Comparative Effects of Interval and Continuous Aerobic Training on Haematological Variables Post-stroke – A randomized clinical trial

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SUMMARY

Stroke induces changes in the haematological variables of post-stroke patients. Pathological changes in haematological variables can be reversed using aerobic exercise. This study assessed and compared the effects of Interval Training (IT), Continuous Training (CT) and a Combination of Interval and Continuous Training (CICT) modes of aerobic exercise on selected haematological variables of stroke survivors (SSv).

Sixty-nine consecutively recruited SSv participated in this single blind randomized controlled trial. They were randomly assigned into one of the IT (n=25), CT (n=21) and CICT (n=23) groups. All the participants underwent aerobic training at 40 – 70% of heart rate reserve using a bicycle ergometer for eight consecutive weeks following the American Heart Association/American Stroke Association protocol. White blood cell count (WBC), red blood count (RBC), haemoglobin concentration (Hg), platelet count (PC) and mean platelet volume (MPV) were determined using PROCAN PE-6800. Data was analysed using descriptive statistics, one-way ANOVA, ANCOVA and paired t-test at $\alpha_{0.05}$.

No significant difference was observed in all the baseline variables across the three groups ($p>0.05$). All the pre- and post-intervention haematological variables were significantly different in all the groups ($p<0.05$) except WBC in the CT group ($t=-0.538$, $p=0.596$). Post-intervention WBC ($5.71\pm1.31*10^3/\mu L$; $6.00\pm1.22*10^3/\mu L$; $5.87\pm1.38*10^3/\mu L$), RBC ($4.64\pm0.42*10^6/\mu L$; $4.64\pm0.38*10^6/\mu L$; $4.76\pm0.42*10^6/\mu L$), haemoglobin (12.69 ± 1.53g/dL; 11.90 ± 1.47g/dL; 12.30 ± 1.57g/dL), PC ($291.40\pm63.73*10^3/\mu L$; $260.48\pm60.15*10^3/\mu L$; $301.57\pm64.23*10^3/\mu L$), and MPV ($9.78\pm0.99$fl; 10.47 ± 1.02fl; 10.14 ± 0.97fl) were significantly different across the IT, CT and CICT groups respectively. The IT was the most effective in decreasing WBC and MPV and also the most effective in increasing Hg and PC.

The IT, CT and CICT modes are effective in significantly improving the haematological variables of stroke survivors after eight weeks of aerobic training, the IT mode is, however, the most effective.

KEY WORDS: aerobic training, stroke survivors, haematological variables

INTRODUCTION

Stroke is a leading cause of disability worldwide (WHO, 2017). Post-stroke disability appears complex; low fitness and other impairments interact to drive post-stroke activity limitations and participation restriction (Saunders et al, 2014). Physical inactivity is a major modifiable risk factor of stroke (Tikk et al, 2014; O'Donnell et al, 2016) and also a major determinant of post- stroke disability and prognosis (Wondergem et al, 2017). There is a strong relationship between physical inactivity and abnormalities in haematological indices (Wirth et al, 2017; Daniele et al, 2018). Having a stroke has been shown to induce changes in haematological variables such as white blood cell count, red blood cell count, platelets as well as their differentials (Heikinheimo et al, 2015; Ioana, 2015; Du et al, 2016).

There is a direct association between white blood cell count and the incidence of stroke (Wu et al, 2016; Furlan et al, 2014). Elevated white blood cell count is also an independent predictor of outcomes after ischaemic stroke (Furlan et al, 2014; Heikinheimo et al, 2015) and other inflammatory disorders such as atherosclerosis, myocardial infarction and heart failure (Swirski and Nahrendorf, 2013), which are comorbidities of stroke. According to the Texas Heart Institute (2016), moderate elevation in red blood cell count can be a risk factor for stroke. A high level of red blood cell count (polycytaemia) has also been associated with poor prognosis of stroke (Ioana, 2015). Mean platelet volume and platelet count are independent risk factors of ischaemic stroke (Mayda-Domac et al, 2010). Platelet count has been observed to have changed significantly following a haemorhhagic stroke (Mayda-Domac et al, 2010). Increase in mean platelet volume and decrease in platelet count have been reported as features of both acute and non-acute phases of cerebral ischaemia, which may have preceded the vascular events (Ghahremanfard et al, 2013; Du et al, 2016).

