

Combined morphine-clonidine adjuvant in epidural analgesia support role of supraspinal modulation in opioid tolerant patient



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ABSTRACT

Acute pain patients with complicated pain-related experiences would need more than just a pain reliever, especially those with behavioral opioid usage. Latest findings revolving supraspinal modulation are not only taking experts and pain physician into a different stage of understanding but also making theories and management revisited. A 41-years-old Australian male underwent plate and screw fixation of his right femur. He was overweight with a history of behavioral opioid

usage. He was given epidural analgesia for postsurgical management with bupivacaine 0.1% with morphine 2 mg and clonidine 30 mcg every 12 hours as adjuvants. Hemodynamic curves were in normal limits, no paralysis, urinary difficulties, or pruritus. He was discharged on the fourth day. The combined morphine-clonidine adjuvant in epidural analgesia technique was an effective choice to alleviate pain response in this opioid-tolerant patient.

Keywords: *combined morphine-clonidine adjuvant, supraspinal modulation, opioid tolerant*

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INTRODUCTION

The pain would be a challenging issue especially in acute patients with difficult experiences. Even though the direct correlation between activation and nociceptors and the sensory experience of pain is not always apparent, nevertheless emotional state, the degree of anxiety, attention and distraction, past experiences, memories, and other factors can either enhance or diminish the pain experience.

Recently, experts are getting interested in the supraspinal pathway. Supraspinal modulation is one path of pain pathway that would be happened during pain modulation. It is a specific system in pain pathway that blocks pain transmission in the central nervous system which consists of the periaqueductal gray (PAG), periventricular areas, raphe magnus nucleus (RMN), and pain inhibitory complex (PIC). Another important thing to be considered is that the pain process is an intertwined process that could not be cut abruptly. While we are elaborating and defining a pathway, it also contributes to other pathway and induces other things as well. This matter would be taken into concern when applied to pain management.

CASE REPORT

A 41-year-old man admitted to hospital with a closed fracture of the right femur and he underwent plate and screw fixation under anesthesia.

A pre-anesthetic lookup summarized that he was obese (his body mass index was 30 kg/m²) with a history of behavioral opioid usage and sedatives. His pain score upon admission was reached 80/100 mm which was measured using a visual analog scale (VAS). He was dissatisfied with pain management efforts consisting of high dose morphine combined with pregabalin, NSAID, and paracetamol. Upon evaluation, he was able to spontaneously open his eyes, agitated, with markedly elevated pulses 134-140 beats per minutes and respiratory rate 14-16 per minutes.

The surgery went unremarkable. For postsurgical pain management, the epidural analgesia was given with bupivacaine 0.1% and 2 mg of morphine as an adjuvant. The VAS score slightly decreased to 70/100 mm. But still, he was not satisfied. We finally gave him the combination of bupivacaine 0.1% with 2 mg of morphine and 30 mcg of clonidine in 10 ml solution every 12 hours. VAS was markedly decreased to 20/100. Hemodynamic curves were in normal limits, no complaints of paralysis, urinary difficulties, post-operative nausea and vomiting (PONV), or pruritus. He was discharged on the fourth day postsurgical with crutches.

Conventional workup showed that the patient was amphetamine and heroin user, complicated with an anxiety disorder. Complete pain resolution was seen in seven days postsurgery without any additional intravenous opioid or even antianxiety medications.

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DISCUSSION

Pain is a vital function in providing our body with a warning of potential or actual injury. It is both sensory and emotional experiences and strongly affected by psychological factors such as past experiences, belief, fear or anxiety. A patient who had been exposed with previous pain experiences and anxiety would need much more than just a pain reliever through opioid acts. The inherent pain memory had already perceived and rooted in the perception stage, and as we had reviewed, would be complicated with anxiety and fears. Their history of opioid usage and anti-anxiety medications would be taken into consideration when elaborating an effective and adequate pain regimen.^{1,2}

Supraspinal modulation is a complex pathway that happens during pain modulation. It is a specific system in pain pathway that blocks pain transmission in the central nervous system which consists of the periaqueductal gray (PAG), periventricular areas, raphe magnus nucleus (RMN), and pain inhibitory complex (PIC).¹ The periaqueductal gray and periventricular areas of the mesencephalon and upper pons surround the aqueduct of Sylvius (periaqueductal) and portions of the third and fourth ventricles (periventricular). On the other hand, the RMN is a thin midline nucleus located in the lower pons and upper medulla, and the nucleus reticularis paragigantocellularis, located laterally in the medulla. Pain inhibitory complex is located in the dorsal horn of the spinal cord consists of multiple short enkephalinergic neurons that terminate on central endings of pain conducting afferent fibers.¹

The analgesia occurs as in the thalamus, hypothalamus and cerebral cortex send neuronal signals to the periaqueductal grey area. The PAG projects neurons containing aspartate and glutamate that stimulate RMN. Then RMN projects serotonergic neurons, in addition to noradrenergic neurons projected from adjacent medulla to dorsal horn. They will block pain signals by activating PIC. When this complex is stimulated, enkephalin would be released, and caused pre and postsynaptic inhibition of pain transmission.¹

Supraspinal modulation process is also related to opioid receptor modulation. The opioid peptides are morphine-like substances that act by binding to opiate receptors in the analgesic system and dorsal horn of the spinal cord on the central ending of pain conducting pain fibers. The opioid peptides consist of endorphin, enkephalin, dynorphin, and endogenous morphine. Neurons using endorphin or enkephalin are found in PAG where they inhibit GABA-ergic interneurons that normally suppress the anti-nociceptor neurons. Enkephalin is used by interneurons in lamina II responsible for inhibiting

the lamina-I nociceptor-specific spinothalamic neurons.^{1,3} Dynorphin could be found in the hypothalamus, PAG, reticular formation, and dorsal horn, while endogenous morphine is in terminals forming synapses with neuron having μ -opioid receptors in pain modulation.²

