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Research Dissemination Reports

衛生及醫護服務研究基金

研究成果報告

Mental health
精神健康

Reference standards
參考標準

Traditional Chinese medicine
傳統中醫藥

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Health and Health Services Research Fund

Research Dissemination Reports

Traditional Chinese Medicine

Dissemination reports are concise informative reports of health-related research supported by funds administered by the Food and Health Bureau, namely the *Research Fund for the Control of Infectious Diseases* (RFCID) and the *Health and Health Services Research Fund (HHSRF)*.* In this edition, 11 dissemination reports of projects related to mental health, reference standards, and traditional Chinese medicine are presented. In particular, three projects are highlighted due to their potentially significant findings, impact on healthcare delivery and practice, and/or contribution to health policy formulation in Hong Kong.

Individuals with poor mental health may also have poor compliance with treatment. Research suggests that self-stigma is a significant disincentive for psychosocial treatment compliance. Tsang[1] examined the underlying mechanism of self-stigma and treatment compliance and developed and tested the effectiveness of an interventional programme for reducing self-stigma, enhancing readiness for change, and treatment compliance. In a study of 105 Chinese subjects with schizophrenia, he found that self-stigmatised individuals were less willing to seek psychiatric services due to anticipated stigma, and that such individuals possessed poor insight with respect to the beneficial effects of psychiatric treatment. The intervention programme was not effective in enhancing treatment compliance, which emphasises the complex nature of poor mental health and the need to further augment psychosocial intervention in this vulnerable group.

Growth standards are useful for monitoring whether a child's health care needs are being adequately met or not. Schooling et al[2] examined how the 2006 World Health Organization (WHO) criteria for an optimal nurturing environment impacted infant growth in Hong Kong Chinese children. They found that parental socio-economic status was positively associated with length and body mass at 9 months. At 36 months, local children were generally shorter and fatter than the WHO growth reference. The authors caution that as rapid infant growth is associated with adult obesity and metabolic risk, attention should be paid to ensuring Hong Kong children achieve appropriate linear growth without becoming overweight.

Constipation is a common gastrointestinal complaint for which Chinese herbal medicine is becoming a more popular form of treatment. Bian et al[3] conducted an 18-week prospective, randomised, double-blind, placebo-controlled clinical study of a Chinese herbal medicine for treatment of functional constipation in 120 Hong Kong Chinese suubjects. The herbal remedy was superior to placebo and no serious adverse effects were reported.

A research impact evaluation was conducted 2 years after the project end date for many of the studies reported in this supplement. Impact was reported through publications in peer-reviewed journals, gain of additional qualifications for project team members, career advancement, additional research funding obtained, stimulation of other research groups to conduct related research, and impact on policy and health care practices through changes in behaviour of health care professionals and/or other decision makers.

We hope you will enjoy this selection of research dissemination reports. Electronic copies of these dissemination reports and the corresponding full reports can be downloaded individually from the Research Fund Secretariat website (http://www.fhb.gov.hk/grants). Researchers interested in the funds administered by the Food and Health Bureau also may visit the website for detailed information about application procedures.

* In December 2011, the RFCID and HHSRF were consolidated into a new fund called the *Health and Medical Research Fund* (HMRF) with an expanded scope to include advanced medical research.

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HWH Tsang 曾永康

Stages of change, self-stigma, and treatment compliance among Chinese adults with severe mental illness

Key Messages

1. Individuals with higher global functioning, better readiness for action, and lower self-esteem decrement tend to have better psychosocial treatment participation.
2. Individuals with lesser psychiatric symptoms are more likely to have better treatment attendance.
3. Self-stigmatisation undermines treatment compliance. Its indirect effects can be mediated via stages of change and insight.
4. The self-stigma reduction programme may reduce self-esteem decrement, promote readiness for changing own problematic behaviours, and enhance psychosocial treatment compliance. However, its therapeutic effects were not maintained during the 6-month follow-up.

Introduction

Self-stigma is a significant predictor of psychosocial treatment compliance.[1] The present study hypothesised that in individuals with schizophrenia self-stigmatised ideas impede their stages of change for seeking treatment.[2] Understanding of the mechanism helps formulate appropriate treatment to counteract negative consequences.

This study aimed to (1) examine the relationship between stages of change, self-stigma, insight, self-esteem, and psychosocial treatment compliance among Chinese adults with schizophrenia; (2) develop an interventional programme to reduce self-stigma and enhance readiness for change and treatment compliance; and (3) test the effectiveness of the self-stigma reduction programme.

Methods

This was a cross-sectional study (for relationship exploration) and entailed a randomised controlled trial (in the form of a self-stigma reduction programme). Institutional ethical approval and informed consent from each patient were obtained. Between March 2007 and January 2008, 51 men and 54 women with schizophrenia were recruited using convenience sampling by occupational therapists, social workers, and nurses from the Baptist Oi Kwan Social Services, the Richmond Fellowship of Hong Kong, the Stewards Company, the United Christian Hospital, and the Yung Fung Shue Psychiatric Centre. All the recruited patients had at least an elementary level of education, and their mean age was 42 (standard deviation, 9) years.

Participants were assessed using the Psychosocial Treatment Compliance Scale (PTCS), the Brief Psychiatric Rating Scale (BPRS), the Global Assessment of Functioning Scale (GAF), the Chinese Self-stigma of Mental Illness Scale (CSSMIS), the Change Assessment Questionnaire for People with Severe and Persistent Mental Illness (CAQ-SPMI), the Scale to Assess Unawareness of Mental Disorders (SUMD), and the Chinese General Self-efficacy Scale (CGSS). Stepwise multiple regression was used to explore the relationship between treatment compliance (dependent variable) and potential contributing factors. The contribution of each significant independent variable in predicting participation/attendance was reflected by the magnitude of each standardised regression coefficient (β). Two hypothetical path models for self-stigma, insight, readiness for change, and psychosocial treatment compliance were compared (Fig). Relative chi-square (χ^2/df), comparative fit index (CFI), and root mean square error of approximation (RMSEA) were used to test the goodness-of-fit of the models. The goodness-of-fit obtained with the two path models were compared, and the P value determined.

The self-stigma reduction programme comprised 16 sessions (12 group sessions plus four individual follow-ups). It integrated psychoeducation, cognitive behavioural therapy, motivational interviewing, social skills training, and goal attainment components. The programme was pilot-tested at the psychiatric wards of Kowloon Hospital by an experienced occupational therapist and research associate. The feedback was positive. Participants who suffered

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from self-stigmatisation as indicated by the CSSMIS were eligible. Between October 2008 and December 2009, 66 individuals with schizophrenia recruited from the Baptist Oi Kwan Social Services, the Richmond Fellowship of Hong Kong, the Stewards Company, and the New Life Psychiatric Rehabilitation Association were randomised to the experimental (n=34) or comparison (n=32) protocol. The two groups were not significantly different (Table 1).

Participants in the experimental and comparison groups received the self-stigma reduction programme and newspaper reading, respectively, delivered by a research associate and an occupational therapist. The newspaper reading included stigma-related issues pertaining to mental illness. A 1-hour session was held twice a week, and every month there was a 15-minute individual follow-up session. The same seven instruments were used to assess outcome before commencement of the intervention, after the 7th and 12th sessions, and 2, 4, and 6 months after the 12th session. The raters were blind to the intervention types.

The active intervention (baseline to post-intervention) and maintenance (post-intervention to third follow-up) effects of the two groups were compared. Repeated measures ANOVA with Bonferroni correction (P value adjustment within each variable by dividing the number of time intervals) was used to determine whether significant differences existed. ANCOVA was used when there were differences in baseline scores between the two groups. Only measures that demonstrated an active intervention effect were included for analysis of the maintenance effect. The potential institutional effect was controlled. Missing data were computed by the principle of last observation being carried forward.

Results

In the cross-sectional study, 14 and 11 independent variables on 'participation' and 'attendance', respectively, reached the Bendel criterion for the regression analyses.[3] Higher global functioning (β=0.410, P<0.001), better

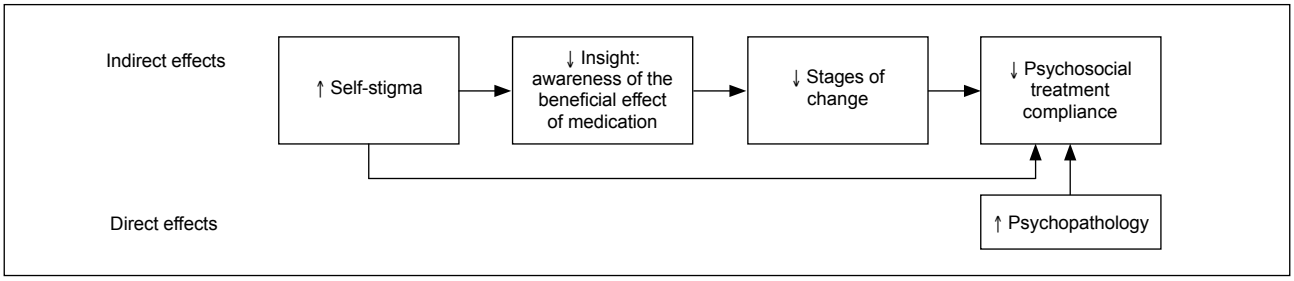

Fig. Hypothetical path model 1 (indirect effects of self-stigma) and model 2 (direct and indirect effects of self-stigma)

Table 1. Demographics of participants*

Parameter	Experimental (n=34)	Comparison (n=32)	χ^2 / t-value	df	P value
Gender			0.77	1	0.559
Male	18 (52.9)	19 (59.4)			
Female	16 (47.1)	13 (40.6)			
Education			2.440	2	0.295
Primary	8 (23.5)	13 (40.6)			
Secondary	22 (64.7)	17 (53.1)			
Tertiary	4 (11.8)	2 (6.3)			
Marital status			4.810	3	0.186
Single	23 (67.6)	26 (81.3)			
Married	5 (14.7)	4 (12.5)			
Divorced	6 (17.6)	1 (3.1)			
Widowed	0 (0.0)	1 (3.1)			
Living condition			2.362	3	0.501
Family	10 (29.4)	14 (43.8)			
Alone	9 (26.5)	6 (18.8)			
Friends	1 (2.9)	0 (0.0)			
Hostel	14 (41.2)	12 (37.5)			
Income			2.860	3	0.414
Family	2 (5.9)	5 (15.6)			
Normal/Higher Disability Allowance	7 (20.6)	6 (18.8)			
Comprehensive Social Security Assistance	25 (73.5)	20 (62.5)			
Others	0 (0.0)	1 (3.1)			
Age (years)	43.91±10.38	46.91±8.92	-1.253	64	0.215
Global Assessment of Functioning score	66.53±8.87	66.59±9.42	-0.029	64	0.977
Brief Psychiatric Rating Scale score	21.76±14.02	26.88±12.47	-1.561	64	0.123

* Data are presented as No. (%) of patients or mean±SD

readiness for action (β=0.310, P<0.001), and lower self-esteem decrement (β=-0.225, P<0.01) were significant predictors for better treatment participation. These factors accounted for 36.6% of the variance in predicting treatment participation. As to treatment attendance, those with lesser psychiatric symptoms (β=-0.260, P<0.01) and females (β=0.204, P<0.05) were more likely to have better attendance. The overall model explained 11.3% of the total variance for predicting treatment attendance.

For path analysis, only the 'self-decrement' subscale of the CSSMIS was significantly associated with insight towards the achieved effect of psychiatric medication (r=0.234, P=0.061). Thus, only this self-stigma test score was included for further analysis. In model 1 (indirect effect of self-stigma), the goodness-fit-statistics (chi-square=6.166, df=3, P=0.104; CFI=0.909 [saturated model], 1.000 [default model]; RMSEA=0.101) did not fit well with this model. Self-stigma explained 5.5% of the variance for insight, and self-stigma plus insight explained 15.4% of the variance for stages of change. The model explained 10.3% of the total variance for treatment compliance. In model 2 (direct and indirect effects of self-stigma), the goodness-fit-statistics (chi-square=5.135, df=5, P=0.400; CFI=0.977 [saturated model], 1.000 [default model]; RMSEA=0.016) fitted well with the proposed path model. Self-stigma was found to exert both direct and indirect effects on reducing treatment compliance. Self-stigma explained 5.5% of the variance for insight, and self-stigma plus insight explained 15.4% of the variance for stages of change. Including the direct effect of psychiatric symptoms, the model explained 20.4% of the total variance for treatment compliance. The results for goodness-of-fit test (P<0.003) suggested that model 2 was significantly superior to model 1.

On the active intervention stage, there were significant differences between the two groups in baseline scores for 'stereotype agreement' [t(64)=2.407; P=0.019], 'self-concurrence' [t(64)=3.267; P=0.002], 'self-esteem decrement' [t(64)=2.717; P=0.008], and 'participation' [t(64)=2.130; P=0.037]. Thus, repeated measures ANCOVA was used to study the changes in these scores. Group x time interaction among the two groups showed overall significance in the self-esteem decrement subscale of the CSSMIS [F (2, 56)=4.916; P=0.011], the stages of change in continuous score of the CAQ-SPMI [F (2, 57)=3.959; P=0.025], and the participation subscale of the PTCS [F (2, 56)=3.501; P=0.037]. Post-hoc comparison suggested a significantly lower self-esteem decrement in the experimental group at mid (F=4.483; P<0.050) and post (F=10.004; P<0.025 with Bonferroni adjustment) assessments. The experimental group also possessed significantly better readiness for change at mid-assessment (F=6.010; P<0.025 with Bonferroni adjustment) and better treatment participation post-assessment (F=6.430; P<0.025 with Bonferroni adjustment). Nonetheless, no overall significance in group x time interaction was found for the SUMD and CGSS (Table 2).

Regarding the maintenance stage, participants in the experimental group demonstrated better self-esteem decrements and treatment participation than those in the comparison group at the post-assessment interval. Repeated measures ANOVA, however, revealed no difference in maintenance of the effect on self-esteem decrement and treatment participation in the two groups (Table 3).

Table 2. Repeated measures ANOVA/ANCOVA on the active intervention phase (group by time interaction)

Instrument*	Mean±SD score						Repeated measures ANOVA/ANCOVA		
	Pre-active		Mid-active		Post-active				
	Experimental	Comparison	Experimental	Comparison	Experimental	Comparison	F-value	P value	Effect size
CSSMIS score									
Stereotype awareness	86.00±14.80	79.78±13.95	74.71±18.13	74.25±14.42	74.82±20.61	74.75±14.22	0.756 (2, 57)	0.474	0.026
Stereotype agreement†	88.76±14.75	79.81±15.46	72.03±19.05	72.81±14.56	70.82±18.91	72.72±18.68	0.735 (2, 56)	0.484	0.026
Self-concurrence†	86.26±15.32	72.63±18.53	65.56±20.95	68.50±15.52	61.47±20.22	69.34±18.05	3.070 (2, 56)	0.054	0.099
Self-esteem decrement†	82.82±16.22	71.56±17.45	65.37±20.12	66.59±20.51	61.38±20.43	67.97±18.83	4.916 (2, 56)	0.011	0.147
CAQ-SPMI stages of change continuous score	8.51±1.57	8.40±1.32	8.78±1.42	7.86±1.25	8.42±1.37	8.15±0.96	3.959 (2, 57)	0.025	0.122
PTCS score									
Attendance	18.12±3.23	17.56±3.11	17.51±3.01	16.78±3.23	18.21±3.25	17.09±3.42	0.650 (2, 27)	0.526	0.022
Participation†	38.80±5.58	35.77±5.98	39.14±5.09	36.03±5.56	41.51±5.91	37.99±5.63	3.501 (2, 56)	0.037	0.111
SUMD score									
Mental illness (current)	2.76±1.91	3.47±1.76	2.94±1.83	3.14±1.82	3.15±1.94	3.69±1.73	1.686 (2, 57)	0.194	0.056
Mental illness (past)	2.50±1.85	3.34±1.70	2.85±1.83	3.03±1.88	3.03±1.95	3.69±1.80	0.992 (2, 57)	0.377	0.034
Medication (current)	1.56±1.33	2.06±1.68	1.14±0.69	2.07±1.58	1.35±1.04	1.91±1.51	0.544 (2, 57)	0.584	0.019
Medication (past)	1.53±1.26	2.03±1.67	1.33±1.00	1.80±1.40	1.41±1.08	1.84±1.42	0.097 (2, 57)	0.908	0.003
Consequence (current)	2.00±1.74	2.09±1.78	1.64±1.49	1.93±1.41	1.62±1.48	2.06±1.68	0.252 (2, 57)	0.778	0.009
Consequence (past)	2.03±1.68	2.03±1.71	1.64±1.49	1.90±1.38	1.62±1.48	2.06±1.68	0.517 (2, 57)	0.648	0.015
CGSS score	21.56±6.45	23.44±5.89	22.44±5.76	23.03±6.98	21.79±6.45	25.81±6.22	1.946 (2, 57)	0.152	0.064

* CSSMIS denotes Chinese Self-stigma of Mental Illness Scale, CAQ-SPMI Change Assessment Questionnaire for People with Severe and Persistent Mental Illness, PTCS Psychosocial Treatment Compliance Scale, SUMD Scale to Assess Unawareness of Mental Disorder, and CGSS Chinese General Self-efficacy Scale

† Repeated measures ANCOVA used

Table 3. Repeated measures ANOVA/ANCOVA on the maintenance phase (group by time interaction)

Instrument*	Mean±SD score								Repeated measures ANOVA/ANCOVA		
	Post-active		1st follow-up		2nd follow-up		3rd follow-up				
	Experimental	Comparison	Experimental	Comparison	Experimental	Comparison	Experimental	Comparison	F-value	P value	Effect size
CSSMIS self-esteem decrement score	61.38±20.43	67.97±18.83	58.21±18.30	66.88±14.46	60.06±17.42	62.81±18.41	65.06±21.85	63.53±17.17	2.204 (3, 62)	0.096	0.096
PTCS participation score	41.51±5.91	37.99±5.63	41.56±5.65	38.37±6.76	40.76±5.64	37.97±6.69	40.09±6.80	38.19±7.45	0.886 (3, 62)	0.453	0.041

* CSSMIS denotes Chinese Self-stigma of Mental Illness Scale, and PTCS Psychosocial Treatment Compliance Scale

Discussion

In the cross-sectional study, among individuals with schizophrenia, self-stigma was a significant predictor for psychosocial treatment compliance. Global functioning was the most significant predictor of treatment participation. Psychiatric symptoms and being female were significant predictors of treatment attendance. Both direct and indirect effects of self-stigma were associated with poor treatment compliance. With regard to the direct effect, self-stigmatised individuals were less willing to seek psychiatric services in anticipation of stigma, believing that the public labels those receiving mental health services as crazy and weak.[1] As to the indirect effect, self-stigmatised individuals have poor insight towards the beneficial effects of psychiatric treatment, particularly when individuals regard such negative aspects of psychiatric treatment as side effects and social stigma. Their poor insight limits their motivation to manage their own mental health problems, which then leads to treatment noncompliance.[4] Individuals with more psychiatric symptoms tend to have poorer compliance.

Caution is needed in the interpretation of these findings, as the relationship of these variables can be explained conversely. For instance, individuals with poor treatment compliance are more likely to be symptomatic and have poor recovery. The decline in personal functioning and the aggravation of psychiatric conditions then further facilitates the stigmatisation process. Individuals with more severe psychiatric symptoms have more difficulty formulating positive beliefs about self. These negative conceptions undermine the motivation to receive treatment.

