The effectiveness of robot-aided upper limb therapy in stroke rehabilitation

A systematic review of randomized controlled studies

Kati Nykänen
Fysioterapian pro gradu -
tutkielma
Jyväskylän yliopisto
Terveystieteiden laitos
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TIIVISTELMÄ

Robottiavusteisen terapian vaikuttavuus yläraajakuntoutuksessa AVH-potilailla – järjestelmällinen kirjallisuuskatsaus
Kati Nykänen
Fysioterapian pro gradu-tutkielma
Jyväskylän yliopisto, Liikunta- ja terveystieteiden tiedekunta, terveystieteiden laitos
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Ohjaajat: Tuulikki Sjögren, Ari Heinonen

Tämän tutkimuksen tarkoituksena oli selvittää järjestelmällisen kirjallisuuskatsauksen perusteella, yläraajoihin kohdistuneen robottiavusteisen terapian vaikuttavuuden näytönaste aivoverenkiertohäiriön (AVH) saaneilla kuntoutujilla.

Kirjallisuushaku suoritettiin CINAHL (1982–8/2008), MEDLINE (1950–8/2008) ja EMBASE (-10/2008) sähköisistä tietokannoista seuraavilla hakusanoilla: aivoverenkiertohäiriö, halvaus, hemiplegia, yläraaja, kuntoutus, fysioterapia, robotti, satunnaistettu kontrolloitu koe. Lisäksi tutkimus sisälsi käsihakua. Tarvittaessa tutkijoihin otettiin yhteyttä tarkentavien tietojen saamiseksi. Kaikki satunnaistetut kontrolloidut tutkimukset, jotka liittyivät robottiavusteiseen yläraajaterapiaan aikuisilla AVH-kuntoutujilla sekä oli julkaistu suomen, ruotsin, englannin tai saksan kielellä otettiin mukaan katsaukseen.

Laadun arviointi perustui van Tulder:n (2003) julkaisemiin kriteereihin.Yksittäisen tutkimuksen laatupisteiden summa voi saada arvon 0-11. Laadun arvioinnissa käytettiin kahta itsenäistä ja sokkoutettua arvioijaa. Meta-analyysi ja suuruudet terapian vaikutukselle (effect size) laskettiin Cochrane Collaboration’s Review Manager Software 5.0.16-ohjelmalla.

Sisäänottokriteerit täyttäviä satunnaistettuja kontrolloituja tutkimuksia löytyi 18, joissa oli yhteensä 545 eri toipumisen vaiheessa olevaa AVH-kuntoutujaa. Tutkimusten laatupisteiden keskiarvo oli 5.5 (SD 1.1) ja vaihteluväli 4-7. Terapiassa käytettiin kymmentä erilaista robottia ja eniten harjoitettiin olka- ja kyynärniveltä. Kaikissa tutkimuksissa harjoittelua verrattiin muuhun fysioterapiaan. Robottiavusteinen terapia paransi tilastollisesti merkitsevästi ($p<0.01$) yläraajan toimintaa motorisia taitoja vaativissa päivittäisissä toiminnoissa akuuteilla AVH-kuntoutujilla. Ero ei ollut merkitsevä myöhäisemmässä toipumisen vaiheessa tai kognitiivisia taitoja vaativissa toiminnoissa. Olka- ja kyynärnivelen motorinen hallinta parani merkitsevästi ($p<0.05$) kaikissa toipumisen vaiheissa. Akuuteilla AVH-kuntoutujilla lihasvoima parani merkitsevästi ($p\leq0.05$) harjoitusta saaneissa yläraajan proksimaalisissa lihaksissa. Yläraajan proksimaaliosien robottiavusteinen harjoittelu ei vaikuttanut distaaliosien motoriseen hallintaan tai lihasvoimaan. Robottiavusteista terapiaa ei todettu vaikuttavaksi yläraajan spastisuuden, nivelliikkuvuuden, kivun, masennuksen tai elämänlaadun osalta.

Robottiavusteinen terapia on lupaava ja turvallinen terapiamenetelmä AVH-kuntoutujan yläraajakuntoutuksessa erityisesti akuutissa kuntoutumisen vaiheessa. Menetelmän käytettävyyttä ja soveltuvuutta kliiniseen käyttöön on tutkittava lisää.

Asiasanat: aivoverenkiertohäiriö, kuntoutus, fysioterapia, yläraaja, robotti

ABSTRACT

The effectiveness of robot-aided upper limb therapy in stroke rehabilitation - A systematic review of randomized controlled studies
Kati Nykänen
Master's Thesis in Physiotherapy
University of Jyväskylä, Faculty of Sport and Health Sciences/Department of Health Sciences
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Tutors: Tuulikki Sjögren, Ari Heinonen

The purpose of this study was to summarise the available evidence of the effectiveness of robot-aided upper limb therapy on upper limb motor function with systematic literature review.

A systematic literature search was performed in CINAHL (1982 to August 2008), MEDLINE (1950 to August 2008) and EMBASE (to October 2008). Search terms were stroke, cerebrovascular accident, paresis, hemiplegia, upper extremity, rehabilitation, physiotherapy, robotics and randomized controlled trial (RCT). Other relevant studies were searched by hand. An inquiry was sent to authors in a case that the article was lacking of relevant information. All RCTs that investigated adult upper limb stroke physiotherapy with robotic device and were published in Finnish, Swedish, English or German were included in the study.

The quality assessment of RCTs was based on the criteria adapted by van Tulder et al. (2003). The quality score for each RCT could vary from 0 to 11. A meta-analysis was performed and treatment effects were calculated with Cochrane Collaboration's Review Manager 5.0.16 Software.

From total of 31 clinical studies 18 RCTs fulfilled the inclusion criteria involving 545 patients representing all recovery stages. The average methodological score was 5.5 (SD 1.1), ranging 4-7. Ten different types of robotic apparatus were used and shoulder and elbow were the most trained body structures. In all statistical comparisons robot-aided therapy was compared with other physiotherapy modalities. Robot-aided therapy significantly ($p<0.01$) increased the motor function of the arm in the acute stroke patients but not in the later stages of the recovery or in any other areas of daily functions. Shoulder and elbow motor control increased significantly ($p<0.05$) in all recovery stages. Similar trend was seen in acute stroke patients whose muscle power increased significantly ($p\leq0.05$) in trained proximal muscles of the paralysed arm. No differences between the groups were seen in motor control and power of the distal parts of the upper limb. Robot-aided therapy was not superior reducing spasticity of the paralysed upper limb. It does not seem to have increased effect on upper limb active range of motion, pain, depression or quality of life.

It seems evident that robot-aided therapy is promising, safe and task-specific treatment method enhancing upper limb motor recovery especially in the acute stroke population. More studies are needed of its feasibility in clinical use.

Keywords: stroke, rehabilitation, physiotherapy, upper extremity, robotics

CONTENT

ABBREVIATIONS

ADL	activities of daily living
AMAT	Arm Motor Ability Test
ARAT	Action Research Arm Test
ARM-Guide	The Assisted Rehabilitation and Measurement Guide
AROM	active range of motion
BI	Barthel Index
Bi-Manu-Track	Bimanual rehabilitation robot
CVA	cerebrovascular accident
CI	confidence interval
CIMT	constraint-induced movement therapy
df	degrees of freedom
EMG	electromyography
EMG-BF	electromyography biofeedback
ES	electrical stimulation
FDT	Functional Dexterity Test
FES	functional electrical stimulation
FIM	Functional Independence Measure
FM	Fugl-Meyer assessment scale
GENTLE/s	computer assisted visual-sensorimotor training environment
I^2	I-squared
ICF	International Classification of Functioning, Disability and Health
InMotion2	Interactive Motion Technologies Inc. rehabilitation robot
MAS	Modified Ashworth Scale
MCA	middle cerebral artery, arteria cerebri media
MD	mean difference
MeSH	Medical Subject Headings
MI	Motricity Index
MIME	Mirror Image Motion Enabler
MIT-Manus	Massachusetts Institute of Technology-Manus
MRI	magnetic resonance imaging
MRC	Medical Research Council
MSS	Motor Status Score

N	Newton
NDT	neurodevelopmental treatment
NeReBot	the Neuro-Rehabilitation-Robot
NMES	neuromuscular electrical stimulation
PFST	positional stimulation feedback training
RCT	randomized controlled trial
REHAROB	the robotic rehabilitation system for upper limb motion therapy
RevMan	Cochrane Collaboration's Review Manager Software
RMA	Rivermead Motor Assessment
SD	standard deviation
SIS	Stroke Impact Scale
SMD	standardized mean difference
TENS	transcutaneous electrical nerve stimulation
TES	therapeutic electrical stimulation
TIA	transient ischemic attack
ULEM	Upper Limbs´ Encircling Motion
VAS	visual analogue scale
WHO	World Health Organization
χ^2 test	chi-squared test for heterogeneity

1 INTRODUCTION

A total of 14 000 individuals are affected with stroke in Finland each year. The prevalence rate will increase as the population ages (Pajunen et al. 2005). Economically stroke is the third most expensive disease in Finland as approximately 40 percent of stroke patients will need intensive rehabilitation in the acute phase and as many as 30 000 stroke patients will need continuous rehabilitation (Aivoverenkiertohäiriöt numerotietoina 2009, Kaste et al. 2006). The type of the rehabilitation is dependent on the severity of the stroke (Pyöriä 2007, 71). As a result of stroke about 50 percent will suffer from permanent sensory and motor impairments (Kaste et al. 2006). Motor recovery of the upper limb after stroke is often incomplete compared to lower limb recovery (Hiraoka 2001). Upper limb paralysis will remarkably reduce the independence on the ability to perform activities of daily living and quality of life of an individual (de Kroon et al. 2005).

The most appropriate and effective treatment methods as based on the evidence-based medicine should be used for patient care in stroke rehabilitation (Kelan järjestämän vaikeavammaisten 2006). The studies in stroke rehabilitation are mostly based on randomized controlled trials (RCT) (Kauhanen et.al. 2003). It seems evident that stroke patients with upper limb paralysis will benefit from physiotherapy (van der Lee et al. 2001). However there are several treatment interventions used in clinical practise that are lacking scientific evidence (Lannin & Herbert 2003, van der Lee et al. 2001) or the approach is not effective (Paci et al. 2003). The best practise and exercise dose for the rehabilitation of the paretic upper limb remains unclear (Barreca et al. 2003, Stein 2006).

New treatment methods have been developed to utilise the technology available. Rehabilitation robots are interactive and user-friendly devices that can facilitate motor recovery by evaluating and delivering measurable therapy for stroke patients (Krebs et al. 2006). Robot-aided upper limb therapy seems a promising method in stroke rehabilitation but is lacking scientific evidence of its effectiveness. The purpose of this study was to summarise the available evidence of the effectiveness of robot-aided upper limb therapy on upper limb motor function with systematic literature review.

2 LITERATURE REVIEW

2.1 Stroke

2.1.1 Epidemiology

In Finland there are about 14 000 stroke incidents per year in which two thirds of the patients are over 65 years old (Kaste et al. 2006). Stroke is the third most common cause of death and it causes a greater loss of quality-adjusted life years than any other somatic diseases (Aivoverenkiertohäiriöt numerotietoina 2009). The prevalence of stroke increases with the age (Pajunen et al. 2005). The prevalence of stroke also doubles in the low socioeconomic population compared to citizens with higher economic status (Sivenius et al. 2002). It is estimated that the prevalence will decrease in the future by well-implemented prevention and care (MacKay et al. 2004, 50). According to the study by Pajunen et al. (2005) the incidence and mortality of first-ever stroke among Finns over 35 year old has already decreased. Risk factors are high blood pressure, high blood cholesterol, coronary heart disease, arterial fibrillation, tendency to thrombosis, smoking, unhealthy diet, physical inactivity, diabetes and advancing age (Stroke WHO 2009). The majority of ischaemic strokes can be prevented by early recognition of risk factors and healthy living habits with moderate amount of exercise (MacKay et al. 2004, 62).

Economically stroke is the third most expensive disease group in Finland and the expenses in stroke rehabilitation are about 6.1 percent of the total health costs (Kaste et al. 2006). About 40 percent of all incidents will need intensive rehabilitation in the acute phase and as many as 30 000 chronic patients will need continuing rehabilitation (Aivoverenkiertohäiriöt numerotietoina 2009). Approximately 80 percent of stroke survivors will benefit from inpatient or outpatient rehabilitation whereas 10 percent of patients receive no benefit from any treatment (Zorowitz 2006). About 15 percent of stroke survivors remain in institutions (Aivoverenkiertohäiriöt numerotietoina 2009) whereas about 20 percent of stroke survivors will return to working life (Kaste et al. 2006).

2.1.2 Aetiology and clinical symptoms

Stroke or cerebral vascular accident (CVA) is a term used for disorders of the cerebral circulation including any disease of the vascular system that causes transient ischemic attach (TIA), ischemia or infarction of the brain or spontaneous haemorrhage into the brain or subarachnoid space (MacKay et al. 2004, 18). It is estimated that up to 80 percent of all the stroke cases are caused by infarctions in Finland (Kaste et al. 2006). Haemorrhage is the reason in 10 percent of the cases and 10 percent of all CVA cases are caused by bleed into the subarachnoid space (Kaste et al. 2006). A blood vessel burst or a clot in a blood vessel will cause temporal interruption of the blood supply to the brain (Stroke WHO 2009). This will lead to damage in the brain tissue as the supply of oxygen and nutrients is temporary limited or totally disturbed.

Stroke can cause permanent neurological brain damage, complications and even death if not appropriately treated. The most common symptom of a stroke is sudden weakness or sensory loss of the face, arm or leg, most often on one side of the body (Stroke WHO 2009). This is known as hemiplegia. About 75 percent of all acute stroke cases will have sensory and motor impairment with upper and/or lower limb paralysis (Kaste et al. 2006). The location and the area of the lesion will correlate with the severity of the paralysis (Blanton & Wolf 2006). Other symptoms may be confusion, difficulty of speaking or understanding speech, problems with vision or walking, dizziness, loss of balance or coordination, severe headache, fainting or unconsciousness (Stroke WHO 2009). Depending on the site of the lesion other secondary complications may also occur (Table 1). These clinical symptoms need to be taken into consideration when planning the treatment and rehabilitation interventions as they may influence the recovery.

Table 1. Secondary complications related to stroke

Symptom	Implications to daily functions
agnosia	problems in perception
aphasia	speech and language difficulties
apraxia	difficulties in learnt functions
ataxia	co-ordination problems in extremities

cognitive deficits	problems in cognitive functions such as memory problems, learning difficulties
dysphagia	difficulty in swallowing
incontinence	loss of regular control of the bowels and/or bladder
neglect	carelessness or unable to pay attention to the hemiplegic side, can be present in all senses (vision, touch etc.)
spasticity	muscular hypertonicity
psychological problems	depression
vision impairments	visual inattention, blurry vision, homonymous hemianopia (partial blindness resulting in a loss of vision in the same visual field of both eyes)

2.1.3 Rehabilitation and recovery after stroke

The main goal for stroke rehabilitation is to maximize patients´ independent functioning and quality of life preferably in patients´ own home (Peppen et al. 2004a). The type of the stroke rehabilitation is dependent on the severity of the stroke and the physical and cognitive impairments caused by the stroke (Pyöriä 2007, 71). Successful recovery after a stroke is dependent on the extent (Jørgensen et al. 1995) and location (Shelton & Reding 2001) of brain damage and the admission to intensive rehabilitation. The active role of a patient in rehabilitation is essential. Together with motivation, personal qualities such as age, gender, educational background, profession, lifestyle and habits may influence the result of rehabilitation. Recovery is also influenced by the age, presence of incontinence, upper limb recovery and cognitive stage (Kaste et al. 2006). Participation of the patient's family in the rehabilitation process is essential for successful outcome. Initial recovery is based on a decrease of swelling in the central nervous system and brain plasticity (Bütefisch 2004).

