

The Challenges for Anesthesiologists in the Operating Room Managing Patients on Buprenorphine for their Addiction

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Abstract

Addiction in the United States has become a national crisis. While physician and other providers are decreasing the amount of opiates that are being prescribed for either acute or chronic pain we, as a country still see many patients abusing opiate-based medications. One form of treatment for these patients with substance use disorder would be medical assisted treatment. Medical assisted treatment can certainly help stabilize the patient as they start the road to recovery. One portion of the medical assisted treatment would be medication management. Medication management for these individuals can be either methadone or buprenorphine. Both these medications can be challenging for physician and anesthesia providers given the fact that they block opiate receptors. This blockade of opiate receptors certainly can assist with sobriety but in terms of acute pain management can be a complicating factor.

Given these facts that many patients are now presenting to the emergency room as well as operating room on these medications we are left as an anesthesiologist and anesthesia providers on how to manage these patients correctly. This paper will hopefully give some insight on how to treat these challenging patient's undergoing surgery.

Keywords: *Buprenorphine; Addiction*

Introduction of Buprenorphine

Buprenorphine acts as antagonist as well as partial agonist for kappa opioid and mu receptors. It is about 30 times as potent as morphine sulfate. The activity at the mu receptors is low efficacy, demonstrated by an attenuated maximal clinical response through a range of clinical doses, which is characteristic of partial agonism. The observed terminal half-lives ranged from 19 - 28 hours in one study, although the range of the observed half-life of buprenorphine is broad, ranging from 20 - 70 hours (typically referenced as approximately 37 hours). The sublingual buprenorphine formulations are used for cure of opioid dependence and addiction. Certain medications such as Subutex and Suboxone have been developed for this core purpose. The formerly mentioned medication is marketed in form of tablets either of 2 mg or 8 mg while the latter one is a conjugate of buprenorphine and naloxone in 4:1 ratio i.e. 2 mg with 0.5 mg to 12 mg with 3 mg, which were developed to reduce the potential abuse of buprenorphine [1].

Buprenorphine preparations

Buprenorphine is derived from thebaine, an alkaloid of morphine, and possesses partial agonism to mu as well as delta receptors with variable affinity and also exhibit antagonist ability to kappa receptors on the other hand. It should be noted that the activity at mu-1 versus mu-2 receptors specifically is unclear. Due to its relatively more significant potential than morphine sulfate, it has reduced withdrawal symptoms when discontinued [1].

Buprenorphine as pain killer

A diverse range of parenteral and transdermal formulations of buprenorphine are currently available at commercial scale for the remedy of chronic pain that include Buprenex, Belbuca and Butrans. In contrary, sublingual or buccal buprenorphine are independent of CSAT/SAMHSA or DEA waiver [1].

Perioperative considerations in patients on buprenorphine formulations

Buprenorphine/naloxone therapy is very effective in maintenance of patients dependent upon opioid and treating withdrawal with lower abuse potential as well as pharmacodynamic advantages to methadone. Relatively higher dosage of buprenorphine/naloxone is required than usual opioid dosage for the control of cases with severe acute pain. Discontinuing buprenorphine/naloxone therapy to treat acute pain requires at least 72 hrs of monitoring for potential overdose. Buprenorphine therapy is a more reliable alternative which can be used in place of conventional methadone therapy for treatment of chronic pain as well as opioid-dependence. Traditional intravenous opioids that are used for sedation and post-operative maintenance of pain are ineffective within the patients which would be taken under buprenorphine therapy. There are two strategies which are used for the peri-operative management of buprenorphine/naloxone:

1. **Continue buprenorphine:** Supplement with short-acting opioids such as fentanyl. Divide buprenorphine maintenance into every 6 - 8 hrs.
2. **Discontinue buprenorphine:** 72 hrs prior to the surgery while for analgesia, traditional opioids can be used.

This can be either a rapid or slow taper with the goal of 72 hrs without buprenorphine before the surgery [1].

