

Perioperative concerns in neurosurgical patients with human immunodeficiency virus infection

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ABSTRACT

Background: The perioperative management of human immunodeficiency virus (HIV) infected patients undergoing neurosurgery is challenging due to the presence of HIV-related multi-system derangements, opportunistic infections and malignancies, history of substance abuse, and adverse effects of anti-retroviral therapy (ART), together with the inherent risks of neurosurgery. The possible adverse impact of HIV disease on the anesthetic outcome due to the associated co-morbidities, and conversely, the role of surgery and anesthesia in HIV disease progression due to their immunosuppressive effects, and also, the fear of HIV transmission among the attending medical personnel are the important perioperative concerns in such surgeries.

Aim: To present our experience in the perioperative management of HIV-infected patients who underwent neurosurgery at our institute in the past 5 years and highlight the relevant perioperative issues.

Materials and Methods: A retrospective analysis of the records of HIV-infected neurosurgical patients was undertaken to determine their HIV status and ART, anesthesia and surgery details, perioperative complications, and instances of postoperative worsening of HIV disease or its transmission, if any.

Results: Seven HIV infected patients with variable severity of HIV infection and systemic disease underwent neurosurgery for different indications. Their perioperative management was modified in accordance with the co-morbidities and the type of neurosurgery. There was no obvious adverse impact of the HIV disease on the anesthetic outcome, no obvious clinical evidence of post-surgery worsening of the HIV disease, and no instance of HIV transmission in our patients.

Conclusion: A good understanding of the HIV disease and its perioperative implications during neurosurgery helps in better patient management and enables a safe outcome.

Key words: Anesthetic considerations, anesthetic outcome, human immunodeficiency virus, neurosurgery, perioperative concerns

Introduction

The global population of patients infected with human immunodeficiency virus (HIV) is rising significantly with a reported estimate in 2009 of 40 million patients worldwide and 5.2 million in India.^[1] HIV disease progresses from an

asymptomatic seropositive state to the serious Acquired Immunodeficiency Syndrome (AIDS) in about 10 years, leading to severe multi-system derangements, wasting syndrome, fulminant opportunistic infections and malignancies, and ultimately death of the affected patients. However, effective combination anti-retroviral therapy (ART), also referred to as highly active anti-retroviral therapy (HAART), has significantly increased the lifespan of patients with HIV disease and these patients are now living longer,^[2] and also presenting to hospitals in increasing numbers for elective and urgent surgical procedures. Nearly 20-25% of HIV seropositive patients undergo surgery during their lifespan;^[3] these surgeries include neurosurgical operations, both for non-HIV-related central nervous system (CNS) disorders and those directly attributed to the HIV infection.

Surgery in HIV-infected patients primarily raises three important concerns regarding its risks and outcome: (a) HIV disease could potentially impact the outcome from surgery,

Access this article online

Quick Response Code:



Website:

www.asianjns.org

DOI:

10.4103/1793-5482.145050

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mainly due to the multi-system derangements caused by the disease itself, or induced secondary to the associated substance abuse, opportunistic infections and malignancies, and ART side effects and drug interactions; (b) anesthesia and surgery could cause postoperative worsening of the HIV disease secondary to their known immunosuppressive effects;^[4] and (c) there is the dreaded risk of transmission of HIV infection to the attending medical personnel.^[5] These concerns assume greater significance in inherently high-risk procedures like neurosurgery, and hence a thorough understanding of the HIV disease and its perioperative implications in neurosurgical patients is important. While HIV-related perioperative concerns during general surgery have been addressed before,^[3-8] there is insufficient literature focusing on the specific concerns pertaining to neurosurgery; most available neurosurgery reports only discuss the surgical aspects.^[9-19] We present here our experience in the perioperative management of HIV-infected patients who underwent neurosurgery at our institute in the past 5 years and discuss the relevant perioperative issues along with the relevant medical literature.

