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ORIGINAL ARTICLE

Leukocytosis after routine cranial surgery: A potential marker for brain damage in intracranial surgery

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ABSTRACT

Aims and Objectives: Leukocytosis after intracranial surgery may create concern about possible infection, especially when associated with fever. Knowledge of the expected degree of leukocytosis after surgery would assist in the interpretation of leukocytosis. It was hypothesized that the degree of leukocytosis after intracranial surgery correlated with the extent of brain damage inflicted during the surgery.

Materials and Methods: In this prospective study conducted over 6 months, consecutive patients undergoing either elective resections of brain tumors (having significant collateral brain damage) or aneurysm clipping (with minimal collateral brain damage) were studied. Total blood leukocyte count was checked daily in the morning for the first five postoperative days in both the groups. The mean of the leukocyte count ratio (postoperative leukocyte count/preoperative leukocyte count) on each day was calculated for each group.

Results: There were 76 patients, 46 in the test group and 30 controls. Both groups were well matched in age, sex, duration of surgery, and intraoperative fluid balance. The mean leukocyte count ratio on POD1 in the tumor group was significantly higher (1.87) as compared to 1.1 in the aneurysm group ($P = 0.001$). This difference in the leukocyte count ratio between the groups was maintained on the second and third postoperative days, with decreasing level of significance after the third day.

Conclusions: This study shows that intraoperative brain injury is associated with leukocytosis in the immediate postoperative period. This can assist in the interpretation of leukocytosis after intracranial surgeries and could be a quantitative marker for brain injury in patients undergoing intracranial surgery.

Key words: Brain damage, brain injury, brain tumor, intracranial surgery, leukemoid reaction, leukocytosis, marker, total leukocyte count

Introduction

In no other discipline does the outcome depend on the skill and knowledge of the surgeon as much as in Neurosurgery. Brain has an extremely low tolerance for trauma and even minimal brain handling during surgery can lead to radiologically evident complications such as brain edema, venous engorgement, and venous infarcts.[1-7] However, there are no markers to assess the magnitude of intraoperative brain injury in routine cranial surgeries. In our experience, marked leukocytosis is seen in the immediate postoperative period following major intracranial surgeries. In fact, leukocytosis as high as 50,000/mm^3 is routinely seen in the postoperative period following hemispherectomy for intractable epilepsy. This has previously raised concerns about possible infection, especially when associated with fever, although an infective cause was rarely found. We, therefore, hypothesized that the degree of leukocytosis after intracranial surgery could correlate with the extent of brain damage inflicted during the surgery. This study was, therefore, designed to explore the role of postoperative leukocyte counts as a potential marker for intraoperative brain damage.

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Materials and Methods

This was a prospective controlled study carried out in the Department of Neurosurgery, All India Institute of Medical Sciences, over a 6-month period. Informed consent was taken

from all patients for participation in the study. Consecutive patients undergoing routine major cranial surgery during the study period were enrolled into the study. Patients who underwent minor procedures like biopsies, shunt placement, and stereotactic procedures or surgery for an infective pathology (e.g. abscess) were excluded from the study. Patients with diabetes or with liver diseases, immunodeficiency syndromes, leukemia, and lymphoma were also excluded. Patients who developed infection(s) in the immediate postoperative period were also excluded from the study. An immediate postoperative infection was defined as culture positivity in urine, CSF, or tracheal secretions within 5 days of surgery.

Patients were divided into two groups based on the probability of collateral brain injury during surgery. The control group consisted of patients undergoing aneurysm surgery (where collateral brain damage during surgery is thought to be minimal) and the test group consisted of patients undergoing surgery for intra-axial brain tumors (where significant collateral brain damage may occur). Intraoperative parameters like fluid balance, blood loss, and blood transfusions were recorded along with the duration of surgery in minutes. Use of steroids and their duration of use preoperatively were also recorded for all the groups. All patients in the control (aneurysm) group were operated by the same surgeon (BSS).

In all patients, a peripheral blood sample was taken 24 h prior to surgery and leukocytosis measured. The blood was subsequently sampled for leukocyte count in the morning following the surgery (POD1) and every 24 h thereafter for a total of five postoperative days (POD1-POD5). All leukocyte counts were done in the same lab on an electronic leukocyte counter and the values were recorded.

