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# Refractory Raised Intracranial Pressure: A Case-Based Therapeutic Review in Resource-Limited Setting

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## 1. Abstract

**1.1. Background:** Raised Intracranial Pressure (ICP) often presents with series of symptoms which adversely affects patient and their family members. It usually leads to a life-threatening condition that requires immediate medical attention. With disease progression, patients tend to experience severe, persistent, and refractory symptoms.

**1.2. Objectives**: To review available pieces of evidence for raised intracranial pressure in malignant conditions on a background of the clinical scenario.

**1.3. Clinical Scenario and Results**: We came across a 36 yr old gentleman diagnosed with malignant melanoma and presented with large cerebral mass refractory to disease-modifying treatment (RT/ CT/ Surgery) and regular conservative management. He presented with persistent refractory raised ICP features requiring administration of medications beyond their recommended schedule. All available treatment modalities failed to achieve adequate symptom relief. Medico-legal and clinical complexities added burden to management. Consideration of palliative sedation was found to be a good option near the end of life.

**1.4. Conclusion**: Palliative sedation should be considered as a therapeutic option in the terminally ill patient where the goal is to relieve and comfort from severe, intractable sufferings.

## 2. Introduction

Raised ICP is a common neurological complication in patients with primary or secondary brain lesions, affecting a person's physical, cognitive and social functioning and quality of life [1]. Possible etiologies include an increase in either volume of the brain, cerebral blood flow, or Cerebrospinal Fluid (CSF). The rigid non-compressible nature of the human skull often adds to increasing ICP. Resting ICP represents an equilibrium pressure between CSF production and absorption. The Monroe- Kellie hypothesis states that change in intracranial brain volume reciprocally changes volume in one of the components, either blood or CSF [2].

In most cases, raised ICP can be managed conservatively using optimal treatment with steroids, anti-edema therapies, analgesics, anti-emetics, and other supportive medications. This may be followed by radiotherapy or chemotherapy or neurosurgery (decompressive craniotomy or ventriculoperitoneal shunting if ventricles are dilated). Other available measures: hypothermia, hypertonic saline, hyperventilation, barbiturate coma can be considered according to availability. Very rarely patient presents with persistently raised ICP features refractory to available treatment modalities. This increases symptom burden and distress to patients and their families. Inability to achieve adequate symptom control often increases distress among the care team.

This article depicts a case-based therapeutic review in a patient who had persistent features of refractory raised ICP. Every available treatment modality has been tried for optimal symptom control. Failure to achieve good symptom benefit lead to continuing medications post their recommended schedule.

## 3. Case Summary

A 36-year-old gentleman, Mr. S presented with a subcutaneous nodule over the left leg. The diagnostic evaluation suggested malignant melanoma of the left leg with lung metastases. Prior treatment history includes palliative radiotherapy and advice for palliative chemotherapy. However, the patient defaulted and started

himself on alternative medications. After two months he presented with lymphadenopathy over an inguinal and pelvic region with increased left leg nodular swelling. Despite advice for palliative chemotherapy, the patient defaulted. After one month he presented with left lower limb weakness with a history of recent onset convulsion, headache, vomiting, and double vision. Post stabilization, Magnetic Resonance Imaging (MRI) of the brain showed a large peripherally rim enhancing lesion in right parieto-occipital lobes and left occipital lobe. Both lesions were associated with marked perilesional edema and a midline shift towards the left side. Ophthalmological examination showed moderate bilateral papilloedema. A decision about Whole-Brain Radiotherapy (WBRT) with the involvement of the palliative care team had been taken and was conveyed to the patient and family members. Due to concerns involved regarding post-WBRT memory loss, neurological dysfunction, and inability to manage financial and personal dealings, Mr. S requested to manage symptoms conservatively. Thorough counseling regarding the need for WBRT, the urgency of the situation, effect on memory and other neurological functions, possible consequences of inadequate therapy had been done. Mr. S understood all these things and took discharge against medical advice. He was advised to visit the Emergency Room (ER) in case of any symptom worsening and was discharged with supportive medications including anticonvulsants. Meanwhile, nodular swelling over the left leg had increased to a large fungating ulceroproliferative lesion of approximately 10 cm x 10 cm. After ten days, Mr. S presented to ER with features suggestive of raised ICP. His symptoms were controlled with conservative medical decompressive therapy (MDT) with intravenous (IV) injections of dexamethasone 8 mg, mannitol 100 ml, ondansetron 8 mg, paracetamol 1 gm, and has been re-counseled for WBRT. Mr. S agreed to go ahead with WBRT and received 20 Gray/ five fractions. An opinion from the medical oncology team has been sought for the feasibility of palliative chemotherapy. But due to the extensive nature of the disease and poor likelihood of benefits, chemotherapy was deferred and he was referred back to the palliative care team. A neurosurgery opinion was also ruled out for any role of surgical intervention.

