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Multimodal Analgesia for Postoperative Pain Management

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1. Introduction

The experience of pain is complex, multifaceted, and "an unpleasant sensory and emotional experience," as defined in part by the International Association for the Study of Pain. It is a personal, subjective experience that involves sensory, emotional and behavioral factors associated with actual or potential tissue injury (Rawal). The differential behavior response to surgical incision can be influenced by many variables including global (i.e., personality, gender, age, cultural background, pre-existing pain syndromes, genetic makeup, kind and type of surgical approach, cultural background) and specific (i.e., fear, anxiety, depression, anger, and coping) psychological factors (Eccleston, 2001). Only by considering all concomitant factors can physicians provide optimal treatment.

Millions of surgeries are performed on an annual basis, necessitating the frequent use of acute postoperative pain management. There are many types of surgery and, with few exceptions, all are painful. Fear of uncontrolled pain is among the primary concerns of many patients who are about to undergo surgery.

One of the most important factors in determining when a patient can be safely discharged from a surgical facility, and that also has a major influence on the patient's ability to resume his/her normal activities of daily living, is the adequacy of postoperative pain control. Pain is a predictable part of the postoperative experience. Unrelieved postoperative pain may result in clinical and psychological changes that increase morbidity and mortality as well as costs and that decrease quality of life (Carr& Goudas, 1999).

The guidelines for acute pain management in the perioperative setting published in 1992 and 1995 (Acute Pain, 1992; American Pain, 1995; Practice Guidelines, 1995) promoted aggressive treatment of acute pain and educate patients about the need to communicate unrelieved pain. Nonetheless these guidelines appear to have had little influence on practice patterns or on improved pain control for patients. In a study of Warfield and Kahn (Warfield&Kahn, 1995) they found three of four patients reported experiencing pain after surgery, and 80% of these patients rated pain after surgery as moderate to extreme. Since their study, newer drugs, techniques and protocols for postoperative pain management have been developed, and minimally invasive surgical techniques, such as endoscopic procedures, are used more frequently. These changes in practice patterns thought that they could affect the management of postoperative pain and patient attitudes about pain. But in a recent study (Apfelbaum, 2003) that assessed patients' postoperative pain experience and

the status of acute pain management in a random sample, approximately 80 percent of patients said (not very different the previous study mentioned above) they experienced acute pain after surgery. The authors concluded that; despite an increased focus on pain management programs and the development of new standards for pain management, many patients continue to experience intense pain after surgery.

Effective and appropriate pain management requires a proactive approach using a variety of treatment modalities to obtain an optimal outcome with respect to facilitating rapid recovery and returning to full function, allowing early discharge from hospital, improving quality of life for the patient and reducing morbidity (Rawal). Protocols for postoperative pain treatment should be made with considering patients' needs, surgical indications, and institutional resources. It is important to use effective state-of-the-art techniques combined with hospital protocols for early rehabilitation and recovery.

Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and nonopioid) analgesics and regional (i.e., neuraxial and peripheral) analgesic techniques. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects of sole administration of individual analgesics (Kehlet&Dahl, 1993). It also refers to concurrent application of analgesic pharmacotherapy in combination with regional analgesia (Elvir Lazo&White, 2010).

This chapter's aim is to overview on the topic of multimodal analgesia for postoperative pain management and to provide an update on the drugs and techniques used for this approach.

2. Consequences of postoperative pain

When an appropriate analgesic treatment is not given for postoperative pain, various adverse effects might occur in the respiratory, cardiovascular, gastrointestinal, urinary, endocrinological systems, as well as in patient's metabolisms and mentality. These changes were relievable with application of appropriate types of analgesic regimens.

