Continuous vs Intermittent Albuterol, at High and Low Doses, in the Treatment of Severe Acute Asthma in Adults*

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Adult patients suffering from acute asthma presenting to the Emergency Department with an FEV_1 of less than 40% of predicted were randomized into four treatment groups. They were treated with nebulized albuterol at a high (7.5 mg) or standard (2.5 mg) dose given either continuously through 1 h, or intermittently every hour, for 2 h. When the FEV_1 improvements for the different groups at 2 h were compared, the groups treated with continuous nebulization had the greatest improvement. The improvements (1.07 L for the high-dose group, and 1.02 L for the standard-dose group) were significantly greater than the improvement seen with standard-dose intermittent treatment (0.72 L; $p<0.05$). The improvement in FEV_1 of the high-dose, hourly treated group was intermediate in magnitude between these (0.90 L). There was no difference in the improvement seen between the two groups treated with continuous nebulization. The potassium fall, present in all groups, was more pronounced in the groups treated with high doses of albuterol. Only one person (high dose, continuous treatment group) developed hypokalemia of less than 3.0 mmol/L. The high-dose hourly treated group had the highest incidence of side effects, and the standard-dose continuously treated group had the lowest. The standard-dose continuous-treatment regimen had the greatest improvement in FEV_1 with the least number of side effects. ***(CHEST 1996; 110:42-47)***

Key words: albuterol; asthma; β-agonist; bronchodilator; continuous nebulization; Emergency Department

Abbreviations: ED=Emergency Department; NSS=normal saline solution

Inhaled β-agonists are the treatment of choice for patients with acute asthma presenting to the Emergency Department (ED).[1] The choice of nebulized medication in most EDs has been nebulized albuterol. Even though the package insert for albuterol recommends only 2.5 mg administered 3 to 4 times per day, common practice in the acute setting is to give the medication more frequently and in higher doses. Current recommendations are to give three nebulization treatments of albuterol, 2.5 mg (0.5 mL in 2 to 3 mL of saline solution) within the first 1 to 1.5 h.[1] Theoretically, the more frequent the administration of inhaled treatment, the earlier the delivery of medication to progressively distal regions of the tracheobronchial tree, *ie*, as bronchoconstriction is alleviated proximally, more medication is delivered distally. When the medication is administered continuously, this process is maximized. Higher doses may be justified in severe bronchoconstriction as it is likely that a smaller percentage of inhaled medication reaches the β-adrenergic receptors in this setting.

High-dose, continuously administered nebulized albuterol has been shown to be safe and effective in children.[2] Recent studies have compared the effect of continuous vs intermittent delivery of albuterol in adults presenting with acute asthma using different doses of albuterol.[3-5] Superiority of continuous delivery was demonstrable only in poststudy subgroup analysis in patients who had more severe asthma.[4,5] We sought to examine both the dosage of albuterol used for nebulization and the method of delivery, either continuously or intermittently, prospectively in ED patients who presented with an FEV_1 of less than 40% of predicted.

Materials and Methods

The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. Patients were recruited from the ED of Parkland Memorial Hospital by the treating physician if they met the following entry criteria: (1) a diagnosis of acute asthma;[6] (2) an initial FEV_1 of less than 40% of predicted; (3) development of asthma at an age younger than 45

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Table 1—*Patient Characteristics

