Review Article

Opium Abuse and its Problems in Anesthesia Practice: a Review from Bench to Bedside

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Abstract

Opium is a derivative of opium poppy; the species of plant which its extract is used for preparing opium. Opium abuse is considered under drug dependency classification of psychiatric diseases and opium abusers have a number of major challenges before, during and after anesthesia for surgical operations (i.e. the perioperative period). This article reviews these clinical challenges during the perioperative period to discuss the new clinical findings for these patients and to demonstrate some of the main problems that physicians are encountered.

Keywords: opium, abuse, anesthesia

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Introduction

Opium is one of the oldest substances being abused worldwide. It has been mentioned as an anesthetic medication many years ago, including the citations to opioid by Shahnameh and Avicenna (1-5). However, in the modern medical practice, opioid derivatives are used just as their pharmaceutical compounds and those patients abusing opium impose a great challenge for the medical team especially during the course of an operation (3, 6-9). In this review, we have focused on the problems related to the clinical management of opium abuser patients during anesthesia based on the available evidence in this field.

Evidence Acquisition

The data of this study was gained through a systematic search in PubMed. The search strategy included the following keywords: opium, anesthesia, and anesthesiology. This search was limited to the last 10 years i.e. from 2005 to 2015. For "(opium) AND (anesthesia)", the search resulted in 35 items while for "(opium) AND (anesthesiology)" the search resulted in 31 manuscripts. Then, the overlaps between the two search results were cleared and the final number of manuscripts without being repeated in search query was 50. Throughout the study, we found 40 complementary articles which were in direct relation during the search to the primary 45 articles; so they were added to our primary sample and finally we had 95 articles related to "(opium) OR (anesthesia)" or "(opium) OR (anesthesiology)".

Discussion

Based on the available evidence, we categorized the current studies. For this purpose, we will discuss:

1. **Basic studies** related to problems of opium abuser in anesthesia; which is primarily involved with those researches in basic science

1-1- Genetic factors in pain management for opium abusers

1-2- Receptor response in pain management for opium abusers

1-3- Immunologic mechanisms for pain management in opium abusers

1-4- Anatomic classification for pain control in opium abuser

2. Then, we have described the **clinical challenges** of opium abusers in anesthesia; so, we have used the time course of patient management during a surgical operation as the basis for the clinical classification:

2-1- preoperative period: before the operation

2-2- intraoperative period: at the time of the surgical procedure

2-3- postoperative period: after surgery

1- Basic studies related to problems of opium abuser in anesthesia

These studies explain how chronic opium abuse causes a number of cellular changes in pain perception. First we discuss mechanism based changes, then, we consider 3 anatomic sources for pain control: brain, spinal cord and peripheral nerves. Although these studies have been classified here in a number of sub-classes, often these classifications have overlaps.

1-1- Genetic factors in pain management for opium abusers:

there are a number of genes that predispose people to opium abuse; these genes are the focus for further studies; we should believe in "genetic predisposition" when treating opium abusers during the perioperative period. Also, manipulating these genes could be a potential, but very effective method for changing the behavioral patterns of opium abusers. Possibly, in near future, we could at least detect these genes to treat opium abusers undergoing anesthesia in a more appropriate manner or even, we will be able to produce much more appropriate pharmacologic agents for managing opium abusers undergoing anesthesia (10-12)

1-2- Receptor response in pain management for opium abusers:

It is including the changes in neural receptors that have occurred in opium abusers. These changes affect the pain receptors at the cellular and sub-cellular level. In other words, the receptors of opium have changed their response from a normal response to pain to an abnormal response. These changes have a number of mechanisms, resulting from the reaction of receptors to repeated opium exposure; i.e. opium attachment to the receptor does not elicit the normal intracellular RNA production process; which would result in synthesis of different and abnormal proteins; the resulting change in protein synthesis causes different clinical responses like pain intolerance, hyperalgesia, allodynia or other clinical phenomena seen in these patients which are primarily due to modifications in receptor response; these mechanisms are under further research and contribute an active field of studies which could create new horizons not only for opium abusers but also for other chronic pain patients and include: up-regulation of substance P, up-regulation of Calcium Gene Related Peptide (CGRP), changes in inhibition of Nitric Oxide, modifications in inhibitors of cyclooxygenase, abnormal inhibition of Protein kinase C, modifications in antagonistic response of NMDA (N-methyl-D-aspartate) receptor, changes in antagonism of alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA) receptor, antagonism of cholecystokinin (CCK), changes in L-type Calcium channel response (L-type Ca channel could be blocked with amlodipine to overcome some effects of opium tolerance) (13-17).

1-3- Immunologic mechanisms for pain management in opium abusers:

It includes the interactions of the immune system due to repeated opium exposure. In opium abusers, there are a number of well demonstrated changes in immunologic mediators. Immunologic cells and other components of the immunologic system can induce pain intolerance. Some major immunologic responses in opium abusers include: increased ratio of pro-inflammatory interleukins compared to anti-inflammatory interleukins, expression of NK-1 receptor in the dorsal horn of the spine, facilitating pain conduction, the role of Toll-like receptors especially TLR-5 in chronic pain and its modulation and other components of both innate and adaptive immunology system.

These changes will results in partial ineffectiveness of anesthetic agents, needing extra-normal anesthetic drugs or inability to control stress response which its control is an important goal in anesthesia care during perioperative period (18-21).

1-4- Anatomic classification for pain control in opium abusers**:**

It includes brain, spinal cord and peripheral nerves.

Brain related mechanisms: these are due to changed response of brain to neurotransmitters, cellular signal transduction, signal processing and other neural circuit changes in the brain leading at times to partially permanent trophic changes that result in really great challenges in the clinical field. These changes create an abnormal pattern of signal transmission in different parts of brain including thalamus, locus coeruleus and other nuclei. For example: changes in cholecystokinin level in the rostral ventromedial medulla in repeated exposure to opioids results in up-regulation of CCK; increased CCK will activate facilitation of descending pain pathways, which is relayed via the dorsolateral funiculus, leading to hyperalgesia (13, 17, 22-24), the neurons located in locus coeruleus have specific relation with mu receptor and they are coupled with K channels; while, increased excitatory neurotransmission through nucleus paragigantocellularis could be among the mechanisms that make opium tolerance more severe (13, 22-25), opium by itself could induce brain apoptosis which may be associated with defects in some parts of brain function (26)

neuroplastic and neurotrophic changes are those cellular level changes due to repeated opium exposure that show themselves as different response to opium and opioid agents; these changes are not as much severe as apoptosis; however, they create abnormal patterns of brain function and are so called "pronociceptive changes" (27, 28).

Spinal cord related mechanisms: these are including ascending and descending pathways in the spinal cord and also, local spinal neuronal circuits. Generally speaking, we could classify them into the following mechanisms: pain elicited through descending facilitation which is a main source of spinal cord-elicited pain in opium abusers (17, 29), up-regulation of spinal dynorphin which could also have interactions with bradykinin receptors; the final result would be aggravated hyperalgesia with neuroexcitatory effect and the resulting pronociceptive pain in the spinal cord (29, 30), excitatory neurotransmitters which their release induces severe pain through spinal cord mechanisms (29, 30), role of mitogen activated protein kinase (MAP kinase) family, especially the role of TGF-β activated kinase 1 in inducing pain through spinal cord (16, 30).