Rehabilitation is a learning process requiring experiences and practise with multiple repetitions (Shumway-Cook & Woollacott 2001, 27, Schmidt & Wrisberg 2008, 11). Motor learning will produce synaptic reorganisation and regeneration in the central nervous system (Bütefisch 2004). Learning is considered as permanent change in motor control that will help patient to overcome in various tasks and environments (Shumway-Cook & Woollacott 2001, 27, Gallahue & Ozmun 2006, 15). Motor control is defined by Shumway-Cook and Woollacott (2001, 1-2) as the ability to regulate or direct the mechanisms essential to movement. These neural, muscular, biomechanical and perceptual mechanisms are essential for motor learning (Gallahue & Ozmun 2006, 16). Rehabilitation is a cognitive process where memory and motivation will play an important part in the recovery (Shumway-Cook & Woollacott 2001, 25). During the rehabilitation process stroke patient will learn variety of movement skills and this motor performance can be measured through some form of outcome measures (Gallahue & Ozmun 2006, 16).

Motor learning results from an interaction of the individual, the task and the environment (Shumway-Cook & Woollacott 2001, 49, Schmidt & Wrisberg 2008, 16-21). Somatosensory training with intensive task-related practice will provide the possibility for the stroke patient to select, attend to and respond to relevant sensory inputs (Carr & Shepherd 2000, 145-146). Therefore stroke patients should be encouraged to use their affected upper limb despite the sensory or motor loss. Trained tasks should be challenging enough so that training is progressive (Page et al. 2004). The trained skills and tasks should be similar needed in daily living in individuals´ own environment so that the patient can transfer learnt skills to his home environment (Talvitie 2008). The patient will also need visual and verbal feedback both during the training and on completion of the task (Shumway-Cook & Woollacott 2001, 35; Talvitie 2008). There is evidence that stroke patients will benefit from training in the enriched environment of specialized stroke units with a multidisciplinary approach (Kwakkel et al. 1999, Jörgensen et al. 2000, Sivenius & Tarkka 2008).

The recovery after stroke has traditionally been divided into acute, subacute or postacute and chronic stage. The speed and quality of the recovery and also treatment guidelines varies in each phase (Peppen et al. 2004a).The acute phase will last up to two weeks from the onset of stroke. In this stage patient is mainly immobilized and not stable enough for vigorous exercise as there will be swelling present in the central nervous system (Peppen et al. 2004a). Passive limb mobilisations and positioning should be started immediately to prevent body and limb dysfunction and activate the somatosensory system. Intensive multidisciplinary rehabilitation should commence as soon as the patient is stable enough (Peppen et al. 2004a). It should include a holistic approach to patient’s motor and cognitive function (Sivenius & Tarkka 2008).

There is evidence that increasing the intensity of therapy can enhance motor recovery (Schaechter 2004). Patients with upper limb deficits will benefit of intensive upper limb training in the acute phase (Feys et al. 1998). The patient is encouraged to use his hemiplegic side in all activities and compensatory functions should be avoided (Kaste et al. 2006). The reliable prognosis of the rehabilitation can be estimated within one to three weeks of the onset of stroke and it should be done by a multidisciplinary team (Kwakkel et al. 1996). According to study by Kwakkel et al. (2003) the optimal prognosis for upper limb dexterity can be made within the first four weeks after the onset of stroke.

The subacute phase is considered as time till six months from the onset of CVA. The first three months are the fastest phase of recovery (Jørgensen et al. 1995). The final phase the chronic stage is from six months onwards. At this stage motor recovery is still possible but changes will be slower. There is evidence that the abilities in function can be improved with intensive out-patient rehabilitation after one year of discharge from hospital (Green et al. 2002), therefore out-patient rehabilitation should be continued as long as progress will occur.

2.2 Stroke and upper limb dysfunction

Upper extremity function is the basis for the fine motor skills required for feeding, dressing and grooming (Shumway-Cook & Woollacott 2001, 447). Upper limb function also plays an important role in walking and the ability to recover balance (Shumway-Cook & Woollacott 2001, 448). Therefore upper limb paralysis will remarkably reduce the ability to independently perform activities of daily living and decrease the quality of life of an individual (de Kroon et al. 2005). Reaching movements are the major actions of the arm (Carr & Shepherd 2000, 126). Critical muscles for reaching are shoulder and elbow muscles that transport the arm and wrist and finger muscles that are critical for object manipulation (Carr & Shepherd 2000, 249; Krebs et al. 2007b). Optimal muscle tone, muscle strength, flexibility and co-ordination are essential of the muscles surrounding the shoulder and scapula for successful reach (Shumway-Cook & Woollacott 2001, 456).

Somatosensory impairments may be a major cause of functional disability of the hand (Carr & Shepherd 2000, 223). Losses of tactile and proprioceptive sensation as well as pain and diminished temperature sensation are often associated with stroke. Problems with discrimination and interpretation of information regarding movement, force, texture or stereognosis of an object can be related to somatosensory deficits after stroke (Carr & Shepherd 2000, 222-223). The large representation areas of the upper limb and hand in the somatosensory cortex will illustrate the amount of detailed information needed to execute actions of the upper extremity (Shumway-Cook & Woollacott 2001, 66).

The lateral corticospinal tract will monitor the function of the upper limb, especially its distal parts (Sivenius 2001). Eighty-five to ninety percent of the fibres of the lateral corticospinal tract will cross over in contralateral side in pyramidal decussation (Soinila 2006). Therefore they will co-ordinate the muscle function and sensory in the opposite side of the body. The damage of this tract can cause total or incomplete paralysis of the opposite upper limb (Sivenius 2001). As middle cerebral artery (MCA) is predominantly affected in stroke it is more likely to result in upper limb paralysis than lower limb dysfunction (Kaste et al. 2006).

Motor recovery of the upper limb after stroke is often incomplete compared to lower limb recovery (Kwakkel et al. 2003). Recovery of upper limb motor control seems develop proximal to distal (Peppen et al. 2004b) and the distal parts will recover less well than proximal parts (Sivenius 2001). The initial grade of the paresis seems to be the most important predictor of motor recovery (Blanton & Wolf 2006) but the accuracy of prediction rapidly improves during the first few days after stroke (Hendricks et al. 2002). The other factors that can complicate motor recovery of paretic upper extremity are gross sensory deficiency, shoulder pain, limited shoulder range of motion and increased muscle tone (Blanton & Wolf 2006). The recovery period in patients with severe stroke can be twice as long as with mild hemiplegic patients (Hendricks et al. 2002). Patients who developed some voluntary movement over the lower extremity in the first week after stroke had about 74 percent chance of regaining some dexterity in the upper extremity (Kwakkel et al. 2003). It is estimated that if there is no activity in the upper limb within a week after onset of stroke, there is 80 percent of possibility that the arm will remain non-functional (Kaste et al. 2006). If there is no activity in the fingers and wrist after a month since the incident there is strong likelihood that the hand remains permanently disabled (Sivenius 2001, Blanton & Wolf 2006). Typically stroke survivors with initial upper limb movements respond better to treatment because they can voluntarily engage the limb in various activities (Blanton & Wolf 2006).

Stroke and upper limb paralysis may cause various impairments in the upper extremity. Inferior glenohumeral joint displacement, generally referred to as shoulder subluxation, is caused by gravitational pull on the humerus and stretching of the capsule of the shoulder joint as the muscles around the shoulder are weakened by paralysis (Ada & Foongchomcheay 2002). Spasticity in the muscles surrounding shoulder can correct the subluxation but it also tends to pull the humerus into internal rotation (Ada & Foongchomcheay 2002). In both cases traction of various nerves, inflammation and impingement of passive and active range of movement may occur. Subluxation appears to be related to the degree of paralysis in the muscles of the upper limb (Ada & Foongchomcheay 2002). Incidence of subluxation is highest with flaccid upper limb and can be as high as 81 percent among the stroke patients (Ada & Foongchomcheay 2002). As many as 84 percent of the hemiplegic patients experience shoulder pain in some stages of recovery (Turner-Stokes & Jackson 2000) and there is correlation between shoulder pain and range of movement (Page et al. 2003). Therefore pain can be a limiting factor of functional use of upper extremity. It is often hypothesised that one of the underlying causes for shoulder pain is subluxation but Snels et al. (2002) found no relationship between shoulder subluxation and pain. Therefore the aetiology of pain remains unclear.

Pathologically increased muscle tone or as often referred to as spasticity is one manifestation of the upper motor neurone syndrome. Spasticity is traditionally described as a motor disorder characterized by a velocity-dependent increase in monosynaptic stretch reflex with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex (Shumway-Cook & Woollacott 2001, 597). The syndrome has so-called positive features including muscle hypertonia, sometime painful muscle spasms, tendon hyperreflexia (such as clasp-knife phenomenon and clonus) and abnormal patterns of muscle activity during voluntary movement. The negative features are muscle fatigability, decreased dexterity particularly for fine manipulation, weakness or impairment of independent and co-ordinated movements (Carr & Shepherd 2000, 137). Often spasticity is mixed with muscle stiffness and muscle contracture (Carr & Shepherd 2000, 137). Upper limb spasticity may inhibit the fine use of hand in variety of functions.

Swelling and hand oedema are common problems among stroke patients. As many as 73 present suffer from some degree of hand swelling (Boomkamp-Koppen et al. 2005). Hand oedema may occur as an isolated problem or as a part of shoulder-hand syndrome (Geurts et al. 2000). Oedema affects mainly paretic arm with hypertonia in fingers and impaired sensibility (Boomkamp-Koppen et al. 2005). The pathophysiology remains unclear but it seems a multifactorial problem (Geurts et al. 2000). Hand oedema may affect especially the fine use of hand.

2.3 Upper limb physiotherapy interventions in stroke rehabilitation

2.3.1 Neurotherapies

There is various treatment interventions used in upper limb stroke rehabilitation. Traditionally neurotherapies such as neurodevelopmental treatment (NDT) as also called as Bobath approach is widely used with patients with hemiplegia (Carr & Shepherd 2000, 16).) Neurotherapies are facilitation techniques that are used with people who have central nervous system insults that create difficulties in controlling movement. With manual guidance the therapist inhibits abnormal muscle tone and facilitates normal movement and the role of the patient remains relatively passive (Shepherd 1997, 46). As rehabilitation is based on learning where the involvement of the patient as an active participant will play an important part, it can be assumed that the carry over of these techniques is only short-term.

In the literature five systematic reviews (Hiraoka 2001, van der Lee et al. 2001, Barreca et al. 2003, Paci 2003, Luke et al. 2004) analyzed the effectiveness of NDT approach with other physiotherapy interventions or a placebo. It seems evident that the NDT technique is not superior to conventional physiotherapy in any recovery phase in stroke physiotherapy in three systematic reviews out of five. In one systematic review NDT was compared with no therapy but the results were contradictory (Luke et al. 2004).

2.3.2 Task-related practice and bilateral movement training in various environments

The goals for adult stroke patients in upper limb rehabilitation are usually re-learning bimanual skills required in activities of daily-living such as eating, washing, grooming, dressing and writing. Task-related practice with meaningful tasks and a high amount of repetitions is considered the most crucial component for recovery of stroke (Carr & Shepherd 2000, 141, Winstein & Stewart 2006). There is evidence that intensive and meaningful, task-specific training will be effective compared to traditional neurophysiological treatment approaches (Sivenius 2001). Task-specific training focuses on improving the performance of functional tasks through repetition and goal-oriented practise (Winstein & Stewart 2006, Zorowitz 2006). This involves the patient's active role and motivation in the therapy. There is evidence that new areas in cerebral cortex will activate as the affected upper limb is used intensively in meaningful functional tasks (Sivenius 2001). Skill practise in an enriched environment with meaningful tasks related to patients' every-day life should be an essential part of upper limb stroke physiotherapy (Carr & Shepherd 2000, 249, Shumway-Cook & Woollacott 2001, 44).

Two systematic reviews (French et al. 2007, Urton et al. 2007) have searched for evidence of the effectiveness of repetitive task training after stroke in improving upper limb function. Mostly exercises were functional such as reach and grasp, leaning, punching a ball, dressing, hair-combing, moving objects, using a keyboard or writing tasks. In one trial they used the Motor Relearning Programme by Carr and Shepherd (2000). There were also tasks to improve motor control such as hand-eye co-ordination, stretching and strengthening exercises. Interventions lasted from 30 minutes to six hours per day, five to seven days a week for total of two to 20 weeks. Total amount of repetitive training varied from five to 84 hours.

The results of two systematic reviews are conflicting. The largest and a high quality systematic review by French et al. (2007) found evidence that repetitive task training is no more effective than conventional therapy in improving arm and hand function or sitting balance and reach. Urton et al. (2007) found that repetitive task training is equally effective to conventional therapy but more effective than Bobath approach. They suggest that repetitive task training is more effective in the acute stage with mild stroke. On the other hand French et al. (2007) presented that there is no relationship between the effect of repetitive task training and dosage of task practise, time since stroke or type of task training. They also did not find any adverse effects whereas Urton et al. (2007) reported an increase in upper limb pain with passive range of movement.

It is necessary to practise bimanual actions since the two upper limbs work co-operatively in most every day tasks (Carr & Shepherd 2000, 143). Bilateral movement training is based on the assumption that voluntary movements of the intact limb may facilitate voluntary movements in the paretic limb by activating similar neural networks in both hemispheres (Stewart et al. 2006). A recently published good-quality systematic review by Stewart et al. (2006) found strong evidence that bilateral movement training is beneficial alone or in combination with rhythmic auditory cueing or electrical stimulation in the subacute and chronic stages of motor recovery post-stroke. Results can be generalized only to the patients with right hemiparesis though. Bilateral movement training consisted of 50 to 90 minutes training sessions for total of 18 to 50 trials with block placements, simulated drinking, peg targeting, reaching, dowel placement tasks or active wrist/finger extensions. Interventions lasted for six days to eight weeks. There were no adverse effects.

Virtual reality is a relatively new treatment method in upper limb rehabilitation after stroke. It is a computer-based, interactive, multisensory simulation environment that occurs in real time (Henderson et al. 2007). Activities and environments imitate real world situations (Weiss et al. 2006). It will provide a virtual environment for task-related unilateral and bilateral arm training. According to Weiss et al. (2006) and Henderson et al. (2007) a term immerse virtual reality is used when the user has a strong sense of presence of the environment in a concave computer screen with additional interface devices (i.e. computer mouse, joystick, force sensor). In non-immersive virtual reality the user interacts to different degrees with the virtual environment with or without interface devices. There is only one systematic review published about the upper limb training in virtual reality (Henderson et al. 2007). Results are based on two RCT`s and four clinical trials. Initial results are promising that immersive virtual reality may have an advantage over no therapy in arm function even in chronic stroke population. There were no adverse effects.

Mirror therapy is used for bilateral training in upper limb rehabilitation. Patients are asked to move the non affected arm while looking in a mirror that give the impression that the paretic limb was moving (Peppen et al. 2004b). In the study by Altschuler et al. (1999) symmetric upper limb movements were performed using a mirror for 15 minutes twice a day for six times a week during a four week period. A control group performed similar movements using transparent plastic sheet. No evidence was presented but there were tendency that mirror therapy may be beneficial for the chronic stroke population. No side effects were reported. In the most recent RCT by Dohle et al. (2009) subacute stroke patients with severe hemiparesis completed a protocol of six weeks of additional mirror therapy for 30 minutes a day, five days a week compared to control group. Their results indicated that mirror therapy is a promising method to improve sensory and attention deficits and to support motor recovery in a distal paretic limb.

