Recent Advances in Multimodal Analgesia

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KEYWORDS

- Injectable acetaminophen and ibuprofen
- Topical NSAIDs for multimodal analgesia • Capsaicin
- Tapentadol • Depot formulation of local anesthetic

Multimodal analgesia captures the effectiveness of individual agents in optimal dosages that maximize efficacy and attempts to minimize side effects from one analgesic. This important concept uses the theory that agents with different mechanisms of analgesia that may have synergistic effects in preventing or treating acute pain when used in combination. These regimens must be tailored to individual patients, keeping in mind the procedure being performed, side effects of individual medications, and patients' preexisting medical conditions.[1] The concept and theory of multimodal analgesia is not new; however, several novel pharmacologic agents have emerged and can be added to the drugs that can be used in this manner. It is vital to realize that blocking the neuronal pathway during surgery with local anesthetics does not decrease the humeral biochemical responses that occur during surgery, which have to be inhibited by administering systemic pharmacologic therapy.[2] This review focuses on the recent advances in pharmacologic agents for multimodal therapy.

ACETAMINOPHEN

Oral acetaminophen has been used for several decades and believed to have a central role of action in analgesia because of its antipyretic properties and confers several mild analgesia antiinflammatory properties.[3] Paracetamol, an intravenous (IV) formulation of acetaminophen, became available in 2002 and has been studied in Europe. Göröcs and colleagues[4] administered a single dose of 1 g of IV paracetamol (Perfalgan) before the termination of surgery and observed high patient satisfaction and good tolerance of the drug in 601 patients undergoing minor outpatient surgical procedures. Nearly half of these patients (42.7%) received the lone dose of

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paracetamol as monotherapy for postoperative pain. Salihoglu and colleagues[5] randomized 40 patients undergoing laparoscopic cholecystectomy to 1 g paracetamol (after intubation and before incision) or saline infusion. Significant improvements in outcomes in the paracetamol group included lower visual analog score (VAS), lower morphine consumption, and shorter stay in the recovery room (32 $\pm$ 11 vs 48 $\pm$ 14 minutes). Approved by the US Food and Drug Administration (FDA) in November 2010, IV acetaminophen (Ofirmev) has been studied and shown to be safe. IV acetaminophen endorses a quick onset with meaningful pain relief achieved 25 minutes after administration in patients undergoing laparoscopic surgery,[6] 25 to 27 minutes after total hip arthroplasty.[7] Ender and colleagues[8] retrospectively evaluated the use of a fast-track protocol (which included IV acetaminophen) for cardiac surgery in 421 patients compared with matched controls who were not fast-tracked and did not receive IV acetaminophen. Acetaminophen was administered, 1 g every 6 hours, postoperatively. Significant results included shorter times to extubation (75 vs 90 minutes), shorter intensive care units stays (4 vs 20 hours), shorter intermediate stays (21 vs 26 hours), and shorter hospital stay (10 vs 11 days). The ability of these compounds to shorten hospital stays, while providing safe and effective analgesia, should garner the attention of not only anesthesiologists but also hospital administrators keen on cost-effective care. The oral administration of acetaminophen can probably achieve the same results as IV acetaminophen in patients who have a functioning gastrointestinal system. However, it is also to be noted that the analgesic effect is much more rapid than oral because of the pharmacokinetics.

As based on current research, combinations of acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) have been investigated and may offer enhanced effects. In 55 children undergoing hernia repair, 30-mg ketorolac and 20-mg/kg acetaminophen resulted in significantly lower postoperative fentanyl consumption and less sedation and vomiting.[9] A systematic review of this subject determined that when used as a combination, NSAIDs and paracetamol "offer superior analgesia compared with either drug alone,"[10] and 18 of 21 studies included had positive results with regard to lowering VAS and/or use of rescue analgesics. The combination was more effective than paracetamol (85% of studies) or NSAIDs (64% of studies) alone.