Several studies have shown that aerobic exercise can be used to improve haematological indices in cardiac patients (Sandor et al, 2014), sedentary adults (Belviranli et al, 2017; Kumar and Choudhary, 2017), athletes (Tekin et al, 2012), and young women (El-Lithy et al, 2015). A systematic review by Hamzat and Ekechukwu (2015) revealed that there is a gap in literature on the effects of aerobic training on the haematological profiles of stroke survivors and the best mode of aerobic training for improving these haematological variables. This study therefore compared the effects of three modes of aerobic exercise (interval, continuous and combined) on the haematological profiles of stroke survivors.

METHOD

Participants

A total of 69 stroke survivors participated in this study. Only stroke survivors with a diagnosis of first-time (ischaemic or haemorrhagic) unilateral stroke, with no other known neurological disorder (e.g. Parkinson’s disease), were included in this study.

Instruments

The following instruments were used for data collection:

i. **Fully Auto-Haematological Analyser (PROCAN PE-6800, USA).** This was used for the haematological analysis.

ii. **Monark Bicycle Ergometer (Model AB 827E, China).** This was used for the aerobic exercise training. It has a pulse rate detector as well as a timer and indicators for variables such as calories, distance covered, etc.

Research Design

The study adopted the randomized controlled trial design. Eligible participants were randomly assigned to the Continuous Training Group (CT), Interval Training Group (IT) or Combination of Continuous and Interval Training Group (CCIT) modes of aerobic exercise.

Sampling

Sample size was determined using an effect size of 0.4, power of 0.8 for three groups and two measurements. A minimum sample size of 66 was thereafter determined. Consecutive sampling technique was used to recruit the stroke survivors.

Procedure for Data Collection

Ethical approval was sought and obtained from the Ethical Committee of the University of Port Harcourt Teaching Hospital, Port Harcourt before the commencement of the study. The trial was registered with the Pan African Clinical Trial Registry (PACTR201511001359344). The procedure was described to the participants and their informed consent obtained before participation. Willing participants were screened and those eligible were randomly assigned to one of the three training groups. Baseline measurements of the anthropometric and haematological profiles of all the participants were obtained before the commencement of the aerobic training (intervention). After eight weeks, post-test measurements of all the participants were taken.

Haematological Profile: Haematological parameters were assessed as follows:

The PROCAN PE-6800 fully auto-haematology analyser was used to analyse the sample of blood contained in an

EDTA K3 blood collection tube. Pre-test (24 hours before training) and post-test (24 hours after training) blood samples were obtained in the morning after 12 hours fasting. The analyser uses electric resistance method for counting, haemoglobin-cyanide method and SFT method for haemoglobin. The count principle of the instrument is based on the measurement of changes in electrical resistance produced by a particle passing through an aperture sensor. The haematological parameters analysed were white blood cell count (WBC), red blood count (RBC), haemoglobin concentration, platelet count (PC) and mean platelet volume (MPV).

Intervention

The training protocol was based on the physical activity and exercise recommendations for stroke survivors by the American Heart Association - AHA (Billinger et al, 2014). This study adopted a gradual progression of intensity (40% to 59% HRR for the first two weeks and 60% to 70% HRR for the remaining six weeks). The target heart rate was determined using the heart rate reserve method (HRR) or Karvonen formula (Karvonen et al, 1957).

