



Are we Sure about the Benefits of Opioid Free Anesthesia?

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When reading the article by Bohringer, et al. [1], I thank authors for detailed review of non-opioid analgesics, also for bringing up some interesting points for discussion. There is currently an opioid epidemic in the United States that results in increased opioid misuse and opioid-related deaths [2]. Regulatory authorities at federal and state levels and health professionals are looking for measures to reverse this opioid crisis. In 2018, the Food and Drug Administration (FDA) launched the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) program that requires training be made available to all healthcare providers in terms of how to reduce the risk of abuse, misuse, addiction and fatal overdose due to prescription opioid analgesics [3]. Some anesthesiologists started to avoid the use of opioids during anesthesia [4-7]. However, we knew the side effects of opioid long before the current opioid problem. In anesthesia practice, we always say “it is not about which drug, it is about how you use the drug”. So, before blaming opioid, should we do some self-reflection?

What Contributes to the Current Opioid Epidemic?

Opioids are a class of pain-relieving medications which cause euphoria and have high risks for addiction and overdose. There should be a strict surveillance system for prescribing and using these “controlled substances”. Nevertheless, some physicians open “for-profit” clinics and write opioid prescriptions without conducting a thorough evaluation of the patient. These “pill mills” may contribute to the current opioid epidemic. Another fact is 76% of nonmedical users reported getting medications that had not been prescribed to themselves [2]. This is consistent with the report from the U.S. Department of Health and Human Services (HHS) in that most (53.1%) misusers obtained the last pain reliever they misused from a friend or relative [8]. This phenomenon indicates that drug diverting is a major problem in opioid abuse and opioid-related deaths. Although opioid prescriptions written by physicians increased annually by 3.0% from 2006 to 2010 which may be a contributing factor to opioid misuse, abuse,

overdose and death, the Centers for Disease Control and Prevention (CDC) 2018 report did not differentiate these prescriptions for acute pain or chronic pain management. However, CDC did indicate that “the current epidemic of drug overdoses began in the 1990s with overdose deaths involving prescription opioids being driven by the dramatic increase in prescribing opioids for chronic pain” [9]. Except for prescription opioids, “illicitly manufactured fentanyl” also involved in synthetic opioids overdose deaths [9].

An early analysis of the trend in medical use and abuse of five opioid analgesics (fentanyl, hydromorphone, morphine, oxycodone and meperidine) using the databases of Drug Abuse Warning Network (DAWN) from 1990 to 1996 did not show an increase in opioid abuse with an increase in opioid use [10]. Later, when the data of DAWN was compared again to the years 1997 to 2002 [11] and 2004 to 2011 [12], the authors found a significant increase in abuse and misuse of opioids with increased medical opioid use. Meanwhile, the authors realized that increased opioid prescribing coincided with the period of generous opioid use for chronic non-cancer pain management [12] and increased drug diversion might be the explanation of increased drug abuse [11]. Therefore, besides socioeconomic reasons, it is likely that “pill mills” and drug diverting from over prescribed opioids for chronic pain has a higher contribution rate to the current opioid epidemic and opioid related death, although over prescribing opioid for acute surgical pain may exist as well [13].

Shah, et al. examined the probability of long-term opioid use (1 year and 3 year) after opioid-naïve patients were treated with an opioid. If the initial period of opioid therapy was at least 1 day, the probability of continued opioid use was 6.0% at 1 year and 2.9% at 3 years. If the initial period of opioid therapy was more than 8 days, the person had a 13.5% chance of becoming a chronic opioid user at 1 year [14]. However, the study population consisted of patients with head pain, neck pain, back pain and joint pain, not acute pain patient from surgery. Furthermore, the information on pain intensity or duration were not recorded. Because

perioperative pain management and chronic pain treatment are two different entities, we should not mix them up when we do “root-cause analysis” of the current opioid epidemic. Drug use, either illegal or prescription, does not automatically lead to abuse or addiction. Drug abuse/addiction or severe “substance use disorders” defined by DSM-5 are certain symptoms one has resulting from continuous use of a substance, despite experiencing problems as a result. The activation of the brain’s reward system leading to cravings and urges to use the substance is central to substance-use problems. The amount, frequency and duration of drug use are less important in the diagnosis of substance use disorders [15]. A study in a single academic institution showed that chronic opioid usage in surgical patients is almost 5 times as high as that in the general population. It is possible that patients had preoperative pain that required surgery or persistent postsurgical pain that warranted opioid treatment [16]. So, chronic opioid use may not represent opioid abuse.

