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Efficiency of physical therapy on postural imbalance after stroke: study protocol for a systematic review and a meta-analysis.

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ABSTRACT (300 words)

Introduction: Balance disorders are frequently seen after stroke and lead to limited physical activities and worse autonomy. Current physical therapies (PT) aiming at reducing postural imbalance have shown a large variety of effects with low levels of evidence. The objectives are to determine the efficiency of PT in recovering postural imbalance in patients after stroke and to assess which PT is more effective.

Methods and analysis:

We will search Medline, Embase, Pedro, Cochrane Central Register of Controlled Trials, Pascal and Francis from inception to October 2015. There will be no restriction in language or publication type. Only randomised controlled trials assessing PT to recover from post-stroke postural imbalance in adults will be considered.

Outcome measures will be the Berg Balance Scale (BBS), the Postural Assessment Scale for Stroke (PASS), static posturographic parameters (in sitting or standing conditions) and all other measurements of weight bearing distribution on the lower limbs.

Two independent reviewers will screen titles, abstracts and full-text articles, evaluate the risk of bias, and will complete data extraction. In addition to the outcomes, measures of independence as the Barthel Index (BI), the Functional Independence Measure (FIM), the scale for Instrumental Activities of Daily Living (IADL) and the scale for Activities of Daily Living (ADL) will be analysed. This study will aim to determine effects of PT on the function (posturography), the activity (BBS, PASS) and the independence of patients. Subgroup analysis will be planned according to the location of brain lesions (hemispheric, brainstem or cerebellum), the type of approaches (top-down or bottom-up), the methodological quality of studies and the overall time of PT.

Ethics and dissemination: No ethic statement will be required. The results will be published in peer-reviewed journal. This meta-analysis aims to manage the rehabilitation of postural imbalance by PT after stroke.

Trials registration number: Prospero CRD42016037966

Strengths and limitations of this study:

- To our knowledge, there is few systematic reviews and meta-analyses in literature that assess the evidence of the physical therapy for rehabilitation of postural imbalance after stroke.
- This study compares the efficiency of all the rehabilitation's techniques used after stroke to one another.
- A series of subgroup analyses (localisation of brain lesion, side of supratensorial lesion, quality of studies) will address clinical relevant questions.
- There are several posturographic outcomes to assess postural imbalance that may limit comparison across studies.
- The results of this meta-analysis will be helpful for clinician to define strategies of rehabilitation to improve postural imbalance after stroke.

Key words: meta-analysis, efficiency, physical therapy, postural imbalance, balance, stroke.

INTRODUCTION

Background

Stroke was defined as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24h or leading to death with no apparent cause other than that of vascular origin".(1) Stroke is the third cause of death and the first cause of acquired adult disability in the world (WHO). In the USA, 795 000 people suffer from a stroke every year.(2) Stroke leads to a long-term limitation of activity and disability. In France, 80,5% of the people with self-report stroke relate a limitation (light or severe) in activities of daily living (ADL) and one in three stroke survivors are dependent.(3) In New-Zealand, 71% of 5 years poststroke patients present a neurologic impairment (NIH Stroke Scale). A restriction of activity was present in 31,4% of the patients assessed by the Modified Rankin Scale and in 35,4% assessed by the Barthel Index (BI).(4) Among limitations of activity, the postural imbalance is frequently found. 83% of acute stroke patients present a postural imbalance.(5) The fall risk is increased by 73% in the 6 months following a stroke.(6) At a chronic stage, the quality of life is associated with the postural imbalance.(7) The postural rehabilitation seems to be essential to achieve independence in activities of daily living after stroke.

Human posture refers to the relative disposition of body parts.(8) Postural control aims to maintain body stabilization based on a sensory-motor complex skill and body orientation, based on internal representation of body scheme.(9, 10) Postural imbalance following stroke is defined by: i) a postural asymmetry characterized by a larger weight-bearing asymmetry toward the unaffected limb, in a quiet standing posture;(11-18) ii) an increased body sway of the center of the pression (COP);(12, 13, 15, 19) iii) limits of stability (LOS) decreased;(12, 20) iv) an excessive reliance on visual input and a loss of capacity to select the relevant sensory information;(21-24) and v) anticipatory postural adjustments and postural reactions after external perturbations impaired.(25, 26)

State of the art

Different physical therapies (PT) aim to reduce postural imbalance. Current recommendations are limited for daily clinical practice: the level of evidence is too low and they are based on few systematic reviews and meta-analyses. The recommendations in the French evidence-based clinical practice guidelines for PT in patients after stroke were based on only 16 clinical studies.(27) Furthermore, these guidelines are not specific to postural disability and propose a rather global rehabilitation.(28, 29) It is therefore necessary to assess the efficiency of PT in the recovery of postural control after stroke.

Regarding the literature, some meta-analyses have evaluated the effects of one technique on postural imbalance like balance training using platform with biofeedback,(30) functional electrical stimulation,(31) repetitive task training,(32) water-based exercises,(33) virtual reality,(34-36) ankle-foot orthosis,(37) aerobic exercises,(38) physical fitness training,(39) whole body vibration(40, 41). In view of the tremendous growth in the number of randomised controlled trials, it seems to be essential to evaluate one PT compared to another or the association of PT compared to control or usual care. Veerbeek *et al.* (2014)(42) have evaluated the effects of PT after stroke on all outcomes based on the International Classification of Functioning, Disability and Health (ICF) and not only the balance. Pollock *et al.* (2014)(43) have investigated the function and mobility recovery by PT after stroke. They have investigated the different physical rehabilitation approaches and excluded single specific treatments as orthosis and functional electric stimulations. One of all outcomes have evaluated the functional balance (Berg balance Scale). No evaluation of PT on posturographic parameters has been carried out so far. Consequently, the measurement of the PT impact on different characteristics of

the postural imbalance, such as function (posturographic parameters), activity and ADL might be contributive. Lastly, the PT methods might be classified in two distinct types: the pragmatic 'top-down' methods, aiming to improve the postural imbalance by acting on the patient's awareness of the deficit, and the physiological 'bottom-up' methods aiming to modify the sensory-motor dimension of posture, in bypassing the central awareness deficit. This distinction was applied in a recent Cochrane review assessing the effects of rehabilitation methods of spatial neglect.(44)

OBJECTIVES

The aims are: i) to determine the efficiency of PT on the recovery of postural imbalance in adult patients after stroke and ii) to assess which PT is more effective when compared with one another.

METHODS

We will use the guide from The Cochrane Collaboration entitled "Cochrane Handbook for Systematic Reviews of Interventions" (version 5.1.0)(45) and the software (RevMan 5.3) to construct this meta-analysis. The recommendations from PRISMA statement will also be used.(46) No ethic statement will be required for this review and meta-analysis.

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials. The allocation between two or several groups will have to be correctly randomised. Trials without control group or these with quasi-random allocation will be excluded.

Types of participants

We will included all trials which have included human adult patients (over 18 years old) after a first or recurrent stroke. Stroke is defined, according to the World Health Organisation, as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin".(1) Therefore, the positive diagnosis is based on the clinical examination. The imaging diagnostic is not compulsory to include. Transient ischemic accidents (TIAs) will be excluded because, all neurologic symptoms disappear ("TIAs are brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.").(47)

Types of interventions

All types of PT will be included whatever the aim of therapy (upper-limb, lower-limb, posture, gait, spasticity …). The PT is defined by the World Confederation for Physical Therapy (WCPT) as "services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan" and "physical therapy is concerned with identifying and maximising quality of life and movement potential within the spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation" (http://www.wcpt.org/policy/ps-descriptionPT).

