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Editorial

Update on Opioid Addiction for Perioperative and Critical Unit Care: Anaesthesiologists Perspective

Introduction

Drug addiction remains a challenge in perioperative management for a surgical procedure for anaesthesiologists. Anesthesiologists are increasingly encountering patients with current or previous history of drug abuse in their day-to-day practice, both in the ED (emergency department) or ICU (intensive care unit) and the OR (operating room) [1]. The understanding of such addiction is important not only for patients safer outcome but also better perioperative pain management. Hence, anesthesiologists need to be aware of the possibility of drug abuse and its adverse effects on various body systems and be adequately trained to effectively manage the crucial perioperative period. Greater precautions need to be taken in patients with multiple or combination drug addiction, as opioids are commonly abused with tobacco, alcohol, cocaine and marijuana.

Opioids commonly abused

The risk of opioid addiction increases if it is taken daily in escalating doses. In view of their euphoric and analgesic effects, their abuse continues unabated, leading to rapid development of tolerance, narcotic abstinence syndrome, physical and psychological dependence. The opiates commonly abused include either *prescription opioids* like morphine, fentanyl, sufentanil, meperidine, dextro-propoxyphene, codeine or hydrocodone**;** *illicit drugs* like heroin; and *de-addiction opioids* like buprenorphine and methadone. Heroin, also called *diamorphine or di-acetylmorphine* is commonly abused [2]. There are numerous ways in which heroin can be abused, with its different street-names: sniffing (*snorting*); smoking (*chasing the dragon*); subcutaneous injection (*skin popping*); intravenous injection (*Mainlining*); oral intake; or in combination with cocaine (*Speed Ball*). *Naturally-occurring* opioids like opium, morphine and codeine are derivatives of the poppy plant, *Papaver somniferum,* grown in several parts of the world. Morphine is the main ingredient of opium. The break-down products of opium *(phenanthrenes and isoquinolines)* do not have abuse potential due to lack of central neural effects. *Semisynthetic* opioids which are derived from natural opioids include heroin, hydromorphone, oxycodone and hydrocodone. *Heroin* is often mixed with additives or impurities (known as cutting agents) like sugar, starch, acetaminophen, procaine, quinine, steroids, clenbuterol (a banned beta-2 agonist) and sometimes even synthetic opioids like fentanyl, leading to a multitude of unpredictable effects. Meperidine, dextropropoxyphene, fentanyl, alfentanil, sufentanil, carfentanil, pentazocine and butorphanol are *synthetic opioids* (prepared in laboratory). Meperidine has significant abuse liability [3]. Its neurotoxic byproduct (*1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine*) has the potential to produce irreversible Parkinsonian-like syndrome. *Fentanyl* abuse was first noted amongst the medical community. Due its very high potency, its abuse is less common in non-health care addicts, due to fear of fatal overdose. Fentanyl and its analogues (especially the transdermal or the transmucosal preparations) can be injected, snorted, swallowed or smoked. In order to decrease the abuse potential of *pentazocine*, it is mixed with naloxone (an opioid anatagonist) to counter the morphine-like effects if its tablets are dissolved and injected. Methadone was initially synthesized due to shortage of morphine and later utilized for narcotic de-addiction. Since in high doses it can block the effects of heroin, it is ideal for detoxification and maintenance programs. It is being increasingly used for chronic pain management and it can be abused with other prescription agents like benzodiazepines and alcohol.

Adverse effects and overdose of opioids

Anesthesiologists may be frequently involved in the care of patients with acute drug-overdose or with chronic opioid addiction, presenting either for elective or emergency surgery or critical care. Not only do these drugs cause physiological damage to vital organs, but also permanent damage to immune system and brain areas responsible for memory and pain mediation. The lungs, heart and kidneys are at significant risk from the use of injected or inhaled illicit drugs. There increased incidence of pulmonary infections, granulomatous diseases, barotrauma, aspiration pneumonitis and non-cardiogenic pulmonary edema [4]. Heroin inhalation can produce severe and life-threatening exacerbations of asthma. There can be excessive sympathetic stimulation during drug-induced withdrawal from opioids, precipitating myocardial ischemia in susceptible population. In view of their central nervous system (CNS) depression, overdose can cause stuporous states, especially when abused with alcohol or sedatives. Coma can lead to pressure-induced muscle damage and *rhabdomyolysis*. Clinically, opioid overdose can be diagnosed by slow respiratory rate, increased tidal volume and *miotic pupils* [5]. It is treated with intravenous opioid-antagonist, Naloxone (0.4-0.8 mg, upto a maximum of 2 mg) for reversal of respiratory and CNS depression. Sometimes, endotracheal intubation with short-term mechanical ventilation is required to tide