Materials and Methods

Between August 2007 and July 2012, seven HIV-positive patients underwent neurosurgical interventions for various CNS lesions at our institution. Anesthesia charts and surgical records of these patients were retrospectively reviewed and the following relevant data obtained: Preoperative general condition and nutritional state of the patients, extent and severity of neurological involvement, severity of HIV disease based on the Cluster of Differentiation (CD4) cell counts, presence of multi-organ dysfunction and opportunistic diseases, ART medication used and its side effects, medical consultations sought, details of anesthesia and surgery, the perioperative course and complications, development of any postoperative infection or clinical worsening of the patient's HIV state during their hospital stay, and any instance of HIV transmission among the attending medical staff.

Results

The demographic profile and relevant preoperative data of our patients are depicted in Table 1. Patients presented for

Table 1: Demographic profile and preoperative data of our patients

Case	Age/sex/weight	Neurological evaluation	HIV status	Systemic involvement	MRI	Proposed surgery
1	33 years/ male/40 kg	Headache, vomiting, vertigo, unstable gait, normal GCS, positive cerebellar signs	CD4~102 cells/mm ³ , on ART with zidovudine, lamivudine, navirapine for 6 months	Recurrent chest infections, weight loss, smoking, alcohol intake, substance abuse, Hb~8 gm%, TLC~2800/dl, serum creatinine~1.8 mg%, blood urea~58 mg%, normal LFT, coagulation profile, platelets and chest X-ray	Cerebellar mass with obstructive hydrocephalus	Craniotomy and tumor decompression
2	47 years/ male/52 kg	Fever, diarrhea, seizures, right hemiparesis, 7 th cranial nerve palsy	CD4~115 cells/mm ³ , detected as HIV positive first time during PAC	On ATT for 5 months, old Koch's evident on chest X-ray, ultrasound abdomen~multiple lymph nodes in para-umbilical region, blood urea~50 mg%, serum creatinine~1.3 mg%, marginally raised liver enzymes, total serum proteins~5 gm%, normal bilirubin	Multiple, variable-sized, thin-walled enhancing lesions with peri-lesional edema, possibly tubercular or inflammatory granulomas [Figure 1]	Focal craniotomy and biopsy of lesion
3	45 years/ male/42 kg	Progressive weakness of all four limbs, thinning of hand muscles over 6 months	CD4~143 cells/mm ³ , on ART for 14 months	Frequent respiratory infections, quadriparesis, Hb~9 gm%, TLC~3200/dl, evidence of depression present, psychiatric consultation sought	C2~C3 IDEM with left para-vertebral extension through widened neural foramina	Excision of IDEM
4	40 years/ male/56 kg	Headache, altered sensorium	CD4~436 cells/mm ³ , diagnosed HIV positive during PAC, ART started	ECG~ST-T changes, concentric LVH and normal EF on Echo, hypertension detected and treatment started	Left MCA aneurysm with SAH	Craniotomy and aneurysm clipping
5	21 years/ male/48 kg	Headache, diplopia, altered sensorium	CD4~210 cells/mm ³ , diagnosed HIV positive in PAC, ART started	Fatigue, weight loss	Pineal region mass with hydrocephalus	VP shunt
6	10 years/ male/20 kg	Headache, drowsiness, vomiting	CD4~180 cells/mm ³ , diagnosed HIV positive in PAC, ART started	Cough, low-grade fever, loss of appetite, weight loss, on ATT for 1 month, Hb~8.2 gm%	Tubercular meningitis	VP shunt
7	35 years/ male/44 kg	Headache, seizures	CD4~383 cells/mm ³ , on ART for 4 months	Alcohol intake, chronic smoker, history of pulmonary Koch's 2 years back, took ATT for 9 months, raised liver enzymes	Right fronto-parietal mass	Craniotomy and excision of mass

HIV – Human immunodeficiency virus; CD4 – Cluster of differentiation 4; ART – Anti-retroviral therapy; GCS – Glasgow coma scale; Hb – Hemoglobin; TLC – Total leukocyte count; LFT – Liver function tests; PAC – Pre-anesthetic checkup; ATT – Anti-tubercular treatment; IDEM – Intradural extramedullary; ECG – Electrocardiogram; LVH – Left ventricular hypertrophy; EF – Ejection fraction; Echo – Echocardiography; MCA – Middle cerebral artery; SAH – Subarachnoid hemorrhage; VP – Ventriculoperitoneal

neurosurgery for HIV-induced as well as coincidental CNS lesions. The commonest observed co-morbidities included derangements of liver, kidney, and hematological system, and opportunistic respiratory infections. HIV disease severity, as determined by the CD4 counts, was variable; viral load testing was not available. Medical, gastrointestinal, nephrology, hematology, and psychiatric consultations were sought for help in preoperative patient management.

