

CASE REPORT

Combination of Low Dose Ketamine, Paracetamol, and Tramadol for Opioid Induces Hyperalgesia in Lung Cancer with Intra Abdominal Metastases

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ABSTRACT

Background: Opioid induced hyperalgesia or OIH is one of exaggerated response to pain secondary to using of the opioid itself. High dosage of opioid in long term (days to weeks) relate to increased OIH occurrence.

Case: Female, 58 yrs, BMI 17.77, complained severe abdominal pain with NRS 8/10. Patient suffered from lung cancer stage 3 with intra abdominal metastases. Previously patient had received analgesic paracetamol 1gr TID, dexketoprofen 25mg TID, parecoxib 40mg OD, morphine 10mg BD and fentanyl patch 50 µg. Then fentanyl was given 25 µg IV twice with interval of 15 minutes. Patient still complained for pain and eventually pain severity increased to NRS 10/10. Afterwards patient was given low dose ketamin 0.1mg/kg slow IV push, paracetamol 1gr IV, and tramadol 50mg IV. After 15 minutes observation, pain decreased to NRS 5/10.

Discussion: Decreasing total dose of opioid consumed may decreased OIH. It may be performed by improving analgesia by using combination of analgesic and intervention strategy.

Conclusion: combination of low dose ketamine (0.1mg/kg), paracetamol, and tramadol may be benefit for patient with opioid induces hyperalgesia in lung cancer stage 3 with intra abdominal metastases.

Keywords: abdominal metastases; abdominal pain; low dose ketamine; numeric rating scale; opioid induced hyperalgesia

INTRODUCTION

Opioid is recently, significantly and frequently used in chronic cancer and non cancer pain treatment. Using long term opioid may lead to some problems. First, no supportive evidence for its effectiveness in long term treatment, second: it is known well for possibility of misuse opioid and opioid is related to unwanted event including hyperalgesia (opioid induced hyperalgesia or OIH).

Hyperalgesia is defined as increasing pain response to stimulus that causing pain.¹ OIH is sensitivity to nociceptive receptor secondary to opioid. Initially in OIH opioid will treat the pain, but eventually patient become more sensitive to pain stimulus. In other words, in adding analgesic effect, opioid produce opposite effect of pain stimulus. OIH patient probably experience pain that might be similar to pain in patient using opioid or other type of pain. Tolerance is defined as decreasing response on medicine progressively, so additional dosage will be needed to achieve desirable analgesic effect. Increasing dosage of medicine will not overcome OIH.

OIH is one of exaggerated response to pain secondary to using of the opioid itself. Tapering the dose or discontinuing the opioid may decrease OIH, while increasing the dose may increase OIH. OIH is reversible, but it will take long time to get free from the opioid.² Using high dosage of opioid in long term (days to weeks) relate to increased OIH occurrence, but in few case short term treatment may generate some effects.^{3,4} For example, after initial use, analgesic effect will be seen in 1-5 hours, followed by decreased threshold pain and last in few hours or days.³ Therefore using in short or long term may generate OIH.

OIH secondary to high dose of morphine (opioid) is mediated by 2 non-opioid receptor, glycine and NMDA receptor in spinal cord. This was proven by the evidence that opioid antagonist does not affect OIH secondary to high dose opioid.⁴

CASE

A female, 58 years old, BMI 17,77 complained of severe abdominal pain with NRS 8/10. Patient suffered from lung cancer stage 3 with abdominal metastases. Previously patient took paracetamol 1gr TID, dexketoprofen 25mg TID, parecoxib 40mg OD, morphine 10mg BD and fentanyl patch 50µg.

Subsequently fentanyl 25µg IV was given twice with interval 15 minutes. Patient still complained of abdominal pain, and eventually increased pain to NRS 10/10. Then low dose ketamine 0.1µg/kg slow IV bolus, paracetamol 1gr IV, and tramadol 50mg IV were given. After 15 minutes patient experienced decreased pain to NRS 5/10. Furthermore, ketamine 0.1µg/kg/hour was continued and metoclopramide 10mg TID were added. On our observation, NRS maintain in NRS 4-5/10. Patient refused for invasive treatment and decided to continue palliative care. Patient experienced minimal pain and eventually died after 4 days.

DISCUSSION

Mechanism of OIH

The exact mechanism of OIH has not been defined yet. But there are 2 mechanism in OIH, which are central mechanism, such as NMDA receptor activation, spinal dynorphin, descending facilitation, decreased reuptake,

enhanced nociceptive response, and other mechanisms.