2.3.3 Constraint-induced movement therapy

Constraint-induced movement therapy (CIMT) is a term used to describe various treatment modalities that all focuses on restraining the unaffected upper limb while forcing the use of the affected upper extremity to promote purposeful movement (Bjorklund & Fecht 2006). It is based on assumption that after paralysis the patient will learn not to use the weaker arm with possible stiffness and sensory loss. Six systematic reviews have been released about the CIMT in upper limb after stroke (Hiraoka 2001, Van der Lee 2001, Barreca et al. 2003, Hakkennes & Keating 2005, Bjorklund & Fecht 2006, Bonaiuti et al. 2007). Five out of six reviews found that CIMT is an effective treatment method both in the acute and chronic stage after stroke compared to other physiotherapy interventions or no treatment.

The technique involves the restraint of the intact upper limb with a mitten, glove or hand splint and arm sling for as long as 90 percent of the waking hours in combination with a large number of repetitions of task-specific training of the affected upper limb (Bjorklund & Fecht 2006). According to the systematic reviews the total amount of training varied between 30 minutes to six hours per day for three to six times a week as long as two to 10 weeks. The results should be generalised to people with preserved cognitive function and sitting balance, no severe spasticity and with 10° of active finger and 20° of active wrist extension. In the review by Hakkennes and Keating (2005) burns and skin lesions in the restraint limb as well as muscle soreness in the affected limb after the intensive use were reported. Compliance can be poor as the constraint can make normal bimanual functioning impossible. Due to long-term involvement to therapy it may not be always clinically feasible. Therefore some modifications have been tried out to reduce the daily participation time and lengthen the overall treatment period form the original protocol. It appears that modified CIMT is effective improving upper limb function following stroke (Hakkenness & Keating 2005). Nevertheless the optimal treatment protocol remains unclear.

2.3.4 Electrical stimulation and electromyography biofeedback

In upper limb stroke rehabilitation the electrical stimulation is often used for improving the motor control and thus increasing the muscle power of the paralysed hand. Various terms are used unclearly to describe the given stimulation depending on the purpose of the treatment. When Therapeutic Electrical Stimulation (TES) is used the purpose is to achieve sensory response to treatment but in the literature it has also been used to describe motor stimulation (Mc Donough & Kitchen 2002). In Neuromuscular Electrical Stimulation (NMES) the stimulation is applied in a pre-programmed scheme, resulting in repetitive muscle contractions without active involvement of the patient (Mc Donough & Kitchen 2002). It can be utilized with or without functional movement. When NMES is used for facilitation the movement will require active participation from the patient (Baker et al. 2000, 58). Functional Electrical Stimulation (FES) is a term used to describe the stimulation together with patient active involvement where functional movement is the main purpose (Mc Donough & Kitchen 2002, Gorman et al. 2006). Often NMES and FES are used synonymously. Transcutaneous Electrical Nerve Stimulation (TENS) can also be used for motor stimulation when parameters are adjusted to evoke muscle contraction (de Kroon et al. 2005).

Electromyography (EMG) and electrical stimulation can be used together. EMG biofeedback (EMG-BF) will register patients volitional muscle contraction and full range of movement can be performed with the help of stimulation (Hesse & Werner 2003). Similar to EMG-triggered electrical stimulation is Positional Stimulation Feedback Training (PFST). It also requires patients active muscle contraction where electrical stimulation is added to increase a joint's full range of movement after patient has actively moved the joint beyond the pre-set threshold (de Kroon et al. 2005). Electroacupuncture is a method used for stimulation also where both surface and needle electros are used (de Kroon et al. 2005).

Seven systematic reviews have reported results of the effectiveness of electrical stimulation in improving motor control and function in the upper limb after stroke (Hiraoka 2001, de Kroon et al. 2002, Barreca et al. 2003, Handy et al. 2003, de Kroon et al. 2005, Pomeroy et al. 2007, Urton et al. 2007). De Kroon et al. (2005) did not study the effectiveness of electrical stimulation as such as they concentrated the relationship between the characteristics of stimulation to the effect of stimulation. In five out of seven systematic reviews it was found that there is strong evidence that electrical stimulation is an effective treatment method compared to no treatment or other physiotherapy interventions in all stages after stroke (de Kroon et al. 2002, Barreca et al. 2003, Handy et al. 2003, de Kroon et al. 2005, Urton et al. 2007). Electrical stimulation seemed to be effective in increasing motor control such as active range of motion, strength and fine dexterity of the hand. No gains were measured in functional ability. The most used stimulation method was NMES. TENS was included in three systematic reviews and PFST as well as electroacupuncture were used in two systematic reviews. The stage after stroke or severity of the paralysis did not seem to affect the effect of electrical stimulation (de Kroon et al. 2002, de Kroon et al. 2005). In many original trials participants were required to have some residual wrist movement. As treatment required good commitment, patients with cognitive deficits were often left out of the study. Muscles that were mostly stimulated were wrist and finger extensors, elbow extensors, shoulder abductors and both wrist and finger extensors and flexors. There were suggestions that electrical stimulation might be more effective if elbow and/or shoulder muscles were stimulated together with wrist and fingers (de Kroon et al. 2005).

De Kroon et al. (2005) found that specific stimulus parameters may not be crucial in determining the effect of electrical stimulation. Therefore it can be assumed that in improving muscle control it is more important to gain visible muscle contraction than set the specific stimulation parameters. In the analyzed studies frequency varied from 20Hz to 100Hz, except with TENS and electroacupuncture were low frequencies was used. Pulse duration was mostly reported to be 200-300μs. The rest periods between the stimulation periods were either same length or double the time of the treatment period. Ramp up and down varied from between one to three seconds. Amplitude was generally set according to the patient comfort. Treatment times ranged from 30 minutes to six hours per day, four to five days a week for two to eight weeks in total. Total hours or frequency of the stimulation did not reveal a difference for positive results (de Kroon et al. 2002, de Kroon et al. 2005). No adverse effects were reported of electrical stimulation.

There was one older (Moreland & Thompson 1994) and three more recently published systematic reviews (Hiraoka 2001, Barreca et al. 2003, Woodford & Price 2007) investigating the efficacy of the EMG-BF compared to other physiotherapy intervention or no treatment. According to three out of four reviews there is moderate evidence that EMG-BF is an effective treatment method in stroke rehabilitation in all recovery stages. A good quality review by Moreland and Thomson (1994) presented that EMG-BF is not an effective treatment method compared to conventional therapy for improving upper limb function. Whereas three recently published systematic reviews (Hiraoka 2001, Page & Lockwood 2003, Woodford & Price 2007) demonstrated that EMG-BF is effective together with conventional physiotherapy compared to physiotherapy alone increasing shoulder range of movement and upper extremity function. Treatment times varied from 20 to 45 minutes for three to five times a week in total of 10 to 28 sessions for two to 11 weeks. There were no adverse effects of EMG-BF.

2.3.5 Treatment interventions for shoulder pain and subluxation

Eight systematic reviews have been released for the various treatment interventions preventing and treating shoulder pain and subluxation following hemiparesis (Price & Pandyan 2000, Ada & Foongchomcheay 2002, Snels et al. 2002, Turner-Stokes & Jackson 2002, Barreca et al. 2003, Handy et al. 2003, Page & Lockwood 2003, Ada et al. 2005). The conclusions are based on 51 original studies of which 36 are RCTs and one is systematic review (Price & Pandyan 2000).

There is strong evidence that electrical stimulation (ES) of deltoid and/or supraspinatus muscles is effective in preventing shoulder subluxation in the acute stage and treating pain in the chronic stage compared to other physiotherapy interventions (Price & Pandyan 2000, Ada & Foongchomcheay 2002, Turner-Stokes & Jackson 2002, Barreca et al. 2003, Handy et al. 2003). ES was also effective in increasing pain free range of movement of the shoulder. Shoulder area ES did not seem to affect upper limb spasticity. No adverse effects were reported of ES in treating shoulder subluxation and pain. It is impossible to summarize the treatment times for various treatment modalities due to their heterogeneity.

Four systematic reviews have been done of the other methods treating post-stroke shoulder subluxation and pain (Snels et al. 2002, Turner-Stokes & Jackson 2002, Page & Lockwood 2003, Ada et al. 2005). Strapping of the shoulder joint especially if it is done within 48 hours after stroke seems promising in delaying onset of pain, but does not prevent pain to occur (Turner-Stokes & Jackson 2002, Page & Lockwood 2003, Ada et al. 2005). Steroid injections, oral medication, upper limb handling and positioning or use of arm slings did not prevent or decrease the pain in the shoulder (Snels et al. 2002). Injections also caused some side effects and were not supported as a treatment method for painful shoulder after stroke (Snels et al. 2002, Turner-Stokes & Jackson 2002, Page & Lockwood 2003). It was reported that slings caused over and under correction of the shoulder joint or even joint displacement (Turner-Stokes & Jackson 2002). A variety of exercise and therapy methods were investigated but there seemed to be no one method superior to the other. Overhead pulleys should be avoided in paralysed upper limb training as they can injure rotator cuff muscles (Turner-Stokes & Jackson 2002).

2.3.6 Treatment interventions for hand oedema and hand splinting

The evidence of the effectiveness of various treatment methods for hand swelling and oedema is limited. Systematic review by Geurts et al. (2000) included studies that investigated NMES, continuous passive motion, oral medication, injections and trauma prevention in treatment of hand oedema. No any specific treatment method was more advantageous over the other. There were no reports of the side effects, the recovery phase or the stage of paralysis. Roper et al. (1999) in their RCT found that intermittent pneumatic compression is not an effective treatment method for the swollen hand after stroke. It seems that prevention of swelling is the most successful option at present. Early recognition of the clinical signs and symptoms of oedema of the hand and care for the hand and shoulder are essential to prevent diminishing functioning, delay in the rehabilitation process and the occurrence of shoulder hand syndrome (Boomkamp-Koppen et al. 2005). Appropriate positioning in wheelchair or walking and active movement training should be encouraged.

Orthotics and splints are passive or powered external devices that support loads or assist or restrict motion (Krebs et al. 2006). Hand and wrist splints are widely used to prevent muscles from contracture in stroke rehabilitation (Carr & Shepherd 2000, 147). There is need for the evidence of the effectiveness of the use the splints as they can also inhibit the use of the affected limb and cause muscle shortening in the antagonist muscle groups. Lannin and Herbert (2003) assessed the effectiveness of hand splinting on the hemiplegic upper extremity following stroke. Results showed no difference in contracture formation in wrist and finger flexors compared to controls who received prolonged stretches for upper limb twice a day for 30 minutes, five days a week for six weeks. Authors' conclusions were made of 21 original trials of which only five were RCTs. Therefore the evidence remains insufficient. There was no evidence for adverse effects. The participants were from all recovery stages and there was no data of the severity of paralysis in the upper extremity. A variety of types of splints were used such as dynamic, resting, dorsal, dorsal-volar, finger spreader/adductor, cone, inflatable pressure or lycra splints.

2.3.7 Motor imagery training

Mental practise or motor imagery was initially developed for athletes but it has been used also in stroke rehabilitation to support motor recovery (Zimmermann-Schlatter et al. 2008). Motor imagery is an active training during which action is reproduced without any real movements and same brain areas are activated as during functional tasks (Zimmermann-Schlatter et al. 2008). No harmful effects have been reported and method is easy to apply to patients at all stages of the recovery after stroke (Carr & Shepherd 2000, 147, Zimmermann-Schlatter et al. 2008). There have been two systematic reviews published about the mental practise or imagery training (Barreca et al. 2003, Zimmermann-Schlatter et al. 2008). They all reported positive results compared to control interventions and therefore can be said that there is a moderate evidence of the effectiveness of imagery training in all stages of stroke upper limb rehabilitation. Imagery training varied from relaxation to audiotape listening and task analysis in addition to conventional occupational therapy or physiotherapy. Treatment sessions varied from 10 minutes to one hour per day, for three to five times a week for period of three to six weeks.

2.3.8 Additional training and home exercises

Two systematic reviews (van der Lee et al. 2001, Barreca et al. 2003) of low scientific quality searched for evidence of additional therapy time in upper limb rehabilitation. They increased the training time from 30 minutes to two hours a day for four to five days a week for a total of five to 20 weeks. Their conclusions were contradictory and therefore there is no evidence of the effect of increasing training volume or frequency in therapy.

Two systematic reviews investigated the efficacy of home based exercises compared to no therapy (van der Lee 2001, Barreca et al. 2003). There is little evidence of the effectiveness of home based exercises as only three RCTs has been published. Yet there is some evidence that home based exercises may be effective if the stroke patient does not receive any other therapy. Stroke patients had a 90 minute programme including self-range of movement exercises, functional retraining and self-pacing that they completed three times per week for eight weeks.

2.4 Robot-aided upper limb physiotherapy

New treatment methods have been developed to utilise the technology available. Rehabilitation robots are mechanical devices that are designed to interact with the human providing assistance both for the patient and the therapist in the rehabilitation process (Masiero et al. 2006, Lum et al. 2006). Mostly they are used and studied in the stroke upper limb rehabilitation (Masiero et al. 2006). Rehabilitation robots can facilitate upper limb motor recovery by repetitive goal-directed movements where the patient is actively involved the training (Hogan et al. 2006). Robot will guide patients the upper extremity movements smoothly providing thousands of repetitions without the involvement of the therapist (Krebs et al. 2000, Daly et al. 2005, Kahn et al. 2006a). Consequently they allow patients to practice independently and to improve on their own functional level as the robot can assist, support or resist the desired action (Krebs et al. 2000). Most of the robot-mediated therapy does not necessary require patient’s own active movement as robot can assist the movement as required (Hogan et al. 2006). Therefore method is suitable for all stroke patients with different type of upper limb functional levels.

Patients can perform unilateral or bimanual upper limb training for functional tasks depending on the type of the robot (Krebs et al. 2000). Most of the robotic devices are designed to practice the paralysed shoulder and elbow but recently new techniques have been introduced for wrist and hand rehabilitation (Krebs et al. 2007). In most robotic systems, more than one modality is incorporated into a single device. A robot provides progressive and high-intensity training with multiple repetitions and will give immediate feedback of the performance both for the patient and the therapists (Krebs et al. 2006, Prange et al. 2006). Robot can also provide valuable data of the changes in movement kinematics, forces and patients involvement the training (Fasoli et al. 2003, Kahn et al. 2006a, Krebs et al. 2006). There is evidence that treatment compliance has improved by introducing games and other virtual environments with robotic training (Kwakkel et al. 2008).

Movements with the robot can be set beforehand and the robot can assist the weak limb through stereotyped movement patterns (REHAROB, NeReBot) or a system may allow free reaching movements with variety of degrees of freedom (MIME, ARM-Guide, MIT-Manus, InMotion2). MIT-Manus, Bi-Manu-Track and MIME robotic devices can provide resistance for desired movement. In the upper limbs´ encircling motion (ULEM) a patient is asked to grasp the rod and move it against the resistance of the springs with an inferior-posterior-superior-anterior sequence in a circle (Wang et al. 2007). Generally during the therapy the patient sits in front of the computer screen and speakers that will provide visual and auditory feedback indicating correct movements, with trunk supported and strapped by a harness into a custom foam-lined chair or a wheelchair. In some models patient may lie on his side while training with the robot (NeReBot) (Masiero et al. 2007). Elbow and wrist are supported in a neutral position and fit in a connecting trough to the robot. Hand and fingers are attached by straps or orthotics to a handle.