Post-WBRT, his symptoms were well under control. He was discharged on oral medications in a clinically stable condition. Family members were educated regarding wound care. After a week, he presented to ER with worsening features of raised ICP and severe nociceptive pain over the left leg wound. Upon inquiry, he was found to have very poor medical compliance. The reinstitution of conservative medical management achieved optimal symptom control. Inadequate pain control with weak opioids leads to consideration of strong opioids like fentanyl to achieve proper analgesia. Repeat ophthalmology opinion showed marked bilateral papilloedema. Laboratory investigations revealed increased white blood cell count. Wound swab culture/ sensitivity confirmed the diagnosis. Appropriate antibiotics controlled the infection. He was discharged in a clinically stable condition with symptoms well under control. Mr. S was on regular follow-up with the palliative care team with frequent home visits and phone follow-up. For the next three weeks, his symptoms were well under control and he was able to manage his office work from home.

Post three weeks' period, he presented to ER with worsened symptoms. He was admitted for supportive care and received immediate conservative MDT. Other supportive measures for his symptoms were continued with regular wound dressing. Head positioned to 300. Repeat ophthalmology examination showed persistent marked papilloedema. A maintenance dose of 24 mg/day dexamethasone, 24 mg/ day of ondansetron, 3 mg/day haloperidol (increased from 1.5 mg/day), 300 ml/day mannitol, 4 gm/day of paracetamol with 25 mcg/hr of fentanyl transdermal patch was continued. However, even after 5 days of optimal treatment, his symptoms persisted. Repeat brain imaging showed a marked increase in bilateral cortical mass with extensive perilesional edema and a new lesion at the left occipital area. There was no evidence of dilated ventricles or obstructive hydrocephalus, hence a neurosurgery opinion was ruled out. A decision to start on 3 % hypertonic saline infusion was taken with serum sodium levels maintained in the range of 145-155 mEq/L. Along with this, he was started on fentanyl infusion of 1000 mcg/24 hrs mixed with 10mg/day haloperidol. Dosage of rest medications (dexamethasone to 32 mg/day, ondansetron to 32 mg/day) was increased. For the next two days, Mr. S felt better with rarely any symptoms. Multiple counseling sessions were held with the patient and family members regarding disease prognosis. After three days of treatment, his laboratory parameter showed severe hypernatremia (serum sodium levels- 158 mEq/ L) with clinical features of hypertension. Hence a decision to withhold 3% hypertonic saline infusion was taken. Even after optimal treatment, his symptoms persisted and were considered refractory. His general condition continued to deteriorate.

Because of persistent, refractory symptoms and deteriorating general condition, a decision of palliative sedation and end-of-life care was taken and agreed upon. He was started on continuous IV infusion (CIVI) of 1000 mcg fentanyl + 15 mg haloperidol + 10 mg midazolam. Other medications were continued as before. After two days of being clinically better, his symptom started worsening. Features of raised ICP continue to increase and Mr. S experienced symptoms even worse than before. Due to deranged laboratory parameters (mainly hypernatremia) and worsening of symptoms, he was again started on a short course (3 days) of mannitol. The dose of fentanyl and midazolam was increased to 1200 mcg/ 24 hrs and 15 mcg/24 hrs respectively with a maintained dose of haloperidol. The dose of dexamethasone was also increased to 36 mg/day. After 3 days of IV mannitol and with normal serum sodium levels, he was shifted to 3% hypertonic saline. Post mannitol withdrawal, his symptoms recurred which was controlled by reinstitution of mannitol. However, patient remained to be conscious and alert with a

good response to commands. Because of insomnia and distress due to disease prognosis, the dose of midazolam was escalated further. Meanwhile patient expressed his wish to be at home during his last breath. Hence meeting with family members was organized. Due to the need for continuous IV infusion, non-availability of full-time trained nursing support, financial constraints, and the inability of the wife to handle the husband's acute condition, a decision regarding the place of care was reconsidered. Mr. S was informed about possible difficulties in the care process and consented to hospital care. With a continued high dose of dexamethasone, Mr. S developed gastritis-like features being inadequately controlled with 80 mg/ day of pantoprazole. An infusion of pantoprazole 120 mg/ day was started with peroral sucralfate suspension to cover gastric mucosa. Mr. S was on three separate infusions (fentanyl + midazolam + haloperidol; pantoprazole; and parenteral nutrition) for his optimal symptom control. With this, he felt more comfortable and found himself actively involved in decision-making and managing his important personal dealings. The family was also relieved with optimal symptom control. Achieving good clinical and symptomatic benefit with CIVI and other supportive measures, the family again requested to reconsider the place of care to be at home. A thorough discussion regarding current disease status, need for continuous IV medications and opioid availability with trained nursing staff was held with the active participation of the patient and family members. A decision to taper the dose of IV infusion with simultaneous oral medications (maintaining constant daily dose of all medicines) was taken. Change to the oral route was not tolerated with recurrence of symptoms. Hence he was restarted on IV injections with the same dosage. Symptoms were stabilized with immediate IV doses. Post stabilization, a meeting was held with family members regarding goals of care and place of care. It was decided to provide end-of-life care at the hospital with continued palliative sedation. Mr. S was continued on CIVI for two weeks in a stable clinical state following which, his general condition deteriorated. After three days, Mr. S expired without experiencing any symptoms. The family was satisfied with good symptom control near the end of life and decreased distress.