NSAIDs

The use of NSAID in the perioperative period has been well established taking into consideration the adverse effects of bleeding. The utility of cyclooxygenase 2 inhibitors in this scenario has been demonstrated to be a benefit.[1,2] A randomized, double-blind, placebo-controlled study comparing celecoxib, 200 mg, with placebo in 37 patients undergoing major plastic surgery demonstrated the ability of celecoxib to reduce VAS and postoperative morphine consumption. More importantly, the treatment groups had earlier return of bowel function (2 vs 3 days), resumed normal physical activities earlier (4 vs 6 days), and had higher patient satisfaction scores.[11]

More recent formulations of NSAIDs include intranasal (IN) ketorolac spray, IV ibuprofen, and topical diclofenac. Southworth and colleagues[12] conducted a randomized double-blind trial of varying dosages of IV ibuprofen (Caldolor) versus placebo in 406 patients who underwent an elective abdominal or orthopedic surgery. Those receiving ibuprofen, 800 mg every 6 hours, consumed 22% less morphine postoperatively. IV ibuprofen, 400 mg every 6 hours, seemed to attenuate postoperative pain

for up to 24 hours but had no benefit thereafter when compared with placebo. Aside from dizziness, IV ibuprofen was generally well tolerated.

In a randomized, double-blind, placebo-controlled study comparing IN ketorolac with placebo in 40 patients undergoing third molar extraction, Grant and Mehlisch[13] demonstrated that 31.5-mg IN ketorolac resulted in higher pain relief scores and greater patient satisfaction. Sixty percent of participants in the study group reported good to excellent pain control compared with 13% in the placebo group. IN ketorolac, 31.5 mg every 6 hours for 48 hours and then up to 4 times daily (up to 5 days), in patients undergoing abdominal surgery decreased morphine use over 48 hours and resulted in a higher quality of analgesia scores.[14] The investigators of this study indicated that pain relief occurred within 20 minutes of administration, which may be because of higher blood-brain penetration of ketorolac via the nasal route (cribriform plate). The availability of IN ketorolac can now be used in the ambulatory setting after discharge from hospital, taking the same general precautions as IV formulation.

Topical diclofenac exists in several forms, including diclofenac epolamine 1% topical patch (FLECTOR Patch), diclofenac sodium 1% topical gel (VOLTAREN Gel), and diclofenac sodium 1.5% w/w liquid (PENNSAID). A thorough review by Massey and colleagues[15] showed that topical NSAIDs are not only safe but also efficacious in the treatment of acute soft tissue injuries and localized regions of pain, acute or chronic. The investigators did find a difference between placebo and topical NSAIDs with regard to local skin irritation, but the systemic side effects were less with topical NSAIDs. In fact, most current research point to the fact that topical application of diclofenac could lead to decreased systemic absorption and therefore less gastrointestinal and renal adverse events associated with this class of drug. This research has even led to the National Institute for Health and Clinical Excellence (UK) to recommend topical NSAIDs, along with acetaminophen, as first-line treatment of osteoarthritis pain.[16]

A review of diclofenac epolamine topical patch by McCarberg and Argoff[17] discussed the benefits of a patch, as opposed to NSAID gels or creams. These benefits included application of a defined dose of diclofenac, drug delivery over an extended period of time (typically 12 hours), and ease of application. Barthel and colleagues[18] investigated the application of diclofenac sodium 1% gel versus placebo vehicle (identical composition to the gel component of the study drug) applied 4 times daily for 3 months for the treatment of osteoarthritis pain. Results of their study indicated superior analgesia from 1 to 12 weeks and improved function for the same duration. Diclofenac gel was tolerated as well as placebo. With regard to diclofenac 1.5% w/w liquid, the gel has been shown to be as efficacious as oral diclofenac in treating arthritis pain.[19] Gastrointestinal side effects were significantly less common, with local skin reactions being more common. A prospective study by Shainhouse and colleagues[20] established the safety of topical diclofenac 1.5% w/w in a study in which 793 subjects were followed up for an average of 204 days; 144 subjects were followed up for 1 year. Application of the study drug, 40 drops 4 times daily, resulted in local skin reactions (dry skin, contact dermatitis, or dermatitis with vesicles) in 45.1% of study participants. Twenty-four volunteers indicated a similar overall experience when using diclofenac gel and diclofenac liquid. However, the investigators found the gel to have a less desirable scent and found the consistency to be more greasy and sticky than the diclofenac liquid.[21] When side effects have limited oral NSAID use in a multimodal analgesia, it may be that IN, IV, and topical formulations of NSAIDs could prove to be of benefit in the perioperative period and should be considered as tools that are emerging for multimodal analgesia.

