Comparison of the Changes of D-Dimer and FDP Serum Levels in Ischemic Brain Stroke Patients with and without Malignancy

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Abstract

Introduction: Cerebral artery diseases are the third cause of death in the U.S. proceeded only by the heart diseases and cancer. It is the most prevalent neurological disorder leading to illness and death. Stroke is a syndrome characterized by the initiation of acute neurological disorders lasting at least for 24 hours. It reflects the focal involvement of central nervous system induced by blood circulation disorders in brain. This study was designed to study D-Dimer and FDP serum levels in ischemic brain stroke patients with and without malignancy. Method of study: This is a randomized clinical trial in the form of a case-control study. The population of study consists of all cases admitted in the neurology department of Imam-Khomeini Hospital in Urmia who included in the study via randomized allocation after obtaining their consent. Cases with underlying malignancy were grouped in case group and those with no malignancy were grouped in control group. Results: In this study, 60 and 120 cases were studied in the case and control groups, respectively. There was a significant difference in mean D-Dimer (P=0.01), mean FDP (P=0.02), mean ESR (P=0.01) and mean CRP (P=0.01) between case and control groups. Lung cancer was the most prevalent cancer (31.7%) in the case group. In addition, diabetes mellitus, hyperlipidemia and hypertension risk factors were reported in the case group with a frequency of 28.3%, 33.3% and 30%, respectively. Conclusion: In patients with ischemic stroke and malignancy, the serum levels of D-dimer and ESR was elevated and risk factors such as DM, HLP, and HTN had a high rate in these patients, so in patients with cancer, occurrence of cerebral ischemia is higher compared to patients without malignancy. So knowing mechanisms, type and stage of cancer is critical for survival of these patients.

Keywords: Diabetes mellitus, D-Dimer, ESR, Hyperlipidemia, Hypertension, Ischemic stroke.

Introduction

Cerebral artery diseases are important health problems across the world. They are the third cause of death in the U.S. proceeded only by the heart diseases and cancer. They accompany with physical, functional and emotional effects, especially with depression. It is the most prevalent neurological disorder leading to death [1-5].

Cerebral artery disease term refers to any cerebral abnormality induced by a process of blood vessel damage with three main processes: thrombotic obstruction of arteries, embolic obstruction of arteries and vascular rupture. The clinical feature of all the above states has been identified, especially when they are initialized acutely [6]. Generally, brain strokes are divided into two ischemic and hemorrhagic strokes. The former is the most prevalent stroke induced by the local thrombosis or embolization of far regions such as heart.

Stroke is a syndrome characterized by the initiation of acute neurological disorders lasting for at least 24 hours. It reflects the focal involvement of the central nervous system induced by blood circulation disorder in the brain [7, 8]. If such symptoms last less than 24 hours, it is referred to as transient ischemic attack (TIA) [9]. Brain stroke-induced cell death happens due to the obstruction of arteries and limited blood circulation and in turn no supply of oxygen and nutrient required by neurons [10].
Every year, 750000 new stroke cases are added to the U.S. population and 150000 cases die due to stroke. It is the third and the leading cause of death in Chinese rural and urban population, respectively. The prevalence of brain stroke increases as age increases so that almost two third of brain strokes occur in people aged >65. The prevalence of stroke is higher in males than females and in blacks than whites [1, 11].

According to estimations, brain stroke will be the second cause of death across the world by 2020 [12].

Hypertension, hypercholesterolemia, smoking, drinking alcohol and consuming anti-pregnancy drugs are among the risk factors of stroke. In recent decades, the rate of brain stroke has been decreased due to improvements in hypertension treatment [1, 7, 13]. However, the number of cases with brain stroke and relevant deaths and disabilities increases every year in the world [14]. Generally, three factors can cause focal ischemia in the brain: vascular disorders, heart disorders and hematologic disorders [7, 15].

According to studies, the number of cancer patients is on the rise. On the other hand, cerebrovascular accidents (CVA) occur in cancer patients generally due to the increased probability of artery obstruction arising from coagulopathy and metastases so that 15% of cancer patients experience a thromboembolic event during clinical treatment. Therefore, the increase of cancer patients among cases with brain stroke is expectable [1, 16-19].

The essential mechanisms of brain stroke in cancer patients are unknown to a large extent. Therefore, the prevention and proper treatment of brain stroke in cancer patients demands the complete perception of clinical, radiological and patho-mechanism features of this disease [20]. There are contradictory reports on the risk factors of ischemic brain stroke in cancer patients compared with non-cancer patients [16]. In cases with brain stroke, different cancers are prevalent where lung cancer is the most frequent cancer followed by gastric and colorectal cancers [9].