	Continuous Tx		Intermittent Tx		
	High Dose (n=37)	Standard Dose (n=38)	High Dose (n=40)	Standard Dose (n=42)	p Value
Age, yr (±SD)	34.6 (±10.6)	32.4 (±10.8)	35.3 (±10.7)	35.1 (±10.4)	NS
Female, No. (%)	21 (57)	20 (53)	17 (42)	22 (52)	NS
Race, No. (%)					
Black	25 (68)	27 (71)	30 (75)	30 (71)	NS
Hispanic	4 (11)	8 (21)	7 (18)	7 (17)	NS
White	6 (16)	3 (9.6)	3 (7.5)	3 (7)	NS
No. of medications	2.5 (±1.1)	2.2 (±1.2)	2.3 (±1.2)	2.2 (±1.3)	NS
No. (%) taking inhaled steroids	19 (51)	16 (42)	18 (45)	20 (48)	NS
Duration of attack prior to ED visit (days)	3.5 (±2.5)	3.6 (±3.6)	3.2 (±3.4)	3.1 (±2.9)	NS
Initial vital signs					
Systolic BP, mm Hg	130 (±21)	133 (±22)	129 (±20)	129 (±17)	NS
Diastolic BP, mm Hg	88 (±10)	86 (±12)	83 (±12)	86 (±13)	NS
Pulse rate, beats/min	96 (±19)	89 (±13)	100 (±20)	95 (±17)	NS
Respiratory rate, breaths/min	23 (±5)	23 (±5)	23 (±8)	24 (±6)	NS
Room air oxygen saturation					
Pulse oximetry	96 (±3)	95 (±4)	96 (±4)	96 (±4)	NS
Initial spirometry					
FEV_1 (±SD)	0.88 (±0.33)	0.88 (±0.26)	0.96 (±0.44)	0.89 (±0.29)	NS
% predicted	26 (±7.6)	26 (±7.5)	29 (±12.8)	27 (±7.5)	NS

*Tx=treatment; NS=not significant.

years; (4) at least 18 years of age, not pregnant or breast feeding, and not incarcerated; (5) no history of allergy to albuterol; and (6) able to speak and understand English.

One of the investigators then obtained written informed consent and randomized the patient into one of four groups while the respiratory therapist prepared the nebulization treatment. The four possible treatment groups consisted of the following: (A) high-dose (7.5 mg/h), continuous albuterol; (B) standard-dose (2.5 mg/h), continuous albuterol; (C) high-dose (7.5 mg), hourly albuterol; and (D) standard-dose (2.5 mg), hourly albuterol.

To achieve continuous delivery (groups A and B), albuterol was diluted to allow the desired delivery rate. The disposable reservoirs used for nebulization (Airlife Misty-Neb Nebulizer; Baxter Healthcare Corporation; Valencia, Calif) delivered medication for 12 min when 3.0 mL of solution was used at an airflow rate of 6 L/min. Thus, 15.0 mL was required for 1 h of continuous nebulization. For group A, 7.5 mg (1.5 mL) was diluted with 13.5 mL normal saline solution (NSS). For group B, 2.5 mg (0.5 mL) was diluted with 14.5 mL NSS. For these continuous treatment groups, the nebulization canister (capacity of 5 mL) was refilled as needed. For the hourly treatment groups, the albuterol was diluted to constitute 3 mL of solution. For group C, 7.5 mg (1.5 mL) was diluted with 1.5 mL of NSS (1:1 dilution), and for group D, 2.5 mg (0.5 mL) was diluted with 2.5 mL of NSS (standard 1:5 dilution).

Albuterol solution for each group was prediluted and placed in bottles marked A, B, C, or D. Other than that A and B were to be given continuously and C and D hourly, neither the investigator, the therapist, or the patient knew which bottle corresponded with which treatment group.

Nebulization treatments were given by a registered respiratory therapist using disposable reservoirs and mouthpieces that generate particles 1.45 μm in diameter when attached to high-pressure wall air flowing at a rate of 6 L/min. Oxygen was administered if the patient's oxygen saturation dropped below 92% saturated.

FEV_1 values were measured using a 12-L volume displacement spirometer (P. K. Morgan, Andover, Mass) and analyzed by a computer (IBM compatible AT) and software (P. K. Morgan WYVERN software; P. K. Morgan Inc) FEV_1 values were measured by a registered respiratory therapist using the standard American Thoracic Society protocol.[7] The best of three attempts by the patient was recorded. Predicted FEV_1 values for each patient were calculated using the following formulas: 0.094(height)−0.0281(age)−1.59 for men (subtracting 0.15 times this for black men), and 0.0676(height)−0.023(age)−0.918 for women, where height is measured in inches and age in years. These values were then used by the computer system to determine each patient's percent predicted FEV_1. Patients were entered only if the percent predicted FEV_1 was less than 40%.

All patients were placed on a cardiac monitor. BP, pulse, respiratory rate, and pulse oximetry measurements were monitored every 15 min. An ECG and electrolyte determination were done prior to and after 2 h of albuterol treatment. All received methylprednisolone (Solumedrol), 125 mg IV, and a tapering dose of prednisone on hospital discharge. Other diagnostic tests were at the discretion of the treating physician. Patients were treated for 2 h on the study protocol. After this time, the need for additional treatment was determined by the patient's treating physician.