ANTICONVULSANTS

The use of adjunct agents to treat pain includes the use of anticonvulsants such as gabapentin and pregabalin. Clarke and colleagues[22] studied the effects of varying doses of gabapentin given preoperatively and postoperatively in addition to femoral/sciatic nerve blocks and celecoxib in 36 patients undergoing total knee arthroplasty. When administered preoperatively and postoperatively, gabapentin decreased morphine consumption on postoperative days (PODs) 2 to 4 and increased the amount of active knee flexion on PODs 2 to 3. This occurred without an increase in side effects. A randomized, double-blind, controlled trial of gabapentin in children undergoing spinal fusion determined that preoperative and postoperative gabapentin resulted in decreased morphine consumption and improved pain scores through the early stages of recovery up to POD 2.[23] However, this attenuation of opioid use and decreased verbal pain scores were temporary. An evaluation of gabapentin's ability to prevent not only acute but also chronic pain by Sen and colleagues[24] revealed that gabapentin, 1200 mg, administered preoperatively decreased morphine consumption; reduced incisional pain at 1, 3, and 6 months; and improved patient satisfaction when compared with placebo. Comparing varying dosages of gabapentin in lumbar laminectomy, Khan and colleagues[25] concluded that the timing of dosing (preoperative vs postoperative) did not affect analgesic efficacy. Gabapentin administered, 900 mg or 1200 mg preoperatively or postoperatively, reduced morphine consumption in the first 24 hours after operation and VAS scores without increase in side effects.

The use of a similar anticonvulsant, pregabalin, has gained attention because of more favorable pharmacokinetics, which includes improved bioavailability and faster achievement of therapeutic levels. Thirty patients undergoing laparoscopic cholecystectomy were randomized to receive pregabalin, 150 mg 1 hour preoperatively, or placebo by Agarwal and colleagues.[26] Fentanyl use and VAS scores were measured up to 24 hours postoperatively. Both VAS scores and narcotic use were significantly lower in patients who had received pregabalin. No significant difference in side effects was noted. Mathiesen and colleagues[27] studied a single preoperative dose of pregabalin, 300 mg, versus pregabalin, 300 mg, plus dexamethasone, 8 mg, in 120 patients undergoing total hip arthroplasty. Although pain scores were unaffected, the 2 groups receiving pregabalin preoperatively had significantly less morphine consumption at 24 hours postoperation. The investigators did notice that those receiving pregabalin had more sedation. A randomized, placebo-controlled, double-blind trial comparing pregabalin (300 mg preoperatively with a tapering dose postoperatively for 14 days) with placebo in 240 patients undergoing total knee arthroplasty has recently been published.[28] Immediate effects observed were decreased epidural drug consumption and increased sedation and confusion on PODs 0 and 1. Long-term outcomes included reduced neuropathic pain at 3 and 6 months. A meta-analysis by Zhang and colleagues[29] demonstrated that pregabalin administered preoperatively and/or postoperatively decreases 24-hour morphine consumption while having no effect on postoperative pain scales. Analysis also revealed that pregabalin administration led to lower rates of postoperative nausea and vomiting. The only significant side effect observed was visual disturbances with trends toward more sedation and dizziness/headache in pregabalin-treated groups. This meta-analysis did not include any studies of prolonged (more than 2) doses of pregabalin.

TRPV1 AGONIST: CAPSAICIN

Capsaicin, the active component of chili peppers, selectively stimulates unmyelinated C fiber afferent neurons and causes the release of substance P. After initial

depolarization, continued release of substance P in the presence of capsaicin leads to the depletion of substance P and subsequent decrease in C fiber activation. Capsaicin is a nonnarcotic that acts at TRPV1 receptor as an agonist peripherally. It does not affect the A delta and A alpha fibers. Capsaicin causes calcium-dependent desensitization.

An ultrapurified capsaicin (ALGRX 4975, 98% pure) has been investigated in a randomized, double-blind, placebo-controlled study on the analgesic efficacy of a single intraoperative wound instillation of 1000 μg of capsaicin after open mesh groin hernia repair.[30] The VAS pain scores assessed as area under the curve was significantly lower during the first 3 days postoperatively, but this effect was not observed after 72 hours. The local application of capsaicin during hernia repair does not lead to loss of sensory function in patients[31] and has been demonstrated in animal studies not to cause neurotoxicity.[32] Further clinical trials have been performed in patients undergoing total knee and hip arthroplasty, but the entire data have not been published to date. When capsaicin is used in the perioperative setting, the clinician must administer capsaicin well before the end of anesthesia to allow for resolution of the acute burning sensation that occurs immediately after its application. The prolonged duration of analgesia obtained by capsaicin could be extremely valuable in facilitating earlier rehabilitation after painful orthopedic surgery procedures. In contrast to local anesthetics, capsaicin does not affect the motor or autonomic functions and therefore does not interfere with postoperative rehabilitation. The capsaicin patch (NGX-4010), although used for various neuropathic chronic pain conditions, may be useful in acute pain in a multimodal manner. This needs further large-scale randomized controlled trials.

