EFFICACY OF NEBULISED TOBRAMYCIN IN CYSTIC FIBROSIS MANAGEMENT: A SYSTEMATIC REVIEW

Abstract:

Cystic Fibrosis (CF) is a progressive clinical condition associated with decreased functionality of glands that produce mucus, sweat, and intestinal secretions. CF is one of the most common recessive genetic diseases that affect all ethnic groups without any known identified cure, having variations in the severity of symptoms. In the treatment and management of CF, The choice and routes of administration of antibiotics taken is important in assessing effectiveness at different populations. In the light of this, current study was undertaken to determine the efficacy of Nebulised Tobramycin (NT) in the treatment of mild to moderate CF within 8years study period. Study was achieved by searching known repositories and electronic databases of various sources. Randomized Clinical Trials (RCTs) that compares patients treated on NT and placebo were selected, including six (6) RCTs comprising 609 participants to the review. Study noticed significant clinical and methodological heterogeneity among trials with NT, varying over a total of 8years study period. Also, there were recorded evidences of improvement in pulmonary function in most of the patients, following completion of the study. This review revealed inconclusive evidence in the efficacy of NT in the treatment of mild to moderate CF. It is thus clear, that long term use of NT in mild to moderate CF can provide sustained improvements in pulmonary functions

Keywords: Cystic Fibrosis, Nebulised Tobramycin, Randomized Clinical Trials

INTRODUCTION

Cystic Fibrosis (CF) is an incurable hereditary disorder that causes the body to secrete abnormally thick, sticky mucus that clogs the pancreas and the lungs, leading to problems with breathing and digestion, infection, and ultimately, death [1&2]. Three decades ago most babies born with cystic fibrosis died in early childhood, but advances in diagnosing and treating the disease have significantly improved its prognosis [3]. Today more than 60 percent of babies born with cystic fibrosis reach adulthood, and further advances, particularly in the field of gene therapy, may produce even better treatments in the coming years.

Global records estimate that in the United States, cystic fibrosis occurs in about one in every 3,900 babies, with about 1,000 new cases diagnosed each year, usually before a child reaches three years of age [4&5]. Approximately 30,000

American children and young adults have cystic fibrosis. The disease affects white people more often than black people, in an accounted value of one in every 3,300 white babies reportedly born with cystic fibrosis. However, only one in every 15,300 black babies is born with the disease [6].

Cystic fibrosis is caused by a defect in the gene responsible for manufacturing *cystic fibrosis transmembrane conductance regulator* (CFTR), a protein that controls the flow of chloride ions into and out of certain cells. In healthy people, CFTR forms a channel in the plasma membrane through which chloride ions enter and leave the cells lining the lungs, pancreas, sweat glands, and small intestine. In people with cystic fibrosis, malfunctioning (or absent) CFTR prevents chloride from entering or leaving cells, resulting in production of a thick, sticky mucus that clogs ducts or tubes in these organs [7]. In the lungs, this mucus blocks airways and impedes natural infection-fighting mechanisms, eventually turning the body's immune system against its own lung tissue. Similar blockage prevents crucial digestive enzymes produced in the pancreas from reaching the intestines, impairing the ability to break down certain foods. In healthy people most of the chloride in sweat is reabsorbed, but in people with cystic fibrosis, sweat glands cannot take up chloride ions, enabling excessive amounts of salt to escape in the sweat [8&9].

Cystic fibrosis is an autosomal recessive genetic disorder. This means that to have the disease, a child must inherit two copies of the defective gene, one from each parent. Many people carry a single cystic fibrosis gene, although they do not experience any significant health problems as a result; in the general population, approximately 1 in 31 Americans carries the gene [10]. The disease can only occur in babies with two carrier parents. When both parents are carriers, they have a 25 percent chance with every pregnancy of passing two copies of the defective gene to their child. Prospective parents may elect to undergo genetic testing to determine if one or both of them carry the defective gene [11].

Researchers identified the gene responsible for cystic fibrosis in 1989. Since that time more than 200 different defects in the cystic fibrosis gene have been described, many of which produce cystic fibrosis in varying degrees of severity. Researchers also learned that two different gene defects—one from each parent—can combine to produce varying effects.

