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Does integrated cognitive and balance (Dual-task) training improve balance and reduce falls risk in individuals with cerebellar ataxia?

Stanley Winser,[1] Marco Pang[1], Jessica S Rauszen,[1] Anne YY Chan,[2] Chen Huijun Cynthia[3] and Susan L Whitney[4]

1. Department of Rehabilitation Sciences, Hong Kong Polytechnic University
2. Division of Neurology, Prince of Wales Hospital and Honorary Clinical Assistant Professor Dept. of Medicine and Therapeutics, Chinese University of Hong Kong
3. Saw Swee Hock School of Public Health, National University of Singapore
4. School of Health and Rehabilitation Sciences, University of Pittsburgh

Abstract

Frequent falls in people with cerebellar ataxia (CA) is a significant problem because it increases the burden of disease to both the individual and the healthcare system. Therefore, an intervention that could improve balance and reduce the number of falls is of paramount importance from the patients' perspective. Although the incidence of CA in the population is not as high as the other neurological disorders such as stroke and Parkinson's disease, the disability and its negative impact on quality of life are significant for those suffering from CA. Moreover, research that results in more knowledge regarding the factors that contribute to falls and the efficacy of treatments that reduce falls in this population could inform research into fall prevention in other populations of individuals at risk for falls, including otherwise healthy elderly adults. Combining cognitive training with physical training to improve balance is a new approach for reducing the risk of falls in patient populations who are at risk for falls. To determine if adding structured cognitive demands to conventional balance and coordination training we designed the Cognitive-coupled Intensive Balance Training (CIBT) program. We found that the more intensive and focused CIBT intervention reduced dual-task cost, improved balance, and reduced the number of falls in a sample of individuals with CA. Important next steps in our research program are to evaluate the efficacy and cost-effectiveness of the CIBT in improving balance and reduce falls using a fully powered clinical trial. We hypothesize that (1) CIBT will improve balance and reduce falls; (2) reduction in dual-task cost of balance and cognitive performance will mediate a reduction in the number of falls in CA and (3) CIBT will be a cost-effective treatment option for improving balance and reduce falls. To test these hypotheses, a randomized controlled trial (RCT) with economic evaluation will be conducted. This paper reports the findings of our study testing the feasibility of the CIBT program, rationale for testing our hypothesis and an overview of our future study design to test the effectiveness and cost-effectiveness of the CIBT program.

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Key words: Dual-task, cerebellar ataxia, balance training, fall prevention and economic evaluation

Background and significance

Cerebellar ataxia (CA) is an umbrella term that includes health conditions with genetic or non-genetic inheritance affecting the cerebellum or its connections resulting in postural instability, gait disturbance, incoordination and cognitive impairment.[1 2] The prevalence of health conditions resulting in CA is estimated as 8.22/100000.[3] Spinocerebellar ataxia, a genetic disorder resulting in CA has a prevalence of 0.9-3.0 /100000.[4] Poor balance and walking difficulties are hallmarks of diseases associated with CA.[2 5] Nearly 93% of people with CA report at least one fall over the past 12-month period.[6] Falls are very common in spinocerebellar ataxia type 3.[7] An estimate of the annual excess cost of medical expenses per person with CA is € 18776.[8] However, the cost of falls and falls related consequences are not well understood.

Why is rehabilitation important and challenging in CA? Therapeutic exercises are regarded as the first line intervention for individuals with CA.[9] Evidence-based guidelines in this population is limited.[2] This is due primarily to the limited number of high-quality studies in this field,[5] as well as the heterogeneity of the health conditions resulting in CA.[9] Intact cerebellum, plays a key role in motor adaptation and regulation of balance.[10] However, people with CA show limited motor re-learning.[11] In contrast, some studies show evidence for motor re-learning with repeated practice.[12 13] Therefore, understanding the potential for motor re-learning is critical for designing therapeutic intervention in this population.

Cerebellar influence during dual task paradigm: A recent systematic review reported that dual tasking, that is, simultaneous performance of two tasks involving physical and cognitive tasks,[14] predicts falls in people with cognitive impairment.[15] A recent study involving healthy adults found additional activation of the cerebellum during dual tasking and reported that the cerebellum is likely to control the neural networks responsible for such activities.[16] Dual tasking is found to deteriorate the performance of either or both tasks in people with neurological disorders.[17 18] This deficiency in dual-task performance relative to single-task performance is referred to as dual-task cost.[19] Training balance using dual-task is found to improve the ability to perform dual-task, that is, reduce the dual-task cost among people with stroke,[20] Parkinson's disease[21] and traumatic brain injury.[22] In individuals with CA, dual tasking is associated increased risk for falls[23] and gait disturbance.[24] Clinical studies on individuals with CA found that adding cognitive demand to a physical task increases the dual-task cost.[23 25 26] Difficulty in performing dual-tasks is due to the increase in demands in motor and cognitive resources.