Does Perioperative Opioid Use Result in More Drug Abusers?

Among chronic non-cancer pain patients who had no previous or current history of addiction/illicit drug use, 0.19% will become drug abusers/addicts after exposed to chronic (average 26 months) opioid analgesic treatment. Even though the reported incidence of opioid abuse/addiction on all patient who had chronic opioid analgesic therapy is 3.27% [17], this number is well below the prevalence of lifetime drug abuser (7.7%) in general population [18].

In the presence of the opioid epidemic, the critical question to ask is “how many patients become drug addicts because of perioperative pain treatment with opioids?” Although there is no accurate data on the rate of addiction among inpatients who received opioids for acute and subacute pain [19]. A Medline literature search from 1966 to 1996 by Drayer’s group led to 17 studies which discussed addiction due to medically used opioids. There was no consensus definition of “addiction” in these studies, the patient was considered to be “addicted” after treatment as long as the patient did not show any evidence of drug abuse prior to treatment. The incidence of “iatrogenic addiction” was between 0% and 5.4% if we do not take into consideration the 7 studies on chronic pain patients [20]. According to the National Survey on Drug Use and Health (NSDUH) report, the numbers of new substance users in 2017 were 4.9 million for alcohol, 3.0 million for marijuana and 2.0 million for misusers of prescription pain relievers [8]. So, more people started using alcohol and marijuana than pain relievers.

Although there are no clinically confirmed predictors for patients at risk of addiction, risk factors found in lit-

erature include personal or family history of addiction, psychiatric disorders, childhood history of abuse [21], treatment in a drug rehabilitation facility [22] and use of multiple drugs [23]. Vulnerability to addiction also has a genetic predisposition [24]. Based on available data, there is no convincing evidence that short term use of perioperative opioid analgesics is a risk factor for long term drug abuse.

Is Opioid Free Anesthesia Better than Opioid Based Anesthesia?

Balanced analgesia or multimodal analgesia was first proposed by Hehlet and Dahl [25] to improve pain relief and decrease the side effects of each drug, not only the side effects of opioids. Clinical studies have demonstrated that nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors reduced pain intensity and opioid use from 20% to 40% in 24 hours after surgery, and opioid-related side effects, such as nausea, vomiting and sedation [26,27]. However, when NSAIDs and COX-2 inhibitors are added to the pain management regimen, severe bleeding and renal failure, although rare, are not theoretical risk [26]. In this situation, the risk of non-opioid analgesics may outweigh the benefit. It has also been estimated conservatively that there are 16,500 NSAID-related deaths among patients with rheumatoid arthritis or osteoarthritis every year in the United States [28].

In face of the opioid crisis, opioid-free anesthesia (OFA) has been carried out. Early clinical experience has suggested that OFA could be performed with preemptive ketamine analgesia and local anesthesia by surgeon in office based plastic surgeries [29]. However, the theory that 50 mg of preemptive intravenous ketamine totally blocks infra-tentorial *N*-methyl-D-aspartate (NMDA) receptors and pain arousal of cerebral cortex needs to be proved by further study [30]. The addictive potential of ketamine should not be overlooked. Recently, studies with dexmedetomidine have emerged with miscellaneous results. A study on opioid-free total intravenous anesthesia (TIVA) with propofol, ketamine and dexmedetomidine in patients undergoing bariatric surgery demonstrated that opioid-free TIVA significantly reduced postoperative nausea and vomiting compared to general anesthesia with volatile agent and opioids. However, both groups required similar amounts of postoperative opioid [5]. Compared to remifentanyl, dexmedetomidine does not decrease visual analogue scale (VAS) scores for postoperative pain in the post anesthesia care unit (PACU) in patients who had a total laparoscopic hysterectomy [4]. It seems that dexmedetomidine decreases the VAS pain scores and opioid consumption within 2 hours after surgery, but not during 4 and 6 hours in patient who had a laparoscopic cholecystectomy [6]. The trade-off is the dexmedetomidine