Depending on the disease's severity, symptoms may be apparent soon after birth, or they may escape detection for months or years. In nearly 20 percent of all cases, the first symptom is *meconium ileus*, intestinal blockage in newborns. In other babies, the first evidence of cystic fibrosis is bulky stool, poor weight gain, flabby muscle tone, or slow growth, all products of low levels of digestive enzymes in the intestines. About half of all children with cystic fibrosis first see the doctor for coughing, wheezing, or respiratory tract infections [12]. Teenagers with cystic fibrosis may grow slowly and enter puberty later than their peers. Cystic fibrosis often causes impaired reproductive function. About 98 percent of adult men who have cystic fibrosis produce little or no sperm, and females have decreased fertility and are more likely to experience complications during pregnancy and childbirth. Cystic fibrosis patients of all ages are prone to dehydration because they lose so much salt in their sweat [13]. Infections, particularly in the lungs, plague people with cystic fibrosis throughout their lives. These chronic infections destroy lung tissue, a complication that ultimately takes the lives of most people with cystic fibrosis.

The earlier a diagnosis is made the better so that early treatment can slow the progression of lung damage caused by infection. Prenatal tests are available to determine if a baby will be born with cystic fibrosis. In newborns, blood tests indicating high levels of digestive enzymes suggest cystic fibrosis, but a certain diagnosis requires a sweat test to determine the amount of salt in the sweat. Sweat tests provide a valid diagnosis in babies over 24 hours old, and this test is also used to confirm diagnosis in older children and adults [14].

Cystic fibrosis remains incurable; existing treatments aim to relieve discomfort and delay the devastating and inevitable effects of the disease. Meconium ileus, the intestinal obstruction occurring in newborns, may require surgery. Patients with pancreatic blockage must take pancreatic enzymes with meals. Even with such enzymes, people with cystic fibrosis must consume adequate amounts of protein, vitamins, and higher-than-normal amounts of fat to ensure growth [15]. Those with respiratory infections are treated with antibiotics, often in aerosol form. When inhaled, these medicated vapors fight infection and relieve constriction of the airways. Using a procedure called chest physical therapy or postural drainage, caregivers of people with cystic fibrosis repeatedly and vigorously pound on the patient's back and chest to dislodge mucus obstructing the airways. Increasingly,

cystic fibrosis patients with severe, irreparable lung damage turn to lung transplantation surgery. Although complications with transplantation surgery may pose problems for some patients, lung or combination heart and lung transplants provide nearly 80 percent of cystic fibrosis patients with severe lung damage an entirely new lease on life [16].

Although no cure has yet been found, cystic fibrosis presents one of the most promising areas of research in modern medicine. Scientists are investigating the use of gene therapy to introduce healthy copies of the CFTR gene into the cells of patients with cystic fibrosis. Scientists hope that once inside the cells, healthy copies of the gene will manufacture functional CFTR protein, permitting the flow of chloride into and out of cells in affected organs and restoring healthy function. Just one of many new treatment strategies under investigation, such research provides the cystic fibrosis community—scientists, patients, and families—with hope that more-effective treatments and possibly a cure may soon be discovered [17]. In the light of this, current study was undertaken to determine the efficacy of Nebulised Tobramycin (NT) in the treatment of mild to moderate CF within 8years study period. As a progressive clinical condition associated with decreased functioning of glands that produce mucus, sweat, and intestinal secretions, CF is one of the most common recessive genetic diseases that affect all ethnic groups. There is no known identified cure, and there is variation in the severity of symptoms. The choice and routes of administration of antibiotics taken in the treatment of CF is important in assessing their effectiveness with different populations.

AIM

There seems to be very little conclusive evidences about the efficacy of NT in the treatment of mild to moderate CF. There are various reports about the long term efficacy, but still not conclusive. This study was designed to systematically review the efficacy of Nebulised Tobramycin (NT) in the treatment of mild to moderate CF within 8 years study period. The review determined the evidence of NT efficacy in the treatment of mild to moderate CF, plus recommend possible changes in the treatment modalities of mild to moderate CF.

Materials and Methods

Study Design

RCTs comparing improvement in pulmonary function (PF) following mild to moderate CF in patient treated with NT and those treated with placebo. Study drew its participants from the community of clinically diagnosed mild to moderate CF patients with no other co-morbid conditions. CF patients within the age 6-18 years were also sought after.