Perioperative pain management

It is not recommended to hold buprenorphine (including preparations with naloxone) for extended durations prior to the procedure. Using the longest documented half-life for buprenorphine products, some institutions have implemented holding for 14 days, conferring increased risk of withdrawal as well as relapse of opioid. Therefore, it is not recommended to continue buprenorphine products throughout the perioperative period in procedures where there will likely be a considerable opioid requirement. Postoperative pain is treated with exceedingly high amounts of opioid in attempt to "treat through" buprenorphine products. Using this method, there is a concern for abrupt respiratory depression when enough buprenorphine has been eliminated from the body to allow the high amounts of supplemental opioid to bind to the mu receptors. This often necessitates ICU level care for close respiratory monitoring. In the event that a patient has not appropriately held buprenorphine preparation, elective procedures should warrant a discussion with the patient and surgical team regarding possible rescheduling to ensure better postoperative pain control. For non-elective surgery, regional anesthesia should be considered when applicable and non-opioid adjuvant therapy should be used as the main line of analgesia (as described above). Management of buprenorphine prescriptions can solely be done by specialized practitioners and contact with the primary prescriber can be difficult. Thus, communication with the primary licensed prescriber of buprenorphine products should be performed as early as possible when the decision to have an operative procedure is made, and the primary prescriber should work with the patient to hold the medication for the necessary amount of time. The patients with high risk of relapse, the primary care provider could prescribe a one day dose of an alternative pure opioid agonist if the patient begins to experience opioid withdrawal towards the end of the holding period [1].

Buprenorphine plays vital role in the cure of OUD with the help of its sublingual formulation having 30 to 50 percent bioavailability while that of the PO formulations is decreased by 3 to 14 percent because of the extensive first-pass elimination. Cytochrome-P450, a liver 3A4-enzyme, is responsible for the metabolism of this drug by producing a metabolite, norbuprenorphine, as a byproduct which is known for its opioid activity whereas, significance and potency is unclear. This particular metabolites interacts bile at the first then excreted out in form of feces [2].

Half-life of buprenorphine

Half-life of buprenorphine is entirely dose as well as route-dependent. In case of BMT, high dosage is required whereas, in that of chronic pain, low dosage plays significant role. The estimated half-life of buprenorphine is around 20 to 70 hrs for former dosage while 2 to 6 hrs for the latter one. In opioid-dependent healthy males, plasma of sublingual buprenorphine reduces to half of its concentration

within 26 hrs and with the help of computed analyses, considerable variations in half-lives of plasma were observed i.e. between 6 to 96 hrs. Though, the time taken among ingestion and maximum level of plasma lies between 30 minutes to 3 hours.

The diversity among dosage is the most crucial factor in therapeutics. As about 2 mg to 4 mg of dosage is needed against cancer or chronic pain for over a day in consecutive 6 hours. While in case of BMT, it is utilized in excessive concentration up to 32 mg within a day. Beyond 32 mg/24hr, a ceiling effect in terms of analgesia occurs due to the partial agonist effect of buprenorphine at the opioid receptor.

The mentioned drug is found commonly in medical history of patients which might cause complications in perioperative settings of such patients. The same properties that make buprenorphine advantageous for management of addiction and chronic pain present a challenge to anesthesiologists [2].

Management of perioperative pain within BMT-stabilized patients

Some of the steps for management of perioperative pain within patients stabilized by BMT are as follows;

1. BMT needs to be maintained as prescribed along with the addition of short interacting opioids. The patient might need increased dosage of opioids as an agonist in order to attain anticipated effect.
2. Division of dosage of BMT to be administered thrice a day for utilizing their analgesic characteristic. This procedure is highly recommended to the patients who treatment encounters several hurdles or complications and ultimately leads to invasiveness and is not usually painful.
3. BMT needs to be stopped while opioid agonists have to be administered in place of it for the assessing of withdrawal.
4. Convert into methadone (30 to 40 mg per day) for deterring the withdrawal symptoms. It should be prescribed for curing pain at the first place than deterring withdrawal.

While maintaining a patient by buprenorphine, short-acting opioids have to be supplemented as well as titrate in order to control the pain as the effective dosages might be a lot higher that may cause the respiratory depression risk to the patient. Instead of reverting to methadone prior to surgery, certain other means of control are also available such as low dose ketamine infusion, NSAIDS, utilizing the indwelling peripheral nerve catheters and maximizing the regional techniques [2].

Buprenorphine, a partial agonist, is relatively safer than that of the methadone, a complete agonist. As far as it is concerned, the decline in respiratory depression as well as euphoria was observed. The formulations of buprenorphine were marketed in 2002 in different forms, some with the naloxone which only gets active, when the drug is either directly injected into body (intravascular) or snorted.

Post-operative pain management strategies

The collaboration with prescriber of buprenorphine is of immense importance for stopping this drug and consult any full agonist as substitute. It is already known that time span of approximately 60 hours is required by μ receptors in getting rid of this drug. In case of getting back to buprenorphine, there should have to be a period, opioid-free, for over a day. This could only be beneficial or appropriate in the cases of mild to moderate pain [2].

