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NEUROLOGY AND NERVOUS SYSTEM

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Evaluation of Neuroinflammatory and Neurocognitive Effects of Noninvasive Ventilation Modes in COVID-19 Patients

By Esra Demir Unal & Berna Arlı

Abstract- Background and Aim: Coronavirus disease (COVID-19) is a fatal disease that affects all systems, especially the pulmonary system and its cerebro-pulmonary interaction. In this study, we compared the effects of High-Flow Nasal Cannula Oxygen (HFNC) and Non-Invasive Mechanical Ventilator (NIMV) use on COVID-19 severity scales and determined its relevance with the neuro-inflammatory parameters and the cognitive system.

Material and Methods: This study was conducted on 50 patients using HFNC (n:25) or NIMV (n:25), who followed up with COVID-19 pneumonia in the Neurology Intensive Care Unit (ICU) in September 2020. Demographic data, COVID-19 severity scales (Brescia-COVID Respiratory Severity Scale (BCRSS), Rapid COVID-19 Severity Index (QCSI), H-Index), serum neuro-inflammatory parameters, Coronavirus Anxiety Scale (CAS) and Montreal Cognitive Assessment Scale (MOCA) were evaluated and compared on the first and seventh days in both groups. In addition, thorax computed tomography (CT) findings and Total Lung Severity Score (TLSS) were evaluated.

Keywords: Cognitive assessment; COVID-19 pneumonia; HFNC; NIMV.

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Esra Demir Unal^a & Berna Arlı^a

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Results: Both groups were homogeneous in terms of age, gender, and education level. Each participant had at least one RT-PCR test of positivity. At the end of the 7th day, QCSI and H-Index were higher in the NIMV group. Also MOCA was lower and CAS scores were higher in the NIMV group. ESR, NLO, pro-calcitonin, and troponin values from neuro-inflammatory parameters were higher in the NIMV group on the 7th day ($p<0.05$). The distributions in these groups are statistically significant ($p<0.05$).

Conclusion: In this study, it is predicted that the noninvasive oxygen module to be selected on behalf of patients to be monitored in intensive care conditions may affect COVID-19 severity, neuro-inflammatory levels and cognitive processes. In this aspect, the use of HFNC should be given priority in patients considered for noninvasive ventilation. New studies are needed in this area.

Keywords: Cognitive assessment; COVID-19 pneumonia; HFNC; NIMV.

I. INTRODUCTION

Noninvasive ventilation is an alternative approach that was developed to avoid complications in patients with acute respiratory failure (1-6). It is often used for acute exacerbations of chronic obstructive pulmonary disease, because such exacerbations may be rapidly reversed and because the hypercapnic ventilatory failure that occurs in patients

with this disorder seems to respond well to noninvasive ventilation (5,7-13). The value of HFNC for acute hypoxemic respiratory failure (unrelated to COVID-19) has been extensively studied. Of eight meta-analyses published since 2017, we concluded HFNC was associated with reduced rates of MV compared with conventional oxygen therapy or NIPPV in the setting of acute hypoxemic respiratory failure (14, 15, 16, 17). Four meta-analyses evaluated the use of HFNC after liberation from MV (17-19, 20); and demonstrated a reduction in the need for re-intubation and re-initiation of MV (20). No meta-analysis of HFNC use, either before or after MV, found HFNC to be associated with worse outcomes. In this study, we investigated the central and peripheral effects of the non-invasive ventilation module to be selected in the management of COVID-19 patients. In this context, we evaluated the effect of (HFNC) and NIMV use on COVID-19 severity scales and neuro-inflammatory markers in terms of peripheral exposure, as well as the relationship between COVID-19 anxiety and changes in MOCA scales in terms of central involvement in acute and subacute stages.

II. MATERIALS AND METHODS

a) Study Design and Patient Cohort

This single-center, prospective study was conducted with 50 patients older than 18 years of age who were hospitalized in the Neurology ICU in September 2020 in Ankara City Hospital because of COVID-19. The study was carried out after obtaining the written consent of each participant. Patients who were followed up with HFNC or NIMV in intensive care conditions and who were able to comply with cognitive impairment tests were included. Demographic data including age, gender, education level, history of central neurological disease, history of peripheral neurological disease, symptom onset time, number of positive RT-PCR, the time between positive RT-PCR finding and symptom onset, and neurological complaints were recorded. The relevant data were collected using a standardized case-report form. All data were performed by the corresponding researcher (E.D.U.). All the patients included in this study were tested for influenza A virus, influenza B virus, respiratory syncytial virus, and parainfluenza virus, and these infections were excluded

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by a serological test. Nasal and/or pharyngeal swab specimens were collected from all patients, and RT-PCR assays were performed. The patients have received the diagnosis by positive RT-PCR and chest imaging findings for COVID-19. In this study, we classified and compared the patients into two groups according to NIMV or HFNC usage. Hospitalization, treatment, management, and discharge of the patients were decided according to the guidelines of the Turkish Ministry of Health.

b) *Imaging Analysis*

Thorax computed tomography (CT) information was obtained from the images during the application to the emergency department. Revolution CT (GE Healthcare, Illinois, U.S.A) CT devices with 64 and 128 detectors were used. The evaluation was made by the corresponded investigator (E.D.U) on the images uploaded to the system by PACS (Picture Archiving and Communication System software) installed on the computer. Each participant's CT was evaluated for viral or bacterial pneumonia and the TLSS score was calculated.

c) *Evaluation of plasma acute inflammatory reactants*

Serum samples were taken from each participant on the first and seventh days. Serum acute phase reactants including erythrocyte sedimentation rate (ESR), neutrophil/lymphocyte ratio (NLO), C-Reactive protein, pro-calcitonin, interleukin-6 (IL-6), ferritin, fibrinogen, triglyceride, aspartate aminotransferase, D-Dimer, and troponin values were measured, and both groups compared. Related tests were carried out by Ankara City Hospital Medical Biochemistry Laboratory and evaluated by the responsible researcher (E.DU).

d) *Evaluation of COVID-19 severity scales*

COVID-19 severity scales were included in this study and compared between two groups, including the BCRSS, QCSI, and Hscore. The BCRSS, QCSI, and HScore were evaluated using laboratory information in the emergency department during the admission process on the first day and in the Neurology ICU at the end of the seventh day. In our study, we aimed to calculate the sensitivity and specificity values according to the cut of values in the literature, as well as find the best cut-of value of the scores. The cut of values in the literature were used for these calculations. The BCRSS and Hscore values were 3, ≥ 1 , and >169 in the calculations, respectively (21–23,24, 25, 26, 27). Consistent with the existing literature, we consider using the worst parameters available in the first 24 h during admission (21–23, 24, 25, 26, 27).

BCRSS: The BCRSS was developed in Brescia, Italy, during that nation's COVID-19 crisis. This prediction rule uses patient examination features and the need for escalating respiratory support levels to suggest treatment recommendations. The scale allows clinicians to compare patients, track the trend of a patient's

respiratory severity level over time, and monitor patients nearing a critical action point (28). The BCRSS uses clinical criteria to rank non-intubated patients. It assigns patients a score of 0–3 based on 4 test criteria: (1) dyspnea or staccato speech, defined as being unable to count rapidly up to 20 after a deep breath, at rest, or during minimal activity, such as sitting up in bed, standing, talking, swallowing, or coughing; (2) respiratory rate of >22 breaths/min; (3) PaO₂ of <65 mmHg or SpO₂ of $<90\%$ with supplemental oxygen; and (4) significant worsening of chest radiography. In intubated patients, PaO₂/FiO₂ below 150 mmHg determines whether the score is 5 or above, and the use of adjunctive therapies including prone positioning and neuromuscular blockade agents further increase the score (28, 29)

QCSI: The QCSI score was derived from a dataset of hospitalized COVID-19 patients in the Northwestern United States. Its primary purpose is to predict critical respiratory illness at 24 h, as defined by high oxygen requirements, non-invasive ventilation, invasive ventilation, or death (30). It is a 12-point scale that uses only three variables available at the bedside: nasal cannula flow rate, respiratory rate, and minimum documented pulse oximetry. The patients were then assigned to four risk strata (0–3) based on the following 217 scores: 0–3 low risk, 4–6 low-intermediate risk, 7–9 high-intermediate risk, and ≥ 10 high risks (30).

Hscore: The Hscore is composed of nine variable components as follows: three clinical variables (high fever, organomegaly, underlying immunosuppression), five biochemical variables (triglycerides, ferritin, serum transaminases, fibrinogen, presence of cytopenia), and one cytological variable (findings of hemophagocytosis in the bone marrow) (31). Although there are different cut-off values, the most reliable one in hemophagocytic syndrome (HPS) was 169, and it accurately classified 90% of patients with 93% sensitivity and 86% specificity (31).

e) *Evaluation of cognitive function rating scale and COVID-19 anxiety scale*

All 50 patients were subjected to the neurocognitive assessment scale on the first and seventh days. Compliance with the test was confirmed by performing a full physical and neurological examination of each patient before the test application. Patients who could not comply with the test were excluded from the study. For the neurocognitive evaluation, MoCA test (8), which has proven effective in COVID-19 patients, and CAS scales (32), which are significant in eld studies in terms of COVID-19 anxiety were used.

MoCA: The MoCA is a widely used screening assessment for detecting cognitive impairment (33). It is a one-page 30-point test administered in approximately 10 minutes that assesses: Short-term memory,

visuospatial abilities, executive functions, attention, concentration, working memory, and language (34). Scores on the MoCA range from 0 to 30 and ranges indicate ≥ 26 = normal, 18–25 = mild impairment, 11–17 = moderate impairment and ≤ 10 = severe impairment. According to the validation study, the sensitivity and specificity compared with 18% and 100% respectively for the MMSE. Subsequent studies in other settings were less promising, though superior to the MMSE (35,36)

CAS: The CAS is a 5-item scale with robust reliability and validity based on a study conducted with 775 adults (37). It includes the cognitive (i.e., repetitive thinking; worry; processing biases; dreaming; planning), behavioral (i.e., dysfunctional activities; avoidance; compulsive behaviors), emotional (i.e., fear; anxiety; anger), and physiological (i.e., sleep disturbances; somatic distress; tonic immobility;) dimensions of coronavirus anxiety. Each item was rated on a 5-point scale to react to the frequency of the symptom, ranging from 0 (not at all) to 4 (nearly every day).

f) Statistical Analysis

SPSS 25 (IBM Corp. Released 2017) statistical package program was used to evaluate the data. In the study, descriptive statistics (mean, standard deviation, median, minimum-maximum values, number, and percentile) were given for categorical and continuous variables. The homogeneity of the variances was checked with the Levene test. Normality assumption was checked with the Shapiro-Wilk test. The differences between the two groups, 'Student's-T Test' if the parametric test prerequisites are met; If not, the 'Mann Whitney-U' test was used. Relationships between categorical variables were analyzed with Fisher's Exact Test and Pearson Chi-Square test. The relationship between two continuous variables was evaluated with the Pearson Correlation Coefficient and Spearman Correlation Coefficient. A $p < 0.05$ level was considered statistically significant.