over the crisis. The renal effects of heroin abuse include the following: glomerulonephritis, secondary amyloid deposits, *heroin-associated nephropathy* (HAN) progressing to end-stage renal failure, *human immunodeficiency virus-associated nephropathy* (HIVAN) and nephrotic syndrome [6]. For the opioid-abusing parturient, intra-uterine drug exposure can cause fetal intra-uterine growth retardation (IUGR), congenital anomalies, fetal distress and neonatal opioid withdrawal. Complications occurring due to mode of drug abuse include infectious diseases, pyogenic abscesses, cellulites, non-healing ulcers and peripheral aneurysms. There is an ever present risk of viral infections in intravenous drug abusers, like hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV/ acquired immunodeficiency syndrome (AIDS) [7]. Hence, *universal precautions* should be taken by all health workers caring for these patients and complete asepsis should be practiced during any procedure in them.

Pharmacotherapy for opioid de-addiction

Anesthesiologists need to be aware of the drug therapy and the timing of its last dose, in-order to decide their plan of management. Pharmacotherapy for opioid de-addiction includes:

- Opioid maintenance programs;
- Treatment of withdrawal symptoms;
- Prevention of craving and management of overdose or toxicity.

Drugs commonly used for pharmacotherapy include methadone, LAAM (levo-alphacetyl-methadol) and buprenorphine. *Methadone* is available as oral solutions, tablets and injections [8]. Even though it blocks the narcotic effects and reduces craving, it provides the classic euphoric state of heroin. Its dose is 30-40 mg per day, with duration of action of 24 hours. It is administered in outpatient treatment programs under strict supervision on a daily basis. Due to its ability to produce tolerance and dependence, stopping of methadone maintenance can precipitate withdrawal. *LAAM* is a synthetic opioid, structurally similar to methadone and longer half-life, allowing for less frequent dosing. Since it has greater abuse potential and risk of cardiovascular toxicity, it is not used as a first-line agent in pharmacotherapy. *Buprenorphine*, a semi-synthetic (partial-agonist) opioid, has several advantages, including long duration of action, oral administration, less respiratory depression, presence of ceiling effect and improved safety profile. It can be combined with a pure opioid antagonist, Naloxone (*Suboxone*), which can be injected intravenously. Suboxone does not need daily supervision and has greater therapeutic window [9]. Some opioid-dependent patients may be treated with opioid antagonists, like naltrexone. Since the development of its long-acting, extended-release form (*Vivitrol*), naltrexone can be given as monthly injections so as to improve patient compliance. Withdrawal symptoms can be treated with clonidine (alpha-2 agonist), loperamide, diphenhydramine and doxepine. Clonidine acts by replacing opioid-mediated CNS inhibition with alpha-2 agonist mediated inhibition [10].

Preoperative evaluation

Pre-anesthetic evaluation, apart from routine investigations, must focus on establishing the existence of opioid abuse, pharmacotherapy for detoxification (current drug, dosage and time since last dose), organ system evaluation, viral markers screening and, if required, detailed psychiatric assessment. There are several constraints of urinary drug testing (UDS), as many standard tests report only as positive for certain opiates and fentanyl cannot be detected [11]. Only current or recent abuse can be detected and not past abuse. Immunoassays for specific opioids can have false-positive results and they must be confirmed by gas chromatography, which is both time-consuming and expensive. The *modified* Conjoint screening questionnaires for alcohol and other drug abuse (*CAGE-AID*) questionnaire can also be utilized to elicit opioid abuse [12]. Detailed questioning must also be done in a "*clean addict*", who was previously an opioid addict and successfully undergone withdrawal therapy and is currently not on any pharmacotherapy. Nowadays, hair analysis is being contemplated in addicts for detecting chronic drug abuse [13]. If a patient is on preoperative methadone maintenance therapy, it is advisable to continue methadone till the morning of surgery. *Naltrexone* should be discontinued atleast 24-72 hours prior, if opioid based anesthesia is planned [14]. It should then be restarted after 5-7days, remembering to cover the intervening period with non-opioid analgesics. If these agents are continued, then it is better to avoid intra-operative opioids to prevent precipitation of withdrawal or other adverse reactions.

