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Research Dissemination Reports

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研究成果報告

Mental health and neurology
精神衛生和神經學

Traditional Chinese medicine
傳統中國醫學

Viral hepatitis
病毒性肝炎

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Viral Hepatitis

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, 12 dissemination reports of projects related to mental health and neurology, traditional Chinese medicine, and viral hepatitis are presented. In particular, three projects are highlighted owing to their potentially significant findings, impact on healthcare delivery and practice, and/or contribution to health policy formulation in Hong Kong.

In Hong Kong, until recently mental health services had been characterised by low resources, high caseloads, and relatively heavy reliance on inpatient care. Early intervention for psychotic disorders aims to improve the long-term outcome by early detection so as to reduce delay in treatment. Previously, early intervention studies were only 1 to 2 years in duration and often conducted on a small scale. This limited the extent to which the results could be generalised. Chen et al[1] aimed to compare the 3-year outcome in patients enrolled into the Early Assessment Service for Young People with Psychosis with a matched cohort treated prior to introduction of this programme. The primary hypothesis was that the early intervention would improve functional outcome and reduce suicides and hospitalisations. Overall, the 3-year outcome in the early intervention group compared favourably with that of standard psychiatric care, particularly with respect to functional outcome and reduction in hospitalisations, suicides, and disengagements. However, early intervention did not appear to reduce the rate of relapse.

Traditional Chinese medicine (TCM) has long been an integral part of Hong Kong culture. However, western allopathic medicine (AM) is the accepted legitimate local medical system. Given the important role of TCM in primary care and to foster collaboration between AM and TCM in line with government policy, Griffiths et al[2] investigated the attitude of Hong Kong western medicine doctors toward TCM and its integration with western medicine using both quantitative and qualitative methodologies. Some 1130 western medicine practitioners responded and diverse opinions on the use of TCM were received. Over one third of respondents used TCM themselves, and one fifth has considered referral to TCM practitioners. It appears that Hong Kong western medicine doctors emphasise evidence-based practice over patient choice when considering TCM, while many AM practitioners expressed a lack of exposure to the practice and scientific basis of TCM during western medical training. The authors concluded that better understanding of the regulations might promote more collaboration between western medicine and TCM practitioners. Establishing a platform for TCM and AM interprofessional collaboration may help the development of integrated care, which could in turn be more responsive to the health behaviours of the Hong Kong population.

Viral hepatitis B infection is a major health hazard in end-stage renal disease patients on dialysis. The direct costs of hepatitis B infection and its long-term impact on morbidity and mortality are substantial. In patients on dialysis, the traditional intramuscular recombinant vaccine (40 μg Engerix-B at months 0, 1, and 6) attains a seroconversion rate of 44 to 76%. Chow et al[3] compared the conventional dose (40 μg) with an extra-high dose (80 μg) of Engerix-B vaccine in peritoneal dialysis patients in terms of primary seroconversion and long-term seroprotection. The rates of seroconversion (hepatitis B surface antibody level of ≥10 IU/L 3 months after treatment) were not significantly different between the two regimens. The amount of dietary protein intake, as measured by normalised protein nitrogen appearance, was predictive of the response. Thus, although the extra-high-dose regimen had no significant clinical benefit, improved protein intake may improve the immune response to hepatitis B vaccination in peritoneal dialysis patients.

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 may visit the website for detailed information about application procedures.

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Case management to improve quality of life of older people with early dementia and to reduce caregiver burden

Key Messages

1. Case management was not effective in improving quality of life of mildly demented people or reducing family caregiver burden.
2. Case management reduced depressive symptoms in mildly demented people in the short term.
3. Case management encouraged family caregivers to seek outside help.

Introduction

Psychosocial interventions are important adjuvant therapies that may offer additional benefits for persons with dementia.[1] A combination of cognitive behavioural approach for functional and skill training, coupled with caregiver intervention on problem-solving skills for neuropsychiatric symptoms have shown promise in improving cognitive and behaviour parameters. To optimise potential therapeutic benefits, these interventions should be initiated early.[2] Nonetheless, intensive therapeutic psychosocial interventions in demented subjects are difficult to sustain, because of limited resource and the underlying disease process. A more feasible approach is case management whereby available resources within both the family and community are used for the benefit of the demented persons and their families. By offering regular contacts and support, the case manager helps the demented persons and their families to adapt to the evolving level of disabilities.

We proposed a case management model for mildly demented persons. In this model, the case manager (occupational therapist) performed functional assessments, advised on coping strategies, skills training and behavioural management, and encouraged the demented persons to be registered with a local social service centre so that the family can tap into the locally available social services. Through regular contacts by telephone or home visits, and a telephone hotline, the progress of the family can be monitored. A randomised controlled trial was performed to evaluate the impact of the programme on the quality of life of the mildly demented older people and on caregiver stress.

Methods

This study was conducted from March 2005 to January 2008. Community-dwelling people aged ≥65 years with mild dementia (Chinese Mini-Mental State Examination (MMSE) score of ≥15 and a Clinical Dementia Rating of 1) and their family caregivers were recruited from a psychogeriatric outpatient clinic and memory clinics of the Prince of Wales Hospital. After baseline assessment, the subjects were randomly assigned to receive case management (intervention) or usual care (control). The intervention included assessment and continual support by a case manager via home visits and telephone calls, a 3-month home-based cognitive stimulation activities, and a telephone hotline to access the case manager.

All subjects were followed up at months 4 and 12. The primary outcome measures were Personal Wellbeing Index for Intellectual Disability (PWI-ID)[3] of the demented elders and the Zarit Burden Interview (ZBI) score of the family caregivers. Seondary outcome measures entailed the Cornell Scale for Depression in Dementia (CSDD),[4] Neuropsychiatric Inventory (NPI), general health questionnaire (GHQ), and Personal Wellbeing Index for Adult (PWI-A) for family caregivers. Cost analyses of the direct and indirect expenses of the family caregivers and the public health care costs were also performed.

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Results

Of 102 subjects recruited, 59 were randomly assigned to the intervention and 43 to the control groups. At the end of 12 months, 6 and 4 subjects dropped out from the respective groups (Table 1).

At the 4-month follow-up, the CSDD scores decreased significantly for the intervention group (z= –3.17, P=0.002, Wilcoxon signed rank test) but not for the control group, whereas the NPI total scores decreased significantly in both groups (Table 2). For the quality-of-life measures, change in PWI-ID was not significant in both groups. For caregiver stress, changes in the PWI-A, ZBI, and GHQ scores were not significant in both groups.

At the 12-month follow-up, the Chinese MMSE scores decreased significantly in both groups (P<0.05, Wilcoxon signed rank test), whereas changes in the CSDD, PWI-ID scores in the demented subjects were not significant in both groups (Table 2). The GHQ scores for caregivers in the intervention group improved significantly (z= –2.20, P=0.028, Wilcoxon signed rank test).

At the baseline, the use of paid helpers and day care services was not significantly different in the two groups. At the 4-month and 12-month follow-up, the use of paid helpers and day care services increased significantly in the intervention group (P<0.05, Chi squared test). Home help and respite care were seldom used by either group (Table 3).

Table 1. Demographics of subjects and caregivers at baseline*

Parameter	Intervention (n=59)	Control (n=43)	P value
Subject			
Age (years)	78.6±6.4	78.2±5.5	0.74
Female	35 (59)	24 (56)	0.72
Use of dementia-related drugs	18 (31)	14 (33)	0.83
Use of antipsychotics	9 (15)	3 (7)	0.23
Use of antidepressants	14 (24)	12 (28)	0.65
Mini Mental State Examination score	17.6±5.2	18.0±5.1	0.69
Cornell Scale for Depression in Dementia score	4.8±6.0	4.3±3.8	0.52
Neuropsychiatric Inventory score	18.9±17.2	20.4±17.1	0.63
Personal Wellbeing Index for Intellectually Disabled	69.6±20.0	72.2±18.6	0.53
Caregiver			
Spouse	13 (22)	15 (29)	0.18
Zarit Burden Interview score	33.2±17.8	32.3±15.8	0.81
Personal Wellbeing Index for Adult	63.6±15.1	61.2±18.6	0.46
General Health Questionnaire score	13.1±5.4	14.2±6.6	0.70

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

Table 2. Change in demented persons' quality of life and caregiver stress at 4- and 12-month follow-up

Parameter	Mean±SD change from baseline to month 4		Mean (95% CI) group difference	Mean±SD change from baseline to month 12		Mean (95% CI) group difference
	Intervention (n=57)	Control (n=42)		Intervention (n=53)	Control (n=39)	
Subject						
Mini Mental State Examination score	-0.46±3.42	0.39±2.95	0.57 (-1.47, 2.60)	1.45±4.17	1.76±3.44	0.23 (-2.24, 2.71)
Cornell Scale for Depression in Dementia score	2.45±5.00†	1.03±3.40	-0.85 (-2.15, 0.45)	0.94±6.47	1.08±3.57	0.65 (-1.11, 2.42)
Neuropsychiatric Inventory score	8.75±14.23†	9.25±14.15†	-1.23 (-7.65, 5.18)	4.62±17.23	10.15±15.43†	3.47 (-3.10, 10.03)
Personal Wellbeing Index for Intellectually Disabled	-3.39±22.89	0.35±20.92	-0.28 (-8.71, 8.16)	-5.48±24.83	-2.49±18.93	-0.67 (-9.68, 8.34)
Caregiver						
Zarit Burden Interview score	-1.12±13.03	-1.95±14.38	0.46 (-6.44, 7.36)	-2.68±15.22	-1.05±14.34	3.06 (-4.34, 10.46)
Personal Wellbeing Index for Adult	-1.80±11.46	1.18±11.78	5.19 (-1.33, 11.71)	1.91±16.42	0.15±11.58	2.46 (-5.03, 9.94)
General Health Questionnaire score	-0.81±4.98	0.25±5.56	0.09 (-1.98, 2.17)	-1.87±6.29*	0.03±4.54	1.22 (-1.09, 3.53)

* P<0.05, Wilcoxon signed rank test
† P<0.005, Wilcoxon signed rank test

Table 3. Use of additional support for dementia care

Support	No. (%) of demented persons					
	Baseline		Month 4		Month 12	
	Intervention	Control	Intervention	Control	Intervention	Control
Paid helpers	19 (32.2)	7 (16.3)	27 (47.4)*	6 (14.6)	21 (39.6)*	7 (17.9)
Day care	28 (47.5)	18 (39.1)	44 (77.2)*	18 (43.9)	37 (69.8)*	14 (35.9)
Home help	5 (8.5)	5 (11.6)	4 (7.0)	3 (7.3)	3 (5.7)	3 (7.7)
Respite care	0 (0)	1 (2.3)	1 (1.8)	0 (0.0)	3 (5.7)	0 (0.0)

* P<0.05, Pearson Chi squared test

The median public health care cost was significantly greater in the intervention than control group (HK$8526 vs HK$5993, P=0.023, Mann-Whitney *U* test), primarily because of the cost of case management. From the family caregivers' perspective, the median incremental direct costs per month were significantly greater in the intervention than control group (HK$170 vs HK$50 at month 4; HK$240 vs HK$7 at month 12; P<0.05 for both). The median incremental indirect costs per month increased in the intervention group at month 4 (HK$0 [interquartile range, HK$0-3750] vs HK$0 [interquartile range, HK$0-950] but not at month 12.

Discussion

Dementia is a common disease of old age. The global deterioration in cognition and independent functioning leads to increased caregiver stress and institutionalisation. The usual care for the demented elders is not suited to community-dwelling persons with mild dementia. The medical service is not geared to early detection of dementia, and treatment is limited by drug budgetary constraints. Psychosocial interventions are not normally available except in the few specialised memory clinics where multidisciplinary therapeutic interventions are provided for a limited number of patients for a limited period of time. We proposed an interdisciplinary approach, based on a community case manager supported by a medically oriented psychiatric or memory clinic. The case manager offered professional advice from cognitive stimulation, behavioural management, carer support to liaise with different welfare agencies.

For mood symptoms, the intervention group showed a positive effect at the 4-month follow-up, but the effect was not sustained at 12 months. There was no significant improvement in quality of life and caregiver burden in the case management approach, despite some therapeutic effects. This may be important for the management of motivational mood symptoms in persons with mild and moderate dementia. The case manager advised on coping strategies, skill training, and behavioural management in the initial few months. Subsequent interventions were less intensive. This may explain the lack of sustainability in mood improvement. Therefore, continual community support for families with demented subjects, especially those with co-existing depression is important.

The use of supportive care could be an indicator for the impact of case management. The intervention group became more well informed and active in seeking support. The reported rate of using a paid helper at home and community day care services increased significantly at both 4- and 12-month follow-up. Although costs of care increased in case management, early use of communtiy care services may help to delay institutionalisation.[3]

The compliance of the home-based programme on cognitive stimulation was limited by the accessibility and communication skills of family caregivers, and the cooperation of the demented persons. This might have contributed to the psychological stress and burden by the caregivers. It may be more effective if cognitive training was to be administered by trained staff in day care centres.

The perceived burden and personal wellbeing of family caregivers did not improve with case management. There was some deterioration in psychological health as indicated by a signficant increase in the GHQ score. This was not surprising as the cognitive function of the demented person deteriorated, costs of care would increase.

A high proportion of intervention group subjects had already received some day care services. The amount and quality of day care was likely to have a direct impact on the psychological stress experienced by family caregivers. During the study period, most of the day care services for the demented were not funded by subvention. Therefore, there was a problem in accessibility and affordability. With further development in dementia day care, this case management model may have a bigger impact. Ideally, the day care centres should take over case management when demented clients start attending on a regular basis.

The small sample size of this study limited its statistical power and precluded the use of hierarchical linear models. Further studies are needed.

Conclusions

Case management was not effective in improving quality of life of early dementia patients or reducing caregiver burden, but did encourage family caregivers to seek help (paid helpers and day care services). Case management and home visits appeared to reduce depressive symptoms of demented subjects, but the effect was not sustained.

Acknowledgement

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Three-year outcome of phase-specific early intervention for first-episode psychosis: a cohort study in Hong Kong

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Key Messages

1. The 3-year outcome of 700 first-episode psychosis patients who received phase-specific early intervention were compared with that of 700 matched historical controls who received standard psychiatric care.
2. Patients in the early intervention group had longer full-time employment or study (P<0.001), fewer days of hospitalisation (P<0.001), less severe positive symptom (P=0.006), less severe negative symptom (P=0.001), fewer suicides (P=0.009) and fewer disengagements (P=0.002) than the historical control group. In addition, more patients in the early intervention group experienced a period of recovery (P=0.001), but the two groups had similar rates of relapse (P=0.08) and durations of untreated psychosis (P=0.72).
3. The 3-year outcome in phase-specific early intervention compared favourably with that of standard psychiatric care, particularly with respect to functional outcome and reduction in hospitalisations, suicides, and disengagements. However, intervention did not appear to reduce the rate of relapse.

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Introduction

Early intervention for psychotic disorders[1] aims to improve the long-term outcome for psychotic disorders by early detection to reduce delay in treatment[2,3] and phase-specific intervention during the early phase of the disorders. In one of the most comprehensive controlled studies of early intervention, the OPUS trial,[4] 547 first-episode psychosis patients were randomised to either intensive early intervention or standard treatment. At 2 years, the former group had a medium effect on improving negative symptoms, a small effect on improving positive symptoms, and 22% reduction in average hospital stay.[4] However, at 5 years, the effect on symptom levels had diminished, whereas the effect on hospitalisation was still significant.[5] Another randomised controlled study found that some of the improved outcome that resulted from an early specialised service at 18 months was not maintained at 5 years.[6,7]

Most early intervention studies are limited to 1 or 2 years.[8] In addition, early psychosis programmes often operate on a smaller scale and limit the generalisability of results.[3] The development of population-based clinical services and media education does not easily accommodate randomised controlled studies. Together with the overwhelming consensus that early intervention should not be withheld, ethical concerns have restricted the set up of randomised controlled studies.[9] Under these circumstances, the optimal approach to estimate the real-life impact of the programmes may be by a historical control design comparing patients who receive early intervention with those who are managed by standard care prior to the introduction of early intervention. A small number of historical control studies on early intervention programmes have reported reduction in negative symptoms and suicidal behaviour, and improved quality of life.[10,11] Nonetheless, one limitation of these studies is that the cases may not match the controls. Most of these studies are based on western populations with more mental health resources and their results might not be applicable to other populations.

In Hong Kong, until recently mental health services had been characterised by low resources, high caseloads, and relatively heavy reliance on inpatient care.[12] The Early Assessment Service for Young People with Psychosis (EASY) programme was launched in 2001.[13-15] We aimed to compare the 3-year outcome of a cohort of patients who received this service with a matched cohort treated prior to the introduction of the programme. The primary hypothesis was that the early intervention would improve functional outcome, as well as reduce suicides and hospitalisations.

Methods

Study design and setting

The study was approved by relevant local institutional review boards and ethics committees. A historical case-control design was adopted, as the territory-wide nature of the programme precluded a concurrent control group.

The EASY programme was introduced in Hong Kong in 2001. It was

directed at patients aged 15 to 25 years who presented with a first episode of psychotic symptoms. It consisted of five specialised teams, each composed of two clinicians and three case managers. Together, the five teams managed approximately 1400 cases at any one time. The phase-specific intervention included intensive medical follow-up and a protocol-based psychosocial intervention. A case management approach was adopted, in which a case manager provided psychosocial interventions according to the patient's stage of illness and needs. Psychosocial intervention aims to help patients develop a more positive attitude to the illness in order to facilitate recovery. Case managers aim to establish early therapeutic alliances with patients and their families, provide individual or family intervention in response to emotional maladaptation and coping difficulty, and provide psychoeducation. During the course of recovery, case managers also aim to guide patients to develop goals, maintain social networks, establish routines, and cope with stressful situations.[13-15] Standard care service was characterised by its high service volume, brief consultation time, and limited community support.[12]

Sample

From the Psychiatric Case Register, 700 consecutive cases who received the EASY programme between 2001 and 2003, and 700 controls who received standard care between 1998 and 2001 were identified. To minimise the potential cohort effect, cases and controls were individually matched for gender, diagnosis, and age (±3 years).

Cases were those who had any of the following diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10): schizophrenia (ICD-10 code F20), acute and transient psychotic disorders (ICD-10 code F23), schizoaffective disorders (ICD-10 code F25), psychosis not otherwise specified (ICD-10 codes F28 or F29), and affective disorders with psychotic features (ICD-10 codes F30.2, F31.2, F31.5, F32.3 or F33.3). Patients with any severe organic condition, drug-induced psychosis, or mental retardation were excluded, as were those with >1 month of prior psychiatric treatment before presentation. Informed consent from each patient was waived by the institutional review boards and ethics committees of the hospitals.

Data acquisition procedure

Between 2006 and 2007, clinical records of the 1400 patients were retrieved systematically. Only data that could be reliably extracted from the records were retrieved and analysed. Outcomes were determined each month in the 3 years following first contact, unless otherwise specified.

Baseline data included age, gender, diagnosis, education (years of formal education completed), premorbid occupational functioning (impaired or not impaired), smoking status (smoker, non-smoker, or ex-smoker), and duration of untreated psychosis (DUP) [from appearance of first psychotic symptom to treatment].

Symptomatic outcome measures included positive and negative symptom levels according to the Clinical Global Impressions-Severity Scale (CGI-S).[16] Relapse was defined as an increase in the level of positive symptoms leading to a change in medication management or hospitalisation. Recovery was defined as having a CGI-S positive symptom score of ≤2 (borderline ill), having a CGI-S negative symptom score of ≤3 (mildly ill), and working or studying full-time for at least 12 consecutive months. Functional outcome was measured by engagement of full-time employment or study. Suicidal behaviours included suicide attempts and completed suicides. Participants were categorised by whether they had exhibited the target risk behaviour during the study period. Service utilisation measures included number of hospitalisations, duration of hospitalisations, compulsory hospital admissions, number of outpatient and paramedical contacts, length of engagement with service, and disengagement from service (defined as having no psychiatric contact at the end of the study).