Considered outcome was the therapeutic efficacy of NT in the management of mild to moderate CF. this was assessed through an appreciable improvement in the PF. The improvement assessed as thus; Increased Forced Expiratory Volume in 1 second (FEV-1), Increased Forced Vital Capacity (FVC-1), and Increased Forced Expiratory Flow (FEF) at the midpoint of Vital Capacity (VC). Other measured outcome includes; decreased density of Pseudomonas aeruginosa in the sputum, reduced duration and frequency of hospitalisation and reduced need for concomitant antipseudomonal therapy. The efficacy of NT was assessed by;

Efficacy   =   [1 – Relative Risk (RR) of infection in the intervention group
compared to placebo group] X 100%

Population

Selected studies in this review were carried out in seven continents, and all were urban-based. The number of participants in the studies varies from twenties to four hundreds, and age ranges overlapping. All the RCTs tested participants with mild to moderate cystic fibrosis, although the criteria for distinction vary between studies. Similar methods were used for follow-up in all the studies, although there is about 8 years follow-up and length of studies range between studies. The male to female ratio of participants are similar, though the proportion of females doubles that of males in the study by Ramagopal.

Data Collection

Study followed the systematic type of research design, and systematically reviewed literatures, with structured review question to conduct the literature search. The multiple sources of data considered were;

i. Electronic Databases

ii. Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) [1946 to present]. Available from: http://ovidsp.tx.ovid.com.eresources.shef.ac.uk/sp-3.5.1a/ovidweb.cgi?&S=GCADFPJOLLDDDGALNCALHHOBIJHKAA00 &New+Database=Single%7c13. Accessed 10th April,2012 – see Appendix B for details

iii. EMBASE [1974 to 2012 April 06]. Available from: http://gateway.ovid.com. Accessed 10th April, 2012 – see Appendix C for details

iv. Cochrane Library [1991 to date] Network (Systematic Review of research in health care). Available from: http://www.thecochranelibrary.com/view/0/index.html. Accessed 11th April, 2012 – see appendix D for details

v. Centre for Reviews and Dissemination (CRD). Available from: http://www.york.ac.uk/inst/crd/index_databases.htm. Accessed 12th April, 2012. Using search terms "Cystic Fibrosis" AND "Inhaled OR Nebulised OR Aerosolised" AND "Tobramycin OR Nebcin OR Tobi" – see appendix E for details

vi. CINAHL via EBSCO [1982 to Date] Network (Nursing and Allied health literature). Available from: http://web.ebscohost.com.eresources.shef.ac.uk/ehost/search/advanced?sid=2 244df47-0737-4d30-8341-57f8b341c7bc%40sessionmgr11&vid=1&hid=12. Accessed 14th April, 2012 – see appendix F for details

vii. Trial Registers [British Medical Association: Clinical Trials in the UK. Available from: http://www.bma.org.uk/patients_public/clinicaltrialuk.jsp and Accessed 7th April, 2012

viii. The World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). Available from: http://apps.who.int/trialsearch/. Accessed 13th April, 2012- search terms were "Nebulised Tobramycin" AND "Cystic Fibrosis"

ix. metaRegister of Controlled Trials (mRCT). Available from: http://www.controlled-trials.com/mrct/mrct_about. Accessed 9th April, 2012 – search terms were "Nebulised Tobramycin" AND "cystic fibrosis"

x. References from identified articles

xi. Hand searching of key journals based on database search results: these highlighted journals were searched, considering the number of related articles that were found on the database search;

    xii. Cystic fibrosis: manual of diagnosis and management (2000 to date) using the search terms "cystic fibrosis" in the keywords column.

    xiii. Cystic fibrosis: manual of diagnosis and management. 2nd ed. (2000 to date) using the search terms "cystic fibrosis" in the keyword and title columns.

    xiv. Cystic fibrosis in adults: recommendations for care of patients in the United Kingdom/a report of the Royal College of Physicians (2000 to date) using the search term "cystic fibrosis" in the keyword column.

xv. Internet resources like "Google Scholar" were also utilised. This was done via www.googlescholar.com. Available from http://scholar.google.co.uk/. Accessed 6th April, 2012. Search terms used is "Management of Cystic Fibrosis"

Selection Criteria

Study selection was done only by the author, and this may be a source of bias. Cochrane Collaboration tool for assessing risk of bias was used for study to fulfil eligibility criteria. Data extraction form was designed, and two of the identified studies were piloted with it. The process of data extraction is ideally supposed to be double checked for possibility of error, but was not done due to the nature of the review. The same study was noted to have been reported twice, but data from the most recent publication was used.