III. RESULTS

The study was conducted with patients receiving oxygen supplementation with 25 HFNC and 25 NIMV. Patients who were intubated during their follow-up or who had to take HFNC or NIMV support together were excluded. The mean age was 52.5 ± 2 years. Both groups were homogeneous in terms of age, gender, and education level. Among the demographic data, 3 patients had epilepsy and 9 patients had diabetic polyneuropathy. Each participant had at least one RT-PCR test of positivity. PCR negative time was measured in 26 patients. The mean value was 12 ± 2 . The most common complaints among the participants were sleep disturbance (46%), headache (45%), and lightheadedness (45%). Two patients presented with epileptic seizures. During the treatment period, all patients were treated with favipiravir, while 10 patients were treated with anakinra, 3 patients with tocilizumab, and 3 patients with pulse prednol (1000 mg IV). At presentation, 30% of the patients' thoracic CT scans were typical for viral pandemic pneumonia, and 6% were typical for bacterial pneumonia. 14% had viral-bacterial pneumonia superimposition. The TLSS scale for assessing the severity of COVID-19 pneumonia was 2.36 ± 2 in the HFNC group and 2.6 ± 2 in the NIMV group. BCRSS, QCSI, and HScore were evaluated in the evaluation of COVID-19 severity scales between groups. BCRSS 1st and 7th-day measurement and QCSI 1st day measurement did not differ statistically between groups ($p < 0.05$). In Hscore 1st-day measurement, the HFNC group mean was 89.8 ± 2 and the NIMV group mean was 98 ± 2 . HScore 7th-day measurement was lower in the HFNC group than the NIMV group mean. In QCSI and HScore 7th-day measurement, the HFNC group mean was 7.44 ± 2 and the NIMV group mean was 10.52 ± 2 . In QCSI and HScore 7th-day measurement, the HFNC group mean was lower than the NIMV group mean ($p < 0.05$) (Table 1).

Table-1: Comparison of COVID-19 Severity Scales (Day 1-7) in NIMV and HFNC group

| | HFNC(mean \pm 2) | NIMV(mean \pm 2) | P |
|--|--------------------|--------------------|----------------------|
| BRESCIA SCORE 1.Day Measurement | 2,64 | 2,84 | 0,658 [€] |
| BRESCIA SCORE 7. Day Measurement | 2,40 | 2,84 | 0,447 [€] |
| QUICK COVID-19 SEVERITY INDEX (QCSI) 1. Day Measurement | 8,44 | 8,66 | 0,933 [€] |
| QUICK COVID-19 SEVERITY INDEX (QCSI) 7. Day Measurement | 7,44 | 10,52 | 0,04 ^{*€} |
| H SCORE 1.Day Measurement | 89,8 | 98 | 0,042 ^{**} |
| H SCORE 7.Day Measurement | 77,12 | 112 | 0,001 ^{***} |

** $p < 0,01$ * $p < 0,05$

n: Number; %: %: Percentage; € Mann Whitney-U test ¥ Student's t test

MOCA and CAS scores were calculated in the evaluation of cognitive and anxiety status between groups. CAS score and MOCA 1st-day measurement did not differ statistically in HFNC and NIMV groups ($p < 0.05$). MOCA 7th-day measurement values were

19.48 ± 2 in the HFNC group and 15.84 ± 2 in the NIMV group. At the MOCA 7th-day measurement values, the mean of the HFNC group was higher than the mean of the NIMV group ($p < 0.05$) (Table 2).

Table-2: Comparison of MoCA (Day 1-7) in NIMV and HFNC group

| | HFNC(mean \pm 2) | NIMV(mean \pm 2) | P |
|---|--------------------|--------------------|--------------------|
| MONTREAL COGNITIVE ASSESSMENT (MOCA) (1. Day Measurement) | 19,2 | 18,84 | 0,117 [€] |
| MONTREAL COGNITIVE ASSESSMENT (MOCA) (7. Day Measurement) | 19,48 | 15,84 | 0,044** |

** $p < 0,01$ * $p < 0,05$

n: Number; %: Percentage;

€ Mann Whitney-U test ¥ Student's t test

Of those with positive CAS 7th-day measurement, 33.3% were in the HFNC group (n: 12) and 66.7% were in the NIMV group (n: 24) (Table 3). The distributions in these groups are statistically significant ($p < 0.05$).

Table-3: Comparison of CAS (Day 1-7) in NIMV and HFNC group

| | | | | Groups | | Critical Value | P |
|---------------------------------|--------------------|----------|---|--------|-------|----------------|---------|
| | | | | HFNC | NIMV | | |
| Coronavirus Anxiety Scale (CAS) | 1.Day Measurement | Negative | n | 3 | 1 | 1,087 | 0,297 |
| | | | % | 75,0% | 25,0% | | |
| | | Positive | n | 22 | 24 | | |
| | | | % | 47,8% | 52,2% | | |
| | 7. Day Measurement | Negative | n | 13 | 1 | 14,286 | 0,001** |
| | | | % | 92,9% | 7,1% | | |
| | | Positive | n | 12 | 24 | | |
| | | | % | 33,3% | 66,7% | | |

** $p < 0,01$ * $p < 0,05$

n: Number; %: Percentage;

1 Chi-Square Test

Serum acute inflammatory parameters were measured on the first and seventh days of the groups. In the first day measurements; 34.3% of those with a high IL-6 value were in the HFNC group (n:12) and 65.7% in the NIMV group (n:23); 60.6% of those with a high AST value are in the HFNC group (n:20) and 39.4% in the NIMV (n:13) group; those with high troponin values were 44.2% in the HFNC group (n:15) and 55.8% in the NIMV group (n:22). On the seventh day measurements of serum acute phase reactants; 38.7% of patients with high ESR values were in the HFNC group (n:13) and 61.3% in the NIMV group (n:6); 44.4% of those with high

NLO values were in the HFNC group (n:20) and 55.6% in the NIMV group (n:25); 44.2% of those with high procalcitonin levels were in the HFNC group (n:19) and 55.8% in the NIMV group (n:24); 40.5% of those with high troponin levels were in the HFNC group (n:15) and 59.5% in the NIMV group (n:22) (Table 4). Distributions in these groups are statistically significant ($p < 0,05$).

Table-4: Comparison of Serum Acute Phase Reactants (Day 1-7) in NIMV and HFNC group

| | | | | Groups | | Critical Value | p |
|--------------------------------------|-------------------|--------|---|--------|--------|----------------|--------|
| | | | | HFNC | NIMV | | |
| Erythrocyte Sedimentation Rate (ESR) | 1.Day Measurement | Normal | n | 6 | 7 | 0,104 | 0,747 |
| | | | % | 46,2% | 53,8% | | |
| | | High | n | 19 | 18 | | |
| | | | % | 51,4% | 48,6% | | |
| | 7.Day Measurement | Normal | n | 13 | 6 | 4,160 | 0,041* |
| | | | % | 68,4% | 31,6% | | |
| | | High | n | 12 | 19 | | |
| | | | % | 38,7% | 61,3% | | |
| Neutrophil / Lymphocyte Ratio (NLO) | 1.Day Measurement | Normal | n | 0 | 1 | 1,020 | 0,312 |
| | | | % | 0,0% | 100,0% | | |
| | | High | n | 25 | 24 | | |
| | | | % | 51,0% | 49,0% | | |
| | 7.Day Measurement | Normal | n | 5 | 0 | 5,556 | 0,018* |
| | | | % | 100,0% | 0,0% | | |
| | | High | n | 20 | 25 | | |
| | | | % | 44,4% | 55,6% | | |
| Procalcitonin µg/L | 1.Day Measurement | Normal | n | 3 | 2 | 0,222 | 0,637 |
| | | | % | 60,0% | 40,0% | | |
| | | High | n | 22 | 23 | | |
| | | | % | 48,9% | 51,1% | | |
| | 7.Day Measurement | Normal | n | 6 | 1 | 4,153 | 0,042* |
| | | | % | 85,7% | 14,3% | | |
| | | High | n | 19 | 24 | | |
| | | | % | 44,2% | 55,8% | | |

| | | | | | | | |
|---------------|-------------------|--------|---|-------|-------|--------|---------|
| IL-6 pg/MI | 1.Day Measurement | Normal | n | 13 | 2 | 11,524 | 0,001** |
| | | | % | 86,7% | 13,3% | | |
| | | High | n | 12 | 23 | | |
| | | | % | 34,3% | 65,7% | | |
| | 7.Day Measurement | Normal | n | 7 | 4 | 1,049 | 0,306 |
| | | | % | 63,6% | 36,4% | | |
| | | High | n | 18 | 21 | | |
| | | | % | 46,2% | 53,8% | | |
| AST U/L | 1.Day Measurement | Normal | n | 5 | 12 | 4,367 | 0,037* |
| | | | % | 29,4% | 70,6% | | |
| | | High | n | 20 | 13 | | |
| | | | % | 60,6% | 39,4% | | |
| | 7.Day Measurement | Normal | n | 13 | 7 | 3,000 | 0,083 |
| | | | % | 65,0% | 35,0% | | |
| | | High | n | 12 | 18 | | |
| | | | % | 40,0% | 60,0% | | |
| Troponin ng/L | 1.Day Measurement | Normal | n | 6 | 1 | 4,153 | 0,042* |
| | | | % | 85,7% | 14,3% | | |
| | | High | n | 19 | 24 | | |
| | | | % | 44,2% | 55,8% | | |
| | 7.Day Measurement | Normal | n | 10 | 3 | 5,094 | 0,024* |
| | | | % | 76,9% | 23,1% | | |
| | | High | n | 15 | 22 | | |
| | | | % | 40,5% | 59,5% | | |

**p<0,01 *p<0,05
n: Number; %: Percentage;

1 Chi-Square Test

IV. DISCUSSION

In this study, we aim to evaluate to what extent the ventilation module to be selected affects the severity of the disease, the change of neuroinflammatory markers, and cognitive impairment in the acute and subacute periods in COVID-19 patients who have not yet been intubated. In this respect, our study is the first as far as we know.

The etiology of the SARS-CoV-2 is certainly multifactorial, but the exact pathophysiological mechanisms leading to the neurological and psychiatric consequences of COVID-19 are still not clear. Reports about anosmia (loss of the sense of smell) (38) and ageusia (loss of taste) in patients with COVID-19 infection turned attention toward possible affection of the central nervous system (CNS) (39–42). Other early complications include impaired consciousness, agitation, dizziness, and headache (40). Rogers and colleagues (43) conducted a systematic review and found a few studies that did systematic assessments of cognition in patients following SARS-CoV and MERS-CoV infection. During the acute phase, around a third of the patients experienced impaired memory, concentration, or attention (44). After the illness, around one-fifth of all patients had one or more of the aforementioned cognitive impairments. A letter dating from June 2020 (44) reported that a third of their discharged COVID-19 patients showed a dysexecutive syndrome consisting of "inattention, disorientation, or poorly organized movements in response to the command". As more unusual symptoms emerged, it became gradually clear that COVID-19 could affect a wide variety of organs and tissue (45–47). In our study, both central and peripheral nervous system effects of COVID-19 were investigated, and sleep disturbance (46%), headache (45%), and lightheadedness (45%) were found to be the most common symptom of patients upon admission. Two patients were found to have epileptic seizures.

Current observational reports view that a significant proportion of patients with COVID-19 pneumonia can be treated non-invasive (i.e., high flow nasal cannula (HFNC) or non-invasive ventilation (NIV)) instead of invasive mechanical ventilation (IMV). HFNC and NIMV are the leading noninvasive ventilation methods used in COVID-19 patients (48). In our study, HFNC and NIMV were used as non-invasive mechanical ventilation methods in ICU, depending on necessity.

HFNC oxygen therapy refers to the delivery of humidified and heated oxygen at high flows, typically 20–60 L/min, which is titrated to a precise fraction of inspired oxygen (Fi O₂). The advantages of delivering oxygen in this manner include improved comfort by satisfying patients on demand, creating an oxygen reservoir in the upper airway, and reducing physiological dead space (reduced CO₂ rebreathing) (49). Recent

meta-analyses suggest that the application of HFNC in the setting of acute hypoxemic respiratory failure can reduce the risk of intubation and invasive mechanical ventilation by 15% compared with conventional oxygen therapy without affecting mortality. (50). A recent computer simulation study concluded that strategies incorporating HFNC for patients not urgently needing intubation could result in greater mechanical ventilator availability and fewer deaths. Propensity score-matched analyses comparing HFNC and other means of respiratory assistance suggest a lesser likelihood of intubation (51), a higher number of ventilator-free days, and a reduction in ICU length of stay (52) with the former. In previous studies on the use of oxygen support with HFNC in hypoxic respiratory failure, better patient comfort, decreased respiratory distress, regressed tachypnea, better oxygenation and decreased intubation requirement have been found (53).