Among individuals with schizophrenia, the self-stigma reduction programme had modest effects on improving self-esteem decrement, readiness to change one's own problematic behaviours, and psychosocial treatment participation. Furthermore, its therapeutic effects were not be maintained after completion of the programme. Different treatment approaches contributed to the reduction of self-stigmatisation. The readiness for change was enhanced after the participants completed the first half of the experimental protocol. Motivational interviewing may have contributed to the improvement in the experimental group.[5] This modality helped self-stigmatised individuals realise how their stigmatising beliefs and behaviours hindered their life pursuits, and discover the advantages and disadvantages of adopting their present behaviours.[5] Participants of the experimental group demonstrated better psychosocial treatment participation than those of the comparison group at the post-intervention assessment. Self-stigmatised individuals were more likely to endorse feeling of hopelessness and query the beneficial outcomes of psychosocial treatment. It is likely that better participation in treatment was due to improved self-esteem. No significant difference was noted in the domains of insight and self-efficacy. This may be due to the restricted treatment content disseminated.

Although many of the treatment effects were not significant, they had implications for developing effective treatment programmes for individuals with schizophrenia in the future. These could deal with self-stigmatisation by enhancing readiness for change and psychosocial treatment participation. In addition, the treatment effect was not long lasting. Further efforts are needed to strengthen the effect size and the long-term effectiveness of the self-stigma reduction programme. It is important to consider the characteristics and daily experience of participants when designing the treatment protocol. A supportive environment to liaise with participants' corresponding service units should be fostered. Furthermore, helping individuals with schizophrenia to develop a sense of urgency enables them to accept their illness and reject mental illness stigma.

There were several limitations in this study. First, the causality among variables could not be examined using the cross-sectional approach. Second, only a small number of participants were recruited from a small number of psychiatric settings, and may affect generalisation of the results. Third, 'fully non-compliant' individuals were not recruited, and may have led to selection bias. Fourth, a structural clinical interview for DSM-IV to verify the diagnosis of participants was not used. Fifth, certain generic measures (eg self-efficacy) were not sensitive enough to detect changes across time. Sixth, differential effects of different intervention strategies on how each of the intervention components contributed to the clinical

outcomes were not investigated. Seventh, the clinical significance of the programme was not investigated. Eighth, the effects of confounding variables (eg therapeutic alliances) were not accounted for and may have affected the validity.

Acknowledgements

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Pathological Internet use and associated factors among university students in Hong Kong

Key Messages

1. Among university entrants, the prevalence of pathological Internet use (PIU) increased more than three-fold (from 5.0 to 15.7%) after 18 months of university life. Psycho-social factors such as depression, life dissatisfaction, and use of the Internet for recreational purposes were associated with the development of PIU.
2. University health workers should be aware that PIU is associated with inferior mental well-being, increased sleeping disorders, and deterioration of family relationships. Special attention should be given to Mainland Chinese students and those with pre-existing psychological problems, as they are more prone to developing PIU.
3. Most university students with PIU were unaware of the health implications of the condition and thus not motivated to seek help. Health workers must take a pro-active approach.

Introduction

Some university students, particularly those living away from home, engage in unhealthy behaviours (erratic sleeping habits, inadequate physical exercise, poor diet, and uncontrolled alcohol consumption), which often persist or even become worse in adulthood. Pathological Internet use (PIU) is defined as Internet use that causes personal problems, withdrawal symptoms, and mood-altering states. In United Kingdom, up to one fifth of university students suffered from symptoms consistent with PIU.[1] According to the Hong Kong Census and Statistics Department, in 2009 Internet use was almost ubiquitous among individuals aged 15 to 24 years (99.1%), those with post-secondary education (97.0%), and among students (99.3%). Thus, university students in Hong Kong are likely to be at risk of PIU. Media consumption such as television viewing is associated with decreased physical activity, poor diet, and increased obesity. Pathological Internet use is likely to be an even more detrimental health hazard, as it is associated with increased social isolation, mood disorders, and sleep problems.[2,3] This study aimed to determine the prevalence and risk factors of PIU among university students in Hong Kong and examine its association with health problems. The ensuing findings could provide insights for intervention and prevention of PIU in university students.

Methods

This study was conducted from January 2009 to January 2010. The study population comprised full-time undergraduate entrants of The Chinese University of Hong Kong in 2007. Non-Chinese speaking students or exchange students were excluded. In July 2007, self-administered questionnaires were randomly delivered to 50% of all registered entrants. Completed questionnaires were collected when the students presented for health check in August 2007. Student ID numbers and email addresses were collected for use during follow-up. In February 2009 (1.5 years later), the students were invited through email to complete a follow-up online survey. To increase the response rate, HK$40 cash coupons were provided to students who completed the survey. Several reminders were sent to non-respondents through email and instant messengers.

During the baseline survey in 2007, student ID numbers, email addresses, instant messenger accounts, and telephone numbers were collected for case identification and follow-up. Socio-demographics such as major of study, age, gender, birthplace, residential status, household income, parental education level, and academic results were collected. A validated 26-item Chen's Internet Addiction Scale (CIAS) was used to assess PIU; a score of ≥64 was considered diagnostic of PIU.[4] Other Internet-related questions included average weekly hours of Internet use, preferred online activities, self-perceived impact of the Internet, and having met strangers from the Internet. Lifestyle factors including sleep patterns and physical activity levels were collected. Respondents were considered physically active if they reported having 20 minutes of vigorous activity at least 3 days per week or 30 minutes of moderate activity at least 5 days per week. Daytime sleepiness was assessed by the Hong Kong Chinese version of the Epworth's Sleepiness Scale. Mental well-being was assessed by the Satisfaction with Life Scale, Rosenberg's Self-Esteem Scale (6-item version),

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The Chinese University of Hong Kong: School of Public Health and Primary Care
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social anxiety subscale of the Self-Consciousness Scale, and Center for Epidemiologic Studies Depression Scale (short form) [CESD-10].

The follow-up questionnaire in February 2009 contained most items of the baseline questionnaire and the following additional items: present living quarters (student hostel or not), academic results (the first-year grade point average), time spent on studying in a week, satisfaction with various aspects of university life, self-perceived level of problematic Internet use, and the Short Form-12 health survey to measure overall health status.

The prevalence and cumulative incidence of PIU was determined. Stepwise multiple logistic regression analysis was used to assess the association between potential risk factors and PIU, after adjusting for socio-demographic factors. Association of different factors with PIU was assessed using the Chi-square test (for categorical outcomes) and independent sample *t*-test (for continuous outcomes).

Results

In the 2007 baseline survey, 1262 students completed the questionnaire (response rate, 78.2%) and 1027 (81.4%) of them completed the follow-up survey in 2009. There were no significant differences between 2007 and 2009 participants in terms of gender, age at matriculation, origin (local vs. mainland China students), or field of study.

The prevalence of PIU in 2007 and 2009 were 5.0% and 15.7%, respectively. Using a stepwise logistic regression model, risk factors for PIU were being a Mainland Chinese student (OR=1.89, P=0.026), dissatisfaction with university life (OR=1.98, P=0.012), higher baseline levels of depressive symptoms (OR=1.08 per 1 point increase in CESD-10 score, P<0.001), and using the Internet for recreational and interactive activities such as gaming, gambling, chatting, downloading music and videos (OR=1.68-6.70, P<0.05).

Using logistic regression analysis, PIU was positively associated with late sleeping (sleep after 1 am on a weekday; OR=1.85, P=0.004) and meeting strangers from Internet (OR=3.83, P<0.001). Students with PIU were more likely to suffer from daytime sleepiness (OR=1.57, P=0.016). The association between PIU and physical inactivity was not significant (P=0.162). Although PIU students spent less time studying (25.5 vs. 29.2 hour/week, P=0.22), their mean grade point average was similar to non-PIU students (3.02 vs. 3.06, P=0.267). Students with PIU had worse physical and mental well-being, as indicated by significantly lower scores for SF-12 physical and mental components and life satisfaction, and higher levels of social anxiety, stress, and depression (P<0.05).

Regarding self-perceived PIU status, among non-PIU students, 63.7% did not regard their Internet use to be a problematic behaviour, 35.2% thought they were 'somewhat problematic', and only 1.1% reported it as 'very problematic'. The corresponding percentages of PIU students were 28.4%, 56.8%, and 14.8%. Among non-PIU students, 68.9% expressed lack of interest in learning skills to control their Internet use (compared to 46.2% in the PIU group), whereas 29.2% reported that they were 'somewhat interested' (versus 42% in the PIU group) and 2.0% were 'very interested' (versus 11.8% in the PIU group).

Discussion

The prevalence of PIU in these university entrants increased more than three-fold (from 5.0 to 15.7%) after 18 months of university life. Development of unhealthy lifestyles during university is attributable to greater autonomy and less stringent parental control.[5] This was partially supported by the higher prevalence of PIU among students from Mainland China, but the association between hostel living and PIU was not significant. This suggests that lower parental supervision per se was not a risk factor for PIU among Hong Kong university students. Pathological Internet use was associated with psychosocial factors and use of the Internet for recreational activities such as online gaming and gambling. The associations between PIU and baseline depressive symptoms and life dissatisfaction suggest that psychosocial factors affected the development of PIU among Hong Kong university students. Similar to substance abuse, pathological Internet use may be a convenient coping mechanism for dysphoric feelings. In addition, PIU was associated with adverse health effects in physical, mental, and social health dimensions. Health workers including student counsellors and clinical staff should be mindful of this emerging health issue in students who seek assistance for psycho-social or even physical health problems.

Lack of awareness of PIU and its potential effects on other health domains was common among university students. Therefore, they are unlikely to seek help to curtail such behaviour. Being unaware appears to be a key barrier to prevent PIU. The health education curriculum of secondary schools should include PIU to foster awareness of its potentially deleterious consequences.

Conclusions

Pathological Internet use is an underappreciated health problem affecting university students in Hong Kong. It is a risk factor for common physical and psychosocial problems. Primary prevention of PIU should start in the early period of university life, given its relatively low prevalence at that stage. University health workers should become acquainted with this common health issue, and consider Internet use patterns when dealing with student health issues. Further attention should be given to vulnerable groups, such as non-local students and those with pre-existing mental health problems.

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Use of electroacupuncture to accelerate the antidepressant action of selective serotonin reuptake inhibitors: a single-blind, randomised, controlled study

Key Messages

1. Patients treated with dense cranial electroacupuncture stimulation (DCEAS) had a significantly greater reduction in the 17-item Hamilton Rating Scale for Depression scores and clinically significant response to treatment than those having sham acupuncture (19.4% vs. 8.8%).
2. Neither sham acupuncture nor DCEAS had effects on the platelet serotonin system.
3. In the early phase of selective serotonin reuptake inhibitor treatment for depressed patients, DCEAS could be used as an additional therapy.
4. Neurobiological mechanisms responsible for DCEAS effects warrant further investigation using neuroimaging.

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Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment for depressive disorders, but their outcomes are unsatisfactory.[1] A large proportion of depressed patients cannot obtain a full remission and experience relapse and functional impairment. Moreover, the delay in the onset of the action of SSRIs prolongs patients' suffering and exposes them to the risk of suicide. These shortcomings have led to the search for alternative strategies to enhance the antidepressant efficacy of SSRIs, particularly in the early phase of treatment.[2]

Acupuncture is efficacious for various types of depressive disorders, particularly in alleviating associated pain, autonomic dysfunction, sleepless, and low moods. This is thought to be associated with the fast, direct modulation of multiple central neurochemical systems. Adrenergic and serotonergic (5-HT) mechanisms in the brainstem, as well as neuronal and hypothalamic neuroendocrine systems play a pivotal role in the pathophysiology of major depression. We therefore hypothesised that electroacupuncture may enhance the antidepressant activity of SSRIs in the early phase of treatment.

Dense cranial electroacupuncture stimulation (DCEAS) involves electrical stimulation of dense acupoints on the forehead mainly innervated by the trigeminal nerve. Such acupoints modulates multiple central transmitter systems via the trigeminal sensory-brainstem adrenergic and 5-HT neuronal pathways.[3] Pilot studies have shown that DCEAS is effective in improving refractory obsessive-compulsive disorder, major depressive disorder (MDD), post-stroke depression, and MDD-associated residual insomnia.

Human platelets are terminally differentiated 5-HT-synthesising cells and are similar to 5-HT neurons in terms of synthesis, release, and receptors. Platelets have been widely used as a peripheral model for investigation of psychiatric disorders associated with the central 5-HT system. We hypothesised that DCEAS as additional treatment could produce greater clinical improvement in the early phase of SSRI treatment in patients with MDD, and that the antidepressant effects of DCEAS may be associated with changes in the platelet 5-HT system.

Methods

This single-blind, randomised, controlled trial was conducted in the Department of Psychiatry at the Kowloon Hospital of Hong Kong between May 2009 and March 2011. The study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Based on our recent meta-analysis, a sample size of 35 patients per group could provide approximately 80% power to detect an estimated difference in the 17-item Hamilton Rating Scale for Depression (HAMD-17) score of 3 points, with an α set at 0.05 and an estimated standard deviation of 4.5 at the endpoint of 3-week treatment.

Fluoxetine (FLX) is one of the most prescribed SSRIs for major depression worldwide.[4] Unmedicated patients in both groups received orally administered FLX for 3 weeks. The dosage was initiated at 10 mg/day and escalated to an optimal dose within 1 week, based on patient response; the maximum dose was 40 mg/day. Information about the equivalent efficacy of FLX was provided to the patients.

Of 188 outpatients referred by psychiatrists, 73 were eligible and randomly assigned to receive sham acupuncture (n=35) and DCEAS (n=38). Informed consent was obtained from each patient. Each patient received nine sessions of intervention (three sessions per week) during FLX treatment. For DCEAS, acupuncture needles were inserted into six pairs of forehead acupoints and affixed with adhesive tapes to ensure allocation concealment. Electrical stimulation at a comfortable level was then delivered for 30 minutes. The acupoints were Baihui (Du-20) and Yintang (EX-HN3), left Sishencong (EX-HN1) and Toulinqi (GB15), right Sishencong (EX-HN1) and Toulinqi (GB15), bilateral Shuaigu (GB8), bilateral Taiyang (EX-HN5), and bilateral Touwei (ST8) [Fig 1]. For sham acupuncture, Streitberger non-invasive acupuncture needles were applied and affixed in the same way.[5] The forehead acupoints were outside the visual field of the subjects to ensure blinding. Patients were not told about the potential response of both procedures. To ensure consistency in acupuncture procedure, the principal investigator provided a training workshop about the acupuncture protocol. Acupuncture was performed by two registered acupuncturists who had practised Chinese medicine for over 3 years.

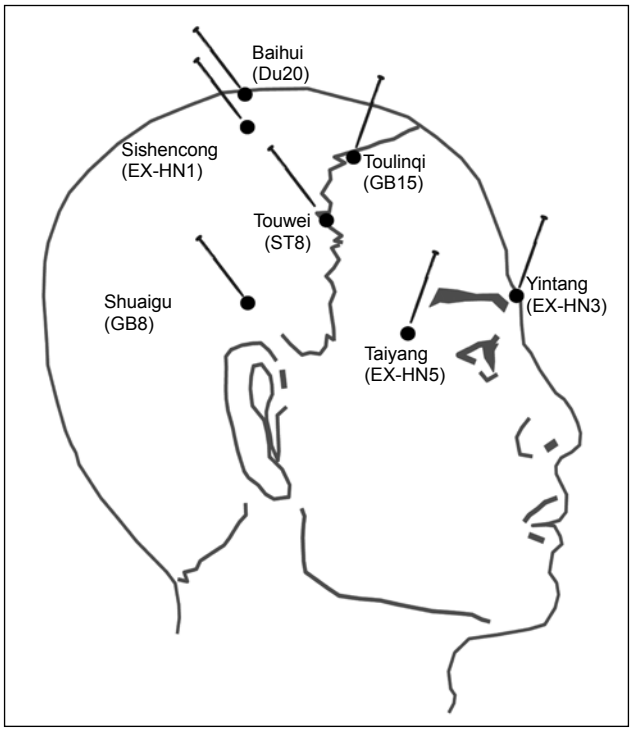

Fig 1. Acupoints used in dense cranial electroacupuncture stimulation

Outcome was assessed using the HAMD-17, the Clinical Global Impression-Severity (CGI-S), and the Chinese-version Self-rating Depression Scale (SDS) at baseline and at days 3, 7, 14, and 21. Secondary outcome measures included the treatment response and remission. Safety and tolerability were assessed using the Treatment Emergent Symptom Scale, in which adverse events were recorded at each visit. All assessments were completed by the same rater. A training workshop was provided to the rater. Both the patients and the rater were blind to the treatment allocation.

Two 10-ml blood samples were collected at baseline and day 14. Blood samples were also collected from age- and gender-matched healthy controls. Platelets and platelet-poor plasma were separated and the number of platelets was counted. The contents of platelet serotonin type 2A receptors and serotonin transporter were measured using Western blot. The concentrations of 5-HT and its metabolite 5-hydroxyindoleacetic acid were measured using reverse-phase high-performance liquid chromatography coupled with a fluorescence detector.

Results

Of the 73 patients, 63 (86%) completed the 3-week assessment. One patient in the sham group who had a history of cocaine use and two patients in the DCEAS group who did not have post-baseline assessment were excluded from analysis (Fig. 2). The proportion of females assigned to the sham group was significantly greater (97.1% vs. 69.4%, P=0.006, Chi-square test). Other baseline variables were similar in both groups (Table 1). Compliance with treatment was nearly 95%.

Changes from baseline in terms of scores of HAMD-17, CGI-S, and SDS over time revealed linear correlations (Table 2). Between-group comparisons revealed that DCEAS-treated patients had a significantly greater reduction in HAMD-17 scores at day 3 through day 21 ($P \leq 0.025$) and in SDS scores at day 3 (P=0.037) and day 21 (P=0.004). The response and remission rates were similar in both groups.

Adverse events occurred in at least 5% of the patients in both groups (Table 3). Two patients in the DCEAS group discontinued due to intolerance of acupuncture stimulation. The credibility rating in the two groups did not differ significantly.

The two groups did not differ significantly at baseline and day 14 for all platelet 5-HT parameters (Table 4).