Central Mechanism NMDA receptor activation

NMDA receptor plays an important role in pain signal. Some opioid and its metabolite have an agonist effect on NMDA receptor in spinal cord. As opioids activate NMDA receptor, they generate an influx of calcium which increases the excitability of the neuron. The increased neuronal excitability will facilitate transmission of pain impulses which are caused by every pain stimulus. In this event, the influx of calcium that activates PKC (protein kinase C) is generated by phosphorylation and opioid receptor activation. In addition, the influx of calcium activates NO synthesis in neurons which decreases opioid effect such as morphine.⁵⁻⁹

Spinal Dinorphin

Spinal dinorphin is an endogenous opioid which is mostly active in kappa receptors of opioids and binds to NMDA receptors.¹⁰ Spinal dinorphin levels were seen to increase in continuous infusion of opioids, such as morphine. Increased spinal dinorphin leads to neuropeptide spinal excitatory such as Calcitonin Gene Related Peptide (CGRP) of primary afferents on spinal cord.¹¹ Increased release of neuropeptide excitatory after pain stimulus will generate OIH.¹² Therefore, the analgesic effect of morphine can be relieved by blocking spinal dinorphin effect using antiserum of dinorphin.¹⁰

Descending Facilitation

Rostral Ventromedial Medulla (RVM) is one of the descending pathways, on which modulation of transmission and pain stimulation on the dorsal horn level of spinal cord occur. RVM has 3 different types of neurons: on-cell, off-cell, and neutral cell, of which each of them has an effect to

increase, inhibit or none on nociceptive process in the dorsal horn of spinal cord.¹³

Morphine given in sufficient dosage generates analgesia due to activation of off-cells and inhibition of on-cells.¹⁴ This process was observed in a study on rats who were exposed to long-term morphine and eventually experienced increased pain sensation by increasing the sensation of on-cells to pain stimulus. This study probably managed to explain how OIH occurs.¹⁵ A lesion on the dorsolateral funiculus (the brain part which facilitates descending pathways from RVM to dorsal horn) may prevent or relieve OIH.¹⁶

Decrease Reuptake and Enhanced Nociceptive Response

Decreasing reuptake of nociceptive neurotransmitters such as substance P and glutamate of afferent nerves on spinal cord and increasing response of neurotransmitters on spinal cord after long-term opioid may generate OIH.¹⁷

Other Mechanism

Inhibition of important transport systems such as P-glycoprotein, of which a part of secretion of toxins, including morphine and its metabolites released from cerebrospinal fluid, may play a role in initiating, maintaining and aggravating OIH.³ This transport system was inhibited by medication such as verapamil, cyclosporin, ketoconazole and quinin and results in high morphine levels and its metabolites in CSF.¹⁸

In clinical studies, OIH has been observed in patients given high opioid doses, but not in patients given low and medium doses. Many studies explained that in cases where high opioid doses increased fast (intrathecally), opioid metabolites (such as 3-glucuronide morphine) cause neuroexcitation and induced hyperalgesia, where many patients were

reported with increased pain on pain site.¹⁹⁻²¹

Diagnosing OIH

OIH typically was perceived as difused pain and according to distribution pattern. The new pain expand out of intial pain site. Different to tolerance, OIH become severe in high opioid dose. Increased pain is secondary to decreased effective dose and occur relatively slow, while increased pain in OIH occur rapidly and with strong intensity compared to initial pain.²²

In this case patient experienced hyperalgesia secondary to opioid of which opioid (fentanyl and morphine) had been given for almost 2 weeks. Patient suffered from chronic pain secondary to lung cancer with intraabdominal metastases which suggested patient to consume opioid analgesic in long term. But this long term opioid led to a condition named hyperalgesia. Hyperalgesia is increased pain response to stimulus that usually causing pain.

In OIH, there is an increasing sensitivity of nociceptive receptor secondary to opioid use. In this case patient suffered from severe pain, however the pain was not relieved after fentanyl (2.5 µg/kg) given, furthermore the pain tended to be more severe after fentanyl given.

Strategy to Minimize OIH

Decreasing total dose of opioid consumed may decreased OIH. It may be performed by improving analgesia by using combination of analgesic and intervention strategy.²³

Pharmacotherapy

This strategy might be performed by combining anticonvulsant, non steroid anti imflammatory drugs (NSAID) as

well as to treat patient with neuropathy or nociceptive pain.

Intervention Therapy

Intervention therapy may block nociceptive input and give 2 function, which are helping diagnosing etiology of pain and give benefit of therapy. Regional block, peripheral nerve block, spinal cord stimulation or combination of oral analgesic may be considered as alternative strategy on chronic pain treatment.

Additional alternative treatment suggested in this case is epidural analgesic, of which it will increase nociceptive input, hence decrease NRS as well. However patient did not consent for it.

Psychological Therapy

Studies have explained that cognitive behavioral therapy may become an effective treatment strategy in chronic pain condition. By phsychological intervention, pain and disabilities may improved and opioid dose is lessen.