Non-invasive ventilation (NIV) is delivered through a face mask or a helmet that is placed over the patient's head. The helmet interface potentially presents a safer alternative (from an infection control perspective) because it eliminates leaks. In the settings of acute congestive heart failure and acute hypercapnic respiratory failure due to COPD, NIV has been extremely effective in preventing intubation and reducing mortality (54, 55). NIV was associated with higher intensive care unit mortality among ARDS patients with PaO₂ / Fi O₂ 9.5 mL/kg predicted body weight) and poor oxygenation at baseline (PaO₂ /Fi O₂ 9 mL/kg of predicted body weight and PaO₂ /FiO₂ ≤200 mmHg independently predicted NIV failure (54). A post hoc analysis reported a higher risk of intubation and mortality for patients treated with NIV versus HFNC in a group of immunocompromised patients with acute respiratory failure (55). In our study, the central and peripheral system effects of NMIV and HFNC use in COVID-19 patients were evaluated and the effects on COVID-19 severity scales, serum neuro-inflammatory markers levels, and cognitive impairment were compared between two groups. Consistent with the literature so far, it has been statistically proven that the use of HFNC at the end of the 7th day has a positive effect on both the COVID-19 severity scores. We evaluated BCRSS, QCSI, and HScore on the 1st and 7th-day. There is no difference between BCRSS and QCSI scores on the 1st-day. HScore 1st-day measurement was higher in the NIMV group. HScore 7th-day measurement was lower in the HFNC group. In QCSI and HScore 7th-day measurement, the HFNC group mean was lower than the NIMV group ($p < 0.05$).

There is evidence that severe COVID-19 patients show hyper-inflammation, hyperferritinemia, and hypercytokinemia. Siddiqi and Mehra stated that in the hyperinflammation phase of COVID-19, there is a significant increase in biomarkers and inflammatory cytokines such as interleukin (IL)-2, IL-6, IL-7, ESR, NLO,



troponin, CRP, ferritin, PCT, and D-dimer. It has been reported that uncontrolled hyperinflammation can lead to cardiopulmonary collapse and multiple organ failure (56). To determine the effect of COVID-19 on the neuroinflammatory process and to compare the prognostic change of this process, we measured laboratory values on the first and seventh days in both groups. In the first day measurements of serum acute phase reactants; IL-6 values were higher in the NIMV group, and AST and troponin values were higher in the HFNC group. On the seventh day measurements of serum acute phase reactants; ESR, NLR, pro-calcitonin and troponin levels increased in the NIMV group and had a high that reached statistical significance.

Considering current data, patients in various degrees suffer from short-term cognitive impairment following COVID-19 infection. Compared to healthy controls, all the included studies reported that a higher percentage of patients had a global cognitive impairment. Regarding specific cognitive domains, principally attentional and executive functions seem to be prone to impairments (57). Dysfunctions of the higher mentation go unnoticed, especially if they are mild and occur in otherwise asymptomatic persons (58). Such unrecognized deficits have been brought out in asymptomatic subjects in many other diseases by targeted cognitive tests like MoCA (59, 60). The ICU patient follow-up process creates cognitive impairment in patients because it affects the patient's psychological and physical comfort and because COVID-19 inflammation adversely affects the central nervous system. In this process, we believe that the noninvasive ventilation method to be chosen in non-intubated patients can change the cognitive impact of the patients. MoCA scores were compared to cognitive evaluation scales in both groups. The MoCA day 1 measurement was similar in both groups, while the average for day 7 was higher in the HFNC group. There is not enough data to support this statistically significant data in our study, and there is not enough data yet on which noninvasive method affects cognitive influence for the better.

During an infectious disease outbreak, a significant proportion of people tend to experience clinically significant levels of fear and anxiety (61). Consistent with this, acute infection and mortality rates related to COVID-19 caused widespread fear and anxiety (62, 63). Studies conducted in China demonstrate this, reporting that between 50% (64) and 70% (65) of the participants showed moderate to high psychological symptoms (64, 65). Consistent with this, Wang et al. (64) found that approximately one-third of the participants reported moderate-to-severe anxiety, while for Tian et al. (65) the participants reported high scores for obsessive compulsion, interpersonal sensitivity, phobic anxiety, and psychoticism. Many studies have shown that HFNC is tolerated as well and

reduces anxiety better than other means of oxygen supply (66) respected by comfort scores (67), generated noise scores, dryness of the nose scores, and subjective appearance of patient's comfort and complaint (68). The study by Sztrymf et al. (69) included patients who tolerated HFNC for up to 7 days without major side effects. In our study, we compared first and seventh-day CAS scores to measure coronavirus anxiety in the HFNC and NIMV groups. While no statistically significant difference was observed in the first-day scores, we showed that 66.7% of those with high 7th day measurements were in the NIMV group. The present results are in line with data showing that HFNC has a better effect on anxiety.

Limitations of the Study

The present study was based on a detailed interview with the patient (and/or a carer) that was carried out within 7 days of hospital admission for COVID-19 pneumonia. The parameters examined within the study do not include the significance level of the parameters that have reached statistical significance in chronic return of COVID-19 pneumonia. In addition, the limited patient population included in the study brings to mind the idea that different results can be obtained when similar studies are conducted with larger patient groups of different ethnic origins.

V. CONCLUSION

In this study, patients ventilated with NIMV or HFNC were evaluated with demographic data, COVID-19 severity scales, serum acute phase reactant parameters, and cognitive scales. We concluded that COVID-19 severity scales and serum acute inflammatory parameters, which may be important in the follow-up and treatment of COVID-19, increase in patients using NIMV, and that the use of NIMV is related to poor cognitive impairment, which may adversely affect the prognosis in patients and increase the need for treatment. There is not enough data to compare the data on the two noninvasive ventilator modules that we compared in the study. In this respect, our study will contribute to the literature.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Caracterización Clínica Y Neurofisiológica Del Síndrome De Guillain Barré En Los Pacientes Hospitalizados En Octubre 2017 A Octubre 2019. Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja De Seguro Social, Panamá

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Abstract- The study methodology consists of an observational, cross-sectional, descriptive, retrospective study that evaluated patients seen from October 2017 to October 2019, was done at the Complejo Hospitalario Dr. Arnulfo Arias Madrid, Caja de Seguro Social, Panama.

The objective was to describe the clinical and neurophysiological characteristics of Guillain Barré Syndrome in patients hospitalized at the hospital and during the period before mentioned.

The estimated universe is 48 patients.

Palabras Claves: critical care unit, guillain barré syndrome, infections, vaccines, mechanic ventilation.

GJMR-A Classification: DDC Code: 616.8 LCC Code: RC343.4



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Pahola Araujo ^α, Yamizel Esther Castillo Serrano ^ο & Dr. David Dondis ^ρ

Resumen- La metodología del estudio consiste en un estudio observacional, corte transversal, descriptivo, retrospectivo, que evaluó pacientes atendidos de octubre 2017 octubre 2019, fue llevado a cabo en el Complejo Hospitalario Metropolitano Dr. Arnulfo Arias Madrid, Caja de Seguro Social, Panamá.

El objetivo fue describir las características clínicas y neurofisiológicas del Síndrome de Guillain Barré en los pacientes hospitalizados en el hospital y durante el período de tiempo ya mencionado.

El universo estimado fue de 48 pacientes.

Métodos estadísticos EPI INFO, porcentajes y frecuencias, según el tipo de variables, con sus medidas de dispersión.

Conclusiones: El Síndrome de Guillain Barré es más común en el sexo masculino, con un promedio de edad de 54 años. La mayoría tiene antecedentes de un proceso infeccioso previo y son procedentes de la ciudad capital. La variante neurofisiológica más observada es ANSAM a diferencia de los reportes internacionales.

Palabras Claves: infecciones, síndrome de guillain barré, unidad de cuidados intensivos, vacunas, ventilación mecánica.

Abstract- The study methodology consists of an observational, cross-sectional, descriptive, retrospective study that evaluated patients seen from October 2017 to October 2019, was done at the Complejo Hospitalario Dr. Arnulfo Arias Madrid, Caja de Seguro Social, Panama.

The objective was to describe the clinical and neurophysiological characteristics of Guillain Barré Syndrome in patients hospitalized at the hospital and during the period before mentioned.

The estimated universe is 48 patients.

EPI INFO statistical methods, percentages, and frequencies, according to the type of variables, with their dispersion measures.

Conclusions: Guillain Barré Syndrome is more common in males, with an average age of 54 years. Most have a history of a previous infectious process and are from the capital city. The

most observed neurophysiological variant is ANSAM, unlike international reports.

Palabras Claves: critical care unit, guillain barré syndrome, infections, vaccines, mechanic ventilation.

I. INTRODUCCIÓN

El síndrome de Guillain-Barré es una enfermedad inflamatoria inmunomediada monofásica con una incidencia global anual de aproximadamente 1 a 2 por 100.000 personas-año. Más común en el sexo masculino con un riesgo de 1.5 veces más que las mujeres. (3,4). Es un trastorno postinfeccioso, donde 2/3 de los pacientes informan infecciones del tracto respiratorio o gastrointestinal dentro de las 4 semanas previas al inicio de la debilidad. (30).

En cuanto a sus manifestaciones clínicas están debilidad bilateral rápidamente progresiva principalmente de piernas, brazos y/o pares craneales, parestesias distales o pérdida sensorial. Los reflejos están disminuidos o ausentes en la mayoría de los casos, sin embargo, se han reportado casos de reflejos osteotendinosos normales y hasta hiperreflexicos. (5,7) El dolor se informa con frecuencia, puede ser muscular, radicular o neuropático (2).

Existen diferentes variantes: la más común es la variante clásica sensitivo motora (30-85%), la motora pura (5-70%), Paraparéctica (5-10%), braquio-cervico-faríngea (5%), la Variante Miller Fisher (SMF) (5-25%) y la encefalitis de Bickerstaff, que tiene una frecuencia menor del 5%. (2,4,5,10)

En cuanto a las pruebas diagnósticas fueron utilizadas, la punción lumbar y un estudio de electrodiagnóstico.

Los estudios de electrodiagnóstico pueden diferenciar entre los tres subtipos de GBS clásico: polirradiculoneuropatía desmielinizante inflamatorio aguda (AIDP), neuropatía axonal motora aguda (AMAN) y neuropatía axonal sensorial y motora aguda (AMSAN). (2, 4)

El síndrome de Guillain Barré consiste en una de las principales patologías neurológicas atendidas en

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el Complejo Hospitalario Dr Arnulfo Arias Madrid, sin embargo, no se cuentan con datos acerca de esta patología. Por ende, el objetivo principal de este estudio fue la Caracterización clínica y neurofisiológica del Síndrome de Guillain Barré en los pacientes hospitalizados en Octubre 2017 a octubre 2019. Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

II. MATERIALES Y MÉTODOS

a) *Participantes y recolección de datos*

Consiste en un estudio observacional, corte transversal, descriptivo, retrospectivo, que evaluó pacientes atendidos de octubre 2017 octubre 2019, fue llevado a cabo en el Complejo Hospitalario Metropolitano Dr. Arnulfo Arias Madrid, Caja de Seguro Social, Panamá.