Discussion

The use of DCEAS was effective in augmenting the

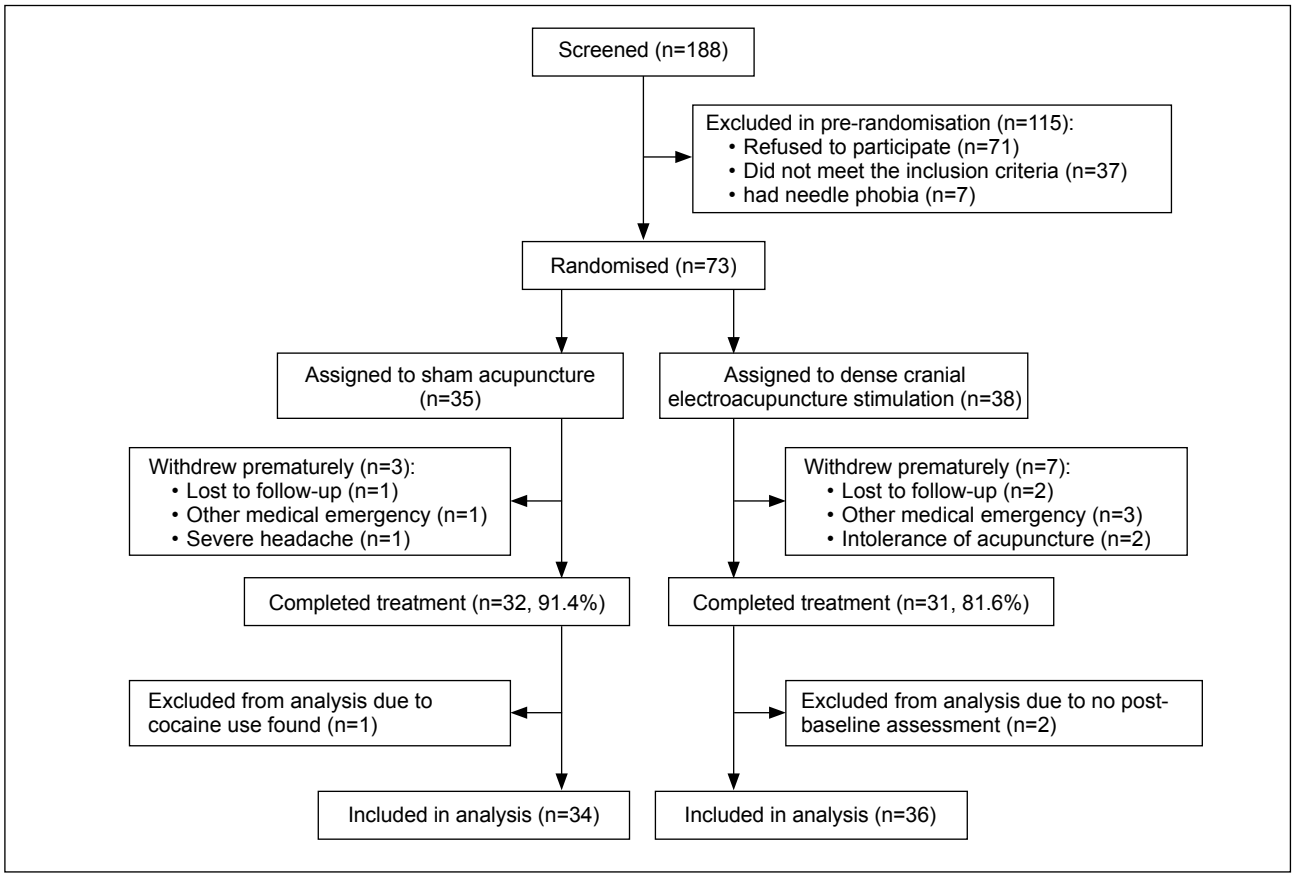

Fig 2. Flowchart of screening and patient recruitment

Table 1. Baseline characteristics of patients*

Variable	Sham acupuncture (n=34)	Dense cranial electroacupuncture stimulation (n=36)	P value (*t* or χ^2 test)
Female	33 (97.1)	25 (69.4)	0.006
Age (years)	48.2±9.8	46.3±9.9	0.414
Duration of major depressive disorder (years)	7.3±7.1	7.9±8.0	0.744
No. of previous depressive episodes	3.6±4.4	4.9±6.1	0.332
Patients with first-onset major depressive disorder	3 (8.8)	2 (5.5)	0.669
Patients with previous psychiatric admission	8 (23.5)	7 (19.4)	0.901
Patients with family members having mental illnesses	9 (26.5)	13 (36.1)	0.800
Patients with previous acupuncture treatment	22 (64.7)	24 (66.7)	0.937
Patients receiving psychotropic medications at study entry (not exceeding 1 week)	6 (17.6)	7 (19.4)	0.909
Selective serotonin re-uptake inhibitors	3	3	
Serotonin-norepinephrine reuptake inhibitors	1	1	
Mood stabilisers	1	1	
Benzodiazepines	2	2	
Baseline 17-item Hamilton Rating Scale for Depression score	23.1±3.6	23.9±3.8	0.321
Baseline Clinical Global Impression-Severity	4.3±0.5	4.4±0.5	0.760
Baseline Self-rating Depression Scale score	40.6±14.5	41.9±14.0	0.704

* Data are presented as no. (%) or mean±SD

antidepressant efficacy of FLX in patients with moderate to severe MDD, as indicated by the significantly greater reduction of HAMD-17 and SDS scores. The effect was observed as early as day 3 (after the first session of treatment). The frequency of adverse events in both groups was comparable, and only two DCEAS-treated patients discontinued treatment, indicating that it was well tolerated and safe.

The possibility of a placebo effect of DCEAS was also explored. There was no significant difference in the credibility of sham acupuncture and DCEAS, suggesting that non-inserted needling stimulation was valid and acceptable, so it was unlikely that the antidepressant

Table 2. Changes in depression scores from baseline

Variables	Mean (95% CI) change in score from baseline			P value (linear mixed effects model)
	Sham acupuncture (n=34)	Dense cranial electroacupuncture stimulation (n=36)	Between-group difference	
17-item Hamilton Rating Scale for Depression				
Day 3	-3.71 (-4.34 to -3.06)	-5.97 (-6.71 to -5.23)	2.27 (1.29 to 3.25)	0.000
Day 7	-5.82 (-6.46 to -5.18)	-6.97 (-7.71 to -6.23)	1.15 (0.17 to 2.13)	0.025
Day 14	-6.41 (-7.05 to -5.77)	-8.44 (-9.18 to -7.70)	2.03 (1.05 to 3.01)	0.000
Day 21	-6.27 (-6.90 to -5.62)	-8.66 (-9.39 to -7.91)	2.39 (1.41 to 3.37)	0.000
Clinical Global Impression-Severity				
Day 3	-0.32 (-0.42 to -0.22)	-0.44 (-0.54 to -0.34)	0.12 (-0.03 to 0.27)	0.116
Day 7	-0.65 (-0.75 to -0.55)	-0.53 (-0.63 to -0.43)	0.12 (-0.03 to 0.27)	0.116
Day 14	-0.71 (-0.81 to -0.61)	-0.71 (-0.81 to -0.61)	0.00 (-0.15 to 0.15)	1.000
Day 21	-0.74 (-0.84 to -0.64)	-0.74 (-0.84 to -0.64)	0.00 (-0.15 to 0.15)	1.000
Self-rating Depression Scale				
Day 3	-6.44 (-8.48 to -4.40)	-9.76 (-12.03 to -7.49)	3.32 (0.26 to 6.38)	0.037
Day 7	-8.82 (-10.86 to -6.78)	-9.12 (-11.39 to -6.85)	0.30 (-2.76 to 3.36)	0.851
Day 14	-11.74 (-13.78 to -9.70)	-12.38 (-14.65 to -10.11)	0.64 (-2.42 to 3.70)	0.679
Day 21	-8.38 (-10.42 to -6.34)	-13.06 (-15.33 to -10.79)	4.68 (1.62 to 7.74)	0.004

Table 3. Adverse events during treatment

Adverse event	No. (%) of patients		χ^2	P value
	Sham acupuncture (n=34)	Dense cranial electroacupuncture stimulation (n=36)		
Dizziness	15 (44.1)	11 (30.6)	0.858	0.354
Tiredness	10 (29.4)	15 (41.7)	0.672	0.412
Nausea	10 (29.4)	10 (27.8)	0.013	0.910
Excessive sweating	9 (26.5)	6 (16.7)	1.403	0.236
Headache	8 (23.5)	10 (27.8)	0.018	0.894
Transient tachycardia	8 (23.5)	9 (25.0)	0.018	0.892
Insomnia	7 (20.6)	9 (25.0)	0.024	0.877
Discomfort during needling sensation	7 (20.6)	14 (38.9)	1.985	0.159
Vomiting	4 (11.8)	3 (8.3)	-	0.706*
Unsteadiness	2 (5.9)	6 (16.7)	-	0.266*
Somnolence	2 (5.9)	6 (16.7)	-	0.266*

* Fisher Exact test was used

Table 4. The effects of dense cranial electroacupuncture stimulation on platelet 5-HT parameters

Variable	Mean±SD value				
	Healthy controls (n=22)	Sham acupuncture (n=34)		Dense cranial electroacupuncture stimulation (n=36)	
		Baseline	Week 2	Baseline	Week 2
Platelet					
Serotonin type 2A receptors	1.3±0.2	2.6±1.5*	2.5±1.5	2.6±1.5*	2.5±1.5
Serotonin transporter	1.6±0.2	2.3±1.5	2.0±1.5	2.2±1.8	2.1±1.8
5-HT (ng/10^9)	527.2±111.1	81.8±92.8*	81.6±91.8	84.3±62.2*	87.0±74.2
5-hydroxyindoleacetic acid (ng/10^9)	632.9±214.6	192.3±129.0*	231.7±196.1	215.2±149.5*	249.6±203.3
Turnover	0.9±0.3	0.7±1.2	0.7±0.7	0.6±0.6	0.6±0.6
Platelet-poor plasma					
5-HT (ng/ml)	9.3±1.6	4.8±1.5*	5.3±1.2	5.5±2.3*	5.4±2.4
5-hydroxyindoleacetic acid (ng/ml)	10.4±2.3	6.7±2.9*	7.5±3.6	7.0±3.0*	7.1±3.3
Turnover	1.0±0.3	0.8±0.5	0.8±0.4	0.9±0.4	0.9±0.5

* vs. healthy controls, P<0.01, one-way analysis of variance

benefits of DCEAS were derived from placebo effects.

There were several limitations in the present study. First, most subjects were females. There may be gender- and ethnic-differences in acceptance and credibility of acupuncture, suggesting a form of demographic bias. Single-blind treatment allocation might lead to effects mediated by the non-blind acupuncturists. Second, DCEAS only achieved a clinically meaningful (but not significant) difference in terms of the response rate (DCEAS: 19.4% vs. sham: 8.8%). This may be related to the relatively short-term (3-week) treatment. Long-term studies of antidepressant efficacy of DCEAS are warranted. Finally, no significant changes in platelet 5-HT parameters (baseline

to post-treatment) were noted in DCEAS-treated patients, suggesting that DCEAS may have minimal effects on platelet 5-HT systems. Evaluation of DCEAS effects on the brain 5-HT neuronal system may provide insight into central mechanisms responsible for the antidepressant effects of DCEAS. Several baseline 5-HT parameters of depressed patients differed significantly from those of healthy controls, and correlated significantly with the severity of depression symptoms. The platelet 5-HT indices seem to be potential biomarkers, reflecting the clinical status of major depression, although they are not directly involved in the physiopathology of major depression.

Implications

As patients with moderate and severe major depression have a higher risk of suicide and symptom worsening in the early phase of SSRI treatment, DCEAS can be an additional therapy. Neurobiological mechanisms responsible for DCEAS effects may warrant further investigation using neuroimaging approaches.

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Assessing mental capacity for everyday decision-making in the Chinese older population

Key Messages

1. The abilities to make everyday decisions may be reliably measured in the local elderly population.
2. The Chinese version of the Assessment of Capacity for Everyday Decision-Making is a reliable tool to assess these abilities.
3. Significant proportion of participants with mild dementia was mentally incapable in making decisions on everyday tasks. Global cognitive functioning appeared to be an important prerequisite for intact mental capacity.

Introduction

With population ageing, the prevalence of cognitive impairments in older people is expected to increase. Clinicians are often requested to assess a person's fitness for independent community living. Clinical assessment by psychiatrists and psychologists is a standard approach to assess one's mental capacity, but it can be unreliable.[1] A multidimensional structured assessment may enhance the reliability. The MacArthur Competence Assessment Tools for Treatment (MacCAT-T) and for Clinical Research (MacCAT-CR) were recommended as standard instruments for measuring mental capacity. Based on the framework of both instruments, a new instrument to measure everyday decision-making capacity—the Assessment of Capacity for Everyday Decision-Making (ACED)—has been developed.[2] The ACED is the first semi-structured interview for assessing everyday decision-making in western older populations with cognitive impairments.

This study aimed to: (1) develop a culturally appropriate ACED for Chinese older persons in Hong Kong; (2) identify profiles of performance in mental capacity in older persons with different degree of cognitive impairment; (3) evaluate the association between mental capacity for judgement of functional abilities with actual performance in everyday tasks; and (4) determine the cognitive pre-requisites for competent decision making in everyday tasks.

Methods

This study was approved by relevant institutional ethical review boards and conducted from November 2009 to October 2010. Participants were recruited from social centres for elders in Hong Kong. Three groups of subjects were recruited: those with intact cognitive function, those with amnestic mild cognitive impairment (MCI),[3] and those with mild dementia (MD) as rated by the Clinical Dementia Rating of 1.[4] Those with moderate to severe dementia or poor ability to communicate were excluded.

The ACED focused on three areas of activities of daily livings (medication management, meal management, and money management) and measured four decision-making abilities (understanding, appreciation, reasoning, and expressing a choice). The ACED questionnaire was translated into Chinese and back-translated using a standard procedure. Two focus groups were held to evaluate the appropriateness of the instrument, and two modifications were made. First, the option "someone could double-check how you spend your money" was changed to "someone you trust would plan the spending of your money for you." Second, the option "someone else could manage your money completely" was changed to "someone you trust would manage your money completely." The changes were made because these financial issues appeared to be sensitive in the local context. Each participant was interviewed with the ACED for decision-making capacity on everyday activities. The recorded interviews of 100 subjects were assessed independently by a geriatric psychiatrist and an occupational therapist for inter-rater reliability. All participants were independently assessed by a psychiatrist with respect to their capacity in making decisions about their medication, meal, and money managements. The participants were rated as 'fully incapable', 'incapable', 'capable', or 'fully capable'. The ACED ability scores

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were compared with the corresponding clinician ratings for estimation of concurrent validity.

To compare the decision-making abilities across different capacity domains, participants were also interviewed with the Chinese version of the MacCAT-T. The recorded interviews were also rated independently by a geriatric psychiatrist.

Cognitive assessment was made using the Cantonese version of the Mini-Mental State Examination (MMSE),[5] the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-cog), the 10-minute delayed recall, the category verbal fluency test (CVFT), and digit and visual spans. Functional assessment was made using the Disability Assessment for Dementia (DAD).

In a western study, the correlation of the three major dimensions measured by ACED with MMSE scores ranged from 0.48 to 0.60.[4] It was estimated that a sample size of 53 in each group could attain a power of 80% (alpha value=0.05). Based on the Chinese MacCAT-T, 97% of cognitive normal subjects, 73% of subjects with MCR, and 46% of subjects with MD were competent to make decision on medical treatment. The estimated number of subjects required for each group was estimated to be at least 60 to achieve a power of 81%. For psychometric properties of the ACED in Chinese elderly, inter-rater reliability was assessed by the intra-class correlation coefficients. The internal consistency of each dimension of the ACED was examined. The summary scores of the MacCAT-T were used for evaluation of construct validity. The correlation between each decision-making ability in MacCAT-T and ACED was calculated. Correlations with clinician ratings were used for concurrent validity. One-way ANOVA was used to evaluate differences in ACED ability scores between different subject groups (normal cognition, MCI, and MD). Correlations between decision-making abilities, cognitive and functional performance were evaluated.

Results

A total of 291 participants were recruited. Participants in the MD group were significantly older and less educated (Table 1). Of all participants, 291, 288, and 287 finished the ACED for medication management, meal management, and money management, respectively (Table 2).

The intra-class correlation coefficients for medication, meal and money managements ranged from 0.84 to 0.94 for understanding, 0.83 to 0.88 for appreciation, 0.89 to 0.94 for reasoning, and 0.55 to 0.71 for expressing a choice. The Cronbach's alpha coefficients for medication, meal and money managements ranged from 0.75 to 0.79 for understanding, 0.53 to 0.64 for appreciation, and 0.74 to 0.77 for reasoning.

Table 1. Demographics of the participants (n=291)

Characteristics	Cognitively intact (n=97)	Mild cognitive impairment (n=99)	Mild dementia (n=95)	One-way ANOVA	
				F	P value
Mean±SD age (years)	74.2±6.5	78.15±6.9	82.27±6. 6	35	<0.001
Mean±SD education (years)	4.3±3.7	3.17±3.51	1.62±3.24	14.19	<0.001
No. of male/female	10/87	28/71	14/81	11.73	0.003
Mean±SD Mini-Mental State Examination score	26.6±2.4	25.3±2.5	19.5±2.7	208.29	<0.001
Mean±SD Alzheimer's Disease Assessment Scale – Cognitive subscale total score	10.2±3.2	14.5±3.7	25.8±6.1	308.14	<0.001
Mean±SD 10-minute delayed recall score	6.3±1.1	2.6±1.5	0.9±1. 6	367.73	<0.001

Table 2. Assessment of Capacity for Everyday Decision-Making (ACED) scores of the participants

ACED ability	Mean±SD score			One-way ANOVA	
	Cognitively intact	Mild cognitive impairment	Mild dementia	F	P value
Medication management	n=97	n=99	n=95		
Understanding	7.00±1.68	5.84±2.13	4.22±1.96	49.92	<0.001
Appreciation	7.33±1.18	6.81±1.48	5.69±1.79	29.76	<0.001
Reasoning	8.87±1.48	8.46±1.76	6.96±2.88	25.27	<0.001
Expressing a choice	1.99±0.10	1.97±0.17	1.84±0.49	6.67	0.001
Meal management	n=97	n=98	n=94		
Understanding	7.88±1.64	6.96±1.85	5.21±2.40	44.61	<0.001
Appreciation	7.61±0.82	7.18±1.10	6.24±1.67	30.44	<0.001
Reasoning	9.43±1.34	8.85±1.74	7.49±2.50	25.92	<0.001
Expressing a choice	1.97±0.23	1.95±0.26	1.89±0.40	1.56	0.211
Money management	n=97	n=97	n=94		
Understanding	7.05±1.62	6.31±1.72	4.34±2.12	55.75	<0.001
Appreciation	7.33±1.21	6.66±1.57	5.51±2.00	30.61	<0.001
Reasoning	8.87±1.72	7.92±2.22	6.21±2.66	34.79	<0.001
Expressing a choice	1.99±0.10	1.96±0.23	1.85±0.49	5.45	0.005

With regard to concurrent validity for medication management, clinician ratings correlated significantly with the ability score for understanding (r_s=0.42, P<0.001), appreciation (r_s=0.38, P<0.001), reasoning (r_s=0.39, P<0.001) and expressing a choice (r_s=0.23, P<0.001). For meal management, the clinician ratings correlated significantly with the ability score for understanding (r_s=0.44, P<0.001), appreciation (r_s=0.35, P<0.001), reasoning (r_s=0.39, P<0.001) and expressing a choice (r_s=0.15, P=0.01). For money management, the clinician ratings correlated significantly with the ability score for understanding (r_s=0.45, P<0.001), appreciation (r_s=0.39, P<0.001), reasoning (r_s=0.49, P<0.001) and expressing a choice (r_s=0.22, P<0.01).

With regard to construct validity for medication management, the area under the curve (AUC) was 0.76 (95% confidence interval [CI], 0.69-0.84) for understanding, 0.74 (95% CI, 0.66-0.83) for appreciation and 0.78 (95% CI, 0.71-0.85) for reasoning. For meal management, the AUC was 0.78 (95% CI, 0.70-0.86) for understanding, 0.72 (95% CI, 0.63-0.81) for appreciation and 0.77 (95% CI, 0.70-0.84) for reasoning The highest point estimate for the AUC was for money management, which was 0.81 (95% CI, 0.75-0.87) for reasoning, 0.79 (95% CI, 0.72-0.86) for understanding and 0.75 (95% CI, 0.67-0.82) for appreciation (Table 3).

With regard to clinician ratings for medication management, 97.9% of the cognitively intact group, 96% in the MCI group, and 57.9% in the MD group were mentally capable The last two groups differed significantly (chi-square=40.06, P<0.001). For meal management, 97.9% of the cognitively intact group, 93.9% in the MCI group, and 56.8% in the MD group were mentally capable. The last two groups differed significantly (chi-square=36.34, P<0.001). For money management, 95.9% of the cognitively intact group, 93.9% in the MCI group, and 50.5% in the MD group were mentally capable The last two groups differed significantly (chi-square=46.02, P<0.001).

Predictive power of each ACED ability score was evaluated using linear regression analyses. The ability score was entered as a dependent variable, with the corresponding summary score in the MacCAT-T, age, years of education, CDAD, MMSE, CVFT, backward digital span, and backward visual span entered as independent variables. Across all participants, the relationship among these measures accounted for 27.5% (appreciation) to 41% (understanding) of the variance of the ACED scores on medication management, 29.1% (appreciation) to 47% (understanding) on meal management, and 36.3% (appreciation) to 52% (understanding) on money management.

