

Treatment options of acute viral bronchiolitis in two Iraqi pediatric hospitals with a recent montelukast treatment option.

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Abstract:

Bronchiolitis is a virally induced acute bronchiolar inflammation. It is the most common lower respiratory tract infection in infants with ages less than 1 year.

The most common virus responsible for bronchiolitis is respiratory syncytial virus (RSV). The mainstay of management is oxygen and fluid administration. Pharmacological interventions including corticosteroids and bronchodilators have not been shown to improve outcome.

Is to evaluate the effect of montelukast and to verify the efficacy of bronchodilators and anti-inflammatory drugs among infants presenting with acute viral bronchiolitis in two Iraqi pediatric hospitals.

This was a randomized, prospective study in two Iraqi pediatric hospitals. Sixty infants with age range (2-24months) with a first episode of acute bronchiolitis were randomly divided into four treatment groups: oxygen plus intravenous fluid, montelukast pediatric chewable tablet, salbutamol given in combination as oral plus nebulized salbutamol, and dexamethasone IV injection. Control infants with non respiratory diseases were also studied for comparisons. The measured outcomes included: respiratory rate, heart rate, oxygen blood saturation, and times to resolution of illness, duration of oxygen & intravenous fluid therapy, and length of hospital stay.

These parameters were measured for each infants from hospital admission until discharge.

All groups were comparable at baseline. There are significant improvements in the respiratory rate, heart rate, blood oxygen saturation and rapid resolution of illnesses in the patients group that received oxygen plus IV fluid & the patients group that received montelukast tablet compared to other treatment options.

Length of hospital stays was shorter in these two treatment options compared to other treatment options.

The results observed effect of montelukast & oxygen plus intravenous fluid on the measured parameters compared to other treatments options in these two hospitals.

Key words: *Montelukast, Bronchiolitis, Respiratory Syncytial Virus*

الخلاصة :

التهاب القصبيات الحاد عند الاطفال هو مرض شائع يصيب المجاري التنفسية الصغيرة في الجهاز التنفسي، وهو يحدث خلال السنتين الأوليين من الحياة، وذروة حدوثه في الأعمار الصغيرة ذات الستة شهور، ويكثر في فصل الشتاء وأوائل الربيع، واحيانا يحدث في الفصول الأخرى ولكن بشكل أقل ويمكن ان يكون بشكل وباء نتيجة لتفشي ذلك الفيروس المسبب له. أكثر ما يحدث التهاب القصبيات عند الرضع الذكور بين اعمار 3 - 6 اشهر والذين لم يتغذوا من اثناء امهاتهم والذين يعيشون في المناطق المزدحمة، عادة ما يكون مصدر الالتهاب الفيروسي هو من أحد افراد العائلة المصابين بمرض تنفسي بسيط، حيث ان الأطفال الأكبر سنا والبالغين يتحملون هذا الالتهاب بشكل أفضل من الرضع الذين يعانون الكثير من

هذا المرض نتيجة لصغر المجاري وقلة المناعة لديهم، وعدم قدرتهم على طرد البلغم كالكبار وفي العادة ليس هناك علاج معين لهذا المرض ولكن هناك علاجات داعمة تتلخص باعطاء السوائل عن طريق الفم او عن طريق الوريد وكذلك اعطاء الاوكسجين حيث يكون التعافي من التهاب القصيبات الحاد البسيط والمتوسط تلقائيا دون الحاجة الى معظم العلاجات المستخدمة في علاج هذا المرض. من اهم الادوية التي تستخدم في العلاج هي موسعات القصبات والكورتيكوستيرويدات . تم تصميم هذه الدراسة لمقارنة الفعالية والسلامة سريريا لاقراص المونتيلوكاست (الذي ينتمي الى حاصرات مستقبلات الليكوترينات) والمعطى على شكل اقراص فموية للمضغ بجرعة خاصة للرضع، وكذلك لعمل مقارنة بين البروتوكولات المستخدمة (موسعات القصبات الهوائية والكورتيكوستيرويدات) لعلاج هذا المرض.

