

# Efficacy of cromoglycate in persistently wheezing infants

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## Abstract

**A prospective study was undertaken to evaluate the efficacy of (sodium) cromoglycate in the treatment of persistent wheezing in 31 children between 4 and 12 months of age. The subjects were randomised to receive either 40 mg of cromoglycate (n=16) or physiological saline as placebo (n=15) three times a day by wet nebulisation in a double blind fashion for a period of six weeks. The patients were evaluated with daily symptom scores and respiratory function testing measuring maximal expiratory flow at functional residual capacity ( $\dot{V}_{max}FRC$ ) before initiating treatment and upon completion. At baseline, mean (SD) symptom scores between the two groups were comparable (cromoglycate 99.5 (29.8), placebo 104.5 (29.7)) as were  $\dot{V}_{max}FRC$  expressed as per cent of predicted normals (cromoglycate 48 (28), placebo 46 (20)). Upon completion of the treatment protocol, no significant difference could be found between the two groups for either symptom score (cromoglycate 67.6 (40.2), placebo 58.6 (41.4)), or  $\dot{V}_{max}FRC$  (cromoglycate 52 (24), placebo 60 (32)). It is concluded, therefore, that 40 mg of cromoglycate three times a day administered via facemask and wet nebulisation was no more effective than placebo in the treatment of our sample of persistently wheezing infants under 1 year of age.**

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studies have evaluated its use in children under 2 years of age. Henry *et al* reported that children between 18 and 24 months of age treated with cromoglycate showed a trend towards improvement.<sup>5</sup> No published study has evaluated the use of cromoglycate in infants under 1 year of age. This study was designed to evaluate the efficacy of nebulised cromoglycate in a group of chronically wheezing infants less than 1 year of age.

## Patients and methods

In a prospective fashion, patients between 2 and 12 months of age were recruited from an outpatient population referred to the pulmonary clinic at Ste Justine Hospital, a tertiary care referral centre.

Inclusion criteria consisted of the presence of chronic pulmonary symptoms for at least one month before consultation that included wheezing on at least two days per week, thoracic indrawing or cough on at least five days per week, and wheezing documented by a physician on at least one occasion.

Exclusion criteria included the presence of any other chronic respiratory problems such as bronchopulmonary dysplasia, cystic fibrosis, sequelae of severe bronchiolitis, pulmonary manifestations of gastro-oesophageal reflux, or documented immunodeficiency. These conditions were eliminated by questionnaire and physical examination as well as by a preliminary laboratory evaluation consisting of a complete blood count, sweat chloride test, immunoglobulin, IgG subclass status, and a chest roentgenogram. The patient was excluded if the chest roentgenogram demonstrated any abnormality other than hyperinflation or increased bronchial markings. A patient was also considered ineligible for the study if he/she had received corticosteroids parenterally or by inhalation within two weeks before the study.

Patients who met the initial inclusion criteria were discharged with an agenda with week 0 beginning on the day of the initial encounter. Daily respiratory signs and symptoms that included cough, wheeze, thoracic indrawing, and sleep pattern, were recorded for a period of three weeks; the score assigned to each of these parameters is shown in table 1. Parents were instructed on the administration of salbutamol (Ventolin, Glaxo) 0.15 mg/kg by wet nebulisation technique using a Hudson Updraft II nebuliser (particle mass median diameter of 3-4 microns) powered by a DeVilbiss Pulmo-Aide air compressor supplying 5 l/min of compressed air and a facemask. Salbutamol was given every 4-6 hours as

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Persistent wheezing in infants under 1 year of age is a poorly defined clinical entity. While many clinicians are reluctant to label wheezy infants as asthmatic, Tabachnik and Levison suggested that any infant with recurrent episodes of wheezing (three or more attacks) should be considered as having asthma, regardless of age.<sup>1</sup> In a recent consensus report, nebulised (sodium) cromoglycate was proposed as the drug of choice for the treatment of asthma in this age group.<sup>2</sup> The efficacy of cromoglycate in controlling the symptoms of asthma in older children is well established<sup>3,4</sup>; however, few

Table 1 Symptom score\*

	0	1	2	3
Cough	None	Occasional	Often	Continual
Wheeze	None	Faint, close to child	Easily audible close to child	Easily audible
Thoracic indrawing	None	Mild	Moderate	Severe
Sleep	None	Good, but awakens once or twice	Restless, frequent insomnia	Insomnia

\*Symptom score calculated by adding the score for each parameter (for example cough) on a given day and then adding the value obtained on each day to determine a 21 day score.

needed with each administration noted on the agenda.