group had more hypertensive events and increased recovery time [6,7]. Jebaraj's group has shown that dexmedetomidine provided equivalent intraoperative analgesia as fentanyl in patients undergoing robotic urological surgery under TIVA, as demonstrated by same chance and similar dose of intraoperative rescue fentanyl in both groups. But tachycardia was significantly more in the dexmedetomidine group after intubation than in the fentanyl group that suggested unsatisfactory sympathetic block by dexmedetomidine at endotracheal intubation. Furthermore, more patients in the dexmedetomidine group than in the fentanyl group had bradycardia requiring treatment with atropine bolus although the incidence of bradycardia in both groups was not statistically significant. In this study, dexmedetomidine provided the same intraoperative analgesia as fentanyl does, but no pain score and analgesic use in PACU were reported [7]. Increased tachycardia and hypertension with dexmedetomidine may be detrimental to elderly patients and patients with cardiac diseases. Even in selected minimal invasive colorectal surgery, OFA with the laparoscopic transverse abdominis plane (TAP) block, could decrease, but not eliminate postoperative opioid use [31]. In current anesthesia practice, pain management starts prior to surgery with multimodal medications or Peripheral Nerve Blocks (PNBs), with the hope to achieve better postoperative pain control. Adequate intraoperative pain management is also critical for this purpose. Opioids are most effective for treatment of moderate-to-severe pain and should be a component of multimodal analgesia.

While acetaminophen, NSAIDs, COX-2 inhibitors, pregabalin, lidocaine, beta-blockers, dexamethasone, and ketamine etc. either alone or in combination, have been added to opioid-free regimens, most of these medications are metabolized by liver enzymes and excreted by kidneys. Do we know the pharmacological interaction of these medications and the "lasting effect" when we put these non-opioid cocktails into patient's blood? Does any anesthesiologist follow up with patient by checking their liver and kidney functions after they are discharged from PACU? Apparently, long-term outcomes of multimodal analgesia need to be studied.

PNBs have been widely used to optimize postoperative pain control with minimized opioid requirement. However, rebound pain or hyperalgesia after the PNBs can increase opioid consumption once the blocks wear off. The incidence of rebound pain has been reported up to 40% in patients who had single shot brachial plexus blocks [32]. The mechanism of rebound pain after PNBs is unclear, therefore, the best approach to prevent or decrease this complication is unknown. Exparel (liposomal bupivacaine), a sustained-release preparation of bupivacaine, has pain relieving effect for up to 72 hours after surgery. It might decrease rebound pain by pro-

longed analgesia. Unfortunately, Exparel injected locally at the surgical site did not do so [33]. In fact, a recent meta-analysis indicated that PNBs plus Exparel infiltration do not decrease postoperative opioid consumption within 72 hours and length of hospital stay compared with PNBs alone [34]. Researchers have also used intra-articular or intravenous NSAIDs and adjuvant medications in nerve block solutions to reduce incidence of rebound pain with uncertainty [35]. Preemptive opioid analgesia before the block dissipates has been proposed as one of the strategies [35]. Opioid-induced hyperalgesia (OIH), characterized by increased pain sensitivity, is a clinical syndrome that has been mostly observed in experiments with animals and in human volunteers. Its occurrence and relevance in clinical practice remain controversial [36]. Although available literature suggests that the incidence of OIH is higher with the use of remifentanyl, some methods may be used to prevent or reduce OIH, such as gradual withdrawal of remifentanyl infusion [37], coadministration of low-dose butorphanol [38] or naloxone [39]. Other strategies include alternative opioid, limiting opioid dose, coadministration of propofol or nitrous oxide [40].

Normally, pain sensation diminishes to minimal or zero as surgical healing progresses. Persistent, intense pain (PPP) can cause both peripheral and central sensitization, that lead to the transformation of acute to chronic pain [41]. In 10 pain clinics across Scotland, 22.5% of patients related their chronic pain to surgery [42]. In fact, acute postsurgical pain (APSP) is an independent predictor of chronic postsurgical pain (CPSP) [43]. This is a potentially modifiable risk factor through better treatment of surgical pain by perioperative physicians. In current practice, up to 70% of elective operations are performed at day surgery centers [44]. Eighty percent of surgical patients are concerned about postoperative pain. The same high percentage (three quarters) of patients complain of pain immediately after surgery, as well as after discharge [45], suggesting whatever anesthesia technique we used did not provide adequate pain control for patients in the operating room and PACU and after they were discharged. It is imperative to aggressively treat surgical pain to prevent chronic pain from developing, not to mention that adequate treatment of acute pain improves clinical and economic outcomes [45]. As mentioned above, acetaminophen, NSAIDs and COX-2 inhibitors are not strong enough to replace opioid analgesia for major surgery and are not always risk-free; Studies with intraoperative dexmedetomidine had conflicting results and there is no study on dexmedetomidine as a sole postoperative pain medicine. PNBs provide superior postoperative analgesia and fewer opioid-related side effects when compared with opioid analgesia, but with thorny rebound pain that requires increased opioid consumption. With all these dilemmas,