As patients had widely varying preoperative (baseline) leukocyte counts, the ratio of leukocyte count on POD1/leukocyte count preoperative was calculated and similarly derived for each postoperative day (POD1-POD5). The mean of the leukocyte count ratio (postoperative leukocyte count/preoperative leukocyte count) on each day was calculated for each group.

Statistical analysis

All data were recorded in Microsoft Excel spread sheet and analyzed using SPSS version 11.5. The continuous variables were analyzed using one-way ANOVA, and Student's *t*-test was applied for comparison of means. Analysis of repeated measures and adjusted analysis was done whenever necessary.

Results

A total of 76 patients were enrolled during the study period. There were 46 patients in the test (tumor) group and 30 patients in the control (aneurysm) group [Table 1]. Both groups were found to be well matched in age and sex [Table 2]. The duration of surgery, intraoperative fluid balance, and mean hospital stay were also comparable between the two groups [Table 3]. Thirty-eight of 46 patients in the test group received steroids for a mean of 16 days (range 3-92 days) in the preoperative period, while none in the test group received preoperative steroids.

Mean preoperative leukocyte counts were well matched between the control group (11,070/mm^3) and the test group (9831/mm^3) [Tables 4 and 5]. Multivariate analysis showed leukocyte count ratio as the only significant variable between the two groups. The *mean leukocyte count ratio* on POD1 in the test group was 1.87 compared to 1.1 in the control group group ($P = 0.001$) [Figure 1]. This difference in the leukocyte count ratio between the groups was maintained on first and second postoperative days with decreasing level

Table 1: Preoperative diagnoses in the test (tumor) group

Primary diagnosis	Number of patients
Gliomas	21
Post fossa tumors	7
Others	18

Table 2: Demographic profile of patients

Parameters	Test (tumor) group	Control (aneurysm) group	*P* value
Number of patients	46	30	0.15
Mean age	34.2	43.60	0.28
Sex (m/f)	30/16	16/14	0.34
Preoperative steroids	38	00	NA

Table 3: Intraoperative characteristics in both groups

Intraoperative parameter	Test (tumor) group	Control (aneurysm) group	*P* value
Mean operative time (min)	253	247	0.39
Mean input (ml)	3853	4140	0.42
Mean output (ml)	1492	1663	0.38
Mean blood loss (ml)	821	475	0.10

Table 4: Total leukocyte values and characteristics in the control (aneurysm) group

Postoperative days	Blood total leukocyte count values	Ratios (TLC: Preoperative TLC)	Difference (TLC: Preoperative TLC)
Day 0	11,070±3390	1.00±0.00	00
Day 1	11,640±4471	1.10±0.53	570
Day 2	12,983±7819	1.24±0.76	1913
Day 3	13,130±7705	1.27±0.81	2060
Day 4	11,856±6454	1.17±0.65	786
Day 5	11,300±5455	1.13±0.66	230

TLC – Total leukocyte count

of significance ($P = 0.007$) and no statistically significant difference after the third day ($P = 0.1$) [Tables 4 and 5].

Discussion

Recent research has focused on the functional impairment following "minimal" trauma to the brain. Indeed, it has been shown that even minor concussions can lead to life-long cognitive impairment.[2] It is of no surprise that neurosurgeons over the ages have attempted to decrease the amount of damage to the brain while operating upon it. However, objective markers for brain injury are not available at present. Radiological markers are only visible if there are major morphological changes in the brain in the form of brain bulge, edema, mid-line shift, and mass effect. Because of these limitations, the clinical outcome of the patient is taken as a measure of "brain handling" during surgery, which can be argued to be a surrogate measure of the surgical skill of the surgeon. (Yasargil is considered one of the greatest neurosurgeons because he managed to minimize collateral damage to the normal brain while operating). However, even in patients with the so-called "excellent outcome," detailed neuropsychological assessment usually shows subtle cognitive impairment attributed to brain handling during surgery. The International Subarachnoid Aneurysm Trial (ISAT) clearly showed that the "minimal" brain handling which occurs in aneurysmal surgery leads to long-term cognitive impairment as compared to embolization (where there is no brain handling). It is common knowledge that aneurysm clipping by an expert neurosurgeon involves minimal collateral brain injury as compared to operating intrinsic brain tumors where more collateral brain injury is expected. We, therefore, divided patients into two groups based on the probability of collateral brain injury during surgery. We selected aneurysm surgeries as the control group as the surgical exposure is almost the same as craniotomy for intra-axial tumors with minimal collateral brain injury, and hence served as a good control group. In our previous experience too, significant leukocytosis was found to occur following surgeries where extensive collateral brain injury occurred. Another reason for selecting aneurysm and intrinsic brain tumors for the two groups was that these patients were found to match in various parameters like duration of surgery, intraoperative fluid balance, blood transfusions, and hospital stay.