Validity and reliability

Validity and inter-rater reliability for DUP, functioning, and duration of hospitalisation were measured based on 12 independent cases using an intra-class correlation coefficient (ICC). Validity compared ratings between clinicians and research staff (DUP: ICC=0.78; functioning: ICC=0.83; duration of hospitalisation: ICC=0.998). Inter-rater reliability compared ratings between two research staff (DUP: ICC=0.70; functioning: ICC=0.98; duration of hospitalisation: ICC=0.999). All the scores reflected satisfactory concordance in ratings. In addition, weekly consensus meetings among clinicians and research assistants were held during data collection to maintain data quality and resolve ambiguity in information.

Statistical analysis

The large sample size enabled detection of possible difference in suicides, which were rather uncommon events, between the phase-specific early intervention (EI) group and the historical control (HC) group. Demographic and treatment characteristics and outcome variables were compared between the two groups using t-tests and Chi squared tests. To assess the impact of second-generation antipsychotics (SGA) on clinical outcome, functional outcome, and hospitalisation, analysis of covariance and logistic regression were carried out for continuous variables and categorical variables, respectively. Two sets of Kaplan-Meier survival curves were constructed to estimate the proportion of suicide and the proportion of death from any cause, using tests of group difference by log-rank. The risk of suicide and death from any cause were analysed using the Cox-proportional hazards regression model. For patients who discontinued the service, the last observation was used to analyse the positive and negative symptom severities, as this was assumed to be the best approximation of the patient's mental state. Two sets of secondary analyses were performed based on the results of the primary analysis. First, considering that there was a group difference in the

proportion of patients hospitalised at initial treatment, a secondary analysis was performed by comparing outcomes of the two groups only in the patient subset hospitalised within the first month. Second, in view of the increased use of SGA in the EI group and as validation of the use of SGA as a covariate, another secondary analysis was performed, restricted only to those who had used SGA treatment. This analysis compared the 3-year outcome of the two groups using t-tests, Chi squared tests, and survival analyses.

Results

Demographic and treatment characteristics

Clinical records of 839 patients in the early intervention programme and 1318 patients in the standard care were screened. A total of 700 eligible cases from each sample were included in the study. The reasons of exclusion are listed in Table 1. Cases were matched with controls for gender, diagnosis, and age (Table 2). There was no significant difference in premorbid occupational functioning. The EI group had a slightly higher level of education. The absolute difference in education level was small (0.35 years). More EI patients had received at least one SGA (Table 2). The EI patients had significantly longer periods of SGA use during the preceding 3 years. The use of SGA was a covariate in the analysis of clinical outcome, functional outcome, and hospitalisation.

Functional outcome

The EI patients achieved longer durations of full-time employment than HC patients (Table 3). A higher proportion of EI patients engaged in a stable full-time position lasting for ≥6 consecutive months.

Clinical outcome

The EI group had lower overall levels of positive symptoms and negative symptoms than the HC group (Table 3). The cumulative relapse rate was analysed by year. In year 1, fewer EI patients than HC patients relapsed. However, the cumulative rate was equalised by year 2, and was sustained through year 3. Nevertheless, fewer EI patients had multiple relapses (defined as >2 relapses in 3 years) and more EI patients achieved at least a period of recovery.

Suicidal behaviour

There was no significant difference between the EI and

Table 1. Inclusion and exclusion of patients in the early intervention and standard care groups

Criteria	Early intervention	Standard care
Total No. of screened patients	839	1318
No. (%) of patients included	700 (83.4)	700 (53.1)
No. (%) of patients excluded	139 (16.6)	618 (46.9)
Reasons for exclusion (No. [%] of patients)		
Initial presentation outside of the specified period	16 (11.5)	386 (62.5)
Previous episodes or treatment	60 (43.2)	93 (15.0)
Delusional disorder	0 (0)	2 (0.3)
Drug-induced psychosis	6 (4.3)	33 (5.3)
Mental retardation	8 (5.8)	24 (3.9)
Age <15 years	0 (0)	3 (0.5)
Significant organic condition	0 (0)	7 (1.1)
No diagnosis of psychosis	10 (7.2)	28 (4.5)
Eligible cases but unable to be matched	18 (12.9)	8 (1.3)
Unable to retrieve clinical records	21 (15.1)	34 (5.5)

Table 2. Demographics and treatment characteristics of the early intervention (EI) and historical control (HC) groups*

Characteristics	EI (n=700)	HC (n=700)	χ^2/t	P value
Age (years)	21.1±3.4	21.3±3.4	-0.84	0.40
Education (years)	10.9±2.3	10.6±2.4	2.74	0.006
Duration of untreated psychosis (days)	239.8±373.4	232.0±428.3	0.36	0.72
Male	360 (51.4)	360 (51.4)	0.00	1.00
Smoking			4.29	0.12
Smoker	179 (26.3)	185 (27.2)		
Ex-smoker	20 (2.9)	9 (1.3)		
Non-smoker	481 (70.7)	485 (71.4)		
Premorbid occupational functioning†			0.00	0.99
Impaired	49 (7.00)	49 (7.00)		
Not impaired	651 (93.0)	650 (93.0)		
Diagnosis			0.05	1.00
Schizophrenia or schizoaffective disorder	484 (69.1)	486 (69.4)		
Acute and transient psychotic disorder	87 (12.4)	87 (12.4)		
Psychosis not otherwise specified	46 (6.6)	44 (6.3)		
Mania/bipolar affective disorder with psychotic symptoms	54 (7.7)	54 (7.7)		
Severe depressive episode with psychotic symptoms	29 (4.1)	29 (4.1)		
Treatment				
Prescribed at least one second-generation antipsychotic medication	424 (60.6)	179 (25.6)	174.86	<0.001
Use of second-generation antipsychotic medication (days)	403.5 (454.8)	125.2 (291.9)	13.63	<0.001

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

† Impaired premorbid occupational functioning refers to unemployment and prolonged educational stagnation

Table 3. Comparison of outcomes in the early intervention (EI) and historical control (HC) groups

Outcome variables	EI (n=700)*	HC (n=700)*	Test results†	P value
Functional outcome				
Full-time employment ≥6 months	450 (64.3)	339 (48.4)	Adjusted OR=1.69 (1.35–2.12)	<0.001
Duration engaged in full-time employment (months)	15.2±12.1	10.5±11.3	*F*=33.63	<0.001
Clinical outcome				
Clinical Global Impressions-Severity Scale (CGI-S) positive symptoms	1.6±0.6	1.7±0.9	*F*=7.62	0.006
CGI-S negative symptoms	1.5±0.5	1.6±0.7	*F*=12.03	0.001
Cumulative relapse rate by year 1	123 (17.6)	147 (21.0)	Adjusted OR=0.69 (0.52-0.92)	0.012
Cumulative relapse rate by year 2	273 (39.0)	264 (37.7)	Adjusted OR=0.82 (0.65-1.04)	0.10
Cumulative relapse rate by year 3	344 (49.1)	330 (47.1)	Adjusted OR=0.82 (0.65-1.03)	0.081
Multiple relapses (>2)	120 (17.1)	128 (18.3)	Adjusted OR=0.66 (0.49-0.90)	0.008
Having at least one period of recovery	255 (36.4)	189 (27.0)	Adjusted OR=1.48 (1.16-1.89)	0.001
Suicidal behaviour				
Suicide attempt	65 (9.3)	80 (11.4)	χ^2/t=1.73	0.19
Completed suicide‡	7	20	Hazard ratio=0.32 (0.13-0.75)	0.009
Death (all-cause)§	8	22	Hazard ratio=0.30 (0.13-0.71)	0.006
Service utilisation				
Duration of hospitalisation (days)	61.6±105.5	113.7±141.6	*F*=99.98	<0.001
No. of hospitalisations	1.0±1.1	1.8±1.3	*F*=178.47	<0.001
Hospitalisation in the first month	328 (46.9)	635 (90.7)	Adjusted OR=0.10 (0.07-0.13)	<0.001
Compulsory admission at first hospitalisation	91/435 (20.9)	264/680 (38.8)	Adjusted OR=0.49 (0.36-0.66)	<0.001
Compulsory admission at second hospitalisation	32/177 (18.1)	81/313 (25.9)	Adjusted OR=0.76 (0.47-1.23)	0.27
No. of medical outpatient visits	26.2±13.5	17.0±12.1	χ^2/t=13.57	<0.001
No. of contacts with clinical psychologist	1.4±3.8	0.7±2.4	χ^2/t=3.79	<0.001
No. of contacts with medical social worker	1.8±2.4	1.7±2.6	χ^2/t=0.48	0.63
Disengagement	161 (23.0)	211 (30.1)	χ^2/t=9.15	0.002
Length of engagement in service (months)	31.8±9.3	28.7±12.7	χ^2/t=5.30	<0.001

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

† Data are presented as adjusted OR (95% CI) by logistic regression, *F* value by analysis of covariance, χ^2/t, or hazard ratio (95% CI) by Cox-proportional hazards regression

‡ The 3-year Kaplan-Meier estimate of the proportion of suicides was 1.1% (95% CI, 0.27-1.95%) in the EI group and 3.4% (95% CI, 1.90-4.90%) in the HC group (χ^2_1=7.64, P=0.006, log-rank test)

§ The time of death was missing in one patient in each group. The 3-year Kaplan-Meier estimate of the proportion of death from any cause was 1.1% (95% CI, 0.27-1.95%) in the EI group and 3.6% (95% CI, 2.02-5.10%) in the HC group (χ^2_1=8.48, P=0.004, log-rank test)

HC groups in terms of the number of patients attempting suicide over the 3-year period (65 vs 80, Table 3). Seven of 700 patients in the EI group and 20 of 700 patients in the HC group committed suicide. The EI group had lower Kaplan-Meier estimates of the proportions of suicide and death from any cause. Compared by Cox proportional hazards regression, the EI group had a significantly lower risk of suicide and death from any cause.

Service utilisation

Patients in the EI group had shorter and fewer hospitalisations in the 3-year period (Table 3). In the first month of treatment, fewer EI patients were hospitalised. The EI group had a lower percentage of compulsory admissions in the first hospitalisation, but not in the second. The EI patients had significantly better medical outpatient attendances and greater degree of contact with clinical psychologists, but a similar degree of contact with medical social workers. The EI patients stayed longer in the mental health system than HC patients. A smaller proportion of EI than HC patients disengaged from the service.

Secondary analysis

As the EI and SC groups differed in the proportion of patients treated as inpatients during the initial episode, 328 EI patients and 635 HC patients who were hospitalised for the first episode of illness (defined as hospitalisation in the first month of service contact) were compared. The results of the secondary analyses paralleled to the primary analyses (except that the two groups no longer differed significantly with respect to the number of patients having multiple relapses). Patients in the EI group also had shorter rehospitalisations and fewer rehospitalisations (Table 4).

The SGA secondary analysis differed from the primary analysis in several ways. The EI group (n=424) and the HC group (n=179) had comparable positive symptom severities (P=0.074), suicide rates (P=0.30), levels of contact with clinical psychologist (P=0.062), proportions of disengagement (P=0.17), and durations of contact with service (P=0.36). In contrast to the primary analysis, the EI group had a lower relapse rate than the HC group by year 3 (55.2% vs 65.9%, P=0.015).

Discussion

During the initial 3 years of psychiatric treatment, patients who received phase-specific intervention were more likely to hold full-time jobs, less likely to commit suicide, and spent less time in hospital than patients receiving standard care. Vocational functioning was significantly better in the EI group. The employment rates in the overall cohort were comparable with other studies.[5,17,18] There was a substantial reduction in hospitalisation (45.8%) in the EI group. This

Table 4. Secondary analysis of outcome in 328 early intervention (EI) patients and 635 historical controls (HC) treated as inpatients during their first episode of psychosis

Outcome variables	EI (n=328)*	HC (n=635)*	Test results†	P value
Functional outcome				
Full-time employment ≥6 months	209 (63.7)	302 (47.6)	Adjusted OR=1.78 (1.33-2.37)	<0.001
Duration engaged in full-time employment (months)	14.4±11.5	10.3±11.2	*F=17.84*	<0.001
Clinical outcome				
Clinical Global Impressions-Severity Scale (CGI-S) positive symptoms	1.5±0.6	1.7±0.9	*F=15.92*	<0.001
CGI-S negative symptoms	1.4±0.5	1.6±0.7	*F=9.36*	0.002
Cumulative relapse rate by year 1	55 (16.8)	133 (20.9)	Adjusted OR=0.66 (0.46-0.96)	0.027
Cumulative relapse rate by year 2	124 (37.8)	238 (37.5)	Adjusted OR=0.79 (0.59-1.07)	0.12
Cumulative relapse rate by year 3	171 (52.1)	297 (46.8)	Adjusted OR=0.94 (0.71-1.26)	0.70
Multiple relapses (>2)	55 (16.8)	109 (17.2)	Adjusted OR=0.70 (0.47-1.02)	0.064
Having at least one period of recovery	127 (38.7)	171 (26.9)	Adjusted OR=1.66 (1.23-2.24)	0.001
Suicidal behaviour				
Suicide attempt	42 (12.8)	71 (11.2)	χ^2/t=0.55	0.46
Completed suicide‡	4	20	Hazard ratio=0.34 (0.12-0.99)	0.049
Death (all-cause)§	5	22	Hazard ratio=0.32 (0.11-0.94)	0.038
Service utilisation				
Duration of rehospitalisation (days)	44.2±95.0	57.5±113.4	*F*=10.85	0.001
No. of rehospitalisations	0.7±1.0	0.8±1.2	*F*=10.81	0.001
Compulsory admission at second hospitalisation	27/147 (18.4)	78/294 (26.5)	Adjusted OR=0.75 (0.45-1.25)	0.28
No. of medical outpatient visits	25.7±12.7	16.5±11.7	χ^2/t=11.13	<0.001
No. of contacts with clinical psychologist	1.3±3.6	0.7±2.4	χ^2/t=2.78	0.006
No. of contacts with medical social worker	1.9±2.2	1.7±2.6	χ^2/t=1.22	0.22
Disengagement	59 (18.0)	193 (30.4)	χ^2/t=17.23	<0.001
Length of engagement in service (months)	33.1±7.7	28.6±12.8	χ^2/t=6.89	<0.001

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

† Data are presented as adjusted OR (95% CI) by logistic regression, *F* value by analysis of covariance, χ^2/t, or hazard ratio (95% CI) by Cox-proportional hazards regression

‡ The 3-year Kaplan-Meier estimate of the proportion of suicides was 1.3% (95% CI, 0.01-2.61%) in the EI group and 3.8% (95% CI, 2.09-5.41%) in the HC group (χ^2_1=4.28, P=0.039, log-rank test)

§ The time of death was missing in one patient in each group. The 3-year Kaplan-Meier estimate of the proportion of death from any cause was 1.3% (95% CI, 0.01-2.61%) in the EI group and 3.9% (95% CI, 2.25-5.61%) in the HC group (χ^2_1=4.76, P=0.029, log-rank test)

suggests that with more intensive support, first-episode psychosis patients could be managed effectively in the community.[19] Significant reduction in rehospitalisation was also noted in the subset of patients who were hospitalised for their first episodes of illness. Nonetheless, the findings might not be generalisable because of the geographical variation in incidence, course, and outcome.[20] Our study has extended the findings on the efficacy of early intervention to a non-western population with limited resources for mental health service.

Our study adopted a historical control design. Although the two comparison cohorts were closely matched for age, gender, and diagnosis, they received different antipsychotic treatments (with greater usage of SGA in the EI cohort). Secondary analyses revealed the potential effect of SGA on outcome. By treating antipsychotics as a covariate in the analyses of the key variables, the effects remained significant, suggesting that the difference in outcome could not be accounted for by differences in the use of antipsychotics.

In our study, the DUP itself did not differ between the two cohorts. This is consistent with one historical control study,[21] but not with two others that reported a shortening of DUP with early intervention.[22,23] One potential reason for the lack of significant difference in DUP could be related to the EI cohort presenting soon after the historical control cohort. There might not be sufficient time for the public awareness programmes to have an impact on the DUP in the population. It was also conceivable that after the launch of the EASY programme, a number of patients who had hitherto had difficulty in accessing care (with long DUP) might have been engaged by the EASY programme because of its improved accessibility.

Whether the observed correlation between long DUP and poor outcome reflects a causal relationship has been contentious.[24] Although this issue has been explored using potential confounding variables such as premorbid adjustment, it has been difficult for intervention studies to separate the two major components of early intervention, namely early detection to reduce DUP and phase-specific intervention. This was because most intervention programmes included both components. The current data were obtained at an early stage of a programme when the impact on the DUP was still minimal. It provided an opportunity to inquire into the extent to which outcome could be improved without a shortened DUP. These improvements in functional outcome and hospitalisation were evident despite unchanged DUP, which suggests that the improvements were likely the result of phase-specific intervention rather than early detection.

In contrast to some studies,[25,26] our study did not detect a reduction in relapse rate in the intervention group, which

was similar to findings from other studies.[5,6,10] Whether the impact of intervention on relapse rate is a function of intervention intensity needs further studies. In addition, some early intervention programmes focused more on cognitive therapeutic approaches, whereas others adopted a more generic approach.[3,27] A number of studies using intensive cognitive therapy succeeded in reducing the number of relapses,[28-30] although some failed even with intensive cognitive therapy.[31,32]

Among early intervention programmes, there were variations in content and intensity. In our sample, the caseload (one case manager to 80 cases) was relatively heavy. The situation is characteristic of some affluent Asian communities, indicating that resources for mental health care may remain significantly smaller than for other health care fields.[33,34] Resource levels in both standard care and early intervention were not comparable with those in locations with more advanced developments in mental health services. This study was of pragmatic relevance to the many locations worldwide where mental health care is still relatively under-resourced.

There were several limitations in the study. As the study was based on clinical records, some potentially important outcome variables (such as quality of life) could not be addressed. A longer period of follow-up could be more informative. The current study design enabled the use of data from large cohorts to demonstrate that phase-specific early intervention, even with a high caseload, could result in improved outcome in the critical period of psychotic disorders, and that this improvement was not dependent on shortening of the DUP.

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Telephone intervention to improve the mental health of community-dwelling women abused by their intimate partners: a randomised controlled trial

Key Messages

1. Intimate partner violence (IPV) is a prevalent public health problem and may go undetected in the community. Depression is one of its most common mental health sequelae.
2. Screening for IPV in the community is important for early detection and timely intervention.
3. An advocacy intervention comprising empowerment and telephone social support was effective in reducing depression and psychological aggression as well as improving perceived social support and safety-promoting behaviour for at least 6 months following the intervention.
4. Participants in IPV advocacy trials should be followed up for years, rather than weeks or months, in order to assess the long-term benefits of the intervention.

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Introduction

According to the World Health Organization, intimate partner violence (IPV) is a global public health problem. It has long-term, negative health consequences for survivors, even after the abuse has ended. Depression is one of its most common mental health sequelae. In the US, a meta-analysis of 18 studies has reported a weighted mean prevalence of depression of 47.6% among abused women,[1] which is much higher than the lifetime rates of 10.2% to 21.3% in the general populations of women. Such an association of depression and IPV has also been found among Chinese women in Hong Kong.

In a systematic review of 10 randomised controlled trials of advocacy programmes for abused women,[2] intensive advocacy interventions (≥12 hours) for women recruited in domestic violence shelters may reduce physical abuse, but its beneficial effects on the women's mental health and quality of life are not yet known. Also, there is insufficient evidence to show whether less intensive interventions (<12 hours) for women who still live with the perpetrators are effective.[2] This study aimed to test the effectiveness of an advocacy intervention for women survivors of IPV in a community setting.

Methods

Between December 2006 and June 2009, 200 community-dwelling, abused Chinese women were randomly assigned to the intervention (n=100) or control (n=100) group. The former group received a 12-week advocacy intervention, whereas the latter received usual community services.

The advocacy intervention consisted of empowerment and telephone social support, based on the Dutton's empowerment model[3] and Cohen's Social Support Theory.[4] The former component was provided at the beginning of the intervention and took about 30 minutes. It included protection and enhanced choice-making and problem-solving skills. The latter was provided via 12 scheduled weekly telephone calls and 24-hour access to a hotline. Women in the control group received the usual community services provided by the community centre including health, social, educational, and recreational services.

