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Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects

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Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects. J.M. Wolter, S.D. Bowler, P.J. Nolan, J.G. McCormack. ©ERS Journals Ltd 1997.

ABSTRACT: In this study, we set out to determine if home intravenous (*i.v.*) antibiotic therapy in adult patients with cystic fibrosis (CF) is a feasible, effective and less costly alternative to hospitalization, and to assess the impact of home therapy on quality of life.

The study was a prospective, randomized, two-factor mixed design involving adults presenting with respiratory exacerbations of CF. Patients were randomized such that they were discharged home after 2–4 days, or remained in hospital.

Seventeen patients had 31 admissions (13 home and 18 hospital). Following 10 days of therapy, there were no significant differences between home or hospital arms with respect to body weight, 12 minute walking distance, sputum weight, pulse oximetry, or improvement in lung function (forced expiratory volume in one second (FEV_1), or forced vital capacity (FVC)). Patients who remained in hospital were less fatigued and noted a greater degree of mastery. Patients discharged early noted less disruption to their family life, personal life and sleeping pattern. The total cost for the home therapy arm was approximately half that of the hospital therapy arm.

Home intravenous antibiotic therapy in patients with cystic fibrosis was a feasible, cost-effective alternative to receiving therapy in hospital. Although there was no clinical compromise associated with home therapy, there were advantages and disadvantages in terms of quality of life.
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As survival in cystic fibrosis (CF) continues to improve, the impact of illness and hospitalization on education, employment and lifestyle is growing. Adult CF patients are almost universally colonized with *Pseudomonas aeruginosa*. Antibiotic therapy during acute exacerbations of pulmonary disease is generally aimed at reducing the concentration of this organism in sputum, and usually involves the use of intravenous (*i.v.*) antibiotics. Patients in this situation are commonly well enough for discharge within a few days, but are obliged to stay in hospital to complete a course of *i.v.* antibiotics. Many of these patients could complete their *i.v.* therapy at home, if this was a feasible option. Although widely-practised, there are no randomized studies comparing home and hospital therapy in CF patients. There are seven studies in the published literature on this topic, the only one which was prospective allocated patients to home or hospital therapy depending on the distance between the hospital and their home [1]. The others were open studies involving retrospective experiences or historical controls [2–7].These studies suggested that home *i.v.* therapy was not associated with any clinical compromise, was preferred by patients and medical staff, and was associated with significant cost-savings. None of the studies examined quality of life (QOL).

We report the findings of a prospective, randomized, two-factor mixed design (group by time) study comparing clinical outcome, QOL and costs in hospital and at home. Our objective was to determine if home therapy, after an initial short period of hospitalization, could be used as an alternative to prolonged hospitalization without any compromise to patient care. Ethics Committee approval was obtained from both participating institutions.

Materials and methods

Subjects

Consenting adolescents and adults with an infective exacerbation of CF, attending two Brisbane hospitals, were enrolled. Respiratory exacerbations were defined by an increase in dyspnoea with or without increased sputum production, fever, or a drop in forced expiratory volume in one second (FEV_1) of 15% compared with previous best. Patients were randomized in blocks of four, by sealed envelope, to home or hospital therapy. Subjects experiencing recurrent episodes automatically alternated treatment arms after initial randomization. Each admission was considered as an event independent of earlier admissions.

Exclusion criteria included: unstable disease; dwelling outside Brisbane; a history of noncompliance; inability to learn treatment techniques, including home physiotherapy; and personal request. Patients with lung transplants or patients on their first admission were also excluded. All patients had colonization of their sputum with *P. aeruginosa*.

Initial antibiotic therapy was with ceftazidime, 2 g 12 hourly, and tobramycin, 4–6 $mg \cdot kg^{-1}$ daily as a single bolus, reflecting standard practice at the time. Therapy was guided by clinical response and treatment continued for a minimum of 10 days.

All patients received physiotherapy twice daily, plus 20 min of aerobic exercise. Other usual therapy, including oral or nasogastric supplementation, was continued unaltered.

Patients randomized to home therapy spent 2–4 days in hospital before discharge and were taught to prepare and administer their own intravenous (*i.v.*) antibiotics. Patients were discharged with medication and equipment for the duration of the proposed course of treatment. Home visits were conducted by research staff to follow progress and to assess and change *i.v.* lines.