Every 15 min, the patients were asked if they experienced any side effects. The side effects were graded on a four-level descriptive scale of (1) just noticeable, (2) uncomfortable, (3) severe but tolerable, and (4) intolerable. The patient and the patient's physician had the authority to stop the trial at any time.

Forty patients in each of the 4 groups were required to allow the study to have sufficient power (0.8) to show a statistically significant (0.05) change in mean FEV_1 of 0.2 L between the different groups. Statistical comparisons were made using analysis of variance for continuous data with more than two groups; Student's t test for continuous data with only two groups; the χ^2 test for percentages; and contingency table analysis for discrete data when more than two groups were present. These were all done on a computer (MacIIsi; Apple Computers; Cupertino, Calif) using a statistical package (Statview; BrainPower Inc; Calabasas, Calif). The data are described in terms of mean±SD. A p value of less than 0.05 was considered statistically significant.

Table 2—*FEV_1 and Changes in FEV_1 With Treatment***

	Continuous Tx		Intermittent Tx		
	High Dose (n=37)	Standard Dose (n=38)	High Dose (n=40)	Standard Dose (n=42)	p Value
Initial					
FEV_1	0.88 (±0.33)	0.88 (±0.26)	0.92 (±0.34)	0.89 (±0.29)	NS
% predicted FEV_1	25.9 (±7.6)	26.4 (±7.5)	27.9 (±10)	26.9 (±7.5)	NS
After 1 h of Tx					
FEV_1	1.64 (±0.77)	1.66 (±0.63)	1.57 (±0.68)	1.36 (±0.54)	NS
% predicted FEV_1	47.3 (±17)	49.7 (±21)	45.8 (±17)	40.9 (±17)	0.15
Change from initial in					
FEV_1	+0.76 (±0.56)	+0.78 (±0.53)	+0.65 (±0.50)	+0.47 (±0.43)	0.026
% predicted FEV_1	+21.4 (±14)	+23.3 (±19)	+17.9 (±15)	+13.9 (±13)	0.042
% change from initial in					
FEV_1	+90% (±67%)	+94% (±73%)	+75% (±65%)	+57% (±53%)	0.049
% predicted FEV_1	+91% (±68%)	+94% (±83%)	+75% (±69%)	+56% (±55%)	0.056
After 2 h of Tx					
FEV_1	1.95 (±0.88)	1.91 (±0.68)	1.81 (±0.74)	1.62 (±0.61)	NS
% predicted FEV_1	55.6 (±19)	56.0 (±18)	53.0 (±18)	48.6 (±19)	NS
Change from first hour in					
FEV_1	+0.31 (±0.23)	+0.24 (±0.25)	+0.25 (±0.28)	+0.25 (±0.21)	NS
% predicted FEV_1	+8.3 (±6.2)	+6.3 (±9.0)	+7.1 (±8.2)	+7.8 (±7.1)	NS
% change from first hour in					
FEV_1	+20% (±15%)	+16% (±19%)	+18% (±20%)	+20% (±16%)	NS
% predicted FEV_1	+19% (±15%)	+17% (±20%)	+18% (±21%)	+21% (±21%)	NS
Change from initial in					
FEV_1	+1.07 (±0.69)	+1.02 (±0.58)	+0.90 (±0.57)	+0.72 (±0.5)	0.046
% predicted FEV_1	+29.8 (±17)	+29.5 (±16)	+25.1 (±17)	21.7 (±16)	0.095
% change from initial in					
FEV_1	+128% (±89%)	+123% (±81%)	+101% (±78%)	+87% (±63%)	0.086
% predicted FEV_1	+127% (±89%)	+121% (±80%)	+99% (±82%)	+86% (±65%)	0.100

*See Table 1 footnote for explanation of abbreviations.

Results

The four groups were similar in terms of demographics, vital signs, and severity of disease (Table 1).

