

The Role of Opioids and Non-Opioids in Postoperative Pain Relief; A Narrative Review

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Postoperative analgesia is one of the important basics of practical recovery after surgery. Pain relief has an important physiological advantage in preventing acute pain turning into a chronic pain and aims at early mobilization with decreasing infection, healing wound time, and hospital stay and /or hospital readmission in addition to eliminating adverse effect related to over sedation. Estimation of postoperative analgesia technique depends on the intensity of dynamic pain and the possible side effects of analgesic medications and techniques which can delay discharge. The key role in improving postoperative pain relates to three steps; 1. Patient education in the decision concerning their specific treatment. 2. Team skills and knowledge for different drugs and technique like acute pain services available towards 24 hours/ day. 3, Physician in communication with the patient is the essential point. Using low dose of opioid drug with NSAIDs or synergistic analgesia or multimodal analgesia at various points along pain pathway to support pain relief with less adverse effect is becoming increasingly common for post-operative pain relief.

keywords: pain management; analgesia; opioids; post-operative pain

Many medical and paramedical staff, unfortunately, believe that pain is a normal, agreeable and innocent outcome of surgery. General causes cited for miserable pain management include unsuitable staff training and knowledge, poor pain assessment, unfamiliarity with the advantages and side effects of pain medications and a false belief that since post-operative pain is often transient and all humans experience pain in life, everyone must "grin and bear it" [1]. Effective control with postoperative pain management is a major problem of the patient, because of physiological response that happens with potential adverse effects on pain from tissue injury and site of surgery. Poor management of surgery outcomes leads to the important clinical complication with increased risk of persistent pain that finally becomes chronic pain [2] and this is common after surgical procedures and about 50% in thoracotomy and mastectomy experience it [3] and recently in US, one study recorded that more than 80% experience post-operative pain and it is the main cause of delayed discharge and functional recovery [4]. Considering pain as the "fifth vital sign" [3] and this sign leads to negative outcomes like myocardial ischemia, poor wound healing, hypertension [5], in addition to pneumonia, deep venous thrombosis, infection, chronic pain and depression [6]. The goal of this review is to know different pharmacological effects, routes, and types for the

treatment of post-operative negative outcomes. The main objective is to reduce or eliminate pain and discomfort with a minimum of side effects and the specific objective is to increase patient rehabilitation, satisfaction with reducing hospital stay and cost [7].

Definition of pain

Pain has been defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (IASP, 1979). And another definition by (John Milton, Paradise Lost) who said "pain is a perfect misery" but Pasero and McCaffery (2010) said that pain is "whatever the experiencing person says it is, existing whenever he/ she says it does". That means the person's self? Pain report represents the most valid measure or "gold standard". Many factors are known to influence the experience of pain including gender, age, culture, and previous experiences. The meaning of pain is something that the person describes it, controlling of pain requires a good cooperation between the patient, and physician and the clinical staff [8].

Assessment of pain

For more than 3 decades many studies have recognized poor outcomes in the evaluation and management of postoperative pain [9-12]. The number of patients whom were evaluated in the studies was low [12]. On the other hand, selecting the suitable tools like verbal rating scale (VRS) and numerical rating scale(NRS), both of which are most commonly used to evaluate post-operative pain, and the patients development, physical, emotional, and cognitive status, has made the new studies more powerful. Both of them are important for assessment and, but visual analog scale(VAS) was used primarily as a research tool [13].

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Opioid Drugs

Pain can be really debilitating and can cause long-term morbidity. Analgesics are a group of various classes of medications which provide relief from pain, and are frequently prescribed medications worldwide. Opioids are the most important pain relieving medications and are used usually as the first line of drugs to ameliorate the post operative pain. And they have been used for centuries to alleviate pain. Opioids, have a great chance of abuse which can be accompanied with severe psychological or physical dependence [14]. In general understanding, the physiological changes that are occurring during life are the first vital steps to reduce the mortality and morbidity related with pharmaceuticals, it means a positive relationship between the age and drug(dose and type) [15-16]. These days we use opioid drugs with short action and plasma elimination like, alfentanil, sufentanil, remifentanyl. Sufentanil is 5-10 times more potent with longer distribution and elimination half-life than fentanyl but the others are less potent and shorter duration of action [17].