All patients were re-evaluated three weeks after the initial visit. The baseline symptom score was tabulated from the agenda based on the 21 days from week 0 to week 3. If this score was greater than or equal to 50, and if the physical examination revealed persistent respiratory distress characterised by tachypnoea, wheezing, or thoracic indrawing, the patient was randomised to receive either cromoglycate or placebo. Those with a baseline symptom score of less than 50 were not included in the study and were subsequently returned to their referring doctor.

Within both the cromoglycate and placebo groups, the patients were further stratified into two age subgroups: below and above 8 months of age. Randomisation was done using a table of random numbers and was blocked within each stratum. In a double blind random fashion, patients within each age group received either cromoglycate (40 mg) 4 ml or placebo (physiological saline) 4 ml three times daily using the same compressor and nebulisation method that had been used to administer salbutamol. Parents were instructed to nebulise the solution to dryness (approximately 20 minutes) and to note whether the child inhaled the medication primarily through the nose or mouth. The addition of salbutamol to the study medication was permitted if the respiratory status of the infant warranted it as judged by the parents. Each nebulisation and medication was noted on the agenda card.

Respiratory function was assessed by measuring maximal expiratory flow at functional residual capacity ( $\dot{V}_{\max}^{\text{FRC}}$ ) using the 'squeeze' technique.<sup>6</sup> Briefly, patients were sedated with chloral hydrate 100 mg/kg body weight (maximal dose 1000 mg) administered by mouth. Using incrementally greater pressures applied by a jacket surrounding the patient's thorax, a maximal flow curve at FRC was sought. When this maximal pressure was found, it was used to obtain three technically correct flow curves at FRC. The curve giving the greatest value for  $\dot{V}_{\max}^{\text{FRC}}$  was used.

Respiratory exacerbation requiring additional medication other than salbutamol during the baseline period resulted in withdrawal from the study. Hospital admissions during the study period were noted but were not cause for withdrawal.

Patients were evaluated three and six weeks after randomisation, that is, six and nine weeks from baseline respectively. While parents were asked to complete the agenda throughout the study, the score at the six week evaluation was not used in the statistical analysis. The baseline symptom score was compared with that obtained at week 9, that is, the final symptom score (the symptom score recorded daily during the final three weeks of the study from week 6 to week 9). Similarly, pulmonary function tests were also compared at these two time points.

Compliance was assessed at the six week and nine week visit by a count of the unused medication vials returned at each visit and

agenda card verification. Between each evaluation, compliance was encouraged via telephone by one of the investigators (SPD).

Unpaired Student's *t* test was used to assess variability between the active and placebo groups for lung function and symptom score at both baseline and after treatment times. Paired Student's *t* test was employed to assess the variability within each group between baseline and after treatment for lung function and symptom score. In addition, non-parametric methods were also used to test for potential differences between total symptom scores at baseline and after treatment; Wilcoxon signed rank test for within group comparisons and Mann-Whitney U test for between group comparisons. Both the non-parametric and parametric analyses resulted in similar levels of significance for both the baseline and after treatment total symptom score. In order to discriminate an improvement of two units/day in the symptom score, we required a sample size of 24 patients. A minimum of six patients per stratum was needed to show a difference of two points on the daily clinical score with a one sided type I and type II error of 0.05 and 0.20 respectively. Therefore, the total sample size required was 24 patients. The level of significance was set at  $p < 0.05$ . All results are represented as the mean (SD) unless otherwise specified.

Written informed consent was obtained from the parents and this study was approved by the ethics committee of Ste Justine Hospital.

## Results

Thirty seven patients were randomised into the study. Three patients were excluded from final analysis because of parental withdrawal and three others were excluded due to poor compliance. No significant difference in the baseline status was found between those excluded and the study population. The demographics of the remaining 31 patients are shown in table 2. There were no statistically significant differences between the control and the study group for any of the baseline parameters evaluated. There were three nose breathers and six mouth breathers in the cromoglycate

Table 2 Baseline data for patients entering study; values are mean (SD)

	Cromoglycate (n=16)	Placebo (n=15)
Age (months)		
4-8	10	8
8-12	6	7
Sex (M/F)	13/3	11/4
Age (months)	7.4 (1.7)	8.3 (1.9)
Length (cm)	70.8 (4.9)	72.2 (4.3)
Weight (kg)	8.8 (1.4)	9.3 (1.3)
Symptom duration (months)*	3.2 (1.8)	4.5 (2.7)
Salbutamol administration (days)†	9.1 (9.2)	6.9 (8.3)
Daycare attendance	4	7
Atopy‡	12	11

\*Duration of respiratory symptoms before entry into the study as determined on history.