Assessment points and outcome measures

Assessments points were chosen to reflect acute illness, convalescence after standard therapy, and a period of relative well-being. Assessment days were: admission (Day 0); Day 10 of therapy (Day 10); and approximately 10 days after cessation of *i.v.* therapy (Post-Rx). Assessment included spirometry; pulse oximetry (spot reading on room air); 12 min walking distance (12 MWD); sputum production over 12 h; and weight gain. In CF, oxygen desaturation has been shown to correlate with disease severity [8]. It is a simple, noninvasive test that may provide useful information when combined with other parameters of assessment. Weight of collected sputum samples is frequently used as a measure of clinical improvement. Shortcomings include inaccurate collection, and the effects of concurrent collection of saliva or vomit, swallowing of sputum and timing with physiotherapy. The 12 MWD is a simple, reproducible method of testing exercise tolerance in patients with lung disease [9]. Subjects walk along a flat corridor as far as possible in a 12 min period, stopping for rest whenever necessary.

The Chronic Respiratory Disease Questionnaire (CRDQ) [10] was administered on Day 0 and Post-Rx. This is a measure of change in dyspnoea, fatigue, emotion and mastery (feeling of control over the disease and its consequences), and is a widely-used measure of QOL in patients with chronic lung disease. Patients were also asked to grade the degree of disruption to their family and personal life and to their sleeping and eating as a result of their acute illness. This assessment was made at the Post-Rx visit, and was graded out of seven for each parameter.

Serum creatinine was measured on Days 0, 2 and 7. Aminoglycoside levels were performed on Day 2 and Day 7. A significant rise in creatinine was defined as a rise of ≥15% of the initial serum level [11]. Audiology was performed before and after therapy. Significant change was defined as a change of ≥15 dB [12].

Hospital costs were expressed as a charge calculated from CF in-patient stays in our hospital in 1992–1993. In addition, projected diagnostic-related group (DRG) reimbursement figures for DRG 173 (CF) were also considered. This is a system currently used in Australia, which determines reimbursement for public hospitals based on the diagnosis at admission. Costs of antibiotics and equipment used by home therapy patients were determined from consumption of resources based on hospital acquisition costs. Staff costs spent on education or home visits were calculated from hourly wages. Travel costs were determined by a standard $cents \cdot km^{-1}$ fee. Indirect costs to the patient and family were determined by interview.

Statistical analysis

Home and hospital treatment groups were compared using unpaired t-tests for normally distributed variables, and Mann-Whitney tests for skewed variables. Differences over time in outcome variables were determined by repeated measures analysis of variance (ANOVA) models. Nonparametric Mann-Whitney tests were used to consider the significance of the difference in actual costs.

QOL scores were considered to be the main outcome of interest. Since the aim of the study was to determine the equivalence of home and hospital care, sample size calculations were based on a very high type II error rate of only 5% (95% power), so that if no difference was detected between the two modes of treatment, this could be stated with confidence. Twenty subjects per arm were estimated to provide adequate power to detect differences of five or more units in the dyspnoea score with a type I error rate of 5%, assuming a two-tailed hypothesis test and a standard deviation for the distribution of dyspnoea scores of 4.71, based on preliminary results.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS)-PC+ version 4.0 (SPSS Inc., 1990, Chicago, USA).

Results

Patient enrolment

Fifty four patients had 114 admissions during the enrolment period. Thirty eight percent were male, and ages ranged 16–41 yrs (median 23 yrs). Eighty three admissions were excluded from enrolling in the trial for reasons of: noncompliance (20%); home outside the Brisbane metropolitan area (19%); an unrelated admission (16%); patient request (14%); too unwell (8%); post-lung transplant (6%); first admission to hospital (6%); no notification of patients admission (2%); non-Pseudomonal infection (3%); and, in three cases, the reason for exclusion was not specified.

Seventeen patients were enrolled in the study and had 31 admissions. Nine patients had one admission, five patients had two admissions, one had three, one had four, and one had five admissions. Ages ranged 19–41 yrs (median 22 yrs).