D-Dimer is the final product of plasma generated due to the destruction of fibrin-rich clots. It increases during disease due to the increased probability of thrombosis and degradation of thrombus. It is used to reject venous thromboembolism (VTE) in diagnosis algorithms. The level of D-Dimer is especially advantageous to other generations of thrombin due to its resistance to the inductions of laboratory environment and having long-term half-life [1, 21]. D-Dimer is separated from plasmin in several stages of fibrin degradation. Therefore, the concentration of D-Dimer indicates the rate of fibrin circulation in blood [22].

Previous studies state that any moderate increase in D-Dimer level indicates increased coagulation, generation of thrombin and increased intravascular circulation of fibrin [23]. Moreover, increased level of D-Dimer associates with the thrombosis of cerebral sinus, pulmonary embolism and intracerebral auto-hemorrhage [24]. Malignancy can result in hyper-coagulation. Therefore, considering the recent measurements of D-Dimer level, it has been used to express the hidden malignancies in cases with ischemic stroke [24, 25]. To this end, we decided to design a paper enabling us to study D-Dimer and FDP serum levels in ischemic stroke cases with and without underlying malignancy.

Method of Study

This is a quasi-experimental study. Sampling was conducted via convenience sampling method where samples were selected among patients admitted in the neurology department of Imam Khomeini teaching-treatment hospital in Urmia. This was a case-control study where all cases admitted in the neurology department of Imam Khomeini hospital included sequentially to the study after obtaining their verbal consent and explaining situation to them.

Cases with underlying malignancy were grouped in case group while those with no malignancy were included in control group. All cases underwent ischemic stroke treatment according to treatment protocols.

To avoid the effect of interfering factors such as consuming heparin and enoxaparin or in the case of using thrombolytic drugs, the measurement of the level of D-Dimer, FDP, ESR and CRP was requested in their primary tests. A total number of 60 and 120 cases were studied in case and control groups respectively in accordance with previous studies.
Inclusion Criteria for the Case Group
- Ischemic stroke cases
- Cases with underlying malignancy

Exclusion Criteria for the Case Group
- Diseases affecting the study such as rheumatologic diseases, auto-immune disease and so on
- Hemorrhagic stroke
- Receiving thrombolytic medicines in recent days
- Cardiovascular diseases affecting the studied factors

Inclusion Criteria for the Control Group
- Ischemic stroke cases
- No background in malignancy

Exclusion Criteria for the Control Group
- Diseases affecting the study such as rheumatologic diseases, auto-immune disease and so on
- Hemorrhagic stroke
- Receiving thrombolytic medicines in recent days
- Cardiovascular diseases affecting the studied factors

After studying the clinical records of cases, the studied data was recorded in the researcher-made questionnaire and was analyzed using SPSS 20.

**Results**

This study assessed 60 patients with confirmed underlying malignancy in the case group and 120 patients in the control group. Of 60 cases with underlying malignancy, 24 cases (40%) were male and 36 cases (60%) were female. Similarly, of 120 control cases, 63 cases (52.5%) were male and 57 cases (47.5%) were female. According to Fisher exact test, there is no significant difference in sex between the case and control groups (p-value=0.07).

### Table 1: Absolute and relative frequency of sex in cases with and without malignancy

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>With malignancy (case group)</td>
<td>24 (40%)</td>
<td>36 (60%)</td>
</tr>
<tr>
<td>Without malignancy (control group)</td>
<td>63 (52.5%)</td>
<td>57 (47.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>87 (48.3%)</td>
<td>93 (51.7%)</td>
</tr>
</tbody>
</table>

The mean age of malignant cases was 53.95±18.04 while that of non-malignant cases was 60.10±13.40. According to independent t-test results, there is a significant difference in age between malignant and non-malignant cases (p-value=0.02)

The mean D-Dimer in the case group was 1.10±1.11 while that of control group was 0.74±0.77. According to t-test results, there is a significant difference in D-Dimer level between the case and control groups (P-value=0.01)

### Table 2: Comparison of the mean and standard deviation of D-Dimer in the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean±standard deviation of D-Dimer</td>
<td>1.10±1.11</td>
<td>0.74±0.77</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The mean FDP in the case and control groups was 16.76±12.93 and 12.36±12.27, respectively. According to independent t-test results, there is a significant difference in FDP level between the studied groups (p-value=0.02)

