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ENDOTHELIN-1 INDUCED FOCAL ISCHEMIA IN ADULT ZEBRAFISH: A MODEL WITH NOVEL ENTITY OF STROKE RESEARCH

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ABSTRACT

Introduction: Stroke is the recurrent threat of mortality worldwide among normal population and 3 fold more in diabetics, requires intense research to investigate new therapeutics.

Objective: Current animal models have restricted reproducibility, less similarity and having technical limitations.

Methodology: In our study, pink zebra-Danio rerio was used for induction of stroke. Diabetes was induced with 111mM D-glucose for 14 days and zebrafish having more than 100 mg/dl blood glucose level were included in study. The experimental stroke was induced with single oral administration of Endothelin-1 3µl/gm of zebra-fish. The swimming, behavioural-patterns and cognitive performance(Y-maze, T-maze) was recorded and analysed with UMA Tracker. The brains were extracted for histopathological investigations.

Results: Administration of ET-1 in normal and diabetic group showed statistically significant ($p<0.001$) change in swimming pattern and movements (circulatory, irregular, disturbed, rotating). Moreover, diabetic ET-1 treated group produced statistically significant ($p<0.001$) change in swimming pattern and recovery time. Behavioural study of ET-1 treated groups showed disturbed cognitive profile and locomotors coordination ($p<0.001$) by increasing in the number of mistakes and reducing total distance travelled in neurocognitive assessment paradigm. Histopathological analysis of ET-1 treated groups indicated cortical lesions, shranked neuronal cells and activated thrombocytes with disturbed normal flora of brain compared to normal control.

Conclusion: Current experimental model exerts more stability, reproducibility and genetic similarity with human stroke pattern over other available rodent models of stroke. Due to its novelty, overcoming technical errors from recent models, reproducibility and genetic similarity, ET-1 induced experimental zebrafish stroke model exerts new horizons for stroke therapeutics and diabetes associated stroke research.

POLY (LACTIDE-CO-GLYCOLIDE) NANOPARTICLE ENCAPSULATING BRAIN-DERIVED NEUROTROPHIC FACTOR PROMOTES NEUROPROTECTION IN AN ACUTE ISCHEMIC STROKE MODEL IN THE RAT

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ABSTRACT

Introduction: Poly (lactide-co-glycolide) (PLGA) nanoparticles (NPs) are biodegradable and biocompatible drug carriers and competent at delivering neuroprotective agents to the brain following intravenous administration. Brain-derived neurotrophic factor (BDNF) could provide neuroprotection in ischemic brain injury. We tested the neuroprotective effect of PLGA nanoparticle-bound BDNF (NPBDNF) on a permanent middle cerebral artery occlusion (pMCAO) model of ischemic rats.

Methods: Sprague-Dawley rats were divided into 4 groups of 7 rats each. Group 1 was subjected to sham operation, group 2, 3, and 4 were subjected to permanent MCAO (pMCAO). Four hours after pMCAO, group 3 and 4 were intravenously (IV) treated with BDNF and BDNF-NPs, respectively. Functional outcome was assessed at 2 and 24 hours after pMCAO, using the modified Neurologic Severity Score (mNSS), and rotarod performance test. Following functional assessments, rats were euthanized by terminal cardiac puncture, whereby blood was taken to assess for neurobiomarker level, the neuron specific enolase (NSE). The brain was evaluated to measure the infarct area.

Results: The NPBDNF treated group demonstrated significant functional improvement in mNSS, evidenced by a mild injury correlated with a decreased in mNSS score by 2.0 and 2.1 times, respectively, when compared with pMCAO and BDNF treated groups. The NPBDNF treated group showed improved rotarod performance, by 2.44 and 2.77 fold increases in latency time to fall on the rotarod, compared to MCAO and BDNF treated groups, respectively. The infarct volume in rats treated with BDNF-NPs was significantly smaller by 1.91 fold compared to the MCAO group and 1.95 fold compared to the BDNF treated group. These results were further corroborated by the NSE level estimates.

Conclusion: NPBDNF exhibit a significant neuroprotective effect in the pMCAO model of ischemia in rat following intravenous administration.