Target heart rate using HRR = intensity (%) x (maximum HR - resting HR) + resting HR

The 8-week exercise training programme included three training sessions per week on a stationary cycle ergometer in the gymnasium of the Department of Physiotherapy, University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt. In each session, participants warmed up for a period of 5 minutes, then proceeded to the main training phase, followed by a cool down phase of 5 minutes. The duration of the training component was 20 minutes during the first 2 weeks, but was increased by 5 minutes every 2weeks.

Continuous Aerobic Training Group (CT): The aerobic training programme followed the general guidelines described above. The intensity of the exercise was set at 40-70% of heart rate reserve. This was in addition to the standard physiotherapy.

Interval Aerobic Training Group (IAT): The target workload for this group was a work intensity of 40-70% HRR (moderate/vigorous intensity) and rest/recovery at 20-29% HRR (low intensity). A work-recovery ratio of 1:2 minutes was chosen. The training was also in addition to their standard physiotherapy.

Combined Aerobic Training Group (CBAT): Participants were, in addition to their standard physiotherapy, trained using both interval and continuous exercise modes. For each session, interval exercise as described above was prescribed for the first half of the session while the continuous mode was prescribed for the remaining half of the session.

The participants were trained three times per week, for twenty minutes each day during the first two weeks. The training was subsequently increased by five minutes every two weeks until the eighth week. Participants in the continuous group were trained at a low intensity of 40 – 59% of HRR for the first two weeks because of the deconditioning effect; the subsequent weeks' training was at a higher intensity of 60-70% of HRR. Participants in the interval group were trained at similar intensities as the continuous group but with a rest intensity of 20-29% of HRR in 1:2 minutes work/rest interval. The participants in the combined group were trained with both interval and continuous aerobic exercise at the above explained intensities.

Data Analysis

Data obtained was analysed using SPSS version 22.0. Descriptive statistics was used to summarize demographic characteristics and to present the pre-test and post-test measurements. One-way ANOVA was used to compare the baseline variables of the participants across the three training groups. ANCOVA was used to compare the effects of the three training modes on the post-intervention variables of the participants using their respective baseline variables as co-variates. Bonferroni pair-wise comparison was done as post-hoc for the ANOVA and ANCOVA tests. The level of significance was set at $\alpha = 0.05$.

RESULTS

Summary of the Haematological Characteristics of the Participants

A total of 69 stroke survivors of mean age 59.33 ± 8.80 years participated in this study. The majority had ischaemic type of stroke (75.4%) that occurred on the right side of the body (59.4%). The mean white blood cell count at baseline and after the 8 weeks of training were $6.03 \pm 1.22 x10^3$cells/μL and 5.71 ± 1.31 $x10^3$cells/μL respectively for the interval training group, 5.97 ± 1.11 $x10^3$cells/μL and 6.00 ± 1.22 $x10^3$cells/μL respectively for the continuous training group, and 6.37 ± 1.46 $x10^3$cells/μL and 5.87 ± 1.38 $x10^3$cells/μL respectively for the combined training group as shown in table 1.

Table 1. Summary of the haematological profiles of the participants at baseline and post-intervention (N = 69)

Variables	Interval Training Group (n=25)			Continuous Training Group (n=21)			Combined Training Group (N=23)		
	Mean ± SD			Mean ± SD			Mean ± SD		
	Pre	Post	Diff	Pre	Post	Diff	Pre	Post	Diff
WBC (10^3/μL)	6.03±1.22	5.71±1.31	-0.32	5.97±1.11	6.00±1.22	0.03	6.37± 1.46	5.87±1.38	-0.50
RBC (10^6/μL)	4.79±0.49	4.64±0.49	-0.15	4.86±0.42	4.64±0.38	-0.22	4.86± 0.43	4.76±0.42	-0.10
Hgb (g/dL)	13.02±1.56	12.69±1.53	-0.33	13.30±1.44	11.90±1.47	-1.40	13.09±1.58	12.30±1.57	-0.79
PC (10^3/μL)	244.68±72.16	291.40±63.73	46.72	239.67±60.26	260.48±60.15	20.81	249.57±64.33	301.57±64.23	52.00
MPV (fl)	10.26±1.25	9.78±0.99	-0.48	10.28±1.03	10.47±1.02	0.20	10.34±0.99	10.14±0.97	-0.20

