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Comparison of Percutaneous Endoscopic Gastrostomy, Megestrol Acetate and Nasogastric feeding in adult patients with Cystic Fibrosis

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Abstract

Background/Aims: Malnutrition remains an important and common problem in cystic fibrosis (CF) patients. In adult CF patients, weight loss is associated with poor lung function, and nutritional status has been found to be an independent predictor of mortality. We compared changes in weight and forced expiratory volume in 1 second (FEV_1) in patients with CF receiving one of three interventions to encourage weight gain: i) oral megestrol acetate (MA); ii) nasogastric (NG) tube feeding; iii) percutaneous endoscopic gastrostomy (PEG), Our aim was to determine and compare the effectiveness of these interventions in i) stabilising weight and ii) stabilising FEV_1 in CF adults.

Methods: We retrospectively collected data from hospital records of patients attending the Manchester Adult Cystic Fibrosis Centre (MACFC) between June 1998 and June 2012. We included adult patients with CF on any of the three nutritional interventions. Decisions regarding requirement for, and type of feeding intervention were made on a case by case basis by a multidisciplinary team with the choice of feeding intervention depending on MDT opinion and willingness of the patient for each intervention.

Results: 53 patients fulfilled inclusion criteria with 12 month follow-up data (17 MA, 14 NG and 22 PEG). Patients showed significant weight gain from baseline for two of the interventions: MA (mean change 2.7 kg, 95% CI 0.5, 5.0) and PEG (mean 2.5 kg, 95% CI 0.7, 4.3). For NG mean weight gain was 2.0 kg (95% CI -0.2, 4.3) which did not reach statistical significance (p=0.073) Analysing change in weight between the interventions no statistically significant differences were identified. Lung function remained stable with small non-significant FEV_1 changes over the 12 months: MA (mean change 0.09, 95% CI -0.08, 0.26), NG (mean 0.02, 95% CI -0.21, 0.26) and PEG (mean 0.04, 95% CI -0.12, 0.21, p=0.58). No statistically significant differences in FEV_1 changes were found between the interventions.

Conclusion: This is the first study to compare 3 different interventions in CF adults. All three interventions appear to be equally effective means of improving nutritional status in this 12 month study. Lung function remained stable but did not improve.

Keywords: Cystic fibrosis; Percutaneous endoscopic gastrostomy; Megestrol acetate; Nasogastric tube feeding; Weight gain

Introduction

Cystic Fibrosis (CF) is a chronic illness with a frequency of 1 in 2500-3200 live births among the Caucasian population [1]. It is the most common life-limiting genetic disorder in Caucasians affecting around 70,000 worldwide and 50,000 in Europe [2,3]. Malnutrition and pancreatic insufficiency are important and common problem in CF patients and often they require nutritional support when oral intake is inadequate to meet their high energy requirements [4,5]. Basal metabolic rate (BMR) in CF patients is estimated to be increased by as much as 30% due to increased work of breathing and energy requirements have been estimated to be 120-150 percent higher than matched individuals.

Improvement in nutritional support is thought to be a vital factor in the increasing longevity and improved quality of life that have been observed in these patients over recent decades [6]. In adult CF patients, weight loss is associated with worsening lung function, which is considered a predictor of early mortality. Weight loss has also been found to be an independent predictor of mortality [7]. Previous studies have shown that the use of supplemental enteral feeding involving percutaneous endoscopic gastrostomy (PEG) tube feeding or nasogastric (NG) feeding results in significant improvement in weight and stabilization of pulmonary function in malnourished CF patients [4,8].

However, PEG tube insertion is an invasive procedure with significant risk of complications including peritonitis and bleeding at the time of the procedure, and stomal infections and tube related problems in the longer term [9]. Overnight NG feeding allows patients to have freedom to perform normal activities during daytime and is safe and effective, however it involves recurrent placement of a nasogastric tube which is uncomfortable and unacceptable to many patients and is associated with a risk of aspiration in these patients with chronic lung disease [10]. Megestrol acetate (MA), a synthetic

derivative of progesterone, is used as appetite stimulant to promote weight in patients with advanced cancers [11]. MA has been used to treat malnutrition and may promote weight gain in CF patients [12]. However, steroid related side effects including adrenal suppression, glucose intolerance and diabetes have been reported [12,13].

To date, there are no studies comparing effects of PEG tube feeding, NG feeding and MA on weight and pulmonary function in CF patients. Given that all three interventions are used to achieve the same goal in CF patients, the aim of this study was to more clearly understand the relative efficacy of each intervention in promoting weight gain and stabilising lung function in adult CF patients.