TELE-CONSULTATION FOR AUGMENTATIVE AND ALTERNATIVE COMMUNICATION IN INDIVIDUALS WITH LOCKED-IN SYNDROME

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ABSTRACT

Introduction: Locked-In Syndrome (LIS) is a rare condition in which a person is aware, but has tetraplegia, dysphagia and aphasia as a result of midbrain and/or pontine stroke. Typically, communication is achieved via vertical eye movements and eye-blinking.

Objective: To illustrate Augmentative and Alternative Communication (AAC) options available to LIS patients, as discussed using tele-consultation.

Methods: Case-series on two individuals with LIS admitted for intensive stroke rehabilitation. An international AAC consultant was sought to review and enhance AAC options via tele-consultation. Recommendations were made to modify existing communication boards and mounting systems, as well as to consider further investigations.

Case Series: Mr. AR is a 50-year old ex-policeman who developed classic LIS due to brainstem and cerebellar infarcts secondary to basilar artery thrombosis. He is able to scan and match pictures, words, letters and numbers consistently by vertical eye movements and generating dual response via blinking once for 'yes' and twice for 'no'. Recommendation on communication involves organizing his alphabet board according to the frequency-of-use alphabets in the Malay language, for energy conservation and efficient communication.

Mr. FB: 46-year old bank-officer who developed brainstem and left cerebellar infarcts secondary to basilar artery thrombosis. He has occasional muscle twitching in his left forearm and index fingers. Vertical eye movements are unreliable as he has oscillatory nystagmus and right divergent strabismus. Dual response is generated by looking upwards for 'yes' and downwards for 'no'. It was recommended that an electromyogram (EMG) using surface electrodes be conducted to detect muscle activity which potentially may activate an EMG switch connected to a switch-scanning AAC device.

Conclusions: Communication deficits in people with LIS require multidisciplinary inputs to augment and facilitate communication between the patient and their partners/carers. AAC techniques need to be customised according to the patients' residual functions, culture, language and available resources.

TELENEUROREHABILITATION DURING COVID-19 PANDEMIC IN MALAYSIA

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ABSTRACT

Introduction: Teleneurorehabilitation is a useful method to deliver stroke care despite the Movement Control Order (MCO) in a pandemic. Patients can still access neurorehabilitation, conduct therapies, receive medications and referrals through teleconsultations. This ensures access and continuity of care for individuals with stroke.

Objective: To describe the use of teleneurorehabilitation during the Covid-19 pandemic MCO in Malaysia for stroke patients scheduled for follow-up appointments.

Methods: A cross-sectional descriptive study was conducted from the 31 March 2020 to 5 May 2020, during the MCO period in Malaysia. Follow-up stroke patients scheduled to attend neurological Rehabilitation clinic in Hospital Rehabilitasi Cheras, Kuala Lumpur, Malaysia were called prior to their appointments using a standard script. Issues which could not be resolved via teleconsultation were given the option to attend clinic for face-to-face review or reschedule their appointments. The issues addressed, continuation of medication and the duration of the teleconsultation were recorded in their medical files.

Results: A total of 291 appointments were scheduled for seven clinic sessions. A third (31.6%) of stroke patients received tele-consultation, comprising medical advice (100%), extension of medical certificates (2.5%) and renewal of medication prescription (34.8%). A third (34%) of them appointed representatives to collect the medications at the clinic, while 66% opted for telepharmacy via local postage. The average teleconsultation time was 8.9 minutes (min 5 minutes, max 20 minutes).

Conclusions: Teleneurorehabilitation is an efficient, value-added tool to ensure continuity of care during a pandemic and may be useful for individuals with logistics issues. Tele-pharmacy is a common component in teleneurorehabilitation consultation.

EVALUATION OF ORAL HEALTH STATUS AND SALIVARY PARAMETERS AMONG STROKE PATIENTS IN HOSPITAL USM, KELANTAN

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ABSTRACT

Introduction: Dental caries and poor salivary function are common in patients with stroke. Few studies of their salivary parameter assessment have been published. This research has been carried out to determine oral health and salivary parameters in stroke patients

Methods: Cross-sectional study was conducted on 54 stroke and 54 non-stroke patients attending Rehabilitation Medicine Unit in Hospital USM. Clinical oral examination was performed using DMFT index and plaque score. Salivary flow, pH and buffering capacity were determined using the Saliva-Check BUFFER kits and salivary cortisol was measured using Cobas E6000 analyzer.