Duration of holding of buprenorphine

The duration of holding buprenorphine prior continues to be a subject of debate. The pharmacokinetic profile of buprenorphine formulations showed similar elimination half-lives ranging from 16.4 to 42 hours. One that appeared to be shorter acting is the buccal film formulation of buprenorphine with naloxone (Bunavail), which reported its elimination half-life of 16.4 to 27.5 hours. Given that it requires 5 half-lives for a drug to be cleared from a system, using the generally accepted half-life of 37 hours would require 185 hours, or 7.7 days of cessation prior to surgery. The difficulty stems from inter-patient variability of the elimination half-life of buprenorphine. Holding buprenorphine for 72-120 hours (as stated in Table 3) allows for approximately 2-3 half-lives to pass, with the goal that the patient's buprenorphine levels have been reduced to a point where high affinity pure μ -opioid receptor agonists can have clinical effect. Patients on the shorter acting buccal film formulation of buprenorphine with naloxone (Bunavail) can potentially hold buprenorphine for a reduced duration of time prior to operative surgery (2 to 3 days versus 3 to 5); however, caution should still be exercised and the patient have to be observed for the withdrawal or relapse as well as difficult perioperative pain control [1].

Managing patients under maintenance buprenorphine treatment

The continual of buprenorphine as a first preference is recommended for BMT along with the use of certain opioid for the analgesia while the titrating with the help of various short acting oral medications such as immediate release (oxycodone or morphine) or opioid analgesic (fentanyl) as per the requirement of analgesic effect. However, the continuous infusions are not favored at this step. The dosage of opioids should be high enough to compete with that of buprenorphine.

On the other hand, the lower dosage of buprenorphine i.e. 2 mg to 8 mg/day after 6 to 8 consecutive hours in order to use it as analgesic agent as well. Moreover, the patients under facial trauma and unconsciousness could not take the sublingual preparations prior to 3 days of surgery. The opioids, that have been used in procedure needs to be re-assessed on regular intervals. The half-life of buprenorphine last for about 3 to 4 days within brain as persistence along with opioid which gradually decreases with the passing day [3].

Advices for the patients getting maintenance therapy with buprenorphine (BMT)

The maintenance buprenorphine therapy is not that common among the clinical experiences while curing the cases of patients with acute pain, hence, the use of this drug seems to be limited. The pain control is a little bit difficult with the use of opioids as they lack the higher affinity to μ receptors, unlike buprenorphine which is usually administered sequentially or concurrently. A broad range of treatment strategies are available for the acute pain with the requirement of opioid analgesia for BMT.

1. The clinical experience of treatment approaches regarding this technique is limited which needs to be elucidated by developing enough experience and involvement in these treatment approaches. All the cases are kept under monitoring for the evaluation of dissociation of buprenorphine from μ receptors to make its conjugated molecule, naloxone, available. The respiration and consciousness level should be checked strictly.
2. The most efficient as well as effective dosage of different drugs have already been optimized which have to be administered in patient to get their effect. However, any dosage less than that might not provide the particular task done i.e. lack of effective analgesia and opioid tolerability that have been getting OAT. Hence, the divided dosage of buprenorphine and opioid for analgesia are in dire need of an additional agonist analgesic of opioid i.e. morphine.
3. The opioid agonism analgesics can be used as an entire therapy with the discontinuity of buprenorphine management therapy for attaining analgesia and avoiding the withdrawal. For instance, immediate release (IR) and sustained release (SR). While, in case of acute pain resolution, all the process goes vice versa and induction protocol would be applied.
4. The management of opioid agonism or withdrawal of BMT can be done by reverting back to methadone therapy (30 mg - 40 mg per day) when the patient is admitted to hospital. The methadone attaches relatively less tightly at μ receptor than buprenorphine and the concentration of methadone is optimum for prevention of the acute withdrawal within numerous patients. Hence, some additional responses by opioid agonism analgesics are expected which involve the increment in analgesia with the elevated dosage. In case of persistence of the withdrawal, the dosage of methadone have to be increased by 5 mg-10 mg subsequently. This strategy provides the titration of opioid analgesia for the control of pain even if the opioid withdrawal is absent. As long as the acute pain gets resolved, this particular treatment therapy needs to be discontinued and buprenorphine maintenance therapy has to be resumed by induction protocol. In case of discharge of patient, opioid agonist analgesics would still be needed with the discontinuity of methadone treatment approach and the cure would be done by process mentioned in 3rd BMT approach. Even if BMT has to be resumed as well as induced once again post-treatment of acute pain, this should not be forgotten that it may precipitate opioid withdrawal as both of these therapies work antagonistically. Similarly, the patient receiving opioid agonist analgesics on routine also give some time after withdrawal and prior to resuming of buprenorphine therapy for maintenance of pain control [4].