Discussion

The Chinese version of ACED demonstrated satisfactory inter-rater reliability in the ability scores, which correlated significantly with their corresponding measure in the MacCAT-T. This supported the construct validity of ACED. The concurrent validity of the ACED was also supported by significant correlations between clinician ratings and the ability scores. The values of AUCs of ACED abilities were comparable with capacity-measuring instruments for other decisions.

The proportion of participants with mental incapacity in the MD group was significantly higher. This highlights the fact that MD can have a profound effect on decisional capacity. This also supports the need to develop proper tools for mental capacity assessment in MD subjects. Each ability score of the ACED correlated with cognitive and functional measures. The MMSE score was a significant factor for mental capacity.

Table 3. MacArthur Competence Assessment Tools for Treatment (MacCAT-T) summary scores and the Assessment of Capacity for Everyday Decision-Making (ACED) scores

ACED ability	MacCAT-T (Spearman's rho)			
	Understanding	Appreciation	Reasoning	Expressing a choice
Medication management (n=291)				
Understanding	0.60†	0.41†	0.49†	0.30†
Appreciation	0.44†	0.39†	0.47†	0.24†
Reasoning	0.36†	0.36†	0.49†	0.17†
Expressing a choice	0.19†	0.19†	0.24†	0.03
Meal management (n=288)				
Understanding	0.53†	0.45†	0.51†	0.25†
Appreciation	0.45†	0.42†	0.43†	0.21†
Reasoning	0.36†	0.32†	0.40†	0.12*
Expressing a choice	0.17†	0.11	0.17†	0.03
Money management (n=287)				
Understanding	0.54†	0.46†	0.53†	0.28†
Appreciation	0.52†	0.46†	0.47†	0.25†
Reasoning	0.49†	0.43†	0.53†	0.22†
Expressing a choice	0.24†	0.20†	0.12	-0.09

* P<0.05
† P<0.01

The findings of this study should be interpreted in the context of its limitations. The group differences in education and age among the subjects may affect interpretation of the findings. The low proportion of males and low education level of our participants may affect generalisability of the findings. The study was also limited by the range of tests studied.

Most of our participants could complete the ACED interview for one decision within 10 minutes. Although clinical assessment is considered the gold standard, the ACED may serve as a useful adjunct and reference.

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Spirometric reference standards for preschool children in Hong Kong

Key Messages

1. Prediction equations and normograms are established using incentive spirometry in a community cohort of 770 Hong Kong Chinese children aged 2 to 6 years.
2. All spirometric parameters depend mainly on standing height. Boys have higher values than girls.
3. Forced expiratory volumes depend on birth weight, place of birth, history of wheezing, and environmental tobacco smoke (ETS) exposure.
4. High urinary cotinine level as a biomarker of ETS exposure is noted in about one tenth of the children.
5. Urinary cotinine level is inversely associated with all spirometric parameters. This supports implementation of the smoking cessation programme.

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Introduction

Spirometry is a standard clinical procedure for assessing the respiratory health of adults and older children. Preschool children have difficulty performing spirometry because of difficulty producing consistent flow volumes, short attention span, low frustration tolerance, and inability to inspire consistently to total lung capacity and exhale completely and consistently to zero flow. Nonetheless, advances in spirometry techniques enable measurements for children as young as 3 years of age.[1,2] The use of animation programmes is one of these technological improvements. The Asthma UK Collaborative Initiative has collated spirometric data from 53 777 healthy children aged 3 to 7 years old from 15 centres across the United States and Europe, in order to establish reference standards for spirometry in Caucasian preschool children.[3] There were only two small reports on spirometric testing in Chinese preschoolers, one in Shenzhen and another in Taiwan. These studies were performed before the availability of any international guideline.[2] This study aimed to establish the spirometric reference standards in Chinese preschool children in Hong Kong and investigate how demographic, anthropometric, and environmental factors influence the reference standards.

Methods

This study was conducted from January 2009 to September 2010 and was approved by the ethics committee of our university. Sample selection was based on stratified (by districts) and clustered (all subjects within a class) random sampling. Nurseries and kindergartens registered under the Education Bureau were randomly selected in proportion to the childhood population residing in the four geographical regions in Hong Kong. Parents of children completed a questionnaire on demographics, environmental exposure, and respiratory health. Our research staff were blind to such information when measuring the children's lung function by incentive spirometry. Exclusion criteria for spirometric references were premature birth (<37 weeks), birth weight <2.5 kg, reported having current wheeze or any history of asthma, congenital cardiorespiratory diseases warranting surgery or long-term medication, and respiratory tract infection within the last 4 weeks.

Each subject's weight, height (standing and sitting), and waist circumference were measured. Lung function was measured using incentive spirometry (Master Screen, Jaeger GmbH, Würzburg, Germany) according to international guidelines.[2] The spirometer was calibrated on-site daily using a 1-litre calibration syringe. Each subject performed at least three forced vital capacity (FVC) manoeuvres. Following data acquisition, the same staff reviewed all computer-derived flow-volume curves for technical acceptability.[2] Spirometric parameters recorded were forced expiratory volume in 0.5 second ($FEV_{0.5}$), $FEV_{0.75}$, FEV_1, FVC, forced expiratory flow at 50% of exhalation (FEF_{50}), and peak expiratory flow (PEF). The highest value of the parameters that were technically satisfactory were reported. Fifteen of the children repeated spirometry within 3 weeks to evaluate between-day reproducibility.

Urine samples of half of the children (randomly chosen) were collected and stored within 4 hours at -20ºC until analysis for cotinine (Calbiotech, Spring Valley, CA, USA) and creatinine (Jaffe method, Roche Diagnostics GmbH,

Mannheim, Germany). Urinary cotinine-to-creatinine ratios were log-transformed. Significant exposure to environmental tobacco smoke (ETS) was defined as cotinine ≥30 ng/mg creatinine.[4]

Spirometric parameters were compared between subgroups using the Student's *t* test or ANOVA as appropriate, and confirmed by linear regression. Multiple regression analysis was used to determine relationship between subjects' best spirometric parameters and physical traits. The regression models were tested for deviation from linear effects of age, height, and weight by means of additive models. Alternative models in which lung function measures and/or the explanatory variables were log-transformed or square-rooted were also carried out. Prediction equations for different spirometric parameters were derived, and sex-specific normograms were constructed using the LMS method.

Results

Out of 4168 eligible preschool children, 2833 (68%) were recruited. In the training phase, 911 (66.4%) of 1371 eligible children consented to participate. Of them, 832 children attempted spirometry and 79 refused testing (Table 1). Only 123 children met ATS/ERS criteria for valid spirometric measurement, 79 of them fulfilled our inclusion criteria. This high failure rate was not unexpected, as all the research staff were new to incentive spirometry. Spirometric data from this phase was not included in the analysis of reference standards. In the research phase, 1922 (68.7%) of 2797 children from 19 nurseries and kindergartens consented to participate. Of them, 12.7% (from four schools) resided in Hong Kong Island, 52.8% (from 10 schools) resided in Kowloon, 22.8% (from four schools) resided in the New Territories East, and 11.8% (from one school) resided in the New Territories West. Excluding subjects with medical and technical problems, a subgroup of 770 (40.1%) could provide spirometric data to establish the reference standards.

The success rates of spirometry varied from 40.6% for those aged <3 years to 95.7% for those aged 6 years. Compared with girls, boys had higher $FEV_{0.5}$, $FEV_{0.75}$, FEV_1, FVC, and PEF values (P<0.001 to 0.010), whereas FEF_{50} and $FEV_{0.5}$/FVC values were independent of gender. The reference standards for individual parameters were thus separately analysed for boys and girls. FEF_{50} was not analysed because of an unsatisfactory R^2 by linear regression. Standing height without any data transformation was the strongest predictor for $FEV_{0.5}$, $FEV_{0.75}$, FEV_1, FVC, and PEF. Table 2 summarises the prediction equations for different spirometric parameters. Bland-Altman plots revealed good between-day agreement for $FEV_{0.5}$ and FVC, with the respective Cronbach's α being 0.985 (95% CI, 0.956-0.995) and 0.995 (95% CI, 0.987-0.998) [P<0.001 for both].

Table 1. Demographic and clinical features of subjects in training and research phases

Characteristic	All children in the training phase (n=946)*	Research phase	
		All children who consented (n=1922)	Children providing spirometric data (n=770)
Mean±SD age (years)	4.5±1.0	4.4±1.0	4.8±0.9†
No. (%) of males	489 (51.7)	1053 (54.8)	417 (54.2)
Anthropometric parameters (mean±SD)			
Body weight (kg)	17.7±3.9	17.5±3.6	18.4±3.9
Standing height (cm)	105.1±8.4	105.2±8.3	107.3±7.7†
Sitting height (cm)	-	58.1±5.6	58.8±5.8
Waist circumference (cm)	49.5±4.5	49.2±4.9	49.8±5.1
Birth history (no. [%] of subjects)			
Born <37 weeks of gestation	70 (7.9)	154 (8.0)	-
Birth weight <2.5 kg	57 (6.4)	160 (8.3)	-
Born outside Hong Kong	64 (6.8)	142 (7.4)	71 (9.2)
Breastfeeding ever (no. [%] of subjects)	462 (48.7)	996 (51.8)	402 (52.2)
Daycare attendance ever (no. [%] of subjects)	129 (13.6)	337 (17.5)	131 (17.0)
Current domestic tobacco smoke exposure (no. [%] of subjects)	382 (40.3)	770 (40.1)	304 (39.5)
Maternal tobacco smoking (no. [%] of subjects)			
During pregnancy	32 (3.5)	76 (4.0)	29 (3.8)
During infancy	79 (8.5)	157 (8.2)	56 (7.3)
Over past 12 months	90 (9.5)	190 (9.9)	66 (8.6)
Dog/cat keeping at home (no. [%] of subjects)			
During infancy	155 (16.3)	192 (10.0)	73 (9.5)
Over past 12 months	129 (13.6)	122 (6.3)	45 (5.8)
History of atopic disorders (no. [%] of subjects)			
Asthma ever	64 (6.8)	99 (5.2)	-
Current wheeze	89 (9.4)	204 (10.6)	-
Rhinitis ever	235 (24.8)	543 (28.3)	197 (25.6)
Eczema ever	299 (31.5)	668 (34.8)	239 (31.0)

* Including 911 consented children and 35 children who returned questionnaires but did not consent for spirometry

† Age distribution for boys: 2 years (n=15), 3 years (n=82), 4 years (n=131), 5 years (n=161), and 6 years (n=28). Age distribution for girls: 2 years (n=13), 3 years (n=75), 4 years (n=120), 5 years (n=110) and 6 years (n=35). Standing height distribution for the 417 boys: <95 cm (n=24), 95-99 cm (n=45), 100-104 cm (n=91), 105-109 cm (n=98), 110-114 cm (n=84), 115-119 cm (n=56), and ≥ 120 cm (n=19). Standing height distribution for the 353 girls: <95 cm (n=23), 95-99 cm (n=38), 100-104 cm (n=75), 105-109 cm (n=94), 110-114 cm (n=68), 115-119 cm (n=43), and ≥120 cm (n=12).

Table 2. Prediction equations for spirometric parameters in Chinese preschool children as a function of: Spirometric index=α + β x standing height

Spirometric index	Height (cm)	α	β	R^2	Residual SD
Forced expiratory volume in 0.5 second ($FEV_{0.5}$) [L]					
Boys (n=417)	83.1-130.0	-1.267	0.019	0.623	0.116
Girls (n=353)	83.0-128.1	-1.387	0.020	0.652	0.109
$FEV_{0.75}$ (L)					
Boys (n=414)	83.1-130.0	-1.534	0.023	0.668	0.126
Girls (n=347)	83.0-128.1	-1.644	0.024	0.703	0.114
FEV_1 (L)					
Boys (n=388)	83.1-130.0	-1.767	0.026	0.700	0.130
Girls (n=327)	83.0-128.1	-1.769	0.025	0.718	0.117
Forced vital capacity (L)					
Boys (n=417)	83.1-130.0	-2.211	0.031	0.727	0.149
Girls (n=353)	83.0-128.1	-2.115	0.030	0.723	0.136
Peak expiratory flow (L/s)					
Boys (n=417)	83.1-130.0	-3.971	0.058	0.530	0.428
Girls (n=353)	83.0-128.1	-4.782	0.065	0.561	0.429

Urine samples were collected from 861 (44.8%) subjects. The cotinine level was high in 92 (10.7%) samples, which were from 77 (23.4%) of 329 children who reported current ETS exposure and 15 (2.8%) of 532 children who reported no such history (P<0.001).

High ETS exposure (high urinary cotinine level) was associated with lower values for all parameters, whereas subjects with parent-reported ETS exposure had higher $FEV_{0.5}$, $FEV_{0.75}$, FVC, and PEF values. An inverse trend was noted between urinary cotinine levels (from lowest to highest quartiles) and values of $FEV_{0.5}$ (P=0.002), $FEV_{0.75}$ (P=0.001), FEV_1 (P=0.016), FEF_{50} (P=0.009), and PEF (P<0.001), but not FVC (P=0.098). Children with recent respiratory tract infections (n=397) had lower $FEV_{0.5}$ values than those without (mean±SD, 0.70±0.21 vs 0.77±0.19 L; P<0.001). Similar findings were observed for $FEV_{0.75}$, FEV_1, FVC, and PEF (P<0.001 for all), but not FEF_{50} (P=0.079) values. Table 3 summarises the effects of demographic, anthropometric, and early-life factors on spirometric variables. Stepwise linear regression revealed that $FEV_{0.5}$ was associated with place of birth (β=0.027; 95% CI, 0.004-0.050; P=0.021) and history of current wheeze (β=0.002; 95% CI, 0.001-0.004; P=0.034), after adjustment for age, sex, residence, standing height, and respiratory tract infection as covariates. A history of asthma was associated with low FEF_{50} (β=0.192; 95% CI, 0.104-0.280; P≤0.001) and $FEV_{0.5}$/FVC (β=4.731; 95% CI, 2.664-6.799; P<0.001) values.

Discussion

Spirometric parameters in Chinese school-age children were up to 12% lower than in Caucasians. This difference may have been due to body size and shape. Chinese newborns had smaller chest circumferences than Caucasian babies, and probably have smaller lungs. However, by superimposing medians and 5th percentile lines for FEV_1 and FVC of Caucasians[3] on our normograms, these parameters were in fact higher in Chinese than Caucasian preschool children. This observation might be attributed to our use of animation programmes as an incentive.

As in other populations, standing height was the best predictor of different spirometric outcomes. Lung function parameters ($FEV_{0.5}$, FEV_1, and FVC) were higher in boys than girls, which was consistent with reports in Caucasian populations.[3,5] Because of small sample sizes, caution is needed when applying the prediction equations to children at extremes of age or standing height.

The Asthma UK Collaborative Initiative lacked sufficient data relevant to the present prediction equations for $FEV_{0.5}$, and the smaller sample size for $FEV_{0.75}$ also limited appropriate interpretation of any sex difference for this parameter.[3] This may be partly due to unavailability of international guidelines at that time. Our study focused on the measurement of FEV_t, as it is more clinically relevant for children, whereas $FEV_{0.5}$ could be measured in all recruited subjects who provided valid spirometric data.

This study had several limitations. Like other preschool spirometric references,[1,3,5] this cross-sectional study had limited interpretation of longitudinal changes in lung function. The retrospective nature of the study made it difficult to distinguish differences in lung function attributable to equipment and measurement techniques from genuine differences. Nonetheless, we performed incentive spirometry according to international guidelines,[2] which should have minimised intra- and inter-observer variability. In terms of subject selection, it was impossible to accurately define the presence of respiratory tract infections unless respiratory samples had been collected to screen for common respiratory pathogens. To overcome this problem, we excluded subjects with fever of ≥38ºC, cough, rhinorrhoea, and sore throat within 4 weeks. Our study population might have over-represented Kowloon children and under-represented those from Hong Kong Island and the New Territories West, when compared with 2006 population by-census statistics. This discrepancy was due to the high refusal rate from schools in the New Territories West, small student numbers in schools on

Table 3. Association between spirometric parameters and potential risk and protective factors in 1402 children with valid spirometric data

Characteristic	Forced expiratory volume in 0.5 second ($FEV_{0.5}$) [L]	P value	Forced expiratory flow at 50% of exhalation (FEF_{50}) [L/s]	P value	$FEV_{0.5}$/ forced vital capacity (%)	P value
Sex		0.002		0.552		0.001
Male (n=770)	0.762 (0.199)		1.352 (0.449)		70.8 (9.1)	
Female	0.730 (0.188)		1.370 (0.685)		72.5 (9.1)	
Born <37 weeks gestation		0.787		0.304		0.353
Yes (n=103)	0.743 (0.179)		1.305 (0.396)		70.8 (9.9)	
No	0.748 (0.196)		1.364 (0.578)		71.6 (9.1)	
Low birth weight <2.5 kg		0.001		0.009		0.434
Yes (n=107)	0.690 (0.195)		1.222 (0.446)		70.8 (10.6)	
No	0.753 (0.194)		1.372 (0.575)		71.6 (9.0)	
Born outside Hong Kong		<0.001		<0.001		0.695
Yes (n=115)	0.855 (0.187)		1.528 (0.472)		71.3 (7.6)	
No	0.738 (0.192)		1.345 (0.573)		71.6 (9.3)	
Breastfeeding ever		0.988		0.236		0.118
Yes (n=722)	0.748 (0.197)		1.377 (0.664)		71.9 (9.1)	
No	0.748 (0.192)		1.342 (0.442)		71.2 (9.2)	
Daycare attendance ever		0.204		0.206		0.257
Yes (n=242)	0.733 (0.202)		1.318 (0.455)		70.9 (9.8)	
No	0.751 (0.193)		1.369 (0.588)		71.7 (9.0)	
Current domestic tobacco smoke exposure		0.520		0.881		0.846
Yes (n=582)	0.752 (0.189)		1.357 (0.436)		71.5 (8.8)	
No	0.745 (0.198)		1.362 (0.645)		71.6 (9.4)	
Maternal tobacco smoking during pregnancy		0.355		0.847		0.663
Yes (n=57)	0.771 (0.178)		1.374 (0.352)		72.1 (8.1)	
No	0.747 (0.195)		1.359 (0.575)		71.5 (9.2)	
Maternal tobacco smoking during infancy		0.984		0.643		0.382
Yes (n=113)	0.748 (0.201)		1.336 (0.453)		70.8 (8.4)	
No	0.747 (0.194)		1.362 (0.577)		71.6 (9.2)	
Maternal tobacco smoking over past 12 months		0.783		0.379		0.069
Yes (n=141)	0.752 (0.193)		1.320 (0.430)		70.4 (8.1)	
No	0.747 (0.195)		1.364 (0.581)		71.7 (9.3)	
Dog/cat keeping at home during infancy		0.259		0.297		0.822
Yes (n=125)	0.746 (0.171)		1.346 (0.393)		71.7 (9.2)	
No	0.748 (0.196)		1.361 (0.579)		71.5 (9.1)	
Dog/cat keeping at home over past 12 months		0.004		0.031		0.493
Yes (n=73)	0.721 (0.177)		1.329 (0.423)		72.1 (9.5)	
No	0.750 (0.196)		1.363 (0.580)		71.5 (9.1)	
History of asthma ever		0.608		0.018		<0.001
Yes (n=76)	0.737 (0.181)		1.210 (0.430)		66.7 (10.4)	
No	0.748 (0.195)		1.369 (0.573)		71.8 (9.0)	
History of wheezing ever		0.431		0.674		0.002
Yes (n=241)	0.739 (0.206)		1.346 (0.954)		69.9 (9.6)	
No	0.750 (0.192)		1.363 (0.448)		71.9 (9.0)	
Current wheezing		0.042		0.369		0.255
Yes (n=153)	0.718 (0.214)		1.321 (1.153)		69.3 (10.3)	
No	0.771 (0.190)		1.379 (0.434)		70.7 (8.2)	
History of rhinitis ever		0.002		0.296		0.469
Yes (n=405)	0.773 (0.197)		1.385 (0.448)		71.3 (9.1)	
No	0.738 (0.193)		1.350 (0.610)		71.7 (9.2)	
History of eczema ever		0.324		0.590		0.972
Yes (n=476)	0.741 (0.197)		1.371 (0.755)		71.5 (9.2)	
No	0.752 (0.193)		1.354 (0.442)		71.6 (9.1)	

Hong Kong Island, and large student numbers in schools in Kowloon. Nonetheless, the body anthropometry (and thus lung volume) of preschoolers in the four geographical regions was similar. As all the subjects did not have asthma/wheezing, they should not have been vulnerable to environmental exposures (eg ambient pollution) that might have differed in these regions.