peripheral nervous system related mechanisms: the peripheral nerves are subject to important changes in opium abusers that mandate more sophisticated attention; the current trend of research is focused on "silencing" the peripheral nerves to improve quality of anesthesia; though the majority of these findings are still in the research phase and have not entered the clinical era (31, 32); these research studies mainly involve: transient receptor potential (TRP) channel family especially TRPV1 (transient receptor potential vanilloid 1) antagonists and TRPA1 transient receptor potential ankyrin (TRPA1) antagonists; it is now demonstrated that pain signaling in peripheral nerves is mainly done through molecular detectors or transducers of TRP family (especially TRPV1 and TRPA1) and this is why TRPV1 antagonists and TRPA1 antagonists have a great role in pain control; in opium abusers we will use possibly in the next years such these drugs to overcome their pain management challenge; some drugs like N-ethyl lidocaine (QX-314) or capsaicin-derived pharmacologic agents work through these channels (32-34), Toll-like receptor (TLR) 5 stimulation which is among the very novel therapies for pain management in some chronic pain patients like opium abusers; which treats pain by targeting TLR-5 in peripheral nerve endings. Molecules like odanacatib (ODN; a cathepsin K inhibitor), flagellin or QX-314 act through these mechanisms (20, 34-36).

Preoperative period: before the operation

The opium abuser patients often have a number of comorbidities, including increased risk for cardiovascular disease especially coronary artery disease and other cardiac problems (6, 37-40), respiratory problems especially periods of hypoxia and lung cancers, obstructive and restrictive diseases of the lungs (6, 41-44), nutritional and gastrointestinal comorbidities including a wide range of lesions starting from erosions and lesions in the upper GI tract to peptic ulcers and increased occurrence of GI cancers (45-48); also, other system diseases (all related to abuse of opium) are more frequently seen in preoperative evaluation of these patients. In general,

opium abusers are more critical compared with general population regarding health issues (49). These studies have demonstrated that patients with history of opium abuse are at increased risk for underlying diseases which is a challenging issue for anesthesiologists who have to manage the patient and to prepare the patient for the operation (3, 6, 37).

Intraoperative period: at the time of the surgical procedure

During the operation, opium abusers need increased anesthetic drugs to tolerate surgery; in fact, the studies related to these patients have demonstrated some clinical findings that confirm the findings in animal studies or other basic researches: chronic opium abuse is a major etiology for receptor changes regarding sensation and pain perception through different mechanisms explained in previous paragraphs. These changes make the opium abusers more resistant to both opioid analgesics and non-opioid analgesics (like local anesthetics); a clinical finding in concordance with other studies demonstrating the effects of chronic opium abuse on the cellular mechanisms of pain sensation and the bizarre, wide changes in the pain perception structures of opium abusers (50-58).

The problem with these patients during the intraoperative period is that excessive opioid use results in increased chance for postoperative apnea and also, delayed emergence from anesthesia after termination of surgery (59). However, a number of other anesthetic drugs have been used successfully in opium abusers with good results; including ketamine, dexmedetomidine and clonidine in order to replace the commonly used analgesic agents, i.e. opioid derivative (51, 60-63):

- Dexmedetomidine: among the above, dexmedetomidine could be really promising with both opium sparing effects and CNS protecting mechanisms. Dexmedetomidine decreases the needed analgesic requirements in the perioperative period and also, has the property to manage opium abusers during perioperative period; especially the opioid induced hyperalgesia phenomenon; studies have demonstrated that dexmedetomidine could be used for treatment of opium withdrawal syndrome (64-68).
- Clonidine has similar chemical properties with dexmedetomidine while it is not exactly the same; however, clonidine and lofexidine, both alpha 2 agonists, could be used for treatment of opium withdrawal in opium abusers (67, 69).
- Ketamine could be used in opium abusers with fewer respiratory depression events leading to opioid sparing results; however, pain control with ketamine may be associated with a number of delirious states that should elicit cautious when using this agent; the clinical solution is to use ketamine as low dose and infusion in order to prevent the untoward effects as much as possible and to have appropriate analgesic properties (51, 60, 70).
- Paracetamol has an efficacious profile for these patients acting through non-opioid analgesic mechanisms.

