

MANAGEMENT OF ACUTE MUSCULOSKELETAL PAIN: A REVIEW

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ABSTRACT

Objectives: Acute musculoskeletal insult (injury and surgery) is very common. It is also one of the commonest sources of acute pain. Unfortunately, this pain is also commonly undertreated. This is because of various factors that include poor understanding of the subject, fear of pharmacologic agents, their uses and limitations. Untreated acute pain evolves to chronic pain which is more difficult to treat; and the result is the younger population of workers lose valuable time and the elderly become more morbid and incapacitated. The purpose of this paper is to discuss the broad principles of multimodal and multi-agent approach to acute pain management for better patient care.

Data Source: The material source is from various published articles in books and journals.

Data Selection/Extraction: This is a review article on general principles. No specific data is given to compare a method or an agent with another.

Conclusions: Control of acute musculoskeletal pain, whether traumatic or postoperative is more likely to be achieved by use of modern protocols that apply existing basic techniques. Staff education and regular assessment of pain using formal scoring systems is critical. Multimodal approach should result into improved quality of care. Parenteral opioids administered by intramuscular injection or by patient-controlled analgesia devices are the recommended approach. Addition of perioperative use of non-steroidal anti-inflammatory drugs enhances pain control. Use of continuous spinal techniques is a useful alternative in selected patients. Combinations of techniques are the most effective with potential benefits in terms of overall patient outcome.

INTRODUCTION

Pain is an unpleasant sensation or feeling caused by noxious stimuli with or without damage to the body. It remains a poorly understood, complex phenomenon that is controlled by neural, cellular, and humoral mechanisms. It has strong emotional and psychologic components to it that require to be addressed in order to effectively control pain. Acute musculoskeletal injuries and surgical operations leave a huge burden of pain on patients and society. The most common musculoskeletal injuries are those caused by sprains, dislocations, and fractures. Ankle and knee injuries are the most common sports and recreational injuries. Orthopaedic procedures involving the spine, hip, knee and shoulder add to this burden. Orthopaedic procedures will induce more intense pain than do other surgical procedures because the periosteum has a lower pain threshold compared to other deep somatic structures (1). Chronic pain from degenerative, inflam-

matory and neoplastic conditions in the musculoskeletal tissues adds to this burden.

Pain is recognized as an undesirable sensory input, the experience which has affective and cognitive repercussions. This perception is determined by factors such as age, gender, personality and previous pain experiences.

Pain can be classified pathophysiologically as nociceptive, neuropathic or mixed. Nociceptive pain is due to stimulation of pain receptors which are either visceral or somatic. The acute pain can be from inflammatory, musculoskeletal injury or of neurovascular origin e.g. ischaemia. Neuropathic pain on the other hand results from a pathophysiologic disturbance of either the peripheral or the central nervous system; common examples include postherpetic neuralgia and diabetic neuropathy. Alternatively, pain may be mixed, that is, having origins that are both nociceptive and neuropathic.

Patients with nociceptive pain are treated pharmacologically as well as nonpharmacologic interventions, whereas patients with neuropathic pain are more likely to respond to adjuvant agents such as anticonvulsants and antidepressants. Pain of mixed origins may respond to administration of agents that treat for both nociceptive and neuropathic pain (2).

Anatomic and physiological considerations of acute pain

The biologic mechanisms by which perception of acute pain develops and how acute pain can progress to chronic pain have been explained. Damage to the tissue integrity is caused by mechanical, chemical or thermal stimulus. The nociceptors, which are specialized peripheral sensory neurons, lead to neurotransmitter release in dorsal horn neurons in the spinal cord. Neurotransmitters, in turn, relay sensory information through the thalamus to the cerebral cortex. At the spinal cord level, the release of neurotransmitters also results into a withdrawal reflex and a heightened physiologic and emotional response to pain. At the same time certain chemicals released by damaged cells which include histamine, bradykinin, prostaglandins, serotonin, substance P, leukotrienes and acetylcholine, sensitize nociceptors to noxious stimuli. Sensitization is the process where the nociceptive threshold to painful stimuli is lowered. This lowering of the pain input threshold result in repeated afferent input into the nervous system. This comes from what may appear as trivial stimulation e.g. minor trauma. The consequence is activation-dependent neuronal plasticity, the ability of neurons to profoundly alter their structure, function, or biochemical profile. Plasticity develops in three stages which overlap. The stages are activation, modulation and modification which begin with major cellular and biochemical changes in the neurons. This is followed by modulation of the pain perception system by alterations in ion channels on the cell surface of peripheral nociceptors, resulting in increased sensitization of peripheral sensory neurons (peripheral sensitization) (3). These processes lead to amplified responses to all sensory input and result in pain evoked by a normally innocuous stimulus (allodynia) or an exaggerated, prolonged pain response (hyperalgesia). Disinhibition of spinal inhibitory mechanisms also occurs.