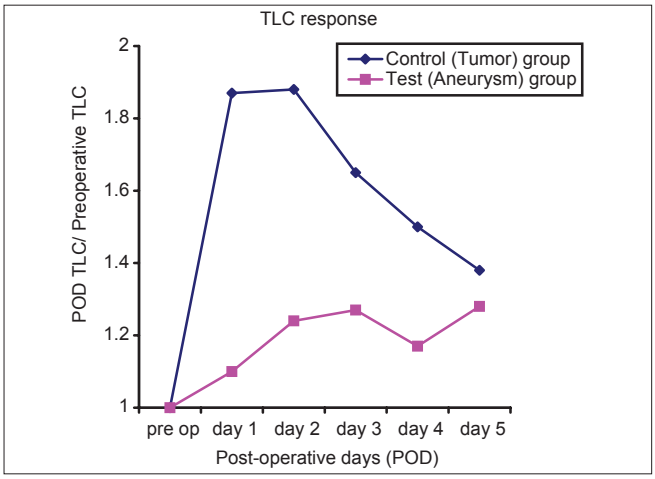

Figure 1: Ratios of blood-leukocyte count against the preoperative leukocyte count value for the respective days

Table 5: Total leukocyte values and characteristics in the test (tumor) group

Postoperative days	TLC values	Ratios (TLC: preoperative TLC)	Difference (TLC-preoperative TLC)
Day 0	9831±3761	1.0±00	00
Day 1	16,610±7377	1.87±1.0	6779
Day 2	16,547±5904	1.88±0.97	6716
Day 3	14,339±4904	1.65±0.87	4507
Day 4	12,889±3762	1.50±0.75	3057
Day 5	11,873±3230	1.38±0.69	2042

TLC – Total leukocyte count

Total leukocyte count is often considered a marker for acute inflammation, and its bulk is constituted by neutrophils. Under normal conditions, more than 90% of neutrophils are in the bone marrow, only 2-3% in the circulation, and rest in the tissues. Half-life of neutrophils is about 7 h.[8] Whenever noxious stimuli are given, cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), colony stimulating factors, compliment fragments, and perhaps the other cytokines are secreted locally causing the recruitment of neutrophils, increasing their percentage in blood and tissues.[8] Thus, leukocytosis observed in these acute conditions is mainly neutrophilic leukocytosis. Whenever there is tissue trauma, local cytokines are released and they cause the redistribution of neutrophils between tissues, marrow, and peripheral circulation, causing leukocytosis.[8] Whenever there is breach in blood–brain barrier and brain parenchymal injury, microglial cells get activated, along with accumulation of pro-inflammatory substances from the blood, and cause an immunogenic response.[9] The levels of cytokines including interleukins and TNF-α thus produced have been found to corre late with the extent of brain injury.[3,7] We similarly hypothesized that brain tumor surgery damages the blood–brain barrier and can cause an inflammatory reaction of the immune system against the brain and the tumor cells, which could also lead to leukocytosis. Aneurysm surgery does not lead to such significant brain barrier damage, and therefore leukocyte count does not rise significantly.

The only confounding factor between the groups was the perioperative use of steroids which were used in almost all cases of the test group and were never used in the control group. Interestingly, even with extensive use of steroids in the test (tumor) group, the *preoperative* (POD0) leukocyte count was actually higher (though not statistically significant)

in the control (aneurysm) group. This is despite the fact that peroperative steroids had been given for a mean period of 16 days in the test group, which would be considered a sufficient period for eliciting leukocytic response (if any) due to steroids. We, therefore, believe that steroids did not contribute to the leukocytosis seen in the immediate postoperative period in operated brain tumor patients and this response is secondary to iatrogenic brain injury.