Types of outcome measures

Outcomes will be selected in the mind of the International Classification of Functioning, Disability and Health (ICF). Immediate outcomes after the end of PT and delayed outcomes after a follow-up time will be included.

Primary outcomes

The Berg Balance Scale (BBS) and the Postural Assessment for Stroke Scale (PASS) are defined as the primary outcomes.

The BBS assesses the functional postural abilities of patients in several conditions (lying, sitting, standing, leaning forward, change of position …). This scale is composed of 14 items. The maximal score, reflecting the best functional postural abilities, is 56 points. The choice of the scale is based on its validation in stroke patients and on its good metrological qualities, doing it a reference scale.(48-52)

The PASS also evaluates the functional postural abilities of patients in several conditions (lying, sitting, standing and during the changes between these positions). This scale is composed of 12 items. The maximal score, reflecting the best functional postural abilities, is 36 points. Its metrological qualities are good, particularly during the first 3 months.(53, 54)

The two scales exhibit a clinical relevance in assessment of postural imbalance in stroke patients. They express the level of activity. Therefore, changes measured by the these reflect modifications of postural abilities of patients in daily living.

Secondary outcomes

The static posturographic evaluation is defined as a secondary outcome. This evaluation can be performed in sitting or standing position but only the posturographic results on a non-moveable platform will be included. The posturography assesses the evolution of the projection of the center of gravity on the floor (center of pression) by a force platform. This technique reflects the function of postural maintenance.(17, 49, 50) All other evaluations of the weight bearing distribution on the lower limbs are defined as secondary outcomes.

The Barthel Index (BI), the Functional Independence Measure (FIM), the scale for instrumental activities of daily living (IADL) and the scale for activities of daily living (ADL), reflecting the level of autonomy, are defined as secondary outcomes.

Only the two primary outcomes, the static posturographic evaluation and the other evaluations of the weight bearing distribution on the lower limbs are considered as the selection criteria of trials. The BI, IADL, ADL, and FIM will be analysed but they will not participate to selection trials.

Search methods for identification of studies

We will search the following electronic bases from their inception to October 2015: Medline, Embase, Pedro, Cochrane Central Register of Controlled Trials, Pascal and Francis. The search strategy will interest in three kinds of terms : these about « stroke », « posture » and « physical therapy». This strategy is described in table 1.

Table 1. Search strategy in Pubmed

1	exercise movement techniques OR physical therapy modalities OR learning OR pract* OR train* OR rehabilitation* OR therapeutic* OR therapy OR therapies OR exercise* OR physiotherap* OR neurorehabilitation OR neurophysiological OR orthopaed* OR treatment OR approach* OR concept OR home rehabilitation OR self-guided program* OR fitness OR stretching OR sport OR program* OR movement OR protocol* OR intervention OR activit* OR regim* OR recovery
2	(occupational OR physical OR manual) AND (therapy OR therapies OR therapist OR therapeutic OR therapeutics)
3	#1 OR #2

4	posture OR equilibrium OR balance OR postural balance OR weight bearing OR weight shift OR lateropulsion OR pusher OR pushing OR postural imbalance OR postural asymmetry OR postural control OR postural stability OR postural instability OR postural perturbation OR postural disorders OR postural deficit OR postural trouble OR postural sway OR postural tilt OR postural shift OR body sway OR upright stance OR (weight AND (distribut* OR transfer*))
5	(cerebrovascular OR cerebro-vascular OR cerebral OR intracran* OR hemispheric) AND (accident OR hemorrhag* OR haemorrhag* OR infarct* OR ischemi* OR thrombotic OR thrombosis OR emboli* OR hematoma OR haematoma OR bleed OR damage OR lesion OR occlus*)
6	stroke OR poststroke OR post-stroke OR hemipleg* OR hemipar* OR paretic OR paresis OR CVA
7	(right OR left) AND brain AND (lesion OR damage)
8	#5 OR #6 OR #7
9	meta-analysis OR review* OR animal* OR child* OR cerebral pals* OR case-report OR traumatic brain injury
10	#3 AND #4 AND #8 NOT #9

All published and unpublished studies, conferences or presentations will be searched without restriction of languages. The library services of three universities (Université Claude Bernard Lyon1, Université Paris 5 Descartes et Université Paris 6 Pierre et Marie Curie) and two hospital centers (Hospices Civils de Lyon, Assistance publique-Hôpitaux de Paris) will be requested to access to the unpublished and published documents.

Data collection and analysis

Selection of studies

The process of selecting the results of the search will be carried out the base on the selection criteria during three successive steps: i) by reading the titles, ii) by reading the abstracts, and then iii) by reading the full study. Each one of these steps will be separately performed by two independent authors (AH and JDM). For the selection by reading the titles, all studies, selected by one of these two authors, will be accepted for the next step of selection. For the two others steps of selection, an agreement between the two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. The authors of trials will be contacted if some informations needed for the selection process are unclear or missed.

The studies published in journals judged as standalone according to the analyse of Jeffrey Beall will be excluded (https://scholarlyoa.com/individual-journals/). Indeed, based on objective and clearly identified criteria (https://scholarlyoa.files.wordpress.com/2015/01/criteria-2015.pdf), he has determined a list of standalone journals, whose the methodological quality is not confident.

Cross-over trials will be included if: i) the order of interventions has been randomised, and if ii) the potential effects of the first intervention have not impacted the potential effects of the second one. They will be considered as randomised controlled trials. Moreover, some cross-over trials can present a special design: One single assessment during the intervention instead of one assessment before and one after as usually. These types of design are specifically used for some kind of intervention (orthosis …). These cross-over trials will be included if: i) the conditions set above about cross-over trials are validated (the randomised order and the absence of impact of the first intervention on the second one) and if ii) a spontaneous recovery is not possible during the time between the two interventions.

No studies will be excluded because of the language of the rapport. The studies rapports written in other languages than the French or the English will be translated by the authors : YX for the Chinese studies, HK for the Persian studies, JP for the Portuguese studies.

Data extraction and management

Data extraction will be separately carried out by two independent authors (AH and JDM). Agreement between these two authors will have be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. The authors of included trials will be contacted if some data are unclear or missed. Data extraction will include :

1. The design of study
2. The details of population: size of population, age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke, the imaging diagnostic with the etiologic and the localisation of stroke lesions.
3. The methodological quality of trials: details of random process, blinding and drop-out.
4. The PT: overall time of PT, the aims and the most important characteristics of each PT.
5. The outcomes: all outcomes measured and specifically the BBS, the PASS, the posturographic outcomes, all outcomes assessing the weight bearing on the lower limbs, BI, FIM, IADL and ADL will be also extracted.
6. The prior submission to an ethics committee or the respect of the declaration of Helsinki on human clinical trials.

Assessment of risk of bias in included studies

The methodological quality of all included trials will be separately assessed by two independent authors (AH and JDM). Agreement between these two authors will have be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. This evaluation will be based on four quality criteria about: i) the random sequence generation, ii) the allocation concealment, iii) the blinding of outcome assessment and iv) the incomplete outcome data. For each one of them, a risk of bias will be determined: i) high level, ii) unclear level, or iii) low level.