There are several manufacturers that have developed variety of robots for rehabilitation purposes (Table 2). These robotic systems are only few examples of the available rehabilitation robots. As the area is relatively new, more robotic systems will be developed for rehabilitation purposes. At the moment there are no rehabilitation robots in therapeutic use in

Finland and there is only one Finnish company that imports the rehabilitation robots to the country.

Table 2. Robotic prototypes used in upper limb rehabilitation

Robot type	Institution	Reference	Country	Type of training
Massachusetts Institute of Technology (MIT)-Manus	Massachusetts Institute of Technology: Newman Laboratory for Biomechanics and Human Rehabilitation	Aisen et al. 1997	USA	Unilateral passive, active-assisted or active resisted shoulder and elbow movements
InMotion2	Interactive Motion Technologies Inc., Cambridge, MA	Daly et al. 2005	USA	Unilateral passive, active-assisted or active-resisted shoulder and elbow movements
Mirror Image Motion Enabler (MIME)	Staubli Unimation Inc, Duncan, SC	Burgar et al. 2000	USA	Unilateral or bilateral passive or active-assisted or active-resisted shoulder and elbow movements
Assisted Rehabilitation and Measurement (ARM) Guide	Rehabilitation Institute of Chicago	Kahn et al. 2006	USA	Unilateral active-assisted reaching movements involving the whole upper extremity
The Neuro-Rehabilitation-Robot (NeReBot)	Padova University	Masiero et al. 2007	Italy	Unilateral passive or active shoulder and elbow movements
REHAROB-system	Budapest University of Technology and Economics, National Institute for Medical Rehabilitation, University of Wales Cardiff, University of Rousse, Zebris Medizintechnik GmbH	Fazekas et al. 2007	Hungary, Wales, Bulgary, Germany	Passive unilateral robot-assisted movements
Bi-Manu-Track	Reha-Stim Company, Berlin	Hesse et al. 2005	Germany	Bilateral passive or active-assisted or active-resisted elbow and wrist movements
ARMOR	Austrian Research Centre, Wien	Mayr et al. 2008	Austria	Unilateral passive or active shoulder, elbow and wrist movements
GENTLE/s robotic system	Haptic Master, FCS Robotics	Coote et al. 2008	Ireland, UK, Slovenia	Unilateral passive or active shoulder and elbow movements
Upper limbs´ encircling motion (ULEM) apparatus	SuTongKang Science and Technology Institution, Nanjing	Wang et al. 2007	China	The patient may train the whole upper extremity with the system by moving the rod with encircling motion

There are two high quality systematic reviews by Prange et al. (2006) and Kwakkel et al. (2008) and two other systematic reviews (Van der Lee et al. 2001, Barreca et al. 2003) which has summarised the effects of robot-aided therapy. Reviews by Van der Lee et al. (2001) and Barreca et al. (2003) included only one RCT by Volpe et al. (2000). Review by Prange et al. (2006) included three RCTs (Lum et al. 2002, Fasoli et al. 2004a, Stein et al. 2004) and five clinical trials (Krebs et al. 2000, Reikensmeyer et al. 2000, Ferraro et al. 2003, Krebs et al.

2004, Lum et al. 2004). It investigated the effects of robot-aided therapy on the upper limb motor control and functional abilities with stroke patients in all recovery stages. The effects of robot-aided therapy seemed to be training-specific as improvements occurred only in the trained shoulder and elbow, not in the wrist or hand. Intervention consisted of repetitive, goal-directed reaching movements partially guided by robotic device three to five hours per week, for six to eight weeks. There is limited evidence that this method is effective for motor control in the short and long term. Robot aided therapy does not seem to be effective in improving functional abilities. It is a promising method both for acute and chronic patient groups but it looks like moderately affected patients are more responsive to treatment than severely paralyzed patients.

Review by Kwakkel et al. (2008) included 10 RCTs (Aisen et al. 1997, Burgar et al. 2000, Volpe et al. 2000, Kahn et al. 2001, Lum et al. 2002, Fasoli et al. 2004, Daly et al. 2005, Hesse et al. 2005, Kahn et al. 2006b, Lum et al. 2006) and it investigated the additional effect of robot-assisted therapy on motor recovery and functional outcome in comparison with conventional treatment forms. Patients represented all recovery stages. Patients practiced with the robot for 20-90 minutes a day for four to 12 weeks. On average, compared to controls the robot-trained group received additional training with the robot. Therefore the amount of exercise is not comparable with the intervention and control groups. As Prange et al. (2006) presented Kwakkel et al. (2008) also found that robot-aided upper limb therapy did not improve upper limb's functional abilities but had a moderate effect on motor recovery measured by Fugl-Meyer upper limb assessment (FM). No adverse effects have been reported of robot-assisted therapy in the literature (Prange et al. 2006, Kwakkel et al. 2008). There is a need for further studies to investigate the effects of robot-aided upper limb therapy on paralysed arm muscle power, spasticity, range of motion and muscle co-ordination.

3 STUDY OBJECTIVE

The purpose of this systematic literature review was to analyze and summarize the available evidence of the effectiveness of robot-aided upper limb therapy on upper limb function, motor control, body functions and participation in adult stroke population based on randomized controlled trials (RCTs). The answers were looked at whether robot-aided upper limb therapy is an effective method on hemiplegic upper limb recovery compared with other physiotherapy methods or placebos? More specifically the research questions were:

1. Is robot-aided upper limb therapy an effective method in improving upper limb function in activities of daily living?
2. Is robot-aided upper limb therapy an effective method in improving hemiplegic upper limb motor control in manual activities?
3. Is robot-aided upper limb therapy an effective method in reducing the upper limb spasticity after stroke?
4. Is robot-aided upper limb therapy an effective method in increasing the muscle power and active range of movement of the hemiplegic upper limb?
5: Does robot-aided upper limb therapy have an effect on pain, depression or quality of life after stroke?

4 METHODS

4.1 Searching of studies

A systematic literature search was performed by a librarian in January to March 2007 in three electronic databases CINAHL (1982 to March 2007), MEDLINE (1950 to January 2007) and EMBASE (to February 2007). The initial search was kept wide to guarantee all possible papers concerning stroke rehabilitation. Search terms (MeSH) were stroke, cerebrovascular accident, cerebrovascular disorders, brain ischemia, brain infarction, hemiplegia, exercise therapy, physical therapy modalities, physical therapy, physiotherapy, functional therapy, occupational therapy, exercise, activities of daily living, recovery of function, motor recovery, disability, rehabilitation, motor control, motor learning, randomized controlled trial, random allocation and clinical trial. An additional and identical search was performed in August to October 2008. Search strategies are in detailed in appendix 1. After these two phases the search terms were specified to upper limb therapy, upper limb physiotherapy/physical therapy, robot and robot-aided therapy. A hand search was completed for relevant references and published reviews that were not identified in electronic search. An inquiry was sent to authors in a case that the article was lacking of relevant information for the inclusion or meta-analysis.

4.2 Selection of studies

In the initial board search three independent assessors (TS / JP / SP) screened the titles and abstracts and selected the relevant studies that fulfilled the inclusion criteria. The same method was used in an additional search (KN and SP). Where there was disagreement between the reviewers the third assessors was consulted (TS). After these wide electronic searches the search was limited to robot-aided therapy and upper limb stroke rehabilitation. This part of the selection was completed by one assessor (KN), who reviewed the relevant titles and abstracts. The same blinded assessors screened the remaining full-text articles for their eligibility.

The inclusion criteria were as follow: 1) adult stroke population in all stages of recovery, 2) robot-aided therapy interventions for the hemiplegic upper limb, 3) randomized and controlled study setting or randomized cross-over setting, 4) compared intervention to other physiotherapy approach, placebo or no treatment, 5) the intervention and control groups were comparable, 6) were published in Finnish, Swedish, English or German and 7) were available in full text format. Exclusion criteria were: 1) participants that had other diagnosis than stroke or included children (under 18 years old), 2) treatment interventions that concentrated to the lower limb robot-aided therapy, 3) no control group for comparison, 4) randomization to intervention and control groups were inappropriate, 5) intervention and control groups were not comparable, 6) no motor deficits of the upper limb, 7) follow-up study or a protocol.

4.3 Assessment of methodological quality

The methodological quality of the selected RCTs was assessed by two independent and blinded assessors (KN and TH) according to the criteria by van Tulder et al. (2003) (Appendix 2). In a case of disagreement the third assessor was consulted (TS). Assessors were blinded for identifying features of article such as authors, journal title, year published and funding source. Quality assessment scale was 11 point scale and each criterion is rated either “yes”, “no” or “?”. Documentation was made of randomization, similarity of experimental and control groups, blinding of the therapist, assessor and patient as well as successful completion of the trial. Consensus on these items was reached by discussion. Kappa statistics for agreement was calculated. Studies that scored “no” in the first section were left outside the study as they did not meet the criteria of randomization. If needed the study authors were contacted to clarify this missing data.

4.4 Data analysis

One independent and blinded assessor extracted the data from the RCTs (KN) and contacted the study authors to clarify data or obtain missing data wherever possible. The second reviewer was consulted in a case of a problem (TS). Documentation was made of patient characteristics, intervention characteristics, control intervention characteristics and outcome measures. According to the control intervention the statistical comparison was made of robot-aided therapy and no treatment or placebo, robot-aided therapy and other treatment, robot-aided therapy and additional treatment versus other treatment and additional treatment. Subgroup analyses were completed if more detailed results were needed.

Outcome data used in the trials were continuous where each individual's outcome is a measurement of a numerical quantity and can have any value in a specific range (Deeks et al. 2008). For continuous outcomes there are two summary statistics available, the mean difference (MD) and the standardized mean difference (SMD). The mean difference is used when studies have reported outcomes in the same scale. If outcomes are reported in different scale the standardized mean difference has to be used. Mean change or final values with standard deviation (SD) for intervention and control groups were entered to the Cochrane Collaboration's Review Manager Software (RevMan 5.0.16). It calculated pooled effect estimates for combinations of single RCT effects. Larger studies with smaller standard deviations were given more weight than smaller studies. In multiple comparisons with two or more treatment groups, the numbers of controls were divided among comparisons.

Mean difference measures the absolute difference between the mean values in two groups and estimates the amount by which the experimental intervention changes the outcome on average compared with the control group (Deeks et al. 2008). That is the treatment effect. When standardized mean difference is used it is necessary to standardize the results of the included studies to a uniform scale before they can be combined, i.e., effects size (Deeks et al. 2008). The random effects model was used for analysis. Overall effect was tested with Z-test, in which a null hypothesis consisted of no difference between intervention group and control group. P-value below 0.05 was considered statistically significant. Effect size more than 0.5 represented large effects, 0.3 to 0.5 moderate effects, 0.1 to 0.3 small effects and below 0.1 was considered not meaningful (Cohen 1988).

RevMan also tested heterogeneity of trials with Cohrans Q statistic or χ^2 test and I^2 statistic. I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). With a value 0 to 40 percent considered not important, 30 to 60 percent represented moderate heterogeneity, 50 to 90 percent indicated substantial heterogeneity and 75 to 100 percent was considerable heterogeneity of intervention effects (Deeks et al. 2008).

5 RESULTS

5.1 Included studies

Out of a total of 12 010 abstracts 570 RCTs were identified in the initial and board search. After screening the abstracts with the specified robot-aided upper limb therapy terms, 31 relevant articles were selected. Thirteen of those needed to be excluded as they did not meet the inclusion criteria (Figure 1). One study was a protocol (Krebs et al. 2007b), one was a review (Krebs et al. 2007a), one follow-up study (Volpe et al. 1999), eight papers were clinical trials (Krebs et al. 2000, Reinkensmeyer et al. 2000, Ferraro et al. 2003, Krebs et al. 2004, Lum et al. 2004, Doornebosch et al. 2007, Siekierka et al. 2007, Stein et al. 2007), in one paper the randomization method was inappropriate (Takahashi et al. 2008) and one trial was a case-based cross-over study (Coote et al. 2008). Eventually 18 RCTs that fulfilled the inclusion criteria were identified (Aisen et al. 1997, Burgar et al. 2000, Volpe et al. 2000, Lum et al. 2002, Fasoli et al. 2003, Fasoli et al. 2004a, Stein et al. 2004, Hesse et al. 2005, Daly et al. 2006, Kahn et al. 2006b, Lum et al. 2006, Masiero et al. 2006 Amirabdollahian et al. 2007, Fazekas et al. 2007, Masiero et al. 2007, Wang et al 2007, Mayr et al. 2008, Volpe et al. 2008). Two studies referred to the same patient sample (Volpe et al. 2000, Fasoli et al. 2004a) but different outcome measures were used. In the trial by Lum et al. (2006) three different robotic interventions were compared to the same control group. In the analysis phase each comparison was considered as individual study. Study by Burgar et al. (2000) was left out after quality analysis as they did not report statistical data of the results and did not respond to enquiries. The included and excluded studies are explained in more detailed in appendix 3.

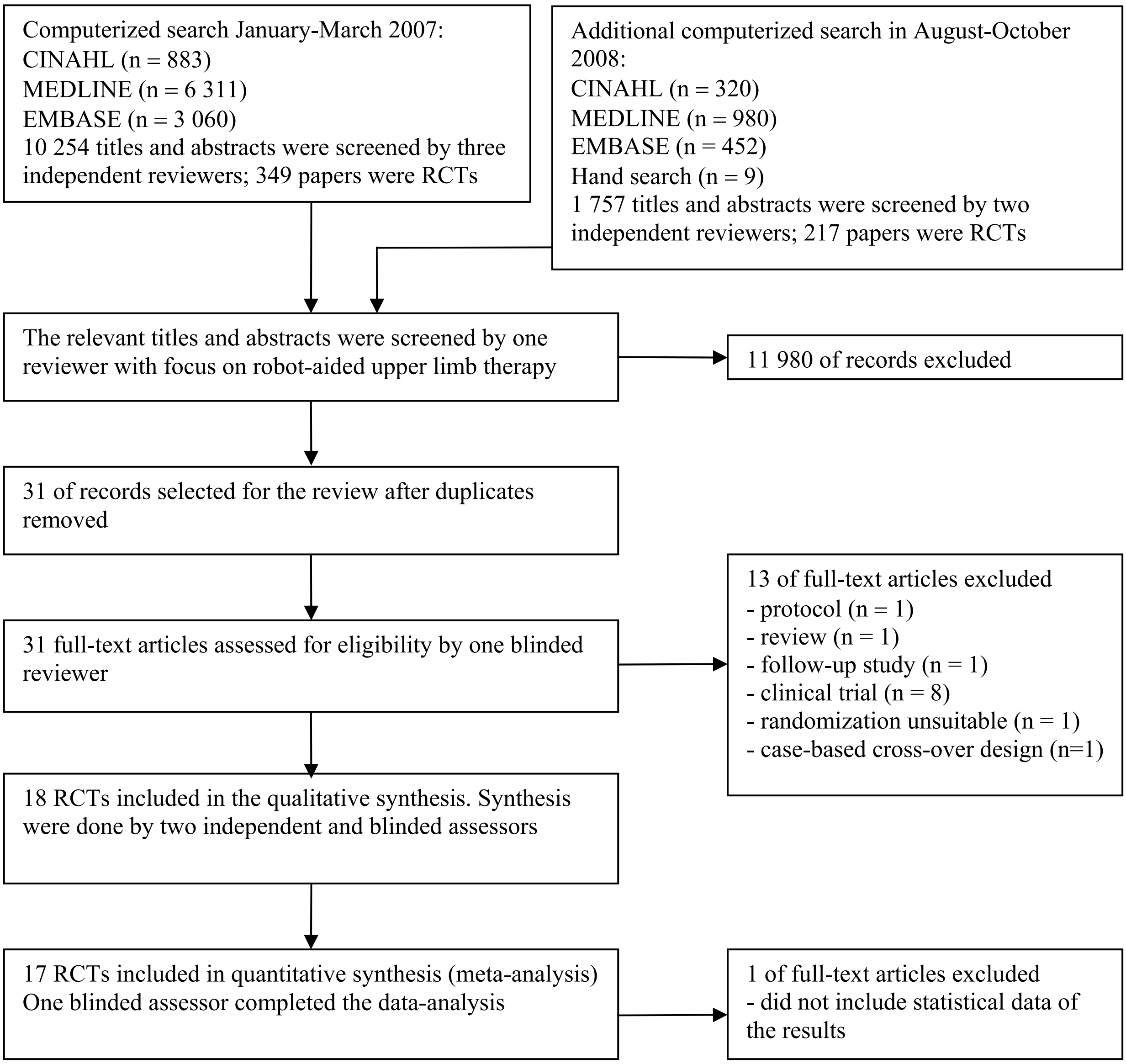

Figure 1. Flow diagram of the selection of randomized controlled studies in the systematic review