Cyclooxygenase-2 (COX-2) is induced in dorsal horn neurons and throughout the central nervous system, including the thalamus, ventral midbrain, and pons with a concomitant increase in production of

inflammatory prostaglandins such as prostaglandin E2 (PGE2). The inflammatory cytokine interleukin-1 (IL-1) also induces COX-2 expression and subsequent PGE2 production in the central nervous system. Therefore, sensitization of the peripheral and central nervous systems, if improperly treated, in the acute phase will result in neuronal plasticity so that highly exaggerated pain responses persist even after the initial injury has resolved (4). This leads to chronic pain in some patients that clinicians find hard to appreciate.

In addition to the sensory input (pain), tissue injury produces stress, which leads to the release of chemical mediators from the injury site, the adrenal cortex, and the immune system. All these interact with mediators of pain, enhancing the response. These endocrine and metabolic changes may cause gastrointestinal symptoms such as nausea and intestinal stasis. They may also cause changes in homeostasis with alterations in blood flow, coagulation, and fibrinolysis. There may also be other systemic changes caused by increased demands on the cardiovascular and respiratory systems.

The stress response may also be accentuated by more pain, anxiety, haemorrhage, and local tissue factors such as tissue necrosis and infection.

Pain under treatment

There are multiple reasons for pain under treatment which include medical personnel lacking formal education on pain management; inadequate pain assessment, mistaken beliefs regarding potential opioid addiction and tolerance, misinterpretation of orders and poor prescription practices. There is also a large inter-individual variation so that a standard dosing regimen will not provide appropriate doses for every patient. The Consequences of under treatment are development of sensitization (chronic pain), reductions in arterial inflow and venous emptying due to sympathetic activity, hypercoagulable state due to immobilization caused by pain and joint splinting. There is also delayed wound repair, muscle spasm and wasting. This creates fear, anxiety and depression in the patient resulting into sleeplessness and depression.

There are social consequences that accrue from under management of a painful episode. This includes delays in discharge from hospital, unanticipated readmissions, delayed in return to work and psychologic disturbances. This may be followed by unnecessary consultations and second opinions that are costly.

The elderly in particular are often either untreated or undertreated for pain. It is like pain is their portion. They are always complaining anyway. This is a bad attitude which discriminates against a segment of the population. The consequences of undertreatment for pain will have a negative impact on the health and quality of life of the elderly, resulting in depression, anxiety, social isolation, cognitive impairment, immobility, and sleep disturbances (5).

Pain assessment

There are pain assessment instruments that are used to evaluate and document pain. Commonly assessed parameters are pain intensity, pain relief and function. There are many such instruments including; Visual Analog Scale (VAS), Patient's Global Evaluation, McGill Pain Questionnaire, American Pain Society Patient Outcome Questionnaire.

The VAS measures pain intensity and pain relief. It consists of a 10-cm horizontal line marked 0-10 with descriptors of "no pain" at 0 and "Worst pain" at 10. When using this scale, physicians will ask patients, "On a scale of zero to 10, with zero meaning no pain and 10 meaning the worst pain possible, how much pain do you have now?" It is a widely accepted and validated method, which is easily added to any existing medical record. VAS is used as a baseline and follow-up measure to gauge response to therapy.

In the postoperative period, there are guidelines which emphasize on provision of analgesia in response to formal assessment of pain experienced by the individual patient. One method is to score the amount of pain and sedation using individual scores and to avoid confusing one for the other. A common refrain is that the patient slept all the time suggesting he/she was not in pain. This is despite the patient persistence complaint of pain. Sleep does not mean painlessness. Bedside assessment of pain is easily combined with the routine postoperative physiological observations. This assessment may be done using VAS or a verbal categorical scale referred to here as the pain score. It is easily understood and quick to administer.