Methods

We retrospectively collected data from hospital records of patients attending the Manchester Adult Cystic Fibrosis Centre (MACFC) between June 1998 and June 2012. We included all living adult (≥ 18 years of age) patients with CF on any of the three feeding interventions. Decision regarding requirement and type of feeding intervention was made on a case by case basis by a multidisciplinary team with the choice of feeding intervention depending on patient status and willingness for individual interventions.

MA

MA was given at the dose of 160 mg BD for a period of 6 weeks. If patients felt a symptomatic benefit further 6 week courses were administered with a minimum of 6 weeks between courses. No patient had greater than 3 courses in the 12 month study period.

NG tube

NG tubes were inserted by patients at night and removed in the morning. Feeds were given 7 nights a week. Each feed was given for 8-12 hours with the aim of providing 500-1500 extra calories, with feed rates governed by patient tolerance, oral intake and estimated requirements.

PEG

PEG tubes were inserted by the gastroenterology department at UHSM. Feeds were given overnight 7 nights a week. Each feed was given for 8-12 hours and provided 500-1500 extra calories, again with feed rates governed by patient tolerance, oral intake and estimated requirements. Patients who did not complete 12 consecutive months on a feeding intervention were excluded. Post lung transplant and patients who died during study period where 12 month data were not available were also excluded. In total, data from 53 cystic fibrosis patients who had received one of three different nonrandomised feeding interventions was analysed for pre and post-intervention weight and FEV_1 at 12 months.

Statistical Analysis

The normality of continuous data was assessed and normally distributed data are summarised using means and mean changes. Baseline characteristics were assessed using one-way ANOVA for age, weight and FEV_1, and Pearson chi-square test for gender. Post-intervention weight and FEV_1, at 12 months, were analysed using analysis of covariance (ANCOVA) models, including feeding interventions, gender and baseline values.

The estimated marginal means and their 95% confidence intervals (CI) are presented, with the overall p-values comparing feeding interventions. To investigate within group changes over time, separate paired ttests for each intervention were performed. The analyses used the conventional two-sided 5% significance level. All statistical analyses were performed using SPSS version 22.

Results

There were no significant differences in age between groups receiving the 3 different feeding interventions (Table 1). For MA 35% of patients were male, whereas for NG 71% were male and for PEG 68% were male.

The differences between feeding interventions and patient gender were statistically significant at the 10% significance level, thus gender was included as a covariate in the following analyses. There was no statistically significant difference in weight at baseline between the groups but there was a significant difference in FEV_1 (Table 1). Specifically NG patients had significantly higher FEV_1 than MA patients.

Age (years)	MA (n=17)	NG (n=14)	PEG (n=22)	p-value
Mean (SD)	28.41 (7.13)	27.71 (7.95)	29.05 (8.84)	0.89[1]
Range	20-42	19-46	18-53	
Gender				
Male	6 (35.3%)	10 (71.4%)	15 (68.2%)	0.061[2]
Female	11 (64.7%)	4 (28.6%)	7 (31.8%)	
Weight (Kg)				
Mean (SD)	47.73 (8.94)	54.18 (9.86)	50.98 (8.56)	0.15[1]
Range	33.00-61.45	36.80-71.05	34.80-63.80	
FEV_1				
Mean (SD)	1.35 (0.62)	2.21 (1.09)	1.55 (0.67)	0.011[1]
Range	0.52-2.30	0.92-4.90	0.70-3.60	

Table 1: Patient baseline characteristics; [1: One-way ANOVA, 2: Pearson chi-square test, SD: Standard Deviation].

	MA (n=17)	NG (n=14)	PEG (n=22)	p-value
Weight at 12 months (Kg)	53.7	52.45	52.77	0.69
Mean (95% CI)	(51.70, 55.70)	(50.23, 54.68)	(51.00, 54.54)	
FEV_1 at 12 months (L)	1.75	1.68	1.7	0.87
Mean (95% CI)	(1.56, 1.94)	(1.46, 1.90)	(1.53, 1.87)	

Table 2: Analyses of post-intervention weight and FEV_1; [All p-values in the above table are derived from ANCOVA models adjusting for gender and baseline values].