why do we give up opioid, a reliable pain reliever we are familiar with?

For the sake of discussion, poorly controlled postoperative pain may lead to an increase in the amount of chronic pain patients [43,46] and more drug abusers since long-term medical opioid users are at higher risk for drug overdose [2]. While it is good intention to “explore the use of non-opioid analgesic drugs to both reduce the risk of developing opioid addiction and the occurrence of opioid related side effects” [1], OFA does not consider the utmost importance of opioid analgesics in anesthesia practice and the lack of credible alternative pain relievers. It has not been proven that addiction can be prevented by restricting access to opioids either.

What Should we do about the Current Opioid Epidemic?

To reverse the current epidemic of opioid addiction and overdose deaths, CDC has proposed prevention strategies that include four components: Education, tracking and monitoring, proper medication disposal, and enforcement. The government requests efforts from all levels at federal, state, local, and tribal groups as well as engagement of parents, youth influencers, healthcare professionals, and policymakers [2]. Education is crucial and may be effective to prevent addiction from occurring, since medical professionals and patients fear becoming addicted to opioids [45].

Identification and monitoring of high risk populations for opioid abuse, misuse and overdose death is important. Except for previously mentioned patients with risk factors, CDC identified that men, persons aged 20-64 years, non-Hispanic whites, and poor and rural populations are high risk individuals as well [2]. Since the chance of long term opioid use is closely related to the duration of initial use [14], perioperative physicians should be extremely cautious in terms of quantity and duration when writing prescriptions. Physicians can play a critical role in curtailing excessive prescription opioid use and preventing misuse and abuse by judiciously prescribing opioid medications, and educating patient and family regarding medical necessity, adverse effects, complications and fatalities associated with opioid treatment. The practice of giving all postoperative patients a prescription for opioids at the time of discharge from hospital should be terminated. More liberal use of opioid should be changed to deliberate use if opioid is needed. CDC guidelines recommend treatment of acute pain with opioids should be for the shortest duration possible (< 3 days) with the lowest dose [47]. Auditing indications for cesarean delivery (CD) and providing feedback to healthcare professionals significantly reduced the rate of CD without adverse effects on maternal or neonatal outcomes [48]. Since increased prescription opioids have now led to increased misuse

and overdose deaths [12], a similar program with close supervision and administrative intervention may apply to perioperative physicians to decrease the number of opioid prescriptions and doses prescribed. In this regard, pharmacies can assist in monitoring opioid quantities used.

Research is an integrated part of translational medicine. Developing new forms of opioid analgesics with same or better analgesic potency and less side effects including reduced tendency to produce dependence and respiratory depression is potentially achievable [49]. Research on the understanding of opioid neurobiology and addiction should be emphasized in order to prevent addiction from developing [50].

As healthcare providers, we are faced with the challenges of balancing the optimal pain management for our patient and minimizing opioid abuse. Studies have shown that we have not made much improvement in postoperative pain control in the last 20 years [45], especially for “minor” surgeries [51]. Because inadequate pain control may cause many undesirable consequences, such as changes in immune system function, poor wound healing, diminished ability to ambulate and coughing, deep vein thrombosis, pulmonary embolism, atelectasis, pneumonia, increased cardiac workload and cardiac ischemia, and myocardial infarction, we need to constantly improve perioperative pain management.

In the absence of evidence that short term perioperative opioid analgesics will cause long term drug abuse, Anesthesiologist should optimize opioid-sparing analgesic modalities for each type of surgery to maximize pain control and minimize the side effects of each drug. Although multimodal analgesia has been shown to be effective and reduce opioid consumption and opioid-related side effects, the main purpose of the therapy is to have satisfactory pain control or analgesia, not to leave opioids out which may compromise patient care.

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