Measures of treatment effect

The statistical analysis will be performed using the software, RevMan 5.3. All outcomes will be continuous variables. The heterogeneity of the effects of trials will be evaluated by the chi-squared test and the I^2 test. Heterogeneity will be considered as substantial if the I^2 statistic $\geq 50\%$ and $p < 0{,}10$. If heterogeneity is not considered as substantial, a fixed-effect model will be used. If heterogeneity is considered as substantial, explications of this heterogeneity will be searched and a random-effect model will be used to compare. A analysis will interest to each outcome measurements made on the same scale. So, the mean difference (MD) and 95% confidence intervals (CIs) will be calculated. To express the size of the PT effect on the function and the activity, it will be necessary to combine the outcomes from some different scales (all static posturographic outcomes and the other evaluations of the weight bearing distribution on the lower limbs for the function, PASS and BBS for the activity). Thus, the standardised mean difference (SMD) and 95% confidence intervals (CIs) will be calculated.

For the trials with results displayed with stratification into subgroups within a same rehabilitation group, no substantial heterogeneity will be checked before mixing the two subgroups of the same PT.

Data synthesis

Because of a diversity of PT, we will plan to group some PT according to their aim and their characteristics. The comparisons will interest the effects of active PT versus: i) no PT, ii) usual care, placebo or control PT and iii) another active PT. They will interest immediate outcomes and delayed outcomes.

Subgroup analysis and investigation of heterogeneity

One first subgroup analysis will be carried out according to the localisation of brain lesion. For this purpose, three subgroups will be identified: i) supratentorial stroke, ii) cerebellum stroke and iii) brainstem stroke. A subgroup analysis will also investigate the effects of PT according to the side of the supratensorial lesion (right/left). A second subgroup analysis will determine the effects of PT based on their types of action: « bottom-up » or « top-down » action. A third subgroup analysis of effects will be carried out according to the methodological quality of trials. Two subgroups will be identified: i) the trials in which all criteria of methodological quality, detailed in the part « Assessment of risk of bias in included studies », will present a low risk, and ii) the trials in which at least one of these criteria will present a unclear or high risk. We will plan a meta-regression of the effects according to the overall time of PT.

Considering the high risk of heterogeneity for the different PT, the network meta-analysis is, at this moment, not studied.

DISCUSSION

This meta-analysis aims i) to determine the efficiency of PT on the recovery of postural imbalance in adult patients after stroke and ii) to assess which PT is more effective when compared with one another.

Postural imbalance is frequent in stroke patients at initial or chronic stage. It affects walking abilities, independency and quality of life.(7) Therefore, reduction in postural imbalance of patients after stroke is a relevant objective of PT, in order to increase the level of autonomy.

For this purpose, this systematic review and meta-analysis aim to upgrade and improve the rehabilitation of postural imbalance by purposing a complete analysis of all PT. In an evidence-based practice approach, we would participate to increase the level of evidence about rehabilitation of postural imbalance by PT. Our purpose is not only to compare the effects of PT but also to improve the understanding of these PT, using subgroup analyses.

Stroke leads to a large range of clinical subtypes of postural imbalance and related underlying disorders. For example, postural imbalance differs depending on the location and the size of the brain damage.(55) The patients with right supratentorial lesions show a greater weight bearing asymmetry and weaker postural functional abilities.(13, 18, 55) Therefore, it will be interesting to determine the effects of PT, not only according to the therapy per se, but also, to the location of the brain lesion. This subgroup analyses could improve the understanding of the key characteristics of each PT, and thus, upgrade the therapeutic aims.

In the same way, examining the effects of PT based on both the function and the activity of the patient will offer an additional asset.

Lastly, the effects of different PT will been analysed according to their ‘top-down’ and ‘bottom-up’ approaches in order to better understand the theory behind postural rehabilitation.

CONTRIBUTORSHIP STATEMENT

Aurelien HUGUES and Julie DI MARCO have participated and performed all steps of this meta-analysis : preliminary search, conception and design of the protocol, and drafting of this publication.

All this work was assisted and supervised by Professors Isabelle BONAN, Francois GUEYFFIER and Gilles RODE.
Perrine JANIAUD has supported Aurelien HUGUES and Julie DI MARCO for the search in electronic data bases.
Yufeng XUE, Jenifer PIRES and Hooman KHADEMI have been in charge to translate the studies respectively in chinese, portuguese, persian languages.

COMPETING INTERESTS STATEMENT

Dr Perrine Janiaud present a conflict of interest with GlaxoSmithKline company. Her PhD thesis was supported by GSK. Dr Perrine Janiaud will contribute in this study by helping to search electronic data bases. She will not participate in the selection process and in the analyses.
All others authors present no conflict of interest.

REFERENCES

1. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;54(5):541-53.
2. Mozaffarian D, Benjamin EJ, Go AS, *et al.*. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;131(4):e29-322.
3. Schnitzler A, Woimant F, Tuppin P, *et al.* Prevalence of Self-Reported Stroke and Disability in the French Adult Population: A Transversal Study. *PLoS One* 2014;9(12):e115375.
4. Feigin VL, Barker-Collo S, Parag V, *et al.* Auckland Stroke Outcomes Study. Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. *Neurology* 2010;75(18):1597-607.
5. Tyson SF, Hanley M, Chillala J, *et al*. Balance disability after stroke. *Phys. Ther* 2006;86(1):30–8.
6. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. *BMJ* 1995;311(6997):83-6.
7. Schmid AA, Van Puymbroeck M, Altenburger PA, *et al.* Balance is associated with quality of life in chronic stroke. *Top Stroke Rehabil* 2013;20(4):340-6.
8. Thomas A. Equilibre et equilibration. Paris: Masson 1940.
9. Amblard B, Crémieux J, Marchand AR, *et al.* Lateral orientation and stabilization of human stance: static versus dynamic visual cues. *Exp Brain Res*. 1985;61(1):21-37.
10. Massion J. Cerveau et motricité, fonctions sensori-motrices. Presses Universitaires de France 1997.
11. Sackley C. The relationships between weight-bearing asymmetry after stroke, motor function and activities of daily living. *Physiotherapy theory and practice* 1990;6:179-85.
12. Pérennou D, Pélissier J, Amblard B. La posture et le contrôle postural du patient cérébrolésé vasculaire : une revue de la littérature. *Ann. Réadaptation Médecine Phys*. 1996;39(8):497-513.
13. Rode G, Tilikete C, Boisson D. Predominance of postural imbalance in left hemiparetic patients. *Scand J Rehab Med*. 1997;29:155-64.
14. Rode G, Tiliket C, Charlopain P, *et al.* Postural asymmetry reduction by vestibular caloric stimulation in left hemiparetic patients. *Scand J Rehab Med* 1998;30:9-14.
15. Cheng P-T, Liaw M-Y, Wong M-K, *et al*. The sit-to-stand movement in stroke patients and its correlation with falling. *Arch Phys Med Rehabil* 1998;79:1043-6.