Analyses of post-intervention weight

At 12 months there were no statistically significant differences in weight between feeding interventions (p=0.69) (Table 2), after adjusting for baseline weight (p<0.001) and gender (p=0.026). There were statistically significant increases in weight at 12 months compared to baseline for MA (mean 2.72 kg, 95% CI 0.46, 4.98, p=0.021) and PEG (mean 2.49 kg, 95% CI 0.69, 4.29, p=0.009). For NG feeding weight gain was similar but not significant at the 5% level, though there was a significant increase at the 10% level (mean 2.04 kg, 95% CI -0.22, 4.29, p=0.073) (Table 3).

	Baseline	12 month follow-up	12 month change	p-value for 12 month change
	Mean (SD) Range	Mean (SD) Range	Mean change (95% CI)	
Weight				
MA (n=17)	47.73 (8.94)	50.45 (9.24)	2.72	0.021
	33.00-61.45	35.40-69.50	(0.46, 4.98)	
NG (n=14)	54.18 (9.86)	56.22 (11.41)	2.04	0.073
	36.80-71.05	39.40-74.00	(-0.22, 4.29)	
PEG (n=22)	50.98 (8.56)	53.48 (8.95)	2.49	0.009
	34.80-63.80	38.40-69.90	(0.69, 4.29)	
FEV_1				
MA (n=17)	1.35 (0.62)	1.44 (0.76)	0.09	0.28
	0.52-2.30	0.60-3.15	(-0.08, 0.26)	
NG (n=14)	2.21 (1.09)	2.24 (1.27)	0.02	
	0.92-4.90	0.85-5.50	(-0.21, 0.26)	0.83
PEG (n=22)	1.55 (0.67)	1.60 (0.61)	0.04	0.58
	0.70-3.60	0.70-2.55	(-0.12, 0.21)	

Table 3: Within-group changes; [All p-values examined using paired sample t-tests analyses of post-intervention FEV_1].

At 12 months there were no statistically significant differences in FEV_1 between feeding interventions (p=0.87) (Table 2), after adjusting for baseline FEV_1 (p<0.001) and gender (p=0.80). There were no statistically significant changes in FEV_1 at 12 months compared to baseline for any of the three feeding interventions: MA (mean 0.09, 95% CI -0.08, 0.26, p=0.28), NG (mean 0.02, 95% CI -0.21, 0.26, p=0.83) and PEG (mean 0.04, 95% CI -0.12, 0.21, p=0.58) (Table 3). Although there were no statistically significant improvements in FEV_1 at 12 months compared to baseline, there were small increases in each of the treatments.

Discussion

Malnutrition is a significant problem in CF patients and optimising nutritional status is thought to improve survival and quality of life by preventing weight loss, reducing the frequency of respiratory exacerbations and stabilizing progressive decline in lung function [8]. The results of this study demonstrated improvement in weight and stabilization in FEV_1 in adult CF patients treated with three commonly used methods of enhancing nutritional intake. The weight gain was similar for all three interventions but only reached statistical significance (p<0.05) for PEG and MA. This is the first study to compare the effect of three different interventions PEG, NG and MA on weight and FEV_1 of CF patients. Our results are noteworthy because whilst there was an improvement in weight with all three interventions, no statistical difference in weight gain was seen between interventions.

There are several studies where PEG tube feeding has been shown to induce weight gain and stabilise lung function in CF patients. Williams et al. found that PEG tube feeding resulted in significant improvement in weights and stabilisation of pulmonary function in 43 adult patients at six months, which remained stable at 12 months; mean weight increased from 37.4 kg to 42.1 kg at 6 months and percentage predicted FEV_1 was 21 (13%-35%) before PEG tube insertion and 20 (13%-35%) at six months which again remained stable at 12 months [8].

Findings from our study were similar, as mean weight gain in patients on PEG feeding was 2.49 kg (95% CI 0.69, 4.29) at 12 months and similarly there were no statistically significant changes in FEV_1 at 12 months. NG feeding has also been used successfully to aid weight gain in CF patients; Daniels et al. used overnight NG feeding in 11 hospitalised CF patients and found significant weight gain but increased weights were not sustained after cessation of NG feeding [15]. In another study by Moore et al. there was significant improvement in the weight (2.72 ± 0.46 kg) of eight CF children (aged 8 months to 13 years) treated with nocturnal home NG feeding for 3 months but again, weight gain was not sustained after cessation of tube feeding [16]. Pulmonary function was not assessed in these studies.