Postoperative pain, especially when poorly controlled, may produce a range of detrimental acute (i.e., adverse physiologic responses) (Vadivelu et al, 2010) and chronic effects (i.e., delayed long-term recovery and chronic pain) (Perkins&Kehlet, 2000). Good pain control after surgery is important to prevent negative outcomes such as tachycardia, hypertension, myocardial ischemia, decrease in alveolar ventilation, immobility, deep venous thrombosis and poor wound healing (Vadivelu et al, 2010; Nett, 2010).

Pathophysiology of acute pain, includes of changes in neuroendocrine, respiratory and renal function, gastrointestinal activity, circulatory and autonomic nervous system activity.

Unsufficient pain management can cause acute and chronic effects:

2.1 Acute effects

- Emotional and physical suffering for the patient
- Sleep disturbance (with negative impact on mood and mobilisation)
- Respiratory system side effects (leading to atelectasis, retention of secretions and pneumonia)
    - Decreased respiratory motion
    - Inhibition of cough and sputum excretion
- Cardiovascular side effects (such as hypertension and arrhythmias)

- Increased oxygen consumption (with negative impact in the case of coronary artery disease, leading to coronary ischemia and myocardial infarction)
- Impaired gastrointestinal motility (while opioids induce constipation or nausea, untreated pain may also be an important cause of impaired bowel movement or postoperative nausea and vomiting-PONV)
- Delays mobilisation and promotes thromboembolism (postoperative pain is one of the major causes for delayed mobilisation)
- Increased sympathetic activity
  - increased release of catecholamines (resulting increase in systemic vascular resistance, cardiac work and myocardial oxygen consumption associated negative effects in patients with coronary artery diseases)
  - reduced blood flow in lower extremities (resulting a higher risk of deep vein thrombosis)

2.2 Chronic effects

- Severe acute pain is a risk factor for the development of chronic pain
- Sleep disturbance (with negative impact on mood and mobilisation)
- Risk of behavioural changes (frequently in children for a prolonged period after surgical pain)
- Poor wound healing
- Delay in long-term recovery

Chronic pain is a potential adverse outcome from surgery. It is costly to society in terms of suffering and disability. For humanitarian and economic reasons, the problem of chronic pain after surgery should be addressed. In a review of Perkins et al. (Perkins&Kehlet, 2000) they showed there was a significant variability in the incidence of chronic pain among surgical procedures (i.e. 3-56% for cholecystectomy, 0-37% for inguinal hernia surgery, 11-57% for breast surgery). They concluded that chronic pain after surgery was common as that has been confirmed with another review (Camann, 1998). Another conclusion of this study is; the intensity of acute postoperative pain was one of the most striking predictive factor for chronic pain, especially following breast surgery (Elia, 2005), thorasic surgery (Carli F,2002; Viscusi, 2004) and hernia repair (Birnbach, 1989).

3. Multimodal approach to postoperative pain

Advances in the knowledge of molecular mechanisms have led to the development of multimodal analgesia and new pharmaceutical products to treat postoperative pain.
Postoperative pain treatment may not be enough to provide major improvements in some outcomes because it is unlikely that a unimodal intervention can be effective in addressing a complex problem such as perioperative outcomes (Boisseau, 2001; Kehlet&Nolte, 2001). The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient's convalescence is implemented (Kehlet, 1997). Pain involves multiple mechanisms that ideally require treatment using a multimodal (or 'balanced') analgesic technique (White&Kehlet, 2010) Principles of a multimodal strategy include control of postoperative pain to allow early mobilization, early enteral nutrition, education, and attenuation of the perioperative stress response through the use of regional anesthetic techniques and a combination of analgesic agents (i.e., multimodal analgesia).

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid-related adverse events. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms at different sites in the nervous system, reducing the incidence of side effects owing to the lower doses of the individual drugs (Buvanendran&Kroin 2009). For example, epidural opioids can be administered in combination with epidural local anesthetics; intravenous opioids can be administered in combination with Nonsteroidal Antiinflammatory Drug (NSAID)s, which have a dose sparing effect for systemically administered opioids. It also refers to concurrent application of analgesic pharmacotherapy in combination with regional analgesia (Elvir Lazo&White, 2010; Rawal).