16. Geurts ACH, de Haart M, van Nes IJW, *et al*. A review of standing balance recovery from stroke. *Gait Posture* 2005;22(3):267-81.
17. Genthon N, Rougier P, Gissot AS, *et al.* Contribution of each lower limb to upright standing in stroke patients. *Stroke* 2008;39:1793-9.
18. Ishii F, Matsukawa N, Horiba M, *et al.* Impaired ability to shift weight onto the non-paretic leg in right-cortical brain-damaged patients. *Clin Neurol Neurosurg*. 2010;112(5):406-12.
19. Dickstein R, Abulaffio N. Postural sway of the affected and nonaffected pelvis and leg in stance of hemiparetic patients. *Arch Phys Med Rehabil*. 2000;81(3):364-7.
20. Di Fabio RP, Badke MB. Extraneous movement associated with hemiplegic postural sway during dynamic goal-directed weight redistribution. *Arch Phys Med Rehabil*. 1990;71(6):365-71.
21. Bonan IV, Yelnik A, Laffont I, *et al*. Sélection des afférences sensorielles dans l'équilibration de l'hémiplégique après accident vasculaire cérébral. *Ann. Réadaptation Médecine Phys*. 1996;39(3):157-63.
22. Bonan IV, Colle FM, Guichard JP, *et al.* Reliance on visual information after stroke. Part I: balance on dynamic posturography. *Arch. Phys. Med. Rehabil*. 2004;85(2):268-73.
23. Bonan IV, Marquer A, Eskiizmirliler S, *et al*. Sensory reweighting in controls and stroke patients. Clin Neurophysiol. 2013;124(4):713-22.
24. Yelnik AP, Kassouha A, Bonan IV, *et al*. Postural visual dependence after recent stroke: Assessment by optokinetic stimulation. *Gait Posture* 2006;24(3):262-9.
25. Di Fabio RP. Lower extremity antagonist muscle response following standing perturbation in subjects with cerebrovascular disease. *Brain Res*. 1987;406(1-2):43-51.
26. Garland SJ, Stevenson TJ, Ivanova T. Postural responses to unilateral arm perturbation in young, elderly, and hemiplegic subjects. *Arch Phys Med Rehabil*. 1997;78(10):1072-7.
27. Haute Autorité de Santé. Accident vasculaire cérébral : méthodes de rééducation de la fonction motrice chez l'adulte Méthode « Recommandations pour la pratique clinique » 2012.
28. American Heart Association/American Stroke Association. Endorsed Practice Guidelines Management of Adult Stroke Rehabilitation Care, A Clinical Practice Guideline Stroke 2015
29. National Health Service. Stroke rehabilitation in adults Clinical guideline 2013.
30. Barclay-Goddard R, Stevenson T, Poluha W, et al. Force platform feedback for standing balance training after stroke. *Cochrane Database Syst Rev*. 2004;18;(4).
31. Glanz M, Klawansky S, Stason W, *et al*. Functional electrostimulation in poststroke rehabilitation: a meta-analysis of the randomized controlled trials. *Arch Phys Med Rehabil*. 1996 ;77(6):549-53.
32. French B, Thomas L, Leathley M, *et al.* Does repetitive task training improve functional activity after stroke? A Cochrane systematic review and meta-analysis. *J Rehabil Med*. 2010;42(1):9-14.
33. Mehrholz J, Kugler J, Pohl M. Water-based exercises for improving activities of daily living after stroke. *Cochrane Database Syst Rev*. 2011;(1):CD008186.
34. Laver KE, George S, Thomas S, *et al.* Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev.* 2015;2:CD008349.
35. Li Z, Han XG, Sheng J, *et al*. Virtual reality for improving balance in patients after stroke: A systematic review and meta-analysis. *Clin Rehabil*. 2016;30(5):432-40.

36. Corbetta D, Imeri F, Gatti R. Rehabilitation that incorporates virtual reality is more effective than standard rehabilitation for improving walking speed, balance and mobility after stroke: a systematic review. *J Physiother*. 2015;61(3):117-24.
37. Tyson SF, Kent RM. Effects of an ankle-foot orthosis on balance and walking after stroke: a systematic review and pooled meta-analysis. *Arch Phys Med Rehabil*. 2013;94(7):1377-85.
38. Pang MY, Charlesworth SA, Lau RW, *et al*. Using aerobic exercise to improve health outcomes and quality of life in stroke: evidence-based exercise prescription recommendations. *Cerebrovasc Dis*. 2013;35(1):7-22.
39. Saunders DH, Sanderson M, Brazzelli M, *et al.* Physical fitness training for stroke patients. *Cochrane Database Syst Rev*. 2013;10:CD003316.
40. Yang X, Wang P, Liu C, *et al*. The effect of whole body vibration on balance, gait performance and mobility in people with stroke: a systematic review and meta-analysis. *Clin Rehabil*. 2015;29(7):627-38.
41. Lu J, Xu G, Wang Y. Effects of whole body vibration training on people with chronic stroke: a systematic review and meta-analysis. *Top Stroke Rehabil*. 2015;22(3):161-8.
42. Veerbeek JM, van Wegen E, van Peppen R, *et al*. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS One* 2014;9(2):e87987.
43. Pollock A, Baer G, Campbell P, *et al*. Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst Rev*. 2014;4:CD001920.
44. Bowen A, Hazelton C, Pollock A, *et al*. Cognitive rehabilitation for spatial neglect following stroke. Cochrane *Database Syst Rev*. 2013;7:CD003586.
45. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
46. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
47. Easton JD, Saver JL, Albers GW, *et al.* Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40(6):2276-93.
48. Tyson SF, De Souza LH. Reliability and validity of functional balance tests post stroke. *Clin. Rehabil*. 2004;18(8):916-23.
49. Pérennou D, Decavel P, Manckoundia P, *et al*. Evaluation de l'équilibre en pathologie neurologique et gériatrique. *Ann. Réadaptation Médecine Phys*. 2005;48(6):317-35.
50. Yelnik A, Bonan I. Clinical tools for assessing balance disorders. *Neurophysiol. Clin. Neurophysiol*. 2008;38(6):439-45.
51. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in Stroke Rehabilitation: A Systematic Review. *Phys. Ther.* 2008;88(5):559-66.
52. Tyson SF, Connell LA. How to measure balance in clinical practice. A systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. *Clin Rehabil*. 2009;23(9):824-40.

53. Benaim C, Pérennou DA, Villy J, *et al*. Validation of a standardized assessment of postural control in stroke patients: the Postural Assessment Scale for Stroke Patients (PASS). *Stroke* 1999;30(9):1862-8.
54. Mao HF, Hsueh IP, Tang PF, *et al*. Analysis and comparison of the psychometric properties of three balance measures for stroke patients. *Stroke* 2002;33(4):1022-7.
55. Pérennou D, Benaim C, Rouget E, *et al*. Postural balance following stroke: towards a disadvantage of right brain-damaged hemisphere. *Rev Neuro* 1999;155(4):281-90.

ETHIC AND DISSEMINATION

No ethic statement will be required for this review and meta-analysis. Results of this research will be published. These results would contribute to ameliorate the therapeutic strategy of stroke patients.

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Efficiency of physical therapy on postural imbalance after stroke: study protocol for a systematic review and meta-analysis.

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ABSTRACT (287 words)

Introduction: Stroke frequently results in balance disorders, leading to lower levels of activity and a diminution in autonomy. Current physical therapies (PT) aiming to reduce postural imbalance have shown a large variety of effects with low levels of evidence. The objectives are to determine the efficiency of PT in recovering from postural imbalance in patients after a stroke and to assess which PT is more effective.

Methods and analysis:

We will search several databases from inception to October 2015. Only randomised controlled trials assessing PT to recover from post-stroke postural imbalance in adults will be considered.

Outcome measures will be the Berg Balance Scale (BBS), the Postural Assessment Scale for Stroke (PASS), the weight body asymmetry" (WBA), the "centre of pressure" (COP) and the "limit of stability" (LOS). WBA, COP and LOS are measured by a (sitting or standing) static evaluation on force-plate or another device.

Two independent reviewers will screen titles, abstracts and full-text articles, evaluate the risk of bias, and will perform data extraction. In addition to the outcomes, measures of independence will be analysed. This study will aim at determining the effects of PT on the function (WBA, COP, LOS), the activity (BBS, PASS) and the independence of patients. Subgroup analyses will be planned according to the location of brain lesion (hemispheric, brainstem or cerebellum), the time since stroke (early, late, chronic), the PT (type, main aim (direct effect or generalization), overall duration), the type of approaches (top-down or bottom-up), and the methodological quality of studies.