Conclusions

This territory-wide community study established normograms and prediction equations by incentive spirometry for Chinese children in Hong Kong. Standing height was the best predictor for FEV, which was higher in boys than girls. High ETS exposure (high urinary cotinine level) was associated with lower values for all measured parameters; FEV were influenced by intercurrent respiratory tract infection, birth weight, place of birth, and a history of wheezing.

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Anthropometric and physiological measurements in healthy children

Key Messages

1. Normal ranges for Ultrasonic Cardiac Output Monitor–derived cardiovascular indices are derived for Chinese children aged 1 to 12 years in Hong Kong.
2. A simple formula for calculating stroke volume is constructed, but the error varies from 8 to 40%.
3. Stroke volume index and, to a lesser extent, the cardiac index generally increase from ages 1 to 5 years, but plateau or fall slightly thereafter.

Introduction

Measurement of cardiovascular parameters is important in the management of critically ill patients. Assessment of cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), and their indices enables differentiation between shock states and monitoring illness progression and responses to therapy. The Ultrasonic Cardiac Output Monitor (USCOM1A; USCOM, Coffs Harbor, NSW, Australia) was introduced for clinical use in 2001. It measures cardiac function in a rapid, safe, and non-invasive means. The USCOM uses Doppler ultrasound to measure blood flow velocity through the aortic or pulmonary valve. Haemodynamic variables are generated after entering various patient parameters such as age, gender, height, and weight, as well as algorithms into the device.[1,2]

Normal paediatric values relating age to peak aortic flow measured with a suprasternal ultrasonic device have been published, but this device did not produce values for SV, CO, or SVR.[3] This study aimed to use the USCOM to determine the range of values for these vital signs and the derived cardiovascular indices, adjusted for age and gender, in Hong Kong Chinese children aged 1 month to 12 years, and to construct formulae relating to age, weight, other anthropometric measurements, vital signs, and cardiovascular indices.

Methods

This observational study was part of a prospective cross-sectional study titled "Healthy children's vital signs and USCOM values" conducted between October 2010 and July 2011. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Healthy Chinese children aged 1 to 12 years were recruited through kindergartens and schools in the Shatin district of Hong Kong. Eight kindergartens and six primary schools agreed to participate. Exclusion criteria were lack of consent, non-Chinese children, current symptoms of illness (eg respiratory tract infection, gastroenteritis), congenital or long-term conditions (eg diabetes, asthma, congenital heart disease), and current use of medication (whether over-the-counter or prescribed by a physician or Chinese medical practitioner).

Three operators were trained to use the USCOM. Standing height was measured to the nearest 0.1 cm using a stadiometer (Harpenden Portable Stadiometer, Holtain, UK). Children too young to stand were measured supine on a flat surface with a tape measure. Body weight was measured to the nearest 0.2 kg in school uniform (shorts and T-shirt) using electronic scales. Blood pressure (BP) and heart rate (HR) were measured in the right arm with an appropriately sized cuff using a standard emergency department oscillometric device (Patient Monitor BX-10ne; Omron Healthcare Co Ltd, Kyoto, Japan). Measurements were made supine at rest. To assess variation, a convenience sample of at least 10% of subjects had repeat measurements of BP and HR within 5 minutes of the first measurement. The first USCOM operator entered the subject's weight, height, and BP using a new account for each child. Scans were obtained using the aortic access area (suprasternal notch), because it was deemed not appropriate to require children to remove their clothing to obtain the pulmonary view. Each scan attempted to obtain at least three good-quality consecutive cycles.

Means and standard deviations (SDs) for cardiovascular indices were

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stratified according to age groups. Unpaired Student's *t* tests were used and statistical significance was set at P<0.05. LMS Chartmaker Pro version 2.3 software (Cole and Pan, Medical Research Council, London, UK) was used to describe the data in percentile curves (2.5th, 10th, 50th, 90th, 97.5th). The relationship between age and USCOM-derived cardiovascular indices was modelled by the (lambda-mu-sigma) LMS method of Cole and Green.[4] MedCalc version 10.4 was used to determine inter-observer reliability for measurement of SV, BP, and HR.[5] Intraclass correlation used the one-way random effects model for absolute agreement of single paired observations with raters selected at random. Bland-Altman limits of agreement were calculated for the percentage difference between observations. Coefficients of variation were calculated as percentage ratios of the SD of the differences between the two measurements and the overall mean. From the results of our pilot study, the mean and SD for SV were used to calculate a sample size of 105 subjects in each year group to achieve 95% confidence that the true mean lies within 5% of that observed.

Results

Data were collected from 1353 Chinese children (55% boys) aged 1 to 12 years from eight kindergartens and six primary schools in Hong Kong. Of them, 1197 healthy Chinese children (55% boys) were scanned with USCOM, and formulae were constructed. The reference ranges for HR, systolic BP, and respiratory rate are shown in Table 1, whereas the normal ranges for cardiovascular indices are shown in Table 2.

For inter-observer variation, a second operator independently scanned 1059 (88%) children, and 183 (15%) of them had a second BP and HR measurement. Coefficients of variation, intraclass correlations, and Bland-Altman limits of agreement for SV, BP, and HR are shown in Table 3. By any measure, USCOM yielded less inter-observer variation for BP or HR than the standard automated oscillometric device.

Regarding normal ranges for clinical use in resuscitation, the Figure shows that the SV index and, to a lesser extent, the cardiac index generally increase from ages 1 to 5 years but plateau or fall slightly thereafter.

The most accurate and user-friendly method of presenting the data was by graphs (Fig). The formulae to calculate the lower limit, median, and upper limit of SV were: 10 + (4 x age), 15 + (6 x age), and 20 + (8 x age), respectively, with 13% to 8%, 20% to 12%, and 40% to 9% error as age increased, respectively.

Discussion

This is the largest study to present normal ranges for cardiovascular indices measured using USCOM, and the first study to present USCOM data for a Chinese population. We used 2.5th and 97.5th percentiles to define the expected range of 95% of the population. Thus, there was a probability of 0.05 that a healthy child had USCOM measurements outside this range. Our results were consistent with those in a study using USCOM in 100 children aged 1 to 16 years and in a study using the earlier suprasternal ultrasonic device.[3] In previous studies, normal paediatric ranges for SV measured with echocardiography were based on weight and height (but not age), which prevented direct comparison with our results. It is likely that the normal values for children depended to some extent on extrapolation from values

Table 1. Reference ranges (2.5 to 97.5 centile) measured using the Ultrasonic Cardiac Output Monitor (Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Critical Care Medicine, copyright 2010)

Age group	Heart rate (beats per minute)	Systolic blood pressure (mm Hg)	Respiratory rate (breaths per minute)
Small Toddler (12-23 months)	99-155	75-110	20-45
Pre-school (24-59 months)	80-130	80-120	15-30
School (60-143 months)	65-115	90-135	15-30

Table 2. Normal ranges for Ultrasonic Cardiac Output Monitor–derived cardiovascular indices (Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Critical Care Medicine, copyright 2010)

Age (years)	Systemic vascular resistance (ml.m-2)	Cardiac index (l.min-1.m-2)	Systemic vascular resistance index (d.s.cm-5.m2)	Mean arterial pressure (mm Hg)	Heart rate (min-1)
1-2	31-55	3.5-6.5	750-1600	48-83	93-140
3-4	37-67	3.6-7.1	750-1700	52-86	78-130
5-12	42-76	3.3-6.9	910-2000	61-94	62-110

Table 3. Interobserver variation (Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Critical Care Medicine, copyright 2010)

Parameter	Stroke volume	Systolic blood pressure	Heart rate
Coefficient of variation (%)	11.3	13.0	11.5
Intraclass correlation (95% CI)	0.94 (0.93 to 0.94)	0.50 (0.38 to 0.60)	0.76 (0.69 to 0.82)
Bland-Altman limits of agreement (%)			
Upper limit (95% CI)	22.3 (21.2 to 23.4)	26.1 (22.8 to 29.3)	22.3 (19.5 to 25.1)
Lower limit (95% CI)	-20.5 (-19.3 to -21.6)	-24.5 (-21.3 to -27.8)	-21.9 (-19.1 to -24.7)

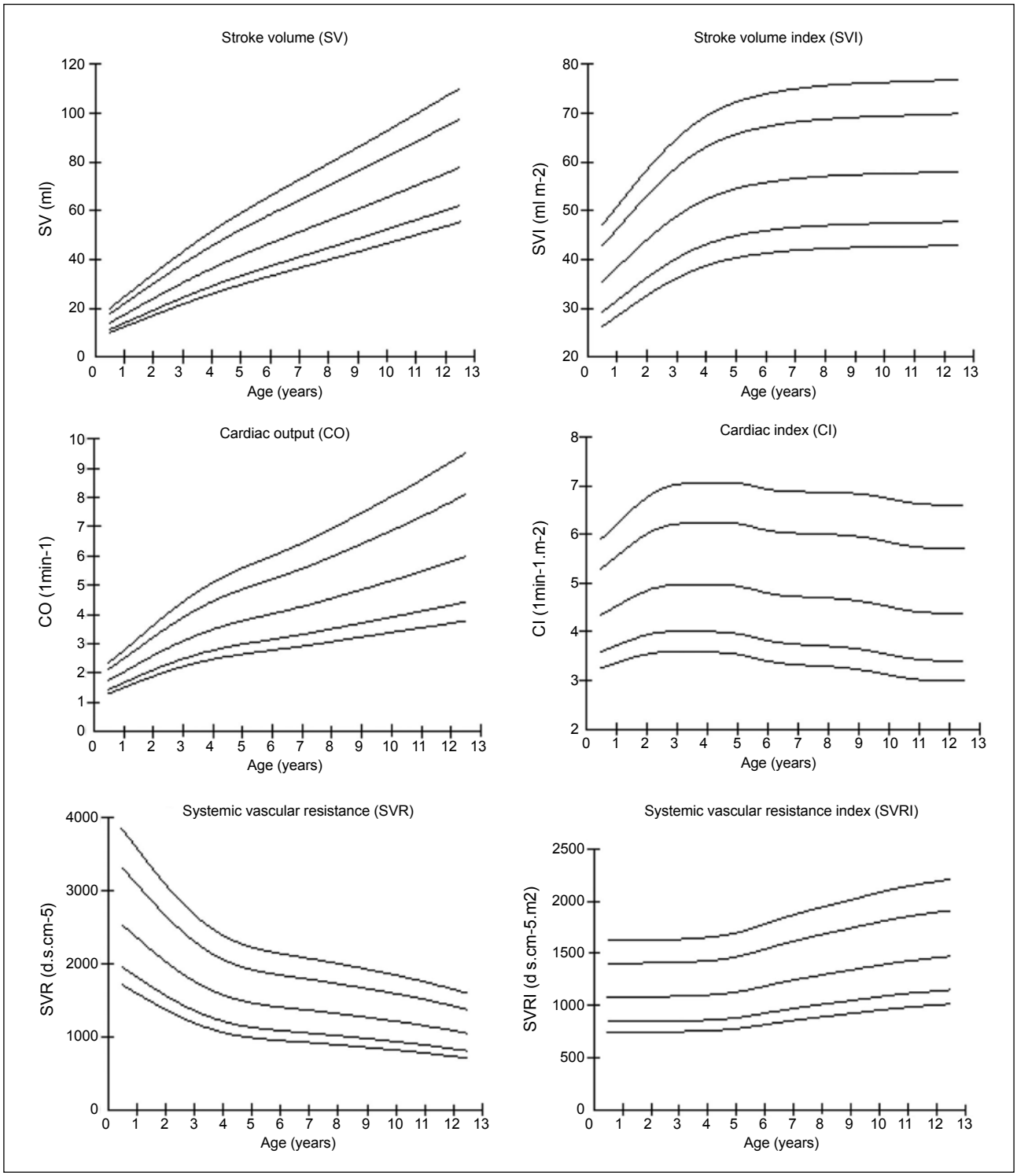

Fig. Ultrasonic Cardiac Output Monitor–derived cardiovascular indices: percentile curves of 2.5th, 10th, 50th, 90th, 97.5th. (Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Critical Care Medicine, copyright 2010)

in adults and critically ill children. The USCOM is non-invasive and can obtain estimates of normal cardiovascular indices in children. However, compared with the gold standard, it may overestimate SV (from which the software derives the other indices).

The inter-rater reliability was good based on three measures: coefficient of variation, Bland-Altman limits of agreement, and intraclass correlation. There was less variability in BP and HR measurements with USCOM than with standard oscillometric devices used in the emergency department.

All scans by the first operator, regardless of quality, were analysed. The quality of each trace was assessed using a scoring system. After approximately 30 scans, each

operator reached a steady state in his cumulative average scan quality.[6] All the scans were conducted after the end of this learning curve, but even highly experienced operators still sometimes failed to obtain a good-quality trace. This may have been due to the compliance or morphology of the subject. The second scans were not used to derive the normal values. In the resuscitation room, it is likely that just one operator uses the USCOM to obtain several views. In our study, each operator obtained three separate screenshots, which represents realistic practice. Sensitivity was determined by averaging values among subjects with two very good-quality scans. Median SVs obtained with better quality, averaged scans were approximately 4% greater than presented. In view of the wide range of normality, this difference was not considered clinically relevant.

This study was limited by the time allocated in the schools and kindergartens. We were unable to obtain two USCOM scans in all children. Nonetheless, children not scanned twice were unlikely to be different from those who were, and therefore we do not consider this a source of bias. Another limitation was that the numbers of children failed to reach the required sample size. Nonetheless, the numbers were more than that in previous studies, and the observed ranges for BP, HR, weight, and height were as expected, which suggests that our sample was representative. We aim to repeat the study in 0 to 2 year olds and in adolescents.

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Are the 2006 World Health Organization standards for infant growth applicable to Hong Kong Chinese? Universalistic standards or epidemiological transition stage-specific norms

Key Messages

1. Parental socio-economic status was positively associated with length and body mass index of Hong Kong Chinese infants at 9 months.
2. Maternal smoking in pregnancy was negatively associated with infant length at 9 months.
3. Some of the World Health Organization (WHO) criteria for an optimal nurturing environment contributed positively to growth. At 36 months, Hong Kong Chinese infants were generally shorter and fatter than the WHO growth references.

Introduction

Infant growth is a key health indicator. Growth standards, particularly for height, can monitor whether child health and care needs are met effectively, such that children can achieve their full growth potential.[1] In 2006, the World Health Organization (WHO) issued growth charts to provide universalistic standards for optimal growth of infants worldwide. Nonetheless, the WHO sample did not include infant populations from China or East Asia. The WHO implicitly assumes that under optimal environmental conditions, infants and children can achieve their full genetic height potential within one generation, although there is evidence indicating a limit to inter-generational height increases and that incremental increases in height take place over many generations.[2] In a population-representative cohort of Hong Kong Chinese infants, their weights at 3, 12, and 36 months matched the 2006 WHO growth references closely, but their heights were shorter at 3 years of age.[3] The rapid and compressed epidemiological transition from essentially pre-industrial conditions a few generations ago to an affluent post-industrial society may not have allowed sufficient generations for infants to realise their full genetic height potential, regardless of an optimal current environment. There is also increasing evidence that rapid infant growth is associated with metabolic disease risk.[4] Given this dilemma, we examined how the WHO criteria for an optimal nurturing environment impacted infant growth in Hong Kong Chinese children.

Methods

This study was conducted from April 2008 to July 2008 and approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board and the Ethics Committee of the Department of Health. In 1997, 8327 infants born in April or May were recruited from 47 government Maternal and Child Health Centres (MCHCs) in Hong Kong. The response rate was 95%, and 88% of all births in that period were included. A self-administered questionnaire was used to collect information on demographics (household type, household size, age, and education levels of parents), birth characteristics (parity, gestational week, and delivery method), tobacco exposure (maternal smoking, second-hand smoking exposure at home and elsewhere) and the infant characteristics (sex, birth weight, birth order, and feeding method). Families were encouraged to bring their infants to the MCHCs a few days after birth and at regular intervals until the age of 6 years for vaccinations and physical examinations (weight and length). The cohort was followed up at 3, 9, and 18 months using a self-administrated questionnaire. In addition, in 2005-6 all recorded weight and length/height measurements were abstracted from the MCHCs by the unique MCHC reference number, and all admissions to public hospitals were extracted from the Hospital Authority records by the unique birth certificate number.

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Infants with growth problems or in poor health attended the MCHCs for health checks more frequently, the closest measurement within one month of the scheduled well-baby checks at 1, 3, 9, 12, 18, 24, and 36 months and the scheduled height checks at 3, 9, and 36 months was used, except for 1 and 24 or 36 months the measurements were within 15 days and 4 months, respectively. We also checked and corrected measurements for errors of transcription if the z-score changed by 1.5 or more within 90 days. Preterm births and multiple births were excluded because their growth trajectory may have differed. Infants with physical birth defects or those not of Chinese ethnicity were also excluded.

Factors considered as potentially affecting growth were the criteria mentioned in the WHO multicentre growth study for an optimal nurturing environment, ie no maternal smoking before and after delivery, no economic constraints on growth, no serious morbidity likely to impact growth, and breastfeeding (Table). Analyses were adjusted for gestational age, birth order, mother's place of birth, and sex as appropriate. To determine the contribution of these factors to weight growth at 0-36 months, a shape invariant model with random effects was used. Relative differences in birth size and growth rate were reported. Multivariable linear regression was used to examine the contribution of these factors to weight and length at 9, 12, and 36 months, expressed as z-scores relative to the 2006 WHO references. Boys and girls were analysed together unless there was evidence of effect modification, ie a significant interaction term or different effect sizes by strata.

Results

Of the 8327 infants recruited, 123 twins and 20 non-Chinese were excluded, as were 99 with birth defects, 377 with a gestational age <37 weeks, 54 with missing gestational age, and six with an unreliably long reported gestational age of over 44 weeks. In each analysis infants with insufficient measurements or missing information were excluded. Preliminary analysis revealed that most factors had similar effects in boys and girls, so boys and girls were analysed together.

