

## CASE REPORT

# Central sensitization: Neurons are awake; are we?

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## ABSTRACT

Central sensitization (CS) is a known entity associated with prolonged intense painful stimulation secondary to neuropathic or inflammatory peripheral disease and manifests as a heightened responsiveness of the patient to even mild peripheral input. Although numerous protocols are available for its treatment, there have been no reports about the patient's behavior under anesthesia while operating for related or non-related surgery and management thereof. These patients might require high doses of anesthetic agents to achieve the required depth of anesthesia for surgery. We present three reports of patients who required high doses of anesthetic agents for optimum operative conditions. Two of these were managed with ketamine.

**Key words:** Central Nervous System Sensitization; Ketamine; Perioperative Period; Anesthetics, General

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## INTRODUCTION

Central sensitization (CS) is often encountered when neuropathic pain persists even after the primary event has healed and represents a dysfunctional operation of nervous system rather than a reaction to pathology.<sup>1</sup> It causes an increased excitability of the spinal neurons such that the response to even harmless inputs is highly enhanced.<sup>2</sup>

CS is an established entity in pain medicine and very commonly associated with conditions such as amputation of limbs, spinal injuries, headache, fibromyalgia, burns etc.<sup>3,4</sup> Chronic bombardment of painful peripheral impulses to higher centers results in neuronal plasticity producing a hypersensitive state. Although many studies have discussed various chronic pain syndromes and the available treatment modalities, there have been no reports about the behavior of these patient under

anesthesia while being operated for related or non-related surgeries. We present case reports of three such surgical patients with possible central sensitization and their perioperative course after taking their written consent.

## CASE REPORT 1

A 67 year male, weighing 50 kg, with paraumbilical hernia presented for pre-anesthetic checkup for herniorrhaphy. Patient was a known case of diabetes mellitus for the last six years and on oral metformin. There were no signs of autonomic dysfunction. He was non-alcoholic and non-smoker with no other significant medical history. He had sustained a fall from a moving train 20 years ago leading to crushing of both legs. Subsequently, he had had 3-4 surgeries for his injuries ultimately landing up with bilateral lower limb amputation.

His general physical examination was unremarkable and the routine investigations (Hb, coagulation profile, blood urea, serum creatinine, ECG) within normal limits. He was advised tablet alprazolam 0.5 mg the night before and on the morning of surgery.

Upon arrival to the operating room, his baseline parameters were recorded after attaching monitors. A peripheral venous access was established and preloading done with lactated Ringer's solution. Inj. glycopyrrolate 0.2 mg and butorphanol 2 mg were administered for adequate sedation and analgesia. Induction with inj. etomidate 0.4 mg/kg (20 mg) IV and halothane 1% in O<sub>2</sub> failed to achieve adequate relaxation. Inj. etomidate was repeated (total 40 mg) but the patient remained in lighter planes of anesthesia. He was still moving and his jaw was tight. The systolic blood pressure (SBP) rose to 170 mmHg, so halothane concentration was increased but to no avail. Inj. propofol 100 mg IV resulted in slight relaxation with normalization of SBP. Inj. succinylcholine 100 mg bolus was administered and patient successfully intubated. Post-intubation, SBP again increased to 180 mmHg. Anesthesia was deepened with halothane and inj. vecuronium 4 mg administered. When SBP came down to 140 mmHg, halothane concentration was gradually reduced. Once again, the SBP started rising and an increase in the heart rate (HR) inspite of adequate hydration. Tears in his eyes could also be appreciated. The patient was afebrile. Due to non-availability of BIS monitoring, clinical signs were related to a lighter plane of anesthesia. Halothane concentration was again increased and diclofenac infusion started. Patient still did not settle down adequately. Inj. butorphanol 0.5 mg was repeated. HR started showing a downward trend. Thereafter, the patient had to be maintained under deep anesthesia keeping SBP between 98/60 to 100/70 mmHg. Inj. paracetamol 1g infusion was administered. On the completion of the procedure, the patient was reversed and extubated. On table, the patient complained of excessive pain and was given inj. tramadol 100 mg IV. In the recovery room, a review of history revealed the occurrence of intermittent phantom limb pain for last many years for which he had been taking some herbal medication. He also had exaggerated response to a pin-prick over the stump area. Postoperatively, the patient had to be maintained under heavy analgesic cover. On reviewing literature we realized that phantom pain is often associated with peripheral and central sensitization leading to hypersensitivity.

## CASE REPORT 2

A 27 years male patient weighing 70 kg was posted for fixation of thoracic spine (T7-T9). The spine injury was 2 months old with history of some loss of sensation and weakness in lower limbs. He was non-alcoholic and non-smoker. Preoperative evaluation was unremarkable. The patient took tab. alprazolam 0.5 mg orally at night and on morning of surgery.

