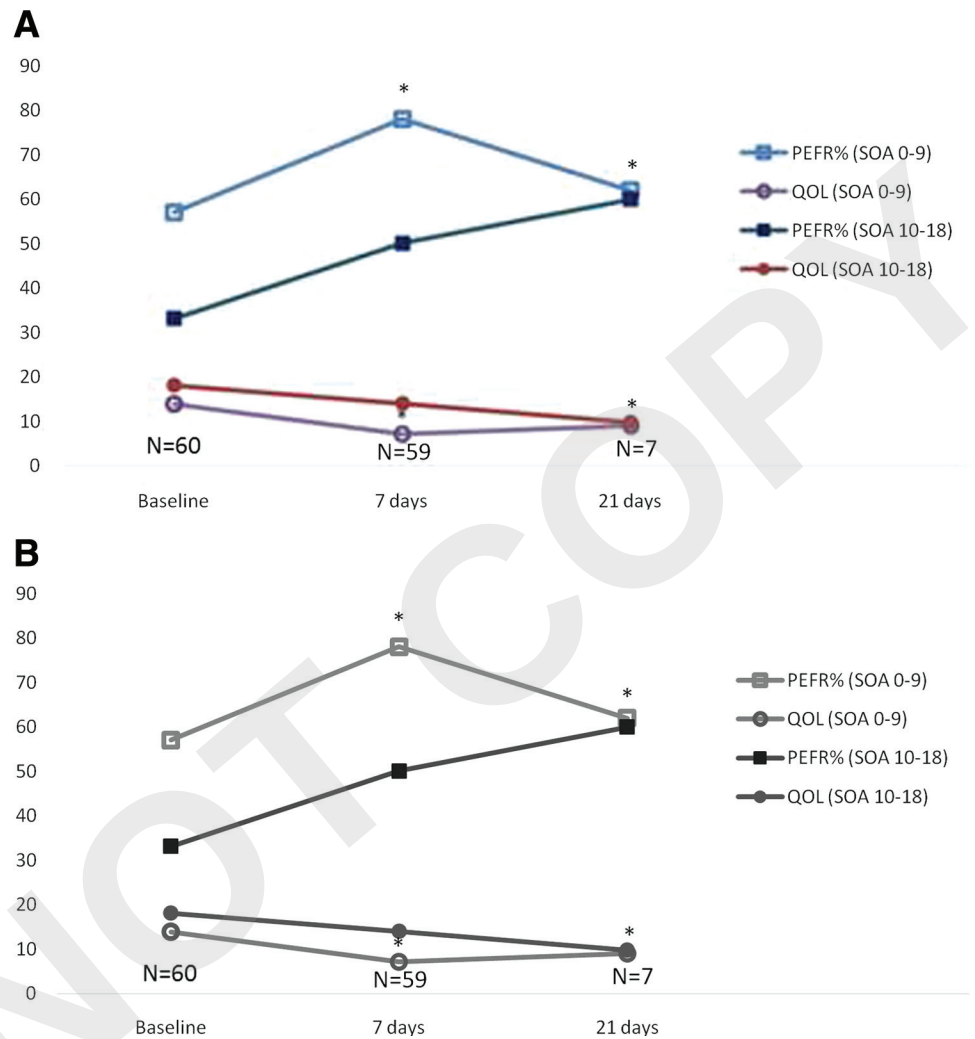


Figure 5. Changes in mean mean peak expiratory flow rate (PEFR) % & quality of life (QOL) score after 7 days and 21 days of systemic corticosteroid treatment in 0–9 and 10–18 severity of asthma (SOA) score sub-groups of acute exacerbation of asthma patients. χ^2 test for comparing pre and post corticosteroid treatment values. * $P < 0.05$ significant in comparison to baseline.

partial responders, indicating a prolonged effect on bronchial epithelial cell survival. Possible reason for this long-term action of systemic corticosteroids on bronchial epithelial cell survival could be that increased inflammatory cells survival and activity is a feature of bronchial asthma exacerbation in the initial stage only, and this feature may not be apparent after the patients have received systemic corticosteroids and the pathology is controlled. In an earlier study, Walsh *et al.*⁵ proposed that corticosteroids increase recognition and engulfment of apoptotic eosinophils by bronchial epithelial cells. Thus, there is a possibility of inverse relationship between the survival of bronchial epithelial cells and that of inflammatory cells as one of the mechanisms of action of corticosteroids in asthma. In our study, the apoptotic markers, Survivin and M30 apoptosense, showed no statistically significant correlation between themselves, possibly due to a more pronounced effect on survival of bronchial epithelial cells as compared with inflammatory cells. The decrease in the level of markers is in accordance with the hypothesis that increased bronchial epithelial cell apo-

ptosis is a feature of acute severe asthma and that systemic corticosteroids increase the survival of these cells as indicated by decreasing serum concentration of the marker for bronchial epithelial cell apoptosis *i.e.*, M30 apoptosense. Thus, increased bronchial epithelial cell survival is one of the mechanisms of action of corticosteroids in asthma.

Also, we tried to explore whether there is any correlation between the biochemical markers of apoptosis with the disease and its symptom severity indicators like the PEFr% and the QOL scores. The serum level of the markers showed no significant correlation with PEFr% and QOL scores.

Nevertheless, as expected, PEFr% and QOL showed statistically significant improvement after systemic corticosteroids treatment. In our study, PEFr% showed significant improvement after seven days as well as after 21 days of systemic corticosteroids treatment, which was in parallel with the improvement in clinical features. Also, PEFr% was negatively (and statistically significantly) correlated with QOL scores.

The study has some limitations like there was no control group to rule out the possible confounding by disease itself as a factor affecting serum Survivin and serum M30 apoptosense levels. Also, the study could not establish the relationship between the markers being used and other indicators like PEFR% and QOL.

In conclusion, in the patients of acute exacerbation of asthma, treatment with systemic corticosteroids for seven days caused a decrease in serum Survivin and M30 apoptosense apoptotic markers indicating decrease in the survival of inflammatory cells and increase in that of bronchial epithelial cells. However, this was more pronounced in patients showing clinical improvement but not in the patients with inadequate clinical improvement. Decreased inflammatory cells survival and increased bronchial epithelial survival after systemic corticosteroids was significant irrespective of baseline severity of bronchial asthma. Systemic corticosteroids improved the objective clinical parameters of acute exacerbation of bronchial asthma as seen by improvement in PEFR% and QOL scores. Studies with larger sample size and a control group could better establish the role of systemic corticosteroids in survival of inflammatory and bronchial epithelial cells in patients with acute exacerbation of bronchial asthma.

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