Figure 1 shows the progression of FEV_1 values for the four groups with treatment. The changes in FEV_1 and percent predicted FEV_1 with treatment are shown in Table 2. After the first hour of nebulization therapy, the improvement in FEV_1 was greatest for the two continuously treated groups. The improvement seen in these two groups was indistinguishable. The standard-dose intermittent treatment group showed the least improvement in FEV_1, but still improved by more than 50%. Each group showed a highly significant improvement. Comparisons between groups showed that the overall difference in improvement was statistically significant at a p value of <0.05. Individual comparisons showed both continuous-treatment groups to have improved significantly greater than did the standard-dose hourly group ($p<0.05$). The improvement in FEV_1 of the high-dose hourly group was not statistically different from that of either of the continuously treated groups or from that of the standard-dose hourly group.

During the second hour of treatment, all of the treatment groups continued to improve at approximately the same rate (Table 2). The FEV_1 values at the end of 2 h for all of the groups were approximately 20% greater than they had been at the end of 1 h of treatment. Improvement within each group continued to be significant.

After 2 h of therapy, the differences in FEV_1 improvement overall were statistically significant ($p<0.05$, Table 2). As after the first hour, the comparisons between each of the continuously treated groups

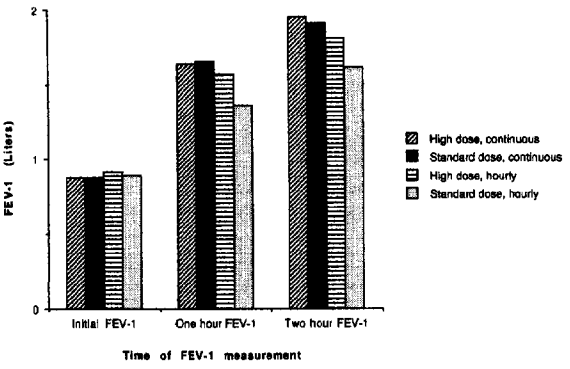

Figure 1. Progression of FEV_1 values with treatment. FEV_1 before treatment, after 1 h of treatment, and after 2 h of treatment given, for each of the four treatment groups.

Table 3—*Comparison of Intermittently Treated Groups

	High Dose (n=40)	Standard Dose (n=41)	p Value
Initial			
FEV_1	0.92 (±0.34)	0.88 (±0.28)	NS
% predicted FEV_1	27.9 (±10)	26.9 (±7.6)	NS
Immediately after first Tx			
FEV_1	1.43 (±0.59)	1.34 (±0.51)	NS
% predicted FEV_1	42.45 (±16)	40.6 (±15)	NS
Change from initial Tx			
FEV_1	+0.51 (±0.41)	+0.46 (±0.37)	NS
% predicted FEV_1	+14.6 (±15)	+13.7 (±11.4)	NS
Before the second Tx			
FEV_1	1.56 (±0.68)	1.36 (±0.54)	NS
% predicted FEV_1	45.8 (±17)	41.2 (±17)	NS
Change from after first Tx			
FEV_1	+0.14 (±0.24)	+0.03 (±0.16)	0.019
% predicted FEV_1	+3.4 (±7.2)	+0.61 (±5.5)	0.054
Immediately after second Tx			
FEV_1	1.73 (±0.70)	1.56 (±0.55)	NS
% predicted FEV_1	50.5 (±16)	46.8 (±17)	NS
Change from before second Tx			
FEV_1	+0.17 (±0.27)	+0.2 (±0.28)	NS
% predicted FEV_1	+4.6 (±6.9)	+5.6 (±7.9)	NS
1 h after second Tx			
FEV_1	1.81 (±0.74)	1.62 (±0.62)	NS
% predicted FEV_1	51.8 (±17)	48.6 (±19)	NS
Change from after second Tx			
FEV_1	+0.08 (±0.20)	+0.06 (±0.23)	NS
% predicted FEV_1	+2.5 (±6.6)	+2.3 (±4.7)	NS

*See Table 1 footnote for explanation of abbreviations.

and the standard-dose intermittent group were the ones that were statistically significant. For all of the groups, most of the 2-h improvement in FEV_1 (65 to 75%) occurred during the first hour of treatment.

Comparing the two hourly treatment groups, the improvement in FEV_1 immediately after the first treatment was substantial for each group, and constituted most of the total FEV_1 improvement at 2 h (Table 3). The high-dose group improved by slightly more than did the standard-dose group (0.51 L vs 0.46 L), but this was not statistically significant. During the wait till the second treatment, the FEV_1 of the high-dose group improved by a small amount, 0.14 L or by 9.8%, which was significantly more than the improvement in the standard-dose group ($p<0.05$). There was no difference in FEV_1 improvements after the second hourly dose.