Type of Opioid

1. Full Agonists

Full agonists join to opioid receptor, stimulate the effects of endogenous opioids, or endorphin, for example, morphine, codeine, methadone, hydromorphone, and meperidine. Full agonists have no ceiling dose, that means by increasing the dose to get more analgesia, results in no further increase in analgesia hence; their dose can be steadily increased to relieve pain [18]. Opioid like sufentanil is used in surgery and post-operative pain control in patients that are taking high dose buprenorphine for chronic pain because it is the only opioid that has a potency and binding affinity strong enough to displace buprenorphine from the opioid receptors in the CNS and provide analgesia [19]. One clinical trial suggested that sufentanil in low doses produces less and shorter-lasting respiratory depression than fentanyl with better patient comfort and produces greater and longer-lasting analgesia than fentanyl [20]. Recently showed sedation with remifentanyl-propofol was compared with fentanyl – propofol in 63 adult cardioversions and in 29 children undergoing 60 procedures, in both of them, there was no difference in sedations effectiveness [21].

2. Mixed Agonists–Antagonists Analgesic

This group produces potent analgesia and sedation, but without the euphoria, drugs can act similar to opioids and relieve pain (agonist effect) when administered to the patient who has not taken pure opioids. And also, they can block opioid analgesics when administered to the patient who has been taking pure opioids (antagonist effect). These drugs include dezocine, pentazocine hydrochloride, butorphanol tartrate, and nalbuphine hydrochloride. They block the mu-receptor site and activate a kappa-receptor site. If the patient has been receiving mu-agonist (morphine) every day for few weeks it leads to inactivation at the mu-receptors and pain enhancement. These drugs have a ceiling effect (larger doses of a medication have gradually smaller effects) that limits the dose [18]. Pentazocine has limited application because it is associated with a high incidence of post-operative nausea and vomiting and it provides limited analgesia, and it can produce undesirable cardiovascular and psychotomimetic effects [22].

3. Partial Agonists

Have a ceiling effect too. For example, buprenorphine (Buprenex) blocks the mu-receptors and binds at a kappa-receptor site, Buprenorphine has good analgesic potency and is used as a standby drug to methadone for opioid maintenance treatment programs. They are active analgesics for relieving of moderate to severe intensity and must be given on a regular basis to prevent chronic pain [18].

High Risk over Sedation

This problem can happen more in patients with a history of sleep apnea, morbid obesity, snoring [18, 23] and also in old patients at risk," 2.8 times higher for individuals aged 61-70, 5.4 times higher for age 71-80, 8.7 times higher for those over age 80" [18, 23-25]. When a person reaches 70 s the majority of healthy older adults experience a 40% to 50% decline in kidney function despite an absence of underlying kidney disease [26]. Serum creatinine is not a dependable indicator of kidney function in older adults because of sarcopenia (loss of muscle tissue as a natural part of the aging process results in inaccuracy low creatinine levels [27]. Instead, GFR is a better index [28]. This old age kidney dysfunction can lead to high blood level of opioids which are excreted from the kidney [18].

Non-Opioid Drugs

Nonsteroidal anti-inflammatory drugs (NSAID) are a group of medications that have analgesic, anti-inflammatory, and antipyretic properties. They are useful analgesics for postoperative pain. Effectiveness of NSAIDs, are comparable or even better than narcotic analgesics [29]. Overall understanding of their pharmacology, their efficacy, and their adverse effects are essential for the successful use of this important group of medications in the treatment of postoperative pain [30]. NSAIDs are broadly used during operative pain control but have a slight effect on surgical stress responses and organ dysfunction [31]. On the other hand, it is certain that NSAIDs exhibit moderate postoperative analgesia and there by an opioid-sparing effect of 20–30% [32]. Also, non-opioid therapy is preferred for the treatment of chronic pain according to the recent CDC report [33]. This clinical property of NSAIDs may decrease the rate of opioid-related side effects (respiratory depression, sedation, nausea and vomiting, ileus, urinary bladder dysfunction and possibly sleep disturbances). Prostaglandins possess several physiological functions, including the protection of gastric mucosa, function of renal tubules and vasodilatation, and bronchodilation. Endothelial prostacyclin, provides vasodilation and prevents platelet adhesion, and platelet thromboxane. Such physiological role is at most regulated by COX-1 that is responsible for many of the adverse effects related to NSAID use. Surgical tissue damage prompts COX-2 generation as a result of prostaglandins that cause pain and inflammation. Inflammation and nerve injury secondary to surgery may freely excite postoperative pain and lead to central sensitization and continue postoperative pain [34], however, correlated adverse effects can occur, such as peptic ulcer disease, change of liver function, gastrointestinal hemorrhage, renal dysfunction and platelet dysfunction. These adverse effects impede the use of these agents in many patients during the operation period but we can use an