Pain score

- 0 = No pain at rest or upon movement
- 1 = No pain at rest, slight pain upon movement
- 2 = Slight pain at rest, moderate pain on movement
- 3 = Moderate pain at rest, severe pain on movement
- 4 = Severe pain at rest and upon movement

Similar assessments can be used

Charting of assessments is important so that trends can be followed, particularly for the sedative and respiratory depressant side-effects of opioids.

Sedation score

- 0 = Alert
- 1 = Mild drowsiness
- 2 = Moderate sedation (frequently drowsy but easy to rouse)
- 3 = Severe sedation (difficult to rouse)

Modalities of treatment

The complexity of the pain pathways involved in the perception and transmission of pain coupled with the emotional components that alter response to pain call for a multimodal approach particularly to severe pain. This is essential to prevent development of peripheral and central sensitization and chronic pain. Multimodal therapy is employment with two or more approaches which have different modes of action. This may include two or more analgesics that will work additively or synergistically (6).

The holistic and interdisciplinary pain management programme results in an effective pain control in most patients. Nonpharmacologic approaches to pain management are essential and include physical cum manipulative therapy, exercise, cognitive behavioral therapy and spiritual interventions. A well designed physical therapy programme is effective in rehabilitating back to normal function limb and body. The type of techniques and the extent of intervention must be tailored to the individual.

A clinical psychologist is a key team member of the care team; offering cognitive-behavioral therapy to teach coping skills in these patients. They use a structured systemic approach conducting six to ten sessions as per individual requirement. Lastly, for many patients, there is a spiritual dimension to the source, cause and direction of the incident or illness that causes pain. Evidence exists as to the value of spirituality in management of chronic pain (7). The same argument can be extended for use of religious counseling in supporting patients with acute pain. Appropriate counseling or referral to clergy may be helpful in the management of patients, particularly those with inordinate symptoms.

Pharmacologic intervention

The bark of the willow tree was the predecessor to aspirin, which was first synthesized in 1860. In the mid-nineteenth century, morphine and codeine were purified as alkaloids from opium. Acetaminophen (paracetamol) was first used medically in 1893. In the late 1970s, ibuprofen was the first propionic acid derivative to be used in the United States. Naproxen, ketoprofen, and others followed in the 1980s.

Although pharmacologic intervention for pain management is the principal treatment modality, adverse drug reactions are a significant risk. Along with considering age-associated changes of pharmacokinetics and pharmacodynamics, physicians must consider the likelihood of drug-drug and drug-disease interactions. Lesser dosages may be effective in elderly as compared with effective dosages in younger patients.

The general approach is to start with nonopioid medication for treating patients with mild pain, advancing to opioids for those with moderate to severe pain. The use of placebos is unethical, and placebos should not be used in pain management (8). The common pharmacologic approaches are:

1. Opioids; administered IM, IV or continuous intravenous delivery using pumps.
2. Centrally acting nonopioids, paracetamol in particular.
3. Nonsteroidal anti-inflammatory drugs (NSAIDS).
4. Muscle relaxants may be used as adjuvant to NSAIDS in the management of pain and stiffness arising from degenerative musculoskeletal disease.
5. Epidural injections and nerve blocks are increasingly being used for surgery of the lower limbs; with an appropriate agent like bupivacaine that will last for several hours.

Opioids, centrally acting non-opioids and NSAIDS are discussed in more details below.

Opioids

Commonly used opioids are morphine, pethidine, fentanyl, methadone and tramadol. Opioids are available as parenteral, sublingual (buprenorphine hydrochloride), suppository (oxycodone hydrochloride), and transdermal (e.g. fentanyl patch) products. Opioid analgesics are effective in treating patients with moderate to severe nociceptive pain.