All operations were undertaken on an emergent basis due to progressive deterioration in the neurological condition of the patients, and high-risk consent for surgery and anesthesia was obtained. The preoperative fasting period was limited to ≤ 8 h and ART was continued till the start of surgery. The patients were anesthetized with intravenous (IV) fentanyl (1-2 $\mu\text{g}/\text{kg}$ initial dose, 0.5-1 $\mu\text{g}/\text{kg}$ hourly boluses), midazolam (0.025-0.05 mg/kg), ondansetron (0.1 mg/kg), thiopentone (3-5 mg/kg), atracurium (0.5 mg/kg initially and 4-5 $\mu\text{g}/\text{kg}/\text{min}$ infusion), isoflurane (0.5-1%), and an oxygen and nitrous oxide mixture. Ventilation was controlled. Intraoperative monitoring of invasive arterial pressure, arterial blood gases, serum electrolytes, neuromuscular junction (NMJ) function, and anesthetic depth with bi-spectral index (BIS) monitor was deployed besides other routine monitoring. Positioning for surgery was done carefully and the pressure points were well padded. Patients with multi-organ dysfunction were administered anesthesia drugs in titrated doses with the help of BIS and NMJ monitoring; blood was transfused in cases 1 and 3 because of their preoperative anemia, and mannitol and fluids were administered as per requirement. Surgery was performed under stringent aseptic measures. The patients were extubated at the end of surgery and were closely monitored postoperatively. IV paracetamol was used for pain relief and ART was re-started within 24 h. Universal Precautions for prevention of infection transmission were followed strictly throughout the procedure with special emphasis on maximal use of disposable surgical items, careful cranial bone drilling to avoid blood spills, and thorough cleaning and disinfection of the operating room after surgery.

The intraoperative course in all patients was largely uneventful with no significant instance of hemodynamic instability, fluid/electrolyte/acid-base imbalance, excessive blood loss, delayed awakening from anesthesia, or requirement for postoperative ventilation. Transient, mild psychosis was observed in case 3 on the first postoperative day. No patient developed postoperative fever or other features of infection or any clinical evidence of worsening of the HIV disease during their hospital stay; CD4 counts were not repeated postoperatively. There was no report of HIV transmission to any operating room staff. The histopathology reports of the surgical specimens revealed a non-Hodgkin's lymphoma in case 1, tuberculoma in case 2 [Figure 1], schwannoma in case 3, and lymphoma in case 7.

Discussion

HIV is a lentivirus subtype of human retroviruses that preferentially infects and destroys the host T helper lymphocytes (CD4 cells) leading to impairment of cell-mediated immunity and thereby enhancing the susceptibility of the host to opportunistic infections and malignancies. Central and peripheral nervous system involvement in HIV disease, caused by the HIV infection itself or by the opportunistic infections, is well known [Table 2]. Diagnostic

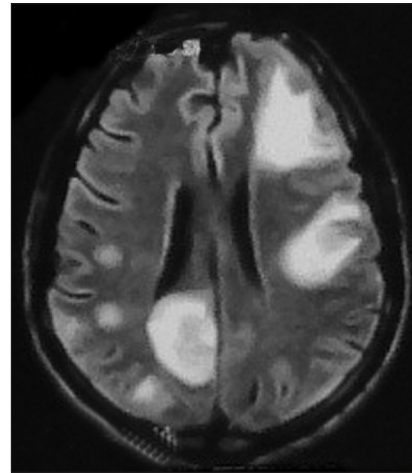


Figure 1: MRI brain of case 2 showing multiple, variable-sized, thin-walled enhancing lesions with peri-lesional edema