Data were collected at baseline and the 3 and 9-month follow-up. No subjects were lost to follow up. The instruments used included the Chinese Abuse Assessment Screen, the Beck Depression Inventory version II (range, 0-63; higher scores indicate higher levels of depression), the Interpersonal Support Evaluation List (range, 0-36; higher scores indicate higher perceived social support), the Short-Form Health Survey (range, 0-100; higher scores indicate better health-related quality of life), the revised Conflict Tactics Scales (range, 0-6 for each item; higher scores indicate higher levels of IPV), the Safety-Promoting Behaviour Checklist, and the Utilisation of Health Services Questionnaire. Depression was the primary outcome measure. The secondary outcome measures were perceived social support, health-related quality of life, IPV, safety-promoting behaviours, and utilisation of health services.

Results

At baseline, the intervention and control groups were comparable in all respects, except that significantly more women in the intervention than control group received comprehensive social security assistance (CSSA) [33% vs 9%, P<0.001, Table 1]. The instrument scores of both groups were compared at baseline and after intervention (Table 2).

Depression

The Beck Depression Inventory version II scores of both groups decreased significantly from month 3 to month 9 (mean, -8.14; 95% CI, -9.72 to -6.57; P<0.001). The decrease was significantly greater in the intervention than control group (mean, -2.66; 95% CI, -5.06 to -0.26; P=0.031), and the effect was sustained even after adjusting for the baseline difference (in CSSA) and removing an outlier (mean, -2.80; 95% CI, -5.32 to -0.28; P=0.030).

Table 1. Demographics of study participants at baseline*

Demographics	Intervention (n=100)	Control (n=100)	P value
Subject age (years)	38.18±7.61	37.99±6.79	0.872
Partner age (years)	45.2±9.81	44.08±9.07	0.543
Age difference (partner - subject) [years]	6.82±5.73	6.35±6.77	0.255
Education level			0.558
No education or primary education	25 (25)	30 (30)	
Middle or high school	71 (71)	65 (65)	
Tertiary or above	4 (4)	5 (5)	
Place of Birth			0.391
Hong Kong	33 (33)	43 (43)	
Mainland China	65 (65)	56 (56)	
Other	2 (2)	1 (1)	
Years of living in Hong Kong			0.474
<1	1 (1)	2 (2)	
1-2	9 (9)	7 (7)	
3-6	11 (33)	16 (16)	
≥7 (permanent resident status)	65 (65)	73 (73)	
Two-way permit (temporary resident status)	1 (1)	0 (0)	
Refused to answer	1 (1)	2 (2)	
Marital status			0.099
Single	5 (5)	3 (3)	
Married or cohabited	88 (88)	91 (91)	
Divorced or separated	7 (7)	6 (6)	
No. of children			0.647
0-1	46 (46)	51 (51)	
2-3	51 (51)	44 (44)	
>3	3 (3)	5 (5)	
History of chronic illness	15 (15)	11 (11)	0.531
Partner with chronic illness	11(11)	8 (8)	0.629
In paid job	30 (30)	32 (32)	0.886
Partner with paid job	76 (76)	78 (78)	0.882
Financial hardship reported	72 (72)	73 (73)	0.865
Receiving comprehensive social security assistance	33 (33)	9 (9)	<0.001
In need of financial support	65 (65)	58 (58)	0.391

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

Table 2. Instrument scores of the intervention and control groups at baseline, month 3, and month 9

Instrument	Mean±SD score						Estimate (95% CI) adjusted between-group difference†	P value
	Intervention (n=100)			Control (n=100)				
	Baseline*	Month 3	Month 9	Baseline*	Month 3	Month 9		
Beck Depression Inventory version II	37.88±14.90	24.38±14.45	16.10±10.69	39.33±15.60	26.25±12.70	18.25±11.40	-2.66 (-5.06, -0.26)	0.031
Interpersonal Support Evaluation List	7.13±8.42	15.94±8.19	21.09±7.02	6.73±7.92	13.51±8.51	19.49±7.20	2.18 (0.48, 3.89)	0.013
Short-Form Health Survey								
Physical Component Summary score	43.28±7.67	42.37±7.22	44.35±7.64	43.32±7.59	42.39±7.37	43.55±7.30	0.37 (-0.91, 1.65)	0.576
Mental Component Summary score	26.58±7.64	34.79±8.87	38.26±8.56	25.44±7.66	34.39±8.26	37.89±8.08	0.80 (-1.16, 2.77)	0.424
Revised Conflict Tactics Scales								
Psychological aggression	18.54±10.20	23.67±15.89	10.07±5.91	18.95±10.36	20.84±10.45	12.11±8.57	-1.87 (-3.34, -0.40)	0.014
Physical assault	1.68±4.21	1.27±3.22	0.23±1.27	1.55±4.10	3.21±6.07	0.45±1.74	-0.35 (-0.80, 0.10)	0.130
Sexual coercion	0.68±3.32	0.33±1.29	0.03±0.30	0.14±0.73	1.11±2.70	0.14±0.75	-0.02 (-0.12, 0.09)	0.602

* No baseline difference (P≥0.125)

† Estimated between-group difference (intervention - control) from month 3 to month 9 after adjusting for baseline values

Perceived social support

The Interpersonal Support Evaluation List scores of both groups increased significantly from month 3 to month 9 (mean, 5.56, 95% CI, 4.66-6.47; P<0.001). The increase was significantly greater in the intervention than control group (mean, 2.18; 95% CI, 0.48-3.89; P=0.013), and the effect was sustained even after adjusting for the baseline difference (in CSSA) and removing an outlier (mean, 2.23; 95% CI, 0.43-4.03; P=0.016).

Health-related quality of life

No significant between-group differences were noted from month 3 to month 9 before and after adjusting for the baseline difference (in CSSA) and removing an outlier (Physical Component Summary (PCS) score: mean, 0.37 vs 0.30; 95% CI, -0.91-1.65 vs -1.04-1.64; P=0.576 vs P=0.665; Mental Component Summary (MCS) score: mean, 0.80 vs 1.13; 95% CI, -1.16-2.77 vs -0.92-3.18; P=0.424 vs P=0.282).

Intimate partner violence

Overall IPV in both groups decreased significantly from month 3 to month 9 (mean, -0.43; 95% CI, -0.81 to -0.05; P=0.027). The decrease in psychological aggression was significantly greater in the intervention than control group (mean, -1.87; 95% CI, -3.34 to -0.4; P=0.014). No significant between-group differences from month 3 to month 9 were noted for physical assault (mean, -0.35; 95% CI, -0.80-0.10; P=0.130) or sexual coercion (mean, -0.05; 95% CI, -0.25-0.15; P=0.602). Similar effects were noted after adjusting for the baseline difference (in CSSA) and removing an outlier of psychological aggression (mean, -2.34; 95% CI, -3.87 to -0.81; P=0.003), physical assault (mean, -0.44; 95% CI, -0.91-0.03; P=0.067), or sexual coercion (mean, -0.04; 95% CI, -0.21-0.13; P=0.649).

Safety-promoting behaviours

The number of safety-promoting behaviours increased significantly from month 3 to month 9 (mean, 0.54; 95% CI, 0.10-0.97; P=0.016). The increase was significantly greater in the intervention than control group at month 3 (mean, 3.80; 95% CI, 2.84-4.77; P<0.001), and the effect was significantly more pronounced at month 9 (mean, 4.72; 95% CI, 3.76-5.69; P<0.001). The effects were sustained even after adjusting for the baseline difference (in CSSA) and removing an outlier of month 3 (mean, 3.70; 95% CI, 2.72-4.68; P<0.001) or month 9 (mean, 4.64; 95% CI, 3.65-5.62; P<0.001).

Utilisation of health services

No significant between-group differences were noted from month 3 to month 9 before and after adjusting for the baseline difference (in CSSA) [mean, -0.02; 95% CI, -0.12-0.09; P=0.749].

Discussion

The abused women reported significantly more reduction in depression and psychological aggression, and more improvement in perceived social support and the use of safety-promoting behaviours after receiving the advocacy intervention than usual community services. The advocacy intervention was also significantly more useful in helping women to improve their relationship and handle conflicts with their intimate partners. However, there was no evidence that the advocacy intervention resulted in more significant improvement in health-related quality of life or reduction in utilisation of health services.

In our study, nearly all the women had not disclosed their IPV experience to or had not sought help from social or health services professionals. This suggested that violence against women may remain hidden as long as no direct questions were asked. Yet, in light of the severe levels of depression reported at baseline, the women were clearly in need of help. This study raised public awareness of the health consequneces of IPV and screening for IPV in the community setting. Although only usual community services were provided to the women in the control group, there was improvement in their depression. It is probable that just abuse screening by itself may have a beneficial effect for abused women.[2]

There is inconsistent evidence as to whether advocacy intervention improves social support in the short term for abused women who have actively sought help.[2] In our study, women who received the advocacy intervention reported more improvement in perceived social support. By helping the women to access services and by non-judgmental listening, the advocacy intervention may have convinced the women that help was available should they need it. During the weekly telephone sessions, most women expressed needs related to parenting problems rather than couple relationship problems. This suggested that Asian couples tend to frame their relationship issues in the context of raising children. It is therefore important not to overlook the need to address parenting problems when providing intervention to Chinese women living in abusive intimate relationships.

Our study showed that a less intensive advocacy intervention (and usual community services) also appeared to improve safety-promoting behaviours for abused women who were not actively seeking legal protection. Exposure to the safety-promoting behaviours checklist during the repeated-measurement process may have an effect similar to that of the intervention. This has implications for practice.

The low PCS and MCS scores of the abused women support previous findings that IPV adversely affects health-related quality of life of abused women by lowering their physical performance and their ability to function socially and emotionally. Financial hardship (as expressed by many of the participants) may have prevented them from functioning socially, owing to the lack of funds and/or

diminshed contact with friends or relatives due to unpaid debts and/or poor self-esteem.

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Cognitive training for Hong Kong Chinese with schizophrenia in vocational rehabilitation

Key Messages

1. A randomised controlled trial was conducted to determine the effectiveness of a computerised, errorless, learning-based, training programme to enhance schizophrenic patients' cognitive functions and vocational outcomes.
2. A total of 80 Chinese with schizophrenia were randomly assigned to a 4-week, computer-assisted, errorless-learning (CAEL) group, a therapist-administered (TA) group, or a control group.
3. Participants were assessed pre-test, post-test, and at the 3-month follow-up. Cognitive, emotional, and vocational outcomes were measured using standardised validated instruments.
4. Participants in the CAEL and TA groups performed better than controls with respect to certain aspects of neurocognition. The CAEL group also had better self-efficacy (social skills and personal appearance) in work training and positive affect than the control group. The effectiveness of the intervention in the TA and CAEL groups was not similar. Vocational outcome after training was best predicted by both cognitive and emotional factors.
5. Combined use of an errorless learning and a computerised approach may be effective in enhancing the cognitive functioning and thus vocational outcome of Chinese patients with schizophrenia.

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Introduction

Work is important to everyone's life. It has beneficial effects to self-esteem, symptoms, economic standing, and satisfaction with finances, sense of recovery, and quality of living.[1] In the realm of mental health, work is important both in maintaining mental health and in promoting the recovery of those who have experienced mental health problems.[2] Nonetheless, people with mental disorders such as schizophrenia have impairment in work function, despite the desire to work.[1] Employment rates of people with severe mental illness range from 10 to 30% only.[1,3]

Basic cognitive function (attention, language comprehension) and higher cortical functions (reasoning such as similarity and judgement) are important predictors for vocational outcomes.[4,5] In addition to social skill and vocational skill training, cognitive training enhances the vocational outcomes and thus recovery and mental health of people with schizophrenia. Computer-assisted, cognitive rehabilitation programmes have been successfully applied to patients with schizophrenia and have provided equivalent or better training effect than traditional drilling methods, which use a trial-and-error approach and usually neglect the cognitive aspect of these patients. Committing errors during the learning process may be problematic for some persons with severe mental illness, as many of them have difficulties attending to a task, filtering out relevant information, or staying with a difficult task, and thus they endure multiple failures. Errorless learning is thus used to encourage active participation and to enhance the results by preventing errors. It is a better learning method than those depending on trial and error.[6]

This study aimed to compare a computer-assisted, errorless-learning (CAEL) training programme with a conventional therapist-administered (TA) errorless-learning programme and a control group for enhancing mental health and vocational outcomes of Hong Kong Chinese with schizophrenia. It was hypothesised that cognitive remediation using the errorless-learning approach delivered through a computerised mode or a therapist-administered mode could be efficacious interventions, and that the effect achieved by a computer-assisted and a therapist-administrated training programme would differ, despite using the same errorless-learning approach and the same content.

Methods

This randomised, controlled, double-blinded trial was conducted from October 2007 to December 2009. All participants were informed about the study and signed a consent form before commencement. Of 90 subjects with schizophrenia aged 18 to 55 years who were mentally stable and calm and had a basic attention span of at least 3 minutes, 80 completed the study and 10 dropped out (owing to early discharge, incomplete training or data set). The patients were randomly assigned into the CAEL (n=27), TA (n=23), or control (n=30) group (Table 1) and were assessed by independent raters pre-test, post-test, and at the 3-month follow-up. The patients and assessors did not know the expected results of the training programmes.

Patients were excluded if they had (1) impaired physical functions inhibiting the operation of a keyboard or mouse, (2) visual impairment such as blindness, partial blindness and other visual problems, (3) other neurological problems such as epilepsy, (4) pre- and post-morbid mental retardation of severe or moderate grades, (5) previous training of similar computerised programmes, or (6) a deviation quotient of <85 in the Test of Nonverbal Intelligence version III (TONI-3),[7] which is a language-free intelligence test that measures abstract/figural problem-solving ability.

The 12-session CAEL and TA programmes were developed based on the work scenario of a convenience store worker involving four major tasks: stock keeping, cleansing, food servicing, and cashiering. Five principles of errorless learning were applied: (1) the to-be-learned task was broken down into components, (2) training began on simple tasks and proceeded gradually to more difficult ones, (3) high levels of success were maintained at each stage with use of aids and abundant positive reinforcement, (4) each component was over-learned through repetitive, successful practice until performed nearly automatically, and (5) the learned components were recombined, adding one component at a time, until the task was trained entirely. The TA programme was produced by print-screening the scenes of CAEL to form an administration handbook for each session. Thus the two programmes were of similar content and structure, but different in the mode of delivery.

Outcome measures included: (1) the Wisconsin Card Sorting Test (WCST) computer version 4,[8] which assesses executive function—the abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies. It was used to obtain information of the subject's learning ability by the cognitive level of flexibility to learn in response to a changing environment. (2) The Neurobehavioral Cognitive Status Examination (NCSE) Chinese version,[9] which is a standardised examination of global cognitive function. It assesses multiple domains of cognitive functioning, namely: orientation, attention, language, construction, memory, calculation and reasoning. It was used to detect changes in the global cognitive functioning of the subjects after training. (3) The Vocational Cognitive Rating Scale (VCRS),[10] which measures cognitive impairment that clients with chronic mental illnesses may experience in the workplace. It includes 16 items that are phrased with behaviourally based anchors. It was used to compare vocational cognitive functioning of subjects. (4) The self-efficacy scale, which is a 10-item questionnaire to rate subject's self-efficacy on the ability to perform tasks of a convenient shopkeeper. It was used to detect the difference of subjects' self-efficacy in being a shopkeeper after training. (5) The Chinese Work Personality Profile (CWPP),[11] which is a behavioural rating instrument for use in employment settings that provides a broad assessment of the vocational circumstance. Five domains of work behaviours (task orientation, social skills, self-control, attitude towards supervision, and personal appearance) were assessed in the work settings. It was used to reflect effectiveness of the training on the actual working performance and to detect any changes in the working personality of the client. (6) The Positive and Negative Affect Scale (PANAS) Chinese version,[12] which independently measures positive and negative moods. It consists of 20 adjectives (10 each for positive and negative mood states). It was used to detect positive and negative emotional responses of the subject. (7) The vocational outcomes, which is defined by five categories: open employment, vocational training, supported employment, sheltered workshop, and unemployment.

Results

The CAEL, TA, and control groups were not significantly different with respect to subject demographics (gender, medication, marital status, and TONI-3 score), except

Table 1. Demographics of schizophrenic patients in the computer-assisted errorless-learning (CAEL), therapist-administered (TA), and control groups*

Variable	CAEL group (n=27)	TA group (n=23)	Control group (n=30)
Age (years)	34.9±8.5 (19-49)	41.6±7.7 (24-54)	35.1±10.2 (18-50)
Deviation quotient (Test of Nonverbal Intelligence version III)	88.7±14.3 (75-135)	87.7±17.7 (63-135)	90.6±12.5 (64-116)
Gender			
Male	15 (56)	14 (61)	21 (70)
Female	12 (44)	9 (39)	9 (30)
Education			
Primary	3 (11)	0 (0)	6 (20)
Secondary	23 (85)	23 (100)	20 (67)
Post-secondary	1 (4)	0 (0)	4 (13)
Marital status			
Single	23 (85)	18 (78)	24 (80)
Married	3 (11)	3 (13)	6 (20)
Widowed	1 (4)	0 (0)	0 (0)
Divorced	0 (0)	2 (9)	0 (0)
Medication			
Typical	9 (33)	9 (39)	11 (37)
Atypical	18 (67)	11 (48)	18 (60)
Both	0 (0)	3 (13)	1 (3)

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

Table 2. Instrument scores of schizophrenic patients pre-test, post-test, and at the 3-month follow-up*

Instrument	Computer-assisted errorless-learning group			Therapist-administered group			Control group		
	Pre-test (n=27)	Post-test (n=27)	Follow-up (n=18)	Pre-test (n=23)	Post-test (n=23)	Follow-up (n=15)	Pre-test (n=30)	Post-test (n=30)	Follow-up (n=24)
Vocational Cognitive Rating Scale	53.7±9.3	54.7±8.6	-	52.7±9.0	52.1±9.2	-	53.5±13.7	54.0±13.6	-
Wisconsin Card Sorting Test									
Total correct	63.5±19.3	69.6±18.6	64.2±16.4	67.3±20.4	61.7±18.9	63.6±11.6	70.9±18.2	70.0±15.5	70.5±19.9
Total error	58.7±26.1	48.6±27.4	49.7±31.0	54.7±26.2	54.5±30.8	40.0±30.9	52.5±22.6	44.5±25.9	46.3±24.7
% of error	46.8±19.1	39.1±20.0	40.3±22.3	43.9±19.3	44.1±22.3	35.1±21.1	41.9±16.6	36.7±18.3	38.7±18.6
Preservative error	29.1±19.2	25.5±20.0	21.6±20.1	29.3±21.2	27.4±20.4	18.4±13.4	29.7±19.0	24.6±20.0	27.0±20.7
% of preservative error	23.2±14.6	20.5±15.1	17.6±15.1	23.4±16.1	22.1±15.3	16.1±9.0	23.6±14.4	20.2±15.0	22.3±15.7
Conceptual level response	46.4±26.4	54.3±26.7	50.0±24.5	50.6±27.9	45.2±27.8	50.1±22.3	54.4±23.7	55.7±21.6	56.3±25.1
Categories completed	2.7±2.1	3.3±2.5	3.2±2.6	3.1±2.4	2.9±2.7	3.7±2.9	3.5±2.2	3.8±2.4	4.0±2.4
Neurobehavioral Cognitive Status Examination									
Orientation	11.3±1.0	11.6±0.8	11.7±0.5	10.9±1.6	11.3±1.3	10.0±2.2	11.2±1.2	11.4±1.2	11.4±1.2
Attention	8.0±0.0	8.0±0.2	8.0±0.0	8.0±0.0	8.0±0.0	8.0±0.0	7.7±1.5	7.7±1.2	7.8±0.7
Language	20.7±4.3	22.4±3.3	23.0±3.1	21.0±4.2	22.0±3.9	20.9±5.1	21.5±3.6	21.9±2.9	21.6±3.4
Construction	4.9±1.7	5.3±1.0	5.3±1.0	4.3±1.7	4.7±1.7	4.6±2.1	5.3±1.1	5.1±1.5	5.0±1.7
Memory	9.6±3.3	9.6±3.4	9.8±3.4	8.6±3.4	9.0±3.7	8.8±3.9	9.1±3.2	9.2±2.8	9.2±3.5
Calculation	3.7±0.7	3.9±0.3	3.9±0.3	3.4±1.2	3.9±0.5	4.0±0.0	3.5±1.1	3.6±1.0	3.6±0.9
Reasoning	12.3±2.4	13.2±1.6	12.2±2.6	11.9±2.6	12.7±2.5	12.5±3.0	10.5±3.0	10.8±2.6	11.0±3.1
Chinese Work Personality Profile									
Task orientation	73.4±7.4	75.1±8.4	-	73.0±8.0	71.8±8.5	-	68.9±15.3	69.1±15.2	-
Social skills	41.6±5.0	42.7±5.7	-	41.1±6.4	41.0±7.2	-	37.7±6.8	37.9±6.5	-
Self control	20.9±2.2	21.3±2.2	-	20.7±1.7	20.8±2.2	-	20.0±3.5	20.0±3.6	-
Attitude towards supervision	26.8±3.3	27.7±3.6	-	27.1±4.2	26.9±4.1	-	25.4±4.8	25.3±4.4	-
Personal appearance	6.1±1.2	6.0±1.0	-	6.3±1.1	6.0±1.1	-	6.5±0.9	6.5±0.9	-
Self-efficacy scale	72.0±18.3	79.7±6.3	-	69.5±20.8	72.6±18.6	-	68.0±19.1	65.2±20.9	-
Positive and Negative Affect Scale									
Positive	30.2±6.5	31.0±6.3	30.5±6.5	29.3±7.5	27.6±6.1	26.1±7.7	29.3±7.5	29.1±7.5	29.9±6.7
Negative	24.0±9.4	20.9±8.2	25.0±7.3	22.4±8.6	22.4±10.3	20.1±6.2	20.6±7.4	21.9±8.4	22.6±7.8
Vocational outcome at follow-up									
Vocational training	-	-	15 (33)	-	-	10 (67)	-	-	-
Sheltered workshop	-	-	1 (6)	-	-	3 (20)	-	-	-
Supported employment	-	-	2 (11)	-	-	2 (13)	-	-	-

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

for age (F=4.40, P=0.015) and education level (Chi-square=10.54, P=0.032) [Table 1]. The three groups were also not significantly different in terms of baseline outcome measures (VCRS, WCST, NCSE, NCSE, PANAS, and the self-efficacy scale), indicating comparable pre-test status (Table 2). Interacting effects were not significant in the VCRS and WCST, even when repeated analysis of variance (ANOVA) was applied, age was adjusted, and education levels were stratified.

