Journal of the Neurological Sciences 367 (2016) 18–21

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

The curative effect comparison of two kinds of therapeutic regimens on decreasing the relative intensity of microembolic signal in CLAIR trial

Q.Q. Deng [a,1], J. Tang [b], C. Chen [c], H. Markus [d], Y.N. Huang [e], H. Zhao [f], D. Ratanakorn [g], K.S.L. Wong [h,*,1], J.H. Fu [b,i,**,1]

[a] Department of Neurology, Jing'an District Central Hospital of Shanghai, Shanghai, China
[b] Department of Neurology, Huashan Hospital affiliated to Fudan University, Shanghai, China
[c] Department of Pharmacology, National University of Singapore, Singapore
[d] Department of Clinical Neuroscience, St George's, University of London, London, UK
[e] Department of Neurology, Peking University First Hospital, Beijing, China
[f] Department of Neurology, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou, China
[g] Ramathibodi Hospital, Bangkok, Thailand
[h] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China
[i] Department of Neurology, Pudong hospital, Shanghai, China

ARTICLE INFO

Article history:
Received 13 January 2016
Received in revised form 26 April 2016
Accepted 20 May 2016
Available online 21 May 2016

Keywords:
The relative intensity
Microembolic signals
Aspirin
Clopidogrel
Large artery stenosis
Transcranial doppler

ABSTRACT

Background: Microembolic signals (MESs) are direct markers of unstable large artery atherosclerotic plaques. In a previous study, we found that the number of MESs is associated with stroke recurrence and that clopidogrel plus aspirin more effectively reduce the number of MESs than does aspirin alone. Stroke recurrence is associated with not only the number of MESs but also the size of the MES, which can theoretically be estimated by monitoring the MES intensity *via* transcranial doppler (TCD). Thus, we compared the effects of clopidogrel and aspirin with aspirin alone on MES intensity using TCD.

Methods: We recruited 100 patients who experienced acute ischemic stroke or transient ischemic attack (TIA) within 7 days of symptom onset. All patients also had large artery stenosis in the cerebral or carotid arteries and the presence of MES as revealed by TCD. The patients were randomized to receive either aspirin or clopidogrel and aspirin for 7 days. MES monitoring was performed on days 2 and 7.

Results: Intent-to-treat (ITT) analysis (46 patients in the dual therapy group, 52 patients in the monotherapy group) and per–protocol (PP) analysis (25 patients in the dual therapy group, 31 patients in the monotherapy group) were performed on 98 patients. The primary finding was that the MES intensity was dramatically reduced in the dual therapy group. ITT analysis of the dual therapy group revealed that the MES intensity was 8.04 (0–16) dB before treatment, 0.00 (0–17) dB on day 2, and 0.00 (0−12) dB on day 7 ($P = 0.000$). In the monotherapy group, the MES intensity was 9.00 (0−20) dB before treatment, 8.25 (0–17) dB on day 2, and 7.0 (0–18) dB on day 7 ($P = 0.577$). PP analysis revealed similar results. No severe hemorrhagic complications were detected. The two patients in this study who experienced stroke recurrence were in the monotherapy group.

Conclusions: Clopidogrel and aspirin more effectively decrease the MES intensity than aspirin alone in patients with large artery stenotic minor stroke or TIA.

1. Introduction

Anti-platelet therapy is a valuable treatment for patients with ischemic symptoms, and clopidogrel and aspirin are the most common drugs of choice [1]. However, the effects of pharmacological intervention require additional clinical data [2–6]. Microembolic signal (MES) monitoring using transcranial doppler (TCD) indicates the prognosis of patients with arterial stenosis who develop a stroke or transient ischemic attack (TIA) [7–10]. For instance, Gao et al. found that the number of MESs was an independent factor of stroke recurrence [11]. Thus, based on the number of MESs, we previously found that the combination of

* Corresponding author.
** Correspondence to: J.H. Fu, Department of Neurology, Huashan hospital affiliated to Fudan University, No 12, Middle Urmqi Road, Jing'an District, Shanghai, China.
E-mail addresses: qqd19871314@163.com (Q.Q. Deng), 173700329@qq.com (J. Tang), phccclh@nus.edu.sg (C. Chen), hmarkus@sgul.ac.uk (H. Markus), huangyn@outmail.net.cn (Y.N. Huang), wzhanzhao@yahoo.cn (H. Zhao), radrt@mahidol.ac.th (D. Ratanakorn), ks-wong@cuhk.edu.hk (K.S.L. Wong), jianhuifu@123.com (J.H. Fu).
[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.jns.2016.05.042
0022-510X/

clopidogrel and aspirin more effectively reduces embolization than aspirin alone in patients with predominantly intracranial symptomatic stenosis [12].

The MES intensity, as determined by TCD [13], which reflects the microembolism size [14] and should be examined to validate our previous results. Martin et al. [15] and Russell et al. [16] demonstrated the consistency between the MES intensity and the microembolism size *in vitro* and *in vivo*, respectively. Clearly, large microemboli are more likely to occlude small vessels and cause ischemic symptoms. Therefore, in this study, we focused on the MES intensity to further investigate the clinical efficacy of clopidogrel and aspirin for patients with predominantly intracranial symptomatic stenosis.