As shown in the Table, 4.5% of the mothers smoked in pregnancy, 16.5% of the infants were exclusively breastfed for at least 1 month, and 1.3% of the infants had serious morbidity. The mean birth weight in boys (3.29 kg) and girls (3.18 kg) was below the WHO standard (by z-scores equivalent to 58 g in boys and 49 g in girls). Maternal education and breastfeeding were associated with faster growth. Serious morbidity had little association with growth. Infants of mothers who smoked in pregnancy were smaller at birth, but grew faster. By 9 months (n=3404) infant length was associated with parental education and tobacco smoke exposure, but not with breastfeeding or serious morbidity. Infants whose parents had grade 12 or higher levels of education had similar length as the WHO reference and were longer than infants whose parents had grade 9 or lower levels of education by a mean of 0.30 cm (difference in z-score, 0.14; 95% confidence interval (CI), 0.04-0.24). Infants of more educated parents also had higher mean body mass index by 0.15 kg/m^2 (difference in z-score, 0.10; 95% CI, 0.00-0.20) than infants of parents whose education level was grade 9 or lower. The latter also had a higher mean body mass index by 0.42 kg/m^2 (difference in z-score, 0.29; 95% CI, 0.23-0.36) than the WHO references. On average, infants whose mothers smoked in pregnancy were shorter at 9 months than infants with no pre- or post-natal tobacco smoke exposure by about 0.41 cm (difference in z-score, -0.18; 95% CI, -0.01-0.35). However, these differences in length associated

Table. Adjusted relative birth weights and growth rates at 0-36 months among 3071 boys and 2765 girls in Hong Kong

Variable	% of children	Adjusted relative birth weight* (95% CI)	Adjusted relative growth rate* (95% CI)
Father's education			
Grade 9 or below	42.2	1.00	1.00
Grade 10 to 11	34.3	1.01† (1.00-1.01)	0.98† (0.96-0.99)
Grade 12 or above	23.5	1.00 (0.99-1.01)	0.99 (0.97-1.01)
Mother's education			
Grade 9 or below	38.8	1.00	1.00
Grade 10 to 11	45.2	1.00 (1.00-1.01)	1.04† (1.02-1.05)
Grade 12 or above	16.0	1.01† (1.00-1.02)	1.05† (1.02-1.07)
Tobacco smoke exposure			
No	29.4	1.00	1.00
Second-hand smoking exposure in utero only	33.2	1.00 (1.00-1.01)	1.01 (1.00-1.02)
Second-hand smoking exposure at home after birth	32.9	1.00 (0.99-1.01)	1.01 (0.99-1.02)
Mother smoked during pregnancy	4.5	0.98† (0.96-0.99)	1.04† (1.01-1.07)
Exclusive breastfeeding‡			
No	83.5	1.00	1.00
Yes	16.5	0.99 (0.99-1.00)	1.02† (1.01-1.03)
Hospitalised for diarrhoea by 18 months			
No	98.7	1.00	1.00
Yes	1.3	0.99 (0.98-1.00)	1.02 (1.00-1.04)

* Adjusted for sex, gestational age, birth order, and mother's place of birth
† P<0.05
‡ Breastfeeding was based on the duration of exclusive breastfeeding (0-183 days) and included as a time-dependent variable, thus giving an estimate of the effect on growth for the duration of breastfeeding.

with parental education and tobacco smoke exposure were no longer evident at 36 months (n=2612). These toddlers had consistently lower height but higher body mass index values than the WHO references, regardless of parental education, tobacco exposure, breastfeeding, or serious morbidity.

Discussion

Regarding the 1997 cohort of Hong Kong Chinese infants, their birth weight was on average lower than the 2006 WHO references. Parental socio-economic position, tobacco smoke exposure, and to some extent breastfeeding were associated with different growth rates. Infants whose parents had grade 12 or higher levels of education were similar to the WHO 2006 references in terms of length at 9 months. On average, these infants had a higher body mass index than infants of less educated parents who also had a higher body mass index than the WHO references. Maternal smoking in pregnancy was associated with faster growth, but these infants were smaller at birth. Infants whose mothers smoked in pregnancy were shorter than infants without any tobacco smoke exposure at 9 months. By 36 months our toddlers were shorter and fatter than the WHO references, regardless of parental education, tobacco smoke exposure, or serious morbidity.

This study confirmed that several of the WHO criteria for an optimal nurturing environment were associated with infant growth differences. Hong Kong Chinese infants did not achieve the WHO height standards at 36 months. In infants of educated parents who achieved WHO standards of length growth at 9 months, their body mass index was higher than the WHO reference. Thus, attributes of the current environment appeared not to have contributed to the generally shorter height at 36 months. However, information on diet was not collected, so we cannot rule out the possibility that these infants and toddlers generally had a diet that was low in nutrients that specifically promote linear growth. These infants also had lower birth weights than the WHO references, which may also have been reflected in their birth length, with corresponding implications for infant length and toddler height. In well-nourished populations, maternal diet is not strongly related to birth weight. It is possible that a cultural preference for slimness in the mothers resulted in inadequate nutrition during pregnancy, which constrained the offspring's linear growth potential. Alternatively, birth weight may also reflect childhood living conditions in previous generations,[5] so another possible pathway is that these infants' linear growth was constrained by living conditions in previous generations, ie by epigenetic constraints. Finally, we cannot rule out the possibility that Hong Kong Chinese are genetically shorter, although the current strong trend in height suggests that Hong Kong Chinese have not yet reached their full genetic height potential. Given that rapid infant growth is associated with adult obesity and metabolic risk, attention should be paid to ensuring Hong Kong infants achieve appropriate linear growth without becoming overweight.

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Electroacupuncture for ileus after laparoscopic colorectal surgery: a randomised sham-controlled study

Key Messages

1. Electroacupuncture at acupoints of Zusanli, Sanyinjiao, Hegu, and Zhigou is more effective than no acupuncture and sham acupuncture in stimulating early return of bowel function and reducing analgesic requirement after laparoscopic colorectal surgery.
2. Electroacupuncture is more effective than no acupuncture in reducing the duration of hospital stay.
3. Receipt of electroacupuncture is an independent predictor of shorter duration of ileus and hospital stay after laparoscopic colorectal surgery.

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Introduction

Ileus after colorectal surgery adversely influences patient recovery and prolongs hospital stay.[1] Laparoscopic colorectal surgery is associated with better short-term clinical outcomes (including more rapid return of gastrointestinal function) than open surgery.[2,3] Nonetheless, the duration of postoperative ileus (time to first bowel motion) can be up to 4 days after laparoscopic surgery and 5 days after open surgery. Further measures are warranted to enhance the gastrointestinal recovery and reduce the duration of hospital stay and hence costs.

Acupuncture is effective in managing postoperative nausea and vomiting and various functional gastrointestinal disorders.[4] Its role in treating postoperative ileus is less known. This randomised sham-controlled study aimed to evaluate the efficacy of electroacupuncture (EA) in reducing the duration of ileus and hospital stay after laparoscopic colorectal surgery.

Methods

This study was conducted from October 2008 to October 2010. The study protocol was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. Consecutive patients aged >18 years who had the American Society of Anesthesiologists grading I to III and underwent elective laparoscopic resection of colonic and upper rectal cancer without the need of conversion were included. Patients who underwent laparoscopic resection of mid and low rectal cancer were excluded, as were those who underwent complex or combined laparoscopic procedures, had stomas created, developed intraoperative problems or complications, received epidural anaesthesia or analgesia, had a cardiac pacemaker, were allergic to acupuncture needles, or had received acupuncture previously.

A standard perioperative protocol (including preoperative mechanical bowel preparation) was followed. Laparoscopic surgeries were performed under general anaesthesia. After the surgery, patients were randomised to receive either EA (acupuncture and electrical current stimulation) or sham acupuncture (SA) by an experienced acupuncturist, or no acupuncture (NA). The patients randomised to the EA and SA groups underwent one session of treatment daily from day 1 to day 4, or till the time defaecation occurred, whichever was earlier. In the EA group, sterile acupuncture needles were inserted to a depth of 20 mm in the acupoints relevant to the treatment of abdominal distension and constipation, including Zusanli (stomach meridian ST-36), Sanyinjiao (spleen meridian SP-6), Hegu (large intestine meridian LI-4), and Zhigou (triple energiser meridian TE-6). Effective needling was indicated by a radiating sensation with paraesthesia known as *De Qi*. Electrical stimulation with a frequency of 100 Hz was then used. Each session of EA lasted for 20 minutes. In the SA group, shorter needles were placed 15 mm away from the acupoints at a shallower depth to avoid *De Qi*. Pseudostimulation was given by incorrectly connecting the output socket and thus no flow of electrical current. The postoperative management was standardised. Postoperative analgesia (pethidine 1 mg/kg) was given 4-hourly on demand. Early ambulation was encouraged. Oral feeding was resumed as early as possible. No gum chewing was allowed. Patients were discharged when they

tolerated diet and were fully ambulatory.

The primary outcome measure was the time to defaecation (number of hours after the end of laparoscopic surgery to the first observed passage of stool). The secondary outcome measures were the time to first passing of flatus, time elapsing till the patient tolerated solid diet, time till the patient walked independently, duration of hospital stay, visual analogue scale score for pain on the first 3 postoperative days, and receipt of postoperative analgesia. Data were recorded and measured by an independent research assistant according to the intention-to-treat principle. Two null hypotheses were tested using Student's *t*-test in a stepwise fashion. In the first, EA was hypothesised to be no more efficacious than NA in reducing the duration of postoperative ileus. In the second, EA was hypothesised to be no more efficacious than SA. Multivariate analysis with stepwise multiple linear regression was used to identify independent predictors of outcome. According to our previous randomised controlled trial on laparoscopic resection of rectosigmoid carcinoma, the mean time to first defaecation in the laparoscopic arm was 4 days, with a standard deviation of 1.7 days.[2] Assuming that the difference in mean time to first defaecation between the EA and NA groups is 1 day, a sample size of 55 patients in each group is needed to yield a power of 80% with a significance level of 0.025 (two pair-wise comparisons). Thus a sample size of about 165 patients is derived.

Results

Out of 208 patients, 43 were excluded after surgery for various reasons and 165 were randomised to receive either EA (n=55), SA (n=55), or NA (n=55). There was no withdrawal or drop-out, so all recruited patients were available for analysis. No adverse event related to the use of acupuncture was reported. The study groups were similar with respect to demographics, prevalence of underlying comorbidities, types of surgery performed, operation time, and operative blood loss (Table 1). There was no significant difference in the overall postoperative complication rates in the three study groups (P=0.318).

Compared to the NA group, the EA group had significantly shorter time to defaecation (P<0.001) and time to resume a normal solid diet (P=0.01) and earlier hospital discharge (Table 2). Compared to the SA group, the EA group also had significantly shorter time to defaecation (P=0.007). Other outcome measures including time to walk

Table 1. Baseline demographics of the three groups

Parameter	Electroacupuncture (n=55)	Sham acupuncture (n=55)	No acupuncture (n=55)
Mean±SD age (years)	67.4±9.7	67.4±10.7	68.5±10.6
No. of males/females	35/20	33/22	31/24
Mean±SD body mass index (kg/m^2)	22.8±2.9	22.9±3.4	23.4±3.1
American Society of Anesthesiologists grading (no. of patients)			
Grade I	17	14	11
Grade II	36	30	32
Grade III	2	11	12
No. (%) of patients with comorbidities	29 (52.7)	34 (61.8)	37 (67.3)
Types of surgery (no. of patients)			
Right hemicolectomy	15	12	17
Left hemicolectomy	12	12	10
Sigmoid colectomy	7	7	8
Anterior resection	21	24	20
Mean±SD operative time (minutes)	157.3±39.2	158.6±46.5	164.1±52.5
Median (range) blood loss (mL)	20 (0-200)	20 (0-200)	20 (0-600)
No. (%) of patients with complications	6 (10.9)	5 (9)	10 (18.2)

Table 2. Outcome measures in the three groups

Outcome (mean±SD)	Electroacupuncture (n=55)	Sham acupuncture (n=55)	No acupuncture (n=55)	P value (electroacupuncture vs no acupuncture) [Student's t-test]	P value (electroacupuncture vs sham acupuncture) [Student's t-test]
Time first passing flatus (days)	2.0±0.9	2.3±1.1	2.6±1.1	0.003	0.095
Time of first bowel motion (hours)	85.9±36.1	107.5±46.2	122.1±53.5	<0.001	0.007
Time to resume normal diet (days)	4.0±1.1	4.1±0.8	4.8±2.0	0.010	0.695
Time to walk independently (days)	2.8±1.5	3.3±1.1	3.8±1.8	0.001	0.028
Hospital stay (days)	6.5±2.2	6.8±1.7	8.5±4.8	0.007	0.491
Pain score					
Day 1	5.6±2.0	5.8±1.9	5.5±2.3	0.689	0.655
Day 2	3.2±1.6	4.6±2.0	4.2±2.0	0.004	<0.001
Day 3	2.1±1.2	3.4±2.2	3.2±1.8	<0.001	<0.001
Postoperative analgesic requirement (no. of injections of 50 mg pethidine)	2.7±2.3	5.2±4.7	5.0±4.5	0.001	0.001

independently, pain scores, and analgesic requirement were also significantly more favourable in the EA group. The duration of hospital stay, however, was similar in the EA and SA groups.

On multivariate analysis with stepwise multiple linear regression, the presence of complications was an independent predictor of longer time to defaecation (regression coefficient, 39.3; 95% CI, 18.8 to 59.7; P<0.001), whereas the use of EA predicted a shorter time to defaecation (regression coefficient, -27.8; 95% CI, -42.3 to -13.4; P<0.001). Independent predictors of shorter duration of hospital stay were absence of complications (P<0.001), the use of EA (P=0.002), and the use of SA (P=0.016).

Discussion

In the present study, EA was more effective than NA and SA in stimulating an early return of bowel function and reducing analgesic requirement after laparoscopic colorectal surgery. Furthermore, EA was an independent predictor of a shorter duration of postoperative ileus. On multivariate analysis, both EA and SA were independent predictors of shorter duration of hospitalisation, with EA being a stronger predictor. The EA and SA groups had similar length of hospital stay despite a shorter time to defaecation and ambulation in the EA group. The sample size and power of this study may not have been adequate to show significant differences between the EA and SA groups for all parameters.

This study had several limitations. First, the study population who underwent uncomplicated elective laparoscopic resection of colonic and upper rectal cancer constituted a highly selected group. Patients with mid and low rectal cancer or those undergoing complex or combined laparoscopic procedures were excluded. Complicated cases are more likely to develop prolonged ileus and morbidity after surgery, and it is uncertain whether EA could be effective in them. Second, a fast-track perioperative programme was not used,[5] as it was not the standard of care in our institution.[2] The combined effects of EA and fast-track programme on clinical outcomes after laparoscopic colorectal surgery warrant further research. Third, a cost-effectiveness analysis was not conducted to evaluate the economic impact of resorting to EA on the hospital system. Laparoscopic colorectal surgery is costly.[2] Further studies are needed to address whether faster recovery brought about by EA reduces the financial burden to the hospital/healthcare system.

Acknowledgement

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Long-term efficacy of electroacupuncture for chronic neck pain: a randomised controlled trial

Key Message

Electroacupuncture is a safe treatment for chronic neck pain. Nonetheless, one month after treatment, improvement of neck pain is similar to that in placebo-treated controls. This suggests that the efficacy may not be due to specific effect of the treatment procedure.

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Introduction

Acupuncture may be more effective than placebo in producing immediate relief of neck pain, but controversies exist as to whether it has any long-term benefit. This study aimed to evaluate the long-term efficacy of electroacupuncture for chronic neck pain, and document any possible side effects.

Methods

This double-blind, randomised controlled trial was conducted from November 2006 to April 2009. Patients, practitioners, and the assessor were blind to the treatments. Adult subjects with chronic mechanical neck pain for ≥3 months were included. Patients with surgery to the neck, neurological deficits, a history of malignancy, congenital abnormality of the spine, systemic diseases, and those treated by acupuncture in the last 6 months were excluded.

A total of 206 Chinese patients (mean age, 45.8 years) with chronic neck pain (mean duration, 75.4 months) were randomised to receive electroacupuncture (n=103) or sham laser acupuncture (n=103) three times per week for 3 weeks. Randomisation took into account the age, gender, and degree of disability due to neck pain using computer software. An intention-to-treat analysis was performed.

Sterile acupuncture needles 25 to 40 mm long with a diameter of 0.25 to 0.30 mm were inserted into Hegu (LI4, x2), Houxi (SI3, x2), Feng Chi (GB20, x2), Jiangjing (GB21, x2), and Bailao and stimulated with an electroacupuncture machine for 45 minutes. Two additional points could be chosen from tender points or acupuncture points immediately near the tender points. Sham laser acupuncture was delivered via a mock laser pen that only emitted a red light. Neither the patients nor the practitioners were informed that the laser pen was inactivated. Each point was treated for 2 minutes, with the pen at a distance of 0.5 to 1 cm from the skin.

The primary outcome measure was the change in neck pain specific disability index, as measured by the Northwick Park Neck Pain Questionnaire (NPQ). Secondary outcome measures were (1) the change in maximum pain related to motion, regardless the direction of movement, on a 100-point pain scale, (2) quality of life assessment using SF-36 health survey, (3) use of medication for neck pain, and (4) sick leave for neck pain. Adverse effects and the credibility of real and sham treatments were assessed by a blind assessor before and after treatment.

Results

Of 103 patients in each group, 91 in the treatment group and 84 in the control group completed the treatment sessions. At the end of six months, 84 and 76 patients, respectively, had completed all follow-up assessments (Fig). About 70% of the patients were female. Over 90% of the patients had secondary school or higher levels of education, and about 40% of them worked in an office. The baseline characteristics of the two patient groups were similar (Table).

