Relation of High Plasma Fibrinogen Level in Stroke

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ABSTRACT

INTRODUCTION: Fibrinogen has emerged as an important contributor in the development of coronary, peripheral and cerebral vascular disease due to its involvement in both atherogenesis and thrombosis. The objective of this study was to assess plasma fibrinogen level in ischaemic and haemorrhagic stroke.

METHODS: This is a cross sectional case control study of stroke patients. 40 cases of stroke (Ischaemic and haemorrhagic) with the history of sudden loss of consciousness and weakness, were taken as case and admitted consecutively in medical ward of Bir Hospital through emergency department. Similarly 40 cases, without history of strokes were included as control group from OPD. Blood sample were taken within 24 hour of stroke. The study period was 1 year, from July 2006 to July 2007.

RESULTS: In this study, high plasma fibrinogen level was found in 32 (80%) patients in stroke and 11 (27.5%) in control group, with the P value is <0.001. Among the stroke, there were 55% ischaemic stroke and 45% haemorrhagic stroke. The mean value of fibrinogen level in ischaemic stroke is 441 mg where as in haemorrhagic stroke is 384 mg.

CONCLUSION: High plasma fibrinogen concentration is a risk factor for stroke, due to its involvement in both atherogenesis and thrombosis. Incidence of ischaemic stroke is high if the level of fibrinogen is increased more than normal value.

KEY WORDS: Stroke, plasma fibrinogen

INTRODUCTION

Fibrinogen or coagulation factor I, is a large fibrous glycoprotein present in plasma at a concentration ranging between 200-400 mg/dl. Fibrinogen, the precursor of fibrin, plays a major role in haemostatic. Conversely inappropriate activation of haemostatic function within the vasculature may endangers life if vessels such as the coronary or cerebral artery are occluded by a thrombus. Fibrinogen is a coagulant and if it is high, significantly increase the risk of stroke. High blood pressure and high fibrinogen levels appeared to be the most dangerous combination, elevating a person’s risk of stroke even more.

Plasma fibrinogen is an important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow. Increasing evidence from epidemiological studies suggests that elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular disorders, including ischaemic heart disease (IHD), stroke and other thromboembolism.

The concentration of plasma fibrinogen is regulated by both genetic and environmental influences. Factors that are positively associated with plasma fibrinogen include age, female gender, smoking, stress, obesity, menopause, oral contraceptives, LDL, cholesterol (Folsom, 1995; Folsom et al., 1991; Moller & Kristensen, 1991). Fibrinogen and its derivatives have...
been shown to be involved in the initiation and growth of atherosclerotic lesions. The coagulation protein fibrinogen has emerged as an important contributor in the development of coronary, peripheral and cerebral vascular disease due to its involvement in both atherogenesis and thrombosis.\

Large-scale epidemiological studies have consistently demonstrated that an increased fibrinogen concentration is an independent risk factor for future cardiovascular events.\

It is well established that raised levels of fibrinogen increase the risk of coronary heart disease. For stroke, however, data are much more limited and restricted to overall stroke.

**METHODS**

This is a cross sectional case control study of stroke patients. 40 cases of stroke (Ischaemic and haemorrhagic) with the history of sudden loss of consciousness and weakness, were taken as case and admitted consecutively in medical ward of Bir Hospital through emergency department. Similarly 40 cases, without history of strokes were included as control group from OPD. Blood sample were taken within 24 hour of stroke. The study period was 1 year, from July 2006 to July 2007.

Patients presenting in emergency departments with signs and symptoms of stroke (loss of consciousness, weakness, disturbance in speech and language) included in this study, after taking informed consent. Patients were admitted within 24 hours of development of symptoms, suggestive of stroke, and only CT Scan proved stroke patients were included in this study. Thorough clinical examinations were done for screening from other diseases. Basic investigations carried out in the following manner according to the need. Non consenting patients, patients with renal failure (uremia), infection, active hepatic disease, severe dehydration, myocardial infarction and surgery within past 3 month were excluded because it may alter the level of fibrinogen concentration.

**RESULTS**

All the cases were followed up in the medical ward of the hospital till the end points, which were either death of the patients or discharge from the hospital.

In this study, high plasma fibrinogen level in stroke found in 32 (80%) patient and 11(27.5%) in control group. The P value is <0.001.