Potassium levels were drawn before and after 2 h of treatment in all patients. They decreased in all treatment groups. The greatest decrease was seen in the high-dose continuously treated group followed by the high-dose intermittent group, then the standard-dose continuous group, and the standard-dose intermittently treated group (Table 4). The overall changes were statistically significant for each group, but the differences among groups was not.

Of the 165 patients entered, only 1 patient, who had been given high-dose continuous treatment, developed hypokalemia less than 3.0 mEq/L. The pretreatment serum potassium level of 4.5 fell to 2.8 after 2 h. There were no ECG changes. The patient did have a very good bronchodilator response, as her FEV_1 improved from 0.70 L to 2.17 L. She was given 40 mEq orally and 40 mEq KCl IV (over 2 h). Repeated serum potassium level was 3.5 mEq/L. She remained asymptomatic from the hypokalemia and was discharged from the hospital.

The changes in BPs, pulse rates, respiratory rates, and room air oxygen saturations were variable. The mean values for these variables changed by only slight amounts, and differences were not statistically significant among groups.

Twenty-eight percent of the enrolled patients had at least one side effect. Most of these (41%) were in the high-dose hourly treatment group ($p=0.14$). The most common side effect was "tremor," which was experienced by 14% of all entered patients. The patients in the high-dose groups experienced significantly more tremor than those in the standard-dose groups: 24% in the high-dose hourly group and 20% in the high-dose continuous group, compared with 9.3% in the standard-dose hourly group and only 2.5% in low-dose continuous group ($p<0.05$). The vast majority of side effects were graded as "noticeable" (lowest severity grade) by the patients. The difference in incidence of total side effects among the four groups was not significant. None of the side effects were graded as intolerable.

Discussion

High-dose (7.5 mg) albuterol delivered continuously over each hour is similar to the National Heart Lung and Blood Institute Expert Panel's recommended initial treatment of acute asthma of three 2.5-mg nebulization treatments over the course of 1 or 1.5 h.[1] Surprisingly, the effect of this treatment was matched by the improvement in FEV_1 seen with the standard-dose (2.5 mg) albuterol treatment diluted to last an hour. Both continuously treated groups improved their FEV_1 values by approximately 90% after the first hour and by 128% by the second hour. The very dilute mixture of albuterol used in the standard-dose continuous group (0.5 mL, or 2.5 mg, in 14.5 mL saline solution, *ie*, a 1:29 ratio) was able to bronchodilate as effectively as a solution three times as concentrated, if administered continuously.

The improvement in the FEV_1 of patients given single, hourly nebulized treatments of standard-dose (2.5 mg) albuterol was less than that seen with either of the continuously treated groups ($p<0.05$). After 1 h, the absolute magnitude of the difference in improve-

Table 4—*Changes in Serum Potassium With Treatment**

	Continuous Tx		Intermittent Tx		
	High Dose (n=40)	Standard Dose (n=41)	High Dose (n=41)	Standard Dose (n=42)	p Value
Serum potassium, mEq/L					
Initially	4.3 (±0.41)	4.4 (±0.54)	4.1 (±0.39)	4.2 (±0.55)	NS
After 2 h	3.8 (±0.44)	4.1 (±0.46)	3.7 (±0.35)	4.0 (±0.46)	<0.05
Change	-0.51 (±0.44)	-0.24 (±0.51)	-0.43 (±0.43)	-0.29 (±0.46)	0.11

*See Table 1 footnote for explanation of abbreviations.

ment was 0.3 L, or 39%. After 2 h, the difference was 0.38 L, or 31%.

High-dose intermittent treatment resulted in FEV_1 improvements at 1 and 2 h that were intermediate between that seen with the continuous-treatment groups and that of the standard-dose intermittent group. The difference between FEV_1 improvements of the high- and standard-dose hourly groups at 1 and 2 h were small and not statistically significant. Immediately after the first treatment, the high-dose intermittent group improved it's mean FEV_1 only slightly more (0.51 L vs 0.46 L, or by 0.05 L) than did the standard-dose group. The difference was not statistically significant. After the second treatment, the standard-dose group actually improved by a nonsignificant small amount more than the high-dose hourly group. The only statistically significant difference was that during the wait between the first and second treatments, the high-dose group improved by slightly more than did the standard-dose group (0.14 L vs 0.03 L; $p<0.05$). There was no such difference during the wait after the second treatment. If there is any benefit from the use of a concentrated single treatment, it would seem that it would be with the initial treatment only.