For NCSE, after adjusting for age, the group effect was significant in the reasoning domain only (F=6.460, P=0.003, multivariate ANOVA [MANOVA]), and the CAEL and TA groups performed significantly better than the control group. For subjects with primary education, the group effect was significant in the language domain (F=7.480, P=0.034, MANOVA), and the CAEL group performed significantly better than the control group (t=2.443, P=0.045). For those with secondary education, the group effect was significant in the reasoning domain (F=6.561, P=0.003, MANOVA), and the CAEL and TA groups performed significantly better than the control group in the ANOVA and post-hoc (Bonferroni) test. For those with post-secondary education, no significant group effect was noted on all domains.

For CWPP, after adjusting for age, the group effect was significant in the social skill domain only (F=3.98, P=0.023, MANOVA), and the CAEL group (but not the TA group) performed significantly better than the control groups. For the other four domains, there was no significant group effect. For those with secondary education, the group effect was significant in the social skill domain (F=3.46, P=0.037, MANOVA). For those with post-secondary education, the group effect was marginally significant in the personal appearance domain (F=15.64, P=0.058, MANOVA).

For the self-efficacy scale, after adjusting for age, no significant group effect was noted (MANOVA). For those with primary education, the group effect was marginally significant (F=3.865, P=0.097, MANOVA). For those

with secondary education, the group effect was significant (F=3.909, P=0.025, MANOVA). The CAEL group had better self-efficacy than the control group (ANOVA and post-hoc test), whereas the CAEL and TA groups did not differ significantly (F=4.232, P=0.018). For those with post-secondary education, no significant group effect was noted (MANOVA).

For PANAS, group effect was significant for positive scores only (F=3.53, P=0.043) among patients with secondary education. The CAEL group had a better positive affect than the control group, and the CAEL and TA groups were not significantly different (ANOVA and post hoc test).

For vocational outcome, the CAEL, TA, and control groups were not significantly different at the 3-month follow-up (Chi-square=3.378, P=0.497). Most patients were still receiving vocational training (n=46 [15+10+21, respectively], 80.7%), whereas others were attending a sheltered workshop (n=6, 10.5%) or having support employment (n=5, 8.8%). There were significant differences in self-efficacy, WCST, NCSE, and PANAS scores among patients in each of the three vocational outcomes. Thus, discriminant analysis was carried out to determine whether post-training outcome measures at the 3-month follow-up could help to predict vocational outcome.

The canonical correlation between self-efficacy and vocational outcome was low (0.112), as were the classification function coefficients of self-efficacy versus each of the vocational outcomes (vocational training, sheltered workshop, and supported employment). The values were 0.146, 0.156, and 0.13, respectively. From the classification table, if only self-efficacy was used to predict the vocational outcome, the overall classification rate was only 36.8%. Similarly, for discriminant analysis, the canonical correlations between WCST and vocational outcome were not high (0.403 and 0.231, respectively). The classification function coefficients of WCST (categories completed) and percentage of errors with the three vocational outcomes (2.14, 2.11, and 2.06, respectively) were higher than that for the percentages of preservation errors and conceptual level responses. If WCST subtests including categories, percentage of errors, percentage of preservation errors, and conceptual level response were used to predict the vocational outcome, the overall classification rate was at the acceptable level of 54.4%.

The classification function coefficients of NCSE (attention) and NCSE (calculation) with each of the vocational outcomes were higher, compared to other NCSE components. From the classification table, if all NCSE components were used to predict the vocational outcome, the overall classification rate was high (75.4%).

The canonical correlation between PANAS (positive and negative) score and vocational outcome was low (0.187 and 0.025, respectively). The classification function coefficients of positive and negative PANAS scores with each of vocational outcomes were lower, because the coefficients were <1. If PANAS positive and negative scores were used to predict the vocational outcome, the overall classification rate of 56.1% was acceptable.

Discussion

The short-duration training (CAEL or TA) did not result in significant differences in VCRS and WCST. The VCRS may not be a sensitive tool in detecting changes when subjects were being observed in doing real work tasks. The training intensity may be too low for positive transfer of skills, and the content may not be relevant. The ecological validity of WCST (a laboratory-based test, assessing abstract reasoning, and execution of card activities on a computer screen) is questionable and may also limit its use in real-life, work-related task.

For global cognitive function as indicated by NCSE, only the component score of reasoning was better in the CAEL and TA groups than controls. For those having primary and secondary education, the CAEL group performed better than controls in both NCSE (language) and NCSE (reasoning). Therefore, limited but positive changes in cognitive functions were indicated, and the CAEL group was more effective.

For CWPP (social skills), the CAEL group performed better than controls. For patients with secondary and post-secondary education, the CAEL group performed better than controls in social skills and personal appearance, respectively. This suggested that computer training provided an efficacious training effect on work behaviour (social skills, personal appearance) for those with better education.

For self-efficacy, in patients with primary and secondary education, those in the CAEL group performed better in shop keeping than controls, whereas the CAEL and TA groups were not significantly different. This suggested that the computer training content was able to change subjects' self-evaluation of their own competence in performing the required task, as comparable to the documented therapist's face-to-face role in motivation and provision of positive feedback. This computerised training approach may be an alternative means of motivating patients in job training.

For PANAS, no significant change in positive and negative affect among the three groups was noted, except that the CAEL group had a more positive affect than controls after training. This suggested that computer training itself may influence the subjects' affect. Although CAEL and TA entailed similar content, the computer programme seemed to provide an additional benefit to the emotional adjustment of the subjects.

For vocational outcome, there was no significant

difference in the three groups at the 3-month follow-up. Vocational outcome was limited to three of the five pre-set categories (vocational training, supported employment, sheltered workshop). None of the patients had open employment. The training programmes may be too content-specific (restricted to manual work) to empower them for successful open employment. Other pertinent factors predicting successful work placement should also be considered.

In the discriminant analysis, both cognitive (WCST, NCSE) and emotion functions (self-efficacy, PANAS) were equally important in predicting vocational outcomes. Future training programme or discharge plans for persons with schizophrenia should provide well-balanced cognitive and self-efficacy training, which can be achieved by an increased awareness and emphasis on innovative cognitive training and by conventional training in social skills, assertive training, and group therapy.

Due to the limited time and the number of subjects, the sample size was not large enough, especially at the 3-month follow-up. Although the dosages of antipsychotic drugs were maintained at the same level before and during the study period, the medication effect might have made them feel tired and less motivated, which might not be the best time point to conduct the training. In the TAG, the investigators had to conduct face-to-face delivery of the feedback that was similar to the CAELG training programme, but there was no standardised training method for the therapists.

Suggestions for future studies are: (1) training could be increased to six sessions per week to a total of 20 sessions or more, so as to enhance the over-learning effect and help the participants become familiarised with the tasks. (2) A well-defined scoring system should be incorporated into the computer programme. (3) A placement of convenient shopkeeper's tasks should be included as an outcome measure at the end of each week for more precise evaluation of the participants' actual performance. (4) In the TA group, the investigators should formulate a general rule about feedback to the participants during the training.

Conclusions

Although the CAEL group did not show a significant effect with respect to most of the cognitive, emotional, and vocational outcomes, improvement in the component scores of NCSE (reasoning, language), self-efficacy, and PANAS (positive affect) demonstrated possible learning of cognitive skills in relation to vocational tasks. Learning may be enhanced by the errorless-learning method and may be feasibly delivered by a computerised training programme. Through examining the new vocational outcome predictors of cognition (reasoning and problem solving), the vocational rehabilitation treatment programme can be more specific and tailor-made for schizophrenic patients.

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Long-term neurocognitive outcomes of children prenatally exposed to low-dose methylmercury

Key Messages

1. It has been suggested that low-dose prenatal mercury exposure as measured by umbilical cord blood mercury concentrations of >29 nmol/L causes adverse long-term neurocognitive outcomes.
2. Of 608 children, 491 (81%) had umbilical cord blood mercury concentrations of >29 nmol/L. However, umbilical cord blood mercury concentrations were associated with only two out of 23 neurocognitive subtests.
3. There is no strong evidence to support restriction in fish consumption in pregnant women to reduce prenatal mercury exposure.

Introduction

It has been suggested that low-dose prenatal methylmercury exposure can give rise to long-term adverse health outcomes.[1] Two of the largest cohort studies have shown conflicting results.[1,2] Pregnant women are advised to regulate fish intake to limit fetal methylmercury exposure.[3] Using an umbilical cord blood mercury concentration cut-point of 29 nmol/L,[1] 78.4% of children in our locality were at risk of adverse neurocognitive outcomes.[4] Nonetheless, maternal seafood consumption has beneficial long-term neurocognitive effects in children.[5] Therefore, associations between long-term childhood neurocognitive outcomes and both prenatal mercury exposure and fish consumption behaviour are crucial for recommendations about fish consumption. We investigated whether there were any associations between low-dose prenatal mercury exposure and neurocognitive outcomes in Hong Kong children. We hypothesised that our local population was at risk of adverse neurocognitive effects from low-dose prenatal mercury exposure as a result of high fish consumption behaviour.

Methods

This study was conducted from October 2007 to September 2009. Subjects from our previous study[4] were recruited for neuropsychological tests. The tests were performed and interpreted by clinical psychologists who were blinded to the subjects' mercury exposure. The tests involved several standardised techniques to measure general intellectual function (verbal and non-verbal), learning and verbal memory, fine motor coordination, and attention. Associations between cord blood mercury concentration and neurocognitive outcomes were determined using multivariate analyses.

Results

Of 608 children assessed, 491 (81%) had umbilical cord blood mercury concentrations of >29 nmol/L and 117 had lower concentrations. Using the Student's *t* test, the two groups did not differ significantly in any of the neurocognitive subtests. In multivariate linear regression analyses for each subtest of each neurocognitive assessment, after adjusting for confounders, cord blood mercury concentration was positively associated with the Sky Search – time per target subtest of the TEACH and negatively associated with the Picture Arrangement subtest of the HK-WISC. Further in-depth analyses of the neurocognitive outcomes are required to identify any pattern of clustering of effects.

Discussion

Demographics and fish consumption characteristics were similar between those recruited and not recruited. The cord blood mercury concentrations differences between the two groups were small (50 vs 46 nmol/L), but statistically significant.

Although the follow-up rate in our study was only 58%, it was still adequately powered to detect the small effects demonstrated in the Faroese cohort (adverse effects).[1] Our results were consistent with those of the Seychelles cohort (no

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adverse effects).[2] In Hong Kong, mercury exposure occurs mainly as a result of high and steady fish consumption.[4] This pattern of fish consumption is similar to that of the Seychelles cohort.[2,3] In the Faroese cohort, the episodic consumption of pilot whales gave rise to a pattern of mercury exposure that was more erratic and interspersed with high spikes.[3] This may be part of the reason why the Hong Kong population did not show substantial adverse neurocognitive outcomes as a result of prenatal mercury exposure. Restriction of fish consumption during pregnancy may be undesirable as fish is a good source of many nutrients. In our previous study,[4] 78.4% of children had umbilical cord blood mercury concentrations of >29 nmol/L.[3] However, this study showed no strong evidence to support restriction in fish consumption during pregnancy, as the risks of reduced fish consumption may outweigh the benefits of reduced mercury exposure.

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Marital satisfaction among Hong Kong couples

Key Messages

1. Interest in sex was highly predictive of sexual satisfaction and frequency of sex in marriage.
2. For husbands, age was negatively correlated with the frequency of a married couple having sex.
3. For wives, holding a full-time job resulted in a lower frequency of sex.
4. Marriage counsellors should pay attention to the different needs of both individuals in a couple.

Introduction

Marriage satisfaction is associated with sexual satisfaction, and frequency of sex is related to marital sexual satisfaction.[1,2] In western societies, common predictors of sexual satisfaction in marriage are age and medical condition of the couples. Nonetheless, such empirical studies in Chinese societies are limited.

This study aimed to address whether the predictors of sexual satisfaction within marriage in western societies (marital sexual satisfaction and frequency of sex) were applicable in a Chinese society. The research questions were: (1) what were the factors that influence sexual satisfaction for married Hong Kong Chinese couples?; (2) what were the factors that influence frequency of sex for married Hong Kong Chinese couples?; and (3) what were similarities and differences in the factors associated with marital sexual satisfaction and frequency of sex among married Hong Kong Chinese couples?

Methods

Path analysis was used to test the research hypotheses. The main advantage of path analysis over regression analysis is that predictors for sexual satisfaction and the frequency of sex can be tested simultaneously to compare similarities and differences.

A large dataset from the eighth Knowledge, Attitude and Practice (KAP) Survey conducted by the Family Planning Association of Hong Kong in 2002 was used. Marriage and sexual satisfaction were two key variables. Stratified sampling was used to randomly select participants to ensure that the sample characteristics were similar to those at the societal level.

About 1600 married or cohabiting women aged 15 to 49 years were successfully interviewed. The spouses of these women were invited to participate. The total number of pairs of couples was 1124. Missing data were dealt with using the full information maximum likelihood method.[3] If the data were missing at random, maximum likelihood could provide efficient and unbiased estimates on the parameters.

A question "are you satisfied with your sexual life?" was used to measure the sexual satisfaction of the husbands and wives. The response scale was from 'very unsatisfied' (1) to 'very satisfied' (5). The answers given by the wives on the question "in the past 30 days, how many times have you had sex?" were used as proxy on the frequency of sex, which was assumed to be the same for the couples. Variables were grouped into several categories. (1) Demographic variables included age, place of birth (Hong Kong SAR vs Mainland China), educational level, having a full-time work, and having been married more than once. These variables were measured separately for the husbands and wives. (2) Family variables included family income, number of children, and years of marriage. These variables were assumed to be the same for the couples. (3) Medical history related to sex included having sought medical help related to sex (husbands and wives) and having an abortion (wives only). (4) The psychological variable, namely 'interest in sex', was measured separately for husbands and wives.

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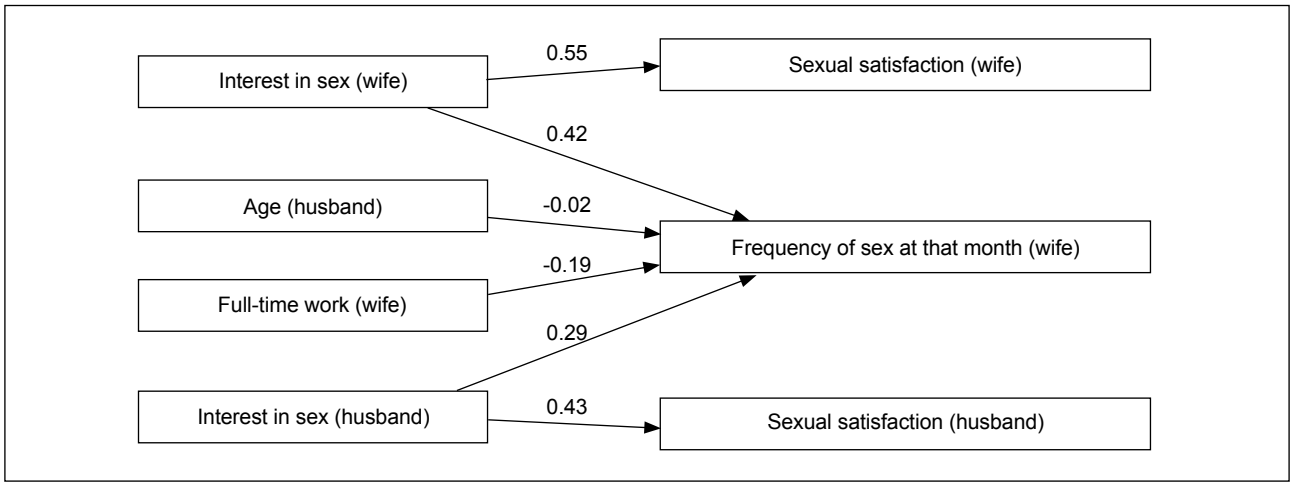

Fig. Path model of sexual satisfaction and frequency of sex*

* Coefficients represent the unstandardised path coefficients significant at α=0.01. Non-significant variables are not included.

Results

A path model with three dependent variables was fitted. The significant paths (α=0.01) of the unstandardised coefficients are shown in the Figure. The residuals of the dependent variables were significant suggesting that the predictors were not sufficient to explain all the association among the predictors.

Interest in sex was the strongest predictor in predicting sexual satisfaction of husbands and wives and of the frequency of sex. It was the only significant predictor for both sexual satisfaction and frequency of sex. For the husbands, age was negatively correlated with frequency of sex, but not with sexual satisfaction. This effect was not observed in the wives. Wives with a full-time job had sex less frequently than those without a full-time job. This effect was not observed in the husbands.

Discussion

This is the first empirical study on sexuality within marriage in Hong Kong. One possible reason for a lower frequency of sex in wives with a full-time job is that wives in Hong Kong are expected to be responsible for household chores and most parenting duties. Even if they have full-time employment, their involvement in parenting and domestic duties remains high. This may lead to high levels of stress. Readers may refer to the study by Cheung et al[4] for more details.

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Attitude toward traditional Chinese medicine among allopathic physicians in Hong Kong

Key Messages

1. Hong Kong western medicine doctors emphasise evidence-based practice over patient choice when considering traditional Chinese medicine (TCM).
2. The lack of opportunity to expose to the practice and scientific basis of TCM during western medical training should be redressed.
3. Better understanding of the regulations might promote collaboration between western medicine and TCM practitioners.
4. Establishing a TCM and allopathic medicine inter-professional collaboration platform may help the development of integrated pluralistic care, which could in turn be more responsive to the health behaviours of the Hong Kong population.

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Introduction

Traditional Chinese medicine (TCM) is a part of Hong Kong culture. Nonetheless, western allopathic medicine (AM) is the accepted legitimate local medical system. Policy initiatives to develop TCM in line with that in mainland China increase TCM popularity among the public. Given the role of TCM in primary care and to foster collaboration between AM and TCM in line with government policy, we set out to investigate the attitude of Hong Kong western medicine doctors toward TCM and its integration with western medicine using both quantitative and qualitative methodologies.