In the OR after attaching monitors, the vital signs were; BP-138/96, HR-83/min. IV line was secured with ringer's lactate solution. Inj. midazolam 2 mg, glycopyrrolate 0.2 mg and butorphanol 1 mg were injected IV as premedication.

After preoxygenation, induction started with inj. propofol 130 mg and isoflurane 2%. Abnormal upper limb movements occurred and patient's body became stiff instead of relaxing. Propofol 50 mg was repeated and isoflurane concentration increased without much success requiring another bolus of propofol (60 mg) to achieve relaxation. To avoid succinylcholine (risk of dangerous hyperkalemia in spine injury), we decided to use vecuronium bromide (0.1 mg/kg bolus) for intubation. After intubation and positioning, surgery was started. Soon after, the patient's SBP and HR started rising (SBP 186/116 mmHg; HR 116/min). Anesthesia was deepened with isoflurane along with inj. butorphanol 1 mg but patient did not respond much and even required vecuronium top-ups every 10 min. Diclofenac sodium 75 mg was infused. Still SBP remained high (even upto 190 mmHg and HR 125 bpm) making operative conditions difficult. Nothing seemed to work on the patient. While considering hypotensive agents, we also thought of central hypersensitivity due to our past experience and the proven effectiveness of ketamine for these states. As the accompanying hemodynamic effects of ketamine could be a cause for concern in this patient, we kept esmolol infusion ready and administered 50 mg of ketamine IV. Paradoxically within 10 min, the HR and SBP started settling down and almost normalized. Thereafter, the patient remained stable under deep anesthesia with small supplemental doses of ketamine. His requirement of vecuronium too decreased. On completion of surgery, patient was reversed and extubated uneventfully. Postoperatively, he was maintained under good analgesia. A meticulous history-taking revealed episodes of severe burning pain in his lower limbs for the past 2-3 weeks despite sensory loss. Although he had decreased sensations in the

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lower limbs, he had a heightened perception of pin-prick and touch in the upper limbs.

### CASE REPORT 3

A 13 years male child (weight 34 kg) with history of burns 6 years ago and a prior surgical intervention for the same presented for burn contracture release on left foot. In the OR, monitors were attached and intravenous access secured with dextrose normal saline (DNS). On adequate preloading, glycopyrrolate 0.2 mg and butorphanol 0.5 mg were injected as premedicants. After preoxygenation, induction was begun with propofol 100 mg along with halothane 1% in O<sub>2</sub>. Patient did not relax properly and required an additional 50 mg of propofol. Intubation was done with vecuronium bromide (0.1 mg/kg). Thereafter, anesthesia was maintained with O<sub>2</sub>/N<sub>2</sub>O/halothane and vecuronium, but patient displayed signs of light anesthesia. In the absence of BIS monitoring, we relied on clinical signs like high HR, BP only. Supplemental analgesia was administered with paracetamol 500 mg infusion. He required frequent vecuronium top-ups (every 10 minutes). Given his past history of burns, surgical intervention and our previous experiences, we suspected CS and injected ketamine 30 mg IV. The patient settled down within five minutes. Subsequently, he remained comfortable with additional increments of 10 mg ketamine. On completion of procedure reversal and extubation was done. Patient was shifted to RR with stable vitals. Postoperatively, tramadol 50 mg was injected followed by ondansetron 3 mg IV. Later in the ward, history and examination demonstrated hyperalgesia on painful stimulation around the vicinity of the wound.

### DISCUSSION

Central sensitization occurs as a result of prolonged intense noxious stimulation which may be a result of tissue injury, inflammation or nerve injury (peripheral, spinal cord or higher centers) manifesting as reduction in pain threshold, exaggerated pain responses and expansion of the receptive fields.<sup>5</sup> Increased activity of the peripheral nociceptors initiates long term modulations and modifications in the central nervous system causing peripheral as well as central sensitization. Peripheral sensitization involves the increased excitability of nociceptors brought about by the inflammatory mediators released as a result of tissue damage. Central sensitization occurs due to hypersensitivity of dorsal horn neurons to the increased peripheral

input, such that even touch is perceived as pain (allodynia) and painful stimuli are highly amplified (hyperalgesia).<sup>1</sup> All these changes are chemically mediated by the NMDA receptors and its transmitter glutamate.<sup>1,6</sup>

All our patients displayed clinical signs of light anesthesia and an increased requirement for anesthetic/analgesic drugs. Therefore, we analyzed the various causes of awareness during anesthesia which could range from a faulty anesthesia equipment to drug resistance in the patient. We checked our machine, the circuits, vaporizers and the drug delivery systems but nothing was out of place. All procedures had been conducted in different ORs at different times.

Another cause in our first patient could be an altered sensation of pain or abnormal hemodynamic responses to anesthetic drugs due to peripheral or autonomic neuropathy as a result of diabetes mellitus. A detailed review of history revealed that his disease was six years old and properly controlled without any signs of neuropathies, retinopathy or nephropathy.