Opioid analgesic activity is mainly located within the central nervous system, in the dorsal horn of the

spinal cord and in the mid-brain, where there are high concentrations of receptors for opioid agonists (3). (An agonist is a chemical that binds to a receptor of a cell and triggers a response by that cell. Whereas an agonist causes an action, an antagonist blocks the action of the agonist and an inverse agonist causes an action opposite to that of the agonist). These agonists include exogenous opioid drugs, endogenous compounds (endorphins and enkephalins). The three major classes of opioid receptors are mu (μ) (to which morphine binds), kappa (κ), and delta (δ). The μ agonists confer most clinical analgesia, but are not specific to pain pathways; they also produce alterations in mood and sleep but at therapeutic doses do not alter unconsciousness. They are also responsible for reduction in the propulsive peristaltic contractions of both the small and the large intestine with increased sphincteric tone that may lead to constipation. Due to stimulation of the vagal nucleus in the medulla, dose-dependent bradycardia may occur.

In addition, there are subtype receptors that include μ_1 which produces supraspinal analgesia, μ_2 affects respiratory, cardiovascular, and gastrointestinal function. The kappa and delta receptors also produce spinal analgesia, and sedation.

Patient-controlled analgesia (PCA)

Intravenous opioids are used for PCA, using a programmable IV pump with a reservoir that delivers small predetermined doses at the request of the patient, using a press button. Each dose is delivered within seconds. A predetermined lockout period must lapse before another dose is delivered to avoid abuse and self overdosing.

Adverse effects of opioids

There are other concentrations of opioid receptors in the body that are not associated with analgesia. Stimulation of these sites results in opioid side-effects such as pruritis, nausea, sedation and respiratory depression. They may interfere with normal sleep patterns and aggravate pulmonary function episodic nocturnal arterial oxygen desaturation for several days following general anaesthetic. Renal impairment enhances adverse effects and doses should be decreased if creatinine clearance is $< 30 \text{ mL/min per } 1.73 \text{ m}^2$.

Morphine

Morphine is the standard opioid against which others are judged. It offers effective analgesia with an

acceptable side-effect profile and remains the opioid analgesic of choice after major traumatic event. It is both familiar and cheap. To achieve clinical analgesia, it is necessary to maintain the minimum effective analgesic concentration (MEAC), which is the plasma morphine concentration above the threshold level for pain. There is considerable inter-individual variation in MEAC which ranges from 6 to 33ng/ml. This variation cannot be predicted by weight or similar patient variables so an individually flexible dosing regimen is required. Exceeding plasma morphine MEAC significantly will result in more adverse effects.

Morphine has an active metabolite, morphine-6-glucuronide (M6G), which is more potent than morphine. Intrathecal M6G is 10-20 times more potent than morphine. This metabolite contributes to the analgesic effect of morphine by its action through a different receptor subtype. M6G can accumulate causing unexpected degree and duration of effect of in patients with impaired renal functions. The glucuronidation of morphine is not affected significantly in cirrhosis, although the kinetics and dynamics of morphine metabolism are altered in precoma states.

Morphine acts most rapidly when given intravenously (IV) and so ideally an intravenous loading dose is individually titrated to achieve analgesia followed by a regular intramuscular (IM) or IV doses to maintain MEAC.

Pethidine

Pethidine is the only other strong opioid drug in common use. It has a lower maximum analgesic ceiling compared to morphine and exhibits similar inter-individual variation in plasma MEAC. The adverse effect profile is similar to morphine except for some anti-cholinergic properties that confer some anti-emetic activity. Pethidine has a metabolite called norpethidine which may cause tremor, twitching, agitation and convulsions. These effects increase with multiple dosing and in the presence of impaired renal function. It has a shorter effective half-life, necessitating more frequent dosing. It is inferior to morphine for routine use by PCA.

Fentanyl

Fentanyl is another opioid with analgesic properties similar to pethidine and morphine. It has slightly faster onset of activity when given intravenously; more commonly used during anaesthesia. Can be used for post-operative analgesia by PCA but there is a potential

risk of overdose because fentanyl dose range is very small (mcg).

Tramadol

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic used in treating severe pain. Tramadol possesses weak agonist actions at the μ -opioid receptor, releases serotonin, and inhibits the reuptake of norepinephrine. Tramadol is converted to *O*-desmethyltramadol, a significantly more potent μ -opioid agonist. Opioids are chemical compounds which act upon one or more of the human opiate receptors. The opioid agonistic effect of tramadol and its major metabolite(s) are almost exclusively mediated by the substance's action at the μ -opioid receptor. This characteristic distinguishes tramadol from many other substances (including morphine) of the opioid drug class, which generally do not possess tramadol degree of subtype selectivity.