N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

N-methyl-D-aspartate (NMDA) receptor antagonists, including ketamine and memantine, have been studied as adjuncts for acute and chronic pain management. Ketamine has options for routes of administration, including IV or IN. Remérand and colleagues[33] demonstrated that an IV bolus at the beginning of surgery followed by a 24-hour infusion decreased morphine consumption in patients undergoing total hip arthroplasty. Also, in patients receiving ketamine, the incidence of chronic pain was decreased. At 6 months, 21% of placebo and 8% of ketamine-receiving patients had persistent pain. Loftus and colleagues[34] found similar results, albeit in opiate-dependent patients undergoing lumbar spine surgery. A ketamine infusion of 10 μg/kg/min was started at the beginning of surgery after a bolus of 0.5 mg/kg was administered and terminated at skin closure. Significant results included decreased postoperative morphine requirements and lower pain scores at 6 weeks after operation.

Memantine was first synthesized in the 1960s and found to antagonize the NMDA receptor in the 1980s. The major site of action is the blockade of current flow through the NMDA receptor channel. Memantine is completely absorbed from the gastrointestinal tract, with maximal plasma concentration occurring between 3 and 8 hours after oral administration. Food does not influence the bioavailability of memantine. Approximately 80% of the administered dose remains as the parent drug. The mean terminal elimination half-life is 60 to 100 hours. The recommended initial dose of memantine hydrochloride for the treatment of moderate to severe dementia of Alzheimer disease type is 5 mg orally once daily. The dose should be increased in 5-mg increments to 10 mg/d. The minimum recommended interval between dose increases is 1 week. The recommended maintenance dose is 10 mg twice daily (20 mg/d). There is not an established dose for the treatment of chronic pain states, but case reports and

medication trials that have started at 5 to 10 mg twice a day with increases at 1-week intervals to 30 mg/d have been examined. Ketamine causes memory deficits, reproduces with impressive accuracy the symptoms of schizophrenia, is widely abused, and induces vacuoles in neurons at moderate concentrations and cell death at higher concentrations. Memantine, on the other hand, is well tolerated; although instances of psychotic side effects have been reported, in placebo-controlled clinical studies the incidence of side effects is remarkably low.

Memantine, an orally administered noncompetitive NMDA receptor antagonist, may prove to be more useful than ketamine as an analgesia adjunct. In one study, daily doses of memantine, 30 mg, decreased phantom pain by up to 80% at 1 month after upper extremity amputations (in combination with brachial plexus block.)[35] However, in patients who have developed phantom pain, the pain relief obtained is temporary. Once chronic pain from surgery is established, such as phantom limb pain, memantine has not been shown to provide analgesia for these patients.

Magnesium seems to exert its analgesic mechanism via inhibition of calcium influx, antagonism of NMDA receptors, and prevention of enhanced ligand-induced NMDA signaling in a state of hypomagnesemia. In addition, magnesium may attenuate central sensitization after peripheral tissue injury or inflammation because of dorsal horn NMDA receptors. Magnesium sulfate is available as a 500-mg/mL preservative-free solution for injection. Magnesium administered intravenously lacks efficacy at 4 g; however, 50 mg administered intrathecally has been demonstrated to be effective.[36] Perioperative IV magnesium sulfate at very high doses has been reported to reduce postoperative morphine consumption but not postoperative pain scores. A dose-finding study for IV magnesium determined that administration of magnesium at 40 mg/kg before induction, followed by a 10-mg/kg/h infusion, resulted in a reduction in perioperative analgesic requirements without any major hemodynamic consequences.[37] Higher infusion doses did not offer any advantage. However, because the magnesium ion poorly crosses the blood-brain barrier in humans, it is not clear whether the therapeutic effect is related to NMDA antagonism in the central or peripheral nervous system. This needs to be investigated further.

