RESEARCH PAPER

Nebulized Hypertonic-Saline *vs* Epinephrine for Bronchiolitis: Proof of Concept Study of Cumulative Sum (CUSUM) Analysis

NEERAJ GUPTA, *ASHISH PULIYEL, AYUSH MANCHANDA AND JACOB PULIYEL

*From the Department of Pediatrics and Neonatology, St Stephen's Hospital, Delhi, India; and * Tech Guru gonzoBuzz, Singapore. Correspondence to: Dr Neeraj Gupta, Registrar, Department of Pediatrics, St Stephen's Hospital, Tis Hazari, Delhi 110 054, India. drneeraj79@yahoo.co.in*

Received: March 29, 2011; Initial review: April 26, 2011; Accepted: August 11, 2011.

Objective: To apply cumulative sum (CUSUM) to monitor a drug trial of nebulized hypertonic-saline in bronchiolitis. To test if monitoring with CUSUM control lines is practical and useful as a prompt to stop the drug trial early, if the study drug performs significantly worse than the comparator drug.

Design: Prospective, open label, controlled trial using standard therapy (epinephrine) and study drug (hypertonic-saline) sequentially in two groups of patients.

Setting: Hospital offering tertiary-level pediatric care.

Patients: Children, 2 months to 2 years, with first episode of bronchiolitis, excluding those with cardiac disease, immunodeficiency and critical illness at presentation.

Interventions: Nebulized epinephrine in first half of the bronchiolitis season (n = 35) and hypertonic saline subsequently (n = 29). Continuous monitoring of response to hypertonic-saline using CUSUM control-charts developed with epinephrine-response data.

Main outcome measures: Clinical score, tachycardia and total duration of hospital stay.

Results: In the epinephrine group, the maximum CUSUM was +2.25 (SD 1.34) and minimum CUSUM was -2.26 (SD 1.34). CUSUM score with hypertonic-saline group stayed above the zero line throughout the study.

There was no statistical difference in the post-treatment clinical score at 24 hours between the treatment groups {Mean (SD) 3.516 (2.816): 3.552 (2.686); 95% CI: -1.416 to + 1.356}, heart rate {Mean (SD) 136 (44): 137(12); 95% CI: -17.849 to +15.849) or duration of hospital stay (Mean (SD) 96.029 (111.41): 82.914 (65.940); 95% CI: -33.888 to +60.128}.

Conclusions: The software we developed allows for drawing of control lines to monitor study drug performance. Hypertonic-saline performed as well or better than nebulized epinephrine in bronchiolitis.

Key words: *Bronchiolitis, Control limit lines, CUSUM, Randomized Control Trials, Stopping rule.*

Clinical Trial Registration No.: CTRI/2008/091/000233.

Published online: 2011, October 30. PII: S097475591100270-1

Nebulized epinephrine is commonly used for treatment of bronchiolitis in children having significant respiratory distress. Nebulized hypertonic saline is another modality of treatment [1,2]. It has previously been studied in the context of cystic fibrosis (CF) [3]. The various mechanisms of action of hypertonic saline have been reviewed by Mandelberg and Amirav [4]. Nebulized hypertonic saline with or without bronchodilators has been demonstrated to reduce hospital stay and improved clinical severity [5,6]. Studies directly comparing nebulized hypertonic saline with nebulized epinephrine are lacking.

The best answer to this question, of which of the two alternative interventions is better, can be studied in a double blind Randomized Control Trial (RCT) comparing the new drug (nebulized hypertonic saline) against standard therapy (nebulized epinephrine). However, RCT's have inherent problems, especially in the context of trials in children. According to Mc Culloch and colleagues, RCTs involve difficult blinding, require large samples, long duration, and are very expensive [7]. Others have noted that it is difficult to recruit cases [8].

Drug trials often include a provision of interim analysis and stopping of the trial if large differences between treatment groups are detected. We did this study to see if instead of such interim analyses, Cumulative Sum (CUSUM) can be used for continuous monitoring of the use of the study drug.

Cumulative Sum (CUSUM) is a statistical technique used in industry for quality control. Positive weights are given for successes and negative weights for failures such that, as the process continues, the cumulative score stays close to the zero line. Control lines are drawn so that if there are more failures or success than would be expected by chance, the lines would be crossed. These lines can be drawn using boot-strapping methods, as the sequence of failures and success depends on chance. By repeatedly

reordering the same data randomly in say 10,000 iterations, the limits of the CUSUM that can occur by chance can be defined [9]. The highest CUSUM and the lowest CUSUM is noted for each iteration. The upper limit of CUSUM is considered the mean upper CUSUM +2 SD and the lower limit is considered as the mean lower CUSUM-2SD.