A failure in supraspinal modulation would contribute to central sensitization. Central sensitization occurs when pain pathways in the spinal cord become hyperexcitable and are augmented, rather than blocked, in the thalamus and other brain centers. This leads to a cascade of neuroinflammatory, neuroendocrine, and autonomic dysregulation.^{1,3}

The concept of supraspinal modulation which consists of a descending pain modulatory system provides many targets for the development of analgesic drugs or adjuncts that enhance the effects of existing analgesics. Opioids act throughout the neuraxis and can relieve pain through activities at cortical and subcortical sites, at which affective and somatosensory aspects of the pain experience can be modified, as well as by activating descending pain inhibitory circuits. As seen on our patient, the addition of morphine as an adjuvant could activate the descending pain inhibitory circuits which in turn would help the local anesthetic work in neuraxial scope.¹

Meanwhile, activation of descending noradrenergic projections from the locus coeruleus and other noradrenergic sites produces antinociception. Accordingly, α_2 -adrenergic receptor agonists have been shown to produce antinociception as well as to potentiate the antinociceptive effect of opioid. Our patient was given combined adjuvant morphine with α_2 -adrenergic receptor agonist clonidine to potentiate morphine effect and suppress the locus coeruleus. Locus coeruleus pontine is the most abundant place of alpha-2 receptors, an important source of sympathetic innervation of the forebrain, and a vital alert center. The effects of sedation are due to inhibition of coeruleus nucleus.² Clonidine is able to provide analgesia effects both peripherally, spinally, and supraspinal. The mechanism of clonidine analgesia at spinal level is, among others, through constraints of excitation on primary afferent nerves at the central terminal, resistance to release of substance-P and hyperpolarization, and a decrease in spontaneous activity of dorsal horn nerve.² On the other hand, supraspinal level analgesia is reached through resistance to afferent nerve substantia gelatinosa and some nuclei in the brainstem. Peripheral level analgesia is also achieved by weakening the excitation of A-delta and C fibers and blocking conduction through increasing potassium conductance.⁵

Clonidine at supraspinal level affects the nucleus in the brain stem activating alpha-2-postsynaptic adrenoceptor and nonadrenergic imidazole bonds in lateral reticular nucleus resulting in a reduction of sympathetic tone. Clonidine at the peripheral level also act on adrenoceptor alpha-2-presynaptic and reduces the release of norepinephrine in sympathetic nerve terminals thereby causing dilatation of blood vessels and reducing the chronotropic effect on the heart.¹⁸ But those negative effects on hemodynamics were not found in our patient.⁵

These modulatory pathways help to explain how personal experience and emotional state, as well as societal beliefs, may alter the experience of pain in which happened in patients with previous discomfort experiences.⁵

In this case report, we used the clonidine the co-administration of clonidine reduces the dose of bupivacaine and improves the quality of spinal anesthesia. The antinociceptive properties of clonidine indicate that it might be useful as an alternative to intrathecal opioids for postoperative analgesia, thus avoiding the main adverse effects, such as respiratory depression, pruritus, and urinary retention. The intrathecal application of clonidine increases the duration of both sensory and motor block²⁻⁵ as well as postoperative analgesia. The mechanism of clonidine in spinal anesthesia is reported to be mediated by presynaptic (inhibition of transmitter release) and postsynaptic (enhancing hyperpolarization) effects.⁶

CONCLUSION

Supraspinal modulation has been theoretically explained many years ago. It was totally not only a theory but could be perceived into cases and real practices, in which one of our patients had come into. By combining morphine and clonidine as

adjuvants for local anesthetic in the epidural regimen, the opioid and α_2 -adrenergic receptor agonist worked synergistically as antinociceptive agents and potentiated neuraxial blockade. Somatosensory and opioid receptor modulation were affected by morphine, while sympathetic innervation and activation were blocked by clonidine. Combined adjuvant agents would be beneficial in complicated patients who would not be satiated with only opioids.

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REFERENCES

1. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest*. 2010; 120(11): 3779-87. DOI: [10.1172/JCI43766](https://doi.org/10.1172/JCI43766)
2. Mayer EA. Spinal and supraspinal modulation of visceral sensation. *Gut*. 2000; 47 (Suppl 4): iv69-72; discussion iv76. DOI: [10.1136/gut.47.suppl_4.iv69](https://doi.org/10.1136/gut.47.suppl_4.iv69)
3. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. *Prim Care*. 2012; 39(3): 561-71. DOI: [10.1016/j.pop.2012.06.013](https://doi.org/10.1016/j.pop.2012.06.013). Epub 2012 Jul 24
4. Sikandar S. Peripheral Processing and Central Modulation of Pain. *Annals of the Rheumatic Diseases*. 2016; 75 (Suppl 2): 17. DOI: [10.1136/annrheumdis-2016-eular.6374](https://doi.org/10.1136/annrheumdis-2016-eular.6374)
5. Prasad R, Rao RR, Turai A, et al. Effect of epidural clonidine on characteristics of spinal anesthesia in patients undergoing gynecological surgeries: A clinical study. *Indian J Anaesth*. 2016; 60(6): 398-402. DOI: [10.4103/0019-5049.183395](https://doi.org/10.4103/0019-5049.183395)
6. Racle JP, Benkhadra A, Poy JY, et al. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesth Analg*. 1987; 66: 442-6. DOI: [10.1213/0000539-198705000-00013](https://doi.org/10.1213/0000539-198705000-00013)



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