**Table 1: Distribution of fibrinogen level in stroke patients and control group**

<table>
<thead>
<tr>
<th>Fibrinogen (mg/dl)</th>
<th>Case</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8(20%)</td>
<td>29(72.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>32(80%)</td>
<td>11(27.5%)</td>
<td></td>
</tr>
</tbody>
</table>

In descriptive analysis of the plasma fibrinogen level, in stroke group, the minimum level of fibrinogen is 248 and the maximum level is 570. The mean value of the fibrinogen level is 446.5 with the standard deviation 66.24. Similarly in the control group the minimum plasma fibrinogen level is 168 and the maximum level is 540. The mean value of fibrinogen is 366.28 with stander deviation 95.62. The 95% confidence interval for mean lower bound 425.32 and upper bound 467.68 in stroke where as 335.7 and 396.85 in control group showing the P value <0.001.

**Table 2: Distribution of fibrinogen level in stroke patients and control group**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Group</th>
<th>No</th>
<th>Min.</th>
<th>Max</th>
<th>Mean</th>
<th>S. D</th>
<th>95% Confidence Interval for Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>Case</td>
<td>40</td>
<td>248</td>
<td>570</td>
<td>446.50</td>
<td>66.24</td>
<td>Lower Bound: 425.32, Upper Bound: 467.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>40</td>
<td>168</td>
<td>540</td>
<td>366.28</td>
<td>95.62</td>
<td>Lower Bound: 335.70, Upper Bound: 396.85</td>
<td></td>
</tr>
</tbody>
</table>

Among the stroke, there were 55% ischaemic stroke and 45% haemorrhagic stroke. Out of them there were 2 and 7 mortality in respective group.
Table 4: Fibrinogen level according to type of stroke

<table>
<thead>
<tr>
<th>Stroke</th>
<th>ischaemic stroke</th>
<th>haemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen level (mg)</td>
<td>Min.</td>
<td>Max.</td>
</tr>
<tr>
<td></td>
<td>312</td>
<td>570</td>
</tr>
</tbody>
</table>

The minimum level of fibrinogen in ischaemic stroke is 312 mg and maximum is 570 mg with mean value 441 mg. Similarly in haemorrhagic stroke, the minimum level is 248 mg and maximum is 520 mg with the mean value 384 mg which shows that high level of fibrinogen has tendency of causing ischaemic stroke.

There were 30 patients with smoking habit in the stroke group. Among them 22 patients (73.3%) had high fibrinogen level. There were 25 patients with smoking habit in control group and only 8 patients (32%) had high plasma fibrinogen level.

In this study, there were 33 hypertensive patients in stroke patients and out of which 27 (81.8%) patients had high plasma fibrinogen level. Similarly in control group 29 patients were hypertensive and only 9 (31%) patients had high plasma fibrinogen level.

**DISCUSSION**

Fibrinogen and its derivatives have been shown to be involved in the initiation and growth of atherosclerotic lesions. The coagulation protein fibrinogen has emerged as an important contributor in the development of coronary, peripheral and cerebral vascular disease due to its involvement in both atherogenesis and thrombosis. Large-scale epidemiological studies have consistently demonstrated that an increased fibrinogen concentration is an independent risk factor for future cardiovascular events.\(^5\)

Stroke is the commonest life threatening neurological disease requiring hospitalization and stands out as one of the most important cause of mortality and severe disability. It is the second commonest cause of the mortality after coronary heart disease worldwide. In Bir Hospital, Nepal, stroke comes among the three most common diseases admitted in the medical ward and common cause of mortality.\(^6\)

The Framingham Study provided detailed analyses of the inter-relation of fibrinogen with smoking and cardiovascular disease and estimated that 50% of the cardiovascular harm caused by chronic smoking is mediated through its effect of increasing fibrinogen.\(^7\)

Fibrinogen levels are higher in patients with hypertension than in normotensive similarly, plasma viscosity is elevated in hypertensive persons, and blood pressure readings are positively correlated with this variable. Even when hypertension is mild, fibrinogen levels are higher than in normotensive. The Framingham data revealed a correlation between blood sugar levels and fibrinogen. Fasting glucose also correlates with fibrinogen in non-diabetic persons.

In this study, majority of the patients were ischaemic stroke 22 (55%). Though one patient had normal CT scan finding, it was considered as ischaemic as there may be chance to became infarction after 24 hours. Most of the other studies also have shown the prevalence of the ischaemic stroke. According to the Bomford J. and Gubitz G., about 80% of all acute strokes are caused by cerebral infarction, usually resulting from thrombotic or embolic occlusion of a cerebral artery.\(^8,9\) A retrospective review, from the Tribhuvan University Teaching hospital showed that the total number of stroke patients admitted in four years was 683, out of which 434 (63%) were ischaemic and 249 (37%) haemorrhagic.\(^10\)