Tramadol is available in IV/IM and oral forms. A moderate opioid with some additional non-opioid analgesic activity, which produces less nausea compared to other opioids. It is useful for day surgery use although must be used in caution in the elderly because it may cause dizziness and reduce the seizure threshold.

Centrally Acting Nonopioids

Paracetamol (or acetaminophen in USA) is a widely used over-the-counter analgesic and antipyretic. It can also be used in the management of more severe pain such as post surgical pain and providing palliative care in advanced cancer patients. It has a quick onset of action after oral administration (approximately 11 minutes); with a plasma half-life of 1-4 hours.

It is the active metabolite of phenacetin, but is not considered to be carcinogenic at therapeutic doses. It is generally safe for use at recommended doses (1g per single dose and up to 3g per day for adults). The total dose should be limited to 2g per day in alcoholics (9). Acute overdoses of paracetamol can cause potentially fatal liver damage and, in rare individuals, a normal dose can do the same; the risk is heightened by alcohol consumption. Most mild or moderate pain in the musculoskeletal system responds well to acetaminophen given around-the-clock. This agent is well tolerated in most patients provided that both renal and hepatic functions are normal.

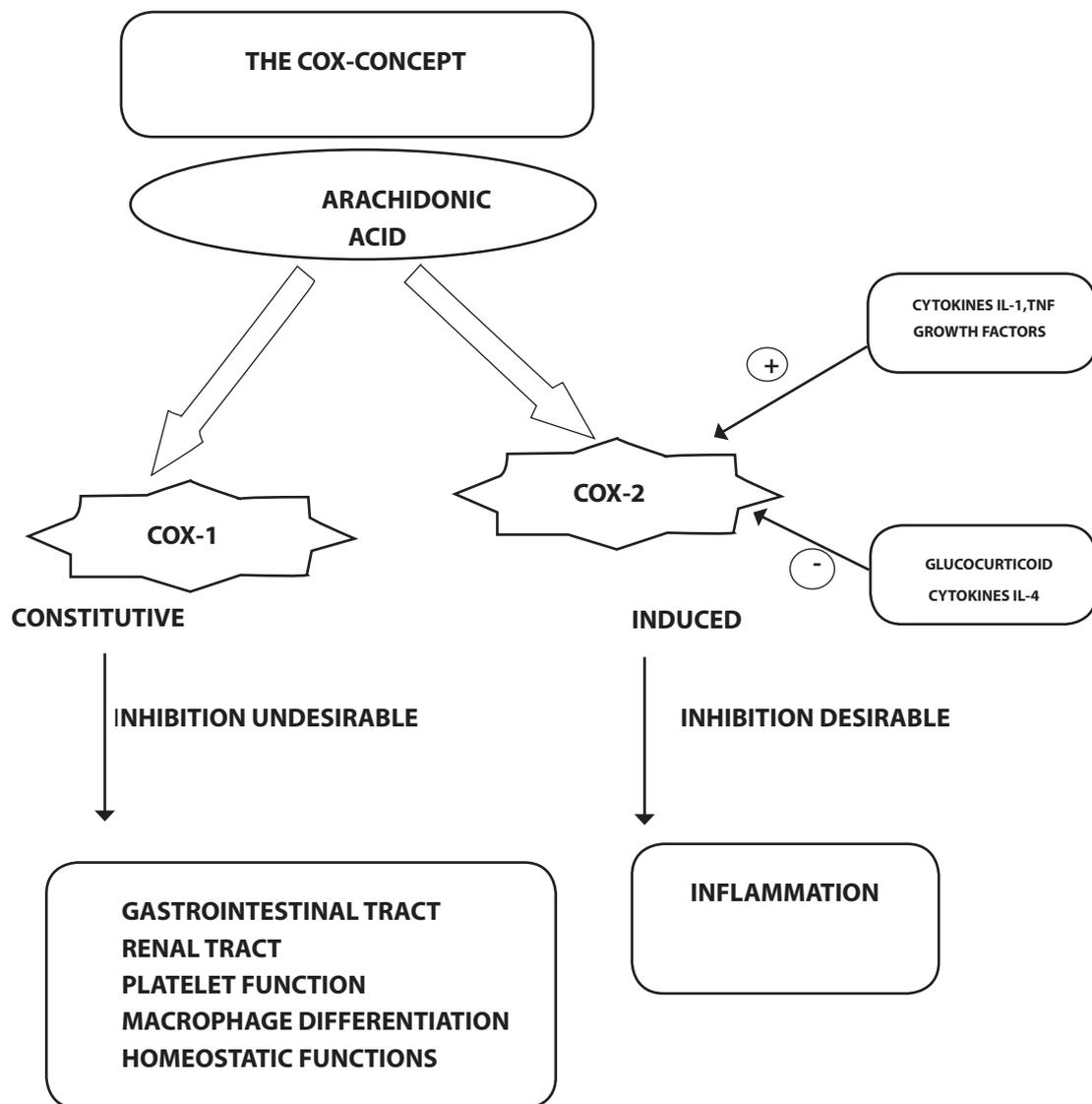
The combination of tramadol and paracetamol has been successfully used to treat moderate to moderately severe acute and chronic pain. This combination has several advantages, including rapid