There were no significant differences between home and hospital admissions with respect to sex or age distributions or the proportions recruited from the two

Table 1. – Comparison of home *versus* hospital populations

		Hospital	Home	p-value
Admissions n		18	13	
Male %		28	39	0.71
Age# yrs		22 (19–41)	22 (19–41)	0.88
Admission FEV1* % pred		44 (19)	41 (19)	0.70
Admission FEV1* % drop in previous best		28 (13)	23 (18)	0.39
Type of *i.v.*	Peripheral	10	8	0.17
	Port-A-Cath	5	5	
	Central line	3	0	

#: median, and range in parenthesis; *: mean, and SD in parenthesis. FEV1: forced expiratory volume in one second; % pred: percentage of predicted.

hospitals (p>0.70 in all cases). Table 1 compares home and hospital populations at the time of admission. There were no statistically significant differences. There were no significant differences in the duration of treatment or use of antibiotics. The median duration of treatment was 11 days (range 7–26 days) for the hospital arm and 12 days (range 10–24 days) for the home arm (p=0.2). Differences in treatment duration reflect the practices of treating physicians and severity of illness. Patients undergoing home therapy spent a median of 3 days in hospital before discharge (range 1–5 days). There was no significant difference in time to next admission between each arm (p=0.68).

Doses of tobramycin were not statistically different between arms (p=0.35). Imipenem was used on seven occasions due to allergy or failure to respond to study drugs. There were no adverse drug reactions. Seventy one percent (hospital) and 46% (home) of patients (p=0.14) continued on low-dose home maintenance antibiotics (in most cases nebulized tobramycin, gentamicin or ticarcillin) after *i.v.* treatment at the discretion of their physician, and remained on these antibiotics until the final assessment day.

Home patients had significantly fewer investigations performed than in-patients (p=0.002), consistent with the observations of other authors [13].

Hospital patients routinely received twice daily physiotherapy. Home patients performed either twice daily physiotherapy or an extended once-a-day session provided by community physiotherapists or family members.

Table 2. – Home *versus* hospital comparisons of changes from baseline in clinical outcome parameters

		Hospital	Home	p-value*
Weight kg	Admission	52.5 (7.5)	53.7 (8.6)	0.10
	Day 10	53.4 (7.6)	54.1 (8.9)	
	Post-Rx	53.2 (7.6)	53.9 (8.7)	
12 min walk m	Admission	1163 (234)	1254 (333)	0.11
	Day 10	1267 (196)	1363 (579)	
	Post-Rx	1326 (239)	1363 (399)	
Sputum weight g	Admission	32.5 (29.5)	54.7 (44.3)	0.09
	Day 10	19.3 (18.1)	37.4 (26.0)	
	Post-Rx	30.6 (31.9)	29.2 (24.2)	
Oximetry %	Admission	94 (3)	93 (3)	0.44
	Day 10	95 (1)	94 (2)	
	Post-Rx	96 (2)	94 (2)	

Values are presented as mean, and SD in parenthesis. *: p-values compare magnitudes of overall changes in the home *versus* hospital arms. Rx: therapy.

Table 3. – Changes in FEV1 and FVC in hospital and home patients

		Hospital	Home	p-value*
FEV1 % pred	Day 0	44 (20)	39 (17)	0.27
	Day 10	50 (21)	45 (22)	
	Day 21	51 (21)	43 (19)	
FVC % pred	Day 0	58 (17)	56 (19)	0.30
	Day 10	64 (19)	58 (21)	
	Day 21	66 (19)	58 (22)	

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: percentage of predicted value. Values are expressed as mean, and SD in parenthesis. *: p-values compare magnitudes of overall changes in the home *versus* hospital arms.

General activity was higher in the home group as patients performed routine household and social duties.

Most patients had three home visits (range 1–5 visits) taking an average total of 4 h per patient (range 2–10 h).

Toxicity and complications

There were no deaths, no short-term readmissions and no events attributable to the drugs used. One patient had a pneumothorax associated with central line insertion. Most patients had peripheral *i.v.* lines (table 1). There were no significant differences in *i.v.* complication rates (p=0.57) or in the number of line changes required (p=0.5) by patients at home or in hospital.

There were no significant changes in serial serum creatinine (16 admissions) or serial audiometric (15 admissions) measurements.