Anesthetic management

Anesthetic implications of the opioid–abusing patient includes:

- Higher analgesic requirements;
- Development of tolerance;
- Management of physical and/or psychological withdrawal symptoms;
- Opoid-induced-hyperalgesia (OIH);
- Complications due to route or mode of opioid abuse;
- Unpredictable drug interactions; and
- Difficult post-operative pain management.

The key to success lies in creating a fine balance, by *avoiding both under-and over dosage*. In opioid addicts, a non-opioid based anesthesia can be safely administered [15]. This regime includes ketamine, benzodiazepines, volatile anesthetics, paracetamol non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 (cyclo-oxygenase) inhibitors. Other adjuvants with opioid-sparing effect and particularly useful for analgesia include, clonidine (0.3 mcg/Kg bolus intravenously, followed by 0.3 mcg/Kg/hour infusion), ketorolac (30 mg intarvenous every 6-8 hours) and pregabalin (150-300 mg/day oral). Caution must be exercised, as opioid abuse causes cross-tolerance to other CNS depressants and decreases the minimum alveolar concentration (MAC) of inhalational anesthetics. Other equally important considerations include difficult venous access, malnutrition, dehydration and electrolyte imbalances (leading to hypotension on induction). Regional techniques are a boon in such patients for both anesthesia and analgesia [16]. Ultrasound-guided nerve or plexus blocks can be performed pre-emptively for decreasing anesthetic requirements and can be extended for post-

operative pain relief. If an opioid- based regime is chosen, then it must be remembered that *the opioid dose requirement is increased by 30-100%* [17]. It is better to *avoid mixed opioid agonist-antagonists* like nalbuphine, butorphanol and pentazocine in patients on opioid withdrawal regime.

The vital peri-operative step in patients chronically on opioids is to calculate their 24-hour dosage [18] and convert it to an equivalent dose (oral or intravenous) for maintenance. The following formula can be used for calculation:

Hourly opioid requirement = Twenty four-hour dose/ 24.

The doses of various addicted drug among opioids may be calculated by their appropriate conversion (Table 1). In perioperative management, the different opioids may be converted into morphine equivalent and then it may be administered to have optimal pain control. The 30 mg of oral morphine is equivalent to oxycodone 20 mg, hydromorphone 6 mg, oxymorphone 10 mg, hydrocodone 20 mg and codeine 120 mg. These oral morphine equivalent may be converted to intravenous morphine with its one-third dose equivalent. Assuming a 30 to 50% increase in acute opiate requirements (as compared to opioid-naïve patients), the total final dosage can then be adjusted as per individual patient.

Early anesthetic consultation during antenatal visits is recommended for the opioid-abusing parturient. Labor epidural with local anesthetics can be given, which can be continued for operative delivery if required [19]. If general anesthesia is warranted for emergency section, then a non-opioid-based anesthesia with full stomach precautions and with preparations for neonatal resuscitation can be administered.

Postoperative pain relief

Ensuring adequate post-operative analgesia is of paramount importance, to prevent relapse to addiction by insufficient analgesia. The secret behind a successful postoperative care is to strike a fine balance between patient safety and comfort. Alternate methods of pain relief must be practiced with co-analgesics like intravenous paracetamol, liposomal bupivacaine, α2 agonists (clonodine and *dexmeditomidine)*, COX2 inhibitors, NSAID`s, pregabalin and gabapentin. Recent research has supported the role of dexmeditomidine, which is 10 times more potent than clonidine, for postoperative sedation and analgesia in opioid addicts [20]. Electronic *patient controlled analgesia* or PCA (intravenous, epidural or continuous plexus blocks) pumps go a long way in gaining the confidence of the patient and giving him a feeling of self-control [21]. For patients on preoperative buprenorphine therapy, there are four broad methods [22] of acute pain management:

1) Continue buprenorphine maintenance therapy, with the knowledge that these patients will require higher than usual doses of short-acting opioid to achieve desired effect due to persistence of buprenorphine on opioid receptors;

2) For less invasive surgeries, buprenorphine itself may be adequate, by dividing it into TDS (three times a day) dosing, as it has inherent analgesic properties;

3) If buprenorphine is discontinued, then full opioid analgesics can be given with careful watch for withdrawal symptoms; or

4) Buprenorphine can be converted to equivalent Methadone @ 30-40 mg/day in standard TDS dosing. This requires detailed documentation of methadone therapy with the authorized de-addiction centres.

