

Original Research:

Efficacy Of Pidotimod In Reducing Recurrent Respiratory Tract Infections In Indian Children

Das D*, Narayanan V**, Rathod R***, Barkate HV#, Sobti V##,

*Consultant paediatrician, Department of Paediatrics, Milestones Paediatric Clinic, Malviya Nagar, New Delhi, India. **Head, Department of Medical Affairs - Medicomarketing, Wockhardt Ltd., ***Medical advisor, Department of Medical Affairs - Medicomarketing, Wockhardt Ltd, Mumbai, India. #Vice-President, India and Emerging markets, Department of Medical Affairs, Wockhardt Ltd, ##Group Product Manager, Department of Respiratory-Marketing, Wockhardt Ltd, Name of the institute where the study was carried out: Milestones Paediatric Clinic, Malviya Nagar, New Delhi 110017.

Corresponding author: Dr Varsha Narayanan, Head, Department of Medical Affairs - Medicomarketing, Wockhardt Ltd, Wockhardt Towers, BKC, Bandra (E), Mumbai. Email: vnarayanan@wockhardt.com

Received: February 23, 2017. Reviewed: March, 27, 2016. Accepted: April, 25, 2017.

Abstract

Objective: Respiratory infections in children are associated with significant economic burden, as well as significant morbidity and mortality. Immunomodulation with pidotimod, a synthetic dipeptide, has been shown to reduce incidence of recurrent respiratory infections (RRIs) in children. This study was conducted to assess efficacy and safety of pidotimod in Indian children with RRIs.

Materials and Methods: In an OPD based study, children aged 2 to 10 years were randomized to pidotimod or control group in a 2:1 ratio. Patients included had RRIs defined as six or more acute respiratory infection episodes in one year. Pidotimod was administered in dose of 400 mg as 7 ml of oral suspension twice daily for 15 days followed by once daily to complete 2 months. Treatments were started on day 1 of infection in addition to standard treatments. Patients were followed for 6 months after completion of treatment. Incidence of respiratory infection episodes were compared to previous rate in either treatment groups as well as between the groups.

Results: In 63 patients, 43 received pidotimod and 20 were controls. Mean age did not differ in two groups. 44.2% patients in pidotimod and 25% patients in control group had known

asthma. In 6-month period, compared to control pidotimod resulted in significantly lower RRI episodes in both overall (mean number of episodes: 0.09 ± 0.29 Vs 2.90 ± 0.64 respectively, $p < 0.001$) and asthmatic (0.05 ± 0.23 Vs 3.40 ± 0.55 respectively, $p < 0.001$) populations. Compared to previous year's mean number of RRI episodes, pidotimod significantly reduced incidence of RRI episodes in 6-months period (mean difference: -7.31 ± 0.96 Vs -4.48 ± 1.09 , $p < 0.001$ in overall population and -7.31 ± 0.96 Vs -4.48 ± 1.09 , $p < 0.001$ in asthmatic population). No adverse effects were reported and treatment was well tolerated.

Conclusion: Pidotimod is effective and safe addition to lower the recurrence of respiratory infections in children including those having asthma and may be recommended in Indian children with RRIs.

Keywords: *Pidotimod, recurrent respiratory infection, treatment, immunomodulation*

Introduction

Amongst various infections, acute respiratory infections (ARIs) are common in children especially below 5 years and are major cause of morbidity and mortality. Worldwide, South-East Asia has highest prevalence of

ARIs. Incidence of ARIs in India is widespread. A study from North India reported ARI incidence of 5.88 per child-year in children below 10 years of age. A South Indian study, reported ARI prevalence of 59.1% (63.7% urban and 53.7% rural). These ARIs tend to be recurrent in children leading to frequent hospital/out-patient visits. Occurrence of six or more ARIs in a year is recognized internationally as recurrent respiratory infections (RRI). Among various predisposing factors, immune immaturity may be an important contributor to recurrence of ARIs in young children. It has been reported that abnormalities of neutrophils and macrophage activity as well as dendritic cells, natural killer (NK) cells, B-cells and T-cells are associated with RRIs.

