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COMPUTER GAME-BASED REHABILITATION FOR POST-STROKE UPPER LIMB DEFICITS- SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: The need for intense rehabilitation protocols with easy applicability to improve for patient adherence and harness the potential neuroplasticity leading to improvement in the quality of life (QOL) in post-stroke patients. Several studies have described the benefits of virtual reality and video games in rehabilitation.

Aims: To explore and determine if Computer game-based rehabilitation for post-stroke upper limb deficits after stroke is superior to conventional therapy in terms of (1) ICIDH based outcomes (2) Intervention duration (3) acceptability and adherence to the intervention.

Methods: This systematic review and meta-analysis followed PRISMA guidelines. Several electronic databases were searched using specific keywords, to measure the effects of computer-game-based therapy in post-stroke patients compared to conventional therapy.

Results: 14 studies were included after a systematic review, out of which 11 were included for analysis. Studies recording Wolf motor function test and box and block test have shown improvements with Computer-game-based therapy in addition to conventional therapy. No improvements were recorded in impairments and patient participation/Quality of life. CGBT was acceptable and reported no adverse effects.

Conclusions: Computer-game-based therapy or non-immersive virtual rehabilitation is effective and acceptable for upper limb rehabilitation after stroke. With significant improvement in 'activity-limitation,' this mode of rehabilitation can be adapted for patient-specific needs. Its effects on impairment and quality of life need further exploration.

Keywords: Stroke, rehabilitation, upper limb, computer games, technological advances, non-immersive rehabilitation.

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INTRODUCTION

The global burden of stroke is on the rise, recording 1.03 crore new strokes and 11.3 crore disability-adjusted life years (DALYs) per year [1]. Approximately 75% of deaths and more than 80% of DALYs occur as a response to stroke in low and middle-income countries (LMICs) [2,3]. Eighty percent of stroke survivors are limited by upper limb disability and only 5-20% show complete functional recovery [4,5].

There is no therapy protocol universally accepted for upper limb rehabilitation after stroke. Rehabilitation practices vary in duration, intensity, and frequency [6]. The intensity of rehabilitation and the rate of recovery post-stroke are directly proportional causing the poor outcome of death or deterioration to reduce [6,7]. Repetitive motor behavior during motor learning can aid to changes in representational organization in the motor cortex [8,9]. Animal (rats) models have suggested that after 2 weeks from the injury, the peri-infarct cortex starts responding to cortical afferents and consequently, limb responsiveness increases by stimulating those locations unrelated to limbs before a stroke. With an appropriate and adequately intense dosage of rehabilitation new connections are formed within cortical circuits (new dendritic spines, axonal connections stimulated by a molecular program on regeneration). Improvement in motor recovery induced by a brain-derived neurotropic factor (BDNF) works by having direct effects on synapses, angiogenesis etc. post-stroke which can also be tapped through neuro-rehabilitation [10]. Studies suggest that therapy needs to be challenging, repetitive, task-specific, motivating and intensive for neuroplasticity to produce recovery [11,12]. Kwakkel et al., 2004 have found a significant effect of augmented therapy on ADL (activities of daily living), especially when therapy begins at least 16 hours within the first six months after stroke [13]. The importance of repetition and intensity of rehabilitation is further described in a review and meta-analysis [14].

The NICE (National Institute for Health and Care Excellence) guidelines [15] and the National clinical guidelines for stroke in the United Kingdom and the Netherlands suggest a minimum of 45 minutes of therapy five times per week for optimal recovery over a period of time as needed by the patient. However, the actual duration of therapy provided is much less, ranging between 22-30 minutes per day [16-18].

One of the many interventions available for post-stroke upper limb rehabilitation is the widely researched CIMT (Constraint-induced movement therapy) and its modified versions. These are presently the best evidence-based physiotherapy approach causing significant neurophysiological changes in the brain and motor improvement with effects lasting at least up to 4-5 months. CIMT requires constraining the non-paretic upper limb for 60-90% of waking hours with 3-6 hours of task-specific therapy activities. (14) Such long duration of constraint leads to poor adherence and frustration in patients and their caregivers [19]. Many of the modified CIMT protocols lack transparency in reporting dosages and the barriers to implementation of such interventions need more exploration. Over the past decade, the use of Robotics, Virtual reality-based rehabilitation (VR) and Computer game-based therapy (CGBT) are supplementing and in some cases replacing conventional therapy approaches [20].