Para la recolección de datos se utilizó un instrumento realizado por los investigadores principales que detallaban las variables que fueron evaluadas.

El universo estimado fue 48 pacientes, tomando como referencia las estadísticas de pacientes hospitalizados con diagnóstico de Síndrome de Guillain Barré evaluados por el servicio de neurología por mes. La muestra dio como resultado 24 pacientes que fueron atendidos en el servicio de neurología durante el tiempo estipulado en el estudio. De estos 24 pacientes se excluyeron 11 pacientes debido a que no se encontraron los expedientes clínicos.

Las variables recolectadas fueron: sexo, edad, lugar de procedencia, mes de admisión, variantes neurofisiológicas del Síndrome de Guillain Barré, antecedente infeccioso, antecedente de vacunación, días intrahospitalarios, ingreso a la unidad de cuidados intensivos, requerimiento de ventilación mecánica, tratamiento, punción lumbar y los hallazgos en la punción lumbar.

Las variantes neurofisiológicas fueron definidas polirradiculoneuropatía desmielinizante inflamatoria aguda (AIDP), neuropatía axonal motora aguda (AMAN) y neuropatía axonal sensorial y motora aguda (AMSAN), síndrome de Miller Fisher, encefalitis de Bickerstaff, variante faringo cervicobraquial (2,4).

El antecedente infeccioso se definió como infecciones del tracto respiratorio o gastrointestinal dentro de las 4 semanas posteriores al inicio de la debilidad. (30)

Por último los hallazgos de la punción lumbar que se tomaron en cuenta fueron disociación albuminocitológica con proteinorraquia y con pleocitosis desde 10 a 50 células por mm³. (8)

b) *Análisis estadístico*

Se utilizó para el análisis de los datos el programa estadístico EPI INFO y se reportaron los resultados en porcentajes y frecuencias, según el tipo de variables, con sus medidas de dispersión.

c) *Aprobación del protocolo*

El protocolo de investigación fue evaluado por el Comité de bioética de la investigación del Complejo Hospitalario Dr. Arnulfo Arias Madrid. (CBI-CHDRAAM-CSS)

III. RESULTADOS

En nuestro estudio, el 61.5% de los casos correspondían al sexo masculino y 38.5% correspondían al sexo femenino, siendo la relación M: F 1.5: 1.

La edad de nuestra población estudiada iba desde los 35 años hasta los 71 años, siendo este último grupo el 23.1% de los casos de este estudio. La media la edad obtenida en nuestro estudio fue de 53,9 años.

Tabla #1. Frecuencia de Síndrome de Guillain Barré según **características epidemiológicas** en los los pacientes hospitalizados en Octubre 2017 a octubre 2019.Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

| Características epidemiológicas epidemiológicas en los los pacientes hospitalizados en Octubre 2017 a octubre 2019.Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá. | | |
|--|------------|------------|
| Sexo | Frecuencia | Porcentaje |
| Masculino | 8 | 61,5 % |
| Femenino | 5 | 38,5% |
| Total | 13 | 100% |
| Edad | | |
| Media | 53,9 años | |
| Mediana | 52 años | |
| Moda | 71 años | |

Base de datos del estudio Caracterización clínica y neurofisiológica del Síndrome de Guillain Barré en los pacientes hospitalizados en Octubre 2017 a octubre 2019.Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

El 76.9% de nuestra población procedía de la provincia de Panamá, la mayoría eran del área oeste y del centro. 15.4% de los casos no se pudo consignar el área de procedencia y el mes que se presentaron la mayoría de los casos, con 46.15%, correspondió a junio seguido del mes de diciembre con 31%. Los casos se presentaron durante temporada lluviosa.

El 84.6% de nuestra población no presentaba antecedentes de vacunación reciente al momento de desarrollar Síndrome de Guillain Barré y 54% de los pacientes presentaban antecedentes de un proceso infeccioso reciente previo al desarrollo de los síntomas.

Tabla #2. Frecuencia de Síndrome de Guillain Barré según **antecedente de vacunación** en los los pacientes hospitalizados en Octubre 2017 a octubre 2019.Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

| Antecedente de vacunación | Frecuencia | Porcentaje |
|---------------------------|------------|------------|
| No | 11 | 84,62 % |
| Sí | 2 | 15,38 % |
| Total | 13 | 100% |

Base de datos del estudio Caracterización clínica y neurofisiológica del Síndrome de Guillain Barré en los pacientes hospitalizados en Octubre 2017 a octubre 2019.Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

Se observó que la cantidad de días intrahospitalarios iba desde 5 días hasta 5 meses. En 15.4% de los casos, se observó que los días intrahospitalarios era entre los 5 y 8 días, respectivamente. En cuanto a la necesidad de requerimiento de ventilación invasiva y el ingreso a la unidad de cuidados intensivos, 61.5% de los pacientes necesitó manejo avanzado de la vía aérea.

Tabla #3. Frecuencia de Síndrome de Guillain Barré según requerimiento de ventilación mecánica invasiva en los los pacientes hospitalizados en Octubre 2017 a octubre 2019. Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

| Requerimiento de ventilación mecánica invasiva | Frecuencia | Porcentaje |
|--|------------|------------|
| No | 8 | 61,54% |
| Sí | 5 | 38,46% |
| Total | 13 | 100% |

Base de datos del estudio Caracterización clínica y neurofisiológica del Síndrome de Guillain Barré en los pacientes hospitalizados en Octubre 2017 a octubre 2019. Complejo Hospitalario Dr. Arnulfo Arias Madrid Caja de Seguro Social, Panamá.

76,9% de los pacientes recibió tratamiento con inmunoglobulinas, 15,4% de los pacientes recibió otro manejo, entre ellos con corticoides y manejo sintomático.

92,3% de los pacientes se le realizó una punción lumbar durante su cuadro de Síndrome de Guillain Barré, de estos 77% presentó disociación albúmino-Citológica en sus resultados. Es importante mencionar, que, aunque a 2 pacientes si se le realizó la punción lumbar, en los expedientes revisados, nose encontró resultados de esta.

Con respecto a la variante neurofisiológica, se observó que el 46,15% de los pacientes presentaron resultados positivos con la variante AMSAN y 38,5% presentaron la variante AIDP.

IV. DISCUSIÓN

Al igual que en el estudio presentado por Palmezano Díaz et al. (36) en Colombia y Chunga-Vallejos et al. (37) en Perú, la mayor parte de la población de estudio correspondía al sexo masculino, en nuestro caso en un 61,5%. En cuanto a la población afectada, el rango de edad iba entre 35-71 años, siendo el promedio de 54 años, resultados similares a los obtenidos por Cea et al, (38) donde el promedio de edad fue de 51,6 años y el rango de su población de estudio era entre 17-81 años.

El estudio realizado en México por de la O-Peña et al (39), la mayoía de sus pacientes procedían del área metropolitana de Guadalajara, similar a los resultados de nuestro estudio, donde la mayoría de los pacientes procedían dela provincia de Panamá, probablemente esto se debe a la facilidad de acceder a este hospital en el centro de la ciudad, además de ser uno de los hospitales de tercer nivel más importantes del país.

Nuestros casos se presentaron durante la temporada lluviosa del país, resultados que coinciden con los publicados por Arami et al. (40) en Iran, donde el 43% de sus casos ocurrieron durante el invierno, sin embargo, difieren de los encontrados por de la O-Peña

et al, donde la mayoría de sus casos ocurrieron en verano.

Un poco más de la mitad de nuestros pacientes tenían antecedentes de algún proceso infeccioso reciente y solo 15,38% tenían antecedentes de vacunación.

En el metanálisis realizado por L.H. Martín Arias y col.(41) pudieron concluir que existió un aumento pequeño pero estadísticamente significativo en el riesgo de desarrollar SGB asociado con las vacunas contra la influenza -estacional o pandémica (RR = 2,2; IC del 95%, 1,1-4,3).

El tiempo intrahospitalario de nuestros pacientes era entre 5-8 días, siendo estos pertenecientes a la variante AIDP. Estos datos son similares a los encontrados en el estudio realizado en Guadalajara (39).

A diferencia de otros estudios realizados, el 92% de nuestros pacientes se les realizó punción lumbar, aunque por dificultad del Sistema de registro de expediente, solo se pudo consignar el 77% de los resultados, donde predominala presencia de discociación albúmino-citológica.

La variante electrofisiológica más observada fue ANSAM con un 46,15% seguido por AIDP con 38,5%, de esto, el 50% de los pacientes con AMSAN y el 60% con AIDP presentaban antecedente de prodromo infeccioso reciente.

Nuestros datos difieren en comparación a los encontrados en los estudios de Palmezano Díaz et al. y Arami et al, donde la variante más observada fue AIDP con 64% y 60% respectivamente. Sin embargo, se asemejan a los encontrados por Chunga-Vallejos et al., donde las variantes axonales fueron las más comunes.

61,5% de nuestros pacientes requirieron Ventilación Mecánica Invasiva. Nuestros valores difieren significativamente en comparación a los encontrados en Colombia y Chile donde solo 27% y 7% de los pacientes, respectivamente necesitaron ventilación mecánica invasiva.



El tratamiento más utilizado fue la inmunoglobulina (76.9%), concordante con el manejo sugerido con las guías actuales sobre el SGB.

V. CONCLUSIONES

El Síndrome de Guillain Barré es más común en el sexo masculino, con un promedio de edad de 54 años.

La mayoría tiene antecedentes de un proceso infeccioso previo y son procedentes de la ciudad capital.

Dentro del abordaje, generalmente se le realiza punción lumbar a los pacientes y la disociación albúmino-citológica es el hallazgo más común.

La variante neurofisiológica más observada es ANSAM a diferencia de los reportes internacionales.

Más de la mitad de los pacientes ingresados con Síndrome de Guillain Barré requirieron ventilación mecánica invasiva.

VI. LIMITACIONES

1. Muestra limitada de pacientes.
2. Dificultad para encontrar los expedientes de los pacientes.
3. Datos incompletos de los expedientes revisados.

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Stimulation of Cerebral Angiogenesis and Neurogenesis by Transcatheter Intracerebral Laser Photobiomodulation Therapy in Alzheimer's Disease

By Ivan V. Maksimovich

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This work is dedicated to the clinical application of transcatheter intracerebral laser PBMT for stimulating angiogenesis and neurogenesis in various Alzheimer's disease (AD) stages.

Keywords: *alzheimer's disease; photobiomodulation therapy; laser; transcatheter intracerebral laser photobio-modulation therapy; angiogenesis; neurogenesis.*

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Stimulation of Cerebral Angiogenesis and Neurogenesis by Transcatheter Intracerebral Laser Photobiomodulation Therapy in Alzheimer's Disease

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Abstract- Background and Objectives: An increase in the life span leads to population aging and an increase in neurodegenerative and cerebrovascular lesions. In the treatment of neurodegenerative and cerebrovascular diseases, it is advisable to stimulate angiogenesis and neurogenesis thereby causing cerebral tissues regeneration. Photobiomodulation Therapy (PBMT) is a promising direction in this area.

This work is dedicated to the clinical application of transcatheter intracerebral laser PBMT for stimulating angiogenesis and neurogenesis in various Alzheimer's disease (AD) stages.

Methods: 210 patients suffering from AD were examined. For this research, we selected 97 patients aged 34-80 (average age 67.5), 34 (35.05%) men, 63 (64.95%) women. The patients were divided into groups according to AD severity: preclinical stage TDR-0 - 10 (10.31%), mild stage TDR-1 - 28 (28.87%), moderately severe stage TDR-2 - 42 (43.30%), severe stage TDR-3 - 17 (17.52%).

Test Group- 48 (49.48%) patients, 17 (35.42%) men, 31 (54.58%) women, received Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT).