Preventive measures like vaccination, hand washing, avoidance of pollutants, and reducing indoor air pollution by avoiding use of solid biomass fuel can contain recurrence in ARIs. However, accomplishing these measures in every household may be lacking. Recurrence of these infections puts additional socio-economic burden to the family and the community. More so, RRIs cause exacerbations in children with airway allergies like asthma. Besides standard therapy and preventive measures, immunomodulation with synthetic dipeptide – pidotimod – has been found effective in RRIs. Pidotimod exerts its immunomodulatory effect by different mechanisms involving adaptive and innate immune responses which include dendritic cell maturation, upregulation of HLA-DR and cytokines like γ -interferon to induce T-cell proliferation, increase in activity of NK cells, promotion of phagocytosis, modulation of airway epithelial cells with upregulation of toll-like receptor-2 (TLR-2) and others. Pidotimod has been found effective, safe and well tolerated in children suffering from RRIs with or without asthma. There is so far no evidence with use of pidotimod in children with RRIs in India. This article represents the first evidence on pidotimod in paediatric RRI from India along with a brief review of its pharmacology and clinical evidence.

Materials And Methods

Study design and patient population

A total of 63 children aged 2-10 years with history of RRI (defined as 6 or more RRIs in preceding year) were divided into treatment and control group in a 2:1 randomization. Children suffering from asthma were also included in both groups. The study was done in the city of Delhi in the months Aug-Jan. Children with diagnosed primary immune deficiency disorders or acquired immunodeficiency states, known systemic disease involving heart, liver, gastrointestinal tract and/or kidneys, receiving potential agents known to interfere with immune response and recent immunization within 3 months before randomization were excluded. Study was conducted with ethical principles according to Declaration of Helsinki

Treatment allocation

Pidotimod in a dose of 400 mg was administered as 7 ml of oral suspension twice daily for 15 days followed by once daily to complete 2 months, to the treatment group. Treatment was started on day 1 of current illness as add-on to standard treatment of respiratory infections. Treatment of asthma was continued in those who had asthma at the time of randomization.

Follow-up

After treatment of 60 days, patients were followed up at monthly intervals for total 6 months to determine the frequency of RRIs. In these 6 months, patients were asked to report any symptoms suggestive of respiratory infection. Besides, they were asked to report any untoward symptoms to document side-effects with treatments.

Outcomes Assessed

Reduction in recurrence of respiratory infections in 6-month post-treatment period and comparison to pre-treatment frequency was the main outcome assessed in this study. Secondary

outcome was safety assessment.

Statistical analysis

The data was analysed using SPSS software for windows version 10. Continuous data was presented as mean and standard deviation and was compared using student's t test. Categorical data was presented as frequency and percentages and was compared using chi square tests. P value <0.05 was considered significant.

Results

From 63 patients enrolled in to the study, 43 received pidotimod and 20 were controls. Baseline characteristics are shown in table 1. Mean age of patients did not differ in two groups ($p=0.335$). 44.2% patients in pidotimod group and 25% in placebo group had asthma. Mean number of RTI episodes in previous year were similar in two groups (7.40 ± 0.95 in pidotimod and 7.48 ± 0.84 in controls, $p=0.933$). Also, the mean number of episodes did not differ in patients with asthma in two groups ($p=0.665$).

Compared to placebo, mean number of RTI episodes were significantly reduced in pidotimod group in a 6-months follow-up period which was evident from first month ($p=0.003$). At 3rd month of follow-up, there were no further RTI episodes in pidotimod group and the difference compared to placebo was significant as shown in table 2. Total number of RTI episodes were significantly lower with pidotimod than in controls (0.09 ± 0.29 Vs 2.90 ± 0.64 , $p=0.001$). Similar results were evident in patients who had asthma as shown in table 2. When compared to pre-treatment frequency of RTIs, mean difference after treatment with pidotimod versus controls was significant in overall population (mean difference -7.31 ± 0.96 Vs -4.48 ± 1.09 respectively, $p=0.001$) and asthmatic patients (mean difference -7.31 ± 0.96 Vs -4.48 ± 1.09 respectively, $p=0.001$) as shown in table 3. Reduction in mean number of RTIs at 6 months was 98.8% with pidotimod and 60.7% in control group in overall population whereas it was 99.3% and 54.7% respectively in asthmatic patients. Figure 3

shows the pre-treatment and post-treatment mean number of RTIs.

There were no side effects reported in any of the patients in either pidotimod or control group. Both treatments were well tolerated.