Key: Pre = Baseline, Post = Post-Intervention, Diff = Difference, WBC = White Blood Cell Count, RBC = Red Blood Cell Count, Hgb = Haemoglobin, PC = Platelet Count, MPV = Mean Platelet Volume

Baseline Comparison of the Haematological Profiles of Participants across the Groups

There was no significant difference between the mean baseline white blood cell count of the participants across the three training groups (F = 0.661, p = 0.520). Also, there was no significant difference in the participants' mean baseline values of red blood cell count (F = 0.187, p = 0.830), haemoglobin concentration (F = 0.198, p = 0.821), platelet count (F = 0.123, p = 0.884) and mean platelet volume (F = 0.035, p = 0.966) across the three training groups as shown in table 2.

Comparison of the Post-Intervention Haematological Profiles of Participants across the Groups

There was significant difference in the post-intervention white blood cell counts across the three training groups (F = 17.66, p < 0.001). The comparison also showed significant differences in red blood cell count (F = 6.693, p = 0.002), haemoglobin concentration (F = 25.11, p < 0.001), and platelet count (F = 7.761, p = 0.001) across the three training groups. There was also significant difference in the mean platelet volumes of the participants when compared across the three training groups (F = 25.092, p < 0.001). The post-hoc analysis of the significant variables showed that the participants in the continuous training group had a significantly higher post-intervention white blood cell count than those in the interval training and the combined training groups. Further, the participants in the continuous training group had a significantly lower post-intervention red blood cell count than those in the combined training group. The participants in the interval training group however, had a significantly higher post-intervention haemoglobin concentration than those in the continuous training group and the combined training group. Participants in the continuous training group had a significantly lower post-intervention platelet count than those in the interval training group and the combined training group but mean platelet volume was significantly lowest in the interval training group as shown in table 3.

Difference between the baseline and the Post-Intervention Haematological Profiles of Participants within the Groups

After eight weeks of aerobic training, there were significant reductions in the white blood cell counts of participants in the interval training group (t = 3.927, p = 0.001) and the combined training group (t = 16.234, p < 0.001); while there was no significant change in the white blood cell count of the participants in the continuous training group (t = -0.538, p = 0.596). There were also significant reductions in the red blood cell counts and haemoglobin concentrations within each of the interval training group (t = 5.191, p < 0.001 and t = 7.124, p < 0.001 respectively), the continuous training group (t = 8.602, p < 0.001 and t = 62.894, p < 0.001 respectively), and the combined training group (t = 60.119, p < 0.001 and t = 44.744, p < 0.001 respectively). Also, there were significant increases in the platelet counts of the participants in the interval training group (t = -4.586, p < 0.001), the continuous training group (t = -140.312, p < 0.001), and the combined training group (t = -312.618, p < 0.001) after eight weeks. Finally, there were significant decreases in mean platelet volume within the interval training group (t = 4.052, p < 0.001), the continuous training group (t = -41.000, p < 0.001), and the combined training group (t = 12.770, p < 0.001) as shown in table 4.