RATIONALE: The applicability of various therapy approaches and their factors that may enhance the use of the arms and hand in activities of daily living (ADL) require further investigation [4]. There is a need for intense rehabilitation protocols with easy applicability for patient adherence and to harness the potential neuroplasticity leading to improved quality-of-life (QOL) in patients post-stroke. Several studies have described the benefits of virtual reality and video games in rehabilitation. The varying movement demands of computer games can be used in rehabilitation settings for tailor-made therapy protocols for stroke [21,22].

In this review and meta-analysis, we focus on the various CGBT used for rehabilitation of post-stroke upper limb impairments. For ease of understanding, we have differentiated between VR and CGBT. We have defined a CGBT as the use of non-immersive computer/video games in intervention while handling and manipulating real-life objects/remote for the tasks being performed (like Nintendo Wii (NW), XaviX, Sony Playstation MOVE etc.) and VR as the use of an immersive Virtual reality set up where a computer is used to generate stimuli to provide interaction opportunities with the environment, similar to real-world situations [23] and the patient interacts with the computer screen through motion and depth sensors, accelerometers, gyroscopes, robotic gloves etc. without grasping or manipulating real-life objects.

Based on these differences, we have included only those therapies which used CGBT and excluded motion sensors, VR, and other therapies. Thus our objective is to explore and determine if Computer game-based rehabilitation after stroke is superior to conventional therapy in terms of (a) ICIDH based outcomes (b) Intervention duration (c) acceptability and adherence to the intervention.

METHODS

Search strategy and selection criteria (Figure 1)

All sources of information were required to meet the following eligibility criteria: **Inclusion criteria** were Studies on CGBT after stroke for gross and fine motor movements of the upper extremity, Rehabilitation initiated not later than 6-month post-stroke, only randomized controlled trials were included, Articles published since January 2000 to August 2019. For Meta-analysis Studies recording Fugl-Meyer-assessment (FMA), Wolf-motor-function-test (WMFT), Box-and-block-test (BBT), Action-research-arm-test (ARAT) and Functional-independence-measure (FIM) scores were included. The **exclusion criteria were** Studies on post-stroke rehabilitation based on virtual reality, Studies reporting on robotic systems being applied in post-stroke rehabilitation, Studies written in languages other than English, Studies published before 2000. Exclusion criteria for Meta-analysis were studies that did not record standard deviations and those recording only the mean differences between and within the groups.

We conducted this review and analysis based on PRISMA guidelines. We searched the following healthcare databases for articles of interest: PubMed, Medline, Embase, Isi Web of Science, ScienceDirect, SpringerLink, Google Scholar, ProQuest, EBSCO, Scopus, CINAHL Complete (i.e., EBSCO), and Cochrane Library (of Systematic Reviews). The systematic search was performed using keywords combined with Boolean operators:

(stroke OR poststroke OR post-stroke OR cerebrovascular accident OR cerebrovascular disease OR apoplexy OR intracerebral hemorrhage OR intracerebral hemorrhage) AND (rehabilitation OR therapy OR treatment) AND (game OR computer game OR commercial game OR video game OR Nintendo Wii OR Wii OR Sony Playstation MOVE OR XaviX) AND (upper extremity OR upper limb OR arm OR hand).

Study selection

Two independent reviewers (DG, AS) evaluated the search results titles and abstracts to select potentially relevant articles. After that, the two authors (DG, AS) went through the full texts of the selected articles (except conference abstracts) to verify they fulfilled the inclusion criteria.

Data extraction

Studies were assessed and data collected for Type, intensity, and dosage of an intervention being applied, outcome-based on scales used in the studies [based on International Classification of Impairments, Disabilities (Activity Restrictions), and Handicaps (Participation Limitations), i.e., ICIDH] and Adherence and acceptability of the intervention by the patients and caregivers

Methodological quality, risk of bias assessment

PEDro checklist was used to assess the methodological quality while the risk of bias was measured using COCHRANE risk of bias tool. Publication bias was assessed according to funnel plots generated.