In this study, high plasma fibrinogen level in stroke was found in 32 (80%) patient and 11 (27.5%) in that of control group. The P value is <0.001. The result is supported by other number of studies. Hazra B et al carried a study showing that an elevated plasma fibrinogen level may be an important risk factor for thrombotic strokes.\(^11\) Mistry et al found the level of fibrinogen to be significantly higher in stroke as compared to those of controlled group.\(^12\)

Similarly, Kumar AR et al showed that plasma fibrinogen level high in patients with ischaemic as well as haemorrhagic strokes (more in ischemic stroke), characteristically increasing with the age. Elevated fibrinogen levels were seen in association with hypertension, smoking and diabetic mellitus in compare to non hypertensive, non smoker and non diabetic.\(^13\)

Finding of our study regarding high plasma fibrinogen were similar to those reported by Wilhelmsen and coworkers, and Kannel and coworkers.\(^14,15\) They analyzed among 202 stroke events extends these findings by showing that a raised level of fibrinogen is associated with an increased risk of fatal and non-fatal stroke.\(^5,7\)
In our study, male were suffering from stroke more than female. The significant male prevalence may be due to the risk factors for the stroke like hypertension, smoking, which are more prevalence in the male population. Similarly maximum number of the stroke cases were above the age group 64-74 years i.e. 27.5%. This is similar finding of other hospital and community base study.

Di Napoli M. et al in their study showed that long-term studies of apparently healthy individuals have shown that increased fibrinogen levels are important factor in future cardiovascular events. Fibrinogen indicates an inflammatory condition in ischemic stroke. Other signs of inflammation in ischemic stroke include increased levels of inflammatory cytokines and C-reactive protein. In multiple logistic regression analysis, higher CRP levels and stroke severity on the Canadian Neurological Stroke Scale were independently associated with death or a new vascular event. The authors concluded that increased levels of CRP are associated with the worst outcome in patients with ischemic stroke.

There are several explanations for the differences in fibrinogen levels between stroke patients and controls being highly significant shortly after the event but mostly in apparent after three months. Fibrinogen concentrations increase as a result of an acute phase reaction, which might explain the higher fibrinogen levels in patients one week after the stroke. This is supported by concomitant changes in C reactive protein. Secondly, other cardiovascular risk factors are associated with higher fibrinogen levels and advancedatherosclerosis.

Fibrinogen levels peak after an acute stroke. An earlylongitudinal trial depicted the time course of these changes and showed that fibrinogen was excessively high in those patients who later died of the disease. In the past, the phenomenon has been attributed almost exclusively to an acute-phase reaction due to brain tissue necrosis. However, plasma viscosity and fibrinogen are significantly increased in patients with transitoryischemic attacks, suggesting that fibrinogen levels are elevated before the stroke.

In the Gothenburg Study, univariate analyses identified smoking, cholesterol, and fibrinogen as risk factors for ischemic heart disease, where as blood pressure and fibrinogen were risk factors for stroke. In a multivariate analysis (adjusting for blood pressure, cholesterol, and smoking), the association between fibrinogen and cardiovascular disease was weaker but still statistically significant for stroke. Fibrinogen was again positively associated with the incidence of ischemic heart disease in a univariate analysis, whereas in the multivariate analysis, stroke and total mortality rate were statistically associated with fibrinogen.

Though Shinishi S. et al did not find a positive association between fibrinogen and risk of ischemic stroke, Moreover, high levels of C-reactive protein were associated with increased risk of both ischemic stroke and coronary heart disease. These findings suggest that the role of fibrinogen as a clotting factor or a marker of inflammation may be less important in the pathogenesis of ischemic stroke. Other factors such as hypertension may be strong determinants. In this meta-analysis has shown a weaker but significant association between fibrinogen levels and ischemic stroke, compared with that of coronary heart disease althoughno single study has reported a significant association with ischemic stroke.

One limitation of the current study is the small number and we think this study should need further evaluation in future. However; we observed positive associations between fibrinogen and risk of stroke. We did not measure other markers of inflammation, such as C-reactive protein, which may increase with fibrinogen as predictors of arteriosclerosis. Lastly we did not measure plasma fibrinogen concentrations repeatedly after baseline. The single baseline measurement may lead to regression dilution bias and underestimate the strength of associations.

**CONCLUSION**

As there is high fibrinogen level in 80% stroke patient, which is associated with the increased risk factor like smoking (only 10 non smoker patients had high fibrinogen) and hypertension (only 5 normotensive patient had high fibrinogen), high plasma fibrinogen concentration is a risk factor for stroke, due to its involvement in both atherogenesis and thrombosis. Incidence of ischaemic strokes high if the level of fibrinogen is increased more than normal value.
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