†Salbutamol administration calculated as the number of days during which at least one salbutamol treatment was required.

‡Atopy defined as presence of eczema, rhinitis, urticaria, or allergy to medication in patient or asthma, eczema, rhinitis, urticaria, or allergy to medication in immediate family.

Table 3 Symptom scores; values are mean (SE) and 95% confidence interval (CI)

	Baseline	After treatment	$\Delta$ SS
Placebo	104.0 (7.7)	58.6 (10.7)*	-45.9 (12.6)
95% CI	88.1 to 121.0	35.6 to 81.5	-73.0 to -18.8
Cromoglycate	99.5 (7.4)	67.6 (10.0)*	-31.9 (13.5)
95% CI	83.6 to 115.4	46.2 to 89.0	-60.6 to -3.0

$\Delta$ SS=change in the symptom score from after treatment to baseline.

\* $p < 0.05$  comparing baseline and after treatment scores within the placebo and cromoglycate groups. Comparison between placebo and cromoglycate groups were not significant.

group and two nose breathers and eight mouth breathers in the placebo group. The remaining children in both groups were classified as both nose and mouth breathers by the parents. There was no significant difference in the number of mouth breathers or nose breathers in comparing both groups. Baseline evaluations consisting of complete blood count, chest roentgenogram, sweat chloride test, immunoglobulin and IgG subclass concentrations were within normal limits for all patients.

Two patients (one in each group) were hospitalised during the treatment period. The first patient, hospitalised for three days because of a respiratory exacerbation, had an uneventful hospitalisation and did not require other medication. The second patient required hospitalisation for three days for roseola. None of the patients required other medications including corticosteroids.

Symptom scores are shown in table 3. When comparing the cromoglycate group with the placebo group, there were no statistically significant differences in the symptom scores at both baseline and after treatment times. Results of pulmonary function testing did not reveal a significant difference in either group at both testing times (table 4). In addition, no significant difference was observed between the two groups for the change from final to baseline in either the pulmonary function test volumes or symptom scores.

Significant improvement of the symptom score was present within both the placebo and the cromoglycate group. Similarly, the pulmonary function tests within each group displayed a trend towards improvement but did not reach statistical significance.

The data were analysed with respect to each age stratification. There was no difference in symptom score or pulmonary function improvement between the cromoglycate and placebo group in both the 8-12 month subgroup and the 4-8 month group.

Salbutamol was administered in a comparable fashion in both study groups during the study.

Table 4  $\dot{V}_{maxFRC}$ ; values are mean (SE) and 95% confidence interval (CI)

	Baseline	After treatment	$\Delta$ SS
Placebo	46 (5)	60 (9)	13 (10)
95% CI	35 to 58	41 to 79	-8 to 34
Cromoglycate	48 (7)	52 (6)	4 (6)
95% CI	33 to 63	39 to 64	-10 to 18

$\Delta$ SS=change in the symptom score from after treatment to baseline.

Data expressed as per cent of predicted normal values.<sup>7</sup>

Comparisons between placebo and cromoglycate groups did not reach statistical significance.

## Discussion

The contribution of the inflammatory component to the pathogenesis of asthma has recently been emphasised.<sup>8</sup> Treatment is now directed towards the use of this component with anti-inflammatory drugs such as cromoglycate. In children, because of its lack of adverse effects, cromoglycate is often proposed as the drug of choice.<sup>2</sup> While the efficacy of cromoglycate in decreasing bronchial hyperreactivity in older children and adults is well established, this has never been established in wheezing infants under 1 year of age. This study demonstrates that cromoglycate administered at a dose of 40 mg three times a day by wet nebulisation for a period of six weeks is an ineffective treatment of wheezing in infants under 1 year of age.

Previous authors have investigated the efficacy of cromoglycate in infants. Henry *et al* administered cromoglycate at a dose of 20 mg three times a day for a period of two months to 20 children with a mean age of 11.8 months.<sup>5</sup> This symptom score was recorded by the parents on a daily basis. Those who appeared to respond to cromoglycate, based on parental judgment, had an average age of 16.4 months. Pulmonary function testing was not performed in this study. In a younger subgroup of patients (age non-specified) from this same study, however, cromoglycate was determined by the parents to be ineffective.