Control Group - 49 (50.52%) patients, 16 (32.65%) men, 33 (67.36%) women, received conservative treatment.

Results: All test group patients showed improved cerebral microcirculation and decreased cerebral involutive changes. The control group did not show consistent positive dynamics.

Conclusion: Laser transcatheter intracerebral PBMT is an effective method for stimulating cerebral angiogenesis and neurogenesis. After this complex procedure, patients in different AD stages demonstrate cerebral capillary collateral revascularization, tissue metabolism improvement, and regenerative processes in the cerebral tissue. Tissue regeneration leads to growth of temporal and frontoparietal lobes volume. Clinically, we observe a long-term dementia decrease, cognitive functions restoration, improved patients' life quality.

Keywords: alzheimer's disease; photobiomodulation therapy; laser; transcatheter intracerebral laser photobiomodulation therapy; angiogenesis; neurogenesis.

I. INTRODUCTION

In economically developed countries, an increase in the life span and a decrease in the birthrate leads to population aging, which is accompanied by an increase in neurodegenerative, cerebrovascular diseases, and dementia. In 60-80% of cases, dementia develops as a result of Alzheimer's disease (AD), which is the most common neurodegenerative disorder. The number of people suffering from this disease is constantly increasing. In 2021, in the United States alone, 6.2 million people aged 65 and over have AD. By 2060, this number can increase to 13.8 million [1].

To date, the etiology and pathogenesis of AD have not been fully understood. The process of AD development is a complex and multicomponent one [2-4]. In recent years, an increasing number of studies have appeared underlying the important role of cerebral angioarchitectonics and microcirculation disorders in AD development [5-13]. These disorders have their own particularities, specific only for this disease.

In AD, vascular lesions show themselves as cerebral small vessel disease (CSVD), which is manifested in Dyscirculatory Angiopathy of Alzheimer's type (DAAT). This angiopathy leads to structural changes in blood supply and microcirculation specific for this disease, which in turn contributes to the development of metabolic disorders of amyloid- β (A β) and tau protein [6-12, 14-18].

Vascular and microcirculatory changes during AD begin to develop many years before the visual symptoms of the disease and are observed in the offspring of patients with AD even at an early age [1,10,19]. These changes in the microvasculature might be hereditary [20].

Reduction of cerebral capillaries play the main role in the development of this process [6-12, 15-17]. In the hippocampus and temporal areas, and, then, in the frontoparietal regions, capillaries become thinner, their branching and their number decrease, which leads to the formation of hypovascular zones [6, 8-12]. These changes result in reduced arterial flow to cerebral tissues and lead to AD-specific hemodynamic changes

[9, 15-17]. Since the blood flowing through the arterial branches cannot pass through the reduced capillary bed, increased "tortuosity" of the intracerebral arterial branches develops [6, 10]. At the same time, there open large arteriovenous shunts, through which arterial blood is discharged into the venous bed [6, 10, 20]. In the temporal and frontoparietal areas, the venous bed overflows, causing venous stasis and impaired venous outflow [10, 20]. The arteriovenous shunts and impaired venous outflow contribute to the deterioration of cerebral hemodynamics even more [9, 10]. Patients suffering from other neurodegenerative and cerebrovascular diseases do not have the combination of these pathological changes [10, 17, 20].

Changes in the cerebral arterial, microcirculatory and venous beds, as well as the developed hypoxia, cause death of mitochondria in the cells of the smooth endoplasmic reticulum and the Golgi apparatus, loss of synapses, degeneration, and death of neurons [9,10,12,15-17,21-26]. The combination of these changes result in a complex lesion of the neurovascular unit (NVU) [7-9, 26]. At the same time, these changes cause blood-brain barrier disorders (BBB) [14, 27, 28].

In turn, hypoperfusion and hypoxia characteristic of AD affect the exchange of amyloid- β , decreasing its excretion and increasing its accumulation. These metabolic disorders lead to the deposition of amyloid- β in the cerebral tissue and vascular wall [7, 9, 12, 27]. These deposits cause a decrease in microvascular elasticity, they narrow the capillary lumen, reduce intracerebral blood flow and lead to an even greater increase in hypoxia and neurodegeneration development [13, 22-26, 29]. The growth of these changes advances AD development and progression [20, 23, 24].

While developing new AD treatment methods, it is necessary to keep in mind improvement of capillary blood supply and stimulation of the development of regenerative processes in the cerebral tissue. To achieve these, it is advisable to apply complex methods of action.

A big step in the development of such new complex AD treatments is the use of laser with low output power of the red or near-infrared (NIR) spectrum (600-1100 nm), which is called laser Photobiomodulation Therapy (PBMT) [30].

As a result of experimental and clinical studies on the treatment of AD, it has been found out that lasers with low output power stimulate metabolic processes in the cerebral tissue, restore the exchange of ATP in the mitochondria of neurons, stimulate physiological angiogenesis causing collateral and capillary cerebral revascularization, stimulate neurogenesis and restoration of cerebral tissues. This complex effect leads to a decrease in the level of dementia, restoration of cognitive functions and improved daily living [31-38].

According to the methods of laser energy delivery, PBMT is subdivided into transcranial, [31, 32, 35] intranasal, often combined with transcranial, [34, 37] and transcatheter intracerebral methods [39].

Previous experimental studies have allowed us to move to the clinical application of transcatheter intracerebral laser PBMT [29, 40-44].

This work is dedicated to the clinical application of transcatheter intracerebral laser PBMT for stimulating angiogenesis and neurogenesis in various AD stages.

II. METHODS

All examinations, conservative treatment methods and intracerebral transcatheter laser interventions in this research were carried out with the approval of the Ethical Review Board (ERB) (Protocol No. 3 of 01-12-2003, Protocol No. 12 of 04-30-2014), as well as with the written consent of patients and their relatives.

The selection of patients for the test and control groups includes:

- Consent of patients, as well as their relatives, for examination and treatment;
- Absence of serious concomitant diseases that could interfere with examination and treatment;
- The somatic state of the patients allowing their examination and treatment;
- Involutive changes in the temporal and frontal parts of the brain corresponding to AD;
- Signs of dementia and cognitive disorders corresponding to AD.

Of 210 people who had been diagnosed with AD in its various stages, we selected 97 patients aged 34 to 80 (average age 67.6 years), 34 (35.05%) men and 63 (64.95%) women. The patients were divided into the test group - 48 (49.48%) patients - and the control group - 49 (50.52%) patients.

All patients of the test and control groups had similar somatic state and severity of dementia and cognitive impairment, in accordance with their AD stages.

Examination plan of patients

The examinations of the patients were carried out according to the following scheme:

- Assessment of the clinical severity of dementia was carried out using The Clinical Dementia Rating scale (CDR) [45];
- Assessment of the severity of cognitive impairment was carried out using the Mini-Mental State Examination (MMSE) [46];
- Assessment of cerebral blood flow and microcirculation was made by means of cerebral scintigraphy (SG) in static and dynamic modes by means of a gamma camera of the "Ohio Nuclear" company, USA, using TC 99M pertechnetate 555;

- Assessment of cerebral perfusion blood filling was carried out using rheoencephalography (REG) on the apparatus "Reospectrum-8", "Neurosoft", Russia; (All of the abovementioned examinations were carried out at patients' admission, then at their discharge, and then in a more distant period with an interval of 6-12 months).
- Laboratory examination was carried out in accordance with the criteria of interventional neuroangiology;
- Assessment of cerebral structural changes was carried out by means of CT and MRI on Somatom (Siemens), Hi Speed (GE), Tomoscan (Philips), Apetro Eterna (Hitachi) using digital program of image processing ATAA (Advance Tomo Area Analysis). The digital processing allows, in percentage terms, to reveal a decrease in the tissue volume of temporal lobes in comparison with their normal volume, thereby showing the severity of involutive changes [6, 10, 41].
- The digital scale of Tomography Dementia Rating scale (TDR) was also used, with the help of which the stage of dementia in AD was morphometrically determined in accordance with the severity of atrophic changes in the temporal lobes detected during CT and MRI [40-42, 47]. Thus, patients were divided into groups: TDR-0 - preclinical AD stage (atrophy of temporal lobes of 4-8%), TDR-1 - mild AD stage (atrophy of temporal lobes 9-18%), TDR-2 - moderately severe AD stage (atrophy of temporal lobes of 19-32%), TDR-3 - severe AD stage (atrophy of temporal lobes of 33-62%) [47]. The examinations were carried out upon the admission of the patient, then, to determine the dynamics of cerebral changes and dementia, at intervals of 6-12 months (the examinations were carried out in independent laboratories);
- Assessment of the intracerebral vascular and capillary bed was carried out using cerebral multi-gated angiography (MUGA) carried out according to the classical technique by transfemoral access using Advantx (GE) devices. The intensity of capillary blood flow was recorded using the digital program of image processing "Angio Vision", which shows changes in the density of capillary blood flow [6, 10, 23, 39, 42]. The primary examination was carried out upon admission of the patient to the clinic and repeated immediately after the PBMT (for the patients of the test group). Further studies were carried out with an interval of 2 to 7 years. In some cases, MSCT angiography (MSCTA) or MR angiography (MRA) was used.

Table 1: Results of examination of patients in the test and control groups

| CHARACTERISTIC OF IDENTIFIED CHANGES | Test Group N - 48 | Control Group N - 49 |
|---|----------------------|-------------------------|
| Clinical Dementia Determination | | |
| CDR - 1 | 16 | 12 |
| CDR - 2 | 21 | 21 |
| CDR - 3 | 7 | 10 |
| Cognitive Disorders | | |
| Decrease to 26-28 MMSE points | 4 | 6 |
| Decrease to 20-25 MMSE points | 16 | 12 |
| Decrease to 12-19 MMSE points | 21 | 15 |
| Decrease to 7-11 MMSE points | 7 | 10 |
| Morphometric determination of dementia stages on TDR scale according to CT and MRI | | |
| TDR - 0 (4-8% temporal lobes atrophy) | 4 | 6 |
| TDR - 1 (9-18% temporal lobes atrophy) | 16 | 12 |
| TDR - 2 (19-32% temporal lobes atrophy) | 21 | 21 |
| TDR - 3 (33-62% temporal lobes atrophy) | 7 | 10 |
| Assessment of cerebral blood flow according to SG | | |
| Decreased blood flow in cerebral hemispheres | 48 | 49 |
| Assessment of cerebral perfusion blood filling according to REG | | |
| Decreased volumetric pulse blood supply | 48 | 49 |
| Dyscirculatory angiopathy of Alzheimer's type (DAAT) according to MUGA | | |
| Reduction of capillaries in the temporal areas | 48 | 49 |
| Development of hypovascular zones in temporal areas | 48 | 49 |
| Decreased arterial flow in the temporal areas | 48 | 49 |
| Development of arteriovenous shunts in the temporal areas | 48 | 49 |
| Development of venous stasis and impaired venous outflow | 44 | 43 |
| Development of increased tortuosity of intracerebral arteries | 38 | 38 |



Treatment methods

The Test Group: 48 (51.61%) patients, 17 (35.42%) men and 31 (54.58%) women, received Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT).

Patients with the preclinical stage of the disease (TDR-0) underwent the intervention against the background of growing memory impairment. Patients with clinical stages of the disease (TDR-1, TDR-2, TDR-3) received their interventional treatment in the period from 1 to 12 years after the diagnosis of AD.