## 4. Discussion

The goal in the management of raised ICP is to identify etio-pathological cause along with measures to reduce ICP (maintaining Cerebral Perfusion Pressure (CPP) and reduction in vasogenic edema) [3]. In clinically evident cases, immediate reduction in ICP is warranted and it often helps to decrease further complications. Regular ICP monitoring may not be possible in many hospitals and should not halt emergency treatment. Treatment protocols often include maintenance of ABCs (Airway, Breathing, Circulation); proper positioning (head elevation of 150-300, avoiding sharp head angulations and tight neck garments) [4–6]; steroids (mainly dexamethasone); osmotherapy/ anti-edema measures (mannitol/ hypertonic saline/ acetazolamide/ glycerol); adequate analgesia; maintaining euvolemia, euglycemia and eunatremia; anti-epileptics for prevention and treatment of seizures; surgical therapies-Cerebrospinal Fluid (CSF) drainage or removal of the mass lesion. Many times raised ICP does not respond to routine treatment measures despite optimal therapy and is often labeled as refractory. Suggested therapies for such cases include sedation (may involve the induction of barbiturate coma [7,8]); hypothermia [9]; hyperventilation; decompressive craniotomy with or without duraplasty.

### 4.1. Anti-Edema Measures

Rapid reduction in ICP and cerebral edema often prevent the development of future complications. Hyperosmolar solutions- Mannitol/ Hypertonic saline/ glycerol acts by removing water from normal brain parenchyma hence lowering ICP [10]. These solutions are effective in the intact blood-brain barrier. Mannitol (18% or 20 %), the most commonly used osmotic agent usually acts by i) increase in cerebral blood flow, hence improving CPP; ii) Hygroscopic action by creating an osmotic gradient between blood and brain; iii) Diuretic action; iv) Red blood cell deformation; v) constriction of brain arterioles and veins. The recommended dose is a loading dose of 1 g/kg over 15-30 min (both in adults and children) followed by 0.25 g/kg every 6-8 hourly. The recommended schedule is not more than 3-4 days. Avoiding dehydration and hypotension are of utmost importance in patients started on mannitol [11–13].

Hypertonic Saline (3 % or 23.4 %) is found to be as effective as mannitol in lowering raised ICP. In addition to osmotic action, it acts via the regulation of vascular blood flow. Recommended dose is: 3%: 5-10 mL/kg; 23.4%: 30 mL/dose. However, there is a risk of rebound effect if being used for a longer duration [12,14,15].

Glycerol is orally available in preparation and acts via osmotic action. It readily crosses the blood-brain barrier. It is mainly useful as maintenance therapy to control the rise in ICP in brain metastases patients. The recommended dose is 1.5 g/kg/day every 4-6 hrly or 120 ml stat dose in acute cases where mannitol is not available. In some cases, it can be used by the intravenous (IV) route. IV injection reduces ICP with an effect lasting for about 70 min without any effect on serum osmolality [16].

### 4.2. Corticosteroids

Steroids mainly act by blocking the outflow of blood components from the capillary bed into brain tissue at the damaged blood-brain barrier. Various corticosteroids have been used in raised ICP cases, out of which dexamethasone is more effective. It does not have mineralocorticoid potency, hence does not lead to sodium and water retention. Due to its less binding to plasma proteins, it is usually found in higher concentrations in CSF as compared to other corticosteroids. The dose of dexamethasone may range from 4 mg/ day to 96 mg/ day. However, studies failed to show the higher efficacy of a drug with higher doses. The usual recommended dose is 24-36 mg/ day in divided doses. Suggested dose in children: initial

dose of 1 mg/Kg followed by a maintenance dose of 0.4-1 mg/kg in divided doses [17–19]. Long-term therapy with dexamethasone should be individualized according to the case basis as prolonged use may cause some serious adverse effects. Hence it is advisable to taper off or discontinue dexamethasone whenever not required.