Similarly, we also found that cromoglycate was ineffective in children under 1 year of age. As Henry *et al* had shown that cromoglycate appeared effective in the older children of his study population,<sup>5</sup> we stratified our study population within the sodium cromoglycate and placebo groups according to age, arbitrarily taking 8 months as a cut off point. Even when considering the children greater than 8 months of age at the onset of the study, we were unable to show a beneficial effect of cromoglycate.

Many factors in this age group can contribute to the non-efficacy of cromoglycate, including poor delivery to the lung due to anatomical considerations, method of administration, and nasal breathing. Furthermore, duration of administration can influence efficacy. Cromoglycate when given for less than six weeks shows no reduction in bronchial hyperreactivity in 7/11 studies.<sup>9</sup> We administered cromoglycate for six weeks, which is a reasonable trial.<sup>10</sup>

Salmon *et al* suggested that young children may be difficult to treat because inadequate amounts of drug reach the lung.<sup>11</sup> In their study, less than 1% of a 20 mg dose of cromoglycate administered by wet nebulisation was absorbed as measured by urinary excretion of the drug in children between 9 and 36 months of age. Furthermore, this amount may even be considered to be an overestimation as some of the cromoglycate may be absorbed through the nasal mucosa. As infants are predominantly nose breathers, the nose may act as a filter reducing pulmonary deposition to a quarter of the value obtained during mouth breathing.<sup>11</sup> While this may have occurred in our patients, the number of nose breathers in both groups

was comparable thereby eliminating this potential bias.

Various aspects of administration including nebuliser type, duration of nebulisation, and quantity of liquid nebulised, contribute to adequate delivery. Consideration must be given to the following factors. Different nebulisers produce aerosolised particles of different diameters that may not be optimal to inhalation and deposition in distal airways.<sup>12</sup> Most of a 2 ml volume of cromoglycate is nebulised within the first five minutes independent of the used nebuliser type.<sup>13</sup> Evaporation accounts for a substantial loss of medication. Finally, the ideal volume of liquid to be nebulised is 4 ml.<sup>14</sup>

For this study, the preceding factors were taken into account. Instead of nebulising the recommended 20 mg dose, we used 40 mg to increase the chances of cromoglycate actually reaching the lung and nebulised to dryness to maximise lung delivery. A Hudson Updraft II nebuliser was used as it produces aerosol droplets with a mass median diameter of 3 to 4 microns,<sup>15</sup> which has been shown to be ideal for penetration into the lung in adult studies.<sup>16</sup> Clinically, patients show a more rapid improvement of respiratory symptoms when larger doses of cromoglycate are used.<sup>17</sup> We used the optimal volume of 4 ml of solution in the nebuliser as recommended<sup>14</sup> and assessed compliance by telephone follow up, verification of agenda card, and unused quantities of medication that were returned to us.

The patients in this study had a thorough history and physical examination upon enrolment, as well as baseline laboratory studies, to eliminate other causes of wheezing in this age group. They did not, however, have invasive examinations such as oesophageal pH meter recording to eliminate reflux. While gastro-oesophageal reflux may be missed on questionnaire, we felt our patient population should reflect the population presenting to a paediatrician's office where the initial investigation would not have included an invasive examination.

During the study period, the amount of salbutamol taken by both the study and placebo group was comparable. Excessive bronchodilator use by the control group could not explain the improvement noted in them.

It is interesting that the symptom score improved significantly within each group. As one might expect in asthma, the evolution of wheezing in infants over a period of six weeks seems to be one of spontaneous resolution.

Pulmonary function testing as measured by the squeeze technique was performed on our

patients. While this test does not represent the respiratory status of the patient throughout the whole treatment period, it permitted an objective measurement of lung function on two different occasions and demonstrated comparable improvements within the two groups. Although, we are aware that this test has limitations,<sup>18</sup> we attempted to minimise the influence of these factors on our results by adhering to a standardised protocol.<sup>6</sup>

In conclusion, cromoglycate administered by wet nebulisation at a dosage of 40 mg three times a day was no more effective than placebo in the treatment of our sample of persistently wheezing infants under 1 year of age. In addition, this study does not support the current recommendation of the consensus report.<sup>2</sup>

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