5.2 Study characteristics

According to the control intervention the studies were classified for "Treatment versus other treatment" category (n=8),"Treatment and additional treatment versus treatment and additional treatment" category (n=10) and "Other" category (n=2). Other category included two studies that compared different type of robotic training. All other than these two studies were analysed in a category "treatment versus other treatment" as control and experimental groups both received some type of a therapy. More detailed information about the intervention classification is in the appendix 4. Experimental interventions included variety of reaching or drawing tasks with a robotic device. Most of the exercises with the robot were active-assisted training (n=17). Assistance was dependant on the activity level of the upper limb. One study (Fazekas et al. 2007) used passive robot-assisted therapy. In two studies (Fasoli et al. 2003, Stein et al. 2004) active-resisted robot training was compared to robot-assisted upper limb training. More detailed description of the intervention characteristics is in the appendix 5. Ten different types of robotic apparatus were used in the trials (Table 3). Shoulder (n=18) and elbow (n=19) were the most trained joints before wrist (n=8) and hand (n=5).

Table 3. Robotic devices used in the RCTs

Robot type	Institution	Country	Study	Trained joint level
Massachusetts Institute of Technology (MIT)-Manus	Massachusetts Institute of Technology, Cambridge, MA: Newman Laboratory for Biomechanics and Human Rehabilitation	USA	Aisen et al. 1997, Volpe et al. 2000, Fasoli et al. 2003, Fasoli et al. 2004	shoulder and elbow
Mirror Image Motion Enabler (MIME)	Staubli Unimation Inc, Duncan, SC	USA	Burgar et al. 2000, Lum et al. 2002, Lum et al. 2006	shoulder and elbow
InMotion2	Interactive Motion Technologies Inc., Cambridge, MA	USA	Stein et al. 2004, Daly et al. 2005, Volpe et al. 2008	shoulder and elbow
Bi-Manu-Track	Reha-Stim Company, Berlin	Germany	Hesse et al. 2005	shoulder, elbow and wrist
The Assisted Rehabilitation and Measurement (ARM) Guide	Rehabilitation Institute of Chicago	USA	Kahn et al. 2006b	shoulder, elbow, wrist
The Neuro-Rehabilitation-Robot (NeReBot)	Padova University	Italy	Masiero et al. 2006, Masiero et al. 2007	shoulder and elbow
REHAROB system	Budapest University of Technology and Economics, National Institute for Medical Rehabilitation, University of Wales Cardiff, University of Rousse, Zebris Medizintechnik GmbH	Hungary, UK, Bulgaria, Germany	Fazekas et al. 2007	shoulder and elbow
GENTLE/s robotic system	Haptic Master, FCS Robotics	Netherlands	Amirabdollahian et al. 2007	shoulder and elbow
Upper Limbs´ Encircling Motion (ULEM) apparatus	SuTongKang Science and Technology Institution, Nanjing	China	Wang et al. 2007	shoulder, elbow and wrist
ARMOR	Austrian Research Centers GmbH, Wien , Landeskrankenhaus Hochzirl, Zirl	Austria	Mayr et al. 2008	shoulder, elbow and wrist

5.3 Patient characteristics

Included studies had a total of 545 patients between the ages 19 to 82. The mean age of the patients in the intervention groups varied from 55.6 years to 72.2 years and in the control groups from 53 years to 68.8 years. Most of the studies investigated the effects of robot-assisted upper limb training for chronic patients (> 6 months post-stroke) (n=9) but also patients in subacute (2-4 weeks to 6 months post-stroke) (n=6) and acute (< 2-4 weeks post-stroke) (n=5) recovery stage were investigated. Most of the studies included patients of all severity stages of the upper limb recovery. Severe impairment was considered if Fugl-Meyer upper extremity score was less than 20 points, moderate between 20 points and 40 points and mild when scored more than 40 points (max 66p). Fazekas et al. (2007), Hesse et al. (2005) and Volpe et al. (2000) included only patients with severe hemiparesis. Most studies included patients with both sided hemiparesis except Mayr et al. (2008) that included patients only with left-sided hemiparesis. A detailed description of patient characteristics will be found in the appendix 6.

5.4 Quality assessment

The results of the methodological quality score of the 18 RCTs are presented in detail in appendix 7. Methodological score represent the original information obtained from research articles and is not influenced by the additional data received from authors. The average scoring was 5.5 (SD 1.1). The methodological quality varied from 4 points to 7 points. The agreement between the assessors was moderate, Cohens kappa for agreement was 0.59 (Brennan & Heyes 1992).

5.5 Outcome measures

The effectiveness of the robot-aided physiotherapy was measured using outcome measures in two main areas according to International Classification of Functioning, Disability and Health

(ICF), body structure and function as well as in activities and participation (Toimintakyvyn, toimintarajoitteiden 2009, 3). Figure 2 presents the outcome measures included in the analysis. More detailed information of the outcome measures used in the included studies is in the appendix 8.

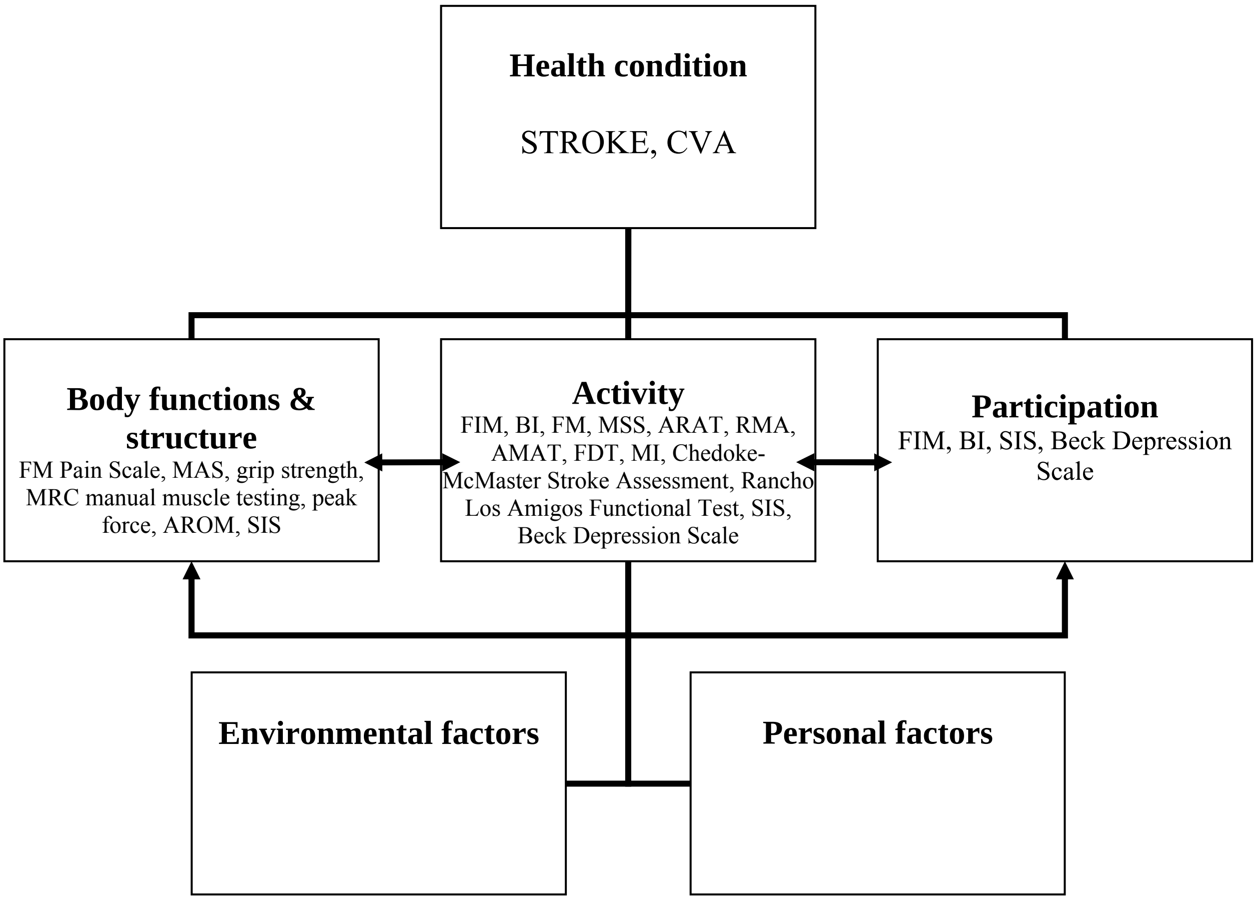

Figure 2. Classification of outcome measures used to assess the effectiveness of robot-aided upper limb training in ICF domains (CVA = cerebrovascular accident, FM = Fugl Meyer, MAS = Modified Ashworth Scale, MRC = Medical Research Council, AROM = active range of motion, SIS = Stroke Impact Scale, FIM = Functional Independence Measure, BI = Barthel Index, MSS = Motor Status Score, ARAT = Action Research Arm Test, RMA = Rivermead Motor Assessment, AMAT = Arm Motor Ability Test, FDT = Functional Dexterity Test, MI = Motricity Index)

5.6 Effectiveness of robot-aided upper limb therapy

5.6.1 Function

Robot-aided upper limb training significantly ($p<0.05$) increased the motor function of the acute stroke patients compared to the controls that had only upper limb exposure with the robot. Motor subsections include self-care and toileting as well as transfers and mobility skills. Robot-assisted upper limb therapy did not have positive effect on transfers and self-care in subacute and chronic stroke patients compared to controls that received NDT approach. There were no effects on cognitive functions either in the acute phase of recovery compared to controls that had upper limb exposure with the robot. Robot-aided therapy did not have positive effect on overall daily functions in any of the recovery stages compared to controls that received either conventional or NDT–based physiotherapy or were only exposed to the robot (Figure 3). Studies by Fasoli et al. (2004a) and Fazekas et al. (2007) were left out the meta-analysis due to the data available.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
4.1.1 FIM motor subsections									
Volpe et al. 2000	25	3.5	30	19.5	3.5	26	39.2%	1.55 [0.95, 2.15]	2000
Masiero et al. 2006	31	7	10	15.4	10.8	10	28.0%	1.64 [0.60, 2.69]	2006
Masiero et al. 2007	33.5	7.5	15	18.5	9.5	15	32.7%	1.71 [0.85, 2.56]	2007
Subtotal (95% CI)			**55**			**51**	**100.0%**	**1.61 [1.16, 2.05]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.96); I² = 0%									
Test for overall effect: Z = 7.08 (P < 0.00001)									
4.1.2 FIM self-care and transfers									
Lum et al. 2002	0.2	0.7	13	0	0.01	14	39.0%	0.40 [-0.36, 1.16]	2002
Lum et al. 2006 III	3.7	2.2	5	3.2	3.4	2	19.1%	0.17 [-1.48, 1.81]	2006
Lum et al. 2006 I	3.1	5.4	10	3.2	3.4	2	21.1%	-0.02 [-1.54, 1.50]	2006
Lum et al. 2006 II	3.7	3	9	3.2	3.4	2	20.8%	0.15 [-1.38, 1.68]	2006
Subtotal (95% CI)			**37**			**20**	**100.0%**	**0.27 [-0.31, 0.86]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 3 (P = 0.96); I² = 0%									
Test for overall effect: Z = 0.92 (P = 0.36)									
4.1.3 FIM cognitive subsections									
Volpe et al. 2000	6	2	30	5.5	2.5	26	100.0%	0.22 [-0.31, 0.75]	2000
Subtotal (95% CI)			**30**			**26**	**100.0%**	**0.22 [-0.31, 0.75]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.82 (P = 0.41)									
4.1.4 FIM total score									
Aisen et al. 1997	25.6	7.23	10	25.7	12.25	10	47.5%	-0.01 [-0.89, 0.87]	1997
Masiero et al. 2007	32.6	7.2	15	25.5	10.5	15	52.5%	0.77 [0.02, 1.51]	2007
Subtotal (95% CI)			**25**			**25**	**100.0%**	**0.41 [-0.34, 1.17]**	
Heterogeneity: Tau² = 0.13; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%									
Test for overall effect: Z = 1.07 (P = 0.28)									
4.1.5 Barthel Index total score									
Lum et al. 2002	1.2	4.3	13	0	0.001	14	47.0%	0.39 [-0.37, 1.15]	2002
Wang et al. 2007	14.3	13.5	22	20	16.5	22	53.0%	-0.37 [-0.97, 0.23]	2007
Subtotal (95% CI)			**35**			**36**	**100.0%**	**-0.03 [-0.77, 0.71]**	
Heterogeneity: Tau² = 0.17; Chi² = 2.38, df = 1 (P = 0.12); I² = 58%									
Test for overall effect: Z = 0.08 (P = 0.94)									

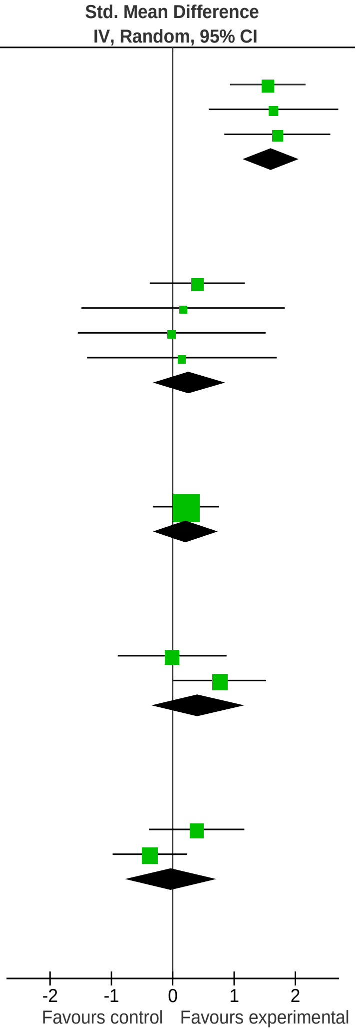

Figure 3. The effects of robot-aided upper limb therapy in function (FIM, BI) (effect size) (FIM = Functional Independence Measure, BI = Barthel Index) [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