Table 2. Baseline comparison of the haematological profiles of participants across the groups using one-way ANOVA (N = 69)

Variables	ITG (n = 25)	CTG (n = 21)	CBTG (n = 23)	F-value	P-value
RBC ($10^6/\mu L$)	4.79±0.49	4.86±0.42	4.86±0.43	0.187	0.830
Hgb (g/dL)	13.02±1.56	13.30±1.44	13.09±1.58	0.198	0.821
PC ($10^3/\mu L$)	244.68±72.16	239.67±60.26	249.57±64.33	0.123	0.884
MPV (fl)	10.26±1.25	10.28±1.03	10.34±0.99	0.035	0.966

Keys: ITG = Interval Training Group, CTG = Continuous Training Group, CBTG = Combined Training Group, BMI = Body Mass Index, WHR = Waist-Hip Ratio, CI = Conicity Index, AVI = Abdominal Volume Index, %BF = Percentage Body Fat, FMI = Fat Mass Index WBC = White Blood Cell Count, RBC = Red Blood Cell Count, Hgb = Haemoglobin concentration, PC = Platelet Count, MPV = Mean Platelet Volume

Table 3. Comparison of the post-intervention haematological profiles of participants across the groups using ANCOVA (N = 69)

Variables	ITG (n= 25)	CTG (n =21)	CBTG (n = 23)	F-value	P-value
WBC($10^3/\mu L$)	5.71 ± 1.31^{a}	6.00 ± 1.22^{b}	5.87 ± 1.38^{ac}	17.660	<0.001*
RBC ($10^6/\mu L$)	4.64 ± 0.49^{ab}	4.64 ± 0.38^{a}	4.76 ± 0.42^{b}	6.693	0.002*
Hgb (g/dL)	12.69 ± 1.53^{a}	11.90 ± 1.47^{b}	12.30 ± 1.57^{c}	25.110	<0.001*
PC ($10^3/\mu L$)	291.40 ± 63.73^{a}	260.48 ± 60.15^{b}	301.57 ± 64.23^{ac}	7.761	0.001*
MPV (fl)	9.78 ± 0.99^{a}	10.47 ± 1.02^{b}	10.14 ± 0.97^{c}	25.093	<0.001*

Key: * = Significant, Items with different superscript (X^a and Y^b) = significant difference post hoc, Items with at least one same superscript (X^a and Y^{ab}) = non-significant difference at post hoc, ITG = Interval Training Group, CTG = Continuous Training Group, CBTG = Combined Training Group, WBC = White Blood Cell Count, RBC = Red Blood Cell Count, Hgb = Haemoglobin concentration, PC = Platelet Count, MPV = Mean Platelet Volume

Table 4. Difference between the baseline and the post-intervention haematological profiles of participants within the groups using paired t-test (N = 69)

Variable	Interval Training Group (n = 25)			Continuous Training Group (n = 21)			Combined Training Group (n = 23)		
	Diff	t-value	P	Diff	t-value	P	Diff	t-value	P
WBC ($10^3/\mu L$)	-0.32	3.927	0.001*	0.03	-0.538	0.596	-0.50	16.234	<0.001*
RBC ($10^6/\mu L$)	-0.15	5.191	<0.001*	-0.22	8.602	<0.001*	-0.10	60.119	<0.001*
Hgb (g/dL)	-0.33	7.124	<0.001*	-1.40	62.894	<0.001*	-0.79	44.744	<0.001*
PC ($10^3/\mu L$)	46.72	-4.586	<0.001*	20.81	-140.312	<0.001*	52.00	-312.618	<0.001*
MPV (fl)	-0.48	4.052	<0.001*	0.20	-41.000	<0.001*	-0.20	12.770	<0.001*

DISCUSSION

There is a direct association between white blood cell count and the incidence of stroke (Wu et al, 2016; Furlan et al, 2014). Elevated white blood cell count is an independent predictor of outcomes after ischaemic stroke (Furlan et al, 2014; Heikinheimo et al, 2015) and other inflammatory disorders such as atherosclerosis, myocardial infarction and heart failure (Swirski and Nahrendorf, 2013) which are comorbidities of stroke. In this study, there were significant decreases in the white blood cell counts of participants in the combined and interval training groups while there was non-significant increase among those in the continuous training group. Also, the combined and interval modes reduced white blood cell count significantly more than the continuous mode. Similar reduction in white blood cell count after aerobic training was reported by Johannsen et al (2012) in their study, though among post menopausal women. The mechanism of exercise-induced control of leucocytosis may be explained through the actions of catecholamines, cortisol, demargination, neuronal transmitters and peptides or purine chemical transmitters (Sand et al, 2013). It is possible that high impact exercises like continuous aerobic exercise may result in lactic acid accumulation which may constitute a source of muscle irritation and thus proliferation of pro-inflammatory markers (leucocytosis). However, interval exercises with its period of rest may induce an anti-leucocytotic effect by regulating catecholamine and cortisol surge. It may therefore be opined that, interval aerobic training may be considered a non-phamacological anti-inflammatory modality through its anti-leucocytotic effect, especially among stroke survivors.