Ethics and dissemination: No ethical statement will be required. The results will be published in a peer-reviewed journal. This meta-analysis aims at managing the rehabilitation after postural imbalance by PT after a stroke.

Trials registration number: Prospero CRD42016037966

Strengths and limitations of this study:

- To our knowledge, there are few systematic reviews and meta-analyses in the literature that assess the evidence of PT for rehabilitation of postural imbalance after a stroke.
- This study will compare the efficiency of all PT used after a stroke to one another.
- A series of subgroup analyses will address relevant clinical issues.
- There are several outcomes to assess postural imbalance (function and activity) that may limit comparison across studies.
- The results of this meta-analysis will be helpful for clinicians to define rehabilitation strategies for improving postural imbalance after stroke.

Key words: meta-analysis, efficiency, physical therapy, postural imbalance, balance, stroke.

INTRODUCTION

Background

A stroke was defined as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24h or leading to death with no apparent cause other than that of vascular origin".(1) Stroke is the third cause of death and the first cause of acquired adult disability in the world (WHO). In the USA, 795 000 people suffer from a stroke every year.(2) Stroke leads to a long-term limitation of activity and disability. In France, 80,5% of the people with self-report stroke declare a limitation (light or severe) in activities of daily living (ADL) and one in three stroke survivors are dependent.(3) In New-Zealand, 71% of 5 years post-stroke patients present a neurological impairment, assessed by the NIH Stroke Scale. A restriction of activity was present in 31,4% of the patients assessed by the Modified Rankin Scale and in 35,4% assessed by the Barthel Index (BI).(4) Among limitations of activity, the postural imbalance is frequently found. Eighty-three percent of acute stroke patients present a postural imbalance.(5) The risk of fall is increased by 73% in the 6 months following a stroke.(6) At a chronic stage, the quality of life is associated with the postural imbalance.(7) Postural rehabilitation seems to be crucial to achieve independence in activities of daily living after stroke.

Human posture refers to the relative disposition of body parts.(8) Postural control aims to maintain body stabilisation based on a sensory-motor complex skill and body orientation, based on internal representation of body scheme.(9, 10) Postural imbalance following stroke is defined by: i) a larger weight-bearing asymmetry (WBA) toward the unaffected limb, in a quiet standing posture;(11-18) ii) an increased body sway of the centre of the pressure (COP);(12, 13, 15, 19) iii) a decrease in the limits of stability (LOS);(12, 20) iv) an excessive reliance on visual input,(21-24) and v) an impairment of anticipatory postural adjustments and postural reactions after external perturbations.(25, 26)

State of the art

Different physical therapies (PT) aim at reducing postural imbalance. Current recommendations are limited for daily clinical practice: the level of evidence is too low and it is based on few systematic reviews and meta-analyses. The recommendations in the French evidence-based clinical practice guidelines for PT in patients after stroke were based on only 16 clinical studies.(27) Furthermore, these guidelines are not specific to postural disability and propose a rather global rehabilitation.(28, 29) It is therefore necessary to assess the efficiency of PT in the recovery of postural control after stroke.

Regarding the literature, some meta-analyses have evaluated the effects of a single technique on postural imbalance like balance training using a platform with biofeedback,(30) functional electrical stimulation,(31) repetitive task training,(32) water-based exercises,(33) virtual reality,(34-36) ankle-foot orthosis,(37) aerobic exercises,(38) physical fitness training,(39) or whole body vibration(40, 41). In view of the tremendous growth in the number of randomised controlled trials, it seems to be essential to evaluate one PT compared to another or the association of PT compared to control or usual care. Veerbeek *et al.* (2014)(42) have evaluated the effects of PT after stroke on all outcomes based on the International Classification of Functioning, Disability and Health (ICF) and not only the balance. Pollock *et al.* (2014)(43) have investigated the function and mobility recovery by PT after stroke. Compared to previous studies, the aim of this systematic review and meta-analysis is to perform a review only focused on the effects of PT on postural imbalance after stroke with identification of different parameters.

Lastly, in this review and meta-analysis, we also propose to categorize the different PT according to the involved "top-down" and "bottom-up" processing. This processing refers to two types of interaction between sensori-motor (implicit) and cognitive (explicit) representations involved in rehabilitation. Top-down approach aims at training the patient to voluntarily compensate for his deficit and requires awareness of the disorder although bottom-up approach does not require awareness of the disorder. This categorization has already been used in a previous Cochrane meta-analysis about cognitive rehabilitation for an another spatial cognition deficit (spatial neglect).(44-46)

OBJECTIVES

The aims are: i) to determine the efficiency of PT on the recovery of postural imbalance in adult patients after stroke and ii) to assess which PT is more effective when compared with one another.

METHODS

We will use the guide from The Cochrane Collaboration entitled "Cochrane Handbook for Systematic Reviews of Interventions" (version 5.1.0)(47) and the software (RevMan 5.3) to construct this meta-analysis. The recommendations from PRISMA statement will also be followed.(48) No ethical statement will be required for this review and meta-analysis.

Criteria for considering studies for this review

Type of studies

We will include all randomised controlled trials. The allocation between two or several groups will have to be correctly randomised. Trials without control group or those with quasi-random allocation will be excluded.

Types of participants

We will include all trials which have included human adult patients (over 18 years old) after a first or recurrent stroke. Stroke is defined, according to the World Health Organisation, as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin".(1) Therefore, the positive diagnosis is based on clinical examination. It is not compulsory to include the imaging diagnosis. Transient ischemic accidents (TIAs) will be excluded because all neurological symptoms disappear ("TIAs are brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.").(49)

Types of interventions

The selection process will not be based on the type or the nature of the PT in trials. We will select all trials assessing a PT whatever it may be and whatever its aim (upper-limb, lower-limb, posture, gait, spasticity …). This meta-analysis will not be limited to PT, the direct and immediate objective of which is to reduce postural imbalance. This possible expand or generalization of effects may be observed after intervention in rehabilitation.

The PT is defined by the World Confederation for Physical Therapy (WCPT) as "services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan" and "physical therapy is concerned with identifying and maximising quality of life and movement potential within the spheres of

promotion, prevention, treatment/intervention, habilitation and rehabilitation" (http://www.wcpt.org/policy/ps-descriptionPT).

Types of outcome measures

Outcomes will be selected following the recommendations of the International Classification of Functioning, Disability and Health (ICF). Immediate outcomes after the end of PT and delayed outcomes after a follow-up time will be included.

Primary outcomes

The BBS assesses the functional postural abilities of patients in several conditions (lying on the back, sitting, standing, leaning forward, change of position …). This scale is composed of 14 items. The maximal score, reflecting the best functional postural abilities, is 56 points. The choice of the scale is based on its validation in stroke patients and on its good metrological qualities, doing it a reference scale.(50-54)

The PASS also evaluates the functional postural abilities of stroke patients in several conditions (lying on the back, sitting, standing and while changing (these) positions). This scale is composed of 12 items. The maximal score, reflecting the best functional postural abilities, is 36 points. Its metrological qualities are good, particularly during the first 3 months.(55, 56)

The two scales exhibit a clinical relevance in assessment of postural imbalance in stroke patients. They express the level of activity. Therefore, measured changes reflect modifications of postural abilities of patients in daily living.