Gliomas are known to produce immunodepression by releasing anti-inflammatory cytokines like IL-10, and soluble factors which have been reported earlier.[10] There were decreased levels of eosinophilic granules and T-helper cells, but higher levels of IgM in the glioma patients, compared to other neoplasms, thus depressing the cellular immunity. In our study, fair variability of tumors [Table 4] has eliminated this likely bias. As shown in Figure 1, leukocyte count values in the test (tumor) group attained their peak on day 1 and then gradually returned to the baseline over a period of 5 days. The peak value of leukocyte count was almost double that of the preoperative value, indicating the acute inflammatory response due to intraoperative brain handling and insult. However, in the controls (aneurysm group), the leukocyte count increased only marginally on the first two postoperative days and remained near baseline over the next three postoperative days.

Excessive brain parenchymal handling or retraction while operation can lead to venous infarcts, venous insufficiencies, postoperative brain edema, and raised intracranial pressure.[11] Search has always been made for a good marker, which can reliably detect the extent of brain parenchymal injury in the postoperative period, so as to predict the outcome and anticipate the complications. Quatocchi has shown decreased production of IL-2 in post head injury patients causing generalized depression of cellular immunity.[12] Suppressor lymphocytes and soluble mediators were held responsible for immunodepression. In another similar study, the same author reported that the cellular arm of immune response, including lymphocyte activation and cytokine production, is suppressed following severe head injury.[11] Another study on head injury patients by Smrcka *et al.* has shown the same findings of depressed cellular immunity in post-trauma patients.[13] This was supposed to be caused due to decreased expression of monocyte DR antigen, and thus the antigen presenting capacity of monocytes. However, none of the studies have dealt with the reasons behind the depressed cellular immunity and also did not assess the acute phase systemic inflammatory response. In our study, we excluded patients who had any documented source of infection within the first 5 days of surgery so as to remove any bias from infection being a cause of leukocytosis.

A good biomarker should satisfy following criteria: (i) should originate in the central nervous system (CNS) with no contribution from extracerebral sources; (ii) should be passively released from damaged neurons and/or glial cells without any stimulated active release; (iii) lack specific effects on neurons and/or glial cells interfering with the initial injury; and (iv) should have unlimited passage through the blood–brain barrier.[6] Serum S-100B and interleukin C have been studied as possible markers for brain damage in head injury and stroke, respectively. Serum S-100B protein, a recent focus of research, as reported in many studies is found to correlate better with the brain injury in brain trauma patients.[1,5] Sawauchi *et al.* have shown that serum S-100B provides clinical assessment of damage and predicts the outcome in traumatic brain injury.[5] However, it has not been studied in tumor surgery in detail. Infarct in cerebrovascular episodes is also associated with disruption of blood–brain barrier, and Smith reported the marker value of IL-6 and C-reactive protein (CRP) in ischemic strokes.[3] He found that IL-6 increased after stroke and CRP values correlate with the infarct volume, stroke severity, and long-term outcome. In another study, he reported that acute phase reactants like IL-6 and CRP are increased in acute stroke and concluded that acute brain injury is a major determinant of the magnitude and variability of acute phase response.[7] It is possible that previous investigators have been barking up the wrong tree and that irrespective of etiology – traumatic, stroke, or iatrogenic – the primary pathology is brain damage which results in a similar cascade of immunogenic and cytogenic responses and is primarily dependent on the quantum of the brain tissue damaged.

Although leukocyte count is by no means the ideal biomarker, our study shows that it can be used as a bedside assessment to evaluate and quantify the brain injury occurring after intracranial surgery and can have immense utility in the day-to-day neurosurgical care. Further studies may be done in head injury and stroke patients to see if our findings can also be replicated in these groups of patients.

Conclusions

Leukocyte count in the postoperative period is found to correlate well with the extent of iatrogenic brain injury during surgery. It peaks on the first postoperative day and gradually returns to the baseline over a period of 4-5 days. It may serve as a good marker for the extent of brain parenchymal injury in the early postoperative period. This study also shows that leukocyte counts done in the postoperative period can be fallaciously high in cases with iatrogenic brain parenchymal injury and should be cautiously interpreted with respect to diagnosis of infection and sepsis.

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