5.6.2 Upper limb motor control

Robot-assisted upper limb training seemed not to have more effect on overall upper limb motor control compared to controls that trained with sling suspension, practised reaching without the robot or received sham robotic training (Figure 4). On the other hand robotic training seemed to improve motor control of the paralysed upper limb when measured with Motricity Index (Masiero et al. 2006). The control group had upper limb exposure to the robot without active training with the paralysed arm. Closer subanalysis revealed that robot-aided upper limb therapy significantly ($p<0.05$) increased the shoulder and elbow motor control

(FM and MSS shoulder/elbow subsections) of the stroke patients compared to the controls that received either NDT approach or upper limb exposure to the robot. Patients represented all stages of the recovery. The small study by Mayr et al. (2008) did not support these results as no effects were found in upper limb proximal motor control in the subacute stage of recovery (Figure 4). Controls received EMG-triggered electrical stimulation. No effect were found to the motor control of the wrist and hand of the paralysed upper limb compared to controls that had either NDT approach, exposure to the robot or EMG-triggered electrical stimulation (Figure 4). Patients represented all recovery stages. At the same time the trial by Volpe et al. (2000) revealed improvement in experimental group also in distal parts of the paralysed upper limb (Figure 4). Patients were in the acute stage of recovery and controls had sham robotic training. Robotic training focused on shoulder and elbow in all studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
7.1.1 Fugl-Meyer Assessment shoulder/elbow									
Volpe et al. 2000	5	2.5	30	4	2	26	23.7%	0.43 [-0.10, 0.96]	2000
Lum et al. 2002	3.3	2.52	13	1.6	1.12	14	18.0%	0.86 [0.06, 1.65]	2002
Masiero et al. 2006	13.1	5.6	10	7.1	8.5	10	15.7%	0.80 [-0.12, 1.72]	2006
Lum et al. 2006 II	4.3	4.2	9	2.5	1.47	2	8.1%	0.41 [-1.13, 1.96]	2006
Lum et al. 2006 I	5.3	3.8	10	2.5	1.47	2	8.0%	0.71 [-0.85, 2.27]	2006
Lum et al. 2006 III	2.4	3.35	5	2.5	1.47	2	7.4%	-0.03 [-1.67, 1.61]	2006
Masiero et al. 2007	12.8	5.5	15	7.5	9.5	15	19.1%	0.66 [-0.07, 1.40]	2007
Subtotal (95% CI)			**92**			**71**	**100.0%**	**0.59 [0.26, 0.92]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 6 (P = 0.95); I² = 0%									
Test for overall effect: Z = 3.53 (P = 0.0004)									
7.1.2 Fugl-Meyer Assessment wrist/hand									
Volpe et al. 2000	1	1	30	0	0.01	26	22.4%	1.35 [0.76, 1.93]	2000
Lum et al. 2002	1.4	1.8	13	1.5	1.87	14	18.7%	-0.05 [-0.81, 0.70]	2002
Lum et al. 2006 III	1.4	1.57	5	3.3	4.65	2	6.9%	-0.64 [-2.35, 1.08]	2006
Lum et al. 2006 I	2.3	1.26	10	3.3	4.65	2	8.1%	-0.49 [-2.02, 1.05]	2006
Lum et al. 2006 II	3.6	3.9	9	3.3	4.65	2	8.1%	0.07 [-1.46, 1.60]	2006
Masiero et al. 2006	2.6	2.6	10	2.4	2.3	10	16.3%	0.08 [-0.80, 0.95]	2006
Masiero et al. 2007	3	2.6	15	2.8	2.6	15	19.5%	0.07 [-0.64, 0.79]	2007
Subtotal (95% CI)			**92**			**71**	**100.0%**	**0.20 [-0.38, 0.79]**	
Heterogeneity: Tau² = 0.35; Chi² = 15.58, df = 6 (P = 0.02); I² = 61%									
Test for overall effect: Z = 0.68 (P = 0.50)									
7.1.3 Fugl-Meyer Assessment total score									
Aisen et al. 1997	14.1	9.7	10	10.1	11.63	10	45.3%	0.36 [-0.53, 1.24]	1997
Amirabdollahian et al2007	3.85	2.45	16	5.09	3.4	15	54.7%	-0.41 [-1.12, 0.30]	2007
Subtotal (95% CI)			**26**			**25**	**100.0%**	**-0.07 [-0.82, 0.67]**	
Heterogeneity: Tau² = 0.13; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%									
Test for overall effect: Z = 0.19 (P = 0.85)									
7.1.4 Motor Status Score shoulder/elbow									
Volpe et al. 2000	8.3	2.5	30	4.4	2	30	100.0%	1.70 [1.10, 2.30]	2000
Subtotal (95% CI)			**30**			**30**	**100.0%**	**1.70 [1.10, 2.30]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 5.59 (P < 0.00001)									
7.1.5 Motor Status Score wrist/hand									
Volpe et al. 2000	0.8	0.8	30	0.4	0.4	30	100.0%	0.62 [0.11, 1.14]	2000
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.62 [0.11, 1.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.36 (P = 0.02)									
7.1.6 Functional Dexterity Test									
Mayr et al. 2008	17.72	35.4	4	-6.92	15.4	4	100.0%	0.78 [-0.70, 2.27]	2008
Subtotal (95% CI)			**4**			**4**	**100.0%**	**0.78 [-0.70, 2.27]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.03 (P = 0.30)									
7.1.7 Rancho Los Amigos Functional Test									
Kahn et al. 2006	-6.28	11.48	10	-2.69	2.02	9	100.0%	-0.41 [-1.32, 0.51]	2006
Subtotal (95% CI)			**10**			**9**	**100.0%**	**-0.41 [-1.32, 0.51]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.87 (P = 0.38)									
7.1.8 Chedoke Mc-Master Stroke Assessment total score									
Kahn et al. 2006	0.2	0.4	10	0.3	0.5	9	100.0%	-0.21 [-1.12, 0.69]	2006
Subtotal (95% CI)			**10**			**9**	**100.0%**	**-0.21 [-1.12, 0.69]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.46 (P = 0.65)									
7.1.9 Chedoke Mc-Master Stroke Assessment shoulder/elbow									
Mayr et al. 2008	-0.5	1.73	4	-1.8	1.26	4	100.0%	0.75 [-0.73, 2.23]	2008
Subtotal (95% CI)			**4**			**4**	**100.0%**	**0.75 [-0.73, 2.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.99 (P = 0.32)									
7.1.10 Chedoke Mc-Master Stroke Assessment wrist/hand									
Mayr et al. 2008	-1.5	1.91	4	-1.5	0.58	4	100.0%	0.00 [-1.39, 1.39]	2008
Subtotal (95% CI)			**4**			**4**	**100.0%**	**0.00 [-1.39, 1.39]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
7.1.11 Motricity Index upper limb subsection									
Masiero et al. 2006	30.4	16.2	10	14	14.5	10	100.0%	1.02 [0.08, 1.97]	2006
Subtotal (95% CI)			**10**			**10**	**100.0%**	**1.02 [0.08, 1.97]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.12 (P = 0.03)									

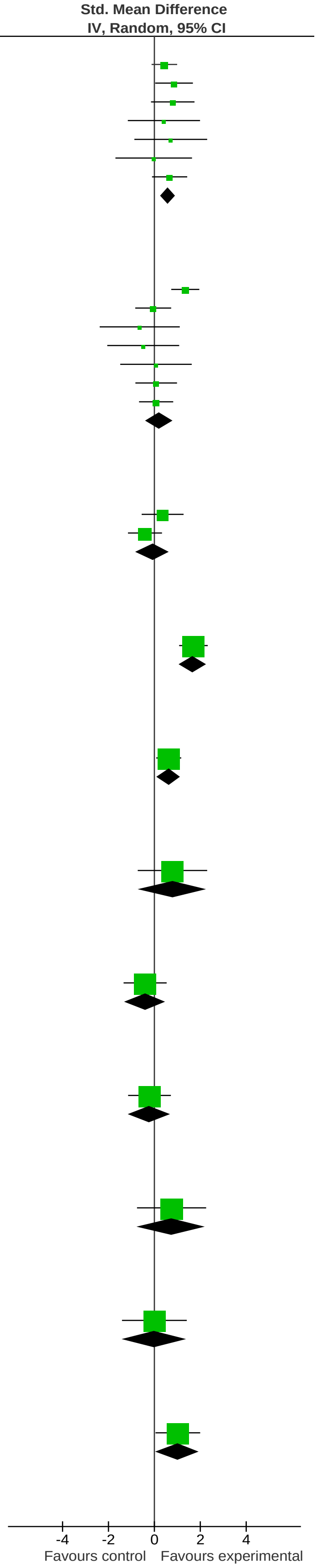

Figure 4. The effects of robot-aided upper limb therapy in upper limb motor control (effect size) [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

Five RCTs (Fasoli et al. 2004a, Hesse et al. 2005, Daly et al. 2005, Fazekas et al. 2007, Volpe et al. 2008) were left out to this meta-analysis due to the data available. According to their results no statistically significant results were found favouring robot-assisted upper limb training in improving upper limb motor control compared to controls. Controls received either EMG-triggered or functional electrical stimulation, intensive movement-based protocol, Bobath approach or had exposure to the robot. Patients were from acute to chronic stages.

Progressive resisted robot training did not have positive effect on upper limb motor control in chronic stroke patients compared to controls that had active-assisted robot training (Figure 5).

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
3.11.1 Fugl-Meyer Assessment total score									
Fasoli et al. 2003	3.71	4.96	7	3.15	3.63	13	42.6%	0.13 [-0.79, 1.05]	2003
Stein et al. 2004	4	4.8	14	4.4	3.4	14	57.4%	-0.09 [-0.83, 0.65]	2004
Subtotal (95% CI)			**21**			**27**	**100.0%**	**-0.01 [-0.58, 0.57]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%									
Test for overall effect: Z = 0.02 (P = 0.99)									
3.11.2 Motor Status Score shoulder/elbow									
Fasoli et al. 2003	0.76	2.59	7	1.44	1.67	13	42.7%	-0.32 [-1.25, 0.60]	2003
Stein et al. 2004	2.4	2.6	14	1.6	1.1	14	57.3%	0.39 [-0.36, 1.14]	2004
Subtotal (95% CI)			**21**			**27**	**100.0%**	**0.09 [-0.60, 0.78]**	
Heterogeneity: Tau² = 0.07; Chi² = 1.37, df = 1 (P = 0.24); I² = 27%									
Test for overall effect: Z = 0.25 (P = 0.80)									
3.11.3 Motor Status Score wrist/hand									
Fasoli et al. 2003	1.86	1.48	7	0.15	0.98	13	38.3%	1.40 [0.36, 2.44]	2003
Stein et al. 2004	1.6	1.1	14	1.3	2	14	61.7%	0.18 [-0.56, 0.92]	2004
Subtotal (95% CI)			**21**			**27**	**100.0%**	**0.73 [-0.46, 1.92]**	
Heterogeneity: Tau² = 0.53; Chi² = 3.50, df = 1 (P = 0.06); I² = 71%									
Test for overall effect: Z = 1.21 (P = 0.23)									

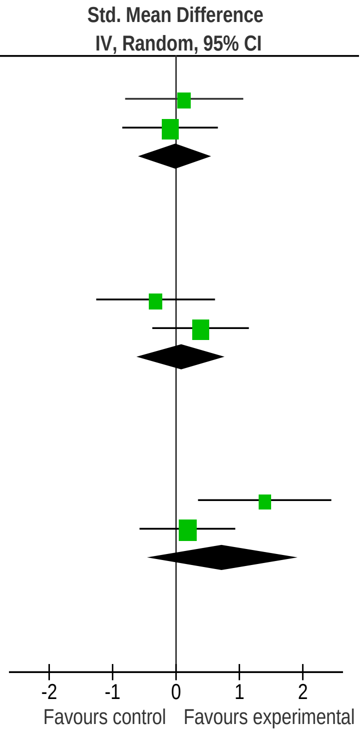

Figure 5. The effects of progressively resisted robot therapy in upper limb motor control in comparison to robot-assisted upper limb training (effect size) [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

5.6.3 Spasticity

Robot-aided upper limb therapy was not more effective than control interventions in reducing the spasticity of the upper limb in subacute and chronic stroke population (Figure 6). Controls received either physiotherapy with Bobath approach, EMG-triggered–physiotherapy or intensive movement-based physiotherapy. The study by Masiero et al. (2007) was not included to the meta-analysis due to the data available. Their individual results support the results of the meta-analysis [effect size 0.00 (95% CI -0.72, 0.72)]. In the trial by Lum et al. (2006) between-group comparisons were not performed because of significant baseline differences between the two groups. In Modified Ashworth Scale lower value represents less spasticity in the muscle or muscle groups.

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
1.1.1 Modified Ashworth Scale upper limb total score									
Hesse et al. 2005	1.7	2.4	21	1.8	1.7	22	67.2%	-0.05 [-0.65, 0.55]	2005
Volpe et al. 2008	6.27	3.32	11	6	4.11	10	32.8%	0.07 [-0.79, 0.93]	2008
Subtotal (95% CI)			**32**			**32**	**100.0%**	**-0.01 [-0.50, 0.48]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%									
Test for overall effect: Z = 0.04 (P = 0.97)									
1.1.2 Modified Ashworth Scale shoulder									
Fazekas et al. 2007	1.2	0.37	15	1.47	0.48	15	79.1%	-0.61 [-1.35, 0.12]	2007
Mayr et al. 2008	0.5	1	4	1.25	1.5	4	20.9%	-0.51 [-1.94, 0.92]	2008
Subtotal (95% CI)			**19**			**19**	**100.0%**	**-0.59 [-1.25, 0.06]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%									
Test for overall effect: Z = 1.77 (P = 0.08)									
1.1.3 Modified Ashworth Scale elbow									
Fazekas et al. 2007	2.13	0.36	15	2.13	0.57	15	80.7%	0.00 [-0.72, 0.72]	2007
Mayr et al. 2008	0.75	0.96	4	1.75	1.5	4	19.3%	-0.69 [-2.16, 0.77]	2008
Subtotal (95% CI)			**19**			**19**	**100.0%**	**-0.13 [-0.78, 0.51]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 1 (P = 0.41); I² = 0%									
Test for overall effect: Z = 0.41 (P = 0.69)									
1.1.4 Modified Ashworth Scale wrist									
Mayr et al. 2008	0.5	0.58	4	2.25	2.06	4	100.0%	-1.01 [-2.55, 0.54]	2008
Subtotal (95% CI)			**4**			**4**	**100.0%**	**-1.01 [-2.55, 0.54]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.27 (P = 0.20)									

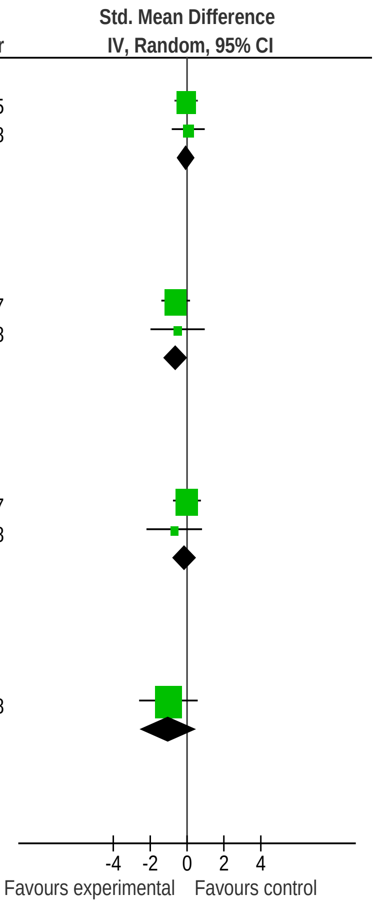

Figure 6. The effects of robot-aided upper limb therapy in upper limb spasticity (effect size) [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

Progressively resisted robotic training did not reduce upper limb spasticity compared to robot-assisted training (Figure 7).