Results: Most stroke patients were Malay (72.2%), male (63.0%), with mean (SD) age of 48.1(14)years while majority of non-stroke patients were Malay (90.7%), female (57.4%), with mean (SD) age of 40.1(16) years. There was a significant difference in caries experience between stroke and non-stroke patients with mean (SD) DMFT of 17.6(4.26) and 15.7(5.38) respectively ($p=0.042$). Stroke patients had significantly less percentage of good oral hygiene (53.7%) compared to non-stroke patients (85.2%); $p=0.001$

The median (IQR) of salivary flow rate was similar in both groups (0.49(0.4)mL/min) and pH was 6.60(0.5) for stroke and 6.60(0.4) for non-stroke patients meanwhile salivary cortisol was 5.21(5.1)nmol/L for stroke and 4.0(3.6)nmol/L for non-stroke patients. Mean (SD) of salivary buffering capacity was 6.06(2.8) for stroke and 5.41(2.4) for non-stroke patients. All salivary parameter showed no significant differences between the two groups; ($p>0.05$). There was no significant correlation between salivary parameter and DMFT; ($p>0.05$).

Conclusion: Oral health status of stroke patients is compromised. Therefore, it is important to take account of salivary parameters and caries experience among stroke patients and the preventive measure in this population should be implemented.

THE NEUROPROTECTIVE EFFECT OF (S)-3,5-DHPG PRECONDITIONING VIA DOWN REGULATORY ANTAGONIST MODULATOR (DREAM) IN ACUTE ISCHEMIC STROKE RATS

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ABSTRACT

Pharmacological preconditioning is an avenue in protecting and reducing the ischemic induced neuronal damage. In vitro studies have shown that prior activation of group I metabotropic receptor (mGluR) with (S)-3,5-dihydroxyphenylglycine ((S)-3,5-DHPG) elicits neuroprotection. This activation of group I mGluR regulates the expression of Down Regulatory Antagonist Modulator (DREAM). This study elucidates the neuroprotective effect of group I mGluR agonist preconditioning, (S)-3,5-DHPG via DREAM in acute ischemic stroke rats.

One, 10, or 100 μM (S)-3,5-DHPG was administered intrathecally to six adult male Sprague Dawley rats 2 hours before the middle cerebral artery occlusion. After 24 hours, the modified neurological severity score (mNSS) and grid walking test were assessed. The rats were sacrificed, and the infarct brain volumes were estimated by 2,3,5-triphenyltetrazolium chloride staining. The serum level of neuron-specific enolase (NSE) was assessed by ELISA. The ischemic penumbra tissue was dissected. The proteins were extracted, and the levels of nuclear and cytoplasmic DREAM were estimated by Western blot. The expression of dream gene was analyzed by qRT-PCR.

One or 10 μM of (S)-3,5-DHPG preconditioning in stroke rats has significantly improved the neurological functions, reduced brain infarction and the NSE level. The DREAM protein has significantly increased in the nuclear compartment after 2 hours of 1 μM (S)-3,5-DHPG administration and in the cytoplasmic compartment after 24 hours of 100 μM (S)-3,5-DHPG administration. 1 μM (S)-3,5-DHPG preconditioning has significantly reduced the level of DREAM protein activity after 24 hours of an ischemic stroke. The expression of dream gene was decreased in 1 μM (S)-3,5-DHPG preconditioning compared to non-preconditioning ischemic stroke rats.

The 1 and 10 μM of (S)-3,5-DHPG preconditioning enhanced the protective mechanism via promoting the nuclear DREAM protein whereas 100 μM of (S)-3,5-DHPG preconditioning exacerbated the ischemic injury. Further studies are warranted to investigate the gene involved in this DREAM-mediated regulation.

THE EFFECTS OF HYPOTHERMIA AND P4 ON GLT-1 AND P62 OF PRIMARY CORTICAL ASTROCYTES FOLLOWING EXPOSURE TO GLUTAMATE TOXICITY.