Discussion

Pidotimod is a synthetic orally active dipeptide and is chemically designated as 3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid. It has immunomodulatory properties. It affects both adaptive as well as innate immunity. Pidotimod is known to induce dendritic cell maturation with release of different cytokines which help in differentiation of T-cell to Th1 phenotype, increase in functional capacity of natural killer cells and promotion of phagocytosis. Further, it enhances defensive functions of airway epithelial cells by upregulation of TLR-2 receptors and increase in secretory IgA secretion.

Pharmacokinetically, oral administration of pidotimod follows first-order kinetics. Rapid absorption occurs after oral intake with bioavailability of 42-44%. Its apparent volume of distribution (aV_d) is 30 L and is not associated with accumulation or auto-induction phenomenon. Unchanged elimination occurs via urine. Plasma half-life is nearly four hours. Different oral formulations of pidotimod like tablets sachets, and vials are reported to be bioequivalent

In this study, we found that pidotimod significantly reduced the recurrence of RTIs compared to controls over 6-month period. Also, there was significant reduction in number of RTI episodes compared to mean number of annual RTI seen in preceding 1 year, with pidotimod compared to control. Similar results were evident in patients with asthma as well. The effectiveness of pidotimod was well supported by excellent safety and tolerability in children as there were no side effects reported by any patient compared to controls. A study from Licariet al., in 100 children with RRs reported that compared to placebo, pidotimod (400 mg/d for 60 days) resulted in

resolution of respiratory symptoms, reduction in medications requirements, increased school attendance and reduction in number of RRIs in significant number of children who had previous RRIs in 120 days follow-up period. Study reported no adverse effects with pidotimod. Similar results were reported in another study from Namazova-Baranova et al., with significant reduction in ARIs in 6 months period. Pidotimod was reported to hasten the recovery in children with RRIs. Careddu P observed persistent effect of drug even after withdrawal with significant reduction in incidence of RRIs with pidotimod compared to placebo. These findings along with our results strengthen the evidence that pidotimod reduces incidence of recurrent respiratory infections and may have prolonged benefits even after discontinuation of therapy. Clinical efficacy of pidotimod have been established in various studies as summarized in table 4.–

Respiratory epithelium is the primary defence against any respiratory illness. The immune response from epithelial cells orchestrate to provide protection to airways and lungs. In asthma, airway epithelium is primarily involved which elicits inflammatory response to both infective and non-infective allergens and thereby results in hyperactivity of airways. We observed significantly better efficacy of pidotimod in reducing RRIs in asthmatic patients as well. Zhao-Li and Xiao-Hong in asthmatic children reported significant improvement in lung function and greater efficacy with pidotimod in addition to background montelukast therapy than montelukast alone. The protective effect of pidotimod in asthma is possibly due to reduction in levels of IL-4 and IgE and increase in interferon- γ . Thus, by reducing the recurrence of respiratory infections and improving lung function, pidotimod may be useful in reducing the recurrent asthma attacks incidence.

In our study, percentage reduction in mean number of RTI episodes in 6-months follow-up was greater with pidotimod in overall as well as in asthmatic populations. This proves its better

efficacy in RRIs. A study from Burgio et al., in children with RRIs found that 34% and 56% of doctors rated excellent and good efficacy of pidotimod as against 5% and 7.5% with placebo respectively. Clinical condition was rated to be greatly improved (50%) and improved (50%) with pidotimod by parents of the children who participated whereas it was rated 5% and 30% for placebo respectively. Thus, pidotimod results in clinical improvements with reduction of RTIs which is well perceived and observed by physicians and parents.

No adverse events were found in any of the children who received pidotimod. This is consistent with other published reports as stated in table 4.

Conclusion

Pidotimod is effective and safe addition to the standard therapy for recurrent respiratory infections in children. Preventing recurrences of RTIs in children is crucial to reduce overall burden of respiratory infections. Efficacy in asthmatic patients as well, is a benefit that may reduce the recurrence of asthmatic attacks besides prevention of RRIs. This first observation in Indian setting provides background for further evaluation of pidotimod in a larger and long duration study to additionally confirm its efficacy and safety in RRIs.

Contributions

Authors have contributed to conducting the study, data collection and analysis. All authors have contributed to manuscript reviewing and editing and approved it in final form.