According to the Texas Heart Institute (2016), moderate elevation in red blood cell count can be a risk factor for stroke. A high level of red blood cell count (polycytaemia) has also been associated with poor prognosis of stroke (Ioana, 2015). In this present study, the three modes of aerobic exercise significantly reduced the red blood cell counts and haemoglobin concentrations of the participants. However, the continuous training mode appeared to have had a superior effect when compared with the other modes. This report differs from the findings of Mazoochi et al (2013) that revealed the interval training mode as having a more profound significant effect than the continuous mode on red blood cell count but non-significant effect on the haemoglobin concentration of Iranian athletes. The disparity in both reports may be due to differences in sample size and study population. The study by Mazoochi et al (2013) had a smaller sample size (24) and investigated athletes while this present study investigated stroke survivors. Further evidence is however needed on the comparative effects of different modes of aerobic training on the red blood cell count and haemoglobin concentration of stroke survivors.

There was significant increase in platelet count and decrease in mean platelet volume in all the treatment groups with the exception of the continuous mode that had a significant increase in mean platelet volume. The combined and interval training modes were more effective in increasing platelet count and decreasing mean platelet volume than the continuous mode. Mean platelet volume and platelet count are independent risk factors for ischaemic stroke (Mayda-Domac et al, 2010). Platelet count has been shown to be inversely correlated with haemorhhagic stroke (Mayda-Domac et al, 2010). Increase in mean platelet volume and decrease in platelet count have been reported as features of both acute and non-acute phases of cerebral ischaemia which may have preceded the vascular events (Ghahremanfard et al, 2013; Du et al, 2016) . Anti-thrombotic drugs have been shown to be useful in reducing the frequency of secondary stroke but they carry potential risk of symptomatic intracerebral haemorrhage during ischaemic stroke (Mayda-Domac et al, 2010). Therefore, in stroke management, the balance between reduction of thrombotic events and the risk of haemorrhage defines benefit (Ungerer and Münch, 2013). The significant increase in platelet count and decrease in mean platelet volume as reported in this study may therefore be of therapeutic value. The aerobic exercise induced increase in platelet count may be as a result of haemoconcentration and by platelet release from the liver, lungs, and, importantly, the spleen (Bakovic et al, 2013). Although, some studies (Scheer et al, 2011; Whittaker et al, 2013; Lippi et al, 2014) have reported an increase in mean platelet volume in response to exercise, other studies (Aldemir and Kilic, 2005; Kratz et al, 2006) appear to have reported otherwise. A systematic review with meta-analysis on the effect of aerobic exercise on mean platelet volume that would estimate the pooled effects of these studies is recommended.

A major limitation experienced in the course of this study was in the compliance of the participants especially during the first two weeks of the training, while some eligible participants were not willing to participate for fear of a repeat stroke despite the efforts to assuage this fear.

CONCLUSION

The interval, continuous and combined modes of aerobic training are effective in improving the haematological profiles of stroke survivors after eight weeks of training. However, the interval aerobic training mode is the most effective mode for improving the haematological variables of stroke survivors after eight weeks of training. The interval aerobic training mode is therefore recommended for use in stroke rehabilitation to achieve the most profound improvement of haematological variables of stroke survivors.

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