Introduction:

Bronchiolitis is the most common infantile respiratory illness resulting in hospital admission with peak prevalence in the winter months (November to March).

The most common pathogen is respiratory syncytial virus (RSV), accounting for over 50-90% of cases^[1].

RSV is so named because of the characteristic syncytial pattern observed in tissue culture^[2].

The usefulness of bronchodilators is controversial, and the limited evidence available does not support the routine use of steroid therapy^[3,4].

The mainstay of treatment is supportive care, consisting of adequate fluid intake, antipyretics to control fever and use of supplemental oxygen if necessary.

Inflammatory mechanisms in bronchiolitis have been documented recently, including increased airway secretion, mucosal edema, and infiltration of inflammatory cells. Cysteinyl leukotrienes (CysLTs) are released during respiratory syncytial virus airway infection in infants, and their levels are significantly elevated. CysLTs are known to cause bronchial obstruction, mucosal edema, and infiltration of eosinophilic granulocytes and to increase bronchial responsiveness. Recently specific CysLT receptor antagonists such as montelukast have become available for use in children. Montelukast was recently shown to be effective when started early in acute viral-induced wheezing in young children and infants.

No study has evaluated the effect of early (1 day of admission) intervention

with montelukast in infants hospitalized with acute bronchiolitis^[5].

The objective of the present randomized, prospective study was to conduct a systematic review of the effectiveness of commonly used treatments for bronchiolitis in infants, and to evaluate the effect of montelukast on clinical progress in infants hospitalized with acute viral bronchiolitis.

Materials & Methods:

This prospective study was conducted in two Iraqi pediatric hospitals. Baghdad Health Office/Karkh, Central Teaching Hospital of pediatrics & Karbala Health Office, Karbala Pediatric Teaching Hospital.

Inclusion criteria were infants' patients aged >8 weeks and <2 years with a respiratory symptom duration of <4 days. Additional inclusion criteria included first episode of wheezing or shortness of breath, randomization within 12 hours of admission and informed consent. Exclusion criteria were any previous hospital admissions with respiratory illnesses, had ever been treated with anti-asthma medications before the current illness, corticosteroids treatment in any form during current illness, and underlying cardiopulmonary disease. Gender, age, weight, height, body temperature, family history in (first-degree relatives), of asthma, atopy, tobacco smoking, usage of kerosene heater, type of feeding, duration of exclusive breast feeding, concurrent diseases, and concomitant medications, were recorded for each infants. A total number of 60 patients with age range 2-24 months, with mild to moderate

bronchiolitis were divided randomly into four treatment groups:

Group A: Ten infants' patients had received oxygen + intravenous fluid. Group B: Ten infants' patients had received study treatment, montelukast pediatric chewable tablet 4mg once daily, if vomiting occurred one additional dose was given. Group C: Twenty infants' patients had received salbutamol given in combination as syrup & by nebulization, (oral salbutamol 0.1-0.3mg/kg/dose q8 hour+salbutamol nebulizer 0.01-0.02 mg/kg /dose q6hour). Group D: Twenty infants' patients had received dexamethasone ampoule (4mg/1ml), with a dose of, 0.25 -0.5 mg/kg/dose q 12 hours intravenously.

The measured outcomes among the infants patient groups included, respiratory rate (RR), heart rate (HR), blood oxygen saturation (S_pO_2), time to resolution of illness (ROI), the presence and duration of noisy breath (wheezing), accessory muscle use (retraction), cough, time to achieve normal sleep & feed, time to resolution of fever & coryza, duration of intravenous fluid therapy, duration of O₂ therapy & the length of hospital stay (LOS in days).

Results:

The following table demonstrated that, there were no significant differences between the groups in terms of demographic variables.

The data were expressed as number (N), and percentage (%).

The following table showed that all the infants admitted to the hospitals have a significantly higher RR than the control infants (infants with non-respiratory diseases). However there were a significant reduction in the RR values at 2, 3 and 4 days compared to preceding day.