alternative drug like metamizole which may be safer for the upper intestinal tract and kidneys than the other NSAIDs, and could instead be used in patients with an increased risk of stomach or renal problems. Hereby, enhanced postoperative pain relief can possibly be achieved [35]. Ketorolac reduces narcotic consumption by 25% to 45% and is a common adjunct in colorectal surgery postoperative protocols [36-37]. A study by Yee et al, defined a dosage of intramuscular ketorolac that can attain pain relief similar to that of morphine, in addition, ketorolac provides sufficient postoperative analgesia after abdominal and pelvic surgery, such as hysterectomy, cholecystectomy, and cesarean sections and even used effectively for analgesia in advanced cancer [38]. Also, ketorolac has a similar effect to tramadol and drug option should rely on their potential side effects and patient co morbidities [39]. On the other hand it has been concluded that I.M injections of 20 mg piroxicam (single dose therapy) could relieve postoperative pain after cesarean section as well as tramadol and it could reduce opioid analgesic requirements with less adverse side effects during the first postoperative 24 hours [40]. Furthermore, it was newly reported that the administration of ketorolac (30 mg) at the incision site to supplement local anesthesia resulted in significantly less postoperative pain, a better kind of recovery, and earlier discharge compared with local anesthesia alone [41]. While Lomo et al, showed that 30 mg ketorolac was effective when combining with paracetamol (1 g t.i.d) in minor surgery [42].

Alpha-2 Adrenergic Agonist

Alpha-2agonists (dexmedetomidine, clonidine) have sedative and analgesic effects via central actions [43]. This group has become more popular as adjuvants to opioid and non-opioid analgesia [33]. Clonidine use is limited because of its side effects like (brady cardia, hypotension and excessive sedation). Dexmedetomidine is more selective and has shorter duration of action, has potent sedative effects without respiratory depression [44]. It is frequently used in patients with high risk of airway obstruction, sleep apnea (morbid obesity) and respiratory depression (opioid uses) and can be used as part of a multimodal analgesic plan in morbidly obese patients undergoing bariatric surgery [45]. On the other hand, dexmedetomidine is used especially in patients susceptible to preoperative anxiety because of its sedative, anxiolytic, analgesic, sympatholytic effects, and stable hemodynamic profile. In addition, its use is associated with reduced oxygen consumption (up to 8%) in the intraoperative period and (up to 17%) in the post-operative period [46].

Gabapentanoids

Gabapentin and pregabalin anticonvulsant drugs are used in the treatment of neuropathic pain, reacting with calcium channel α_2 ligands to inhibit calcium inflow and later release of excitatory neurotransmitters. However, absorption of pregabalin is more rapid and has unlimited bioavailability $\geq 90\%$ in comparison with gabapentin which is $< 60\%$ [47] but both of them improve the analgesic efficacy of opioids (at rest and with movement) and reduce opioid requirement, opioid-related side effects, but with an increased rate of side effects such as sedation and dizziness [48]. A meta-analysis investigating the analgesic efficacy of pregabalin for acute

postoperative pain showed that the use of pregabalin leads to reduction of opioid requirement and opioid-related side effects, but unfortunately no difference in pain intensity [49], but recently it has been shown that gabapentin, (not pregabalin) decreases pain intensity at 24 hours after breast cancer surgery [50]. The use of gabapentin is linked with elevated rates of respiratory depression among patients undergoing laparoscopic surgery. For this reason, when included in multimodal analgesia style, intraoperative opioid dose must be reduced and prudence should be increased for prevention of respiratory depression especially in elderly [51].