Table 2: Central nervous system involvement in HIV disease

Primary involvement due to the HIV infection itself
Aseptic meningitis
HIV-associated neurocognitive disorders, overt dementia
Vasculitis- stroke
Polymyositis
Myopathy
Myelopathy
Peripheral neuropathy
Secondary involvement due to opportunistic infections
Toxoplasmosis
Progressive multifocal leukoencephalopathy
Cryptococcosis
Cytomegalovirus
<i>Mycobacterium tuberculosis</i>
Syphilis
Malignancies
Primary CNS lymphoma
Kaposi sarcoma
Manifestations of CNS involvement in HIV disease
Fever, vomiting, focal neurological deficiencies, raised intracranial pressures, cerebral edema, cerebral hematomas, low Glasgow Coma Scale, loss of sensory or motor function in one or more limbs, proximal muscle weakness, burning sensation in the limbs, paresthesias, ataxia, bladder and bowel involvement, painful proximal muscle weakness, and autonomic hemodynamic instability

and therapeutic neurosurgery has been reported for many HIV-related neurological conditions,^[17] such as primary CNS lymphomas, progressive multifocal leukoencephalopathy, *Toxoplasma gondii* encephalitis, multiple strokes and transverse myelitis, aspergillosis of the base of the skull, cat-scratch disease induced radiculopathy, hydrocephalus due to cryptococcal meningitis, inflammatory peripheral neuropathy, glioblastoma multiforme,^[14] subdural hematoma secondary to thrombocytopenia,^[10] and meningiomas.^[9,16] Of these, primary CNS lymphomas and toxoplasmosis are the commonest lesions. On the other hand, non-HIV-related neurosurgical disorders like neurotrauma, neurovascular diseases, spinal problems, etc., may occur coincidentally in HIV seropositive patients.^[17]

The perioperative management of neurosurgical HIV patients should take into consideration various aspects of the CNS lesion as well as the HIV disease. Preoperative evaluation should specifically document history of drug and alcohol abuse, HIV disease status (CD4 counts and viral load), presence of usually encountered co-morbidities like neurological manifestations [Table 2], systemic derangements and opportunistic infections/neoplasms [Table 3], and details of the commonly used combination ART [Table 4]. Perioperative continuity of ART, achieved by a minimal fasting period enabling uninterrupted medication, is the mainstay in avoiding emergence of post-surgery virus resistance. Intraoperative issues in HIV patients have been discussed before,^[3-8] but those pertaining to neurosurgical procedures need a special mention here. IV access may be difficult in habitual drug users; problems in securing the airway and nasogastric tube insertion may be encountered due to profuse bleeding from Kaposi sarcomas or other oro-pharyngeal lesions; risk of pulmonary aspiration may be exaggerated,

especially in patients with lower cranial nerve palsies, due to increased esophageal reflux and delayed gastric emptying; sudden intraoperative hypotension secondary to autonomic neuropathy, adrenal insufficiency, and drug allergies may worsen the hemodynamic instability associated with posterior cranial fossa and cerebral vascular surgeries; fluid and electrolyte imbalance may develop in patients with colitis and autonomic enteropathy, warranting careful use of mannitol and other diuretics; prolongation of anesthesia drug effects and consequent delayed awakening secondary to hepato-renal involvement and interactions with ART may hamper early postoperative neurological assessment; commonly used drugs in neurosurgery like propofol and steroids can cause severe lactic acidosis and respiratory muscle weakness, respectively, in patients on ART; patient injuries can occur, especially during sitting or prone position neurosurgery, due to the presence of neuropathies and osteonecrosis; increases in the HIV viral load can occur with excessive blood transfusion, and hence erythropoietin and tranexamic acid would be useful in CNS vascular surgeries.^[7] Relevant postoperative issues include development of HIV-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH), possible worsening of the HIV disease due to immunosuppression after use of methylprednisolone and salicylates,^[4] increased chances of ventilator requirement in patients with myopathies and respiratory disease, onset of withdrawal syndrome in substance abusers, and increased chances of developing postoperative hemodynamic instability, high fever, anemia, sepsis, deep venous thrombosis, thromboembolic events, and multi-organ dysfunction. Abnormal behavior changes, rapid neurological deterioration, and death have been reported to complicate the postoperative course in HIV patients.^[14] Early resumption of ART and good pain relief with IV/rectal