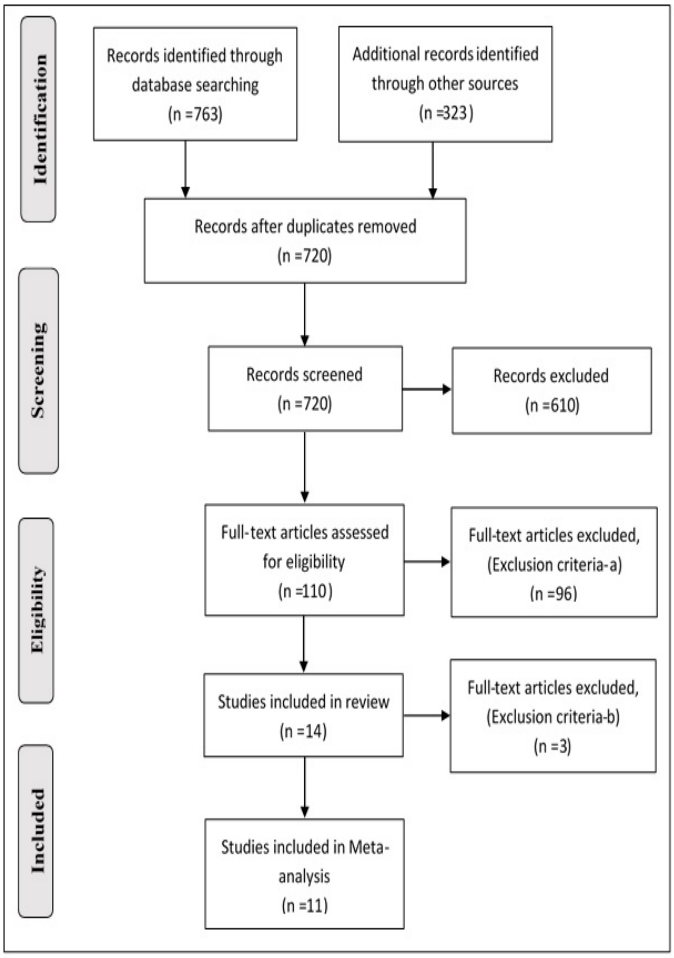

Figure 1: PRISMA flow chart

Statistical Analysis: For the meta-analysis section, all the data were summarised using Mean difference at 95% of a confidence interval. The studies provided 95% CI was transformed into SD, using a statistical formula. The medians and interquartile ranges converted into means and SDs using the appropriate formula [24]. The Log values were converted into original values using the antilog table. The random-effect model was used to analyze the data if the studies were heterogeneous and fixed-effect models for homogeneous studies. The heterogeneity of the studies was calculated by using the Cochrane Q test and assessed by using I^2, which ranges from 0% to 100%. Analyses were conducted using Revman 5.3 by the Cochrane collaboration.

RESULTS

Out of the 14 studies included for this paper (**Table 1**), 4 delivered NW exclusively to the intervention group, 7 delivered either NW/visual feedback exercises/exercises with smartphone tablet/arm support computerized training/hand orthosis in addition to routine care, 2 delivered mental practice/ transcranial direct current stimulation (tDCS) with NW and 1 used video games alone for the experimental group.