onset of analgesia, due to the paracetamol, and a longer duration of analgesia, due to the tramadol.

Nonspecific NSAIDs

NSAIDs are moderators of the response to trauma and inflammation in peripheral tissues with additional analgesic activity in the central nervous system. The primary mechanism of action of nonsteroidal anti-inflammatory drugs is inhibition of prostaglandin production by the cyclo-oxygenase enzyme (COX).

Cyclo-oxygenase is an enzyme that is responsible for formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. COX converts arachidonic acid to prostaglandin H₂ (PGH₂), the precursor of the prostanoids. At present, three COX isoenzymes are known: COX-1, COX-2, and COX-3 9(10). Different tissues express varying levels of COX-1 and COX-2. Although



both enzymes act basically in the same fashion, selective inhibition can make a difference in terms of side-effects. COX-1 is considered a constitutive enzyme, being found in most mammalian cells. COX-2, on the other hand, is undetectable in most normal tissues. It is an inducible enzyme, becoming abundant in activated macrophages and other cells at sites of inflammation.

There are a great number of NSAIDs available. NSAIDs (such as ibuprofen, meloxicam, naproxen, and diclofenac) have a relatively linear structure, and they fit readily into the active site of both COX-1 and COX-2. They are referred to as nonspecific NSAIDs. COX-1 adversely affects the production of prostanoids involved in normal homeostatic mechanisms such as protection of gastric mucosa.

COX-2-specific agents, including celecoxib, rofecoxib, and valdecoxib, have a bulky side chain that binds to the catalytic binding site of COX-2 with substantially greater affinity than it binds to the binding site of COX-1, allowing selective inhibition. Cyclooxygenase-2 (COX-2) is induced in dorsal horn neurons, with a concomitant increase in production of inflammatory prostaglandins such as prostaglandin E2 (PGE2). PGE2 is produced in the gastrointestinal tract; it acts as a vasodilator and plays a key role in defence and repair mechanisms. In the kidney, PGE2 induces diuresis and natriuresis. Additionally, there is widespread induction of COX-2 throughout the central nervous system, including the thalamus, ventral midbrain, and pons. COX-2 is inducibly expressed only in the CNS, kidney, tracheal epithelium, and testicles. There is also inhibitory action on lymphocytes and other inflammatory and allergic response cells, which action mutes the immunological response.

In platelets, thromboxane A2 is the primary metabolite of arachidonic acid. Prostacyclin (PGI2) potently inhibits platelet aggregation and has vasodilator effects. Platelets lack COX-2 and depend on COX-1 to indirectly produce thromboxane. Because nonspecific NSAIDs prevent the formation of prostaglandins through the inhibition of COX-1, the tendency toward bleeding is increased. This may result in increased bleeding and haematoma formation postoperatively; the consequences of which are haemarthrosis, wound dehiscence, infection, poor visualization during arthroscopy, and an increased need for transfusion. Bleeding also has a bearing on rehabilitation because haemarthrosis have a deleterious effect on motion and strength. In acute injuries such as ankle sprain, bleeding causes volumetric changes in addition to pain and inflammation; thus, normal platelet aggregation is again important.