Interventions for improving balance and reducing falls in CA: Intensive balance and coordination training aimed at improving static and dynamic balance, limb and trunk co-ordination are found to be effective in reducing the symptoms of in-coordination, motor performance[27] and a short-term reduction in the number of falls.[28] *However, the available interventions do not address the deficiency during cognitive-motor interaction or dual-task cost in this population.* Dual-task training has been found to improve this interaction in people with neurological disorders.[21 22 29 30] Dual-task training is highly relevant to people with CA due to the presence of poor motor-cognitive interaction and the associated cognitive deficits.[24] Theory-driven claims are available for the use of dual-task training in CA.[23 24] However, to date, there is no study evaluating the effectiveness of dual-task training in people with CA.[24]

Preliminary studies: Previously, we evaluated the effect of Tai-Chi training on improving balance and reducing the number of falls in people with neurological disorders.[31] Tai-Chi, a form of Chinese martial is practised for defence and health benefits. Tai-Chi requires attention in order to engage in the correct sequence of movement and memory to remember the correct moves while practising.[32] This combination of physical activity with cognition (attention and memory) makes Tai-Chi a dual tasking exercise.[32]

The systematic review with meta-analysis we conducted found no studies testing the effect of Tai-Chi for improving balance in CA.[31] Therefore, we conducted a feasibility study to evaluate the preliminary effects of Tai-Chi for improving balance and functional independence in CA; and test the feasibility and safety of the intervention for a future randomized controlled trial (RCT).[33] The feasibility study[33] found beneficial effects of Tai-Chi for improving balance in people with CA. We then conducted an RCT to compare the effectiveness of Tai-Chi compared with usual care control (no Tai-Chi) for improving balance and falls in people with CA. A trained Tai-Chi Master delivered the 8-form Tai Chi as group therapy for 60 minutes, once in 2 weeks for 12 weeks. Participants then complete unsupervised Tai Chi exercise for 60 minutes, twice a week for 6 months. After analysing 6-month follow-up data, we found significant improvement in balance measured with the Berg Balance Scale (BBS) and balance sub-component of the Scale for the Assessment and Rating of Ataxia (SARAbal) scale. However, balance measured with objective laboratory-based assessments (Limits of Stability-LOS and Sensory Organization Test- SOT) did not improve significantly relative to no treatment. In addition, the Tai-Chi did not reduce the number of falls at 6 months post-intervention, relative to no treatment.[34] This lack of improvement in actual falls could potentially be due to (1) a lack of intensity of the intervention with respect to dual tasking; (2) the cognitive demand of the intervention did not reach the threshold to challenge balance; and/or (3) the intervention may not have adequately targeted the specific deficits in individuals with CA.

Pilot study: Given the lack of improvement in the number of falls in the clinical trial, we developed the Cognitive-coupled Balance Training (CIBT) for balance and falls prevention for people with CA to address the potential reasons for the null findings with respect to falls in the RCT we recently completed. The 'Intervention' section of this proposal reports the details of the CIBT program. A literature review revealed no studies combining physical and cognitive training for improving dual-tasking, balance or reducing the number of falls in CA. We then conducted a single group pre-post design (ethic reference ID: HSEARS20180807002) to test the feasibility and safety of the intervention with 5 participants with CA. Dual-task cost of balance performance was measured using the Timed up and go test with the formula: (d-TUG - Standard TUG)/ Standard-TUG) × 100.[35] Functional balance was assessed using the Berg Balance Scale (BBS). Two objective laboratory-based assessments of balance were done using the composite score of the Sensory Organization Test (SOT) and maximal excursion of the Limits of Stability (SOT) test. Ataxia severity was assessed suing the Scale for the assessment and rating of ataxia (SARA) and the number of falls were recorded. We found that the CIBT program was feasible, safe and potentially effective for people with CA. Table 1 summarises the key findings of the pilot study. The post-training assessment reported a reduction in the dual-task cost of balance performance, number of falls and an improvement in functional balance. The findings of the pilot study are very encouraging and support the feasibility and scientific premise of our hypothesis.

Insert Table 1 about here.

Based on the findings from the feasibility study we propose to conduct a randomized controlled trial (RCT) to compare the treatment benefits of the dual-task (experimental: CIBT) training against the single-task (active control: conventional balance, coordination and cognition) training for reducing dual-task cost, improving balance and reduce the number of falls in participants with CA. In addition, we propose to conduct an economic evaluation alongside the RCT at a healthcare perspective of Hong Kong to compare the cost-effectiveness of dual-task training against single-task training, in preparation for the development of any future trials.