Comparing the reduction values of montelukast treated group with other options at day 4 after treatment, the montelukast treated group showed the highest reduction compared to other treatment options, followed by the group that received oxygen plus intravenous fluid.

The values of weight & duration of exclusive were expressed as mean \pm standard error of mean (SEM).

The following table showed, the HR of infants patients group that received oxygen plus intravenous fluid and the group that received montelukast tablet decrease in rapid and pronounced manner compared to other groups of patients.

HR at last day of hospital admission were near to the HR of the control infants.

This could explain the effectiveness of these two treatment options in the management of acute viral bronchiolitis of infancy.

The following table showed, the montelukast treated group showed rapid and consistent elevation in blood oxygenation more than other groups of patients with other treatment options.

Table-1: Demographic data and baseline characters of patients and control infants.

	Patients (N =60)	Control Infants (N =20)
Characteristics	(N, %)	(N, %)
Age <6months.	40, (59)	12, (60)
Age >6months.	20, (41)	8,(40)
Male.	35 ,(58)	14, (70)
Female.	25 ,(42)	6 (30)
Family history of asthma.	30, (52)	8, (40)
Family history of atopy.	38 ,(63)	12,(60)
History of passive tobacco smoking.	44,(74)	16, (80)
Family history of kerosene heating.	46 ,(77)	14 (70)
Presence of pets at house.	26, (45)	10, (50)
Breast feeding.	33 ,(54)	2, (10)
Bottle feeding.	18,(30)	14,(70)
Mixed feeding.	8,(13)	4, (20)
Number of family member< 5.	8,(13)	4,(20)
Number of family member >5.	52,(87)	16,(80)
Mean weight, kg.	7.2 ± 0.79	9.3 ± 1.14
Duration of exclusive breast feeding, months.	4.53± 0.303	8 ± 2.68

Table-2: Respiratory rate for infants' patients with acute viral bronchiolitis receiving different treatment options and for control infants.

Data were expressed as mean ± standard error of mean (SEM). Group A: Oxygen + intravenous fluid. Group B: Montelukast pediatric chewable tablet 4mg/day. Group C: Salbutamol given in combination as syrup & by nebulization. Group G: Dexamethasone ampoule (4mg/1ml). N: Number of patients.RR: Respiratory rate per minute. d1, d2, d3, d4: day 1, day 2, day 3, day 4. *P<0.05: Significant value from the control. Different letters showed significant differences between values. Control infants: Infants with non respiratory illnesses.

Options	N	RR(d1)	RR(d2)	RR(d3)	RR(d4)
Group A	10	53.2*±3.16 a	44.1*±1.51 b	39.5*±1.09 c	
Group B	10	53.7*±2.05 a	45.4*±1.62 b	38.2*±0.93 c	36.8*±0.63 d
Group C	20	57.9*±2.38 a	51.6*±2.39 b	42*±1.56 c	41*±1.09 d
Group D	20	60.2*±2.74 a	48.2*±2.23 b	43.6*±1.67 c	41.5*±0.91 d
RR(control) (20 infants)		31±2.09			

Table-3: Heart rate (HR) of infants' patients received different treatment options and heart rate of the control infants.

Data were expressed as mean ± standard error of mean (SEM). HR: Heart rate.d1, d2, d3, d4: day 1, day 2, day 3,day 4. *P<0.05: Significant value from the control. Different letters showed significant differences between values. Control infants: Infants with non respiratory illnesses.

Options	N	HR(d1)	HR(d2)	HR(d3)	HR(d4)
Group A	10	146.7*±4.83 a	135.2*±4.04 b	117.83*±5.63 c	
Group B	10	142.5*±4.77 a	126.28*±4.67 b	119.92*±3.51 c	116.6*±2.11 d
Group C	20	151.7*±2.62 a	148.2*±2.43 a	135.7*±3.52 b	129.12*±3.3 c
Group D	20	141.1*±3.84 a	135.3*±3.87 a	120.73*±3.23 b	123.62*±3.6 b
HR(control) (20 infants)		105.5 ± 4.2			

Table-4: Blood oxygen saturation of infants' patients received different treatment options and blood oxygen saturation of the control infants.