Study design and methods

This study was conducted from October 2007 to December 2008. A total of 3320 western medicine doctors were randomly drawn from the full and limited registration lists of the Hong Kong Medical Council to undertake a three-phase, cross-sectional mail survey.

Their attitude toward TCM were assessed using (1) a locally adopted version of the Integrative Medicine Attitude Questionnaire (HKTCM-IMAQ-R), with domains of knowledge, evidence, and holism; and (2) questions related to the personal use of TCM, intention with respect to referral to TCM and actual referral to TCM, and open questions for qualitative comments.

Associations between characteristics of western medicine doctors and attitude toward TCM were assessed using multinomial logistic regressions. Group thematic analysis strategy was used for qualitative data analysis.

Results

The response rate was 34% (n=1130). The TCM modality most frequently considered for referral was acupuncture (23.3%), whereas 13.8% of respondents had actually referred their patients (Fig). Favourable attitude toward TCM knowledge and evidence, personal use of TCM, and prior education in TCM were the predictors for potential and actual referral of TCM. Working in the public sector was negatively associated with referrals to TCM. There was a mixed pattern of referral by practitioner age; respondents aged <31 or 41 to 50 years were less likely to refer to TCM, whereas those aged 31 to 40 years were more open to such referrals. In 52 of the respondents, qualitative comments were provided in the areas of (1) paradigm differences between AM and TCM, (2) facilitators for and barriers to collaboration and integration, and (3) the need for policy initiatives to promote integration.

Discussion

Hong Kong western medicine doctors have a diverse range of opinions about TCM. Over one third use TCM themselves, and one fifth have considered referral to TCM practitioners. Personal use of TCM and prior TCM education were

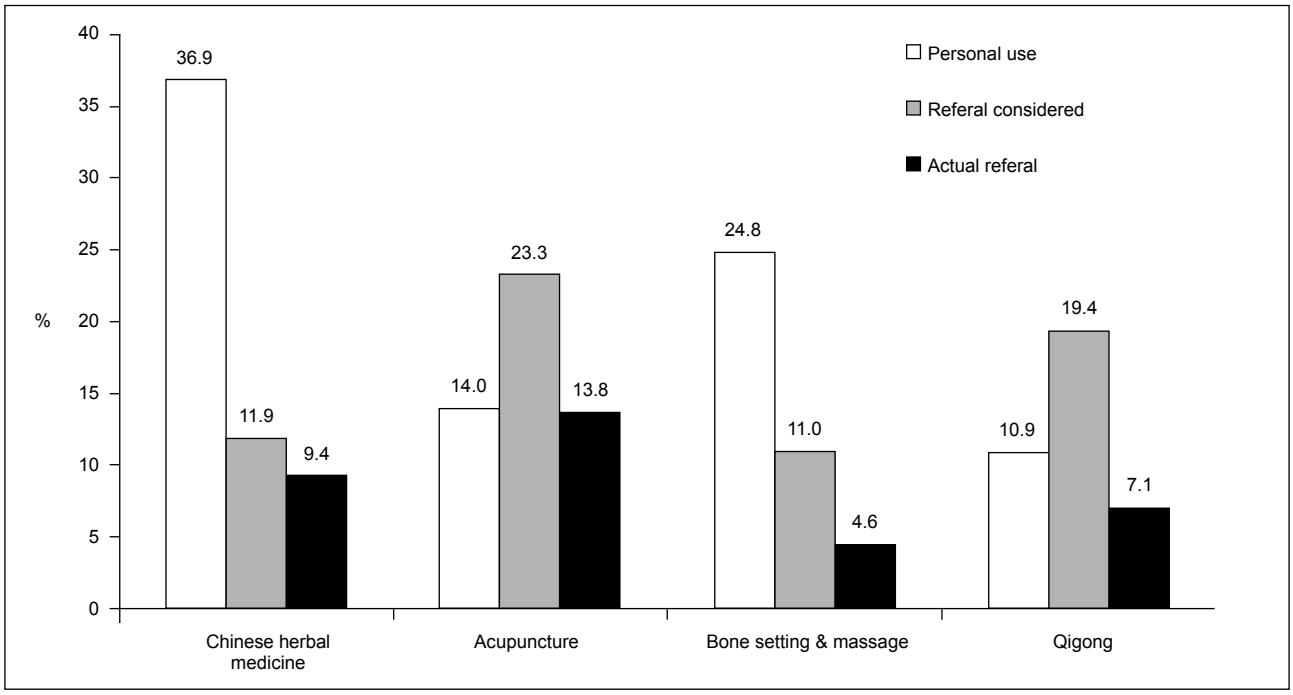

Fig. Western medicine doctors' attitude toward traditional Chinese medicine

associated with a favourable attitude toward integration of TCM and AM. This indicates the potential benefits of future TCM educational strategies for western medicine doctors. The western medicine doctors had concerns about the lack of, and inaccessibility of, the clinical evidence for TCM. Patients' choice of TCM seemed to be of secondary importance. Awareness among western medicine doctors about the TCM regulatory system should be raised. Policy makers may consider establishing an inter-professional collaboration platform to improve coordination between the two systems.

Evidence-based practice over patients' choice

The lack of clinical evidence for TCM hinders referrals to it, especially in the management of conditions for which AM has little to offer. In Hong Kong, TCM as an adjunct to AM is a long-established practice.[1] Western medicine doctors may be inclined to collaborate with TCM practitioners once evidence and patient choice are concordant. However, their awareness of the availability of systematic reviews and randomised controlled trials on the efficacy and safety of TCM remains unknown. The tension between patients' choice and lack of high-quality TCM evidence suggests that allopathic physicians prefer a conservative approach and put more weight on evidence than on patient demand.

In the United Kingdom, randomised controlled trials and evidence of safety of complementary and alternative medicine are considered to be very important in the clinical decision making process among general practitioners and directors of public health, whereas patient demand is viewed as less important.[2] The relevance of scientific evidence in allocation of resources within Primary Care Trusts in the United Kingdom is reflected by their budgetary and clinical integration policies.[3] Based on these observations, in Hong Kong, the lack of, or inaccessibility of, TCM evidence may partly explain the low TCM referral rate among western medicine doctors. In addition, the availability of scientific evidence may also explain the relatively higher referral rates for acupuncture (as oppose to herbal medicine) in Hong Kong.[4]

Traditional Chinese medicine education strategies for allopathic physicians

In this study, knowledge of TCM, prior education, and physicians' self use of TCM were positively related to consideration of referrals and actual referrals. Western medicine doctors were unwilling to refer to TCM until they were properly trained in TCM. They expressed a preference for initiatives to promote integration led by those trained with both western medicine and TCM. This resembles findings from the west and east.[5,6] Although the interaction between TCM knowledge acquisition and self use remained unclear, positive results from a randomised controlled trial testing the effect of complementary and alternative medicine experiential learning for western medicine doctors shed light on their potential synergistic effect. Thus an experiential component could be a critical element in the design of successful TCM education for western medicine doctors in Hong Kong.

In this study, younger physicians (<31 years old) were less likely to refer to TCM. This is consistent with finding that Hong Kong medical students become more negative

toward TCM as they progress from pre-clinical to clinical years.[7] Medical students consider that there is a need to enhance TCM education in the undergraduate curriculum so that future western medicine doctors become competent to serve a population that tends to be pluralistic in choosing health care.[8] In the same vein, middle-aged (41-50 years old) physicians' reluctance to refer to TCM could be due to a lack of TCM education during the colonial period. Continuing professional education about TCM may be a solution to fill this knowledge gap, but how it should be tailored warrants further investigation.

The need for establishing an inter-professional collaboration platform

Structural and organisational constraints within the health system can be an obstacle to integration of TCM and AM. Despite governmental support for developing TCM and the establishment of a statutory regulation system for TCM practitioners, some western medicine doctors remained sceptical about the competency of TCM practitioners or were unaware of relevant regulatory systems. Our study suggested that regulation alone would not lead to inter-professional collaboration between TCM and western medicine. Cross-disciplinary familiarisation and shared education between western medicine and TCM students may foster mutual trust. Nonetheless, mutual trust may not be sufficient, and development of a comprehensive inter-professional collaboration platform is a longer-term solution. Such an initiative may improve the quality of continuity and coordination in primary care. Nonetheless, development of such a platform requires complex, local-context, relevant policy solutions.[9] For Hong Kong, development of such a platform may be strategically linked to the private-public partnership initiative, and the wider health care organisation and financing reform agenda of the government. Nevertheless, proposals to deal with these issues were absent in the two recent health care reform consultative documents in Hong Kong.[10,11]

Implications

For health care policy makers, the lack of evidence for the efficacy and safety of TCM is the major obstacle to collaboration between western medicine and TCM practitioners. Long-term policy initiatives to foster collaboration between the two professions may involve collating, appraising, and disseminating existing clinical evidence on TCM on a dedicated platform targeting western medicine doctors.

For health services managers, inter-professional collaboration platforms can be developed to promote awareness of existing evidence for TCM.

For TCM regulator (Chinese Medicine Council of Hong Kong), awareness of the existing TCM regulatory system should be raised among allopathic physicians. Partnerships with the Medical Council of Hong Kong in the development of inter-professional collaboration platform would facilitate a greater understanding between these modalities.

For TCM and western medicine educators, strategic partnerships between TCM and western medicine schools could be established to design curricula and to promote greater understanding. Early contact and professional familiarisation between TCM and western medicine students should be facilitated, so as to enable informed patient choice between different medical modalities. The possibility of establishing special programmes for developing dual-trained allopathic physicians and TCM practitioners should be explored.

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Auriculotherapy in relieving symptoms of constipation and improving quality of life for the elderly: a pilot project

Key Messages

1. Auriculotherapy was effective in relieving the symptoms of constipation and improving quality of life for elderly people.
2. Auriculotherapy had a significant time effect in relieving symptoms of constipation, a greater reduction in scores for symptoms of constipation and quality of life, and an increased number of bowel movements per week, compared with controls.
3. The methodology of this pilot project was appropriate for future studies on the effects of auriculotherapy for managing constipation in elderly people.

Introduction

Constipation is a common health problem among the elderly in residential care homes (RCHs). It impairs the general health and quality of life (QoL)[1] and is usually managed by laxatives and lifestyle modifications. Auriculotherapy (AT) is a traditional Chinese medicine treatment to alleviate pathological conditions in different parts of the body by stimulating the external surface of the auricle.[2] It has been effective in managing constipation, but major methodological flaws have been identified. Although no conclusion can be drawn regarding its effectiveness, AT appears to be an alternative treatment for constipation. This pilot project aimed to evaluate the effects of AT in relieving the symptoms of constipation and improving QoL for the elderly, and to test the feasibility and appropriateness of the study methodology.

Methods

This single-blind, randomised controlled study was conducted from September 2008 to August 2009. Ethical approval was granted by the Research and Ethics Committee of The Open University of Hong Kong. Permission was obtained from the superintendents of the participating RCHs. A total of 104 elderly persons with constipation from local RCHs were screened for eligibility. Those who (1) were aged >65 years, (2) met the Rome III diagnostic criteria for constipation,[3] (3) were cognitively competent with a score of ≥6 in the Abbreviated Mental Test, and (4) were able to communicate in Cantonese were included. Those who (1) had local lesions in or infection of the ears, or absence of ear(s), (2) had had previous AT within one year, (3) were free from major physical and psychiatric diseases, (4) were being treated with regular laxatives, (5) were undertaking a current bowel training programme, and (6) had an implanted electrical device in the body were excluded. After screening, 39 elderly persons were randomly assigned to receive AT for 3 weeks in an experimental (n=21) or a placebo (n=18) group. The former group used magnetic pellets with a magnetic flux density of ~200 Gauss, whereas the latter group used Semen Vaccariae. Both the participants and the research nurse were blinded to group assignments.

According to the perspective of Chinese medicine, participants were first assessed to be in an 'excess' or 'deficiency' syndrome with regard to constipation. Seven auricular acupoints for the large intestine, rectum, *San Jiao*, spleen, lung, sympathesis, and subcortex were stimulated, because of their positive effect in relieving the symptoms of constipation.[4] Both ears were treated alternately, with one ear taped each time (every 3-4 days), in order to avoid exerting persistent pressure on only one ear. The magnetic pellets and Semen Vaccariae were of comparable diameter, and the translucent auricular plasters were of the same size, colour, texture, and appearance.

During intervention, participants were instructed not to exert manual pressure to the taped acupoints, and to maintain their normal dietary habits and level of physical activity. The participants were also instructed to discontinue taking laxatives 3 days prior to the start of and throughout the intervention, failing which

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they would be withdrawn from the study. The possible side effects of AT were explained. The participants were closely monitored for undesirable effects.

The outcome variables were symptoms of constipation and QoL, which were measured using the Patient Assessment of Constipation – Symptom Questionnaire (PAC-SYM)[5] and the Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL),[6] respectively. The potential confounding variables (physical activity, dietary intake of fruits and vegetables) were monitored using the Physical Activity Questionnaire (PAQ). The drugs taken during the study period were reviewed. Outcomes were collected by face-to-face interviews on day 0 (baseline), day 10 (midway of intervention), day 21 (end of intervention), and then at the 1-month follow-up. The frequency of bowel movements and stool consistency were recorded daily 2 weeks before the intervention until after completion of the intervention.

Results

Of the 39 participants, 17 in the experimental group and 13 in the placebo group completed the intervention. The dropout rate was 23.1%; the reasons were perceptions of no benefit (n=4) and taking of laxatives (n=5).

Baseline characteristics of participants

The participants were of advanced age (mean age, 81; standard deviation [SD], 7.22 years) and mostly females (83.3%). Nearly 80% of them had co-morbidities and in receipt of regular medication. The mean duration of constipation was 4.9 (SD, 7.4) years. All participants were diagnosed to have the 'deficiency syndrome' of constipation. There were no significant differences in baseline characteristics and outcome variables in the two groups.

Effects of auriculotherapy in constipation

The effects of AT were evaluated using the mixed between-within subject analysis of variance. A modified intention-to-treat approach was adopted in which participants who had withdrawn from the study were not excluded so long as they had commenced the intervention. The missing data for the dropouts were replaced by the last observation. These dropouts were expected to be free of further benefit from the intervention.

For effects of the intervention on symptoms of constipation, there were no significant group effects ($F(1,37)=0.14$, $P=0.72$, $\eta_p^2=0.004$) and interaction effects ($F(3,111)=0.28$, $P=0.84$, $\eta_p^2=0.007$), but time effects ($F(3,111)=7.24$, $P=0.000$, $\eta_p^2=0.164$) were significant. Regarding QoL, there were also no significant group effects ($F(1,37)=0.04$, $P=0.85$, $\eta_p^2=0.001$) and interaction effects ($F(3,111)=0.51$, $P=0.68$, $\eta_p^2=0.014$), but time effects [$F(3,111)=5.72$, $P=0.00$, $\eta_p^2=0.134$] were significant.

According to the repeated measures analysis of variance, for PAC-SYM, there were significant time effects in the experimental group (Wilks' Lambda=0.43, $F(3,18)=7.83$, $P=0.001$, $\eta_p^2=0.57$) but not in the placebo group (Wilks' Lambda=0.77, $F(3,15)=1.47$, $P=0.264$, $\eta_p^2=0.227$). The differences between day 0 and day 21, and between day 0 and the 1-month follow-up were significant ($P<0.05$). For PAC-QOL, there were significant time effects in the placebo group (Wilks' Lambda=0.60, $F(3,15)=7.83$, $P=0.049$, $\eta_p^2=0.398$) but not in the experimental group (Wilks' Lambda=0.69, $F(3,18)=2.67$, $P=0.079$, $\eta_p^2=0.307$); only the difference between day 0 and the 1-month follow-up was significant ($P<0.05$). The potential confounding variables (physical activity and dietary intake of fruits and vegetables) had no mediating effects on outcome variables.

Although the between-group differences in symptoms of constipation and QoL were not significant, within-group differences (between baseline and post-tests) in terms of mean scores were significant (Tables 1 and 2). According to the mean scores of PAC-SYM and PAC-QOL in the two groups across time, the experimental group had more improvement than the placebo group in symptoms of constipation and QoL (Fig).

As there were no significant changes in drug history during the study period, a change of drug administration was not considered as a cofounder in interpreting the results. According to the daily bowel records of participants, the number of bowel movement per week increased by a mean of 0.33 (SD, 1.17) in the experimental group but decreased

Table 1. Assessment of Constipation – Symptom Questionnaire (PAC-SYM) scores of the 39 patients during the study period

Time	Mean±SD PAC-SYM scores							
	Total		Abdominal symptoms		Rectal symptoms		Stool symptoms	
	Experimental group	Placebo group	Experimental group	Placebo group	Experimental group	Placebo group	Experimental group	Placebo group
Baseline (day 0)	6.43±4.23	6.72±4.69	0.71±1.10	0.89±1.41	0.48±0.68	0.61±0.98	5.24±3.60	5.22±3.19
Midway of auriculotherapy (day 10)	5.10±4.36	5.06±4.58	0.48±0.98	0.83±1.47	0.29±0.64	0.22±0.65	4.33±3.44	4.00±3.31
End of auriculotherapy (day 21)	4.19±4.46	4.78±4.53	0.48±0.98	0.72±1.45	0.33±0.66	0.39±0.92	3.38±3.47	3.67±3.34
1-month follow-up	3.67±3.89	4.61±4.15	0.57±1.25	0.72±1.45	0.33±0.66	0.22±0.55	2.76±2.74	3.67±2.77
Day 10 – day 0	-1.33±3.32	-1.67±3.99	-0.24±0.62	-0.06±0.94	-0.19±0.40	-0.391±0.85	-0.90±3.55	-1.22±3.08
Day 21 – day 10	-0.90±2.95	-0.28±3.41	0.00±0.45	-0.11±0.96	0.05±0.22	0.17±0.51	-0.95±2.94	-0.33±2.81
1-month follow-up – day 21	-0.52±3.09	-0.17±3.68	0.10±0.94	0.00±0.84	0.00±0.32	-0.17±0.71	-0.62±2.77	0.00±3.36

Table 2. Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL) scores of the 39 patients during the study period

Time	Mean±SD PAC-QOL scores									
	Total		Physical discomfort		Psychosocial discomfort		Worries and concerns		Satisfaction	
	Experimental group	Placebo group	Experimental group	Placebo group	Experimental group	Placebo group	Experimental group	Placebo group	Experimental group	Placebo group
Baseline (day 0)	20.14±7.87	19.22±10.91	2.00±1.90	1.83±2.36	1.00±1.70	0.94±2.07	5.86±3.02	4.78±5.17	11.29±4.24	11.67±2.83
Midway of auriculotherapy (day 10)	17.19±8.91	17.56±14.59	1.33±1.98	1.44±2.53	0.19±0.51	1.06±1.73	5.48±3.96	5.39±7.85	10.19±4.71	9.67±4.78
End of auriculotherapy (day 21)	14.52±8.09	16.50±10.73	1.14±1.90	1.00±2.35	0.33±0.66	0.50±1.54	4.48±3.31	5.28±6.02	8.57±4.12	9.72±3.06
1-month follow-up	14.95±8.18	15.83±11.74	1.29±2.08	1.61±2.38	0.33±0.91	0.44±1.46	3.95±3.37	4.11±5.14	9.38±4.34	9.67±4.27
Day 10 – day 0	-2.95±7.90	-1.67±7.77	-0.67±1.62	-0.39±1.24	-0.81±1.44	0.11±1.68	-0.38±3.07	0.61±4.63	-1.10±5.57	-2.00±4.60
Day 21 – day 10	-2.67±5.48	-1.06±8.56	-0.19±1.12	-0.44±1.10	0.14±0.79	-0.56±1.50	-1.00±1.97	-0.11±3.31	-1.62±4.02	0.06±4.26
1-month follow-up – day 21	0.43±6.65	-0.67±5.22	0.14±1.39	0.61±1.04	0.00±0.95	-0.06±0.87	-0.53±2.14	-1.17±2.57	0.81±3.97	-0.06±3.89

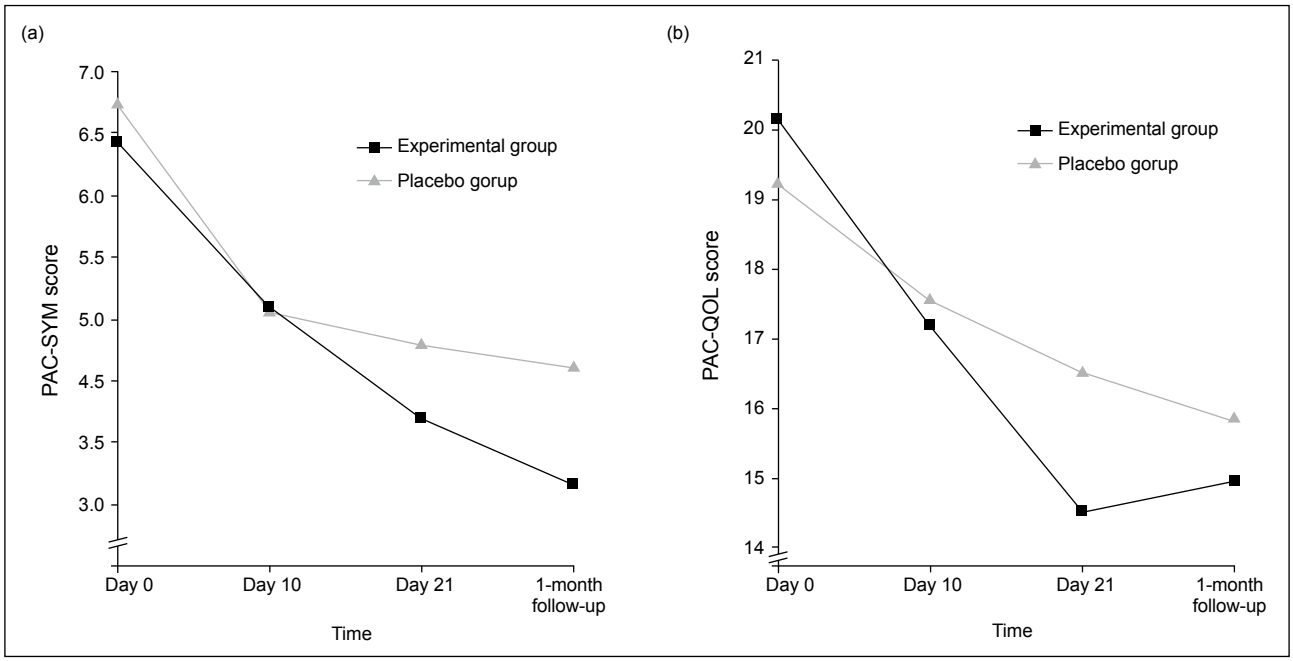

Fig. (a) Patient Assessment of Constipation – Symptom Questionnaire (PAC-SYM) and (b) Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL) mean scores across time for the experimental and placebo groups

by a mean of 0.4 (SD, 1.07) in the placebo group, whereas six and seven participants in the respective groups reported softer stools after the intervention. In addition, two and five participants in the respective groups reported mild, tolerable, and short-term itchiness of the ears after the intervention.