COX-2-specific inhibitors are as effective as nonspecific NSAIDs for managing pain of chronic conditions. They are also as effective as COX-1 in relieving postoperative pain.

Long-term use of NSAIDs, because of their association with gastrointestinal bleeding and renal dysfunction, places a lot of patients particularly the elderly at significant risk. Addition of a proton pump inhibitor reduces the likelihood of bleeding. COX-2-specific inhibitors have greater gastrointestinal safety and tolerability compared to nonspecific NSAIDs.

Multimodal analgesia

Novel approaches to treatment of acute pain have been developed. There is increasing utilization of multimodal analgesia in orthopaedic surgery; this entails a combination of pharmacologic and non-pharmacologic approaches (such as RICE). Multimodal therapy can shorten the hospital stay; lessen the adverse effects of opioids by decreasing individual drug dosage and thereby improving patient outcomes. A number of randomized trials have demonstrated the effectiveness and opioid-sparing properties of nonspecific NSAIDs such as ibuprofen, diclofenac, and piroxicam in the relief of acute postoperative pain (11). A study of the efficacy of intravenous doses of parecoxib (20 and 40 mg), Ketorolac (30 mg) and morphine (4 mg) in relieving postoperative pain following total knee replacement showed that parecoxib and ketorolac have a similar onset of action, duration of analgesia, and level of analgesia. Morphine was similar to parecoxib and ketorolac with regard to onset of action but provided a significantly shorter duration and lower level of analgesia ($p < 0.01$) (12).

Preemptive analgesia

Usually patients are only given pain medications well after the onset of symptoms, locking the gate after the horse has bolted, so to speak. Pain should be prevented other than treated. The concept of preemptive analgesia tries to address this mistake, avoiding causing unnecessary pain particularly postoperatively (13). Doses of analgesics are continuously given at appropriate timings whether the patient is in pain or not. This method is more effective at alleviating pain than the standard "as-needed or PRN" dosing. Furthermore, it creates a lower narcotic requirement, which has obvious benefits. Preemptive analgesia may consist of the following drugs given orally preoperatively:

1. Celecoxib 400 mg once daily
2. Paracetamol 1 g 8 hourly

3. Tramadol 50 mg 8 hourly
4. Pantoprazole or esomeprazole 40 mg once daily before food

An opioid like morphine or pethidine given intraoperatively adds to the postoperative analgesic effect. In the immediate post-operative period (48-72 hours) the following treatment is added:

5. Morphine 2-4 mg IV infusion every hour
6. Ondasentron 4 mg or metoclopramide 10 mg

Accelerated rehabilitation

Rehabilitation means restoration back to health. It is therefore, therapy aimed at improving physical and neurocognitive function that has been lost or diminished by disease or traumatic injury. Accelerated rehabilitation therefore, is shortening the period of rehabilitation so that the patient can gain function and independence as soon as possible. To achieve this goal the patient must be well motivated and without pain. There are prerequisite for patients to participate in an accelerated rehabilitation program. They must be educated on the effect and value of non-pharmacological methods of restoration to function. Even with some pain that most patients would consider unbearable, the motivated patient can power through. The second necessary factor is achieving adequate postoperative pain control. The focus of any rehabilitation protocol should be to control pain because this is the variable that can be manipulated. No amount of encouragement or education will convert unmotivated patient in pain into a motivated one. The fact is that many patients, especially younger, active males, could and should participate in a rehabilitation program on the day of surgery, provided they are medically stable. The benefits include immediate, direct psychologic feedback to the motivated patient, with the ultimate potential of reducing his or her length-of stay.

CONCLUSION

Control of acute musculoskeletal pain, whether traumatic or postoperative is more likely to be achieved by use of modern protocols that apply existing basic techniques. Staff education, regular assessment of pain using formal scoring systems and multimodal approach should result into improved quality of care. Parenteral opioids administered by intramuscular injection or by patient-controlled analgesia devices are the recommended approach. Addition of perioperative

use of non-steroidal anti-inflammatory drugs enhances pain control. Use of continuous spinal techniques is a useful alternative in selected patients. Combinations of techniques are the most effective with potential benefits in terms of overall patient outcome.

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