2. Methods

2.1. Summary of design

The CLAIR study was a randomized, multi-center, blinded outcome controlled clinical trial; its design and operative details were described previously [12]. Briefly, patients from Hong Kong, China, Singapore, Malaysia and Thailand were recruited by local trial ethics committees using the following eligibility criteria: age of ≥18 years; significant (≥50%) extracranial or intracranial internal carotid artery and middle cerebral artery stenosis in the symptomatic territory, as confirmed by carotid duplex, TCD, or magnetic resonance angiography; clinical diagnosis of acute ischemic stroke or TIA; symptom onset within the previous 7 days; not of childbearing potential; and written informed consent obtained from the patient or a legally acceptable representative. The following exclusion criteria were subsequently applied: National Institutes of Health Stroke Scale score of >8; intracerebral hemorrhage on brain computed tomography; current anticoagulation therapy before the onset of stroke or definite indication for anticoagulation therapy; known contraindication for the use of clopidogrel or aspirin; sustained hypertension (systolic blood pressure of >220 or diastolic blood pressure of >120 mmHg) immediately prior to randomization; rheumatic heart disease or metallic heart valve; thrombocytopenia (platelet count of <100,000/mm^3); co-morbid severe systemic disease, such as terminal carcinoma, renal failure (creatinine level of >200 μmol/L), cirrhosis, severe dementia or psychosis; known atrial fibrillation based on electrocardiography (past or present); current participation in another clinical trial; history of intracerebral hemorrhage; and no large artery occlusive disease based on a neurovascular examination.

If positive TCD findings (at least one MES) were present at baseline, the patients were randomized to receive either aspirin alone (75–160 mg once daily) (monotherapy group) or clopidogrel (300 mg on the first day and then 75 mg daily) and aspirin (75–160 mg daily) (dual therapy group) for 7 days. TCD recordings similar to those at baseline were performed on days 2 and 7. Training and assessment for MES interpretation were performed during investigator meetings and during site initiation prior to study commencement.

All TCD recordings were centrally reviewed by a core laboratory experienced in the review of such data for clinical trials. An intensity threshold of 7 dB was used to detect MESs because this threshold has been shown to improve specificity. All analyses were performed by an individual blinded to both subject identity and whether the recording was obtained at baseline or at the 2- or 7-day follow-up examinations.

This trial was registered at the Centre for Clinical Trials of the Chinese University of Hong Kong (www.cct.cuhk.edu.hk/eng/services/TrialReg): CUHK_CCT00164. All patients provided written informed consent, and the study was approved by local trial ethics committees.

2.2. Statistical analysis

The primary subgroup analysis involved measurement of the MES intensity at baseline and on days 2 and 7 because other outcomes and safety evaluations were analyzed previously [12].

The primary analysis was an intention–to–treat (ITT) analysis based on data from the blinded central review of MESs. An additional prespecified per–protocol (PP) analysis was conducted on the MES data for the patients who met the eligibility criteria and adhered to the trial protocol.

All statistical analyses were conducted using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). All significance tests and confidence intervals were two-sided. The proportions between groups were analyzed using the chi-squared test or Fisher's exact test. The mean or median difference between the treatment groups was assessed *via* a two-sample *t*-test or the Mann-Whitney *U* test, depending on the results of the Shapiro–Wilk normality test. Multiple logistic or Poisson regression analysis was performed after adjusting for relevant covariates. The median difference among the three different times was assessed using nonparametric tests for k independent samples, and the comparison between any two medians was assessed using the Student–Newman–Keuls (SNK) test after ranking the cases.

3. Results

The analyses of the patient cohort, side effects, recurrence of stroke and TIA, number of MES-positive patients, and number of MESs, as well as multiple regression analysis, were performed in our previous study [12]. These analyses indicated that combined clopidogrel and aspirin therapy more effectively reduced embolization than aspirin alone in patients with predominantly intracranial symptomatic stenosis without severe side effects. Therefore, we focused on the dynamic changes in the MES intensity during the clinical trial. ITT and PP analysis models were used, which greatly increased the credibility of the results of the clinical trial when they were consistent with each other [17]. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

1 patient was lost to follow up soon after randomization in mono therapy group.

1 patient was inadvertently recruited >7 days after symptom onset in dual therapy group.

We randomly assigned 53 patients to the monotherapy group. One patient was lost to follow-up soon after randomization without undergoing the baseline or post-baseline assessments. Therefore, 52 patients receiving monotherapy were included in the ITT analysis. For reasons such as negative MES at baseline [12], 31 patients were ultimately included in the PP analysis.

One patient was inadvertently recruited >7 days after symptom onset and was withdrawn by the local investigator without undergoing the baseline assessments. Thus, 46 patients in the dual therapy group were included in the ITT analysis, which was planned to include 47

Table 1
Baseline demographic and clinical characteristics of patients.

Characteristics	Dual therapy ($n = 46$)	Monotherapy ($n = 52$)
Mean age(SD), years	59.2 (12.5)	56.4 (12.8)
Male	36(78.3%)	40(76.9%)
Mean systolic BP (SD). mmHg	139.4 (22.2)	148.6 (23.1)
Mean diastolic BP (SD), mmHg	80.1 (11.6)	83.9 (11.6)
Mean time from onset of stroke to randomisation, Day (SD)	2.5 (1.6)	3.2 (1.8)
Site of arterial stenosis		
Intracranial	45 (97.8%)	48 (92.3%)
Extracranial	12 (26.1%)	16 (30.8%)
Both	11 (23.9%)	12 (23.1%)
Previous myocardial infarction	3 (6.5%)	3 (5.8%)
Peripheral vascular disease	4 (8.9%)	2 (3.9%)
Previous angina	5 (10.9%)	4 (7.7%)
Diabetes mellitus	21 (45.7%)	16 (31.0%)
Hyperlipidemia	23 (51.1%)	16 (32.7%)
Hypertension	27 (60.0%)	35 (68.6%)
Never smoke	25 (54.3%)	22 (42.3%)