Analytical Approach

Data analysis – the results of identified trials was properly analysed in this study. The primary analysis was the Relative Risk of mild to moderate CF in 6-18 year old patients treated with NT compared to those treated with placebo. This is assessed at a 95% confidence interval. The secondary analysis was the average RR of mild to moderate CF in the intervention group compared to the control group.

Result

The FEV-1 and FVC are the most frequently used index for assessing airway obstruction. The mean difference in the FEV-1 and FVC at the baseline and at the end of the study in both the intervention and control groups were determined. This mean difference expressed in percent at a particular standard deviation (SD) and confidence interval (CI) was adjusted with the duration of study and number of participants.

The figure below depicts the effect of NT assessed from the mean difference, SD and CI amongst studies;

Assessment using FEV-1;

Study ID	Intervention Baseline Mean+/- SD	Intervention Predicted Mean +/-SD	Intervention Diff in Mean	CI	Control Baseline Mean+/- SD	Control Predicted Mean+/- SD	Control Diff in Mean	CI
Alexander Chuchalin 2007	60.7+/- 14.8	67.5+/- 21.0	6.8+/- 20.0	0.96, 1.76	63.6+/- 15.0	64.4+/-20.5	0.8+/- 19.98	1.92, 3.22
Gerard Lenoir et al 2007	57.7+/- 14.1	73.8+/- 19.5	16.11+/-13.5	10.99, 21.23	59.8+/- 14.6	62.3+/-20.9	2.53 +/- 18.5	-4.48, 9.54
Bonnie W. Ramsey et al	55+/-3.69	58.72+/-5.34	3.72+/- 9.9	4.74, 14.64	60+/-3.20	54.03 +/- 1.34	-5.97 +/- 10.6	4.74, 14.64

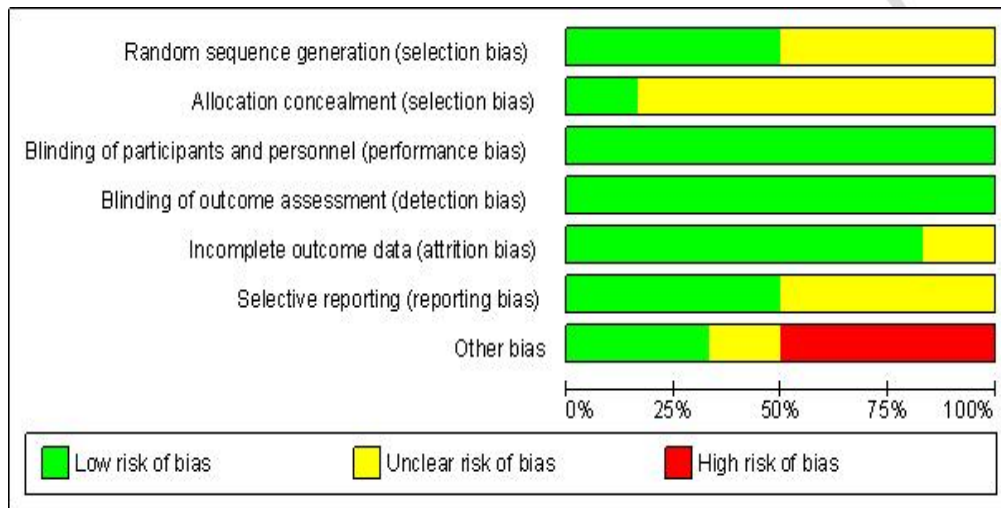| Study ID	Intervention Baseline Mean+/-SD	Intervention Predicted Mean+/-SD	Intervention Diff in Mean	CI	Control Baseline Mean+/-SD	Control Predicted Mean+/-SD	Control Diff in Mean	CI
Timothy D et al 2004	89.1+78.1 /2=83.6	85.1	1.5	Given with each parameter	89.3+81.2 /2=85.3	86.3	81.0	Given with each parameter
Heinz George Weisemann et al 1998	-	78.6+/-33.2	-	-	-	83+/-31.8	-	-
Maya Ramagopal & Larry C. Lands	33-105% of predicted value (66.96+/-21.49)	-	-	-	33-105% 0f predicted value (66.96+/-21.49)	-	-	-