Transcatheter Intracerebral Laser Photobiomodulation Therapy (PBMT)

In catheterization laboratories, under local anesthesia and fluoroscopic control, guiding catheters are used to probe intracerebral arterial branches approaching hypovascular zones [10,23]. Coaxially through these catheters, a flexible laser fiber optic light guide instrument, 25-100 micrometers in diameter and connected to a laser machine, is passed. Laser PBMT is performed using a helium-neon laser ULF-01 (Russia) [39,43,44]. The parameters of intracerebral transcatheter laser exposure: wavelength 632.8 nanometers; laser output power 25-45 mW; fiber output power 24-44 mW; treatment session duration 1200-2400 seconds; beam spot diameter in the vessel 1-2 mm; average dose during treatment 29-106 J [40]. With the transcatheter intracerebral method of delivery, the depth of laser energy penetration into the cerebral tissues is 20-40 mm. [40]. Consequently, power density and energy density are variable [39,43,44].

PBMT is performed on both the right and left hemispheres. If necessary, a solution of a radiopaque substance (Omnipak 350) is injected in small doses for fluoroscopic control.

After PBMT, repeated cerebral MUGA is performed using the digital program of image processing "Angio Vision", which makes it possible to determine changes in the density of arterial and capillary blood flow. The results are used to assess the severity of intracerebral angiogenesis, the degree of collateral revascularization and restoration of microcirculation [23,39,40,43,44]. This program automatically registers the obtained changes in the vascular image in real time, in the corresponding contrast phase.

After transcatheter intracerebral PBMT, according to the generally accepted schemes, the patients underwent disaggregant, anticoagulant, antioxidant, vasodilating and nootropic therapy. The patients received: Aspirin, depending on the parameters of the blood coagulation system, Heparin, indirect anticoagulants, Pentoxifylline 100 mg, Complamin 150 mg, Inosin 200 mg, Nootropil (Piracetam) 1200 mg (or Gliatilin 1000 mg) intravenously, with a drop counter, No. 10-15, followed by pills. In the subsequent period, the courses of pills were repeated twice a year. The patients

did not receive any specific therapy aimed at treating AD.

The Control Group: 49 (50.52%) patients, 16 (32.65%) men, 33 (67.35%) women, received conservative treatment.

The conservative treatment was carried out according to generally accepted schemes [49, 50]. Patients from TDR-0 group received: Nootropil (Piracetam) 2400 mg per day (courses of 3-4 months) or Gliatilin 1200 mg per day (courses of 4-6 months). Patients from groups TDR-1, TDR-2, TDR-3 received Memantine 5-20mg per day or Rivastigmine 3-12 mg per day. At the same time, like patients from the Test Group, all patients from the Control Group received vasoactive drugs Pentoxifylline 800 mg per day in courses of 3 months and Complamin 450 mg per day in courses of 2-3 months, which were repeated twice a year.

Statistical analysis

The result data were processed statistically using the Statsoft Statistica 10 software (StatSoft Inc., USA). In the test and control groups, a contingency table analysis was made by means of the Chi-square test to compare the characteristics of Before / After treatment. Post-treatment indicators significantly differed from pre-treatment indicators in each group ($p < 0.05$), and the statistical significance of the results was significantly higher in the test group ($p = 0.00130$) than in the control group ($p = 0.01044$).

III. RESULTS

The Test Group

Direct results

After transcatheter intracerebral laser PBMT, according to digital MUGA, all 48 (100%) patients showed a direct positive result manifested in pronounced angiogenesis, collateral and capillary revascularization, reduction of arteriovenous shunts, as well as an improvement in venous outflow (Figures 1A, 1B, Figures 2A, 2B).

There were no complications associated with transcatheter intracerebral laser PBMT.

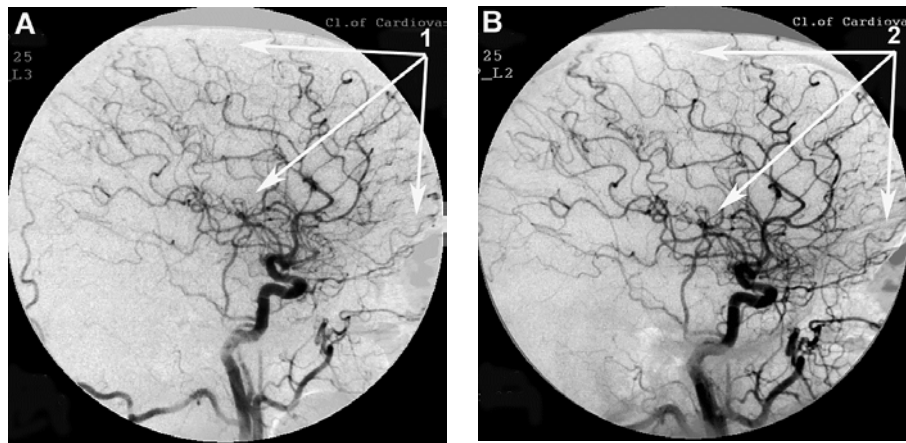


Figure 1: Patient S., 42 years old, male. Medical history of AD - 2 years, TDR-1.

- A. Left internal carotid artery angiogram, arterial phase, before transcatheter Intracerebral laser PBMT: 1. hypovascular areas in temporal and frontoparietal regions.
- B. Left internal carotid artery angiogram, arterial phase, after transcatheter intracerebral laser PBMT: 2. stimulation of angiogenesis, restoration of collateral and capillary blood supply in the temporal and frontoparietal region.

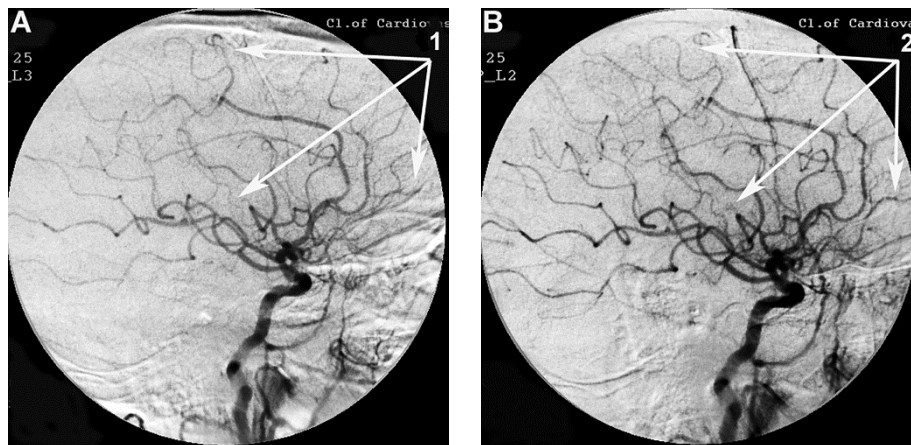


Figure 2: Patient P., 75 years old, female. Medical history of AD - 12 years, TDR-3.

- A. Left internal carotid artery angiogram, arterial phase, before transcatheter Intracerebral laser PBMT: 1. hypovascular areas in temporal and frontoparietal regions;
- B. Left internal carotid artery angiogram, arterial phase, after transcatheter Intracerebral laser PBMT: 2. stimulation of angiogenesis, restoration of collateral and capillary blood supply in the temporal and frontoparietal regions.

Early period (1-6 months) after transcatheter intracerebral laser PBMT

Patients in preclinical AD stage (TDR-0)

Clinically, all 4 (100%) patients showed improvement of memory as well as restoration of cognitive functions to the level of 28-30 MMSE points.

According to CT and MRI data, all 4 (100%) patients had an increase in the volume of the temporal lobes, which was accompanied by narrowing of the Sylvian fissures and restoration of the subarachnoid space.

According to SG and REG data, all 4 (100%) patients demonstrated normalization of blood flow velocity and pulse blood filling in the cerebral hemispheres.

Patients in AD mild stage (TDR-1)

Clinically, all 16 (100%) patients showed a decrease in the level of dementia. Of these, 6 (37.50%) showed an improvement in cognitive functions to the level of 25-26 MMSE points, and 10 (62.50%) to the level of 27-28 MMSE points.

According to CT and MRI data, all 16 (100%) patients had a tendency to an increase in the volume of temporal lobes accompanied by narrowing of the Sylvian fissures and subarachnoid space reduction.

According to SG and REG data, all 16 (100%) patients demonstrated normalization of blood flow velocity and pulse blood filling in the cerebral hemispheres.

Patients in moderately severe AD stage (TDR-2)

Clinically, all 21 (100%) patients demonstrated a decrease in the level of dementia. Of these, 12 (57.14%) showed an improvement in cognitive functions to the level of 19-20 MMSE points, and 9 (42.86%) to the level of 21-22 MMSE points.

According to CT and MRI data, all 21 (100%) patients had a tendency to an increase in the volume of temporal lobes accompanied by narrowing of the Sylvian fissures and subarachnoid space reduction.

According to SG and REG data, all 21 (100%) patients showed signs of restoration of blood flow velocity and pulse blood filling in the cerebral hemispheres.

Patients in severe AD stage (TDR-3)

Clinically, all 7 (100%) patients demonstrated signs of a decrease in the level of dementia, as well as an improvement in cognitive functions to the level of 11-12 MMSE points.

According to CT and MRI data, all 7 (100%) patients had a tendency to an increase in the volume of the cerebral temporal lobes, accompanied by narrowing of the Sylvian fissures and the subarachnoid space reduction.

According to SG and REG data, all 7 (100%) patients showed signs of restoration of blood flow velocity and pulse blood filling in the cerebral hemispheres.

Long-term period (1-7 years) after transcatheter intracerebral laser PBMT

Patients in preclinical AD stage (TDR-0)

One year after transcatheter intracerebral PBMT, all 4 (100%) patients demonstrated sustained

recovery of memory and cognitive functions to the level of 28-30 MMSE points (Table 2).

According to the results of digital processing of CT and MRI images, all 4 (100%) patients had restoration of the volume of the cerebral temporal lobes to the age norm, along with narrowing of the Sylvian fissures and restoration of the subarachnoid space. As a result, all 4 (100%) patients were considered to be practically healthy people without dementia or cognitive impairment.

According to SG and REG data, all 4 (100%) patients showed normalization of blood flow velocity and pulse blood filling in the cerebral hemispheres.

In a longer period of over one year, all 4 (100%) patients demonstrated positive dynamics persisting throughout the observation period (Table 2).

Patients in mild AD stage (TDR-1)

One year after PBMT, all 16 (100%) patients showed no signs of dementia and demonstrated sustained recovery of cognitive functions to the level of 27-28 MMSE points (Table 2).

According to the results of digital processing of CT and MRI images one year after the treatment, all 16 (100%) patients had an 8-10% decrease in the temporal lobes atrophy (Figures 3A, 3B). After 2-4 years, 13 (81.25%) patients showed a further 4-5.5% decrease in the temporal lobes atrophy leading to an almost complete restoration of the temporal lobe volume to the age norm (Figure 3B, 3C). Narrowing of the Sylvian fissures and restoration of the subarachnoid space accompanied the process. In accordance with the abovementioned criteria, all 16 (100%) patients were transferred to Group TDR-0.

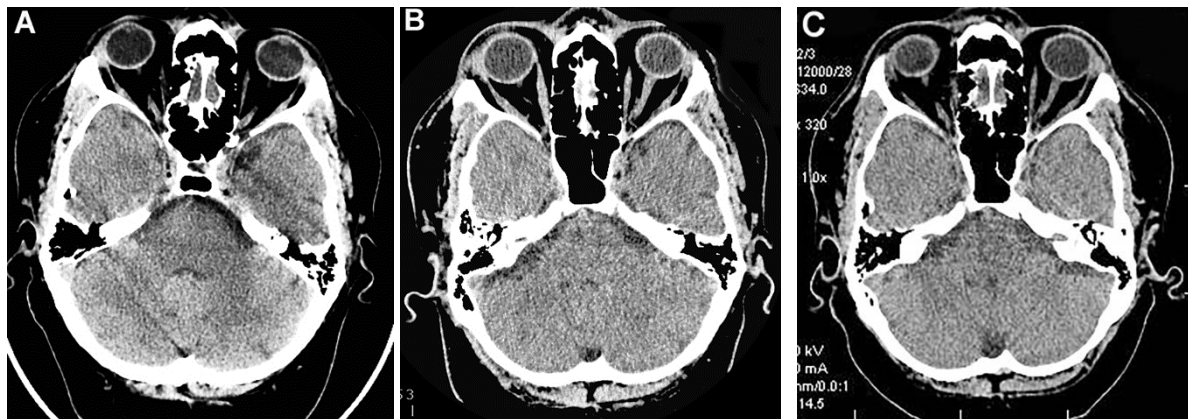


Figure 3: Same patient S., 42 years old, male.