Data were expressed as mean ± standard error of mean (SEM). SPO2: Oxygen blood saturation. d1, d2, d3, d4: day 1, day 2, day 3, day 4. *P<0.05: Significant value from the control. Different letters showed significant differences between values. Control infants: infants with non respiratory illnesses.

Options	N	SPO2(d1)	SPO2(d2)	SPO2(d3)	SPO2(d4)
Group A	10	92.7*±1.05 a	95.5*±1.06 b	95.66*±0.95 b	
Group B	10	93*±0.56 a	95.64*±0.41 b	96.84*±0.39 c	97.2*±0.34d
Group C	20	91.65*±0.41 a	93.8*±0.34 a	95.2*±0.42 b	95.12*±0.4b
Group D	20	91.15*±0.47 a	93.8*±0.54 a	95.53*±0.23 b	96*±0.29 b
SPO2(control) (20 infants)		98.8±0.32			

Table-5: Resolution of symptoms (days); duration of oxygen plus IV therapy and length of hospital stay of infants with acute viral bronchiolitis.

Each value represents the mean ± standard error of mean (SEM) & n = number of patients in each group. A: Significant differences of group from oxygen plus IV Fluid (group A).b: Significant differences of group from montelukast (group B).

Parameters	Group A n =10	Group B n =10	Group C n =20	Group D n =20
Resolution of fever.	1.5± 0.22	1.35 ± 0.13	2 ± 0.15 a b	1.6 ± 0.14
Resolution of cough.	1.5 ± 0.16	1.5 ± 0.13	2.2 ± 0.28 ab	1.8 ± 0.18
Resolution of coryza.	1.1 ± 0.1	1.2 ± 0.12	1.5 ± 0.13 a	1.4 ± 0.13 a
Resolution of wheezing.	1.5 ± 0.22	1.7 ± 0.17	2.2 ± 0.26 a	2.3 ± 0.26 a
Accessory muscle use.	1.6 ± 0.17 b	1± 0 a	2.6 ± 0.18 ab	2 ± 0.25 b
Time to achieve normal feed.	1± 0.01 b	1.3 ± 0.13 a	1.4 ± 0.18 a	1.5 ± 0.13 a
Time to achieve normal sleep.	1.4 ± 0.16	1.2 ± 0.15	1.7 ± 0.23	1.6 ± 0.22
Over all resolution of symptoms.	2.8 ± 0.2	2.5 ± 0.13	4.1 ± 0.25 ab	3.7 ± 0.26 ab
Duration of oxygen therapy.	2.4 ± 0.26	2.1 ± 0.2	2.3 ± 0.22	2 ± 0.2
Duration of I.V therapy	1.5 ± 0.22	2 ± 0.18	2 ± 0.2	2 ± 0.09
Length of hospital stay.	2.3 ± 0.15	2.5 ± 0.17	3.3 ± 0.27 ab	3.1 ± 0.27 ab

Concerning resolution of symptoms in days as shown in table 5; for fever, cough, coryza, wheezing, accessory muscle use time to achieve normal feed & sleep, the duration of oxygen & intravenous therapy, and length of hospital stay in infants with acute viral bronchiolitis; the overall resolution of symptoms in the first two groups (A and B) were significantly lower than most of treatment options.

This could indicate the effectiveness of these two options in resolution of symptoms compared to other options.

In montelukast treated group the resolution of accessory muscle use and overall symptoms were significantly lower than all treatment options.

Regarding the time to achieve normal feed, again the values at the first two groups (A & B) were lower than other treatment options; however, the values were around the other values in respect to the time to achieve normal sleep.

The duration of oxygen therapy and IV therapy depend on

the protocol presented by the physician and hospital, therefore no significant differences were found in the values of the durations in the first two groups (A & B) compared to other treatment options .However the length of stay were lower in the first two groups compared to other groups of treatment options.

The lengths of hospital stay for the group A & B was, 2.3 ± 0.15 & 2.5 ± 0.17 respectively, versus 2.8 ± 0.29 , 3.3 ± 0.27 , 3.1 ± 0.27 and 3 ± 0.24 for other treatment options respectively.