Assessment using FVC;

Study ID	Intervention Baseline Mean+/-SD	Intervention Predicted Mean+/-SD	Intervention Diff in Mean	CI	Control Baseline Mean+/-SD	Control Predicted Mean+/-SD	Control Diff in Mean	CI
Alexander	70.8+/-13.8	76.7+/-18.8	5.9+/-14.2	3.7,8.1	73.6+/-	74.9+/-	1.3+/-	-1.6,4.

Chuchalin 2007					**13.1**	**18.9**	**13.3**	**2**
Gerard Lenoir et al 2007	**59.3+/-14.2**	**73.2+/-19.1**	**13.90+/-15.4**	**10.65,1.94**	**62.1+/-17.9**	**64.7+/-22.0**	**2.62+/-17.9**	**10.65, 19.37**
Bonnie W. Ramsey et al	**73.0+/-3.14**	**75.08+/-4.74**	**2.08+/-9.72**	**1.28, 11.06**	**77.0+/-2.63**	**72.91**	**-4.09+/-10.63**	**1.28, 11.06**
Timothy D et al 2004	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Heinz George Weisemann et al 1998	**-**	**86.8+/-19.4**	**-**	**-**	**-**	**100.4+/-7.9**	**-**	**-**
Maya Ramagopal & Larry C. Lands	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

The figures above show that the effect of NT is statistically significant in studies by Chuchalin, Lenoir and Ramsey at the end of the study. The mean difference between the intervention and control group in these studies are significant. Adequate values for proper assessment were not given in other studies. These differences in the outcome derived are significant enough to be linked to methodological heterogeneity amongst studies.

Risks of bias among included studies expressed in percentage

Risk of Bias among included studies

Effects of Intervention

The Mean difference (MD) between intervention and control group with 95% CI was derived at the end of this study period. A MD >1 depicts NT is high effective in the management of mild to moderate CF, while MD =1 depicts no difference between intervention and controlled group. A MD<1 depicts NT is not efficacious. The efficacy of NT can be determined by [1-MD) x 100% such that a low MD depicts low efficacy. The efficacy of NT at the end of this study differ amongst trials (Lenoir>Ramsey>Chuchalin) when assessed using FEV-1 and FVC in the figure above. These shows there are significant variation in the effect of NT in the management of mild to moderate CF even among included studies.

Discussion

Studies on the efficacy of NT revealed strong evidence that it is efficacious and safe in the management of patients with mild to moderate CF. There is significant difference among trials in this review. This may be ascribed to difference in population size, the strains of NT used, and quality of trial method. The efficacy in this study ranges from 6.0 in Chuchalin to 13.58 in Lenoir (using FEV-1), and 4.6 in Chuchali to 11.28 in Lenoir (using FVC). The follow-up period of studies is from 4 weeks to 8 years. Some factors may explain this variation, as these may include difference in risk of infection in different regions, compliance to medications, and resistance.

A meta-analysis was necessary in this study due to the degree of clinical and methodological heterogeneity, as this makes summary outcomes more coherent.
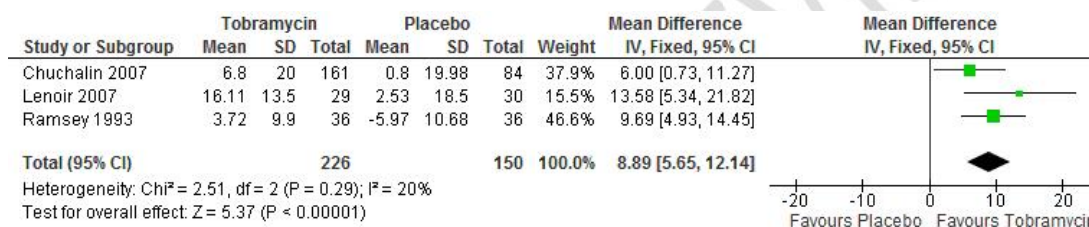
Study or Subgroup	Tobramycin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Chuchalin 2007	6.8	20	161	0.8	19.98	84	37.9%	6.00 [0.73, 11.27]	
Lenoir 2007	16.11	13.5	29	2.53	18.5	30	15.5%	13.58 [5.34, 21.82]	
Ramsey 1993	3.72	9.9	36	-5.97	10.68	36	46.6%	9.69 [4.93, 14.45]	
Total (95% CI)			226			150	100.0%	8.89 [5.65, 12.14]	