Conflict Of Interests: None

Funding Source: None

References

1. Selvaraj K, Chinnakali P, Majumdar A, Krishnan IS: Acute respiratory infections among under-5 children in India : A situational analysis, J Nat Sci Biol Med, 2017, 5:15–20.
2. Krishnan A, Amarchand R, Gupta V, Lafond KE, Suliankatchi RA, Saha S, et al,

- Epidemiology of acute respiratory infections in children - preliminary results of a cohort in a rural north Indian community, *BMC Infect Dis*, 2015, 15:462.
3. Kumar SG, Majumdar A, Kumar V, Naik BN, Selvaraj K, Balajee K: Prevalence of acute respiratory infection among under-five children in urban and rural areas of puducherry, India, *J Nat Sc Biol Med*, 2015, 6:3-6.
 4. Raniszewska A, Górska E, Kotuła I, Stelmaszczyk-Emmel A, Popko K, Ciepiela O: Recurrent respiratory tract infections in children – analysis of immunological examinations, *Centr Eur J Immunol*, 2015, 40: 167-173.
 5. Ferrario BE, Garuti S, Braidò F, Canonica GW: Pidotimod: the state of art, *Clin Mol Allergy*, 2015, 13:8.
 6. Burgio GR, Marseglia GL, Severi F, De Benedetti F, Masarone M, Ottolenghi A, et al, Immunoactivation by pidotimod in children with recurrent respiratory infections, *Arzneimittel-Forschung*, 1994, 44:1525-9.
 7. Careddu P: Role of immunoactivation with pidotimod in recurrent respiratory infection in childhood, *ArzneimForsch*, 1994, 44:1506-11.
 8. Feng-Xin Z, Xin L: The effect of Pidotimod in the prevention and treatment of pediatric bronchial asthma, *Chinese Journal of Biochemical Pharmaceutics*, 2011, 32:3-8.
 9. Correa JBV, Morales SE, Bolañosancona JC, Ale JAF: Pidotimod in recurrent respiratory infection in children with allergic rhinitis, asthma or both conditions, *Mexican Journal of Allergy*, 2002, XLIX:27-32.
 10. Licari A, De Amici M, Nigrisoli S, Marseglia A, Caimmi S, Artusio L et al. Pidotimod may prevent recurrent respiratory infections in children, *Minerva Pediatr* 2014, 66:363–367
 11. Namazova-Baranova LS, Alekseeva AA, Kharit SM, Kozhevnikova TN, Taranushenko TE, Tuzankina IA, et al, Efficacy and safety of pidotimod in the prevention of recurrent respiratory infections in children: a multicentre study, *Int J Immunopathol Pharmacol*, 2014, 27:413–419.
 12. Caramia G, Clemente E, Solli R, Mei V, Cera R, Carnelli V, et al, Efficacy and safety of pidotimod in the treatment of recurrent respiratory infections in children, *Arzneimittel -Forschung*, 1994, 44:1480-4.
 13. Motta G, De Campora E, De Vita C, Esposito S, Galletti C, Incutti V, et al, Immunoactivity of pidotimod against episodes of recurrent tonsillitis in childhood. *Arzneimittel-Forschung*, 1994, 44:1521-1524..
 14. Mameli C, Pasinato A, Picca M, Bedogni G, Pisanelli S, Zuccotti GV, et al, Pidotimod for the prevention of acute respiratory infections in healthy children entering into daycare: A double blind randomized placebo-controlled study, *Pharmacol Res*, 2015, 97:79–83.
 15. Passali D, Calearo C, Conticello S: Pidotimod in the management of recurrent pharyngotonsillar infections in childhood, *Arzneimittel-Forschung*, 1994, 44:1511-1516.
 16. Xiao-Xu M, Xu-Hui S: The effect of Pidotimod on serum IL-4, IFN- γ and IgE in asthmatic children, *Chinese Journal of Biochemical Pharmaceutics*, 2011, 32:400-403.
 17. Zhao-li J, Xiao-Hong L: Clinical Efficacy and Pulmonary Function Research of Pidotimod Combined with Montelukast in Treatment of Children with Bronchial Asthma, *Journal of Hubei University of Science and Technology*, 2016, Article ID: 20954646(2016)02-711643.
 18. Zuccotti GV, Mameli C, Trabattoni D, Beretta S, Biasin M, Guazzarotti L, et al, Immunomodulating activity of Pidotimod in children with Down syndrome, *Journal of Biological*