### Table 3: Comparison of the mean and standard deviation of FDP in the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean±standard deviation of FDP</td>
<td>16.76±12.93</td>
<td>12.36±12.27</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Of 60 cases of the case group, 7 cases (11.7%) had malignant brain tumor, 3 cases (5%) had colon cancer, 6 cases (10%) had thyroid cancer, 12 cases (11.7%) had gastric cancer, 19 cases (31.7%) had lung cancer, 10 cases (16.6%) had breast cancer and 3 cases (5%) had kidney cancer.
The evaluation of different risk factors revealed that of 60 studied cases in the case group, 17 cases (28.3%) had diabetes mellitus, 20 cases (33.4%) had hyperlipidemia and 18 cases (30%) had hypertension. In 5 cases (8.3%) none of the risk factors was reported.

The mean ESR in the case group was 39.88±32.14 while in the control group it was 27.73±32.38. According to independent t-test results, there is a significant difference in ESR level between the studied groups (p-value=0.01).

### Table 4: Comparison of the mean and standard deviation of ESR in the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean±standard deviation of ESR</td>
<td>39.88±32.14</td>
<td>27.73±32.38</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The mean CRP in the case and control groups was 2.30±0.83 and 2.02±0.54, respectively. According to independent t-test results, there is a significant difference in CRP level between the studied groups (p-value=0.01).

### Table 5: Comparison of the mean and standard deviation of CRP in the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean±standard deviation of CRP</td>
<td>2.30±0.83</td>
<td>2.02±0.54</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Discussion

Cancer and ischemic brain stroke are two leading cause of death between aged population and reports have confirmed the relation between them. In cases with active cancer, the incidence of thromboembolic events such as deep vein thrombosis (DVT), pulmonary embolism and brain and heart stroke increases [26].

This study assessed 60 malignant cases with ischemic stroke where the number of malignant females (60%) was higher than malignant males. In addition, the mean age of the studied malignant cases was below 60. The mean D-Dimer level in malignant and non-malignant cases was 1.10±1.11 and 0.74±0.77 mg/l, respectively.

This agrees with the results of Guo et al [25] where the D-Dimer level in cancer cases was higher than non-cancer cases. Another case-control study revealed that the incidence of thromboembolic events is higher in cancer patients than non-cancer ones [27].

Cestari et al [28] showed in their study that D-Dimer increases in embolic stroke and cancer patients and it is a prevalent factor. This agrees with our study in terms of D-Dimer level. Another comparative study showed that the CRP and D-Dimer inflammation indices are higher in stroke cases with cancer than stroke cases without cancer [18].

A retrospective study concluded that there is no significant difference in sex, type of cancer, vascular factors, recent chemotherapy and D-Dimer level between patients with cancer and ischemic brain stroke and patients with no stroke [29]. On the other hand, a study showed that in aged ischemic brain stroke patients with smoking background and increased coagulation factors (D-Dimer and fibrinogen) and CRP, an underlying cancer should be traced [30].

A retrospective study concluded that the increased blood coagulation in cancer patients is the most frequent cause of stroke in such patients. In addition, the mortality rate in such patients was 46.9% in and the remained half of the studied patients showed a weak function which was not associated with the type and stage of cancer [31].

Our study showed the increased level of FDP, CPR, ESR and D-Dimer in stroke patients with malignancy compared with those with no malignancy and the difference is significant.

Our study reported lung cancer, gastric cancer, thyroid cancer as the most frequent cancers in ischemic stroke patients with malignancy. Previous studies reported lung cancer as the most frequent cancer in stroke patients [9].
A Cohort study revealed that age, hypertension, hyperlipidemia, atrial fibrillation, major surgeries and gastric cancer are risk factors of ischemic stroke in patients with gastric cancer [32].

The early diagnosis of brain stroke mechanisms in cancer patients is of high importance because they are different between brain stroke patients with cancer and those with no cancer. It can be conclude from the findings of this study, and previous studies, that D-Dimer and ESR level increases in ischemic stroke patients and several risk factors such as diabetes mellitus, hyperlipidemia and hypertension are frequent in such patients. This is why the chance of ischemic stroke in such cases is higher than cases with no malignancy. Therefore, our respectful colleagues are recommended to identify the mechanisms, type and stage of cancer and relevant risk factors (diabetes mellitus, hyperlipidemia and so on) in cancer patients in future studies.

References