In opium abusers, there is an alternative approach, and this alternative approach is to use regional anesthesia; including spinal, epidural and other methods of regional anesthesia; however, the growing bulk of evidence demonstrates that opium abusers have cross-tolerance to local anesthetics, mainly including lidocaine and bupivacaine; although, the mechanism for tolerance is similar between these agents and possibly other forms of local anesthetics are similar regarding the tolerance phenomenon; this clinical and pharmacological phenomenon presents clinically as shortened duration of action (23, 50, 52, 54, 71). This cross tolerance is a very real problem, encountered both clinically and proved in basic studies; the underlying mechanism stands on the basis of the plastic neuronal changes in the spinal cord which create tolerance to both opioids and local anesthetics (50, 52, 53).

A number of adjuvant drugs have been used with relatively successful results leading to improved regional anesthesia duration and increased analgesic properties; some studies focus on adjuvant drugs to local anesthetics in order to improve their length of analgesia in opium abusers to overcome the rescue analgesia properties (53, 72-80): first of all, opioids combined with local anesthetics in regional anesthesia improve the analgesic potency and decrease the rescue analgesic requirements, the safety profiles for most of these drugs are well established; however, sometimes we need to be more cautious to consider their safety profile, other pharmaceuticals, including magnesium sulfate, neostigmine, dexmedetomidine,

paracetamol, midazolam and others agents have been used for regional anesthesia with acceptable levels of success (53, 61, 62, 81-85).

Final problem with opium is that it may be "significant allergen" and may create some forms of anaphylaxis in operating room; the mechanism of allergy is mainly anaphylaxis and other types of immune reaction are not much common; at times, impaired hemodynamics may ensue; even when opium is used as an oral agent and could cause hypotension (86, 87).

Postoperative period: after surgery

There are a few problems in these patients during the postoperative period. First of all, these patients need much more analgesic than the others; so, care should be given to tailor their analgesic needs in such a way that prevents potential respiratory problems on one hand and their history of opium abuse with the resulting opioid tolerance on the other hand. As mentioned above, other drugs are now available that could help us manage postoperative pain in opium abusers with the use of these "novel, non-addictive or less-addictive pain medications" leading to decreased use of opium abuse (88).

However, increased analgesic requirements should not lead the management team to consider any obligatory withdrawal protocol; since the postoperative period is not a suitable clinical interval for decreasing the demands of these patients for analgesia.

Nonetheless, the increased pain perception and increased analgesic requirements are not the only problems with these patients; increased risk of postoperative delirium and postoperative cognitive disorders are among the other major clinical challenges in the postoperative period for these patients (89, 90). A number of different agents have been introduced (91). Dexmedetomidine is a synthetic novel alpha 2 agonist which could help us manage these patients in order to reduce opium dose and meanwhile, to decrease the chance for postoperative cognitive dysfunction (64, 92-94). Other agents like midazolam, clonidine or chlorpromazine could also be effective when administered as postoperative on-demand patient controlled analgesia infusion (95).

Conclusion

Opium abuse is still a major clinical challenge and we need work much more in order to improve our clinical outcomes; though there are a number of major problems during the perioperative period for opium abusing patients, still some promising points exist which help us look at future with constructive and hopeful inspirations; in summary, we can mention the followings:

1- The newly developed drugs like dexmedetomidine could improve the future of anesthesia for all patients including opium abusers in order to decrease the chance of untoward complications (like respiratory depression and postoperative delirium) while creating good analgesia with acceptable level of patient satisfaction.

2- Other older drugs like clonidine, magnesium and ketamine have demonstrated relatively good results for opium abusers with opium sparing effects.

3- Regional techniques using local anesthetic agents could have more efficacy with the help of adjuvant drugs.

Translational medicine would help us very much in near future, possibly by introducing novel drugs that treat pain through non-conventional methods including cellular and sub-cellular modification of pain and also, reversing the effects of chronic opium abuse, in order to manage these patients more efficiently (21).

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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