Table 1: Study Characteristics

Author/ Year of publication/sample size	Title	Intervention details	Outcomes		
			Impairment/ Others	Activity limitation	Participation restriction
Adie K et al, 2016, 240	Does the use of Nintendo Wii SportsTM improve arm function? Trial of WiiTM in Stroke: A randomized controlled trial and economics analysis	Supervised 6 week home based Wii gaming + CT	None	ARAT, MAL, mRS, EQ-5D 3L	COPM, SIS
Saposnik G et al, 2010, 22	Effectiveness of Virtual Reality Using Wii Gaming Technology in Stroke Rehabilitation: A Pilot Randomized Clinical Trial and Proof of Principle	8 interventional sessions of 60 minutes each over a 14-day period,	Intervention duration and related adverse effects	WMFT, BBT	SIS
R T Viana et al, 2014, 20	Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: A pilot randomized controlled trial	VRT: thrice a week of 1 hour of Wii gaming for 5 weeks. + anodal tDCS (2 mA) applied for 13 minutes over the primary motor cortex of the affected hemisphere.	FMA, MAS, Grip Strength	WMFT	SS-QOL
Nijenhuis SM et al, 2016, 20	Effects of training with a passive hand orthosis and games at home in chronic stroke: a pilot randomised controlled trial	Independent home based rehab, 30 minutes/ day for 6 days/week +SCRIPT dynamic wrist and hand orthosis+SaeboMAS for gravity compensation of proximal arm+ computer with touchscreen displaying gaming exercises.	FMA and grip strength	ARAT, BBT, MAL	SIS
Kong K H et al, 2016, 105	Efficacy of a Virtual Reality Commercial Gaming Device in Upper Limb Recovery after Stroke: A Randomized, Controlled Study	12 sessions of 60 min preselected Nintendo Wii gaming, 4 sessions/week for 3 weeks + routine care	FMA, VAS	ARAT, FIM	SIS
Sapsonik G et al, 2016, 141	Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial	Wii Nintendo gaming system including Wii Sports and Game Party 3-60 minutes each for 2 weeks	mRS, Grip Strength	Abbreviated WMFT, BBT, FIM, BI	SIS
Popovic MD et al, 2014, 20	Feedback-Mediated Upper Extremities Exercise: Increasing Patient Motivation in Poststroke Rehabilitation	30 mins/session, 5 sessions/week for 3 weeks: Visually feedback mediated game-based exercises + 1 hr convenional therapy	RTT	mDT	IMI
Choi YH et al, 2016, 24	Mobile game-based virtual reality rehabilitation program for upper limb dysfunction after ischemic stroke	30 min of conventional occupational therapy (OT) + 30 min of mobile upper extremity rehabilitation program using a smartphone and a tablet PC. 5 sessions/week for 2 weeks	FMA, Brunnstorm stage for arm and hand, MMT	mBI, EQ5D	BDI
Prange GB et al, 2015, 70	The Effect of Arm Support Combined With Rehabilitation Games on Upper-Extremity Function in Subacute Stroke: A Randomized Controlled Trial	6-week Arm support computerized training program, 30 minutes/session, 3 sessions/per week+ regular stroke rehab program	FMA, VAS	SULCS	IMI
Park JH et al, 2016, 30	The effects of game-based virtual reality movement therapy plus mental practice on upper extremity function in chronic stroke patients with hemiparesis: a randomized controlled trial.	5sessions/week for 4 weeks) of Nintendo Wii	FMA	BBT, MAL	None
Simsek TT et al, 2016, 42	The effects of Nintendo WiiTM-based balance and upper extremity training on activities of daily living and quality of life in patients with sub-acute stroke: a randomized controlled study	2 Nintendo-Wii games for upper limb , 45–60 minutes/day, 3 days/week for 10 weeks	None	FIM	NHP
McNulty PA et al, 2015, 41	The efficacy of Wii-based Movement Therapy for upper limb rehabilitation in the chronic poststroke period: a randomized controlled trial	Wii-based movement therapy, 60 min/session for 10 days	FMA	WMFT-tt, MALQO-Mand (BBT)	None
Givon N et al, 2015, 47	Video-games used in a group setting is feasible and effective to improve indicators of physical activity in individuals with chronic stroke: A randomized controlled trial	Video games (Microsoft Xbox Kinect, Sony Play-Station 2 Eyetoy, Sony PlayStation 3 MOVE, Nintendo Wii Fit and the SeeMe VR system) 2 hr sessions/week for 3 months	Compliance,-satisfaction, adverse events, Grip Strength	ARAT	None
Ribeiro NM et al, 2015, 15	Virtual rehabilitation via Nintendo Wii and conventional physical therapy effectively treat post-stroke hemiparetic patients	60-minute/twice a week /2 months, stretching+ NW gaming,	FMA	None	SF-36

*ARAT=action research arm test, MAL(QOM)=motor activity log (quality of movement), mRS= modified Rankin scale, EQ 5D 3L= European Quality of Life, COPM=Canadian occupational performance measure, SIS=stroke impact scale, WMFT (tt)=Wolf motor function test (timed tasks), BBT=box and block test, FMA=Fugl Meyer scale, MAS=Modified Ashworth scale, SS-QOL=Stroke specific QOL, VAS= Visual analogue scale, FIM= Functional independence measure, BI=Barthel index, RTT=received therapy time, mDT=modified drawing test, IMI=Intrinsic motivation inventory, mBI=modified Barthel index, BDI=Beck depression inventory, SULCS=Stroke Upper Limb Capacity Scale, NHP=Nottingham Health profile, SF-36=Short form-36, CT=Conventional therapy

Methodological quality: We scored each study on the PEDro scale (Physiotherapy Evidence Database Scale) and found high quality with a score mean of 8.07 and SD (standard deviation) of 1.07. We used the Cochrane risk of bias tool to present various possible biases.