Discussion:

In the absence of an international consensus view, the management of acute viral bronchiolitis still differs widely from country to country.

All the above treatment options were routinely described by attending Iraqi pediatric physicians to the infants admitted to the hospitals with acute viral bronchiolitis, except for infants group that received montelukast chewable pediatric tablets option. Infants had on average 3.5 days of symptoms before admission, and the main symptom was cough. A total of 32.5% received bronchodilators at home during the current illness. There were no significant differences between the groups in terms of demographic variables.

These results clearly demonstrated the effectiveness of supportive treatment such as oxygen plus intravenous fluid which is the mainstay in the treatment of acute viral bronchiolitis [6-8]. There is no need to expose the infants' patients to multi-drug therapy with resultant increased cost and adverse effects [9-11]. The widespread use of bronchodilators in viral bronchiolitis is likely to be due to the similarity of symptoms and signs of viral bronchiolitis and asthma. The pathophysiology of viral bronchiolitis consists of terminal bronchiolar and alveolar inflammation with airway swelling and luminal debris result in mucosal oedema and mucous plug.

These reasons may explain why bronchodilators are not effective for infants with viral bronchiolitis. Review of trials found no effect of bronchodilators on oxygen saturation, also found that bronchodilators, do not shorten the length of stay in hospital or shorten illness duration at home.

Side effects of bronchodilators include rapid heartbeat and shakiness. Given these side effects and little evidence that they are effective, bronchodilators are not helpful in the management of bronchiolitis [12].

Despite the prominent role that inflammation plays in the pathogenesis of airway obstruction, trials of the use of corticosteroids have consistently failed to show any benefit.

A systematic review of randomised controlled trials of systemic corticosteroids in acute bronchiolitis found no benefit in terms of length of hospital stay or of clinical scores [13].

Bacteraemia is uncommon in infants with bronchiolitis (<1%) and antibiotics are not recommended for the management of infants with bronchiolitis unless assisted ventilation is required and/or bacterial infection is strongly suspected or detected. Inappropriate antibiotic use exposes children to an unnecessary the risk of drug related adverse events and increases the risk of the development of antimicrobial resistance and should be avoided [14, 15].

Hypoxia is the most vital consequence of bronchiolitis. Humidified oxygen should be administered to maintain a minimum saturation of 95%. Pulse oximetry is simple and safe to use for monitoring saturation [6].

Cysteinyl leukotrienes are produced with acute RSV infection and it is argued that administration of a leukotriene receptor antagonist may reduce the incidence and persistence of post infection wheeze [16].

The montelukast treated group in this study showed the highest reduction in RR, HR and rapid and consistent elevation in blood oxygenation compared to other treatment options, followed by the group that received oxygen and intravenous fluid.

This could indicate the effectiveness of these two options in the management of acute bronchiolitis of infancy. Similarly the overall resolution of

symptoms in these two groups were significantly lower than most of treatment options.

The use of unnecessary treatment options results in unnecessary expense for the families and community and in administration of medication that may generate unnecessary distress in the ill infants^[10].

The lengths of stay in the hospitals were lower in the oxygen+ intravenous fluid and montelukast options than other options. These results support the results of other workers, which indicate that oxygen + intravenous fluid is the mainstay option in the treatment of acute bronchiolitis^[6].

The efficacy of montelukast in overall resolution of illness was due to its mild to moderate bronchodilators and anti-inflammatory effects^[17]. Other randomized controlled trial found that the leukotriene receptor antagonist montelukast may give short term, minor symptomatic benefit after acute bronchiolitis^[18].

Conclusion:

Supportive treatment such as oxygenation and hydration was the mainstay in the treatment of acute viral bronchiolitis. Montelukast pediatric chewable tablets 4mg once daily, was effective in reduction of day and night symptoms in infants with acute viral bronchiolitis. The resolution of illness was better and faster in infants that received oxygen plus IV fluid and montelukast tablets, in comparison to other treatment options.

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