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Fasoli et al. 2003	1.95	2.79	7	0.38	3.59	13	46.9%	0.45 [-0.48, 1.38]	2003
Stein et al. 2004	-1.4	2.2	14	0	2	14	53.1%	-0.65 [-1.41, 0.12]	2004
Total (95% CI)			**21**			**27**	**100.0%**	**-0.13 [-1.20, 0.94]**	

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 3.18$, df = 1 (P = 0.07); $I^2 = 69\%$

Test for overall effect: Z = 0.24 (P = 0.81)

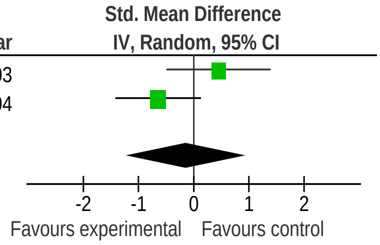

Figure 7. The effects of progressively resisted robot therapy in upper limb spasticity in comparison to robot-assisted upper limb training (effect size) [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

5.6.4 Upper limb muscle power

Active training with the robot increased significantly (≤ 0.05) the deltoid, biceps and triceps muscle power in acute stroke patients compared to control groups that received sham robotic training (Figure 8). In another sub analysis no effect were found to shoulder and elbow muscle power in subacute stroke population. No effect was found in wrist flexor muscle power. Three RCTs (Volpe et al. 2008, Hesse et al. 2005, Fasoli et al. 2004a) were left outside the meta-analysis due to insufficient data available. Hesse et al. (2005) practiced the elbow and wrist with the robot and in addition to proximal muscle power [effect size 2.40 (95% CI 1.60, 3.20)]. They got positive results also at the wrist and hand muscle power [effect size 1.78 (95% CI 1.06, 2.50)].

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
4.1.1 Shoulder flexion/abduction and elbow flexion/extension muscle power									
Aisen et al. 1997	3.88	2.89	10	2.3	2.45	10	44.6%	0.56 [-0.33, 1.46]	1997
Volpe et al. 2000	4.1	1.4	30	1.7	1.7	26	55.4%	1.53 [0.93, 2.13]	2000
Subtotal (95% CI)			**40**			**36**	**100.0%**	**1.11 [0.17, 2.05]**	
Heterogeneity: Tau² = 0.31; Chi² = 3.07, df = 1 (P = 0.08); I² = 67%									
Test for overall effect: Z = 2.31 (P = 0.02)									
4.1.2 Shoulder and elbow muscle power									
Lum et al. 2006 II	10.1	7.2	9	9.3	3.18	2	39.1%	0.11 [-1.43, 1.64]	2006
Lum et al. 2006 III	3.2	2.24	5	9.3	3.18	2	21.7%	-2.09 [-4.42, 0.24]	2006
Lum et al. 2006 I	8.2	3.16	10	9.3	3.18	2	39.3%	-0.32 [-1.85, 1.21]	2006
Subtotal (95% CI)			**24**			**6**	**100.0%**	**-0.50 [-1.60, 0.60]**	
Heterogeneity: Tau² = 0.17; Chi² = 2.44, df = 2 (P = 0.30); I² = 18%									
Test for overall effect: Z = 0.89 (P = 0.37)									
4.1.3 M. deltoid muscle power									
Masiero et al. 2006	1.9	1.1	10	1	1	10	47.9%	0.82 [-0.10, 1.74]	2006
Masiero et al. 2007	2.1	1.1	15	0.7	0.8	15	52.1%	1.42 [0.60, 2.23]	2007
Subtotal (95% CI)			**25**			**25**	**100.0%**	**1.16 [0.55, 1.76]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%									
Test for overall effect: Z = 3.72 (P = 0.0002)									
4.1.4 M. bicpes muscle power									
Masiero et al. 2006	2.1	1	10	1	1.1	10	45.8%	1.00 [0.06, 1.94]	2006
Masiero et al. 2007	1.3	1.3	15	0.9	0.8	15	54.2%	0.36 [-0.36, 1.08]	2007
Subtotal (95% CI)			**25**			**25**	**100.0%**	**0.61 [-0.00, 1.22]**	
Heterogeneity: Tau² = 0.02; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%									
Test for overall effect: Z = 1.95 (P = 0.05)									
4.1.5 Wrist flexors muscle power									
Masiero et al. 2006	1	1.3	10	1.2	0.9	10	47.0%	-0.17 [-1.05, 0.71]	2006
Masiero et al. 2007	1.8	1.3	15	2	1.5	15	53.0%	-0.14 [-0.86, 0.58]	2007
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-0.15 [-0.71, 0.40]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%									
Test for overall effect: Z = 0.54 (P = 0.59)									

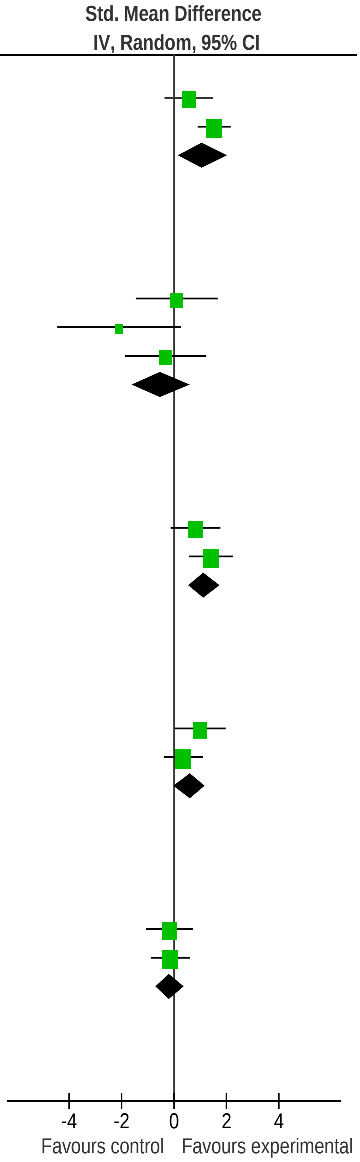

Figure 8. The effects of robot-aided upper limb therapy in hemiplegic upper limb muscle power (effect size). [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

Progressively resisted robot therapy was not superior in improving the muscle power of the upper limb compared to controls that had robot-assisted training (Figure 9). Trials were done with chronic stroke patients.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year	Std. Mean Difference IV, Random, 95% CI
1.3.1 MRC upper limb power total score										
Stein et al. 2004	2.2	1.6	14	1.6	2.3	14	100.0%	0.29 [-0.45, 1.04]	2004	
Subtotal (95% CI)			**14**			**14**	**100.0%**	**0.29 [-0.45, 1.04]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.77 (P = 0.44)										
1.3.2 MRC shoulder and elbow muscle power										
Fasoli et al. 2003	1.57	1.51	7	2.69	1.88	13	100.0%	-0.61 [-1.55, 0.33]	2003	
Subtotal (95% CI)			**7**			**13**	**100.0%**	**-0.61 [-1.55, 0.33]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.26 (P = 0.21)										

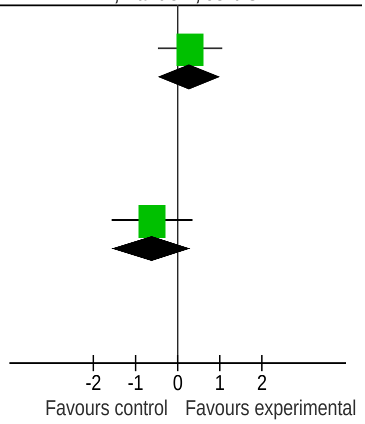

Figure 9. The effects of progressively resisted robot therapy on the power of hemiplegic upper limb compared to robot-assisted upper limb training (effect size). [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

Progressively resisted robot therapy increased the peak force (N) of the shoulder flexion, extension, abduction and adduction in chronic stroke population comparison to controls that received robot-assisted training (Figure 10).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Std. Mean Difference IV, Random, 95% CI	Year	Std. Mean Difference IV, Random, 95% CI
Stein et al. 2004	6.4	2.3	14	4.2	2.2	14	0.95 [0.16, 1.74]	2004	

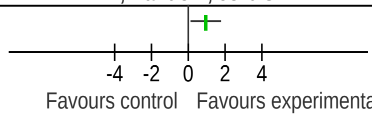

Figure 10. The effects of progressively resisted robot therapy in peak force (N) at shoulder flexion, extension, abduction and adduction in comparison to robot-assisted upper limb training (effect size). [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

Robot-aided upper limb training did not increase the grip strength of the hemiplegic arm in subacute stroke patients with left hemiplegia compared to controls that received EMG-triggered electrical stimulation (Figure 11).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Std. Mean Difference IV, Random, 95% CI	Year	Std. Mean Difference IV, Random, 95% CI
Mayr et al. 2008	-1	5.8	4	-4	3.2	4	0.56 [-0.88, 1.99]	2008	

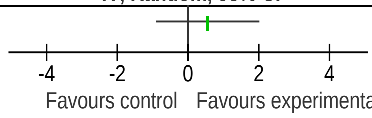

Figure 11. The effects of robot-aided upper limb therapy in hemiplegic hand grip strength (effect size). [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

5.6.5 Upper limb range of movement

Robot-aided upper limb training is not superior in improving the active range of movement of the upper limb compared to controls that received EMG-triggered electrical stimulation (Figure 12). The study by Fazekas et al. (2007) supports the results as the SMD for shoulder flexion was -0.21 (95% CI -0.93, 0.51) and elbow flexion -0.46 (95% CI -1.19, 0.27).

	Experimental			Control			Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	Year
5.1.1 Shoulder flexion								
Mayr et al. 2008	-5	4.2	4	1	10	4	-0.68 [-2.14, 0.78]	2008
5.1.2 Shoulder extension								
Mayr et al. 2008	-4	3.3	4	-1	8.1	4	-0.42 [-1.84, 0.99]	2008
5.1.3 Shoulder abduction								
Mayr et al. 2008	2.5	7	4	2.5	7.6	4	0.00 [-1.39, 1.39]	2008
5.1.4 Shoulder adduction								
Mayr et al. 2008	0.0000001	0	4	-1	2.5	4	0.49 [-0.93, 1.92]	2008
5.1.5 Elbow flexion								
Mayr et al. 2008	-3	8.8	4	0	7.5	4	-0.32 [-1.72, 1.08]	2008
5.1.6 Elbow extension								
Mayr et al. 2008	6.3	10	4	-9	11	4	1.27 [-0.37, 2.90]	2008
5.1.7 Elbow pronation								
Mayr et al. 2008	3.5	18	4	2	5.4	4	0.10 [-1.29, 1.49]	2008
5.1.8 Elbow supination								
Mayr et al. 2008	-16	36	4	0.0000001	0.0000001	4	-0.55 [-1.98, 0.89]	2008
5.1.9 Wrist flexion								
Mayr et al. 2008	-5	3.4	4	-5	5.8	4	0.00 [-1.39, 1.39]	2008
5.1.10 Wrist extension								
Mayr et al. 2008	-17	25	4	-7	5.7	4	-0.48 [-1.90, 0.95]	2008

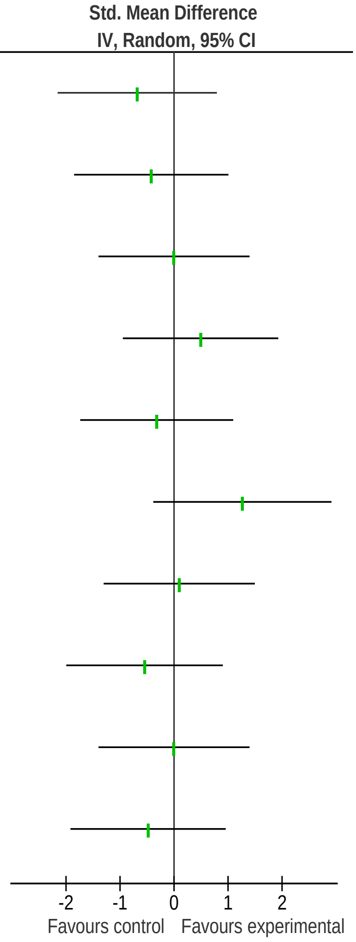

Figure 12. The effects of robot-aided upper limb training on active range of movement of the arm (effect size). [Scale: large >0.5, moderate 0.5-0.3, small 0.3-0.1, <0.1 insubstantial (Cohen 1988)]

5.6.6 Pain

According to Volpe et al. (2008) there were no significant improvements in pain in chronic stroke population as SMD for pain was 0.64 (95% CI -0.24, 1.52). The control group received intensive movement protocol.

5.6.7 Quality of life and depression

According to Volpe et al. (2008) robot-aided upper limb training did not have significant effect on quality of life in Stroke Impact Scale or depression in Beck Depression Scale. SMD for quality of life was 0.20 (95% CI -0.66, 1.06) and depression -0.02 (95% CI -0.88, 0.84). The controls received intensive movement protocol.

5.7 Exercise dose of the robot-aided upper limb therapy

The amount of exercise per session in the robot-trained group varied from 20 to 90 minutes and there were three to five sessions a week for intervention group for total of four to 12 weeks. Weekly therapy times varied from 90 minutes to 450 minutes. The total amount of exercise during the intervention varied from 4.5 hours to 45 hours and the robot provided thousands of reaching repetitions with the hemiparetic arm. In four studies (Aisen et al. 1997, Volpe et al. 2000, Masiero et al. 2006, Masiero et al. 2007) the control group received remarkably less amount of therapy than the group exercising with the robot. More detailed description of the therapy duration is in the appendix 5.

6 DISCUSSION

6.1 Main findings

There have been two good quality systematic reviews of the robot-aided upper limb therapy by Prange et al. (2006) and Kwakkel et al. (2008). In addition to these there have been eight new RCTs that are not included in previous reviews. Therefore this systematic review and meta-analysis will bring some additional and recent evidence of the effectiveness of robot aided upper limb therapy in stroke population. More detailed analysis with several outcome measures was included in this study compared to the previous ones. The purpose of this systematic literature review was to indicate whether robot-aided therapy is an effective method on hemiplegic upper limb recovery compared with other physiotherapy methods or placebos. Effectiveness means incremental clinical benefit gained from the intervention (Glasziou et al. 2001). Results are presented according to the main outcomes which were overall function in daily activities, motor control, spasticity, muscle power and active range of movement of the upper limb. Also outcomes in pain, depression and quality of life were presented. Robot-aided upper limb therapy was compared with other physiotherapy. In some studies the controls were exposed to the robotic device without active exercise but at the same time they also received conventional rehabilitation such as physiotherapy or occupational therapy.

The results of the meta-analysis analysis showed that intensive robot-aided therapy for the proximal parts of the upper extremity significantly improved shoulder and elbow motor control in all stages of recovery. No effect was found in the distal parts of the upper limb. It should be noted that the Fugl-Meyer assessment for wrist and hand was affected with substantial heterogeneity. The previous reviews support this conclusion as Prange et al. (2006) and Kwakkel et al. (2008) demonstrated that the main effect of robot-aided therapy was seen in motor control of the trained arm section not elsewhere in the arm. Meta-analysis also demonstrated that motor function in daily activities such as self-care, toileting, transfers and mobility skills in the acute stroke population improved after robot-aided training. On the other hand in systematic reviews by Prange et al. (2006) and Kwakkel et al. (2008) no treatment effect was found in functional activities. Treatment effect was not superior compared to other physiotherapy methods when participation in activities of daily living was an outcome measure as a whole (FIM total score or Barthel Index). FIM and Barthel Index include cognitive functions that were not affected by robot-aided upper limb training. In this meta-analysis the differences between the experimental and control groups in function and motor control seemed not to be derived from heterogeneity.