Clinical outcome

Although there were some changes from baseline, mean improvements in body weight, 12 MWD, sputum weight and pulse oximetry were not statistically significant between home and hospital groups (table 2).

There were significant differences over time in changes from baseline noted for FEV1 (p=0.006) and FVC (p=0.02). However, there was no statistical difference between home and hospital arms in overall improvement in lung function (FEV1 p=0.27; FVC p=0.30) (table 3).

QOL outcomes

QOL data were divided into four component scores and a total score (table 4). Disruption scores were measured individually and as a total. Overall, there were significant changes from Day 0 to Post-Rx in all scores (p<0.001). These changes were of a similar magnitude for home and hospital arms for dyspnoea (p=0.25), and emotional scores (p=0.11). Hospital patients fared better in terms of fatigue, mastery and total scores (p<0.05). Home patients fared better in terms of family personal, sleep and total disruption (p≤0.005).

Costs of treatments

Most patients, (67% of hospital and 69% of home) were students or invalid

Table 4. – Home *versus* hospital comparison of QOL outcomes

	Hospital	Home	Total	p-value*
Dyspnoea scores	8.2 (5.4)	5.9 (5.5)	7.1 (5.5)	0.25
Fatigue scores	6.8 (4.6)	3.6 (3.4)	5.4 (4.3)	0.04
Emotional scores	8.6 (8.1)	4.4 (5.2)	6.7 (7.2)	0.11
Mastery scores	5.5 (3.8)	2.6 (3.4)	4.2 (3.8)	0.03
Total score	29.5 (16.5)	16.5 (14.8)	23.6 (16.8)	0.03
Family disruption	4.5 (1.3)	6.2 (1.1)	5.3 (1.5)	0.001
Personal disruption	3.8 (1.3)	5.1 (1.0)	4.4 (1.4)	0.004
Sleep disruption	4.4 (1.6)	6.0 (1.3)	5.1 (1.7)	0.005
Eating disruption	5.9 (1.5)	6.6 (0.6)	6.2 (1.2)	0.07
Total disruption	18.3 (3.3)	23.9 (3.3)	20.8 (4.3)	<0.001

Values are presented as mean, and SD in parenthesis. *: p-values compare magnitudes of changes in the home *versus* hospital arms. For dyspnoea, fatigue, emotion and mastery, scores represent change between Day 0 and Post-Rx. For family, personal, sleep and eating disruption, the results represent a single value at Post-Rx. QOL: quality of life; Rx: therapy.

pensioners and did not suffer financially due to loss of income from hospitalization. Home therapy was considerably cheaper for families than hospitalization (mean $23.77, (SD $17.77) per day of hospitalization and $15.08 ($13.48) per day of home therapy).

In 1992–1993 the actual average cost of DRG 173 to this institution was $5028.00 for an average admission of 11.4 days ($440.30 per day). In this trial, the average cost to the hospital of 10 days of home therapy preceded by 3 days in hospital was $2476.00, a difference of $2552.00. This figure includes costs of home physiotherapy, home visits, training, equipment, drugs and bed occupancy.

Discussion

Comparison of home and hospital therapies is confounded by intrinsic differences between the two environments. In this study, extensive attempts to standardize therapies such as exercise, dietary supplements and medication other than antibiotics, received by home and hospital patients were not made. We felt that analysis of treatments under real life conditions was more likely to provide practical information about home treatment.

Variation in dyspnoea scores was higher than originally anticipated (5.4 compared with 4.7). Revision of power calculations to reflect these differences indicated that there was 95% power to detect ≥7 units difference in dyspnoea scores between home and hospital. Differences of ≥5 units could be detected with an acceptably high 75% power. The mean difference in dyspnoea scores between home and hospital treatments was approximately 2.5 units, clinically less than the 5 units difference, which was hypothesized as being an important change. The issue of power is irrelevant for the comparison of total scores, since the observed difference was found to be statistically significant.

Our study demonstrates that clinical improvement over a range of parameters, was similar whether therapy was undertaken at home or in hospital. Overall improvement in lung function was similar for both arms. In addition, time to next admission was not significantly different between therapies. There was no evidence of renal or auditory toxicity; however, conventional audiometry may not detect mild aminoglycoside induced damage, as hair cells associated with very high frequency sound are affected first [14].