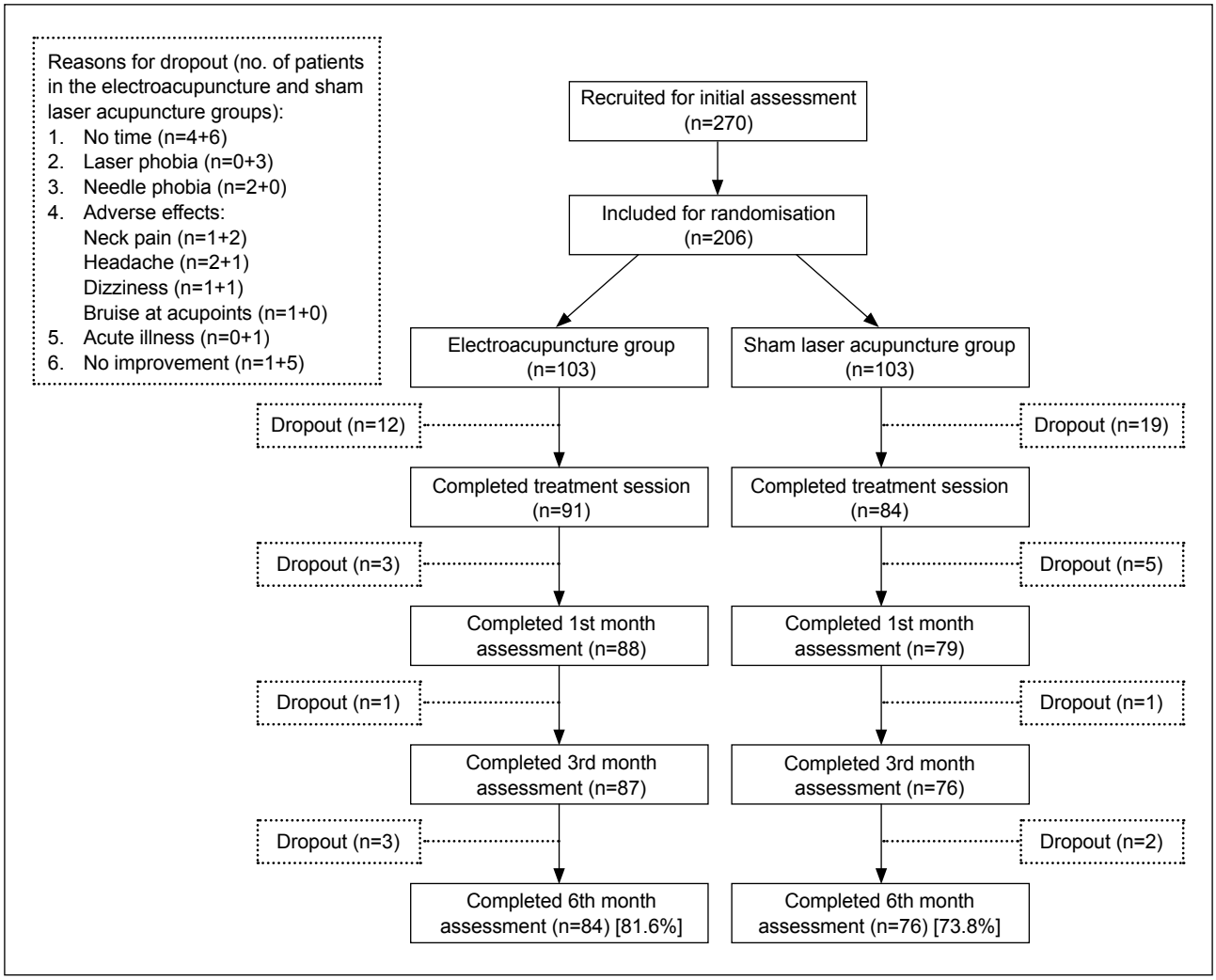

Fig. Consort chart

Table. Changes in neck pain, disability, and quality of life after treatment

Predictors	Electroacupuncture (mean [95% CI])	P value for treatment effect	Sham-laser acupuncture (mean [95% CI])	P value for treatment effect	P value for between-group effect
Northwick Park Neck Pain Questionnaire score					
Pre-treatment	40.7 (38.5-42.9)		41.1(38.7-43.5)		
1 month	35.1 (32.7-37.6)	0.013*	35.7 (32.8-38.6)	0.066	0.791
3 months	32.9 (30.3-35.4)	<0.001*	33.3 (30.1-36.5)	0.002*	0.664
6 months	33.5 (30.7-36.4)	<0.001*	34.3 (31.1-37.6)	0.009*	0.808
Numeric pain intensity scale score					
Pre-treatment	54.7 (50.9-58.4)		51.6 (47.6-55.7)		
1 month	50.8 (46.6-54.9)	0.835	46.9 (42.4-51.4)	0.807	0.813
3 months	46.6 (42.2-51.0)	0.046*	45.1 (40.5- 49.6)	0.234	0.617
6 months	46.8 (42.0-51.5)	0.054	43.6 (38.8-48.4)	0.076	0.813
SF-36 physical component score					
Pre-treatment	52.5 (51.5-53.4)		52.7 (51.9-53.6)		
1 month	52.6 (51.7-53.5)	1.000	53.0 (52.1-53.9)	1.000	0.396
3 months	52.8 (53.0-53.7)	1.000	53.3 (52.4-54.2)	1.000	0.982
6 months	53.0 (52.0-53.9)	1.000	53.2 (52.3-54.0)	1.000	0.559
SF-36 mental component score					
Pre-treatment	43.8 (42.9-44.8)		43.7 (42.6-44.8)		
1 month	45.3 (44.2-46.4)	0.182	44.4 (43.3-45.5)	1.000	0.389
3 months	45.9 (46.0 46.8)	0.015*	45.3 (44.2-46.4)	1.000	0.444
6 months	45.4 (44.5-46.3)	0.146	44.4 (43.4-45.4)	1.000	0.246

* P<0.05, ANOVA

In the treatment group, NPQ scores improved significantly at 1, 3, and 6 months, compared to the baseline value (ANOVA with Bonferroni post-hoc test). Significant improvement was also noted in the bodily pain score of the SF-36 at 1 month, the numeric pain intensity scale score, bodily pain score, vitality, and mental component score and total score of the SF-36 at 3 months, and the bodily pain score of the SF-36 at 6 months. In the control group, NPQ scores improved significantly at 3 and 6 months, as did the bodily pain score of the SF-36 at 1, 3, and 6 months. More items yielded improvements in the treatment than control group (Table).

Using multiple analysis of covariance after controlling for confounding variables (gender, age, duration of pain before treatment, and job nature), the two groups did not differ significantly (P=0.975). All confounding variables had no significant effect. Whether the treatment effect (β5) was significant was determined in the following model: $y = \alpha + \beta1$ (gender) + β2 (age) + β3 (pain duration) + β4 (job nature) + β5 (group) + ε, where y was a vector containing all outcome measures (excluding the reductions in the number of sick leaves and the SF36 total scores) of a respondent and ε a normally distributed random vector representing random errors. The parameters α, β1, β2, β3, β4, and β5 were unknown vectors. The reduction in the number of sick leaves was excluded because such a reduction is an integer and the normally distributed random error was not applicable. The SF36 total score was excluded because it is just the sum of the physical and mental component scores.

The credibility of the test and control treatments was assessed using the Borkovec and Nau scale.[1] At the beginning of the treatment, subjects gave scores of 4 to 4.9 (out of a 6-point scale) for both treatments, indicating good credibility. There was no significant within-group difference before and after treatments, suggesting that the treatment process did not alter the credibility rating significantly. There was a significant between-group difference, indicating that electroacupuncture was perceived as a more credible treatment than laser acupuncture. Nevertheless, concealment of electroacupuncture as the real treatment was successful, as the number of subjects who correctly guessed the nature of treatment received was not significantly different in the two groups (P=0.108). All practitioners believed that laser acupuncture was an active treatment, although they believed that electroacupuncture would be more effective.

Respectively in the electroacupuncture and sham laser acupuncture groups, adverse reactions reported were increased neck pain (n=1+2), headache (n=2+1), dizziness after treatment (n=1+1), bruise at acupoints (n=2+0), pain at acupoint after treatment (n=1+0), chest discomfort after treatment (n=1+0), itching palm after treatment (n=0+1), warm-feeling at the back after treatment (n=0+1). No severe adverse reaction was noted.

Discussion

Compared to sham laser acupuncture, no long-term benefit could be demonstrated for electroacupuncture, although both groups showed small but significant improvements. Whether such improvement was due to spontaneous remission of the disease or the treatment is unknown. The masking of controls was successful for both patients and practitioners. The electroacupuncture treatment was well tolerated and resulted in few adverse effects. The improvements in NPS and numeric pain intensity scale scores in both groups were small (<20%). In chronic pain patients, ≥30% difference is considered clinically significant.[2] Therefore, neither group had clinically significant improvement after treatment.

Several factors may contribute to the improvement of symptoms. First, patient's experience of the treatment process, including patient participation and practitioner attention could have a positive psychological or placebo effect. Second, both treatments might have physiological effects. Electroacupuncture is known to evoke physiological reactions,[3] but physiological reactions to shining a red-light on acupoints has never been evaluated. Sham laser acupuncture had been demonstrated to be inferior to electroacupuncture.[4] Sham laser acupuncture might nevertheless have a small physiological effect equal to electroacupuncture, as it might activate similar parts of the brain involved in pain modulation.[3] Nevertheless, the magnitude of the present effects from both treatment was small. Third, spontaneous resolution of the condition may also account for the improvements.

One limitation of this study was that there was no second control arm, in which participants received no treatment. Thus we were not able to assess the efficacy of the treatment procedure compared to spontaneous remission. In a review of 14 clinical trials of acupuncture for neck pain, short-term effect was demonstrated, but long-term effect was uncertain.[5] Compared to previous studies, our study recruited larger samples and used more stringent methodology, such as concealment of the treatment nature from patients and practitioners, and use of software to ensure a balance of baseline features of the two groups. Our study confirmed that for chronic neck pain there is little, if any, long-term efficacy from electroacupuncture. Owing to the low external validity, our findings may not be generalised to other acupuncture practices, such as manual acupuncture.[6] Our findings have certain implications for clinical research. We initially chose to study the effects of electroacupuncture because the procedures could be standardised and easily replicated in clinical practice. However, the standardisation of procedures also meant that there was little flexibility in the choice of acupuncture regimens, which often change in clinical practices when a patient fails to respond to a particular regimen. For example, a Chinese medicine practitioner may start with electroacupuncture for a patient with chronic mechanical neck pain, but change to manual acupuncture plus moxibustion if the patient does not

respond well. Such flexibility in the choice of regimens is part of the individualised treatment principle in acupuncture practice. We therefore suggest that future clinical research with acupuncture should try to simulate clinical practice as far as possible, so as to improve external validity. Although electroacupuncture for chronic neck pain is safe, it has limited efficacy. Practitioners should be prepared to abandon the treatment if the patient does not respond well.

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Rapid and specific determination of DNA adducts for clinical diagnosis of poisoning and disease associated with aristolochic acid

Key Messages

1. A liquid chromatography–mass spectrometry method was developed to detect and characterise aristocholic acid–DNA adducts in biological samples.
2. The detection of DNA adducts in plasma, urine or the cells found in urine may be useful to support the diagnosis and monitoring of aristocholic acid–associated poisoning and disease.
3. Efforts should be made to improve the sensitivity and specificity of this approach for the detection and characterisation of exposure to other mutagens/carcinogens.

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Introduction

Exposure to aristolochic acids (AAs), derived from the herbal genus *Aristolochia* and *Asarum*, is associated with the development of nephropathy (aristolochic acid nephropathy). Prolonged exposure to AAs has been reported from medicinal applications and the use of AA-related herbs in slimming products. Upon enzyme activation, AAs are metabolised to the aristolactam-nitrenium ion intermediates leading to the formation of the corresponding DNA adducts. Therefore, such DNA adducts may serve as biomarkers of exposure and can be used to confirm ingestion of AAs. Analysis of DNA-AA adducts may support the clinical diagnosis of AA-associated poisoning and disease.

Although the import and sale of herbs *Aristolochia* and related products containing AAs have been banned in Hong Kong since 1 June 2004, certain AA-containing herbs that yield small amounts are still available. Moreover, there is confusion concerning which herbs contain AAs. It is unknown how many people have been exposed to these potentially dangerous herbs and for how long. The possible consequences of long-term exposure to AAs include renal failure and urinary tract cancers. It is therefore important to monitor the long-term outcome of exposure to AAs.

Damage to DNA due to prolonged exposure to AAs significantly increases the risk of cancer in humans. Diagnosis of acute poisoning from AAs is possible, but a retrospective diagnosis is difficult to make. With respect to research on AA-induced kidney disease, a simple and rapid method for detecting DNA-AA adducts is needed. This study aimed to develop a novel assay for analysis of such DNA adducts of AAs in biological samples. The liquid chromatography–mass spectrometry (LC-MS) method was validated and applied to analyse DNA adducts in human kidney tissues, in addition to plasma and urine samples collected from rats dosed with AAs. The feasibility of applying the developed method to study adduct formation in white cell DNA was investigated, and the potential clinical use of such adducts as biomarkers in blood or urine, instead of kidney tissue, was explored.

Methods

This study was conducted from January 2008 to December 2009. In vitro experiments were conducted to produce various DNA adducts of AAs. Sample matrices ranging from oligonucleotides, calf thymus-DNA to animal DNA were used. Animal studies involving oral administration of AAs to rats were conducted to study of AA toxicity. The induction of AAs in single and multiple dosing experiments were carried out. Determination and characterisation of known and unknown DNA adducts of AAs was conducted by exposing rats to AAs via the oral and intravenous route. The formation of AA-DNA adducts in liver and kidney tissue, as well as biofluids (eg urine and plasma) was evaluated. Rat kidney tissues were collected, with a view to extracting and isolating DNA according to the animal study protocols. Liver and kidney tissue samples were collected for the analysis of DNA-AA adducts using the developed LC-MS method. After

method validation, the LC-MS method was also applied for the analysis of rat plasma and urine samples.

Procedures of sample pre-treatment and LC-MS analysis of DNA-AA adducts were developed. Direct analysis of urine samples and simple protein precipitation for plasma samples were combined with solid-phase extraction enrichment and cleanup procedures. Protocols were established to pool certain urine samples together in order to achieve sufficient quantities for analysis. The biological sample extracts were analysed using the LC-MS methods using an existing LC/ion trap mass spectrometer and an LC/quadrupole time-of-flight mass spectrometer. LC separation was important for achieving adequate sensitivity and specificity. For mass spectrometry analysis, both negative and positive electrospray ionisations, along with various instrumental parameters, were investigated and optimised. The obtained LC-MS data on DNA-adducts were validated using traditional ^{32}P-post-labelling analysis.

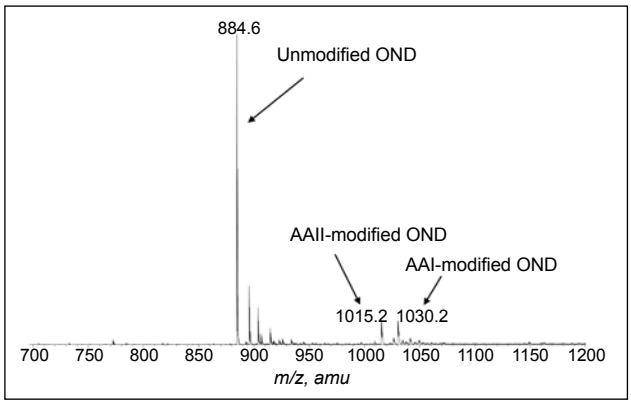

Fig 1. Typical ESI-MS spectrum of 5'-TTTATT-3' modified with 35 equivalents of aristolochic acids (AA) [mixture of AAI and AAII]. Labelled peaks display *m/z* values of the $[M-2H]^{2-}$ ions of the unmodified and AA-modified ODNs.

Results

The in vitro experiments with oligonucleotides and AAs were successful in producing DNA adducts. The DNA adducts produced via in vitro experiments were characterised by electrospray ionisation tandem mass spectrometry. Thus, LC-MS/MS was found to be a powerful technique for the identification and positional mapping of the DNA adducts in oligonucleotides.[1] The developed method was successfully applied to the analysis of unmodified and AA-modified oligonucleotides (Fig 1). The observation of the modified bases (modified adenine and guanine) together

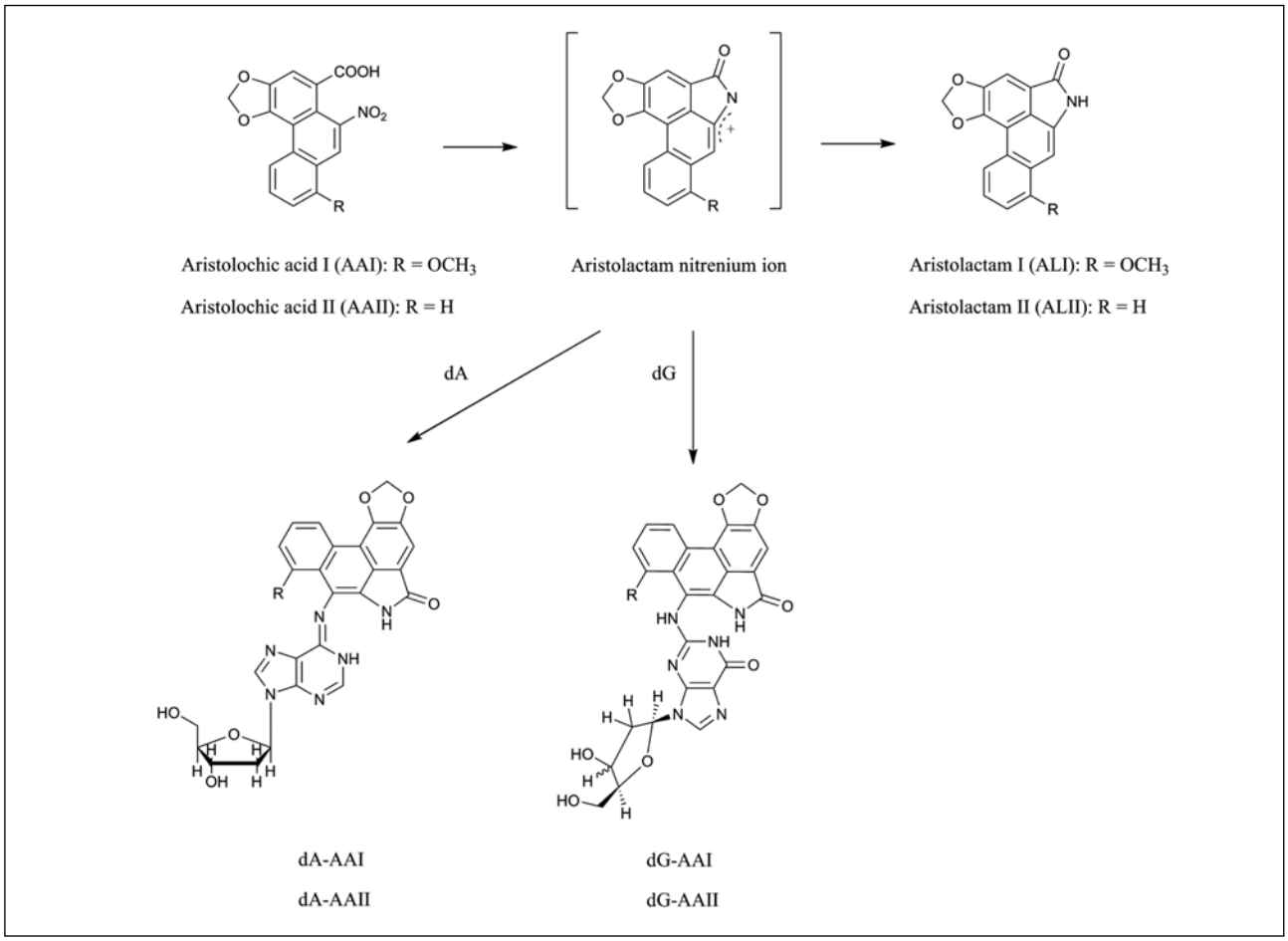

Fig 2. Metabolic activation and DNA adduct formation of aristolochic acids.

with the complementary product ions ([a_n-B^*_n]-, w-) from the cleavage of the 3' C-O bond adjacent to the modified base in MS/MS analyses readily enabled the identification of the AA binding site in oligonucleotides.

The metabolic activation of AAs was investigated. In vitro metabolism studies indicated that AAs were metabolised to *N*-hydroxyaristolactam, which could be either reduced to aristolactams or rearranged to 7-hydroxyaristolactams via Bamberger rearrangement. The intermediates (eg aristolactam-nitrenium) were regarded as responsible for the carcinogenicity of AAs (Fig 2). LC-MS and LC-MS-MS were applied to the analyses of a series of positional isomers of hydroxyaristolactams in both in vitro and in vivo samples. Metabolite identification provided important information for investigating mechanisms of AA toxicity and DNA formation. Prolonged exposure of AAs in rats was associated with development of renal disorder. Renal tubular atrophy and interstitial fibrosis were observed in rats dosed with up to 10 mg/kg/day of AAs for one month. In addition, AA-DNA adducts were detected in the rat kidney tissue.

The LC-MS method was applied to identify and quantify the AA-DNA adducts isolated from kidney and liver tissues of AA-dosed rats.[2] The deoxycytidine adduct of AA (dC-AA), the deoxyadenosine-AA adduct (dA-AA), and deoxyguanosine adduct (dG-AA) were detected and quantified in the tissues of rats with a single oral dose AA (up to 30 mg/kg of body weight). The amount of AA-DNA adducts found in the rats correlated well with the dosage.

Furthermore, a specific method using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) was developed and applied to the determination of 7-(deoxyadenosine-N^6-yl) aristolactam I (dA-AAI) in exfoliated urothelial cells of AA-dosed rats.[3] After the isolation from urine samples, DNA in urothelial cells were subjected to enzymatic digestion and solid-phase extraction on a C18 Sep-Pak cartridge for the enrichment of DNA adducts. The sample extracts were analysed by reverse-phase UPLC-MS/MS with electrospray ionisation in positive ion mode. The quantification of the DNA-AA adduct was performed by using multiple reaction monitoring with reserpine as internal standard. The method was accurate and precise with a detection limit of 1 ng/ml, which allowed the detection of traces of dA-AAI in exfoliated urothelial cells (Fig 3).