Bup/Nal therapy for pain control in patients without opioid dependency

Under the low dosage of buprenorphine, μ opioid receptor gets partially activated. Under moderate dosage, the opioid agonist of buprenorphine hits a limitation so that no further improvement in enhancement of analgesia could be done even with increased dosage. Under the high dosage, the analgesic effect can still be limited further with action of buprenorphine as opioid antagonist. Therefore, Bup/

Nal form of buprenorphine can cause the weak effect for providing the relief to patients from pain in without any opioid addiction that is present in the opioid agonism analgesics [5].

Implications of Bup/Nal in clinical anesthesia and perioperative pain management

Various challenges had been experienced which require detailed examination of perioperative and intra-management by Bup/Nal therapy in patients. Whereas, the implications of this therapy within perioperative management of pain and clinical anesthesia remains unclear. Buprenorphine, being a partial opioid agonist, can restrict the attachment of other opioids to the μ receptors as it exhibits high affinity. Moreover, higher dosage of opioid would be required during the period of perioperative and intra-management. The Bup/Nal therapy seems to be insufficient for providing a standard anesthesia based upon opioid but the adequate analgesia would be produced by some other agents. This therapy might get replaced with some alternative one having opioids from 3 - 7 days prior to postoperative and intra-pain management of anesthesia. The resumption of Bup/Nal therapy postoperatively, after replacing with other opioids preoperatively needs to be managed carefully in order to get the adequate relief from pain maintained. In high dosage of opioids, the induction of withdrawal symptoms needs to be determined whether they were posed either by buprenorphine itself or along with naloxone. There is still very limited information available on impacts of buprenorphine upon the clinical anesthesia till the present date [5].

Strategy for preoperative management of buprenorphine

In most of the cases, the discontinuation of buprenorphine is recommended for the avoidance of analgesic ceiling effect as it lack the clear consensus on the best management strategy otherwise, the increased dosage of opioids would be needed as supplement. The risk of relapse appears with the discontinuity of ORT which would then be assessed upon individual basis. By keeping the increased prevalence of addiction and abuse of such substances in USA, the experts with addictive medicine and their perioperative management could be advantageous for this approach while heading ahead. Within the patients with discontinued medication, the therapy has to be restricted before at least 3 days of surgery. The metabolism of this drug takes sufficient time and takes place in liver then eliminated via biliary system within 72 hours usually. The opioid agonists of μ receptors are more effective when used for post-operative analgesia which clears a fact that several patients are tolerant to them and takes up higher dosage. Even the buprenorphine lasts for 40 hours within body while the half-life of its sublingual dosage is around 37 hours [6].

Buprenorphine safety in curing opioid dependency

The treatment of heroin addicts with sublingual formulation of buprenorphine (8 mg) have not shown any significant morbidity within time span of 36 days. The efficacy of buprenorphine was reported to be same as that of methadone within a random study of patients with opioid dependency during maintenance program. It showed retentiveness in less morbidity of heroin addicts, if the drug was not discontinued for over a year [7].

Treatment with maintenance therapy with buprenorphine (BMT)

The dosage intervals of BMT varies greatly among all the patients. The analgesic duration of this approach might have been shorter than that of the suppression of opioid withdrawal similar to methadone. The division of regular dosage into 3 - 4 times a day could be enough for giving analgesic effect but opioid agonist would still be needed additionally. Buprenorphine, as μ opioid agonist, shows both analgesic as well as anti-hyperalgesic characteristics. The affinity of μ receptors is high along with slow offset kinetics which leads to interference of the resultant blockade by providing effective management of acute pain with the help of some other μ opioid agonists. There is still no evidence regarding continuation or discontinuation of high dosage of buprenorphine within perioperative period but the conflicting recommendations do exist in the meanwhile [8].

Patient's management by BMT

As per available evidence and experience, it is clearly believed that buprenorphine dosage needs to be restricted prior to surgery for the management of patients as first preference which can be attained gradually by reducing the dosage of maintenance therapy within time period of two weeks by decreasing 2 mg of dosage within 2 to 3 days and then discontinued entirely. The discontinuation can also be done for 3 days with immediate effect but it may pose various risks regarding withdrawal symptoms as well as relapse. The patients who cannot tolerate the sudden discontinuation must be provided with any other opioid such as methadone dosage as replacement on buprenorphine prior to surgery [9].