- Regulators and Homeostatic Agents, 2013, 27:253-258.
19. Aivazis VT, Hatzimichail A, Papachristou A, Valeri R, Iuga-Donca G: Clinical evaluation and changes of the respiratory epithelium function after administration of pidotimod in Greek children with recurrent respiratory tract infections, *Minerva Pediatr*, 2002, 54:315–9.
 20. Mantia IL, Grillo C, Mattina T, Zacccone P, Xiang M, Mauro MD, et al: Prophylaxis with the novel immunomodulator pidotimod reduces the frequency and severity of upper respiratory tract infections in children with Down's syndrome, *Journal of Chemotherapy*, 1999, 11:126-130.
 21. Whitsett JA, Alenghat T: Respiratory epithelial cells orchestrate pulmonary innate immunity, *Nature Immunology*, 2015, 16:27-35.
 22. Lambrecht BN, Hammad H: The airway epithelium in asthma, *Nat Med*, 2012, 18:684–692.
 23. Holgate ST: The sentinel role of the airway epithelium in asthma pathogenesis, *Immunological Reviews*, 2011, 242: 205

Table 1: Baseline characteristics in two groups

Characteristic	Pidotimod (n=43)	Control (n=20)	P value
Age (years)			
Mean±SD	5.3±1.9	5.7±1.5	0.335
Age groups			
<5	16 (37.2)	5 (25.0)	0.319
5 to 7	20 (46.5)	12 (60.0)	
>7	7 (16.3)	3 (15.0)	
Known Asthma	19 (44.2)	5 (25.0)	-
RTI episodes (per year)			
Overall	7.40±0.95	7.48±0.84	0.933
In asthmatic patients	7.26±0.87	7.50±1.12	0.665

Table 2: Number of RTIs in 6-months follow-up in two groups

Assessments timeline	Overall population			Asthmatic patient		
	Pidotimod (n=43)	Control (n=20)	P value	Pidotimod (n=19)	Control (n=5)	P value
1 month	0.07±0.26	0.45±0.51	0.003	0.05±0.23	0.40±0.55	0.187
2 month	0.02±0.15	0.55±0.51	0.001	0	0.80±0.45	0.001
3 month	0	0.70±0.47	0.001	0	0.60±0.55	0.023
4 month	0	0.45±0.51	0.001	0	0.80±0.45	0.001
5 month	0	0.35±0.49	0.002	0	0.20±0.45	0.331
6 month	0	0.40±0.50	0.001	0	0.60±0.55	0.023
Total	0.09±0.29	2.90±0.64	0.001	0.05±0.23	3.40±0.55	0.001

Table 3: Change in number of RTIs in pre- and post- treatment period

Assessment	Overall population			Asthmatic patients		
	Pidotimod (n=43)	Control (n=20)	P value	Pidotimod (n=19)	Control (n=5)	P value
Pre-treatment (1 year)	7.40±0.95	7.48±0.84	0.933	7.26±0.87	7.50±1.12	0.665
Post-treatment (6 months)	0.09±0.29	2.90±0.64	0.001	0.05±0.23	3.40±0.55	0.001
Mean diff. (Pre-Post)	-7.31±0.96	-4.48±1.09	0.001	-7.31±0.96	-4.48±1.09	0.001

Table 4: Summary of efficacy and safety pidotimod in children in respiratory infections

Study	Population	Efficacy finding	Adverse effects / Tolerability
Motta et al (1994)	Children with recurrent tonsillitis: Pidotimod (n=177) Vs placebo (n=118)	Significant reduction in inflammatory episodes in upper airways Significant reduction in clinical symptoms and signs Significant reduction in antibiotic usage	Comparable to placebo
Burgio et al (1994)	Children with RRI: Pidotimod (n=52) Vs placebo (n=49)	CD25+ expression was significantly increased	None
Caramia et al. (1994)	Children with RRI: Pidotimod (n=60) Vs placebo (n=60)	Significant trend towards normalization of the immune response Significant reduction in risk of relapses Reduction in hospitalizations Decrease in antibiotics use	None, well tolerated
Passali et al (1994)	Children with RRI: Pidotimod (n=205) Vs Placebo (n=211)	Significant reduction in ·duration and frequency of RTI episodes ·number of days of fever ·severity of clinical symptoms and signs ·need of antibiotics ·absence from school	Excellent safety
La Mantia et al. (1999)	URTI in children with Down's syndrome: Pidotimod (n=14) Vs control (n=12)	Significant reduction in the frequency, severity and duration of infectious episodes	None, well tolerated
Aivazis et al (2002)	Children with RRI: Pidotimod (n=32) Vs no pidotimod (n=18)	Response rate - ≤ 2 recurrence in 9-months period ·87.5% Vs 33.3% ($p<0.001$) Improved clearance from respiratory epithelium in six months· Pidotimod: reduced from 37 mins to 19.5 min Without pidotimod: Reduced from 36.4 min to 31 min ($p=0.01$)	None, well tolerated