Discussion

Constipation is more common among females.[7] In this study, young older adults were under-represented; most participants were old older adults (mean age, 81 years). Nearly 80% of the participants had co-morbidities and in receipt of regular medication. Polypharmacy is a major factor contributing to constipation in elderly people.[7] All our participants were diagnosed to have the 'deficiency syndrome' of constipation. Thus, generalisation of results may be limited to old older adults with the 'deficiency syndrome' of constipation.

The non-significant group effects may be due to the small sample size. Only the experimental group had significant time effects in symptoms of constipation, whereas only the placebo group had significant time effects in QoL. According to the PAC-SYM and PAC-QOL scores, the experimental group had more improvement than the placebo group in symptoms of constipation and QoL. The additional magnetic effects may contribute to the better therapeutic effect in the experimental group.

The significant time effects in symptoms of constipation

in the experimental group indicated that the 21-day intervention period was sufficient to detect a significant time effect.

Many potential participants were excluded because they were unable to communicate in Cantonese or receiving laxatives. Thus, a longer recruitment period or a multi-centre trial may be necessary for future studies. In fact, many elderly people in RCHs had constipation despite taking laxatives. Omitting this particular exclusion criterion (laxatives taking) could have made the samples more representative. As the beneficial effects of AT in managing constipation were inconclusive in previous studies, it is not yet appropriate to withhold the usual care when a new intervention has not been proved to be more beneficial.[8] Therefore, future studies should shift their focus to investigating the complementary effects of AT in managing constipation, which would be more reality-oriented. To prevent the dropout of participants, clear instructions should be given to the participants to increase their compliance.

In this study, there was no control group that received only usual care. The pressure effects from the taped objects and the maturation effect of the disease were not cancelled out. Therefore, inclusion of a usual care group is recommended to address this shortcoming and improve the empirical evidence. Blinding of such intervention could be done by administering the AT but without taped objects on the plasters.

As the practitioner who conducted the intervention was not blinded, the interaction between the practitioner and participants might have affected the results reported by the participants (although they were blinded to their treatment assignment).

Conclusions

There were significant effects of AT across time, but not between groups. The experimental group had greater reduction in PAC-SYM and PAC-QOL scores and an increased number of bowel movement per week. The methodology of this study in terms of randomisation, intervention, data collection process, and instruments was appropriate for future studies on the effects of AT in managing constipation in elderly people.

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Interaction between oseltamivir and herbal medicines used for treating avian influenza

Key Messages

1. In vitro studies were used to investigate the effect of various herbal medicines on the activity of drug-metabolising enzymes, whereas a PBPK model was used to study the interaction between oseltamivir (Tamiflu) and herbal medicines.
2. The biochemical and molecular biological basis of drug-herb interactions were studied by determining the effect of herbal extracts on cellular redox states and gene expression profiles.
3. Herbal extracts may affect oseltamivir treatment in rats. The drug-herb interaction may be related either to the metabolism or uptake of the drug by different tissues. Further studies are necessary to determine whether such interactions also occur in humans.

Introduction

Oseltamivir (Tamiflu) is a cyclopentane neuraminidase inhibitor for treatment of influenza viruses, including the H5N1 avian influenza strain encountered in Hong Kong.[1,2] Oseltamivir is a safe drug with wide margin of safety. It is tolerable in single doses of up to 1000 mg (14 mg/kg/day) for a 70 kg adult and may be given as 500 mg twice daily. Commonly it is administered as the prodrug, oseltamivir phosphate (OP). It is then biotransformed into its active metabolites oseltamivir carboxylate (OC) through ester hydrolysis. Recent reports have shown a strain of Tamiflu-resistant virus.[3-5] In view of this, Chinese herbal medicine was added for combating avian influenza. Herbal medicine that contains *Flos Lonicerae* (金銀花, JYH) and *Folium Perillae* (紫蘇葉, ZSY) and over-the-counter preparation such as *Radix isatidis* (板藍根, BLG) are commonly taken by the public to combat influenza symptoms. The present study investigated a possible interaction between oseltamivir and these herbal extracts and assessed the safety of their combined use.

Methods

This study was conducted from December 2006 to February 2009 using both in vitro (n=6) and in vivo (n=4) samples. It was divided into three parts. In the first part, in vitro studies were used to investigate the effect of various herbal medicines on

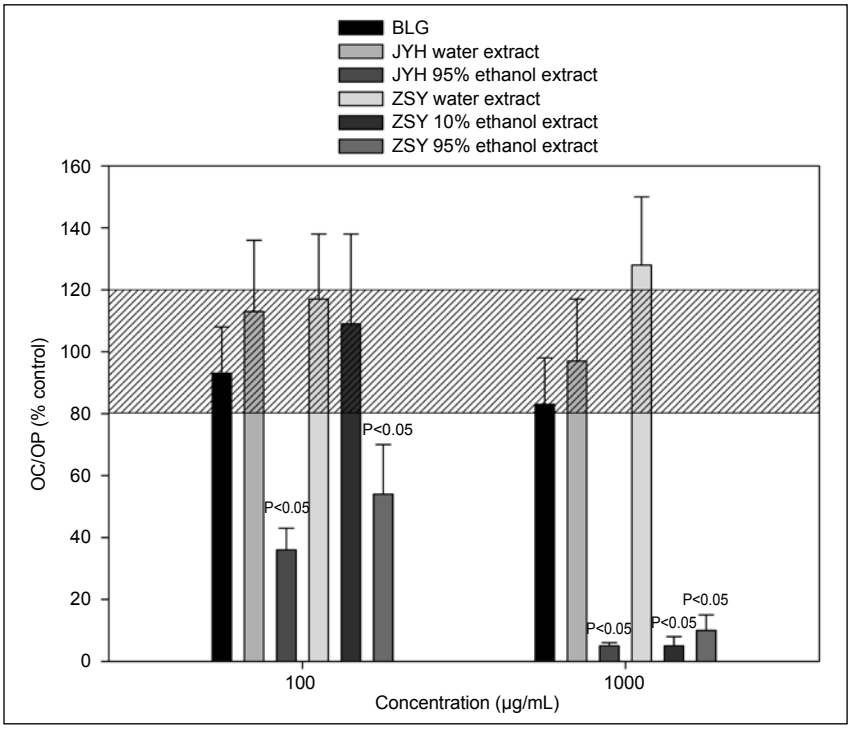

Fig 1. Suppression of plasma carboxylesterase activity on converting oseltamivir phosphate (OP) to oseltamivir carboxylate (OC) following addition of different concentrations (100 and 1000 μg/mL) of herbs
Each value represents the means and SD of four rats. Grey area indicates a ±20% variation range in control value of 100%.

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the activity of OP-metabolising enzymes, which include the carboxylesterase (CE) that activates OP to OC, and CYP450 isoenzymes 1A1, 2C9, 2C19, and 3A4 that metabolise many western drugs. In the second part, a PBPK model was derived to measure tissue distribution of OP and OC and to study any possible interaction between OP and the herbal medicines. In the third part, the biochemical and molecular biological basis of drug-herb interactions was investigated by determining the effect of several herbal extracts (JSY and JYH) on cellular redox states and gene expression profiles. Instruments used included spectrofluorometers, cell culture facilities, high-pressure liquid chromatography, LC-MS-MS, and PCR-microarray analysers.

Results

At high concentration (1 mg/mL), BLG exerted only a slight inhibition on carboxylesterase, whereas JYH and ZSY could significantly suppress the activity of this enzyme (Fig 1). Therefore, BLG was selected for the subsequent animal study.

The kinetic of distribution of OP and OC in various rat tissues was determined by measuring the levels of OP and OC. Most OP and OC were detected in the liver and kidney, with very small amount in the plasma. The OP and OC levels peaked at 2 h following administration. At 6 hr, OP

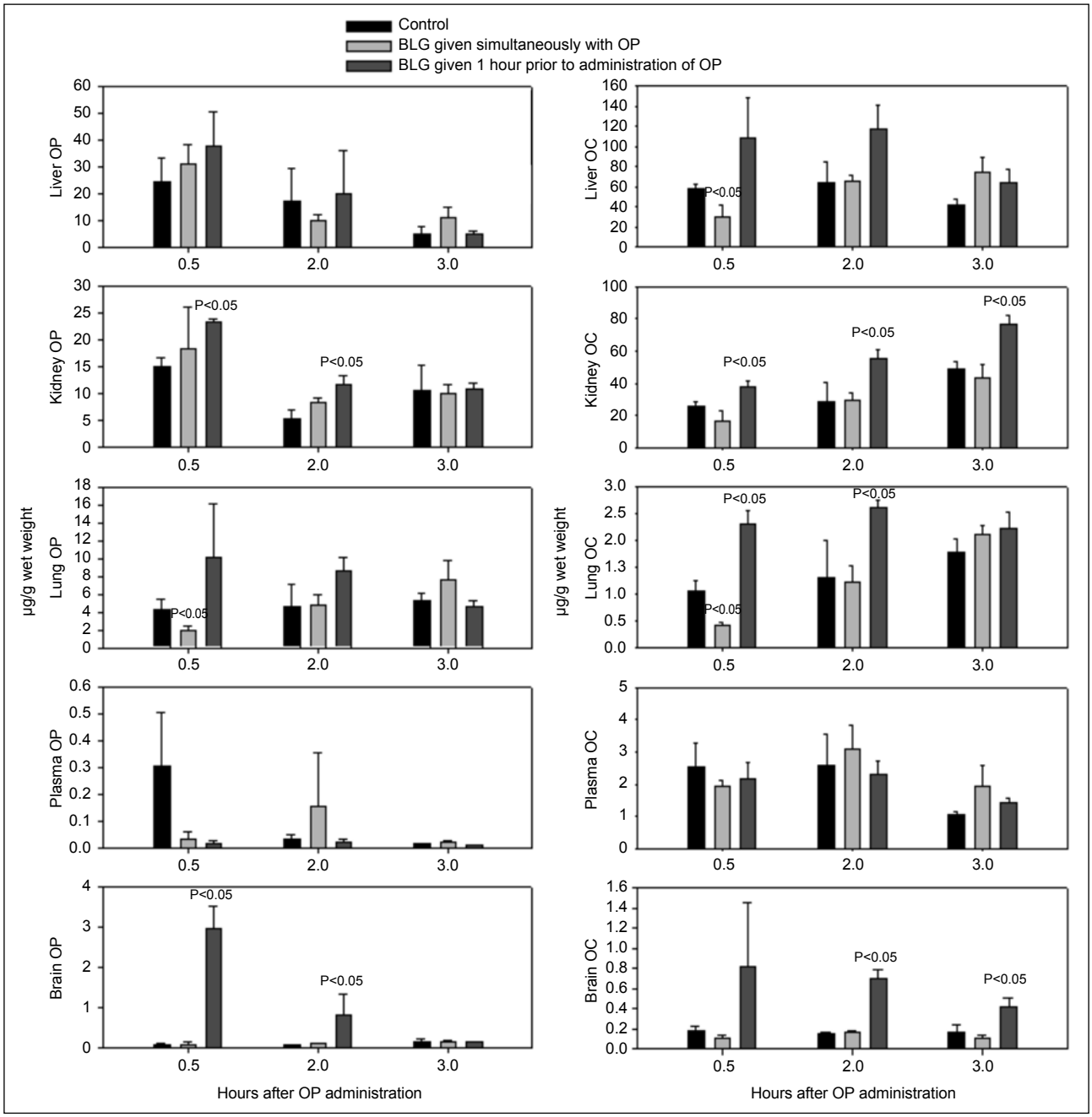

Fig 2. Levels of oseltamivir phosphate (OP) and oseltamivir carboxylate (OC) in rat liver, kidney, lung, plasma, and brain at 0.5, 2, and 3 hours following exposure of OP (50 mg/kg) with *Radix isatidis* (板藍根, BLG) [0.4 g/kg].
Each value represents the mean and SD of three rats.

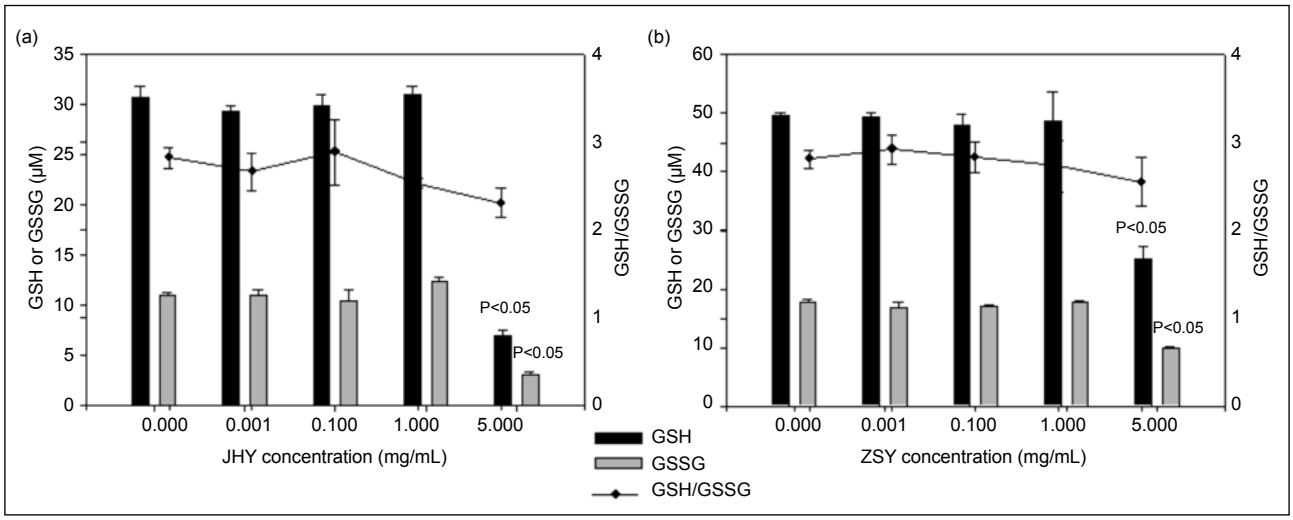

Fig 3. Levels of GSH, GSSG, and GSH/GSSG ratio in the HepG2 cells following exposure to the water extract of (a) *Flos Lonicerae* (金銀花, JYH) or (b) *Folium Perillae* (紫蘇葉, ZSY) for 24 hours.

and OC levels had decreased. These results fitted with the PBPK model constructed in our laboratory. In the presence of BLG, changes were detected in different tissues, with the lung being most affected. When BLG was administered simultaneously, the OC level was significantly reduced during the initial 3 hr. However, if BLG was administered 1 hr prior to oseltamivir administration, the lung OC content was significantly increased. According to the PBPK model, the change may be modified by altering the kinetics of uptake. Thus, BLG may affect the uptake rates of OP and OC in tissues such as the lung. Similar changes were also observed in the brain and kidney but not reflected in the plasma (Fig 2). The results were tested in a PBPK model using a simulation program AcslXtreme OptStat (AEgis Simulation). By fitting the tissue data on the PBPK model, interference with the uptake of OP may be the basic action of BLG.

Although the kinetic interaction effects of JYH and ZSY with oseltamivir was not investigated, the action of these extracts in cultured cells model was studied. In human HepG2 cells, the water extracts of both JYH and ZSY could cause cell death only at very high concentrations (>1 mg/mL for 24 h). At such concentrations, JYH was able to cause depletion of glutathione (Fig 3) and suppress the activity of cytochrome P450 isoenzymes 1A1, 2C9, 2C19, and 3A4.

Discussion

In the rat model, simultaneous administration of BLG and OP orally may reduce the level of OC in lung tissues and thus reduce antiviral activity. Pre-treatment with BLG may help improve oseltamivir uptake in the lung during the initial 3 hr. Nevertheless, this may also increase OC levels in the brain and kidney, but these changes were not reflected in the plasma. High concentrations of water extracts of JYH and ZSY may affect the activity of several CYP450 isoenzymes. This suggested that they should not be taken simultaneously with drugs that are metabolised by these enzymes (eg Panadol).

Herbal extracts may affect oseltamivir treatment in rats. The action may be related either to its metabolism or to the uptake of the drug by different tissues. Further studies are necessary to determine whether such drug-herb interactions also occur in humans.

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Association of polymorphism of human leukocyte antigen alleles with development of hepatocellular carcinoma in Hong Kong Chinese

Key Messages

1. Class I and II genes on homogenous cohorts of normal population controls, healthy hepatitis B virus (HBV) carriers, and HBV-positive hepatocellular carcinoma (HCC) patients were systematically studied using high-resolution human leukocyte antigen typing.
2. Human leukocyte antigen alleles DRB3*0201 and DQB1*050201 were positively and negatively associated with HCC development among carriers, respectively. The former allele was also confirmed to be independent of the HBV genotype.
3. These findings may help stratify the risks among HBV carriers for developing HCC and among the normal population for developing carrier status, thereby enabling more refined surveillance and planning and more cost-effective health resource allocation.