Chronic pain management of patients by buprenorphine

The baseline regimen can be continued by supplementing it with some additional increased dosage of buprenorphine which seems to be an appealing choice which is readily used in cure of opioid addiction for the avoidance of re-exposure to opioids. The concern of ceiling

effect would be useful for prevention of sufficient analgesia as describe by a case report regarding its control of adequate pain with the help of buprenorphine dosage as a supplement. In contrary, buprenorphine can be continued preoperatively with the addition of some traditional opioids, if no issue is experienced with the increased dosage and the inadequacy of pain. An encountered risk to this approach is that the increase in dosage is required which will only then be counteracting the receptors with higher affinity by showing the partial antagonist effects. The significant concerns due to such higher dosages could be respiratory depression and sedation which will also require postoperative monitoring [10].

Evaluation and screening tools for patients

The patients with opioid addiction could be a major challenge for anesthesiologist for starting a surgery. A broad range of strategies are present within subpopulation for analgesia whereas, the foremost step is to obtain a comprehensive and detailed history of the patient in order to avoid complications. The building of trust and communication in good line can ease up the inquiry process a lot which refrains the patients from holding things and allow them to be honest regarding their drug-based history. While taking history of patient, the professionalism and nonjudgmental attitude should be the most privileged attributes [11].

Buprenorphine and methadone for pain management and history of substance abuse

The management of patients with acute pain could be really challenging if they are still on long term maintenance by drugs like buprenorphine and methadone. Several misconceptions exists regarding to the management of patients with acute pain that could generally be by opiophobia, a condition resulted in patients taking opioids as well as other non-opioid analgesics as medication. The other major concerns which cannot be neglected while cure involve addiction relapse, drug diversion and fear of respiratory depression [11].

Intra-operative management

According to PSH model at the day of surgery, anesthesiologists may have the chance of carrying out detailed preoperative examination, assessment as well as management approaches while caring for patients. The finalized plan of anesthesia could be advised to patients and their analgesic regimen involving any opioid dosage should have to be continued till surgery. The nature of pain and information of analgesic agents along with their mechanism have to be noted while tailoring of analgesic plan. Pain due to its complexity and subjective nature is classified into five categories such as idiopathic, mixed, neuropathic, nociceptive and psychogenic [6].

In case of major surgery, even more analgesics would be needed most likely. It is recommended that fentanyl, a short acting opioid (Bup/Nal), can be administered on regular basis as the high dosage of opioids is needed. The increased dosage might help in managing the pain in multimodal analgesic regimen. Unpredictable side effects and results could be obtained while struggling for overpowering buprenorphine effects by using some other opioids. The need of additional opioids can be eliminated by peripheral nerve blocks in case of lower or upper-extremity surgery. The amount of opioids can be minimized by multimodal approach involving APMS at early stage. The anesthesiologist makes the decision whether a drug needs to be continued or not preoperatively. For the effective and safe perioperative care, the coordination and collaboration plays a vital role in complicated population of patients [6].

Buprenorphine and sedation

The deep and moderation sedation plays a crucial role in reducing anxiety and pain during maxillofacial and oral surgery. Combinations of general anesthetics for acquiring amnesia, anxiolysis and analgesia along with short acting benzodiazepines and opioids are required for the sake of outpatient sedation. The effects of opioids are inhibited by strong affinity of buprenorphine i.e. Subutex/Suboxone and messes with sedation techniques including such medications. Additionally, as per ceiling effect of buprenorphine, the routinely utilized opioids cannot be replaced for the sake of outpatient sedation.

The administration of alternate benzodiazepines such as IV midazolam via bolus dosing or propofol infusion are highly recommended in case of the buprenorphine taking patients. The later one infusion approach exhibits onset rapid and short action duration ranging from 3 to 8 minutes. It also possesses certain anti-emetic features which makes it to be used as outpatient anesthesia ideally. The alternates for the sedation include barbiturates, etomidate and ketamine as hypnotics/sedatives along with benzodiazepines [12].

Conclusion

Patient's with a diagnosis of substance use disorder are more common than we think. This paper hopefully will establish a proper way in both diagnosing a particular patient at risk. This paper outlined the importance of the initial office/operating room visit in terms of

managing expectations and managing patients on medical assisted treatment. At times, it might be reasonable to continue their medication management with respect to either methadone or buprenorphine. At times, given the intervention of the surgical procedure it might be more prudent to change the ongoing medical assisted treatment. In either case, using multi modal therapy, antidepressants, antiseizure medications, ketamine, lidocaine infusion, regional and anesthetic blocks and nonsteroidal based therapy are critical.

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