- Cerebral CT before transcatheter intracerebral laser PBMT: Total atrophy of the temporal lobes is 18% of the total tissue volume (TDR-1).
- Cerebral CT in 12 months after transcatheter intracerebral laser PBMT: total atrophy of the temporal lobes decreased to 9% of the total tissue volume (TDR-1).
- Cerebral CT in 4 years after transcatheter intracerebral laser PBMT: total atrophy of the temporal lobes decreased to 5.5% of the total tissue volume.

The patient is transferred to AD group in TDR-0 stage.

According to SG and REG data, all 16 (100%) patients showed normalization of blood flow velocity and pulse blood filling in the cerebral hemispheres.

In a longer period of over one year, all 16 (100%) patients demonstrated that the obtained positive dynamics persisted throughout the observation period (Table 2).

Patients in moderately severe AD stage (TDR-2)

One year after PBMT, all 21 (100%) patients showed a decrease in the level of dementia and an improvement in cognitive functions to the level of 21-22 MMSE points. After 2-3 years, 12 (57.14%) patients had a further decrease in the level of dementia and restoration of cognitive functions to the level of 23-25 MMSE points. 9 (42.86%) patients' cognitive functions remained at the same level equal to 21-22 MMSE points (Table. 2).

According to the results of digital processing of CT and MRI images one year after the treatment, all 21 (100%) patients had a 5-10% temporal lobe atrophy decrease. It was accompanied by narrowing of the Sylvian fissures and subarachnoid space. After 2-3 years, 12 (57.14%) patients had a decrease in the temporal lobe atrophy by another 4-5.5%. 9 (42.86%) patients showed no further pronounced decrease in involutive changes.

As a result, 16 (76.19%) patients were transferred to TDR-1 group, and 5 (23.81%) patients remained in TDR-2 group.

According to SG and REG data, all 21 (100%) patients demonstrated positive dynamics of blood flow velocity and pulse blood filling in the cerebral hemispheres.

4 years after the treatment, all 21 (100%) patients had a tendency to a gradual decrease in cognitive functions.

Patients in severe AD stage (TDR-3)

One year after PBMT, all 7 (100%) patients demonstrated a decrease in the level of dementia. 4 (57.14%) patients had an improvement of cognitive functions to the level of 11-14 MMSE points, and 3 (42.86%) patients to the level of 15-19 MMSE points (Table 2).

According to the results of digital processing of CT and MRI images one year after the treatment, all 7 (100%) patients had a decrease in the atrophy of the cerebral temporal lobes. It was accompanied by narrowing of the Sylvian fissures and subarachnoid space. Of these, 5 (71.43%) patients had a 10-12% decrease (Figures 4A, 4B), and 2 (28.57%) a 6-8% decrease.

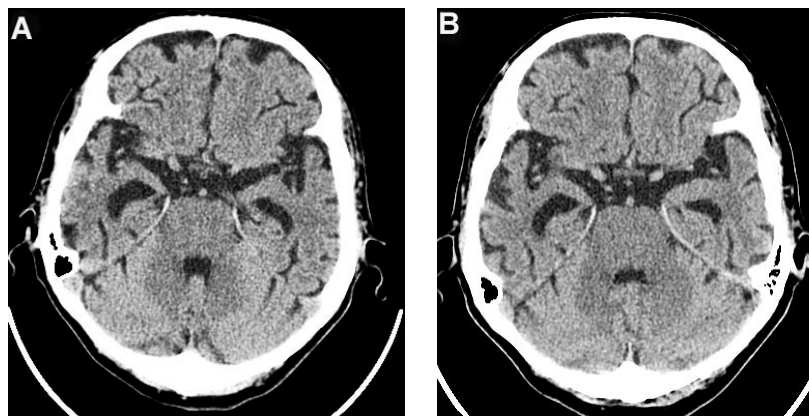


Figure 4: Same patient P., 75 years old, female TDR-3.

- A. Cerebral CT before transcatheter intracerebral laser PBMT: Total atrophy of the temporal lobes is 40% of the total tissue volume (TDR-3).
- B. Cerebral CT 12 months after transcatheter intracerebral laser PBMT: Reduction of the total atrophy of the temporal lobes by 12%. The patient is transferred to AD group in TDR-2 stage.

Accordingly, 5 (71.43%) patients were transferred to TDR-2 group, 2 (28.57%) patients remained in TDR-3 group (Table 2).

According to SG and REG data, all 7 (100%) patients showed preservation of the positive dynamics of blood flow velocity and pulse blood filling in the cerebral hemispheres.

After 2-2.5 years after the treatment, there was a tendency to an increase in dementia and a decrease in cognitive functions.

9 (21.74%) Test Group patients underwent repeated cerebral MUGA in the period from 2 to 6 years after transcatheter intracerebral PBMT. All 9 (100%) patients demonstrated preservation and further progression of angiogenesis, accompanied by collateral and capillary revascularization, was observed in.

Table 2: Long-term results of treating test and control groups patients according to the severity of dementia and cognitive impairment.

| Signs of dementia and cognitive impairment | Test Group before treatment n-48 | Test Group after treatment n-48 | p (chi-square) |
|--|--|---------------------------------------|----------------|
| Practically healthy (MMSE - 29-30 points) | 0 | 4 | p=0.00130 |
| TDR- 0 (MMSE - 26-28 points) | 4 | 16 | |
| TDR- 1 (MMSE - 20-25 points) | 16 | 16 | |
| TDR- 2 (MMSE - 12-19 points) | 21 | 10 | |
| TDR- 3 (MMSE - 7-11 points) | 7 | 2 | |
| | Control Group before treatment n-49 | Control Group after treatment n-49 | |
| Practically healthy (MMSE - 29-30 points) | 0 | 0 | p=0.01044 |
| TDR- 0 (MMSE - 26-28 points) | 6 | 3 | |
| TDR- 1 (MMSE - 20-25 points) | 12 | 5 | |
| TDR- 2 (MMSE - 12-19 points) | 21 | 10 | |
| TDR- 3 (MMSE - 7-11 points) | 10 | 31 | |

The Control Group

Direct results

Immediately after the first course of conservative treatment, all 6 (100%) patients in preclinical AD stage (TDR-0) and all 12 (100%) patients in mild AD stage (TDR-1) showed a trend towards an improvement in cognitive functions. Patients in moderately severe AD stage (TDR-2) and in severe AD stage (TDR-3) had no pronounced positive dynamics.

Early period (1-6 months) against the background of conservative treatment

Patients in preclinical AD stage (TDR-0)

Clinically, all 6 (100%) patients had a tendency to improve memory, as well as to restore cognitive functions to the level of 27-28 MMSE points.

According to CT and MRI data, all 6 (100%) patients had no structural cerebral changes.

According to SG and REG data, all 6 (100%) patients had an improvement in blood flow velocity and pulse blood filling in the hemispheres.

Patients in mild AD stage (TDR-1)

Clinically, all 12 (100%) patients had a tendency towards stabilization of their condition.

According to CT and MRI data, all 12 (100%) patients showed no structural cerebral changes.

According to SG and REG data, all 12 (100%) patients showed signs of improvement in blood flow velocity and pulse blood filling in the hemispheres.

Patients in moderately severe AD stage (TDR-2)

Clinically, 15(71.43%) patients showed a tendency towards a further increase in dementia and a decrease in cognitive functions. 6 (28.57%) patients showed no dynamics.

According to CT and MRI data, all 21 (100%) patients had no structural cerebral changes.

According to SG and REG data, all 21 (100%) patients demonstrated signs of improvement in blood flow velocity and pulse blood filling in the hemispheres.

Patients in severe AD stage (TDR-3)

Clinically, all 10 (100%) patients showed a trend towards a further increase in dementia and a decrease in cognitive functions.

According to CT and MRI data, all 10 (100%) patients had no structural cerebral changes.

According to SG and REG data, all 10 (100%) patients had signs of improvement in blood flow velocity and pulse blood filling in the hemispheres.

Long-term period (1-5 years) against the background of conservative treatment

Patients in preclinical AD stage (TDR-0)

Clinically, within 2 years after the start of the conservative treatment, all 6 (100%) patients had an improvement in memory and stabilization of cognitive functions within 27-29 MMSE points. After 3-5 years, 3 (50.00%) patients showed no obvious signs of dementia. 3 (50.00%) patients had early signs of dementia, as well as a decrease in cognitive functions to 24-25 MMSE points.

According to the results of digital processing of CT and MRI images after 2 years, 1 (16.67%) patient showed no signs of an increase in cerebral involutive changes. 3 (50.00%) patients showed signs of an increase in insignificant involutive changes. 2 (33.33%) patients demonstrated a pronounced increase in involutive changes in the temporal lobes and a 14-18% decrease in tissue volume.

As a result, 3 (50.00%) patients remained in TDR-0 group. 3 (50.00%) patients were transferred to TDR-1 group (Table 2).

According to SG and REG data, all 6 (100%) had persistent moderate positive dynamics of blood flow velocity and pulse blood filling in the brain.

Patients in mild AD stage (TDR-1)

Clinically, within 2-3 years after the start of the treatment, all 12 (100%) patients showed stabilization of the level of dementia and cognitive functions. In the period of more than 3 years, all 12 (100%) patients had an increase in signs of dementia and a decrease in cognitive functions. Of these, 2 (16.66%) patients showed a decrease in cognitive functions to the level of 20-21 MMSE points, and 10 (83.33%) patients to the level of 18-19 MMSE points.

According to the results of digital processing of CT and MRI images in 3 years, 2 (16.66%) patients did not have any intensification of cerebral involutive changes in the temporal lobes. 10 (83.33%) cases had growing involutive changes and a decrease in the volume of the temporal lobes to 19-24%. As a result, 2 (16.66%) patients remained in TDR-1 group, 10 (83.33%) patients were transferred to TDR-2 group (Table 2). Further on, all 12 (100%) cases showed signs of an increase in involutive changes.

According to SG and REG data, all 12 (100%) patients demonstrated weak positive dynamics of blood flow velocity and pulse blood filling.

Patients in moderately severe AD stage (TDR-2)

Clinically, in the period of 1-2 years after the start of the treatment, all 21 (100%) patients showed an increase in dementia and cognitive impairment to 11-12 MMSE points. In the period of 3 years and more, all 21 (100%) patients had a further increase in dementia and a decrease in cognitive impairment to the level of 9-10 MMSE points.

According to the results of digital processing of CT and MRI images after 3 years, all 21 (100%) patients had an increase in involutive cerebral changes and a decrease in the volume of temporal lobes to 34-40%. As a result, all 21 (100%) patients were transferred to TDR-3 group (Table 2).

According to SG and REG, 8 (38.10%) patients had a tendency towards a decrease in cerebral blood flow velocity and pulse blood filling, 13 (61.90%) patients had a clear decrease in cerebral blood flow velocity and pulse blood filling.

Patients in severe AD stage (TDR-3)

Clinically, 1 year after the start of the conservative treatment, all 10 (100%) patients showed an increase in dementia and a decrease in cognitive functions to the level of 7-8 MMSE points.