MA has been used in several studies to try to improve nutritional status and pulmonary function. Marchand et al. conducted randomized, double blind, placebo controlled study of MA in 12 patients with CF for 12 weeks, followed by another 12 weeks of a washout period. Average weight gain was 3.05 kg in MA group compared to 0.3 kg in placebo group. FEV_1 increased by 15.3% in MA group compared to 3.8% taking placebo. The authors concluded that both weight and pulmonary function improved in patients treated with MA [13]. This is similar to the weight gain of 2.72 kg (95% CI 0.46, 4.98) at 12 months we observed, although the duration of treatment was longer in our study [17].

However, the increase in FEV_1 observed by Marchand was not observed in our study, although all 3 feeding interventions groups demonstrated numerical improvement in FEV_1 during our study period which did not reach statistical significance, which could imply that FEV_1 is at least stabilised by these interventions [18]. MA appears to be an effective intervention that obviates the requirements for tube feeding, however significant side effects of the drug have been reported.

Garcia et al. carried out a meta-analysis of 35 trials (which comprised 3963 patients for effectiveness and 3180 looking at the efficacy and safety) of MA for the treatment of anorexia-cachexia syndrome in patients with cancer, AIDS and other underlying diseases including COPD, cardiac heart failure, cystic fibrosis and anorexia nervosa. Both oedema and thromboembolic phenomena were commonly reported adverse events. An increased mortality with MA treatment was also identified (RR1.42 CI 1.04-1.94) however it must be noted that the quality of evidence was poor and there was high levels of heterogeneity between the studies, including the patients type, and further prospective studies of MA use and its impact on long term survival are required [19].

PEG tube placement, although generally considered a safe procedure is also not without risk. Immediate risks include those relating to blind puncture of the abdominal wall such as bleeding and perforation of another viscous eg colon or leakage of feed around the site into the peritoneum can also lead to peritonitis. These severe complications are relatively rare, estimated to occur in less than 0.5% of cases [20]. A review by Schrag et al. of 332 articles looking at complications related to PEG tube placement identified PEG insertion associated with rates of wound infection rate of 3%, significant bleeding of 2.5%, peristomal leakage of 1-2%, tube dislodgement of 1.6 to 4.4% and, buried bumper syndrome in 1.5 to 1.9 [21].

Nasogastric tube feeding has been associated with 0.3% to 8% complications including bronchial placement, intravascular penetration into jugular vein and subclavian artery, intracranial entry and enteral complications including tube knotting, impaction, kinking and perforation and bleeding [22]. Its use is often limited by reluctance of patients to place a tube on a nightly basis with the associated discomfort this can cause.

There are limitations to this study; first it is a retrospective study limited by the small sample size which is often subject to biases and confounding factors in data collection and outcome assessments. However the sample size is larger than many previous published studies; the study of larger groups would likely require multicentre collaboration. Second, the lack of a control group means we cannot be certain that similar weight gain would not be seen without intervention, although given the progressive weight loss observed in these patients prior to intervention despite intensive dietetic input it would seem reasonable to assume that weight gain would not occur without additional nutritional intervention. Performing a randomised controlled trial would be difficult due to ethics involved in withholding a feeding intervention in a group of severely malnourished patients.

Third, there were no formal criteria to choose one feeding modality over another, nor were patient randomised to individual interventions. Choices over the best intervention have historically been based largely on patient preference so bias with regard to choice of intervention may exist, for example patient more motivated to eat and avoid tube feeding may choose MA or patients with more rapid weight loss may have been steered toward tube feeding as clinicians are anxious not to lose ground and to provide the most 'robust' intervention. However, the fact that there was no statistical difference in baseline weight and age between patients is reassuring. Additionally our study did not include patients who died during study period where complete data was therefore not available this may have introduced a degree of unavoidable bias.

Given that all three interventions have similar efficacy in this study, decisions regarding the best modality are likely to be based around complications and side effects associated with each intervention. A possible future study would be examine the efficacy of combination of MA either with PEG or NG feeding which may produce even better results than either intervention alone.

In summary, results of our study demonstrate that all three feeding interventions appear equally efficacious in enabling weight gain and may stabilise lung function in adult patients with CF. Our study is the first to compare these three different interventions. Given the equal effects of all interventions it seems reasonable that the choice of intervention, in patients whom are losing weight despite intensive dietetic input, is based on patient preference and balance of risks and benefits of treatment. Whether the benefits of these interventions to increase body weight would be sustained and ultimately effect survival of malnourished CF patients, and/or delay need for lung transplantation, has not been addressed by this study. Robust prospective studies comparing interventions to and their effects on requirement for transplant, admission rates and mortality are required to help guide decisions regarding nutritional intervention to improve outcomes in these complex patients.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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