CUSUM has been used to study antimicrobial treatment in neutropenic patients [10] and in the qualitative assessment of clinical competence [11]. Watkins and colleagues used CUSUM for the detecting Ross River Virus disease [12]. We have used this novel statistical tool to test if hypertonic saline was better or worse than the standard therapy with epinephrine. In this communication we report the procedure, the software we developed and the results of the study.

METHODS

The study was conducted from November 2008 to April 2009. Children aged between two months and two years, presenting with first episode of acute bronchiolitis and respiratory distress to our hospital emergency room were enrolled in the study after obtaining written informed consent from parents. Children with history suggestive of chronic cardiopulmonary disease, immunodeficiency, past history of respiratory disease requiring nebulization and critical illness at presentation were excluded. Children with a history of use of systemic or nebulized bronchodilators or nebulised hypertonic saline in last 24 hours were also excluded from study. The clinical scoring system described by Uyan, *et al.* [13] was used to clarify severity of respiratory distress (***Web Table* I)**. As per protocol, children with a clinical score of 4 or more, and those with oxygen saturation less than 94% in room air, were advised admission and they were eligible for enrolment in the study. Enrolled children were treated as usual with standard drug; nebulized epinephrine (non racemic solution, 1:1000 concentration,1 mL diluted in 2 mL normal saline) [14] every 6 hours, for first 24 hours. Children whose clinical score increased by 2 points or more (using admission score as baseline), or whose heart rate went above 200/minute were considered treatment failures. If the child improved or did not deteriorate using the above criteria, the treatment was considered useful, for the purpose of our study. In case of failure, the drug was stopped and alternative measures were instituted which could be escalated up to ventilation. Nebulized epinephrine was given during the first 3 months of study. CUSUM data were analyzed to look for failures in standard therapy, to draw control limit lines. In CUSUM, the data were arranged as either treatment success (S) or failure (F) with standard drug (epinephrine). The scores of +1 and -1 were given for each successful or failed treatment respectively. The weightage of each success and failure was calculated such that the cumulative sum of original data, comes to zero. Using boot-strapping technique and by random rearrangement of the sequence we looked at the CUSUM scores in 10,000 iterations. This helped to examine the limits that occur purely on account of chance changes in the sequence of successes. CUSUM scores using the boot-strapping method provided the upper and lower control lines. The mean upper CUSUM score + 2SD provided the upper limit and the mean lower CUSUM score -2SD provided the lower limit.

Children enrolled in the second half of the bronchiolitis season (the next 3 months after the initial 35 patients were recruited to receive standard therapy) received nebulized hypertonic (3%) saline, 3 mL every 6 hours. Clinical score and heart rate were monitored. Success and failures were measured by the same criteria as with epinephrine. The CUSUM score with nebulized hypertonic saline was plotted. It was decided *a priori* that if failure rate crossed the lower CUSUM control line, the trial would be stopped immediately. If however, successes were more and it crossed the upper control line, the study would be continued till the end of bronchiolitis season and it would be clear that new drug is superior to standard therapy. In the absence of suitable software, we developed custom-built open-source software [15] which allows inputting of any initial series data (epinephrine in the study). The software does the boot-strapping and calculates the limits for the control line and the stopping rule.

Conventional statistical methods were employed to examine differences between groups. To compare means and the confidence intervals, we used statistical software (Confidence Interval Analysis) (CIA) [16]. This study was approved by the Hospital Ethics Committee.

RESULTS

64 patients were enrolled in the study; 35 received nebulized epinephrine and subsequently, 29 received nebulized hypertonic saline. Details of children in the two groups are given in ***Table* I**. There was no statistically significant difference in the age, sex distribution, clinical score and heart rate at admission. There was no significant difference in the duration of stay between the groups.

With the initial trial with epinephrine, there were 5 children with 'treatment failure' (2 with worsening of clinical score and 3 with tachycardia). The resultant weightage for success and failure were +0.286 and

TABLE I POPULATION CHARACTERISTICS OF THE TWO GROUPS

Patient characteristic	*Epinephrine group(n=35)*	*Hypertonic saline group(n=29)*	*95% CI for difference between means*	*P value*
Male: Female	25:10	23:6		
Age, mo (SD)	7.1 (6.58)	5.27 (3.82)	-0.886 to + 4.646	<0.05
Clinical score at admission (Mean, SD)	8.2 (2.57)	7.55 (2.28)	-0.549 to + 1.909	<0.05
Heart rate at admission (/min.) (Mean, SD)	149 (41)	143 (16)	-10.168 to + 22.168	<0.05
Clinical score at 24 hours (Mean, SD)	3.5 (2.81)	3.5 (2.68)	-1.416 to + 1.356	<0.05
Heart rate at 24 hours (/min.) (Mean, SD)	136 (44)	137 (12)	-17.849 to + 15.849	<0.05
Duration of stay in hours (Mean, SD)	96.03 (111.41)	82.91 (65.94)	-33.888 to + 60.128	<0.05