Heterogeneity: Chi² = 2.51, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 5.37 (P < 0.00001)

Favours Placebo   Favours Tobramycin

Fig above: Forest Plot comparing outcome (FEV-1) in the intervention and control groups

Study or Subgroup	Tobramycin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Chuchalin 2007	5.9	14.2	161	1.3	13.3	84	57.7%	4.60 [1.01, 8.19]	
Lenoir 2007	13.9	15.4	29	2.62	17.9	30	10.3%	11.28 [2.77, 19.79]	
Ramsey 1993	2.08	9.72	36	-4.09	10.63	33	32.0%	6.17 [1.35, 10.99]	
Total (95% CI)			226			147	100.0%	5.79 [3.06, 8.52]	

Heterogeneity: Chi² = 2.04, df = 2 (P = 0.36); I² = 2%
Test for overall effect: Z = 4.16 (P < 0.0001)
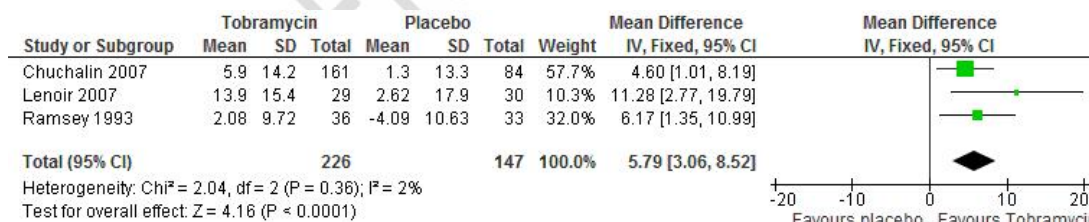
Favours placebo   Favours Tobramycin

Fig above: Forest Plot comparing outcome (FVC) in the intervention and control groups

From the fig above, the pooled mean difference (percentage improvement in pulmonary function) using FEV-1 is 9%, and FVC is 7% (both in favour of tobramycin group). These shows there are 9% and 7% more chances of improvement in pulmonary

function in the tobramycin group compared to placebo group following assessment with FEV-1 and FVC respectively.

The 95% CI while assessed with FEV-1 is 5.65 to 12.14, and 3.06 to 8.52 with FVC. The p-value for overall effects are <0.00001 and <0.0001 respectively. Therefore, we can 95% confident that the mean improvement in pulmonary function was between 5.65 and 12.14% (using FEV-1) and between 3.06 and 8.52 (using FVC) higher in the tobramycin group compared to placebo. These effects are significant at the p<0.05 level.

The Chi-square test for heterogeneity has a p-value of 0.29 with 2degree of freedom (using FEV-1), and 0.36 with 2degree of freedom (using FVC). There is significant heterogeneity at p<0.1 level.

The i value is 20% (using FEV-1) and 2% (using FVC). This indicates a higher degree of heterogeneity in the studies using FEV-1 to assess outcome, compared to the studies using FVC to assess outcome (2% variability may still be explained by chance). Examination of the forest plot shows that all three studies had a higher percentage mean difference in the tobramycin group than placebo group, but the magnitude of this effect varied between studies.

Three of the included studies [13] were not included in the meta-analysis because of their significant clinical and methodological heterogeneity. Study by Ramagopal only recorded the baseline values for FEV-1 as 33-105% of predicted value, and other parameter not recorded even while assessing for FVC. Study by Heinz only gave predicted values and failed to account for the baseline values while assessing both FEV-1 and FVC. Study by Timothy could not account for any of the values while assessing FVC, and equally not precise values for FEV-1.