The outcomes pertaining to balance and postural control will be the WBA, the COP and the LOS. These parameters will be measured by a (sitting or standing) static evaluation on force-plate or another device (17, 51, 52).

Secondary outcomes

The outcomes will be the Barthel Index (BI), the Functional Independence Measure (FIM), the scale for instrumental activities of daily living (IADL) and the scale for activities of daily living (ADL), reflecting the level of autonomy.

Only the primary outcomes will be considered for selection of trials.

Search methods for identification of studies

We will search the following electronic bases from their inception to October 2015: Medline, Embase, PEDro, Cochrane Central Register of Controlled Trials, Pascal and Francis. The search strategy will interest in three kinds of terms: these about « stroke », « posture » and « physical therapy». This search strategy is described in Table 1.

Table 1. Search strategy in Pubmed

1	exercise movement techniques OR physical therapy modalities OR learning OR pract* OR train* OR rehabilitation* OR therapeutic* OR therapy OR therapies OR exercise* OR physiotherap* OR neurorehabilitation OR neurophysiological OR orthopaed* OR treatment OR approach* OR concept OR home rehabilitation OR self-guided program* OR fitness OR stretching OR sport OR program* OR movement OR protocol* OR intervention OR activit* OR regim* OR recovery
2	(occupational OR physical OR manual) AND (therapy OR therapies OR therapist OR therapeutic OR therapeutics)
3	#1 OR #2
4	posture OR equilibrium OR balance OR postural balance OR weight bearing OR weight shift OR lateropulsion

	OR pusher OR pushing OR postural imbalance OR postural asymmetry OR postural control OR postural stability OR postural instability OR postural perturbation OR postural disorders OR postural deficit OR postural trouble OR postural sway OR postural tilt OR postural shift OR body sway OR upright stance OR (weight AND (distribut* OR transfer*))
5	(cerebrovascular OR cerebro-vascular OR cerebral OR intracran* OR hemispheric) AND (accident OR hemorrhag* OR haemorrhag* OR infarct* OR ischemi* OR thrombotic OR thrombosis OR emboli* OR hematoma OR haematoma OR bleed OR damage OR lesion OR occlus*)
6	stroke OR poststroke OR post-stroke OR hemipleg* OR hemipar* OR paretic OR paresis OR CVA
7	(right OR left) AND brain AND (lesion OR damage)
8	#5 OR #6 OR #7
9	meta-analysis OR review* OR animal* OR child* OR cerebral pals* OR case-report OR traumatic brain injury
10	#3 AND #4 AND #8 NOT #9

All published and unpublished studies, conferences or presentations will be searched without restriction in languages. The library services of three universities (Université Claude Bernard Lyon1, Université Paris 5 Descartes and Université Paris 6 Pierre et Marie Curie) and two hospital centres (Hospices Civils de Lyon, Assistance Publique-Hôpitaux de Paris) will be requested to access the unpublished and published documents.

Data collection and analysis

Selection of studies

The process of selecting the search results will be carried out on the base of the selection criteria in three successive steps: i) by reading the titles, ii) by reading the abstracts, and then iii) by reading the full texts. Each one of these steps will be separately performed by two independent authors (AH and JDM). For the selection on the basis of titles, all studies, selected by one of these two authors, will be accepted for the next step of the selection process. For the two subsequent steps of selection, an agreement between the two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. The authors of the trials will be contacted if information needed for the selection process is unclear or missing.

The studies published in journals judged as standalone according to the analysis of Jeffrey Beall (https://scholarlyoa.com/individual-journals/), which is based on objective and clearly identified criteria (https://scholarlyoa.files.wordpress.com/2015/01/criteria-2015.pdf), will be excluded.

Cross-over trials will be included if: i) the order of interventions has been randomised, and if ii) the potential effects of the first intervention have not impacted the potential effects of the second one. They will be considered as randomised controlled trials. Moreover, some cross-over trials can present a special design: a single assessment during the intervention instead of an assessment before and one after, as is usually the case. These types of design are specifically used for some types of intervention (orthosis …). These cross-over trials will be included if: i) the conditions set above regarding cross-over trials are validated (the randomised order and the absence of impact of the first intervention on the second one) and if ii) a spontaneous recovery is not possible during the time between the two interventions.

No study will be excluded because of the language of the report: Those written in languages other than French or English will be translated by the authors: YX for those written in Chinese, HK for those written in Persian, JP for the for those written in Portuguese.

Data extraction and management

Data extraction will be carried out independently by two authors (AH and JDM). Agreement between these two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. The authors of included trials will be contacted if some data are unclear or missing. Data extraction will include:

1. The design of study
2. The details of the population: size of the population, age, gender, time since stroke, side of the paresis, unilateral or bilateral stroke, first ever or the recurrent stroke, the imaging diagnostic with the etiologic and the localisation of stroke lesions.
3. The methodological quality of trials: details of random process, blinding, dropout, reporting and others.
4. The PT: overall duration of PT, the aims and the most important characteristics of each PT.
5. The outcomes: all outcomes measured and specifically the BBS, the PASS, the WBA, the COP, the LOS, the BI, the FIM, the IADL and the ADL will also be extracted.
6. The prior submission to an ethics committee or the respect of the declaration of Helsinki on human clinical trials.

Assessment of the risk of bias in included studies

The methodological quality of all included trials will be separately assessed by two independent authors (AH and JDM). Agreement between these two authors will have to be found. In case of disagreement, three more authors (IB, FG, GR) will have to decide by consensus. This evaluation will be based on the seven relevant domains in the "risk of bias" tool of Cochrane Handbook for Systematic Review of Interventions: i) random sequence generation, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data, vi) selective reporting and vii) others bias.

The level of risk of bias will be determined for each domain: i) high level, ii) unclear level, or iii) low level.

Measures of treatment effect

The statistical analysis will be performed according to the recommendations of the Cochrane Handbook and using the software of Cochrane Collaboration, RevMan 5.3, available from the Cochrane website (http://tech.cochrane.org/revman). All outcomes will be continuous variables. The measurement of effects will be determined based on the change scores from baseline. Initially, a fixed-effect model will be used to compare the outcomes expressed in the same scale. The heterogeneity of the effects of trials will be evaluated by the chi-squared test and the I^2 test. Heterogeneity will be considered as substantial if the I^2 statistic ≥50% and p<0,10. If heterogeneity is considered as substantial, reasons for this heterogeneity will be searched for and a random-effect model could be used for comparison. So, the mean difference, which is the absolute difference between the mean value in two groups in a trial, and its 95% confidence intervals will be calculated. To express the PT effects on the function and the activity, it will be necessary to combine the outcomes measured in a variety of scales (measures of WBA, COP and LOS for the function, PASS and BBS for the activity). Thus, the standardised mean difference (SMD) and its 95% confidence intervals will be calculated. The SMD expresses the size of the intervention effect in each trial relative to the variability observed in that trial. In Revman, the SMD is calculated based on the Hedges' g.

For the trials with more than two PT groups and to prevent a group being counted twice, we will determine which PT groups are relevant for pair-wise comparisons. Or, if all are relevant, a further possibility will be to include each pair-wise comparison separately and to divide evenly the shared group among the comparisons. For the trials for which results for a rehabilitation group are stratified, the absence of substantial heterogeneity will be verified before mixing the two subgroups of the same PT.

Data synthesis

The comparisons will focus on the effects of active PT versus: i) no PT, ii) usual care, placebo or control PT and iii) another active PT. First, immediate outcomes will be analysed, then, delayed outcomes (follow-up tests) if they have been evaluated.