The present findings relating to QOL are of practical interest. Most investigators have concluded that home therapy is associated with better QOL and is preferred by patients. These conclusions have been based on interviews [2, 7] or questionnaires [1, 4] that cannot be evaluated statistically. In the present study, a more sensitive indicator of QOL was used and significant differences between home and hospital arms were demonstrated in some domains (table 3). The CRDQ is a tool developed by GUYATT *et al*. [10] that evaluates four categories relating to dyspnoea, emotional function, fatigue and mastery. It overcomes differences in age, sex and extent of disability by asking the individual to nominate activities for assessment. In the present study, improvements in dyspnoea scores were not significantly different between home and hospital arms, possibly reflecting the effect of antimicrobial therapy in both environments. Hospital patients noted significantly more improvement in fatigue than patients at home. This may reflect increased activity of patients at home, who continue to carry out normal domestic and work-related duties. Contrary to our expectations, there was no evidence of greater improvement in emotional well-being in the home group. Feelings of mastery were significantly better after hospital therapy than home therapy, and total improvement in QOL was higher after hospital therapy. Additional questions relating to effect of treatment on lifestyle, although not a validated QOL tool, gave further insight into the disrupting effects of therapy on lifestyle. As expected, QOL scores showed significantly less disruption to family life, personal life and to sleeping patterns in patients having treatment at home. Eating habits were not significantly affected by either form of therapy.

One possible explanation for these results is the familiarity most adult CF patients have with the hospital environment. Patients in this study were less familiar with home therapy, which may initially have been perceived as more threatening than routine hospitalization. Clearly, although home therapy is more convenient to patients, QOL may be adversely affected. Serial QOL measurements need to be performed to determine if these trends continue after familiarization with home treatment.

Crucial to the success of any home therapy programme is appropriate patient selection. Most patients admitted during the enrolment period of this trial were not suitable for home therapy. Home therapy failures are more likely when patients are noncompliant or have an illness

not treatable in the home setting [15]. These criteria, as well as patient requests to stay in hospital, were the most commonly encountered reason for avoiding home treatment in this trial. In view of the low number of complications in this study, it can be assumed that the selection criteria for patient enrolment were successful in limiting home treatment to suitable indivi-duals. Home therapy was initiated with a 2–4 day stay in hospital to ensure subject skills in managing *i.v.* lines, injections and antibiotics.

There was a range of *i.v.* lines used by patients, most had peripheral lines and there was no difference between *i.v.* line-related complications in home or hospital groups, consistent with findings by others [16, 17].

Ideally, antibiotics used in home therapy should be easily and infrequently administered, require minimal monitoring and have low toxicity. Aminoglycosides, given as a single daily bolus, are easy to administer in the home setting and require minimal monitoring of peak and trough levels [11]. Ceftazidime, given at a dose of 2 g twice daily, has been shown to be effective in serious infections [18, 19], and is suitable in CF since elimination is not increased in these patients [20]. A combination of these two drugs, at these doses, was chosen to reflect convenience of home-administered treatment without compromising therapeutic efficacy. This antibiotic regimen was well-managed by individuals at home and produced clinical improvement in most patients.

There were direct cost benefits when patients were discharged early, even when ongoing costs of home-based therapy were taken into account. Equipment and drugs made up the largest proportion of home therapy costs, whereas accommodation and board accounted for the largest fraction of hospital costs for in-patients, a trend noted by others [21]. Since home visits were performed by the researcher in this study, costs of home therapy to the hospital may have been artificially low and may not reflect the costs of an established home therapy unit employing full-time staff.

Home therapy is rapidly becoming a popular treatment alternative, driven in part by economic imperatives. At present there is lack of supporting evidence for its role from randomized trials. This study confirms the clinical efficacy of home therapy. In contrast to previous studies, we found that, although home therapy causes less disruption to personal, family and social life, hospitalization may be associated with greater improvement in some aspects of quality of life. These results may be clarified by studies involving larger numbers of patients. In view of the enthusiasm of patients, clinicians and economists for home treatment, larger randomized trials need to take place to confirm its efficacy.

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