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Introduction

Human leukocyte antigens (HLA) participate in the selection and establishment of antigen-specific T-cell repertoire and in subsequent activation of those T cells during initiation of immune responses. Classes I and II of HLA are responsible for CD8+ and CD4+ T-cell responses, respectively. They are highly polymorphic, which may contribute to individual variations in susceptibility to immune mediated/controlled diseases. Certain alleles are strongly associated with various infections and their related diseases.[1] In one Hong Kong study, class II alleles were not associated with hepatocellular carcinoma (HCC).[2] In another, multiple alleles were associated with the disease when comparing HCC patients and healthy controls.[3] In fact, >80% of our HCC patients are hepatitis B virus (HBV) seropositive, compared to 18% in the healthy population. This may be related to HBV infection other than HCC.[3] Both studies included HBV seropositive controls for comparisons, but the sample sizes were very limited (about 40). Low-resolution serological HLA typing was primarily used in previous studies. Each serologic HLA type consists of a number of distinct HLA alleles with different biochemical characteristics, such as affinity to antigen, in regard to immune responses to infection. The potential association of HLA with the disease may be masked by opposite effects of the HLA subtypes on disease development. Therefore, the association of HLA with HCC has not yet been critically investigated. Re-assessments of HLA association with HCC using high-resolution DNA typing and increased sample sizes of HBV carriers with and without HCC could reveal the comprehensive biological significances of HLA subtypes related to the disease.

Methods

This two-step case-control study was conducted from October 2005 to October 2007. To evaluate the host immunogenetic risks of viral-driven HCC pathogenesis, the frequencies of HBV genotypes, class I (HLA-A, -B, and -Cw) and class II (HLA-DRB and -DQB1) of HLA subtypes, and genotypes of TNFα were compared systematically between HCC patients with HBV positive and age- and sex-matched asymptomatic HBV carriers, and between the asymptomatic HBV carriers and age- and sex-matched HBV seronegative healthy controls. The first part reflected host genetic risks for developing HCC among HBV carriers, whereas the second part reflected host genetic risks for developing carrier status after HBV infection. Informed consent was obtained from each participant. Two-tailed Fisher's exact test was used, and a P value of <0.05 was considered statistically significant. The Bonferroni correction was applied for testing with multiple comparisons. P values were adjusted by multiplication by the number of comparisons for each HLA group.

Blood buffy coat samples of 100 genetically unrelated Chinese HCC patients with HBV infection (according to the World Health Organization criteria) treated at the Department of Surgery, Prince of Wales Hospital were obtained. According to the guidelines of the Hong Kong Red Cross, blood units donated by HBV carriers are routinely discarded by incineration. In addition, blood buffy coat

samples from 100 healthy HBV carriers matched for age and sex (1:1) with those of HCC patients were recruited and anonymised before further analysis. Non-Chinese and/or hepatitis C virus positive patients or carriers were excluded. Furthermore, peripheral blood samples of 1000 healthy blood donors were obtained from the Hong Kong Red Cross; 100 of these donors were matched for age and sex (1:1) with those of HBV-positive asymptomatic carriers.

DNA was extracted from the blood or blood buffy coat samples of the three groups. High-resolution sequencing-based typing (SBT) of classes I and II of HLA subtype genes was performed according to the International Histocompatibility Working Group protocols. Locus-specific PCR amplification was performed with primer sets according to these protocols, using Taq polymerase (Promega) on 9700 thermal cycler (Applied Biosystems). Specific PCR products were excised from the gels after electrophoresis and purified using a gel DNA extraction kit (Qiagen). A sequencing reaction was then performed using BigDye 3.1 reagent (Applied Biosystems) and resolved on a 3130 sequencer (Applied Biosystems). The sequencing data were analysed using sequence alignment and database matching using the SBTengine software (Genome Diagnostics).

Primers and probes specific to HBV genotypes B and C were designed according to published sequences[4] using Primer Express and synthesised by Applied Biosystems. A Taqman allelic discrimination assay was performed using a 7300 real-time PCR system (Applied Biosystems). Each 25 µl PCR aliquot consisted of 2.25 µl (20 ng) DNA template, 1x Taqman genotyping assay mix consisting of primers and probes, and 1x Taqman Genotyping mastermix. They were all added into Taqman 96-well reaction plates and sealed with adhesive covers. Taqman cycling consisted of 10 min at 50ºC and 10 min at 95ºC, followed by 40 cycles at 92ºC for 15 s and 60ºC for 1 min. The PCR products were detected directly by monitoring the fluorescence intensity. Real-time Taqman analysis was used to monitor the accumulation of the fluorescence throughout the 40 cycles, which produced an amplification plot over the entire course of the reaction. Results were displayed as a Ct (threshold cycle) where the presence of the informative results was recognisable with a Ct number within a specified range and a signal strength Rn>1.

Polymorphism for the TNF gene promoter at nucleotide -308 was determined using a pre-designed Taqman genotyping assay (Applied Biosystems) specific to this site. The Taqman allelic discrimination assay was performed as described above.

Results

Allelic associations with hepatocellular carcinoma among hepatitis B virus carriers

By comparing the allelic frequencies of HBV-positive HCC patients and the healthy HBV carriers, six significant allelic associations were identified. Five of the six associations were in the class II alleles. Associations between HCC development and HBV carrier status were found with DQB1*030302 (P=0.018, odds ratio [OR]=2.262) and DRB3*0201 (P<0.001), whereas protective associations were found with DQB1*050201 (P=0.001, OR=0.390), DRB1*160201 (P=0.011, OR=0.202), DRB4*01010101 (P=0.028, OR=0.603), and the only class I allele, A*1101 (P=0.030, OR=0.075). Notably, the allelic associations of DRB3*0201 and DQB1*050201 remained significant after Bonferroni correction.

Allelic associations with hepatitis B virus carrier status in normal population

By comparing the allelic frequencies of asymptomatic HBV carriers and the seronegative normal population, nine significant allelic associations were identified. All except one were class II alleles. Susceptible associations were found with DRB3*020201 (P=0.016, OR=2.345), DRB1*050201 (P=0.002, OR=2.333), DQB1*020101 (P=0.022, OR=2.455), DRB1*030101 (P=0.019, OR=4.565), whereas protective associations were found with DQB1*030302 (P=0.002, OR=0.369), DRB3*030101 (P=0.016, OR=0.427), DQB1*0401 (P=0.027, OR=0.271), DRB1*150101 (P<0.001, OR=0.157), and the only class I allele, A*0201 (P=0.003, OR=0.292). Among these, only DRB1*150101 remained significant after Bonferroni correction. Although DQB1*030302 and DQB1*050201 were significantly associated with the development of both the HBV carrier status and HCC, they demonstrated opposite trends for this development.

Association of hepatitis B virus genotypes with the development of hepatocellular carcinoma

The frequencies of HBV genotype B and C were found to be the same among the HBV carriers (both at 50%), but there were slightly higher frequencies of genotype C than B among HBV-positive HCC patients (56% vs 44%, P>0.05).

TNFα -308 polymorphism

Most (88%) of the normal population carried only the TNF1 genotype, whereas 11% harboured the TNF1+2 and 1% the TNF2 genotype. There was a significant increase in the frequency of carriage of TNF2 (TNF1+2 and TNF2) among both the HBV carriers (20%, P=0.176) and HBV-positive HCC patients (18%, P=0.857), when compared to the 12% carriage in the normal population. The frequencies were similar (20% vs 18%, P=0.032) in the HBV carriers and HCC patients, suggesting that the increase in frequency of TNF2 carriage was mainly due to the presence of HBV independent of HCC.

Discussion

The two-step approach mimicked the stepwise development of viral carcinogenesis of HCC induced by HBV in Hong Kong Chinese. Many of the previous HLA association

studies were based on relatively low resolution of HLA typing and focused on the outcomes of HBV infections such as viral clearance/persistence and immune responsiveness/non-responsiveness toward HBV vaccination. Studies of viral carcinogenesis are limited by small sample sizes and examination on selective HLA genes only. Few studies assess the interaction between host immunogenetics and viral genotypes. Inconsistencies of observation are attributed to ethnic diversity, variation in the study design, methodology, and the complex nature of immune-regulatory mechanisms. Each serological HLA group consists of a high diversity of different allelic members with very different biochemical characteristics that may confer even opposite immunological properties. Thus, it would not be useful to compare the HLA association findings based on low-resolution serological HLA typing across ethnic groups. Different ethnic groups may have different allelic profiles or HLA structures. This study could clearly delineate which allelic subtypes were involved in the associations.

In this study, most significant allelic associations were found with the class II HLA genes. We observed a significant susceptible association of DRB3*0201 and a significant protective association of DQB1*050201 with the development to HCC in the healthy carriers. Both of these remained significant after Bonferroni correction. Of special interest was the observations on DQB1*050201, where the association with development of carrier status and further change to HCC were in opposite direction. This indicated that although DQB1*050201 was a susceptible marker for HBV carrier status, it conferred resistance to the development of HCC from the carrier state. Similarly, DQB1*030302 showed positive association with HCC but negative association with carrier status. This implied that people harbouring DQB1*030302 may be less likely to develop to the carrier status, but once the carrier status is established, they are more susceptible to further development of HCC. These observations suggested that there may be differential involvements of HLA with HBV chronic infection and the further development to HCC. Given the high resolution on the HLA typing, all the observations regarding association with HCC development in HBV carriers are novel. A*1101 has been found to associate with viral clearance in African Americans and Caucasians. Our finding indicating a protective effect of A*1101 is in line with this observation.

Among the nine significant associations found for the development to the HBV carrier status, only that of DRB1*150101 remained significant after the Bonferroni correction. This is consistent with most previous observations, where DRB1*15 or DRB1*1501/1502 was negatively related to the persistence of chronic HBV infection and liver cirrhosis in the Chinese.[5] However, this is in contrast to one study in Hong Kong, which observed that DRB1*1501 was more common with HCC.[3] In our study, DRB1*150101 was negatively related to development to HBV carrier status but not to the further development of HCC. The findings of susceptible association of DQB1*0201(01) with development to carriers is concordant with other studies.[6] By differentiating the homogeneous cohort of HBV carriers at the healthy, asymptomatic stage from HBV-positive HCC patients, our study delineated and defined the involvements related to HBV infection and to HCC more precisely. It could be concluded that two different sets of HLA genes were involved with HBV infection and the further development of HCC. When the same alleles were involved, they might have quite opposite effects.

The frequencies of the HBV genotypes B and C were similar as reported previously. By including healthy HBV carriers, our study refined the interpretation of involvement of TNF2, which was positively associated with HCC independent of HBV or hepatitis C virus infection in 74 HCC patients in a Taiwan study. This was in contrast to our finding of no significant difference between the HBV carriers and the HCC group (20% vs 18%). Nonetheless, there was a trend of association of TNF2 carriage with HBV carrier status. Thus, in the Taiwan study the association of TNF2 with HCC may be related to the presence of chronic hepatitis viral infection.

Conclusions

High-resolution HLA data are important in association studies for risk stratification of chronic HBV infection and further HCC development. Allelic subtypes might have quite opposite effects on disease developments, and there may be differential involvement of HLA alleles in association with the development to carrier status and HCC. Our two-stage design systematically addressed the specific involvements at different stages. DRB3*0201 and DQB1*050201 were significant alleles that were positively and negatively associated with HCC development among carriers, respectively. The former was also confirmed to be independent of the HBV genotype. DRB1*1501 (01) was a protective allele for development to HBV carrier status in the normal population. These findings enabled risk stratification for HCC development among HBV carriers. Whether HLA genotypes participate functionally in this HBV-driven carcinogenesis or they are markers of some linked disease related genes within the major histocompatibility complex region remains an open issue for further studies.

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Extra-high dose hepatitis B vaccination for peritoneal dialysis patients: a randomised controlled trial

Key Messages

1. The response rate to recombinant hepatitis B vaccine was suboptimal (70.1%) in the peritoneal dialysis population.
2. We investigated whether a three-dose regimen of extra-high dose (80 μg) of Engerix-B would achieve a higher rate of primary seroconversion and more persistent seroprotection in peritoneal dialysis patients, compared with the conventional 40-μg dose.
3. The rates of seroconversion (hepatitis B surface antibody level of ≥10 IU/L 3 months after treatment) were not significantly different between the two regimens.
4. The normalised protein nitrogen appearance was the only predictor for the development of primary seroconversion and persistent seroprotection.
5. Although the extra-high-dose regimen had no significant clinical benefit, improved protein intake may improve the immune response to hepatitis B vaccine in peritoneal dialysis patients.

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Introduction

Viral hepatitis B infection is a major health hazard to end-stage renal disease patients on dialysis. The direct costs of hepatitis B infection and its long-term impact on morbidity and mortality are substantial in such patients. In patients on dialysis, the traditional intramuscular recombinant vaccine (40 μg Engerix-B at months 0, 1, and 6) attains a seroconversion rate of 44 to 76%.

To improve the immunogenicity (seroconversion and seroprotection rates of hepatitis antibody levels) of intramuscular Engerix-B recombinant hepatitis B virus vaccine, various dosages of the vaccine have been compared,[1] but the response rates did not differ significantly. Using a three-dose regimen of 80 μg Engerix-B, there was an absolute risk reduction of 18% for losing the antibody response. Compared with historical controls, this extra-high dose would lead to one extra end-stage renal disease subject with persistent seroprotection (antibody to hepatitis B surface [anti-HBs] level of ≥10 IU/L at one year) for every 5.6 (95% confidence interval [CI], 5.4-5.8) patients treated.[1] The extra-high dose also showed similar benefits in chronic liver disease patients without adverse events.[2] We therefore compared the conventional dose (40 μg) with extra-high dose (80 μg) Engerix-B vaccine in peritoneal dialysis patients in terms of primary seroconversion and long-term seroprotection.

Patients and methods

This multi-centre, randomised, non-blinded clinical trial was conducted from May 2005 to May 2009 at three dialysis units. Written informed consent was obtained from each patient. A total of 109 end-stage renal disease patients (mean age, 60 years) on peritoneal dialysis who were serologically negative for hepatitis B surface antigen and antibody to hepatitis core antigen without previous hepatitis B vaccination were included. Those with active malignancy, alcoholic liver disease, chronic hepatitis C and/or human immunodeficiency virus infection were excluded, as were those expected to survive <6 months, refusing vaccination, or in receipt of immunosuppressive medications.

Patients were randomly assigned to receive the conventional dose (40 μg) or extra-high dose (80 μg) Engerix-B administered intramuscularly into the deltoid muscle at 0, 1, and 6 months. A single booster dose (40 μg) was given to patients who had a negative antibody response 3 months after treatment.

Medications were recorded at the start of the vaccination. The modified Charlson's Comorbidity Index, which was validated in continuous ambulatory peritoneal dialysis patients, was used. Adequacy of peritoneal dialysis was determined by measuring Kt/V using the standard method. Serum albumin was measured using the bromocresol purple method, and normalised protein nitrogen appearance (nPNA) was calculated using the modified Bergstrom formula and normalised to ideal body weight. The residual glomerular filtration rate was calculated as a mean of the 24-hour urinary urea and creatinine clearance using standard methods.

Blood samples were collected 3, 6, and 12 months after completion of vaccination to measure anti-HBs using a commercial kit with enzyme immunoassay (Cobras Core Anti-HBs Quant EIA II; Roche Diagnostics GmbH, Mannheim). All laboratory personnel were blinded to the group assignment of the sera.

Seroconversion and seroprotection were defined as anti-HBs levels of ≥10 IU/L 3 and 12 months after completion of vaccination, respectively. Comparisons were made between patients with an anti-HBs level of ≥10 IU/L or <10 IU/L with regard to the diabetes mellitus rate, Charlson's Comorbidity Index, age, dialysis adequacy, nutritional status, and residual renal function after hepatitis B vaccination.

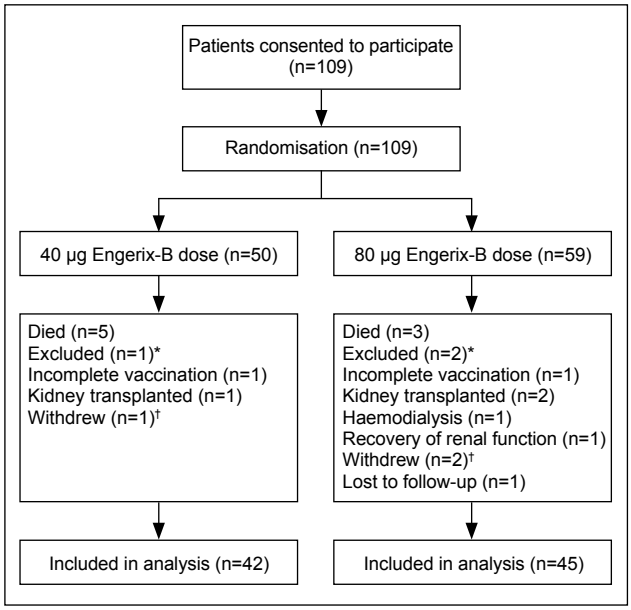

Fig. Enrolment, randomisation, and follow-up of participants
* Missing antibody to hepatitis B surface titres data
† Protocol violation because of occult hepatitis B

Results

Of the 109 patients, 87 completed the vaccination (Fig). Dropouts were related to the physical condition of the patients (death, renal recovery, transplantation, or switch to haemodialysis), protocol violation, or loss to follow-up. None of the dropouts was vaccine- or procedure-related.

Of the 87 patients, 41% were female, and 52% had diabetes mellitus. Forty-two patients received the conventional dose (40 µg) and 45 received the extra-high dose (80 µg) Engerix-B. Baseline characteristics of the two groups did not differ significantly, except for a higher percentage of human recombinant erythropoietin use in the extra-high-dose group.

The immune response was assessed by anti-HBs titre at 3 and 12 months after treatment. Overall, 70.1% of the patients achieved seroconversion; seroprotection rates decreased over time in both groups. At 3 months after treatment, 78.6% of the patients receiving the conventional dose and 62.2% of the patients receiving the extra-high dose achieved seroconversion (P=0.11). At 12 months after treatment, persistence of protective anti-HBs did not differ significantly in the two groups (45.2% vs 51.1%, respectively, P=0.67).

The geometric mean antibody titres were estimated longitudinally. The anti-HBs geometric mean titres elicited 3, 6, and 12 months after treatment did not differ significantly in the two groups (P>0.50 at all time points). For example at 12 months, the anti-HBs geometric mean titres in the respective groups were 18.1 (95% CI, 15.1-21.2) and 18.2 (95% CI, 15.2-21.1) IU/L (P=1.00). Repeated measures analysis of variance confirmed no significant difference in antibody titres between the groups throughout the study period.

Table. Univariate comparison of patients with antibody to hepatitis B surface (anti-HBs) levels of ≥10 IU/L or <10 IU/L 3 and 12 months after completion of vaccination

Parameter	3 months after completion of vaccination			12 months after completion of vaccination		
	Patients with anti-HBs levels of ≥10 IU/L	Patients with anti-HBs levels of <10 IU/L	P value	Patients with anti-HBs levels of ≥10 IU/L	Patients with anti-HBs levels of <10 IU/L	P value
No. of subjects	61	26	-	42	45	-
No. of males:females	33:28	18:8	0.24	21:21	30:15	0.13
Mean±SD patient age (years)	59.1±9.5	60.6±13.4	0.61	58.3±10.8	60.6±10.7	0.32
Median (range) duration of dialysis (years)	0.46 (0.11-1.74)	0.32 (0.09-1.75)	0.65	0.36 (0.11-1.59)	0.36 (0.11-2.08)	0.92
Mean±SD body mass index (kg/m^2)	25.4±6.3	25.7±4.1	0.80	25.5±4.1	25.5±6.2	0.99
% of patients with diabetes mellitus	47.5	61.5	0.25	47.6	55.6	0.52
Mean±SD serum albumin at baseline (g/L)	35.8±5.2	34.0±6.3	0.16	35.7±4.8	34.9±6.2	0.50
Mean±SD Charlson's Comorbdity Index	4.9±1.9	5.7±2.0	0.07	4.9±2.0	5.4±1.9	0.22
% of patients receiving human recombinant erythropoietin	16.4	15.4	1.00	21.4%	11.1%	0.25
Mean±SD haemoglobin level at baseline (g/dL)	9.0±1.4	8.9±1.8	0.82	8.9±1.5	9.0±1.5	0.71
Mean±SD residual glomerular filtration rate (mL/min/1.73 m^2)	3.02±2.37	4.17±3.46	0.28	3.23±2.50	3.38±2.95	0.84
Mean±SD total Kt/V	2.2±0.5	2.1±0.8	0.79	2.3±0.5	2.1±0.6	0.12
Mean±SD normalised protein nitrogen appearance (g/kg/day)	1.16±0.25	0.96±0.23	0.001	1.18±0.24	1.03±0.25	0.007
Mean (95% CI) anti-HBs geometric mean titres 3 months after treatment (IU/L)	-	-	-	357 (356-359)	9 (7-11)	<0.00001

Patients with higher baseline nPNA were more likely to achieve an anti-HBs level of ≥10 IU/L 3 months after treatment (Table). The mean nPNA was significantly higher in patients with seroconversion than in those without seroconversion (1.16±0.25 vs 0.96±0.23 g/kg/day, P=0.001). Patients with an nPNA at least 1 g/kg/day were four times more likely to develop seroconversion (odds ratio, 4.01; 95% CI, 1.48-11.00; P=0.006). Higher total Kt/V and residual renal function did not improve the chance of developing a seroprotective anti-HBs titre. The primary seroconversion rate did not correlate with patient age. Patients with primary seroconversion tended to have a slightly lower Charlson's Comorbidity Index (4.9±1.9 vs 5.7±2.0, P=0.07).