Subgroup analysis and investigation of heterogeneity

Several subgroup analyses will investigate the effects of PT according to:

1. the type/nature of PT (For example: electromechanical devices including biofeedback, robotics, and functional electrical stimulation, virtual reality, task-oriented training, gait training, vibration, non-invasive cerebral stimulation …).
2. The main therapeutic goal of PT. Two groups will be established: i) PT aiming mainly at the recovery of postural imbalance and ii) PT not specifically focused on the recovery of postural imbalance.
3. the localisation of brain lesion. To this purpose, three subgroups will be identified: i) hemispheric stroke, ii) brainstem stroke and iii) cerebellum stroke. A subgroup analysis will also investigate the effects of PT according to the side of the hemispheric lesion (right/left).
4. the type of processing “bottom-up” or “top-down”.
5. the methodological quality of trials. Two subgroups will be identified: i) the trials in which all criteria of methodological quality, detailed in the part entitled « Assessment of risk of bias in included studies », will present a low risk, and ii) the trials in which at least one of these criteria will present an unclear or high risk.
6. the trials assessing or not the level of autonomy (BI, FIM, IADL, ADL).
7. the time since stroke. To this purpose, three subgroups will be identified: i) early (≤30 days), ii) late (<180 days) and iii) chronic stroke (≥180 days).(57)

We will plan a meta-regression of the effects according to the overall duration of PT.

Considering the high risk of heterogeneity for the different PT investigated, a network meta-analysis is, at the present time, not envisaged.

DISCUSSION

Postural imbalance is frequent in stroke patients at early, late or chronic stage. It affects walking abilities, independence and quality of life.(7) Therefore, reduction of postural imbalance in stroke patients is a relevant objective of PT, in order to increase the level of autonomy. This meta-analysis aims i) at determining the efficiency of PT on the recovery of postural imbalance in adult patients after stroke and ii) at assessing which PT is more effective when compared with one another. To this purpose, this systematic review and meta-analysis aims at upgrading and improving the rehabilitation of postural imbalance by a complete analysis of all PT. But our objective is not only to compare the effects of PT but also to improve the understanding of these PT effects, using subgroup analyses.

Stroke leads to a large range of clinical subtypes of postural imbalance and related underlying disorders. One of the major issues regarding the rehabilitation of postural imbalance after stroke is the heterogeneity of stroke and the patients' deficits. For example, postural imbalance differs depending on the location and the size of the brain damage.(58) The patients with right hemispheric lesions show a greater WBA and weaker balance abilities.(13, 18, 58) Moreover, a second major issue is the variety of PT: human practice and/or electromechanical devices, several different (re)learning methods (biofeedback, repetitive tasks, tasks oriented, …), "top-down" and "bottom-up" approaches, …

Therefore, many relevant issues regarding the rehabilitation of postural imbalance after stroke are asked: Which PT is the best? What is the most relevant between specific PT focused on postural imbalance and generalization effects of non-specific PT? Does the postural imbalance rehabilitation only involve a sensory-motor approach? What is the advantage of technology? Which efficiency according to the time since stroke? Which intensity of PT is the most efficient? What are the effects on the autonomy and the quality of life? The previously detailed subgroup analyses could describe the effects of each PT, and thus, contribute to propose a guideline for rehabilitation of postural imbalance in stroke patients. One relevant issue may be to better identify the appropriate PT for one patient at one time after stroke?

CONTRIBUTORSHIP STATEMENT

Aurelien HUGUES and Julie DI MARCO have participated and performed all steps of this meta-analysis: preliminary search, conception and design of the protocol, and drafting of this publication.

All this work was assisted and supervised by Professors Isabelle BONAN, Francois GUEYFFIER and Gilles RODE. Michel Cucherat has supported Aurelien HUGUES and Julie DI MARCO for the statistical processing.

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Yufeng XUE, Jenifer PIRES and Hooman KHADEMI have been in charge to translate the studies respectively in chinese, portuguese, persian languages.

COMPETING INTERESTS STATEMENT

Dr Perrine Janiaud present a conflict of interest with GlaxoSmithKline company. Her PhD thesis was supported by GSK. Dr Perrine Janiaud will contribute in this study by helping to search electronic data bases. She will not participate in the selection process and in the analyses.

All others authors present no conflict of interest.

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REFERENCES

1. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;54(5):541-53.
2. Mozaffarian D, Benjamin EJ, Go AS, *et al.* Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;131(4):e29-322.
3. Schnitzler A, Woimant F, Tuppin P, *et al.* Prevalence of Self-Reported Stroke and Disability in the French Adult Population: A Transversal Study. *PLoS One* 2014;9(12):e115375.

4. Feigin VL, Barker-Collo S, Parag V, *et al.* Auckland Stroke Outcomes Study. Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. *Neurology* 2010;75(18):1597-607.
5. Tyson SF, Hanley M, Chillala J, *et al*. Balance disability after stroke. *Phys. Ther* 2006;86(1):30–8.
6. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. *BMJ* 1995;311(6997):83-6.
7. Schmid AA, Van Puymbroeck M, Altenburger PA, *et al.* Balance is associated with quality of life in chronic stroke. *Top Stroke Rehabil* 2013;20(4):340-6.
8. Thomas A. Equilibre et equilibration. Paris: Masson 1940.
9. Amblard B, Crémieux J, Marchand AR, *et al.* Lateral orientation and stabilization of human stance: static versus dynamic visual cues. *Exp Brain Res*. 1985;61(1):21-37.
10. Massion J. Cerveau et motricité, fonctions sensori-motrices. Presses Universitaires de France 1997.
11. Sackley C. The relationships between weight-bearing asymmetry after stroke, motor function and activities of daily living. *Physiotherapy theory and practice* 1990;6:179-85.
12. Pérennou D, Pélissier J, Amblard B. La posture et le contrôle postural du patient cérébrolésé vasculaire : une revue de la littérature. *Ann. Réadaptation Médecine Phys*. 1996;39(8):497-513.
13. Rode G, Tilikete C, Boisson D. Predominance of postural imbalance in left hemiparetic patients. *Scand J Rehab Med.* 1997;29:155-64.
14. Rode G, Tiliket C, Charlopain P, *et al.* Postural asymmetry reduction by vestibular caloric stimulation in left hemiparetic patients. *Scand J Rehab Med* 1998;30:9-14.
15. Cheng P-T, Liaw M-Y, Wong M-K, *et al*. The sit-to-stand movement in stroke patients and its correlation with falling. *Arch Phys Med Rehabil* 1998;79:1043-6.
16. Geurts ACH, de Haart M, van Nes IJW, *et al*. A review of standing balance recovery from stroke. *Gait Posture* 2005;22(3):267-81.
17. Genthon N, Rougier P, Gissot AS, *et al.* Contribution of each lower limb to upright standing in stroke patients. *Stroke* 2008;39:1793-9.
18. Ishii F, Matsukawa N, Horiba M, *et al.* Impaired ability to shift weight onto the non-paretic leg in right-cortical brain-damaged patients. *Clin Neurol Neurosurg*. 2010;112(5):406-12.
19. Dickstein R, Abulaffio N. Postural sway of the affected and nonaffected pelvis and leg in stance of hemiparetic patients. *Arch Phys Med Rehabil*. 2000;81(3):364-7.
20. Di Fabio RP, Badke MB. Extraneous movement associated with hemiplegic postural sway during dynamic goal-directed weight redistribution. *Arch Phys Med Rehabil*. 1990;71(6):365-71.
21. Bonan IV, Yelnik A, Laffont I, *et al*. Sélection des afférences sensorielles dans l'équilibration de l'hémiplégique après accident vasculaire cérébral. *Ann. Réadaptation Médecine Phys*. 1996;39(3):157-63.
22. Bonan IV, Colle FM, Guichard JP, *et al.* Reliance on visual information after stroke. Part I: balance on dynamic posturography. *Arch. Phys. Med. Rehabil*. 2004;85(2):268-73.
23. Bonan IV, Marquer A, Eskiizmirliler S, *et al*. Sensory reweighting in controls and stroke patients. Clin Neurophysiol. 2013;124(4):713-22.
24. Yelnik AP, Kassouha A, Bonan IV, *et al*. Postural visual dependence after recent stroke: Assessment by optokinetic stimulation. *Gait Posture* 2006;24(3):262-9.