Opioid-induced Hyperalgesia (OIH) and Tolerance

Tolerance is defined as "the need for markedly increased amounts of substance to achieve intoxication or desired effect, and markedly diminished effect with continued use of the same amount of substance" [23]. It is due to desensitization and down-regulation of opioid receptors. *Opiate hyperalgesia or hyperesthesia* is defined as a state of nociceptive sensitization caused by exposure to opioids [24]. It is a paradoxical phenomenon whereby patients on opioid treatment become more sensitive to certain painful stimuli. It should be suspected when the effect of opioid treatment wanes in the absence of disease progression or if the patient develops *allodynia* (pain sensation from a normally non-painful stimulus). *OIH* is due to neuroplastic changes in the peripheral and central nervous system, leading to sensitization of pro-nociceptive pathways. The mechanisms proposed include spinal sensitization to glutamate and substance P as well as NMDA (n-methyl-D-aspartate) receptor activation. OIH can be difficult to treat and involves tapering opioid dosage, substitution with non-opioids and use of NMDA anatagonists, especially ketamine.

Anesthesia for ultra-rapid detoxification

Ultra-rapid detoxification [25] was developed with the idea of circumventing the addicted patient from experiencing the unpleasant effects or withdrawal symptoms of the detoxification process. It is done in a controlled and closely monitored setting, such as the ICU (intensive care unit) or OT (operation theatre). The patient is advised

Table 1: Conversion of opioid doses and calculation of perioperative opioid dose requirements:

Drug	Average oral dose and frequency	Equivalent intravenous dose	Total 24 hour oral dose	Total 24 hour intravenous dose	Hourly requirement
Morphine	30 mg every 4 hr	10 mg	180mg	60mg	~3mg per hour I.V.
Oxycodone	20 mg every 3hrs	-	160mg	-	~ 6 mg per hour oral
Hydromorphone	7.5mg every 4 hours	1.5 mg	45 mg	9mg	~ 0.4 mg mg per hour I.V.
Meperidine	300mg every 4 hours	100mg	1800mg	600mg	25 mg per hour I.V.
Methadone	20 mg every 12 hours	10mg	40mg	20mg	~ 0.8 mg per hour I.V.
Hydrocodone	30 mg every 3 hours	240mg			24 mg per hour oral

NPO (nil per oral) orders from the night before and Clonidine patch (0.2mg) started 12 hours prior to the procedure. Premedication is given in the form of aspiration prophylaxis, anti-emetic and an anti-cholinergic agent. After instituting all standard monitoring, clonidine is administered I.V with the aim of maintaining the heart rate < 60 beats/minute and the systolic blood pressure < 100 mmHg. Rapid sequence induction is facilitated by succinylcholine, propofol or methohexital. Anesthesia is maintained with inhalational agents and further muscle relaxants are avoided. Withdrawal is precipitated with intravenous opioid antagonist, Naloxone. Post-procedure, the patient is extubated, placed under diligent observation and maintained on oral Naltrexone (50mg), which is continued for atleast 6 months. To improve patient compliance, further research is being done to use naltrexone implants and gabapentin after this detoxification process.

Conclusions and Clinical Pearls

As perioperative physicians, anesthesiologists can act as pioneers in the de-toxification process of opioid addicts. Adequate analgesia must never be with-held and a fine balance of optimum anesthesia must be created by avoiding both under-and over-dosage. Attempts must be made to calculate the 24-hour opioid requirements for covering the perioperative period in patients on chronic opioid therapy. With the advancement in scientific knowledge and advent of newer agents, the withdrawal from opioids has been made more tolerable for addicted patients. Creating awareness (both among medical professionals and patients) about the ill-effects of opioid abuse and the various modalities available for de-addiction is the corner-stone of success. Specialized training of anesthesiologists in dealing with drug-addicted patients is the need of the hour to improve the overall perioperative outcome.

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