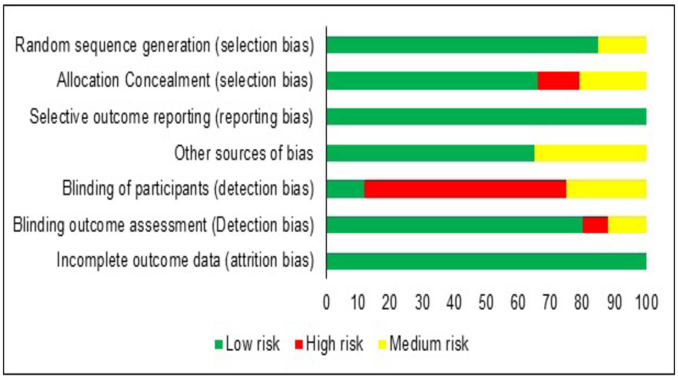

Figure 2: Risk of bias assessment

Quantitative findings: (11 studies)

The outcome measure considered for 'impairment' was FMA score. With 6 studies recording pre-post FMA scores, analysis revealed p-value: 0.26 at 95% CI, with a total mean difference (TMD) of 1.93 (-1.44 to 5.31). The heterogeneity was high at I^2=70%. **(Figure 3)**

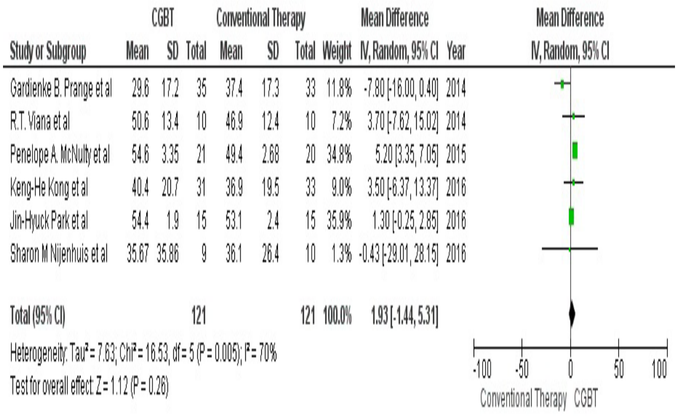

Figure 3: Mean difference of FMA in adjunctive CGBT versus conventional therapy

There were 3 outcomes considered under the 'activity limitation' category of ICIDH: ARAT, BBT and WMFT. ARAT scores for 4 studies showed a p-value of 0.63 at 95% CI, total TMD 0.80 (-2.47 to 4.08) and I^2=0%. **(Figure 4)**

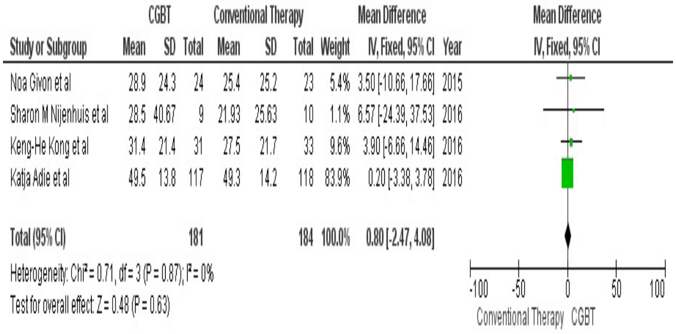

Figure 4: Mean difference of ARAT in adjunctive CGBT versus conventional therapy

Studies reporting WMFT (p-value: 0.002, 95% CI, -3.94 {-6.46 to -1.43}, I^2=0%) **(Figure 5)** and BBT (p-value: 0.04, 95% CI, 3.10 {0.14 to 6.07}, I^2=65%) showed statistically significant differences with additional CGBT for 1/2-1 hour sessions for 10 days-6 weeks. **(Figure 6)**