25. Di Fabio RP. Lower extremity antagonist muscle response following standing perturbation in subjects with cerebrovascular disease. *Brain Res*. 1987;406(1-2):43-51.
26. Garland SJ, Stevenson TJ, Ivanova T. Postural responses to unilateral arm perturbation in young, elderly, and hemiplegic subjects. *Arch Phys Med Rehabil*. 1997;78(10):1072-7.
27. Haute Autorité de Santé. Accident vasculaire cérébral : méthodes de rééducation de la fonction motrice chez l'adulte Méthode « Recommandations pour la pratique clinique » 2012.
28. American Heart Association/American Stroke Association. Endorsed Practice Guidelines Management of Adult Stroke Rehabilitation Care, A Clinical Practice Guideline Stroke 2015
29. National Health Service. Stroke rehabilitation in adults Clinical guideline 2013.
30. Barclay-Goddard R, Stevenson T, Poluha W, et al. Force platform feedback for standing balance training after stroke. *Cochrane Database Syst Rev*. 2004;18;(4).
31. Glanz M, Klawansky S, Stason W, *et al*. Functional electrostimulation in poststroke rehabilitation: a meta-analysis of the randomized controlled trials. *Arch Phys Med Rehabil*. 1996 ;77(6):549-53.
32. French B, Thomas L, Leathley M, *et al.* Does repetitive task training improve functional activity after stroke? A Cochrane systematic review and meta-analysis. *J Rehabil Med*. 2010;42(1):9-14.
33. Mehrholz J, Kugler J, Pohl M. Water-based exercises for improving activities of daily living after stroke. *Cochrane Database Syst Rev*. 2011;(1):CD008186.
34. Laver KE, George S, Thomas S, *et al.* Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev*. 2015;2:CD008349.
35. Li Z, Han XG, Sheng J, *et al*. Virtual reality for improving balance in patients after stroke: A systematic review and meta-analysis. *Clin Rehabil*. 2016;30(5):432-40.
36. Corbetta D, Imeri F, Gatti R. Rehabilitation that incorporates virtual reality is more effective than standard rehabilitation for improving walking speed, balance and mobility after stroke: a systematic review. *J Physiother*. 2015;61(3):117-24.
37. Tyson SF, Kent RM. Effects of an ankle-foot orthosis on balance and walking after stroke: a systematic review and pooled meta-analysis. *Arch Phys Med Rehabil*. 2013;94(7):1377-85.
38. Pang MY, Charlesworth SA, Lau RW, *et al*. Using aerobic exercise to improve health outcomes and quality of life in stroke: evidence-based exercise prescription recommendations. *Cerebrovasc Dis*. 2013;35(1):7-22.
39. Saunders DH, Sanderson M, Brazzelli M, *et al.* Physical fitness training for stroke patients. *Cochrane Database Syst Rev*. 2013;10:CD003316.
40. Yang X, Wang P, Liu C, *et al*. The effect of whole body vibration on balance, gait performance and mobility in people with stroke: a systematic review and meta-analysis. *Clin Rehabil*. 2015;29(7):627-38.
41. Lu J, Xu G, Wang Y. Effects of whole body vibration training on people with chronic stroke: a systematic review and meta-analysis. *Top Stroke Rehabil*. 2015;22(3):161-8.
42. Veerbeek JM, van Wegen E, van Peppen R, *et al*. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS One* 2014;9(2):e87987.
43. Pollock A, Baer G, Campbell P, *et al*. Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst Rev*. 2014;4:CD001920.
44. Bowen A, Hazelton C, Pollock A, *et al*. Cognitive rehabilitation for spatial neglect following stroke. Cochrane *Database Syst Rev*. 2013;7:CD003586.

45. Rossetti Y, Jacquin-Courtois S, Calabria M *et al.* Testing cognition and rehabilitation in unilateral neglect by wedge prism adaptation: multiple interplays between sensorimotor adaptation and spatial cognition. In: Kansaku K, Cohen LG, Birbaumer N, eds. Systems Neuroscience: From laboratory to Clinical Practice. Japan: Springer 2015:359-381.
46. Rode G, Lacour S, Jacquin-Courtois S, *et al.* Long-term sensorimotor and therapeutical effects of a mild regime of prism adaptation in spatial neglect. A double-blind RCT essay. *Ann Phys Rehabil Med.* 2015;58(2):40-53.
47. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
48. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
49. Easton JD, Saver JL, Albers GW, *et al.* Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40(6):2276-93.
50. Tyson SF, De Souza LH. Reliability and validity of functional balance tests post stroke. *Clin. Rehabil*. 2004;18(8):916-23.
51. Pérennou D, Decavel P, Manckoundia P, *et al*. Evaluation de l'équilibre en pathologie neurologique et gériatrique. *Ann. Réadaptation Médecine Phys*. 2005;48(6):317-35.
52. Yelnik A, Bonan I. Clinical tools for assessing balance disorders. *Neurophysiol. Clin. Neurophysiol*. 2008;38(6):439-45.
53. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in Stroke Rehabilitation: A Systematic Review. *Phys. Ther.* 2008;88(5):559-66.
54. Tyson SF, Connell LA. How to measure balance in clinical practice. A systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. *Clin Rehabil*. 2009;23(9):824-40.
55. Benaim C, Pérennou DA, Villy J, *et al*. Validation of a standardized assessment of postural control in stroke patients: the Postural Assessment Scale for Stroke Patients (PASS). *Stroke* 1999;30(9):1862-8.
56. Mao HF, Hsueh IP, Tang PF, *et al*. Analysis and comparison of the psychometric properties of three balance measures for stroke patients. *Stroke* 2002;33(4):1022-7.
57. Stinear C, Ackerley S, Byblow W. Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. *Stroke*. 2013;44(7):2039-45.
58. Pérennou D, Benaim C, Rouget E, *et al*. Postural balance following stroke: towards a disadvantage of right brain-damaged hemisphere. *Rev Neuro* 1999;155(4):281-90.

ETHIC AND DISSEMINATION

No ethical statement will be required for this review and meta-analysis. Results of this research will be published. These results will contribute to improve the therapeutic strategy of stroke patients.

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PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Where find the information? Page	Line numbers
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	1	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2	59
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1	4-20 & 35-38
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9	300-313
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA	NA
Support:				
Sources	5a	Indicate sources of financial or other support for the review	12	447-448
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA	NA
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4	77-119
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4	121-123
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-6	130-172 & 182
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6	174-185
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could	5-6	175-177 & table 1

NA: not applicable

		be repeated		
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7	210-222
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6	187-208
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7	210-222
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7	210-222
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-6-7	157-172 & 210-222
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7	224-231
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7	233-245
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7	233-250
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8	257-276
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)		
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)		

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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NA: not applicable