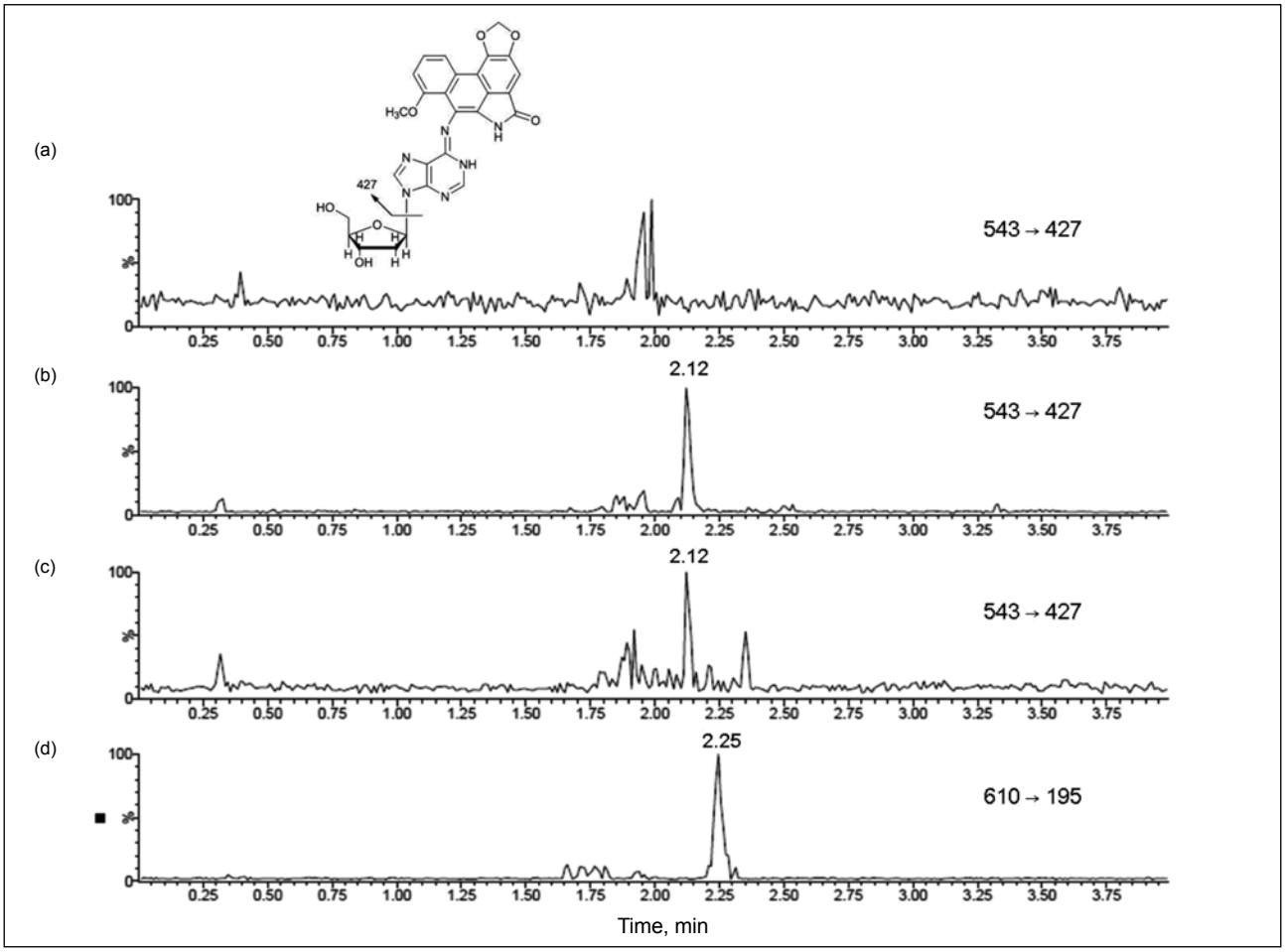

Fig 3. LC-MS/MS chromatograms for the analysis of dA-AAI (2.12 min) in (a) blank sample matrix, (b) spiked in blank sample matrix at a concentration of 60 ng/ml, and (c) exfoliated urothelial cells in urine collected from aristolochic acid–dosed rats. (d) Reserpine (2.25min) was used as internal standard at a concentration of 10 ng/ml.

In addition, a sensitive and rapid method entailing high-performance liquid chromatography with fluorescence detection (HPLC-FLD) was developed.[4,5] The HPLC-FLD method enabled validation of the method and provided an alternative approach for analysis of AAs in Chinese medicinal herbs,[4] as well as biological matrices.[5]

Discussion

Aristolochic acid nephropathy is associated with the prolonged exposure to nephrotoxic and carcinogenic AAs. DNA adducts induced by AAs have been proven to be critical biomarkers for AA-associated diseases. Metabolic activation of AAs produces reactive aristolactam-nitrenium ion intermediates. Electrophilic attack of the aristolactam-nitrenium ion via its C7 position on the exocyclic amino group in the purine bases leads to the formation of the DNA adducts.

Quantitative analyses of in vivo- and in vitro-formed DNA-AA complexes by the LC-MS method were performed with various quantification procedures. The LC-MS/MS method could provide specific and absolute quantification of DNA adducts in rat kidney tissue[2] and urine samples[3] by combining the advantages of LC and multiple reaction monitoring. From rats dosed with AAs, adducts of AAs and DNA were detected in the biological samples, and dA-AAI was detected in urine. Nonetheless, a large volume of rat urine sample was needed for the urine analysis because the DNA-AA adduct levels generated by AA induction were relatively low in urine.

Although the sensitivity of urine samples in detecting the DNA adducts was low, the LC-MS/MS method can be an attractive alternative to the conventional ^{32}P-post-labelling assay for clinical diagnosis of kidney disease associated with AA poisoning, so long as its sensitivity was improved. In particular, a successful urine sample analysis for DNA adducts can provide the diagnosis without a biopsy. Further validation for its applicability to analyse human samples is warranted.

Because AAs can form covalent DNA adducts through metabolic activation, the detection and characterisation of DNA-AA adducts is essential for the monitoring of exposure to AAs and for the investigation of their mutagenic and carcinogenic potential. The DNA adducts may thus serve as biomarkers of poisoning and can be used to confirm previous exposure. Therefore, the LC-MS/MS method for quantification of dA-AAI in exfoliated urothelial cells in urine of AA-dosed rats may be of clinical significance for diagnosing and monitoring AAs-associated disease in human. The detection of the DNA adduct in exfoliated urothelial cells is non-invasive and convenient. This method could also be applied to other DNA-AA adducts by monitoring the various multiple reaction transitions by tandem mass spectrometric analysis. Application of metabolomic approaches are recommended for analysing large amounts of animal data for detection of potential biomarkers associated with AA toxicity.

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Chinese herbal medicine for functional constipation: a randomised controlled trial

Key Messages

1. This was an 18-week prospective, randomised, double-blind, placebo-controlled clinical study on a Chinese herbal medicine—MaZiRenWan (MZRW)—for the treatment of functional constipation.
2. 120 subjects with functional constipation (Rome III criteria) were randomised (60 per arm) into the MZRW and placebo groups. Respective responder rates for the two groups were 43.3% and 8.3% during treatment, and 30.0% and 15.0% in the follow-up period ($p<0.05$). The MZRW group was superior to the placebo group in terms of increased complete spontaneous bowel movement as well as reduction in severity of constipation, straining at evacuation, and use of rescue therapy. No serious adverse effects were reported.
3. The dose of MZRW (7.5 g bid) was determined in a separate clinical trial. This study entailed a dose determination study and then a placebo-controlled clinical trial and can be a good reference for future studies.

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Introduction

Constipation is a common gastrointestinal complaint, and Chinese herbal medicine has become a popular alternative treatment for it.[1,2] MaZiRenWan (MZRW) is composed of *Fructus Cannabis, Radix et Rhizoma Rhei, Radix Paeoniae Alba, Semen Armeniacae Amarum, Fructus Aurantii Immaturus*, and *Cortex Magnoliae Officinalis*. It was first recorded in a Chinese medicine classic—*Discussion of Cold-induced Disorders*—for the treatment of constipation. Current available evidence cannot confirm whether MZRW is effective for functional constipation.[3] This study aimed to determine the efficacy and safety of MZRW for the treatment of functional constipation in Excessive Syndrome (a disease/disorder presentation in Chinese medicine theory).

Methods

This study was conducted from September 2007 to August 2009. An 18-week, prospective, randomised, double-blind, placebo-controlled clinical trial was performed. It entailed 2 weeks of run-in, followed by 8 weeks of treatment, and 8 weeks of follow-up. Patients aged 18 to 65 years with functional constipation in Excessive Syndrome were recruited. Diagnosis of functional constipation was based on Rome III criteria,[4] whereas the diagnosis of Excessive Syndrome was based on the Chinese medicine theory. Participants were required to maintain a diary, in which details of bowel movements, improvement in related symptoms, and/or any adverse effects were recorded. This study was in accordance with the Declaration of Helsinki and approved by the Committee on the Use of Human & Animal Subjects in Teaching and Research of the Hong Kong Baptist University. All patients gave their informed consent and were free to withdraw at any time.

Both MZRW and placebo granules were prepared by PuraPharm International (HK) Limited. The entire manufacturing process was in compliance with the standards of Good Manufacturing Practice. Granules were packed in sealed opaque aluminium sachets and put in a zip lock bag (28 sachets per bag). Only the treatment code and lot number were printed outside the package to ensure successful blinding.

Participants recorded in a diary their stool frequency, stool form, feeling of complete evacuation (yes/no), and the intake of MZRW/placebo granules, rescue drug, or any other medication. They were interviewed at the end of weeks 2, 6, 10, and 18. A 7-point ordinal scale (0=not at all, 6=very severe) was used to measure individual's constipation and related symptoms. Global symptom improvement (improved, same, worse) was defined as a subjective feeling of adequate relief of their symptoms after medication. The primary end point was complete spontaneous bowel movement (CSBM). Participants with a mean increase of CSBM ≥1/week were defined as responders. The safety profiles of MZRW were assessed based on adverse events and clinical laboratory evaluations. The success of blinding was evaluated for both the investigator and patients in the last visit.

In a previous dose determination study, the responder rate of MZRW (7.5 g bid) was 53.1%, and a difference in resolution rate of at least 30% between MZRW and placebo was considered clinically significant.[5] Therefore, 60 patients per

group were needed to achieve 80% power at a significance level of 0.025 and 15% drop-out rate. Analysis was based on an intention to treat. Missing values were imputed by the last observation carried forward method. Continuous variables were calculated with Student's *t*-test, whereas the Chi-square test was used for categorical data. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Of 456 patients screened, 120 were randomised into MZRW (n=60) or placebo (n=60) group (Fig). The baseline variables of the two groups were comparable. Of the 120 patients, 17 (9 from MZRW group and 8 from placebo group) withdrew from the study. The mean number of CSBM per week increased from 0.33 (95% confidence interval [CI], 0.16-0.49) to 1.62 (95% CI, 1.11-2.13) in MZRW group and from 0.52 (95% CI, 0.34-0.69) to 0.72 (95% CI, 0.44-1.00) in placebo group during treatment (P=0.003, Table 1). The responder rates were 43.3% in MZRW group and 8.3% in placebo group (P<0.001, Table 2).

An increase from baseline in the overall number of bowel movements and CSBMs per week was noted in both groups during treatment (weeks 3-10). A sustained increment in the frequency of CSBMs during the follow-up period (weeks 11-18) was noted (Table 1). The responder rates in the follow-up period for the MZRW and placebo groups were 30.0% and 15.0%, respectively (P=0.049, Table 2). Patients receiving MZRW took less rescue drug during and after treatment, compared to baseline values (P<0.05, Table 1).

Compared with the baseline period (weeks 0-2), improvement in the global symptom at week 6 (during treatment), week 10 (end of treatment), and week 18 (end of follow-up) were 81.7%, 80.0%, and 50.0% for the MZRW group, and 46.7%, 53.3%, and 51.7% for the placebo group, respectively. In contrast, five participants in the MZRW group and 11 in the placebo group reported worse symptoms. The scores of individual symptom assessments (including severity of constipation, sensation of straining, incomplete evacuation, sensation of bloating, sensation of abdominal pain/cramping, nausea and passing of gas) were generally lower than at baseline.

Of the 109 participants who attended the last follow-up, 44% correctly guessed the groups they were allocated to, compared with 63.3% by the study investigator. For the 16 subjects who received placebo and made correct guesses, the factors on appearance, colour, texture, taste, and efficacy of the placebo (that did not look like true Chinese herbal medicine) were also determined.

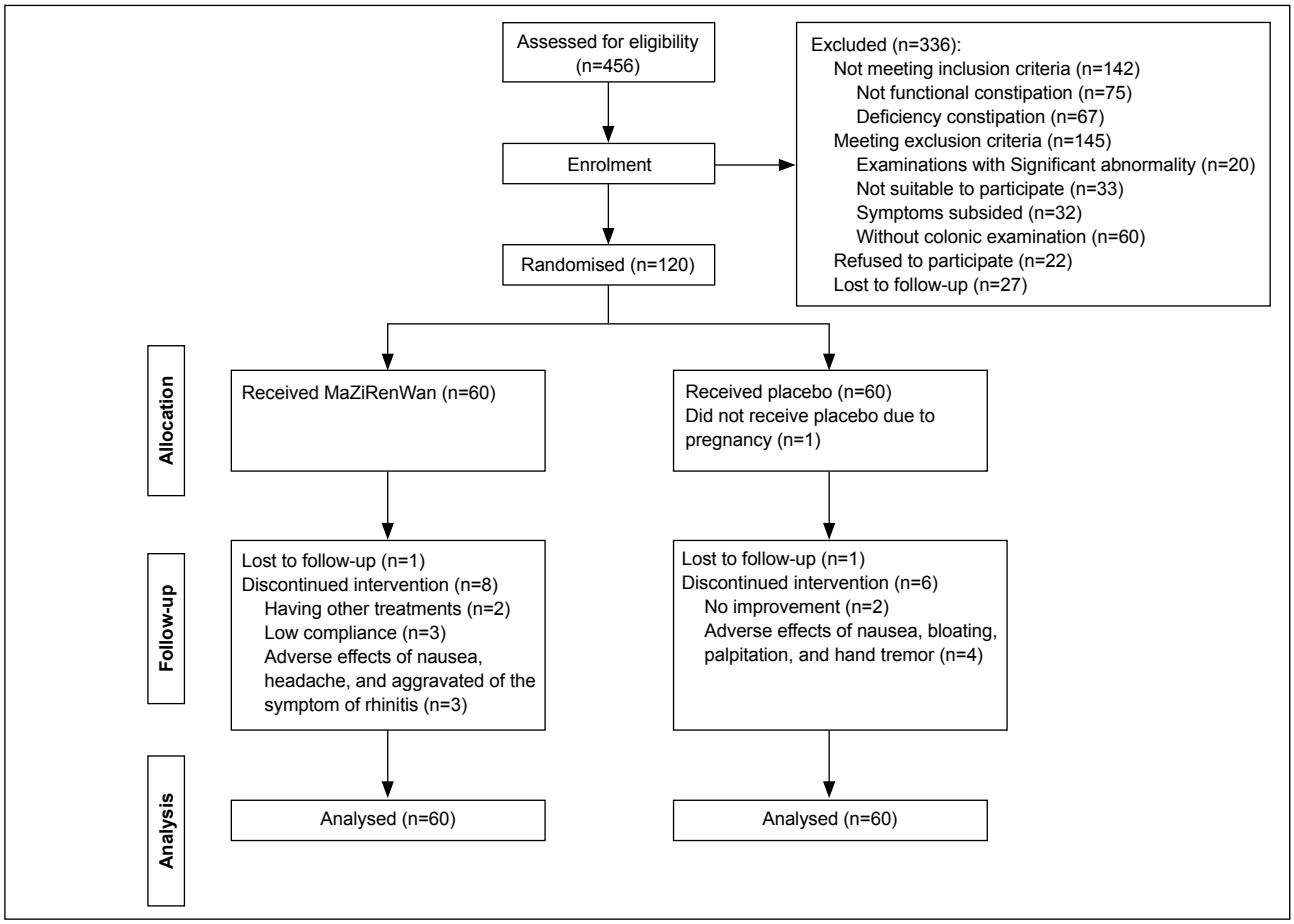

Fig. Flow chart of participants during different stages

Table 1. Comparison of the treatment effects between and within groups

Outcome measure	MaZiRenWan (7.5 g bid) [n=60]	Placebo (7.5 g bid) [n=60]	P value		
			Between groups	Within MaZiRenWan	Within placebo
Mean (95% CI) no. of days taking rescue therapy/week					
Baseline (weeks 1-2)	0.93 (0.59-1.27)	0.84 (0.54-1.14)	0.686	Ref	Ref
Treatment (weeks 3-10)	0.39 (0.18-0.60)	1.10 (0.73-1.47)	0.001	<0.001	0.033
Follow-up (weeks 11-18)	0.68 (0.41-0.95)	1.10 (0.68-1.53)	0.097	0.094	0.088
Mean (95% CI) no. of bowel movement/week					
Baseline (weeks 1-2)	2.79 (2.47-3.12)	3.31 (2.89-3.72)	0.052	Ref	Ref
Treatment (weeks 3-10)	4.72 (4.11-5.33)	3.73 (3.33-4.13)	0.008	<0.001	0.021
Follow-up (weeks 11-18)	3.65 (3.08-4.23)	3.61 (3.20-4.03)	0.902	0.002	0.111
Mean (95% CI) no. of complete spontaneous bowel movement/week					
Baseline (weeks 1-2)	0.33 (0.16-0.49)	0.52 (0.34-0.69)	0.121	Ref	Ref
Treatment (weeks 3-10)	1.62 (1.11-2.13)	0.72 (0.44-1.00)	0.003	<0.001	0.035
Follow-up (weeks 11-18)	1.06 (0.62-1.49)	0.75 (0.44-1.05)	0.246	0.001	0.040

Table 2. Comparison of responder rates during treatment and follow-up periods

Period	Responder rate (% of patients experienced an increase of ≥1 complete spontaneous bowel movement/week compared with baseline)		P value
	MaZiRenWan	Placebo	
Treatment (weeks 3-10)	43.3	8.3	<0.001
Follow-up (weeks 11-18)	30.0%	15.0%	0.049

Most patients tolerated the medication well and no serious adverse effect was noted. There was no impairment of liver or renal function. In all, 11 and 7 patients in the MZRW and placebo groups, respectively, experienced at least one adverse effect (eg abdominal bloating/pain and nausea).

Discussion

During treatment, compared to those taking placebo, patients taking MZRW experienced increased CSBMs as well as reduction in the severity of constipation, straining at evacuation, and use of rescue therapy. Moreover, there were sustainable significant benefits for the MZRW group in terms of responder rates during the follow-up period (P=0.049), although same trend could not be confirmed for global and individual symptom assessments.

By evaluating the feedback from patients and the investigator, correct guesses for MZRW and placebo groups were 59.3% and 29.1% in the patients and 77.8% and 49.1% in the investigator, respectively. Correctly identifying the placebo regimen was less than natural probability (chance). Thus, the blinding process in this study was successful.

Adverse effects affecting the lower gastrointestinal tract (abdominal pain/cramping, bloating, diarrhoea, and passing gas) were more common in the MZRW than placebo group (13.3% vs 3.3%). Such side effects are common among laxatives and may be related to the active compound chrysophanol in *Radix et Rhizoma Rhei*, one of the herbal components of MZRW.

This study addressed the theme of "treatment derived from syndrome differentiation" according to the traditional Chinese medicine theory. In addition, it included a dose determination study and a placebo-controlled clinical trial. Proper dosage is an important prerequisite to determine the efficacy and safety of an intervention; selection based on clinical experience alone may not be optimal. Therefore, it is necessary to explore the optimal dose using a robust method, and then determine the efficacy and safety of an intervention in a separate placebo-controlled trial.

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AUTHOR INDEX

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