N-Methyl-d-Aspartate Antagonists

Ketamine is an NMDA receptor antagonist with effects on central sensitization and neural modulation [52]. To reduce the possibility of central sensitization, a small dose of ketamine (about one tenth of anesthetic dose) is used [53]. Recently one study showed that using ketamine with paracetamol has more efficiency than each one used alone. Adverse effects of ketamine include hypertension, tachycardia, and psychomimetic effects including hallucinations, nightmares, and cognitive dysfunction [54].

Glucocorticoid Steroids

The role of these kind of drugs for analgesia remains controversial. Clinical studies showed that in addition to dexamethasone, betamethasone or methylprednisolone can provide more prolonged postoperative analgesia after surgery when added to a multimodal regimen which also includes NSAIDs [55]. The addition of glucocorticoid also reduces postoperative side effects (e.g. nausea and vomiting) and facilitates the recovery process [56]. Moreover, a recent meta-analysis showed that dexamethasone at doses more than " 0.1 mg/kg is an effective adjunct in multimodal strategies to reduce postoperative pain and opioid consumption after surgery" whereas if given preoperatively, this drug produces less variation of effects on pain outcomes [57].

Preemptive Analgesia

It is referred to the administration of any analgesic medication given before the surgical incision or tissue injury. Active pre-emptive analgesic techniques comprise of various pharmacological agents to diminish nociceptors initiation by preventing or decreasing receptor activation and inhibiting the generation or activity of pain neurotransmitters in addition to preventing central sensitization caused by surgical incision. This analgesia can be provided via many routes (including orally, rectally, intravenously, intrathecally, subcutaneously, intramuscularly), at various times by various medications [58], like opioids (not effective), NSAIDs (effective in 20% [59], COX2 inhibitors, pregabalin, or regional anesthesia. The opioid/local anesthesia or each one alone showed no reduction in pain score [59]. Preemptive pain management drugs can be orally administered or injected approximately 1 hour before surgery [60-61]. Ketamine cannot ameliorate post-operative pain. On the other hand, it is broadly understood that preemptive analgesia may reduce the risk of developing chronic postoperative pain [59].

Preventive Analgesia

It has a wider concept in comparison to preemptive analgesia. The aim of preventive analgesia is to minimize excitation caused by noxious stimuli happening intra/post-operatively so that any interventional analgesia is preventive when having 2 points. Firstly, it is able to reduce the degree of postoperative pain. Secondly, the duration of the effect of the intervention exceeds the clinical duration of action of the target drug [62]. A recent study of systematic review analyzed preventive analgesia with peripheral nerve blocks, transverse abdominal plane blocks, and intravenous (IV) lidocaine infusion. The writer found in this study, that the use of local anesthetic techniques reduced postoperative pain scores and opioid requirements [43].

Multimodal Analgesia

It is the administration of 2 or more drugs (same route or various routes) that act by different mechanisms in producing analgesia [63]. These drugs can be an additive or synergistic combination that act at various points in the pain pathway [64]. Multimodal analgesia is effective after several ambulatory surgical procedures [65] and this analgesic potency differs with the nature of the surgery and finally improves pain with reducing opioid consumption and opioid adverse effects [66]. Therefore, reducing the opioid dose leads to decreasing opioid adverse effects like sedation, sleep disturbances, urinary retention, and respiratory depression [67]. Multimodal analgesia is successful in lessening the postoperative pain, benefits early ambulation, improves recovery, gastrointestinal function, and prevents long duration of hospital stay [68]. Recently it is suggested that, a multimodal analgesic mode that includes liposome bupivacaine can reduce opioid consumption and its adverse effects, reduce the time of hospital stay and total hospitalization costs compared with opioid only analgesia [69]. Moreover, it has been recently reported that a combination of nefopam and opioid drugs enhances the analgesic potency of morphine and prevents opioid-induced hyperalgesia and at the same time, it enhances the analgesia when combined with NSAIDs [70].