The side effects encountered were not serious and did not require discontinuation of treatment. The difference in the incidence of tremor was the only comparison that was statistically significant overall. Side effect profiles may be important in individual patients with specific comorbid conditions. In such cases, the current data support using the standard low-dose continuously nebulized albuterol.

The effect on potassium was dose dependant with a slightly greater decrease in patients getting the continuous delivery of the same dose of albuterol. The incidence of hypokalemia of less than 3.0 mEq/L was rare, as it occurred only once (in the high-dose continuously treated group) and was easily corrected without any adverse effect. It may be wise to check potassium levels in patients getting prolonged treatment with high doses of albuterol. A previous study using 2.5 mg of albuterol nebulized every half hour showed a higher incidence of hypokalemia.[8]

The effect on the BP, pulse, and respiratory rate was inconsistent. Previous reports have noted that, in general, BP and pulse tend to decrease with relief of bronchospasm.[9] There was no clear pattern that developed. Some patients obtained relief of bronchospasm and had normalization in BP and pulse, and others had increases in BP and pulse most likely from the β-adrenergic effects of the medication.

In adults with acute asthma, there have been a few previous reports that have studied continuous vs intermittent delivery of albuterol. Colacone et al[3] showed no difference between the effect of 5 mg albuterol given every hour for 2 h and 5 mg given continuously through each hour for 2 h. Two later studies suggested that continuous albuterol resulted in greater improvements as opposed to intermittent albuterol in patients with more severe bronchoconstriction. Rudnitsky et al[4] treated patients with either 2.5 mg albuterol every 30 min or, after the initial dose of 2.5 mg, 10 mg over 2 h. Overall there was no significant difference in peak flows after 2 h; however, when subgroup analysis was done, patients who presented with peak flows of less than 200 L/min did better by approximately 50 L/min (119% improvement vs 78% improvement).[4] Lin et al[5] used very high doses of albuterol, administering 30 mg over 110 min either continuously or in 5-mg treatments every 20 min, twice the dose of the high dose in the current study. Again, there was no overall significant difference in FEV_1, but the authors were able to statistically show there was a higher rate of improvement in patients who presented with an FEV_1 of less than 50% of predicted.[5] The above three studies all used different doses of albuterol on asthma patients with different severities of bronchoconstriction. We undertook the current study design with four treatment groups to control for both the method of nebulized albuterol administration and the dosage used. The presenting FEV_1 was lower in the current group of patients in an effort to test the hypothesis that continuously delivered albuterol results in a greater degree of bronchodilation in especially sick patients with acute asthma, as had been suggested by the previous studies.

To our knowledge, low-dose continuous nebulization has not been systematically studied previously. A recent retrospective, uncontrolled report on a limited number of pediatric patients documents safety and effectiveness.[10] Our data suggest that it may be the optimal treatment in terms of most rapid improvement in bronchoconstriction with the least side effects. For those with concomitant coronary artery disease or another comorbid condition possibly made worse with high doses of β-agonist, low-dose continuous nebulization may prove to be the best choice.

Though the current study focuses on treatment of acute asthma with β-agonists, anti-inflammatory medication is an irreplaceable component of therapy. In all groups, anti-inflammatory treatment was begun early with the use of methylprednisolone, 125 mg IV at the outset of therapy, and continued after ED, discharge with a tapering dose of oral prednisone.

In conclusion, for the patient population studied (FEV_1<40% predicted, but not requiring assisted ventilation), continuous delivery of albuterol at high (7.5 mg/h) or standard doses (2.5 mg/h) is superior to hourly treatment with the standard 2.5 mg during the first hours of therapy. There was no difference in FEV_1 improvements between the two doses used for continuous treatment, but the standard dose had fewer side effects. The high-dose intermitent-treatment regimen is intermediate in effectiveness and has a lingering effect after initial treatment not seen after the initial standard dose treatment. After the first hour, all groups improved at the same rate.

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