Strategy to Manage OIH Symptoms

Improtant aspect in managing OIH is confirming the diagnosis. Initial step to consider is increased opioid dose and for efficacy evaluation. If pain decreased by increasing the dose, opioid tolerance will be suspected. On contrary, when pain increased, OIH will be suspected.²³

Decreasing Opiod Dose

Decreasing opiod dose will relieve hyperalgesia and pain scale. A benefit strategy was reported on decreasing 40-50% dose and replacing low dose opiod agonist, such as methadone.

Rotation or Shifting Opioid

Shifting new opioid may regain analgesic efficacy of opioid in patient with tolerance in one type of opioid.

The equivalent dose table of analgesic opioid may be helpful for calculating the dosage of which will give analgesic dose almost similar in potency and bioavailability. When shifting an opioid to another one, it is advised to decrease new opioid dose 25-50% for calculating incomplete cross-tolerance. New opioid dose can be titrated gradually when pain increase or become inadequate.

Generally the medicines used are fentanyl, methadone, and buprenorphin.

Fentanyl

With rotation of opioid from derivative phenanthrene such as morphine to piperidine derivative, fentanyl might help some patient with tolerance. Psychochemistry of fentanyl make this medicine ideally given via transdermal. This medicine has low molecule weight, high solubility in lipid, high potency in optimal skin absorption.

Buprenorphin

Buprenorphin might become alternative choice because it is high solubility in lipid and its unique effect as agonist partial on μ -receptor and antagonist on κ -receptor. Buprenorphin might be effective to treat OIH, where it inhibit spinal effect of dinorphin (known as κ -receptor agonist) that will be increased while on opioid given. This medicine is available in transdermal patch or sublingual form.

Methadone

One of low potent NMDA antagonist, hence it will decrease OIH secondary to high opioid dose. Methadone is used in opioid rotation process to decrease severe effect of improper using of opioid. Rotation of opioid to methadone probably help to decrease OIH by its ability as NMDA receptor antagonist and inhibit norepinephrine and serotonin

reuptake. Other benefit of this medicine including cross-tolerance with opioid receptor, relatively long half time (24-36 hours), few variation in plasma level compared to short acting opioid. The limitation of this medicine is drug interaction more often occur compared to other long acting opioid and shifting an opioid to methadone is complex and need experience.

Antagonist NMDA receptor

Ketamin

It is a non competitive antagonist NMDA receptor. There were some evidences based on clinical studies where using low dose ketamine perioperative (pre, intra, and post operative) may decrease hyperalgesia on the wound during post operative period after opioid intraoperative was given.

Ketamin is available as racemic or as S-ketamin isomer. In a evidence based review of ketamin for chronic pain management, Hocking and Michael suggested IV or subcutaneous ketamin dose ranging 0.125-0.3 mg per hour.²⁴ Ketamin has short analgesic effect and need observation during its infusion, therefore it is considered to give orally in patient response to this intervention. Recommended oral dose is started with initial dose 0.5 mg/kg racemic or 0.25 mg/kg S-ketamin then evaluate for its analgesic response and duration of action. The subsequent dose may be increased gradually 0.5-0.25 mg/kg depend on its response and side effects. The average effective dose in the literature is 200 mg a day.

In this case, eventually after giving low dose ketamine (0.1 mg/kg) pain decreased about 50%. Ketamine given to this patient relieved OIH, which ketamine is as NMDA receptor antagonist. Many studies had performed long term opioid

(few days to weeks) will activate NMDA receptor. When NMDA receptor is activated, it will generate influx of calcium and subsequently increase neuron excitability and produce hyperalgesia.

To increase analgesic effect, other analgesic paracetamol and tramadol were added. Paracetamol is known to have important role, especially inhibition on descendant serotonergic and Prostaglandin H₂ Synthase (PGHS). While tramadol as central analgesic with moderate affinity to receptor μ and low affinity to kappa and delta receptor role as descending spinal inhibition as well by decreasing reuptake of norepinephrine and serotonin.

Dextromethorphan

It is a non competitive NMDA antagonist. It can influence peripheral pain transmission on spinal NMDA receptor. There were some studies explained the ability of dextromethorphan suppressed OIH, but clinically not significant.

CONCLUSION

OIH is one of side effect which the mechanism was unknown well secondary to long term opioid use. Nowadays OIH event increase when opioid increase used for chronic pain condition. In the case failed with opioid therapy, OIH should be considered as differential diagnosis. Before treating patient with opioid, informed consent should be obtained.

In this case, combination of low dose ketamine, paracetamol, and tramadol might relieve hyperalgesia and decrease NRS to 50% compared to initial NRS and sustained for about 2 days.

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