The baseline findings (>12% change in FEV-1 and FVC, >25% change in FEF 25-75%) at p=0.93 in the study by Ramagopal. Participants in the intervention group pre-challenged with salbutamol with small sample size of 22. All these necessitate interpreting results with caution.

The participants divided into two groups (6-10 years and 11-15 years) in the study by Timothy. The FEV-1 is between 70-110% and 70-90% of the predicted values in the first and second groups respectively. The FEF 25-75% analysed with covariance, and long follow-up period. All these made the study poorly conducted, and hence needs interpreting with caution. Study by Heinz has recorded no significant difference between the placebo and tobramycin group for most of the outcomes. Most of the results were also adjusted for age, height, and

weight of participants. This review may be prone to errors due to time constraint, and involvement of only the reviewer in all the review processes- literature search, data extraction, and quality assessment.

The FEF at the midpoint of VC depicted by FEF 25-75% was assessed by all the included studies except Ramagopal and Heinz. This parameter as reported by studies [14-16] to be more sensitive than FEV-1 and FVC in measuring small airway obstruction. The FEF 25-75% was noted to be significantly increased versus baseline in the tobramycin group (p<0.001), while no appreciable difference were noted in the placebo group in the studies by Chuchalin and Lenoir. The mean FEF 25-75% increased 8% predicted from baseline in the intervention group, but decreased 2.0% in the control group in the study by Timothy. This contrasting improvement among the groups has made this outcome not included in the meta-analysis.

Analysis of Secondary Outcomes

The mean density of isolated P. aeruginosa strains from the sputum of patients in the intervention group decreased significantly when compared to the control group in all the included studies. Findings from all the studies depicts more than ten-fold decrease, except in studies by Ramagopal and Timothy where the exact figures were not given.

There is significant reduction in the duration and frequency of hospitalisation in the intervention group compared to the control group in all the included studies. Studies by Ramagopal and Heinz did not express these findings as a percentage. The percentage reduction among studies varies from 5-15%. This variation may be ascribed to different factors in each group. There is reduced need for concomitant antipseudomonal therapy in the intervention group compared to control group in all the included studies. Findings almost three times reduction in all the studies, except for studies by Ramagopal and Timothy where the exact values were not given.

The results of this review are not yet concluded, hence cannot serve as an evidence for present facts about the efficacy of NT in the management of mild to moderate CF.
Therefore, the documented efficacy after 28days treatment [16] still remains significant;
   i. Increased value FEV -1 by 9.7% higher than value for placebo, P<0.001
   ii. Increased FVC by 6.2% higher than value for placebo, P=0.014
   iii. Increased FEF at the mid-point of VC by 13.0% higher than value for placebo, P<0.001

iv. Decreased in the density of P.aeruginosa in sputum by a factor of 100, P<0.001

The evidences derived from this study are limited by identified risks of bias in some of the included studies, incomplete data, selectively reported data, and variability in follow-up periods. Cost effectiveness of Nebulised Tobramycin The cost effectiveness of NT in the management of mild to moderate CF was carried out combining the clinical and social reduction of hospital attendances compared to parenteral antibiotics [17&18]. A study [17&18] revealed a drastic reduction in the cost of NT when compared to other parenteral medications. A total cost of 10,010 pounds accrued by delay in prescribing and dispensing was offset by savings of approximately 3500-6200 pounds in the US. This reveals that early diagnosis and management of mild to moderate CF would be cost effective in preventing severe form of the disease, most especially in highly endemic regions.

The results of this review may not be significant enough to suggest new policies in the management of mild to moderate CF. Variations in the trials may be due to factors including race and study locations. Hence, the present modalities in management of mild to moderate CF should be adhere to pending results from new trials and future reviews.

For Further Research

Conclusion

This review shows inconclusive evidence on the effectiveness of NT in the management of mild to moderate CF. Nevertheless, there is weak evidence that the proportion of patients with good response following management in the intervention group is more that the controlled group after a specified period. Though the results were affected by limitations selected studies, and this poses the need for more researches in the future. So the current evidence [19] of 5.7% efficacy after 1 year should be in mind when reviewing future treatment modalities.

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