Our specific objectives will be to: (1) Evaluate the effectiveness of the dual-task (CIBT-experimental) training compared with single task (conventional intensive balance, coordination and cognitive- active control) training on functional balance and number of falls. and (2) Compare the cost-effectiveness of the dual-task and single-task training for preventing falls. We hypothesize that both dual-task and single-task training will improve functional balance, however, the dual-task training will be more effective in reducing the number of falls. Secondly, the dual-task training will be superior in terms of cost-effectiveness than the single-task from a health-care perspective of Hong Kong.

Rationales for testing proposed hypotheses:
Hypothesis 1: Poor attention allocation to balance during dual tasking is a strong predictor of subsequent falls.[36] Improvements in balance and gait facilitate gait automaticity, which in turn allows more attention allocation to the cognitive task resulting in the reduction of risk[36] and fear of falls[37] among the elderly. Our pilot study found a reduction in the number of falls demonstrated by a large effect size (d= 0.91) following 4-weeks of CIBT. We speculate the reduction in the number of falls to task automatization and optimization of attention allocation during walking.[19] Therefore, we hypothesise a greater reduction in the number of falls following dual-task in comparison to single-task training.
Hypothesis 2: Economic evaluations typically relate the cost of the intervention to the potential consequences (both cost- and health-related) of the intervention, compared with current usual care, allowing for estimates regarding the best value-for-money treatment options. Owing to the diversities in culture, economic dynamics and country-specific healthcare policies[38], there is a need to conduct an economic evaluation from the HK healthcare perspective. Such an evaluation will assist decision making on cost-effective treatment options for HK population. Falls are very common in CA and has a significant consequence to the individual.[7] Results of our pilot study demonstrate that the dual-task training (CIBT) program has the potential to reduce the number of falls (d =0.91) in people with CA. Therefore we hypothesise a reduction in the number of falls will result in the reduction in healthcare utility making the intervention (dual-task training) cost-effective for falls prevention.

Summary of the proposed study
Design: An assessor and statistician blinded two-arm parallel group, RCT comparing dual-task (CIBT) to single-task (conventional balance, coordination and cognitive) training will be conducted with 44 participants with CA. Eligible participants will be randomized to study groups and allocation will be concealed. Participants will be randomized to one of the two groups: Group 1: Dual-task (CIBT) training; and Group 2: Single-task active control (conventional balance, coordination and cognition) training.
Sample size calculation: We will enrol 44 participants (22 in each group), allowing 10% attrition rate. For hypothesis 1, using the data from our pilot study, for using dual-task cost of balance performance as a primary outcome measure, assuming 90% power, 5% type I error and allowing

10% dropout, the required sample size is 44 (22 in each group). For hypothesis 2, from the data generated through our pilot study, assuming 90% power, 5% type I error and large effect size (0.91) for the number of falls, the sample size required is 22 (11 in each group).

Participants: Study inclusion criteria include: (1) men and women in the age group of 18-60 years; (2) with a confirmed diagnosis of CA (of any type); (3) able to walk independently with or without walking assistive aids. Study exclusion criteria will be: (1) previous history of other neurological diseases (such as Parkinson's disease, stroke, or polyneuropathies) or musculoskeletal problems severely impairing balance, gait or motor performance; (2) able to walk only with handheld support (3) severe visual impairment preventing from exercise participation and (4) severe cognitive impairment with scores <16 on the Montreal Cognitive Assessment (MoCA) scale.[39]

Randomization and blinding. A person not involved in the study (student helper #1) will randomize participants to study groups in permuted blocks through computer-generated random numbers list prepared by a statistician before the first baseline assessment. The student helper who is not involved in the recruitment, assessment of study variables, or intervention delivery will perform the allocation of participants into the experimental group and active control groups. One HK registered physiotherapist (RA1) will be recruited to provide intervention to participants. Assessments will be performed blinded to the treatment conditions. Statistical analysis will be performed blinded to the treatment condition by the statistician.

Procedure: First baseline assessment (T1) will be completed after written informed consent. Participants will then be requested to return after 6 weeks for a second baseline assessment (T2). Study intervention will not be provided during this six-week period. Consistent with a previous study,[27] in order to allow a prospective number of falls assessment and progress in disease severity, we plan to conduct two baseline assessments at a 6-week interval. Post-intervention assessment will be performed after 4 weeks of intervention (T3) and a follow-up assessment will be performed after 6 months (T4).

***Intervention*:** Treatment will be initiated for both the groups after the second baseline assessment. The exercise intervention will continue for 7 months, beginning with supervised training at PolyU for 1-month. Intervention for both groups will be for 60 minutes, 3 times a week for 4-weeks. At the end of the training phase at PolyU, participants will be asked to complete an unsupervised home exercise programme over the next 6 months, based on the trial intervention.