–1.714, respectively. The highest CUSUM during the trial using epinephrine was +5.429 and the lowest CUSUM was –0.571. Boot-strapping was done with 10,000 iterations. Increasing iterations beyond this number did not significantly alter the CUSUM maximum and minimum values. The maximum CUSUM was +2.253 (SD 1.342) and minimum was –2.259 (SD 1.337). 2 SD (standard deviation) was added to the maximum CUSUM, and 2 SD was subtracted from the minimum CUSUM values, to draw the control lines as shown in ***Fig.* 1**. The CUSUM score while using hypertonic saline stayed above the zero.

DISCUSSION

Many clinical trials include some strategy for interim analysis and early stopping, if large differences between treatment groups are detected. This design feature can reduce the study participants' exposure to inferior treatment in addition to saving time and resources. Interim analyses are done at different predetermined points during the study. Instead of using the traditional form of interim analysis, we used the CUSUM to continuously monitor the new drug (nebulized hypertonic saline). In this 'proof-of-concept study' we monitored the new drug with a view to terminate the study if the drug was less useful than standard therapy with epinephrine in preventing deterioration in bronchiolitis. Other than using CUSUM for this stopping rule, we employed conventional statistical methods to compare the two treatment groups. We found that CUSUM monitoring is possible in the context of clinical trials.

The software we have developed allows CUSUM to be deployed easily in a number of clinical contexts besides drug trials. The use of this software in evaluating the competence of ophthalmic surgeons for cataract surgery has been published [17].

In this study, we found that nebulized hypertonic saline was at least as good as nebulized epinephrine in the treatment of acute bronchiolitis. Deterioration after hospitalization was no more frequent with hypertonic saline than with epinephrine. Previous studies using hypertonic saline have also found it more useful than placebo (normal saline) [1,5,18] or salbutamol alone [19]. This is the first study directly comparing nebulized hypertonic saline with nebulized epinephrine.

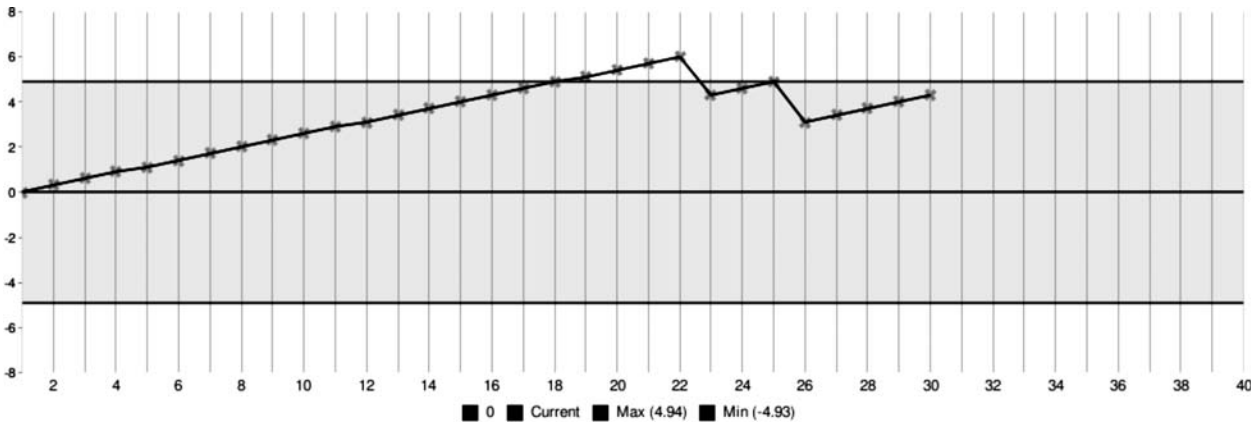

FIG. 1 *Real time CUSUM plot with nebulized hypertonic saline with CUSUM control lines.*

WHAT IS ALREADY KNOWN?

- Nebulized hypertonic saline is better than placebo in bronchiolitis.

WHAT THIS STUDY ADDS?

- Nebulized hypertonic saline is at least as good as treatment with nebulized epinephrine in bronchiolitis.
- A software for easy calculations of CUSUM has been developed that can help monitor new therapies in real time.