### 4.3. Analgesia

Adequate analgesia is required for better symptom control and improved quality of life. Such patients often experience moderate to severe headaches due to raised ICP. Additionally, there might be pain due to disease primary or associated co-morbid conditions. A step ladder approach as recommended by World Health Organization (WHO) is useful to alleviate pain. The initial analgesic used is Paracetamol (up to 4 gm/ day). The role of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) is questionable because of their action on prostaglandin synthesis and vascular bed. Also, negative effects on gastric mucosa along with concomitant use of steroids may add up to the complexity of the situation. Step II medications like tramadol, tapentadol can be considered with precautions for moderate to severe pain. However, the possibility of seizure precipitation should be taken into consideration. For cases where the patient experiences more severe pain, step III medications like morphine, fentanyl can be an option after adequate evaluation and optimization with other medicines [20]. Our clinical experience showed better tolerability and less side effect profile with fentanyl when compared with morphine for pain control [21]. Adjuvant medicines should always be considered for adequate analgesia.

Patients approaching near the end of life should be preferred for non-oral routes- transdermal, subcutaneous, intravenous, per rectal, nasal, or sublingual as per patient's condition and resource availability.

### 4.4. Hyperventilation

By reduction in partial pressure of carbon dioxide (PaCO2), hyperventilation decreases cerebral blood flow (CBF) and cerebral blood volume by vasoconstriction [22,23]. With per mm Hg of PaCO2 change, a 2% change in CBF has been observed. In a normal person where all compensatory mechanisms are intact, hypercapnia causes cerebral vasodilation without an acute increase in ICP [22,24–26]. However, in patients with brain metastases, a reverse phenomenon is usually seen. A minimal rise in PaCO2 levels in such patients causes a marked increase in ICP and thus increased symptom profile. Reduction in cerebral blood flow may induce or worsen cerebral ischaemia [27,28], hence hyperventilation is usually advisable only in a close monitoring neurocritical care setting.

A possible mechanism of benefit from hyperventilation is shunting of blood flow from normo-responsive blood vessels to damaged blood vessels, relieving cerebral ischaemia [22,23]. However, this effect doesn't sustain beyond 24-36 hrs due to compensatory mechanisms in the brain (bicarbonate buffering and readjustment of cerebral smooth muscles to produce cerebral pH milieu).

## 5. Surgery

Neurosurgical interventions are an aggressive form of treatment to surgically remove resectable Space-Occupying Lesions (SOL) or parts of the brain. Outcomes of surgical resection for single brain metastases are found to be superior when compared with WBRT [29,30]. For multiple brain metastases, the preferred choice of treatment is WBRT as compared to any other treatment modality.

Decompressive Craniotomy, a surgical procedure to remove part of a skull and underlying dura mater to overcome the rigid nature of the skull. It benefits from providing extra space for the brain during worsening brain edema. The presence of a mass lesion in the brain causes changes in venous outflow, leading to immediate and dramatic changes in intracranial blood volume and thus ICP. This results in a vicious cycle for increasing brain edema and pressure [31]. Very few studies showed moderate to high evidence of the effectiveness of decompressive craniotomy on reducing raised ICP [32–35]. Possible complications include seizures, subdural hygroma, hydrocephalous, infections, intracranial hemorrhage, etc [31,36,37]. However, the role in advanced cancer patients with non-resectable brain metastases is very limited.

CSF drainage either via Ventriculoperitoneal (VP) shunt or Lumbo-Peritoneal (LP) shunt {External Ventriculostomy}, where a shunt is placed between CSF from a lateral ventricle through a pressure regulating valve and into the atrium or peritoneal or pleural cavity. Though this technique is found to be beneficial in reducing increased ICP levels [38,39], there are chances of infection (0-19%) and hemorrhage (2%) [40,41].

## 6. Palliative Sedation

Palliative sedation is defined as 'the administration of non-opioid drugs to sedate a terminally ill patient to the level of unconsciousness as an intervention of last resort to treat severe, refractory pain or other clinical symptoms that have not been relieved by aggressive, symptom-specific palliation' (National Ethics Committee and Veterans Health Administration, 2006). The most common indication for palliative sedation remains pain, dyspnoea, and terminal delirium. However other sufferings as a result of severe, intractable, refractory symptoms such as vomiting, bleeding, seizures, depression, agitation, existential distress may warrant palliative sedation.

Commonly used medications for palliative sedation, mostly as combination therapy, include opioids (morphine, fentanyl, hydromorphone), benzodiazepines (lorazepam, midazolam- most commonly preferred due to its rapid onset and easiness for titration), neuroleptics (haloperidol, chlorpromazine, levomepromazine), barbiturates (pentobarbital, thiopental, and phenobarbital) and other anesthetic induction agents (ketamine, propofol) [42–45].

In our case, we observed palliative sedation with a combination of adjuvant drugs benefited the patient most.

## 7. Conclusion

In resource-limited settings, treatment for refractory raised intracranial pressure can be individualized with a combination of palliative sedation and adjuvant medications. Palliative sedation should be considered as a therapeutic option in the terminally ill patient where the goal is to relieve and comfort from severe, intractable sufferings.

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