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ABSTRACT

Glutamate excitotoxicity involves the massive release of glutamate extracellularly, thereby inducing glial injuries. Hypothermia offers neuroprotection; however, prolonged time is required to exert its effects as well as variation in the outcomes. Adjuvant therapy with hypothermia may reduce exposure time and obtain consistent outcomes. Progesterone (P4) is a neurosteroid that has been shown to elicit neuroprotection in neuronal cells with ischemic injury. This study investigates the effects of hypothermia and P4 on astrocytes following glutamate-induced toxicity.

The cultured primary cortical astrocyte cells were exposed to 50 μ M of glutamate for 15 minutes followed by incubation under mild or moderate hypothermia with and without P4 for 24 hours. The viability of cells was assessed by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay. The intracellular concentration of glutamate was estimated by the glutamate uptake assay. The levels of S100 β and p62 were measured using ELISA. The membrane protein was extracted and estimated for GLT-1 by Western Blot.

There were significant increases in the percentage of viable cells as well as the concentration of glutamate uptake by the astrocyte cells in mild hypothermia with P4 ($p < 0.01$) and moderate hypothermia with P4 ($p < 0.01$) as compared to normothermia after glutamate-induced toxicity. There was a significant effect of moderate hypothermia with P4 ($p < 0.01$) in increasing the S100 β level in comparison to normothermia across the glutamate-induced toxicity groups and significantly increasing in glutamate uptake ($p < 0.01$) after treated with both mild and moderate hypothermia and P4. There was a significant increase in membrane GLT-1 in both mild hypothermia ($p < 0.01$) and moderate hypothermia ($p < 0.01$) group when compared to the normothermia group. The p62 level was significantly reduced in both mild and moderate hypothermia and P4 ($p < 0.01$) across the glutamate-induced toxicity group.

In conclusion, hypothermia and P4 reduced the glutamate-induced toxicity in the astrocyte cells by increasing glutamate uptake via GLT-1.

ASSESSMENT OF AWARENESS AND ACTION TOWARDS SIGNS AND SYMPTOMS OF STROKE AMONG LAY PUBLIC IN KUANTAN, MALAYSIA: A CROSS-SECTIONAL A STUDY

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ABSTRACT

Background: Stroke remains one of the leading causes of mortality and disability in both developing and developed countries. Lack of awareness towards signs and symptoms of stroke leads to delayed presentation to the hospital, contributing towards increased morbidity and mortality. This study aimed to assess the awareness of and action towards signs and symptoms of stroke.

Methods: A cross-sectional study interview-based survey was performed among 393 lay public (age range: 18-64 years old) in states of Pahang, Kuantan city, Malaysia from June to September 2019. Chi-square tests were used to assess the knowledge of differences between participants with good education and income and those with low education and incomes. as well as logistic regression to obtain the factors effecting to the knowledge of stroke symptoms.

Results: Moajority of respondents (n=309,78,6%) identified sudden face, arms and leg numbness, whereas (n=165,42%) of them identified problems in vision as stroke symptoms. However, (n=39,10.4%) were unaaware of any symptoms, while (n=117,30%) identified appropriate action. Furthermore, (n=349, 88.8%) recognized at least one stroke symptom,(n=108, 27.5%) of them identified all five stroke symptoms, and (n=37,9.4%) of individuals had excellent awareness (aware of all five stroke symptoms and appropriate action “calling an ambulance”). Multivariable logistic regression shows that individuals aged 18-45 years (OR=0.054, 95% CI=0.006-0.500, p=0.010), self-employed (OR=12.430, 95% CI=1.372-31.908, p=0.028), those who were diagnosed with hypertension (OR=0.129, 95% CI=0.025-0.673, p=0.015) and students (OR=35.945. 95% CI=1.745-740.615, p=0.020) were more likely to recognize all the five stroke symptoms and appropriate action.

Conclusion: The awareness and action towards signs and symptoms of stroke is poor among lay public in Kuantan, Malaysia. Therefore, the findings of this study would be a baseline for program interventions that focus on public awareness and policy development on stroke management.