Results

The main result is to increase patient satisfaction with minimal side effects and reduce hospital stays and cost by minimizing the stress response to surgery and speed of recovery to normal function because pain is the major side effect in all types of operations. Improving postoperative pain management requires definitely important changes for each patient, clinicians and hospital organization. Multiple changes which are well confirmed in origin, but have yet to be widely performed. To take one example, the Enhanced Recovery After Surgery (ERAS) group was formed in 2001 to develop the best postoperative patient outcome and early recovery [71]. This group has found a reduction in care time by more than 30% and complications in postoperative period by up to 50% [72]. Thus, using opioid drugs to mitigate surgical stress response is enough to modulate the negative outcome with a preventive effect to the complications such as respiratory depression and ileus, PONV in addition to significant sedation that is not needed and required in current practice. It is preferable to use medications with minimal post-operative hang-over and effects on

gastrointestinal motility. Therefore, long-acting premedications are commonly avoided decreasing the capability of the patient to achieve the immediate post-operative goals. For instance we can use fentanyl perioperatively and TIVA including remifentanyl or short-acting volatile anesthetic agents [73]. On the other hand, the pain control is an important component of an ERAS guideline [74]. In addition, the pain in Surgical Site Infection (SSI) can cause a complex process that appears from a damaging synergy between the patient and the pathogen(s). It can slow healing and magnify wound pain. Thus SSI is responsible for pain severity and has a negative effect on delayed healing [75]. Recognizing it as a common surgical complication occurring in about 3% of all surgical procedures and in up to 20% of patients undergoing emergency intra-abdominal procedures [76], approximately 500,000 SSI occur each year in the United States [77], that causes pain and prolonged hospital stay [78]. Comparing the median duration of hospitalization in infected patients which was 11 days, it was only 6 days in uninfected patients [78]. The pain is one of the signs and symptoms of superficial or deep incisional infections (SSIs) in addition to tenderness, localized swelling, redness and heat [79]. This pain is called either nociceptive pain as a result of tissue damage or neuropathic pain as a result of dysfunction of nervous system. But in the case of pain in SSIs are evident nociception and neuropathic pain and it's a major contributor to chronic pain. Finally, it results in reduction in quality of life and causes sleep disturbance [75]. It can be resolved by many factors like avoiding shaving, bath full body before surgery, glucose control, maintaining normothermia, increasing FIO₂ administered during operative and in the postoperative period [80].

Conclusion

According to the surgical procedure, the multimodal pain management has a key role in the postoperative pain period due to control on peripheral and central pain pathways. There are multiple approaches to control pain in post-operative period such as taking into account the surgical procedure, age, preoperative medical and psychological status. In general, adequate pain relief during the early postoperative period has important clinical implications to prevent developing chronic postsurgical pain, so that timing of analgesic administration depends on the pharmacokinetics of the drug and surgical procedure type. In addition, the choice of analgesic administration does not depend only on analgesic efficacy but on the profile of side effects. Using regional/local analgesia is associated with significant lower pain score than is seen with systemic opioid drugs, that have limited uses due to side effects. Considering the above, systemic ketamine, clonidine, lidocaine, gabapentin, selective COX2, NSAIDs can significantly increase analgesic effect compared with monotherapy because some of the above drugs have inhibitory effects on central sensitization that can be used as motif of preventive and preemptive analgesia. Non-opioid analgesia plays an important role in postoperative pain relief and provides chance to avoid opioid drugs completely, so that opioids should be used as "rescue" analgesic on an "as-needed" basis rather than on a scheduled basis by understanding the clinical pharmacology. The incision size and length of tissue trauma were not related to postoperative pain intensity but related to

better professional education and training of the different members that enhance their skills and knowledge on pain assessment and experience of nursing to control pain and significantly alleviate pain because the pain is soul destroying. No patient should tolerate intense pain unnecessarily. Our goal should be early discharge and improve the quality of life after surgery by reducing the hospital stay and cost, thus facilitating earlier rehabilitation.

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