The next possibility could be a resistance to anesthetic drugs either genetic or drug induced.<sup>7</sup> Genetic resistance could only be ruled out by history, so a detailed history of past anesthetic exposures was obtained in all patients. No history of any abnormal responses to the anesthetics at the time of injury and subsequent amputation was present in the first patient. But the patient had suffered from excruciating pain post crush injury to legs which recurred intermittently over the past 20 years. The third patient had one past surgical intervention under anesthesia which was uneventful, while the second patient did not have any prior history of anesthetic exposure.

Prolonged drug abuse or even multiple anesthetic exposures can lead to enzyme induction manifesting as resistance to anesthetic drugs due to a faster metabolism, thus requiring high doses.<sup>7</sup> Both our adult patients were non-smokers and non-alcoholic. There was no indication of any i.v. drug abuse though the first patient had been taking some herbal medication of unknown origin for pain orally. Past history of multiples anesthetics was present in our first patient about 20 years ago. In third patient the history of anesthetic exposure was quite recent.

Another explanation for the exaggerated responses of our patients under anesthesia could be an induced hypersensitivity due to CS as a result of

extensive tissue and neuronal damage due to trauma.<sup>8</sup> CS is known to occur after amputation, spine injury/stroke and burns leading to an altered perception of the nervous system. Carlton et al have discussed the development of an above-level neuropathic pain in spinal cord injury in addition to the at-level and below-level pain as early as 35 days post-injury. It is characterized by mechanical allodynia and thermal hyperalgesia and causes sensitization of forelimb nociceptors to mechanical and thermal stimulation.<sup>9</sup> Our patients were induced with either etomidate or propofol which are both known for pain on injection. Probably it might be enough to trigger a pain response (the second patient had abnormal upper limb movements with propofol)<sup>9</sup> due to the pre-existing central hypersensitivity later maintained by the surgical manipulation. High doses of anesthetic drugs had to be used to achieve adequate depth of anesthesia during induction as well as throughout the surgical procedures.

The possibility of existence of central sensitization was totally missed in the first patient due to lack of awareness about this phenomenon. In our country, there is a general unfamiliarity regarding the concept of pain clinics amongst doctors as well as patients. On reviewing literature we learnt about this entity and its pre-emptive treatment but no help was available concerning anesthetic management in a patient with prior CS.

Since CS involves the activation of NMDA receptors, ketamine has been advocated for this type of pain since it blocks the NMDA receptors.<sup>10-15</sup> In the second and third patients, we did suspect CS and decided to use i.v. ketamine as a diagnostic measure. In our scenario, the question was whether it could be used in a patient who already had high intraoperative SBP and HR in response to surgical pain. Since ketamine causes a similar hemodynamic response, so theoretically, it could have aggravated the problem. However, there was a miraculous improvement in both the patients and they remained stable thereafter with small top-ups of ketamine.

Various other drugs have been recommended for use in CS like opioids, anti-depressants (tricyclic), anticonvulsants e.g. carbamazepine, gabapentin,

pregabalin (could be started in anticipation if preoperative awareness was there), local anesthetics like lidocaine (for peripheral sensitization) etc.<sup>14</sup> Role of opioids against hypersensitivity is controversial because longstanding CS may actually lead to a downregulation of opioid receptors making opioid analgesia ineffective. In fact, opioid-induced hyperalgesia may occur in some patients.<sup>15,16</sup> In our patients too, opioid analgesia was not effective. The first patient could have been taking opioids in the so called herbal medication, a common occurrence in India. Fentanyl has been found efficacious against CS in some studies so probably it might be a better choice amongst opioids for intraoperative use.<sup>17</sup>

Although a genetic resistance or even enzyme induction due to previous anesthetics cannot be ruled out, it does not explain the events in all our patients. All the patients gave history of some kind of trauma precipitating severe pain and neuronal injury which are proven triggers for the development of CS. Due to the non-availability of BIS monitoring (intraoperatively) and quantitative sensory testing equipment (advocated for evaluation of patients with neuropathic pain), we could not co-relate our clinical observations with these parameters which is a limitation in our case reports. We are suspecting this phenomenon on the basis of patients' history, intraoperative behavior, sensory responses to touch and pin-prick testing, and improvement with ketamine.

To conclude, the object of this case series was to stress upon this issue of increased sensitivity of some patients to painful stimuli while under anesthesia often requiring higher drug doses. In such cases the possibility of CS should be considered if other causes of awareness have been ruled out and there is some co-existing predisposing condition. This is just a hypothesis and further research would be required for better patient outcomes during and after anesthesia.

**Conflict of interest:** None declared by the authors

**Authors' contribution:**

1. K.P - Manuscript preparation, literature search, patient consent
2. G.R - Manuscript Review, Intellectual content
3. S.S - Manuscript editing, manuscript review
4. M.M - Literature research
5. S.J - Literature research

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“All courses of action are risky, so prudence is not in avoiding danger but calculating risk and acting decisively.”

*Machiavelli*