Study	Population	Efficacy finding	Adverse effects / Tolerability
Zuccotti GV et al. (2013)	Acute RTIs in children with Down syndrome: Pidotimod (n=9) Vs placebo (n=9)	All children administered single dose of virosomal-adjuvanted influenza vaccine. Pidotimod ·Upregulated genes involved in activation of innate immunity ·Antimicrobial activity Increment in flu-specific IgG1/G3: Activation of complement dependent mechanisms	None, well tolerated
Caredu P (2014)	Children with RRI: Pidotimod (n=309) Vs placebo (n=327)	Significant reduction in ·number of RRI episodes ·Associated symptoms ·Number of school abstinence days Requirement of antibiotics and other drugs	AEs-vomiting (n=6 Vs 4), diarrhoea (n=5 Vs 4), abdominal pain (n=2 Vs 3), etc. with pidotimodVs placebo; well tolerated
Namazova-Baranova et al (2014)	Children with RRI: Pidotimod (n=78) Vs placebo (n=79)	Significant reduction in incidence of ARIs At 6 months: ARI developed in 92.3% Vs 100% children Better profile of normalization of immunological markers ·Reduced IgE (>1.5 or 2-fold) ·Help switch immune response to Th1 type ·Reduced IL-8 (>1.5 fold) ·Increase in INF- γ (non-significant)	
Licari et al (2014)	Children with RRI: Pidotimod (n=50) Vs placebo (n=50)	Significant reduction in number of children with ·Signs and symptoms of upper and lower airways ·Medication use Increase in school attendance Reduced visits for RRIs	None, well tolerated
Mameli et al (2015)	Healthy Children (3-years age): pidotimod (n=29) Vs placebo (n=28)	No statistical superiority of pidotimod compared to placebo in reducing the acute RTI in healthy children. 22% reduction in rate of acute RTIs with pidotimod Pidotimod reduced usage of antibiotics	In pidotimod- urticaria (n=1), resolved after discontinuation

Study	Population	Efficacy finding	Adverse effects / Tolerability
In patients with asthma			
Vargas Correa et al (2002)	Children with asthma allergic rhinitis or both having RRI (n=73)	Significant reduction in mean number of RRI episodes (from 5.7% to 4.04%, $p<0.005$) within 6 months Significant decrease in number of days affected (from 6.10 days per patient to 4.21 days per patient, $p<0.001$)	
Xiao-Xu and Xu-Hui (2011)	Control (Inhaled budesonide + montelukast) (n=40) Vs Control + Pidotimod (n=40)	Significant reduction in IL-4, IgE ($p<0.05$) Significant increase in INF- γ ($p<0.05$) Significant increase in FEV1 and PEF	
Feng-Xin Z and Xin L (2011)	Children with asthma: Pidotimod + Conventional therapy (n=50) Vs conventional therapy only (n=50)	Total effective rate: 94% Vs 72% ($p<0.05$) Significant increase in IgA ($p<0.01$) Significant increase in levels of CD3+, CD4+, CD8+ and CD4+/CD8+ ratio ($p<0.01$)	None
Zhao-Li and Xiao-Hong (2016)	Children with asthma: Pidotimod + montelukast (n=75) Vs montelukast (n=75)	Total effective rate: 94.67% Vs 81.33% ($p<0.05$) Significant improvement in cough symptom scores Significant improvement in forced expiratory volume in 1 sec (FEV1) and peak expiratory flow rate (PEF)	AE rate: 6.67% Vs 17.33% ($p<0.05$)

Figure 1: Percentage change in mean number of RTI episodes post-treatment in two groups