According to the results of digital processing of CT and MRI images 1 year after the start of conservative treatment, all 10 (100%) patients showed an increase in

cerebral involutive changes and a decrease in the volume of the temporal lobes to 40-45%.

According to SG and REG data, 7 (70.00%) patients had a tendency towards a decrease in the velocity of cerebral blood flow and pulse blood filling, and 3 (30.00%) patients showed a clear decrease in the parameters of cerebral blood flow and pulse blood filling.

IV. DISCUSSION

Test group

The progressive aging of the population and the associated cerebral pathological changes show the need to develop new effective methods of complex treatment of neurodegenerative and cerebrovascular diseases [24,38,39,40]. Transcatheter intracerebral laser PBMT has proved to be highly effective in the treatment of various cerebrovascular lesions, Binswanger's disease (BD), vascular parkinsonism (VP), [40,48] as well as Alzheimer's disease (AD).

During transcatheter intracerebral PBMT, laser energy at a wavelength of 632.8 nanometers with varying power densities passes through the blood, vascular wall, and cerebral tissues, which are essentially "turbid media." As we have noted, the depth of energy penetration is 20–40 mm [39,40,43,44]. As a result, rather large volumes of cerebral tissues are exposed to laser irradiation, which leads to a multicomponent action.

SG, REG and digital MUGA in the test group before, as well as in the immediate and remote periods after transcatheter intracerebral PBMT, shows that helium-neon laser stimulates angiogenesis making arterial and capillary collateral branches open. As a result, revascularization occurs in the hypovascular zones not only in the temporal and frontoparietal regions, but also in other parts of the brain. Improvement in arterial and capillary inflow leads to the closure of pathologically developed arteriovenous shunts and a decrease in venous stasis, which reduces hypoperfusion and restores cerebral hemodynamics.

The conducted research demonstrate the mechanism of action of the laser with low output power of the red spectrum on the vascular and microvascular system of the brain. A similar mechanism works during other methods of conducting PBMT: many authors describe improvement in cerebral blood supply and hemodynamics after transcranial or intranasal PBMT during AD and other neurodegenerative and ischemic lesions [30-38].

Digital processing of CT и MRI images performed before and at different times after transcatheter intracerebral PBMT showed that all 48 (100%) patients in the test group had a persistent decrease in cerebral involutive changes and an increase in the volume of the temporal and frontoparietal lobes. It

should be noted that the cerebral tissue has a normal structure. The results obtained indicate restoration of cerebral metabolism, stimulation of neurogenesis and development of regenerative processes.

The data obtained are confirmed by experimental and clinical works by many authors. These studies have shown that in transcranial and intranasal PBMT, laser energy with low output power of the red or near-infrared spectrum not only improves blood supply, but also restores adenosine triphosphate (ATP) metabolism in the mitochondria of neurons, reduces neuronal death, reduces apoptosis, stimulates neurogenesis and regeneration of cerebral tissues. Clinically, this leads to a decrease in the level of dementia and an improvement in cognitive functions when tested by MMSE and ADAS-cog [31-38].

Thus, transcatheter intracerebral laser PBMT demonstrated a complex positive effect of the lasers with low output power of the red spectrum on the brain of the patients of the test group.

This exposure resulted in stimulated cerebral angiogenesis and neurogenesis for all 48 (100%) patients in various AD stages. As a result, there was an improvement in cerebral hemodynamics, a decrease in involutive changes and an increase in the volume of the temporal lobes, which led to a decrease in the level of dementia and an improvement in cognitive functions and quality of life in all 48 (100%) cases.

The clinical effect after transcatheter intracerebral PBMT, as well as its duration, depends on the disease stages, the initial volume of the affected cerebral tissue and the severity of the initial dementia. Patients in preclinical stage (TDR-0) and mild stage (TDR-1) showed no signs of dementia and had restoration of cognitive functions throughout the observation period. Patients in moderately severe AD stage (TDR-2) and severe AD stage (TDR-3) showed a decrease in dementia and an improvement in cognitive functions within 4-4.5 and 2-2.5 years respectively.

Control group

SG, REG and digital MUGA for patients of the control group before the treatment, as well as at various times after its beginning, shows that moderate positive dynamics of cerebral blood flow and pulse blood filling is observed mainly in the early period of the treatment. In the long term, there was a gradual decrease in the indicators.

Digital processing of CT and MRI images performed before and at different periods of the conservative treatment, not only did not show a decrease in cerebral involutive changes, but, on the contrary, revealed an increase in atrophic changes in cerebral tissues in all 49 (100%) patients.

Conservative treatment is not effective enough and does not reduce the level of dementia or improve cognitive functions. It allows stabilizing the condition of

patients in the early stages of AD for a certain period of time. In the later stages of the disease, the drugs used are ineffective. Similar results have also been described by other authors who carried out similar conservative AD treatment [49, 50].

Pentoxifylline and Complamine allow improving cerebral microcirculation to some extent in cases of early, unpronounced disorders of the cerebral microcirculatory bed.

V. CONCLUSION

Transcatheter intracerebral PBMT is an effective method for stimulating cerebral angiogenesis. After laser exposure, patients suffering from various stages of AD demonstrate arterial and capillary collateral revascularization leading to an improvement in cerebral hemodynamics and a decrease in hypoxia. At the same time, PBMT stimulates neurogenesis and induces regenerative processes in the brain. This complex effect results in declining cerebral involutive changes and growing volumes of the temporal and frontoparietal regions. The patients, show a decrease in the level of dementia, restoration of cognitive functions, an improvement in the quality of life and daily life activities.

The use of Memantine and Rivastigmine, as well as Pentoxifylline and Complamine in the conservative treatment of patients in various AD stages does not have a pronounced effect on the restoration of metabolic and regenerative processes and the improvement of microcirculation in the brain. With this therapy, the improvement of cerebral blood supply is observed only in the early stages of the disease. Clinically, conservative treatment gives a temporary positive effect, which is manifested in the stabilization of the initial condition of patients in early AD stages, while in the late AD stages these drugs are ineffective.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Surgical Management of Coexisting Trigeminal Neuralgia, Hemifacial Spasm, and Glossopharyngeal Neuralgia by Microasterional Approach

By Armando Morales, MD, Shery Lane Sanchez, MD
& Richard Gonzalo Párraga, MD

Abstract- Background: Compression of multiples cranial nerves at the entry zone in the brainstem is called hyperactive dysfunction syndrome. Caused by the dolichoectasia basilar artery that compress V, VII-VIII and IX cranial nerves, in our patient it caused trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia, that its a very rare condition, probably less than 1% of rhizopathies published. There are at less 9 cases reported in the reviewed literature. This case would be the 10th reported case. This is the first case treated with an Microasterional approach with a backup video.

Case Description: In these casewe are reporting a patient diagnosed with trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia, caused by the dolichoectasia basilar artery, caused by microvascular compression. In which case an Microasterional approach was performed. A microsurgical dissection was performed, separating the artery from the nerves, and interposing a non-absorbable sponge between the nerves and vessels.

Keywords: decompression surgery, hemifacial spasm, glossopharyngeal neuralgia, microasterional approach, trigeminal neuralgia.

GJMR-A Classification: DDC Code: 658.4036 LCC Code: HD66, DDC Code: 616.9 LCC Code: RC111



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Surgical Management of Coexisting Trigeminal Neuralgia, Hemifacial Spasm, and Glossopharyngeal Neuralgia by Microasterional Approach

Surgical Management of Hyperactive Dysfunction Syndrome by Microasterional Approach

Armando Morales, MD ^α, Shery Lane Sanchez, MD ^σ & Richard Gonzalo Párraga, MD ^ρ

Abstract- Background: Compression of multiples cranial nerves at the entry zone in the brainstem is called hyperactive dysfunction syndrome. Caused by the dolichoectasia basilar artery that compress V, VII-VIII and IX cranial nerves, in our patient it caused trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia, that its a very rare condition, probably less than 1% of rhizopathies published. There are at less 9 cases reported in the reviewed literature. This case would be the 10th reported case. This is the first case treated with an Microasterional approach with a backup video.

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Conclusion: The microasterional approach and microvascular decompression with a non-absorbable sponge is useful to treathyperactive dysfunction syndromes, with good results, with a resolution of the symptoms in the immediate postoperative period.

Keywords: decompression surgery, hemifacial spasm, glossopharyngeal neuralgia, microasterional approach, trigeminal neuralgia.

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ANNOTATION

- 1) 00:00:00 Title
- 2) 00:08:00 Patient History
- 3) 00:25:14 Preoperative studies
- 4) 00:40:15 Park bench position
- 5) 00:45:15 Park bench position (medical illustration)
- 6) 00:51:05 Microasterional approach (medical illustration)
- 7) 00:56:24 Asterional Zone (medical illustration)
- 8) 01:02:03 Microasterional approach
- 9) 01:06:19 Microasterional approach and dural opening
- 10) 01:11:28 Microdissection of the neurovascular structures
- 11) 01:15:13 Microdissection of the neurovascular structures (medical illustration)
- 12) 01:27:17 Microdissection of the VII-VIII nerves
- 13) 01:38:06 Basilar dolichoectasia artery compressing the VII-VIII nerves (medical illustration)
- 14) 01:55:09 Microdissection to expose the V nerve
- 15) 02:26:00 Basilar dolichoectasia artery compressing the V nerve
- 16) 02:38:24 Placement of non-absorbable sponge in the neurovascular compression
- 17) 03:24:25 Placement of non-absorbable sponge in the neurovascular compression (medical illustration)
- 18) 03:31:21 Placement of non-absorbable sponge in the neurovascular compression at the VII-VIII nerves complex
- 19) 04:39:25 Microdissection to expose the IX-X-XI nerves complex
- 20) 04:53:02 Placement of non-absorbable sponge in the neurovascular compression at the IX-X-XI nerves complex
- 21) 05:30:03 Neurovascular compression solved by microvascular decompression technique (medical illustration)

22) 05:38:25 Postoperative
23) 05:46:28 References

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Author Contributions

Primary surgeon: Richard Gonzalo Párraga. Assistant surgeon: Armando Morales, Shery Lane Sanchez. Medical illustration: Shery Lane Sanchez.

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Conflicts of interest

There are no conflicts of interest.

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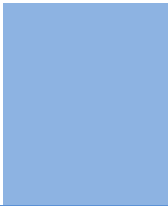
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15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."



Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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BY GLOBAL JOURNALS

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

| Topics | Grades | | |
|-------------------------------|--|---|---|
| | A-B | C-D | E-F |
| <i>Abstract</i> | Clear and concise with appropriate content, Correct format. 200 words or below | Unclear summary and no specific data, Incorrect form Above 200 words | No specific data with ambiguous information Above 250 words |
| <i>Introduction</i> | Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited | Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter | Out of place depth and content, hazy format |
| <i>Methods and Procedures</i> | Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads | Difficult to comprehend with embarrassed text, too much explanation but completed | Incorrect and unorganized structure with hazy meaning |
| <i>Result</i> | Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake | Complete and embarrassed text, difficult to comprehend | Irregular format with wrong facts and figures |
| <i>Discussion</i> | Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited | Wordy, unclear conclusion, spurious | Conclusion is not cited, unorganized, difficult to comprehend |
| <i>References</i> | Complete and correct format, well organized | Beside the point, Incomplete | Wrong format and structuring |



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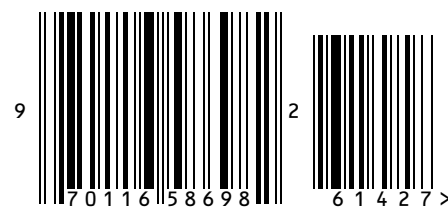
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