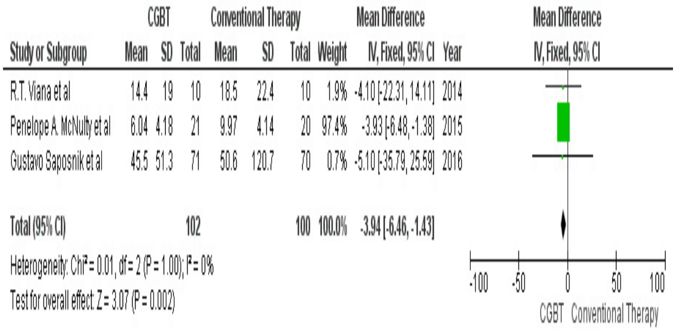

Figure 5: Mean difference of WMFT in adjunctive CGBT versus conventional therapy

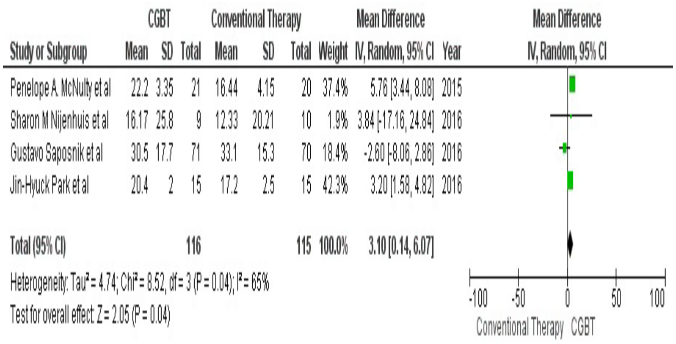

Figure 6: Mean difference of BBT in adjunctive CGBT versus conventional therapy

FIM used for the 'Participation limitation' category of ICIDH showed a p-value of 0.52 at 95% CI, TMD 1.28 (-2.6 to 5.23), and heterogeneity I^2=0%. **(Figure 7)**

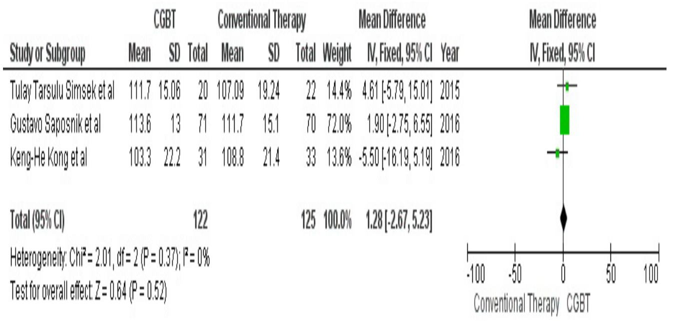

Figure 7: Mean difference of FIM in adjunctive CGBT versus conventional therapy

DISCUSSION

This review and meta-analysis are the first to describe the effects of CGBT (non-immersive-VR while handling and manipulating real-life objects/remote for the tasks being performed) on outcomes based on the ICIDH model. This study has contributed to the existing evidence of technological effects on rehabilitation in stroke rehabilitation in the following ways: (1) has included studies published since 2000, describing specifically the effects of CGBT (refer to introduction for our definition of CGBT). (2) Found CGBT to be effective in improving activity-limitation but having insignificant effects on impairments and participation-restriction.

We have not quantitatively analyzed the effects of duration and intensity of therapy provided; therapy initiated six months post-stroke on the outcomes measured. We have although given a brief and systematic description of these variables as qualitative findings based on the effect of intervention duration on the outcomes, acceptability of and adherence to CGBT and adverse effects if any. **(Table 2)** 10 out of the 14 studies (71.43%) used NW gaming for intervention. The ease of availability and cost-effectiveness of such therapy modes can be exploited to provide effective interventions. 35.71% of the included studies provided intervention for 0.5 hours per session while the rest delivered one-hour sessions, some including the warm-up phase.

Table 2: Qualitative findings

1. Intervention duration versus outcomes

   The total time of rehabilitation therapy among the included studies varied from 8 hours to 31.5 hours. All studies reported improvements in clinical outcome scales after adjunctive CGBT. However, a study on the self administered home-based arm and hand rehabilitation argued the duration of therapy itself is the chief contributor to the upper limb motor improvements.

   The majority of our studies concluded the CGBT to be as effective as conventional therapy (CT) and found no significant differences in functional outcomes. Three studies observed better effects of CGBT compared to standard rehabilitation. A study on a mobile game based VR rehabilitation concluded that patients who underwent thirty minutes of CGBT plus thirty minutes of CT per session performed better in comparison with patients on one hour of CT per session alone (Choi YH et al.). Another study proved the beneficial effects of mental practice consisting of game imagination and relaxation as an adjunctive before playing NW games. Other authors confirmed a favourable impact of visual feedback in addition to physical exercise, stressing the importance of enhanced patient's motivation and enjoyment during the therapy (Popovic MD et al.).