α_2 AGONISTS

Use of α_2 agonists as an analgesia adjunct has gained interest with clonidine and dexmedetomidine. Central and peripheral stimulation of the α_2 receptors is believed to be the basic mechanism behind analgesia. The role of clonidine in neuraxial blockade has been described by several studies. Recently, Lena and colleagues[38] compared a clonidine/morphine spinal plus remifentanil infusion with a sufentanil infusion for analgesia in 83 patients undergoing open heart surgery. The clonidine/morphine spinal group had faster times to extubation and lower pain scores postoperatively, used less patient-controlled analgesia (PCA) morphine, and had improved patient satisfaction.

An infusion of dexmedetomidine, administered before induction through wound closure, decreased postanesthesia care unit (PACU) opioid use in 80 patients undergoing laparoscopic bariatric surgery.[39] In addition to this, nausea and vomiting was decreased and PACU stay shortened. As presumed, higher doses of dexmedetomidine required significantly more rescue doses of phenylephrine intraoperatively, otherwise there were no differences in side effects compared with placebo. Ramadhyani and colleagues[40] reviewed the use of dexmedetomidine in IV regional anesthesia. The investigators concluded that when added to IV regional solutions, dexmedetomidine had the ability to prolong analgesia and extend the duration of motor and sensory blockade.

DUAL-ACTING AGENT: TAPENTADOL

Tapentadol is a novel central-acting analgesic with duel mode of action.[41] It has analgesic action via the μ opioid receptor and norepinephrine reuptake inhibition. Combining both effects in a single molecule eliminates the potential for drug-drug interactions inherent in multiple drug therapy. The analgesic effects of tapentadol are independent of metabolic activation with minimal metabolites. Having limited protein binding, no active metabolites, and no significant microsomal enzyme induction or inhibition, tapentadol has a limited potential for drug-drug interactions. The duel mode of analgesia is synergistic as demonstrated by preclinical work. The immediate release formulation of tapentadol is FDA approved and has been used in the United States since 2008 with 50, 75, and 100 mg. The drug is a Schedule II drug, and, as such, all precautions that need to be followed for other drugs in this category needs to be followed. The equipotent analgesic dose of 100 mg of tapentadol to oxycodone is 15 mg and needs to be administered 4 to 6 hours.

Although this compound has opioid activity, it also has activity at the descending pathway and therefore may prove to be a very useful analgesic as more clinical experience is obtained in the postoperative setting. For equipotent doses of narcotics, tapentadol has decreased incidence of nausea and vomiting compared with oxycodone.[42] The concept of obtaining equipotent analgesia with decreased postoperative nausea and vomiting can be of great benefit in treating postoperative pain and earlier discharge with significant cost savings.[43] However, further clinical trials need to be performed to demonstrate this phenomenon.

EMERGING TECHNOLOGIES IN PAIN MANAGEMENT

Transdermal Fentanyl

The use of patient-controlled delivery has led to the development of other modalities that allow patient control in the delivery of opioid medications. Transdermal delivery systems, such as IONSYS, allow demand dosing of fentanyl at a predetermined interval. The fentanyl hydrochloride iontophoretic transdermal system (ITS) is a patient-controlled approach to analgesic delivery that may avoid some of the problems associated with IV PCA. Fentanyl ITS is a compact, needleless, self-contained system that is preprogrammed to deliver fentanyl, 40 μg, across the skin by means of an imperceptible low-intensity electrical current, a method known as iontophoresis. This needleless system is under further research before being released for human use. Inhaled fentanyl has been trialed in pediatric and adult patients. There are investigations into the encapsulated liposomal inhaled fentanyl for acute pain, the advantage of this being that it can provide rapid onset and sustained release.

Long-Acting Local Anesthetics

A newly developed liposomal long-acting bupivacaine is considered for approval by the FDA. A single injection of the liposomal bupivacaine should last 72 hours and is currently considered for infiltration of the local surgical site. Regional analgesia with this product has yet to be established.

Cannabinoids

These compounds have been shown to be potent analgesics in animal models. There have been several clinical trials, most of them demonstrating no significant analgesic effect superior to placebo.[44] In fact, some of the trials demonstrated increase in VAS with nabilone (oral synthetic cannabinoid) when used in acute postoperative setting. However, these classes of drugs seem to be promising in patients with chronic pain.

SUMMARY

Acute postoperative pain is a predictable response. Recent research has demonstrated that untreated acute postoperative pain can lead to chronic persistent pain. It is imperative that the health care provider managing acute postoperative pain understand the various options such as multimodal analgesia so that acute pain can be treated and development of chronic pain from surgery prevented.

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