Group 1: Dual-task (CIBT- experimental) group participants will receive 10 minutes of warm up, 40 minutes of CIBT training and 10 minutes of cool down exercises. CIBT program includes performing four types of cognitive tasks during sit to stand, standing with feet apart, one leg, tandem standing, multidirectional reaching, stair climbing and walking (10 metres) tasks. The four cognitive tasks will include: counting backwards by subtracting 4 numbers (for mental tracking), naming fruits, vegetables, or animals (for working memory), auditory cues for performing activities, example, perform heel raise when you hear the alphabet H (for improving attention and auditory discrimination), short story telling (for verbal fluency). In addition, falls prevention strategies will be taught. These exercises are consistent with previous studies on dual-task training for people with mild cognitive impairment.[40] The physical tasks selected are in line with the previous published protocol for improving balance, gait and coordination in individuals with CA.[27]

Group 2: Single-task (conventional balance, coordination and cognitive training- active control) group participants will receive 10 minutes of warm-up, 20 minutes of conventional balance and coordination exercises that are in accordance to previously published literature[27], 20 minutes of cognitive training as single-task (same 4 tasks provided for the CIBT) and 10 minutes of cool down. In addition, falls prevention strategies will also be taught.

Outcome measure: Table 2 reports the summary of the proposed outcome measures, domains tested, interpretation and the assessment timeline. We have included standardized and validated measures to assess functional balance (Berg Balance Scale[41] and SARAbal[41]) dynamic stability (LOS[42]), sensory interaction (SOT),[43] number of falls, cognitive function (Montreal cognitive Assessment -MoCA),[44] ataxia severity (Scale for the Assessment and Rating of Ataxia- SARA and SARAbal)[41 45] and quality of life (EuroQol 5 dimension 5 level).[46]

Cost estimation: Participants will be instructed to complete the digital diary once every week. The researcher interface of the digital diary (https://goo.gl/fKHifS) provides a summary of completed items of all included participants. Non-responders will be followed-up over the phone by the research assistant once every week. A printed version of the cost and falls diary will be provided to participants who do not have regular access to the internet. Postage-paid envelopes will be added to each printed cost diary to obtain a better response rate and participants will be instructed to post the completed forms once a month.

Statistical analyses

Hypothesis 1*:* Changes in primary and secondary outcome measure between mean baseline (T2), post-intervention (T3) and follow-up (T4) across the intervention groups will be evaluated using an Analysis of covariance (ANCOVA) at 95% confidence interval. The baseline score will be adjusted for disease duration, ataxia severity and assistive walking device usage (co-variates). Time points 2 and 3 will be compared to establish immediate treatment effects and T2 and T4 will report retention of treatment effect. Hypothesis 1 will be supported if a significant treatment Group X Time interaction emerges, with subsequent univariate analyses showing that scores of the Dual-task (CIBT) group improve significantly ($p<0.05$) more than the active control condition.
Hypothesis 2: The EQ-5D-5L response will be converted into utility scores which will be used to estimate the quality-adjusted life-year (QALY) gain or loss over the follow-up period. The mean QALY gain or loss will be calculated for each group at six months. In addition, the mean incremental QALY gain will be estimated for the intervention groups. The incremental cost-effectiveness ratio (ICER) will be calculated using the mean incremental cost and mean incremental effect by substituting with the formula: $ICER = \Delta C / \Delta E$, where E is the gain in QALY and C is the cost. The cost-effectiveness of the intervention groups will be geographically represented using the cost-effectiveness plane (CE). The threshold (λ) for cost-effectiveness or the amount of money the country is willing to pay to gain one unit of effect (QALY) will be calculated. Hypothesis 2 will be supported if the dual-task (CIBT) training yields cost saving and results in lower healthcare utility following falls and falls related consequences in comparison to single-task training at assessment timeline T4.

Consequences of hypotheses

If the hypotheses we made were found true, the findings of this cutting-edge research are important to the clinicians, researchers, policy-makers and people with CA. This study finding will have important clinical implications by clarifying if adding a cognitive demand to routine balance and coordination training will result in additional benefits on improving balance and reducing falls in comparison with usual care in people with CA. The findings will also have important implications for increasing the efficacy of falls prevention programs in other populations with neurological deficits who are at risk for falls.

Conclusion

People with CA also present with varying degrees of cognitive impairments making it difficult for them to perform dual-tasks in daily activities. Dual tasking has been found to deteriorate the performance of either or both tasks in people with CA. The deficiency in dual-task performance relative to single-task performance referred to as dual-task cost is high in CA. Falls incidence in people with CA increases during daily activities that involve dual tasking. The use of dual-task training to reduce dual-task cost has been found to be effective in stroke, parkinson's disease and the elderly population. The use of dual-task training to improve balance and reduce the number of falls for people with CA is novel and worthwhile testing.

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