It must be emphasized that epinephrine is not used as standard therapy, in the treatment of bronchiolitis universally. In our proof-of-concept study we used epinephrine as 'standard therapy' for the first 3 months to act as controls, and study drug in the second half of the bronchiolitis season. We did not determine the sample size for this study as we felt that the stopping rule would govern numbers of patients recruited for the trial drug. However, we should have used conventional methods to calculate sample size to determine the number of children receiving standard therapy. The study drug trial recruitment could also be continued till the required sample is reached, unless the study has to be curtailed early for breeching the stopping rule. Another major limitation of the study was the comparison of two interventions at different time periods in a sequence. Changes other than the drug might have influenced the results during two different time periods.

This novel technique of using CUSUM helps to stop trials early, if the study drug performs worse than the comparator. This will help limit the risks to study subjects. The parameters to be monitored using CUSUM could be side effects or therapeutic benefits. It can be used for comparisons against placebo or against standard therapy. The new tool can be used within open label RCT to allow for continuous monitoring of the trial. The idea for a clinical CUSUM calculator was taken from industry (quality control mechanism) to provide a simple method to monitor a drug trial. Paradoxically, industry itself may find the simple software we developed, handy for quality control.

Compared to RCT this tool, however, does not allow blinding and randomization easily. Though use of CUSUM provides the advantage of continuous monitoring of the trial, it cannot replace the standard double blind RCTs. We believe that the software we developed for the study allows easy boot-strapping and drawing of control lines and thus has potential for use in many clinical situations.

Contributors: NG, AP, AM and JP conceived the project, NG conducted the clinical trial. AP helped NG and JP in the statistical analysis and development of software.NG, AM and JP were responsible for the write up. JP will act as guarantor.
Funding: None; *Competing interests*: None stated.
Note: The software used in this study was custom built for the study. It can be downloaded free from the internet.

REFERENCES

1. Mandelberg A, Tal G, Witzling M, Someck E, Houri S, Balin A, *et al*. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. Chest. 2003;123:481-7.
2. Tal G, Cesar K, Oron A, Houri S, Ballin A, Mandelberg A. Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. Isr Med Assoc J. 2006;8:169-73.
3. Wark PA, McDonald V. Nebulized hypertonic saline for cystic fibrosis. Cochrane Database Syst Rev. 2000;2:CD001506.
4. Mandelberg A, Amirav I. Hypertonic saline or high volume normal saline for viral bronchiolitis: mechanisms and rationale. Pediatr Pulmonol. 2010;451:36-40.
5. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2008;4:CD006458.
6. Mathew JL. What works in bronchiolitis? Indian Pediatr. 2009;46:154-8.
7. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. BMJ. 2002;324:1448-51.
8. Yeung V. Clinical trials in children. *In*: Pediatric Drug Handling. Available from http://www.pharmpress.com/shop/samples/paeditaric_sample_chapter.pdf. Accessed October 12, 2009.
9. Taylor WA. Change-Point Analysis: A Powerful New Tool for Detecting Changes. Available from: URL http://www.variation.com/cpa/tech/changepoint.html. Accessed October 11, 2009.
10. Kinsey SE, Giles FJ, Holton J. Cusum plotting of temperature charts for assessing antimicrobial treatment in neutropenic patients. BMJ. 1989;299:775-6.
11. Ravn LI, Sprehn M, Pedersen CB. The Cusum score. A tool for evaluation of clinical competence. Ugeskr Laeger. 2001;163:3644-8.
12. Watkins RE, Eagleson S, Veenendaal B, Wright G, Plant AJ. Applying cusum-based methods for the detection of outbreaks of Ross River virus disease in Western Australia.

BMC Med Inform Decis Mak. 2008;8:37.
13. Uyan AP, Ozyurek H, Keskin M, Afsar Y, Yilmaz E. Comparison of two different bronchodilators in the treatment of acute bronchiolitis. Internet Journal of Pediatrics and Neonatology. 2003;3;1.
14. Beck R, Elias N, Shoval S, Tov N, Talmon G, Godfrey S, *et al*. Computerized acoustic assessment of treatment efficacy of nebulized epinephrine and albuterol in RSV bronchiolitis. BMC Pediatr. 2007;7:22.
15. Foresee: CUSUM Calculator for Clinical Control (4-C Software). Available from http://jacob.puliyel.com/calculator/. Accessed August 7, 2011.
16. Confidence Interval Analysis (CIA) Software. Available from http://www.som.soton.ac.uk/research/sites/cia/. Accessed August 7, 2011.
17. Puliyel A, Puliyel J. CUSUM for monitoring competency: computer software is useful for bootstrapping and real time CUSUM plotting. Br J Ophthalmol. 2011;95:295-6.
18. Kuzik BA, Al-Qadhi SA, Kent S, Flavin MP, Hopman W, Hotte S, *et al*. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. J Pediatr. 2007;151:266-70.
19. Luo Z, Liu E, Luo J, Li S, Zeng F, Yang X, *et al*. Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. Pediatr Int. 2010;52:199-202.