At 12 months after treatment, the baseline nPNA was also significantly higher in patients with a persistent seroprotective anti-HBs level of ≥10 IU/L than in those with the level <10 IU/L (1.18±0.24 vs 1.03±0.25 g/kg/day, P=0.007). Patients with and without diabetes did not differ significantly with respect to persistent seroprotective anti-HBs levels. Baseline serum albumin concentration, haemoglobin level, Charlson's Comorbidity Index, total Kt/V, and residual renal function did not influence the persistence of anti-HBs seroprotection. The geometric mean titres of anti-HBs 3 months after treatment differed significantly in patients with and without persistent seroprotection 12 months after treatment (357 vs 9 IU/L, P<0.00001, Table).

Discussion

Although beneficial effects of extra-high dose recombinant hepatitis B vaccination has been reported,[1] this study did not confirm such finding. Primary seroconversion and persistent seroprotective anti-HBs antibody titres were similar in patients receiving conventional or extra-high dose hepatitis B vaccination. By contrast, the amount of dietary protein intake, as measured by nPNA, was predictive of the response.

Increased nPNA was associated with a higher rate of primary seroconversion and maintenance of a seroprotective anti-HBs titre. Reasons for the impaired immunological response in those with protein-energy malnutrition include lower granulocyte-macrophage colony stimulating factor (GM-CSF), among other relevant cytokine responses. Data from animal and human studies indicate that protein-energy malnutrition leads to deficiency or impaired response of GM-CSF.[3] Administration of GM-CSF to end-stage renal disease patients significantly improves the hepatitis B vaccine response rate and achieves an earlier seroconversion following vaccination.[4]

One limitation of our trial related to patient selection. The mean patient age was 60 years, which was much older than the cohort in our previous study (mean age, 43 years).[1] In patients on dialysis, poor response to hepatitis B vaccine correlates with old age.[1] This is further supported by a meta-analysis of end-stage renal disease patients.[5] Therefore, the primary seroconversion rate was lower (70.1%) and long-term immunogenicity was less impressive (48.3% at one year) in this study than in the previous study. Nonetheless, our subjects were representative of the 'real-world' scenario. Recognising the benefits of vaccination at an earlier stage of chronic kidney disease, more younger patients had received hepatitis B vaccination before the start of dialysis therapy.

In conclusion, we found no evidence to support routine extra-high dose intramuscular hepatitis B vaccination, but this needs to be balanced against the fact that our study was underpowered.

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Identification of hepatitis B virus encoding/affecting microRNAs

Key Messages

1. We have discovered a profile of human miRNAs expression from the hepatitis B virus (HBV)–producing cell line HepG2 2.2.15, which can provide more information for the study of the HBV life cycle or HBV-related hepatocellular carcinoma.
2. No HBV-encoded miRNAs were found in the HepG2 2.2.15 cell line.

Introduction

In Hong Kong, hepatitis B virus (HBV) is the major cause of liver cancer, accounting for over 70% of all cases. Over 10% of our population are chronic carriers of HBV, and the risk of these people eventually developing cirrhosis and liver cancer is 100-fold higher than in non-carriers.[1] Many of the factors governing viral latency remain unresolved, and current antiviral treatment regimens are largely ineffective at eliminating cellular reservoirs of latent virus.

MicroRNA (miRNA) is recognised as one of the major regulatory gene families in eukaryotic cells. Virus-encoded miRNAs, which could rapidly accumulate in infected cells, would be a powerful means of modulating viral and cellular gene expression.[2] Several DNA viruses that enter the nucleus during their life cycles have been found to encode miRNAs. Using computational methods, it was predicted that the HBV genome could reasonably encode one candidate pre-miRNA. Experimental evidence also suggests that hepatocytes are the only confirmed site of replication for all members of the hepatitis virus family. This is in line with the characteristics of miRNAs, which are usually expressed in a cell-type and tissue-specific manner.

Based on the insight of miRNA and the fact that regulation of gene expression is not limited to the expression of one or more proteins, we hypothesised that HBV achieved its infection by encoding miRNA(s) or affecting the hosts' miRNA(s). We aimed at identifying HBV-encoded miRNA(s) and HBV-affected host miRNA(s). We report on the analysis of small RNA libraries derived from an HBV-producing cell line and suggest several potential novel miRNAs which are of special interest for future studies.

Methods

This study was conducted from November 2007 to November 2008.

Cell culture of HBV-producing cell line

The cell line HepG2 2.2.15, which was stably transfected with a head-to-tail dimer of HBV DNA (strain ayw), was maintained in Dulbecco's modified Eagle medium (Invitrogen, Carlsbad [CA], USA) and supplemented with 10% heat-inactivated foetal bovine serum and 100 mg/mL penicillin/streptomycin (Invitrogen) at 37ºC under 5% CO_2.

Detection of HBV genes expression in the cell line model

Total DNA was extracted from a HepG2 2.2.15 cell lysate. PCR primers were used to confirm expression of the X, C, Pre-S, and S genes in the cell line. The PCR products were identified by electrophoresis in 2% agarose gels and stained with SyberSafe gel stain (Invitrogen).

RNA isolation and construction of cDNA library of small RNA

According to the manufacturer's protocol, total RNA was extracted from a HepG2 2.2.15 cell lysate using Trizol reagent (Invitrogen). Then, 12% denaturing (7M Urea) polyacrylamide gel electrophoresis was used to size fractionate and enrich the small RNAs to 18 nucleotide (nt) to 26 nt size fractions. Subsequently, small RNAs were cloned using the miRCat-33 microRNA cloning kit (IDT DNA Technologies, Coralville IA). Briefly, 5' and 3' adaptors were ligated

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to the enriched small RNAs. The 5' and 3' ligated small RNAs were then converted into cDNA using SuperScript III reverse transcriptase (Invitrogen) and a specific primer. After reverse transcription, the cDNA was amplified by PCR, and the PCR products were then gel-purified using the Wizard SV Gel and PCR Clean-Up System (Promega, Madison, USA) and cloned into the pCR2.1 TOPO vector (Invitrogen). The positive insert-carrying plasmids were then sequenced using the ABI auto sequencing kit. Sequencing reactions were undertaken with the BigDye Terminator v3.1 Cycle Sequencing Kits (Applied Biosystems, Foster City, USA).

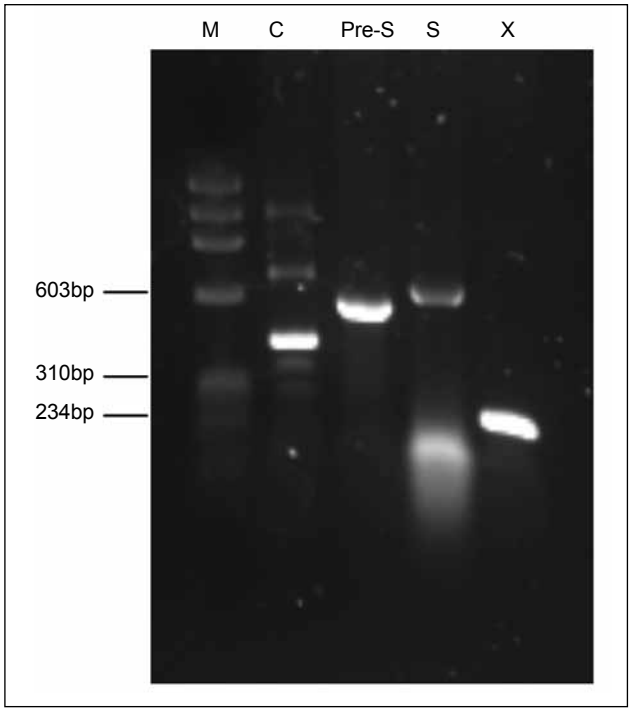

Fig 1. PCR amplification of hepatitis B virus genes (C, Pre-S, S, and X)

Small RNA sequence analyses

Sequence data obtained from cloning were analysed with Bioedit v7.0.4.1 software (http://www.mbio.ncsu.edu/BioEdit/bioedit.html) to identify inserts and orientation. Cloned small RNA sequences of length >17 nt were matched against the published mature miRNAs and stem-loop sequence databases (miRbase - Sanger miRNA database version 12.0, Sep 2008). Then, all the novel nucleotide sequence alignments were carried out by BLASTN searching against non-redundant (nr) and human genome databases (Human build 36.3 version) of the National Center for Biotechnology Information (NCBI). Secondary structures of RNA precursors were predicted from longer genomic sequences of the cloned RNAs using the Mfold software (http://www.bioinfo.rpi.edu/applications/mfold/old/ma/forml.cgi).

Results

Confirmation of HBV genes expression in HepG2 2.2.15 cells

At the beginning of the miRNA cloning experiment, PCR with specific primers were used to confirm that the cell line was HBV producing. All four genes (X, C, Pre-S, and S) were expressed in the cell line (Fig 1). These results ensured that the cell line was a relevant model of chronic HBV infection that could constitutively produce infectious HBV particles.

Analysis of sequence data from the HBV-producing hepatoblastoma cDNA library of small RNAs

A total of 233 clones were subsequently sequenced and databases searched. There were several kinds of RNA fragments. More than 76% of the cloned RNAs represented breakdown products of abundant coding and non-coding RNAs such as mRNA, tRNA, rRNA, sn/snoRNA and other unknown short fragments. About 21% of the cloned RNAs represented known human miRNAs. About 3% of

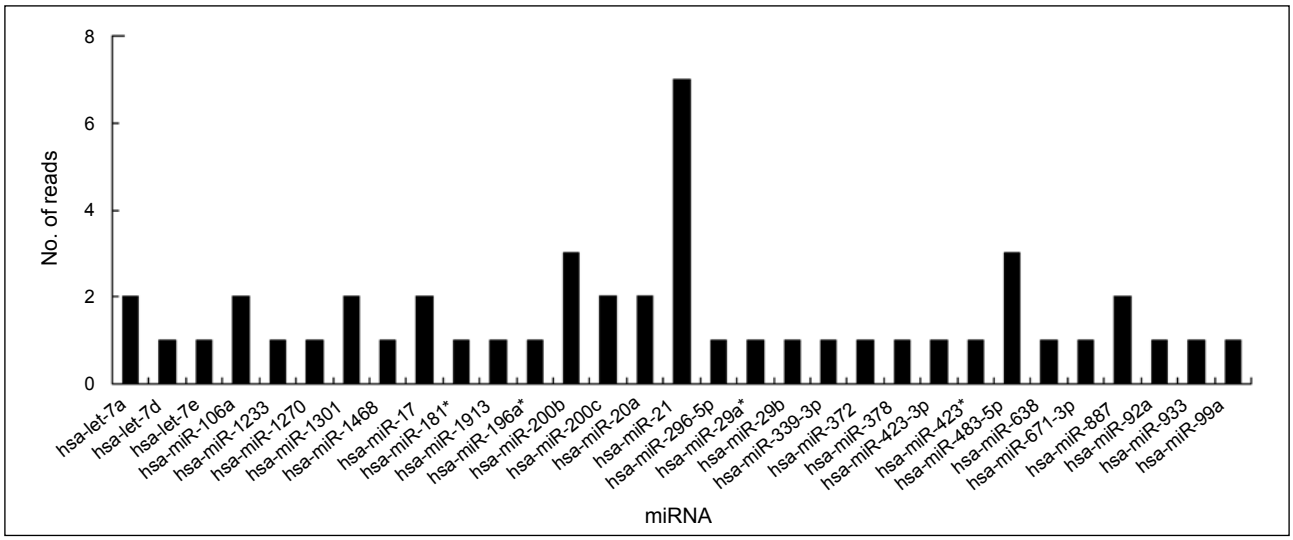

Fig 2. Frequency distribution of cloned and sequenced miRNAs that matched human miRNAs

the cloned sequences were matched with the miRNA of other species or stem-loops of known human miRNA or only matched with human chromosomes. These small RNA sequences might represent novel miRNAs identified in this study. However, no sequence of miRNA was found to be completely identical to that of HBV genome.

Expression pattern of cloned miRNAs

In the chronic HBV infection cell line model, a profile of human miRNAs was obtained (Fig 2). Among the known human miRNAs, hsa-let-7a, hsa-miR-106a, hsa-miR-1301, hsa-miR-17, hsa-miR-200b, hsa-miR-200c, hsa-miR-20a, hsa-miR-21, hsa-miR-483-5, and hsa-miR-887 were the miRNAs that had been sequenced twice or more. The most abundant miRNA was hsa-miR-21, which had been cloned and sequenced seven times. The second most abundant human miRNAs were hsa-miR-200b and hsa-miR-483-5, which were sequenced three times.

Discussion

miRNAs are involved in diverse biological functions, including development, life span, cell proliferation, differentiation, signalling pathways, apoptosis and metabolism.[3] Since the discovery of miRNAs in 2000, more than 6000 miRNA entries across 72 virus, plant, and animal species have been recorded in the miRBase release (version 12.0).

HepG2 2.2.15 miRNA profile

Recent studies have established a crucial role of miRNAs in cancer. We therefore used the miRNA profiling data in HepG2 (without HBV) cells for comparison. As we had used cloning and sequencing methods for miRNA profiling, we assumed that our results (clone count data) could be used for comparison with those of other hepatocellular carcinoma (HCC) miRNA-profiling studies, which might obtained by sequencing or by miRNA microarray profiling.

In one study, the expression of a group of miRNAs (including human miR-21, miR-20a, and miR-34a) was increased more than 2-fold in a HepG2 cell line (without harbouring HBV) when compared with that of normal human hepatocytes. In our study, high-level synthesis of miR-21 and miR-20a were also detected in HepG2 2.2.15 cells.

MiR-21 has been shown to be over-expressed in many different solid tumours, including those of breast, colon, lung, pancreas, prostate, stomach, as well as in cholangiocarcinoma cell lines. Therefore, it is highly

(a)

Clone name	Sequence	Similarity to Stem-loop of miRNAs	Alignment to hairpin miRNAs	Similarity to Chromosome location
P4-615	AAGGATGGCGGAGTGGTCT	rno-mir-349	Our Seq 1 AAGGAUGGCGGAGUGGUCU 19 rno-mir-349 17 AAGGUUGGGGGAGGGGGCU 35	Ch17,
190	AGGATGTCGGAGTGGTCT	hsa-mir-494	Our Seq 1 AGGAUGUCGGAGUGGUCU 18 hsa-mir-494 15 AGGUUGUCCGUGUUGUCU 32	Ch9, 19
128	GAGGATGGCGGAGCGGTCT	hsa-mir-935	Our Seq 18 GACCGCUCCGCCAUCCUC 1 hsa-mir-935 31 GGCCCCUCGGCCAUCCUC 48	Ch1
939	CTCAGGATGGCCCGAGCGGTCT	hsa-mir-212	Our Seq 20 ACCGCUCGGGCCAUCCUGAG 1 hsa-mir-212 51 ACUGCCCGGGCCGCCCUCAG 70	Ch4
P16-704	GGATGGATGGCCGATCG	hsa-mir-412	Our Seq 1 GGAUGGAUGGCCGAUC 16 hsa-mir-412 12 GGAUGGAUGGUCGACC 27	Ch11

(b)

(c)

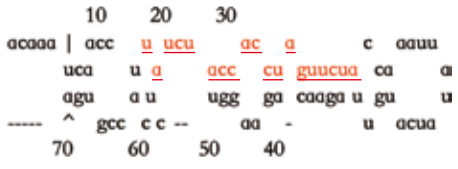

Fig 3. (a) Potential novel miRNA stem-loop sequence alignment, (b) sequence alignment of miRNA clone 311 and mouse mmu-miR-672 precursor miRNA, and (c) fold back precursor sequence of a potential novel miRNA as predicted by the MFold software, with underlined bases representing the mature miRNA sequences

likely that miR-21 plays a fundamental role in tumour cell behaviour and malignant transformation. Our findings were comparable with those of the other tumours in which miR-21 was over-expressed. Moreover, miR-21 has been reported to have anti-apoptotic properties in glioblastoma and cholangiocarcinoma. Thus, altered expression of miR-21 can have several diverse effects in tumour cells.[4]

Another up-regulated miRNA (miR-20a) can induce senescence in mouse embryonic fibroblasts. Senescence has been revaluated as a tumour suppressor mechanism (an alternative to apoptosis). MiR-20a has been suggested to play an anti-apoptotic role via the E2F/miR-20a auto-regulatory feedback loop. The E2F transcription factors play an essential role in the proper regulation of cellular proliferation, and cell cycle progression is critical for the normal development of organisms and the prevention of cancer.

Interestingly, no miR-34a expression was detected in our study. In one study, two different cell lines—SNU-449 (which has HBV DNA integration) and PLC/PRF-5 (which can produce HBsAg but not infectious HBV particles)—also showed a down-regulated miR-34a synthesis.[4] These results were in line with those in another study involving feeding rats with a methyl-deficient diet in order to induce hepatocarcinogenesis.[5] Down-regulation of miR-34a in rat liver during hepatocarcinogenesis was observed.[5] Therefore, HBV production in HCC cell lines might cause miR-34a down-regulation. As miR-34a has been reported to have a tumour suppression function, the relationship between down-regulation of miR-34a in HBV-producing hepatocytes is worth studying.

Another affected miRNA profile was the miR-483-5p, which was sequenced three times in our study, but it was not up-regulated in HepG2 cells in previous studies. As yet, there is no report on their functions in liver cells. Therefore, the effect of HBV on regulating miR-483-5p expression and functions in HCC remains to be discovered.

Moreover, in the miRNA family, let-7 (such as hsa-let-7a, hsa-let-7d, and hsa-let-7e) was relatively up-regulated in HBV-producing HepG2 cells as compared with non-HBV-producing HepG2 cells.[4] An example of the function of the let-7 miRNA family was displayed by hsa-let-7a that modulates interleukin-6-dependent STAT-3 survival signalling in human malignant cholangiocytes by targeting the tumour suppressor gene NF2.[4]

Furthermore, in the miRNA family, miR-17 was up-regulated in both HBV-producing and non-HBV-producing HepG2 cells. Concerning miR-17 miRNA family members, miR-17-5p, miR-20a, miR-93, and miR-106a can regulate mouse STAT3 mRNA in vitro. It has been suggested that STAT3, a known embryonic stem cell regulator, is a target mRNA responsible for the effects of these miRNAs on cellular differentiation in the mouse. Also, temporal regulation of cell cycle progression can be exerted by two miRNAs (miR-17 and miR-20a). Disrupting miR-17 or miR-20a during cell cycle G1 phase progression resulted in premature E2F accumulation, leading to a DNA damage-induced G1 phase checkpoint.

Analysis of potential novel human miRNAs

Among the 3% of potential novel clones, five clones matched the stem-loop sequences of identified human miRNAs (Fig 3a). One of the clones named 311 matched a mouse miRNA (Fig 3b), and another named P6-544 did not match any known miRNAs, but an identical sequence exists in human chromosomes 1. It contains a typical hairpin consisting of approximately 70 nt in length as folded by Mfold software, which is the characteristic for miRNA precursors (Fig 3c).

Conclusions

In this pilot study, we discovered a profile of human miRNAs and identified several potential novel miRNAs, which can provide more information for HBV-related HCC studies. Moreover, no HBV-encoded miRNA was found in the HBV-producing cell line HepG2 2.2.15.

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AUTHOR INDEX

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