Table 3: Multi-system involvement and opportunistic diseases in HIV infection

Organ/system	Disease/manifestation	Required preoperative investigations
Cardiovascular	Coronary artery disease, myocarditis, dilated cardiomyopathy, congestive heart failure, pericardial effusion	ECG, echocardiography, X-ray chest
Respiratory	Sinusitis, bronchitis, interstitial pneumonitis, bacterial, viral, or fungal pneumonia, tuberculosis	X-ray chest, CT scan thorax, pulmonary function tests
Gastrointestinal tract	Candidiasis, Herpes Simplex Virus, cytomegalovirus, oral hairy leukoplakia, aphthous ulcers, gastro-esophageal reflux, delayed gastric emptying, diarrhea, electrolyte imbalance, pancreatitis, hepatobiliary involvement	Liver function tests, endoscopy
Renal	Drug and HIV-induced nephropathy, nephrotic syndrome	Renal function tests
Hematological	Anemia, neutropenia, thrombocytopenia, lymphadenopathy, idiopathic thrombocytopenic purpura, coagulation abnormalities, venous thromboembolism	Complete hemogram, coagulation profile
Endocrine	Lipodystrophy, syndrome of inappropriate ADH secretion, adrenal insufficiency, hypo- or hyperthyroidism, lactic acidosis, hypogonadism	ACTH levels, serum electrolytes, hormone profile, thyroid function tests
Immunologic	Drug allergies, arthralgias, fibromyalgias, HIV-associated arthropathy, osteonecrosis	X-ray of affected joint, arthroscopy
Psychological	Depression, low self-esteem, suicidal behavior	Psychological evaluation, counseling
Neoplasms	Kaposi sarcoma, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, brain, oral, lung, liver, gastric, testicular, cervical, and anal malignancies	Biopsy examination, blood examination for malignant cells, X-ray and CT scan

CT – Computed tomography; ECG – Electrocardiogram; ACTH – Adrenocorticotrophic hormone; ADH – Antidiuretic hormone

Table 4: Anti-retroviral drugs/ART side effects/ART-Anesthetic agent interactions

Group	Drugs
Nucleoside reverse transcriptase inhibitors (NRTI)	Zidovudine, stavudine, lamivudine, zalcitabine, abacavir, tenofovir
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Delaviridine, nevirapine, efavirenz
Protease inhibitors (PI)	Retonavir, indinavir, nelfinavir
Entry inhibitors	Maraviroc, enfuvirtide
Integrase inhibitors	Raltegravir, elvitegravir
ART side effects	Vomiting, diarrhea, lactic acidosis, hepatic toxicity, pancreatitis, dyslipidemia, hyperglycemia, insulin resistance, peripheral neuropathy, myopathy, prolongation of PR and QT interval on ECG, tubular necrosis, nephrolithiasis, osteomalacia, anemia, neutropenia, thrombocytopenia, hypersensitivity, and worsening of the pre-existing infection and associated autoimmune diseases (immune reconstitution inflammatory syndrome)
ART-Anesthetic agents interactions	Enhances the effects of fentanyl, midazolam, calcium channel blockers, lignocaine and vecuronium, increases propofol-induced lactic acidosis and steroid-induced myopathy and respiratory muscle weakness, midazolam contraindicated in patients receiving ritonavir

analgesics and no intramuscular injections is advocated in the postoperative period. Strict perioperative implementation of Universal Precautions^[5,20] is strongly recommended to prevent the feared spread of HIV infection among the attending medical personnel. In case of accidental HIV exposure, prompt deployment of first aid measures should be followed by post-exposure prophylaxis preferably within 2-3 h.^[5]