Statistically significant differences in favour of robot-aided upper limb therapy were also found in muscle power of the deltoid, biceps and triceps muscles of the paralysed arm but not in the distal parts of the upper limb. This will apply to acute stroke population only. Progressively resisted robotic therapy seems not superior to active-assisted robotic therapy. The exception was the study by Stein et al. (2004) in which progressively resisted robot therapy increased the peak force of the shoulder muscles in chronic stroke population compared to controls that received robot-assisted training. Robot-aided therapy was not superior reducing spasticity of the paralysed upper limb compared to other physiotherapy interventions. There was no significant treatment effect on upper limb active range of motion, pain, depression or quality of life. These features were not investigated in any of the previous systematic reviews (Prange et al. 2006, Kwakkel et al. 2008). No adverse effects were reported of robot-aided training. As there was no follow up studies included in this analysis, it did not take a stance on about the long-term effects of this type of therapy. Systematic review by Prange et al. (2006) showed that robot-aided upper limb therapy might have also long-term effects in upper limb motor function.

6.2 Strengths

This meta-analysis was a comprehensive review of the treatment effects of upper limb robotic therapy including 18 RCTs. The purpose of meta-analysis is to estimate effect sizes and provide the best-evidence synthesis of the available scientific research in the area (Muldrow 1996). The literature search was systematic and inclusive as the search terms initially represented the scope of stroke physiotherapy. Also hand search was completed to include all relevant studies in the area. What comes to publication language we limited the articles only written in Finnish, Swedish, English or German. This might have confined the articles available. In our case no studies in rehabilitation robotics were published in any other languages so that bias was avoided in this study. Only the original studies with randomized experimental and control groups were included as they will provide the best evidence of the efficacy of the treatment (Mäkelä 2004, Johansson 2007). The participants were restricted for only adults with CVA, not brain injury or cerebral tumour. To avoid selection bias in each study it was ensured that the intervention and control groups were comparable with age, gender, diagnosis, severity of stroke and recovery stage. Subanalysis was performed to compare effects in different recovery stages.

Each stage and method in this systematic analysis was well described to minimize errors and assure the relevance of the study (Johansson 2007). Blinded assessors in selection phase as well as in quality analysis assured that the detection bias was avoided. Two reviewers were used in quality analysis to make sure that the conclusions were as objective and reliable as possible. Quality assessment of original research articles will increase the reliability of the study (Kontio & Johansson 2007). Quality analysis of the original RCTs was performed so that the poor quality studies could be identified and left out the analysis. In this case all RCTs were of average quality and none of the studies were left out the statistical analysis for quality reasons. Missing data was collected from authors in writing to receive all valuable data and to avoid introducing bias (Oxman 1996). Results of the meta-analysis were reported in detailed and the data outside the statistical analysis was also reported to avoid publication bias (Sterne et al. 2008). We also looked at the adverse effects of robot-aided upper limb therapy but according to the original trials it seems that there were not any negative features with this method.

Random effects model was used in the statistical analysis as it was assumed that the effects being estimated in the different trials were not identical but they followed normal distribution. Even though the studies that were included in the meta-analysis were of similar study setting there were some variations in between the studies. This excessive variation and incompatibility in the quantitative results is also known as statistical heterogeneity (Thompson 1996). This was tested with RevMan I^2 statistic. Heterogeneity more than 50 percent indicated substantial heterogeneity and 75 to 100 percent was considered remarkable heterogeneity of intervention effects (Deeks et al. 2008). Some heterogeneity with the quantitative results was identified but it was not considered significant in any of the analysis.

6.3 Limitations

Quality analysis of the original studies is important so that the weight can be given to the result and their importance (Kontio & Johansson 2007). Even though the quality of the original RCTs in this systematic review was accepted there were some deficiencies in most of the studies. In many articles the reporting was inadequate. Therefore an enquiry was sent to most of the authors of the missing data considering the randomization method, treatment allocation and drop-outs. These sections of the van Tulder criterion (van Tulder et al. 2003) were considered the most important for reliability. We also contacted researches in case of missing statistical data of the results. In most of the cases the author gave the missing information in writing but in three cases there were no reply. Therefore some valuable data had to be left out from statistical analysis. This will increase the risk of attrition bias (Higgins et al. 2008). In this review methodological scores represented the original information obtained from the research articles.

In only five studies out of 18 research articles the randomization method was appropriately described. Only one paper described the treatment allocation so accurately that no further enquiries were necessary. This will rise up the importance of careful and detailed reporting of the study settings and methodological procedures in the research article. On the other hand most of the original articles reported well the group baseline similarities, drop-outs and assessment timing that was identical for all important outcomes. The reason for this might be that the van Tulder criterion (van Tulder et al. 2003) is too demanding and rigid for randomization and group allocation method descriptions. At the same time these are the most important aspects in scientific research regarding the reliability.

In four studies robotic therapy group received additional amount of therapy (robot-aided therapy plus conventional therapy) compared to control group (conventional therapy or less amount of other type of physiotherapy). It is evident that more therapy will results improved motor learning (Kwakkel et al. 1997, Schmidt & Wrisberg 2008, 264) and better motor performance in upper limb use. This difference might have overestimated the effect of robot-aided therapy.

6.4 Reasons for the findings

In this meta-analysis the positive treatment effects of robot-aided therapy were mainly evident in acute patients but not in subacute or chronic patient groups where as Prange et al. (2006) suggested that also subacute and chronic stroke patients can improve upper limb function after robot-aided therapy. According to our meta-analysis it seems that stroke patients will benefit of this type of training within the first weeks or months of intensive in-patient rehabilitation. At the same time it is well known that the fastest recovery phase is the first three months post-stroke (Sivenius 2001). It is also believed that the natural recovery of the upper limb will occur within the first week after the incidence and the fastest recovery phase continues for the next four weeks (Sivenius 2001, Blanton & Wolf 2006). Consequently part of the positive results could be then explained by the natural factors of the stroke recovery and possibly any kind of intensive therapy could have accomplished similar results.

The question is: Are the encouraging results in upper limb muscle power, motor control and performance in motor tasks due to the quality features of the robot therapy or the amount of practise that robotic device can provide? Individual needs to be able to perform various tasks in diverse environments. This is the ultimate goal also in stroke rehabilitation. It is known that the enriched environment will enhance the recovery post stroke (Kwakkel et al. 1999, Sivenius & Tarkka 2008). Furthermore there is evidence that that treatment compliance has improved by introducing games and other virtual environments with robotic training (Kwakkel et al. 2008). The possibilities of the virtual world are enormous in the rehabilitation. The environment can be chosen to illustrate real-world situations where the patient can respond to variety of impulses while training (Weiss et al. 2006). This supports patient's active participation as he will interact with the objects in the virtual environment by using his hemiplegic arm. Moreover the visual and auditive feedback of the performance is immediate enhancing motivation for the training. Motivation and feedback are both essential features in motor learning (Shumway-Cook & Woollacott 2001, 35).

In spite the fact that robot device is sensitive to change in patients activity, robots can not substitute the therapist completely (Kahn et al. 2006a). Therapists are needed to modify the exercise intensity, session duration and changing the tasks so that stroke patient will have periodic change for his exercise routines as needed for motor learning (Page et al. 2004). It is evident that the therapist is unable to perform as many repetitions as required for motor learning as robot is able to provide. Neuromuscular adaptation occurs only after repeated physical activity (Page et al. 2004). With robot patient will perform hundreds of reaching repetitions with the hemiparetic arm within one therapy session. Patients in the experimental group received three to five exercise sessions a week which is similar to previous systematic reviews (Prange et al. 2006, Kwakkel et al. 2008). This did not differ from the amount of exercise sessions the controls received but they never reached the same amount of repetition with sling suspension, electrical stimulation or other control intervention.

The treatment effects were task specific as improvements in muscle power and motor control were only seen in those body functions that were practiced with the robot. This supports the findings of previous systematic reviews (Prange et al. 2006, Kwakkel et al. 2008). Increased proximal power and motor control after shoulder and elbow focused robot-aided upper limb training were promising. Therefore it can be hypothesized that when wrist and hand muscles are exercised with robotic device this might improve the muscle power of the hand. To support this Hesse et al. (2005) practiced the wrist movements with the robot and in addition to proximal muscle power they also measured positive results at the wrist and hand muscle power. Takahashi et al. (2008) found similar results when hand and finger grasping movements were exercised with the robot including virtual games. They also proved with functional MRI that robotic therapy changed sensorimotor cortex function in a task-specific manner (Takahashi et al. 2008). Finger dexterity and muscle power of the distal parts of the arm have effects on functional hand use as hand grip strength, for example, is essential for many every day tasks such as opening a jar or lifting a saucepan (Carr & Shepherd 2000, 143). It is believed that the interventions that combine strength exercises with task practise are likely to be the most effective (Dromerick et al. 2006).

According to findings in this meta-analysis robot-aided upper limb therapy significantly improved the motor function of a stroke patient compared to controls that were exposed to the robot without active training. Barthel Index and FIM were used for functional outcome measures. Measured tasks in FIM were self-care, toileting, transfers and mobility. These are all important skills in activities of daily living (ADL). The other parts of the FIM assessed the cognitive and social functions and speech. No superior treatment effect was found in cognitive subsections after robot-aided upper limb therapy. It is unlikely that these areas would improve with this type of physical training. Robot-aided therapy was not superior compared to the control interventions when total scores in FIM and Barthel Index were analysed. Similar conclusions were done by Prange et al. (2006) and Kwakkel et al. (2008) that stated that robot-aided therapy did not seem to be effective in improving functional abilities (measured with FIM total score) but may have effect on motor recovery measured by FM upper limb assessment.

All of the included studies in this meta-analysis measured motor recovery using Fugl-Meyer assessment for the upper extremity (Fugl-Meyer et al. 1975). It is the most frequently used measure in stroke rehabilitation research and it has been found to be valid assessment tool for upper limb physical performance for the stroke population (Deakin et al. 2003). It evaluates the gross motor function and fine hand use of the paralysed hand (Fugl-Meyer et al. 1975). Specifically designed for measuring motor performance of the upper limb is the enlarged version of Fugl-Meyer Assessment called Motor Status Score. It seems also valid and reliable tool for assessing motor performance after robotic training (Ferraro et al. 2002). These measures are not widely used in clinical work though they seem applicable for physiotherapy practise.

Outcome measures were classified according to the International Classification of Functioning, Disability and Health (ICF) framework (Toimintakyvyn, toimintarajoitteiden 2009, 5). It indicated that most outcome measures used in robot-aided therapy assessed body functions and activities. Body functions are physiological functions of body systems such as power, range of motion and spasticity. Activity is the task or action that individual performs. Outcome measures for motor control of the arm and ADL function represent this domain. Participation is involvement in life situations and participation restrictions are the problems an individual may experience in involvement in life situations after impairment. (Toimintakyvyn, toimintarajoitteiden 2009,10). The most important areas to evaluate should be the intervention effect on individuals´ activity and participation. Those create the quality of life. More this type of outcome measures is needed to clinical work and research. Robot device itself can provide valuable data of the changes in movement kinematics, forces and patients involvement the training (Fasoli et al. 2003, Kahn et al. 2006, Krebs et al. 2006). These measures were used in a few original RCTs. Unfortunately these measurements were so device specific and the data was excessively heterogeneous for quantitative analysis.

6.5 Implications for clinical work and future research

The results in this systematic review can be generalized to Finnish stroke population. The mean ages of the study participants in RCTs were from 53 to 72 years which represented the general distribution of stroke survivors also in Finland. Robot-aided upper limb therapy seems promising method for clinical practise but it has few aspects that need to be investigated more closely. Robotic devices and systems are expensive. What is the cost-effectiveness of this therapy modality? If robots can provide environment where patient can independently practice upper limb skills, would we need fewer physiotherapists? Feasibility studies of using robots in clinical setting for rehabilitation purposes are needed, too. At present the implementation could be feasible in large rehabilitation settings and stroke units, were extensive stroke population would be reached for intensive training with the robot.

More studies are also required to determine the optimal dose – response rate in robot-aided upper limb therapy? What is the intensity needed to gain improved motor function in the upper limb? In RCTs the weekly amount of robotic exercise varied from 90 minutes to 450 minutes. The positive outcomes seemed not to be related to the amount of exercise. In the study by Hesse et al. (2005) robotic group and EMG-ES control group received the same amount of therapy that was only 90 minutes a week. In addition to the intervention they all received standard occupational therapy 30 minutes four times a week and 45 minutes of physiotherapy five times a week. They found that bilateral robotic training for wrist and forearm produced superior improvement in upper limb motor control and power compared with ES in control group. Instead Daly et al. (2005) found no difference between the robot therapy and FES group although they both practiced 90 minutes a day for 5 days a week. In several study settings both groups received additional standard physiotherapy, but the intensity and quality was not reported. Additional therapy input may have an effect on final outcomes and therefore they should be avoided or at least adequately reported in the research papers.

According to earlier findings by Prange et al. (2006) and Kwakkel et al. (2008) it looks like moderately affected patients are more responsive to robot-aided treatment than severely paralyzed patients. In our meta-analysis all stroke patients with variety of muscle activity were included the study. It was impossible to perform analysis for different subgroups as the participants in the original studies were heterogeneous what comes to upper limb activity.

Robotic devices are also designed to provide assistance in the movement (Hogan et al. 2006). Upper limb rehabilitation robots can provide hand-on-hand type of sensorimotor rehabilitation by producing tactile and kinaesthetic feedback of the upper extremity (Hogan et al. 2006). This is based on assumption that impulses from the periphery are necessary for the recovery of the central nervous system. It is also believed that as long as the patient is actively involved the training it should enhance neuromuscular processes that are essential for motor learning (Gallahue & Ozmun 2006, 16). Fazekas et al. (2007) used passive robot-mediated therapy alone for the spastic upper limb but there were no statistical differences between the intervention and control group. Therefore additional studies are needed to investigate the efficacy of the method for all stroke patients with different functional levels even those without any muscle activity.

7 CONCLUSIONS

This systematic literature review indicated that robot-aided upper limb therapy is an effective therapy modality in increasing stroke patient's motor functioning in acute recovery stage but not in the later stages of the recovery or in any other areas of daily functions. In addition improvements in motor control were seen proximally in all stroke patients. Robot-aided therapy significantly increased the muscle power of shoulder and elbow muscles in acute stroke population but not in the subacute or chronic stage of recovery. There was no effect on grip strength of the paralysed hand. No differences between the groups were seen in motor control and power of the distal parts of the upper limb. Progressively resisted robotic therapy seems not superior to active-assisted robotic therapy. Exception was the study by (Stein et al. 2004) were progressively resisted robot therapy increased the peak force of the shoulder muscles in chronic stroke population compared to controls that received robot-assisted training. Robot-aided therapy was not superior reducing spasticity of the paralysed upper limb compared to other physiotherapy interventions. It did not seem to have effect on upper limb active range of motion, pain, depression or quality of life more than any other physiotherapy intervention. The clinical relevance of this meta-analysis was that robot-aided upper limb therapy seems a safe and efficient method in stroke rehabilitation especially in the acute phase. More studies are needed of its feasibility in clinical use.

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