   Nevertheless, a vast number of studies admitted a small sample size to be a limitation to their conclusion over the effects of the CGBT, and whether or not the CGBT is more advantageous to the post-stroke upper limb improvement than standard therapy. Of note is that all of the four included studies with the largest patients populations reported no significant differences between the two rehabilitation approaches (Kong KH et al., Adie K et al., Saposnik G et al., Prange GB et al.).

2. Acceptability and adherence to CGBT compared to routine care

   In general, both the CGBT and standard rehabilitation were well accepted by patients. Some of the studies showed higher levels of satisfaction (Simsek TT et al., Givon N et al.) in the CGBT groups. Further, stronger motivation (on the interest/enjoyment and perceived competence subscales, specifically) was reported in patients with visual feedback mediated therapy, as compared to the CT (Popovic MD et al.). Another study on arm support devices combined with computerized exercises also reported higher gains in interest/enjoyment scores compared to dose matched conventional training (Prange GB et al.). Authors comparing NW based rehabilitation and modified constraint-induced therapy demonstrated higher patient preference, acceptance, and continued engagement in the NW group. Additionally, patients reported high self-perceived improvement and satisfaction with no difference between the groups (McNulty PA et al.). A cohort of patients subjected to a self administered, home-based training with passive dynamic wrist and hand orthosis coupled with computerized gaming exercises perceived positive, yet the equal level of motivation as the group on CT (Nijenhuis SM et al.).

   The adherence to post-stroke rehabilitation was fairly solid. Several studies reported from a zero (Viana RT et al., Choi YH et al.) to a small drop out rate (Saposnik G et al., Kong KH et al., Prange GB et al.). On the contrary, in two of the studies with the largest cohorts, only 87% and 86% of patients completed the therapy protocol (Adie K et al., Saposnik G et al., respectively). No difference in the drop out rates between the CGBT and conventional therapy was observed in any of the studies.

3. Adverse effects

   Zero adverse effects related to both CGBT and conventional therapy were reported in our studies. Moreover, a predominant number of studies reported no unfavorable effects at all (Saposnik G1 et al., Viana RT et al., Choi YH et al., Park JH et al., Simsek TT et al., Givon N et al.). In some studies, adverse effects were not covered (Nijenhuis SM et al., Prange GB et al., Popovic MD et al., McNulty PA et al., da Silva Ribeiro NM et al.). Three of our studies with the largest sample sizes (over one hundred patients each) stated an occurrence of inauspicious events (Kong KH et al., Adie K et al., Saposnik G et al.) and one case of death (Kong KH et al.) unrelated to the therapy.

The symmetry of funnel plots shows low chances of publication bias but good methodological quality.

Our meta-analysis revealed that studies reporting WMFT scores showed a significant improvement with therapy for 10-15 hours over 10days-5 weeks. The three studies considered were homogenous, with all of them using the NW game and 1 using additional trans-cranial direct current stimulation. The three studies, however, have varied sample sizes ranging from 10-71. The four studies reporting BBT were highly heterogeneous, with an intervention duration of 10-18 hours over ten days -6 weeks. Three of these studies used the NW game while 1 used additional passive hand orthosis for assistance. These findings from our meta-analysis suggest the positive effects of CGBT in improving activity-limitation. Larger RCTs using such interventions with varying durations in the various phases after stroke need to be explored. The impairment and participation-restriction categories did not show promising results, although these can partly be attributed to various reasons like heterogeneity in studies, small sample sizes etc.

Limitations:

Our study included only those studies where stroke had occurred a maximum of 6 months before intervention delivery with limited long-term follow-up. There was significant heterogeneity between studies reporting FMA and BBT. Our analysis was based on outcome measures and not on the duration of intervention or the phase post-stroke. These factors may limit the implications of our findings.

CONCLUSIONS

Computer-game-based therapy or non-immersive rehabilitation is effective and acceptable for rehabilitation after stroke. With significant improvement in 'activity-limitation,' this mode of rehabilitation can be adapted for patient-specific needs. Its effects on impairment and quality of life need further exploration.

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