The risks and outcome of anesthesia and surgery in HIV-infected patients are under debate,^[21] and there is as yet limited evidence regarding the actual risks.^[6] While some studies report poorer surgical outcomes in HIV-infected individuals with low CD4 counts,^[21,22] others indicate favorable outcomes irrespective of the HIV serostatus and the type of surgery.^[21,23] No information pertaining specifically to the outcome of neurosurgery in HIV patients was found in medical literature. CD4 cell counts and HIV viral loads are often considered to be determinants of the affected patient's surgical risk. Regardless of the type of surgery, a 1-3% mortality rate has been reported for CD4 counts <50 cells/mm³ and a 0.8% mortality rate for CD4 counts >200 cells/mm³, while patients with high CD4 counts (500-700 cells/mm³) are considered less likely to have perioperative complications.^[6] A viral load of ≥10,000 copies/ml is suggestive of ineffective ART. Some authors, however, consider the patient's poor health and nutritional state (albumin <2.5 g/dl), and presence of systemic derangements to be more reliable predictors of poor surgical

outcomes, than just a low CD4 cell count and a high HIV viral load.^[24,25] Nevertheless, it is still recommended that elective surgery be undertaken after optimizing the ART and improving the CD4 counts.^[21]

It is increasingly recognized that anesthesia and surgery have the potential to adversely impact outcome after cancer surgery by inhibiting important host defense mechanisms and promoting metastasis.^[4,26] Possible progression and worsening of HIV disease due to a similar immunosuppressive mechanism has been postulated, though there is no substantial evidence yet in support of this concern. A recent review of literature on surgical issues in HIV infection by Libman includes several studies showing no progression of HIV infection after major surgery.^[27] Significantly, these studies were from the pre-ART era. With advances in ART and its widespread availability, the possibility of postoperative worsening of HIV status is even more unlikely.

Likelihood of perioperative HIV transmission from a patient to the attending medical personnel is similar to that in other blood-borne infections, but has been a more feared complication for historical reasons. Strict adherence to the Universal Guidelines helps reduce this risk; a low preoperative viral load achieved by an effective ART further mitigates the possibility of dreaded results of transmission.

Our patients presented with low CD4 counts, multi-system derangements, and opportunistic diseases which could not be adequately corrected in time prior to the emergency operations. Despite this, a satisfactory perioperative outcome was achieved in all patients by using a modified anesthesia regime suitable for the co-morbidities, good monitoring of major systemic functions enabling prompt detection and correction of abnormalities, and strict implementation of aseptic measures and Universal Precautions. We did not find any obvious adverse impact of the HIV infection on the results following neurosurgery, no obvious clinical evidence of surgery-induced early worsening of the HIV disease, and no instance of HIV transmission. However, no meaningful conclusions regarding the HIV-related risks and outcome in neurosurgery can be made with this limited data of only seven patients and a clearer picture would emerge only after experience with a larger patient population undergoing a variety of elective and emergent neurosurgical procedures. Meanwhile, a review on surgical decision making in HIV disease by Madiba *et al.* clearly states that the risk of major surgery in HIV-infected patients is like that for any immune-compromised or malnourished patient and the infection should be merely considered as a co-morbid condition requiring an appropriate management.^[24] There are no sufficient grounds for denying surgery to HIV-infected patients for fear of an unfavorable outcome. This could perhaps be valid for neurosurgical operations too.

In conclusion, an improved life expectancy due to HAART can lead to more HIV-infected patients presenting for neurosurgery,

making it necessary for the health care givers to have a detailed knowledge of the related perioperative issues. Implementation of an appropriate perioperative management plan, tailored to the individual HIV patient and the type of neurosurgery, can substantially improve procedural safety.

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How to cite this article: Agarwal J, Ganjoo P, Hansda U, Sharma MU, Tandon MS, Singh D. Perioperative concerns in neurosurgical patients with human immunodeficiency virus infection. *Asian J Neurosurg* 2016;11:103-8.

Source of Support: Nil, **Conflict of Interest:** None declared.