In the literature some different definitions of multimodal analgesia exists. In some contexts, multimodal analgesia refers to systemic administration of analgesic drugs with different mechanisms of action, whereas in other situations it refers to concurrent application of analgesic pharmacotherapy in combination with regional analgesia. Multimodal analgesia is based on to choice paracetamol and NSAIDs for low intensity pain with opioid analgesics and/or local analgesia techniques being used for moderate and high intensity pain as indicated. (Elvir Lazo&White, 2010; Rawal) (Table 1)

<table>
<tr><th>Mild intensity pain</th><th>Moderate intensity pain</th><th>Severe intensity pain</th></tr>
<tr><td rowspan="3">For example:
Inguinal hernia
Varices
Laparoscopy</td><td>For example:
Hip replacement
Hysterectomy
Jaw surgery</td><td>For example:
Thoracotomy
Upper abdominal surgery
Aortic surgery
Knee replacement</td></tr>
<tr><td rowspan="2"></td><td>(i) Paracetamol and wound infiltration with local anesthetic
(ii) NSAIDs (unless contraindicated) and
(iii) Epidural local analgesia or major peripheral nerve or plexus block or opioid injection (IV PCA)</td></tr>
<tr><td colspan="2">(i) Paracetamol and wound infiltration with local anesthetic
(ii) NSAIDs (unless contraindicated) and
(iii) Peripheral nerve block
(single shot or continuous infusion) or opioid injection (IV PCA)</td></tr>
<tr><td colspan="3">(i) Paracetamol and wound infiltration with local anesthetic
(ii) NSAIDs (unless contraindicated) and
(iii) Regional block analgesia
Add weak opioid or rescue analgesia with small increments of intravenous strong opioid if necessary</td></tr>
</table>

Table 1. Treatment options in relation to magnitude of postoperative pain expected following different types of surgery (by permission from Publisher AstraZeneca)

A lower incidence of adverse effects and improved analgesia has been demonstrated with multimodal analgesia techniques, which may provide for shorter hospitalization times, improved recovery and function, and possibly decreased healthcare costs (Buvanendran & Kroin, 2009).

To achieve a maximum short-term and long-term benefits from multimodal analgesic therapies, the pain management would be initiated as a preventive in the preoperative period continued in the early postoperative period and extended into the postcharge period for 3-7 days (Bisgaard, 2006; White et al, 2007). A deficiency in the design of many of the published studies involving multimodal analgesic therapies is that the drug regimens were not continued into the postdischarge period (Ma, 2004). For example, only immediate pre- and postoperative administration of the cyclooxygenase 2 (COX-2) inhibitor rofecoxib as part of a multimodal analgesic regimen in outpatients undergoing inguinal hernia repair provided limited benefits beyond the early postoperative period (White&Kehlet, 2007). However, when the COX-2 inhibitors are administered for 3 to 5 days after ambulatory surgery, (Gan, 2004; Joshi, 2004) the greater benefits were achieved with respect to clinically relevant patient outcomes (eg, resumption of normal activities) and improvements in pain control. Bisgaard et al (Bisgaard, 2006) concluded that a multimodal analgesic regimen consisting of a preoperative single dose of dexamethasone, incisional local anesthetics (at the beginning and/or end of surgery), and continuous treatment with NSAIDs (or COX-2 inhibitors) during the first 3 to 4 days provided the best clinical outcome. Moreover, recent clinical studies suggest that when classical NSAIDs or more selective COX-2 inhibiting drugs were administered for 3–5 days after ambulatory surgery, a significant benefit was achieved with respect to clinically relevant patient outcomes (e.g., resumption of normal activities) and improvements in short-term pain control (Gan, 2004; White, 2007).

A multimodal analgesic regimen should be adjusted to meet the needs of the individual patient by taking into consideration their pre-existing medical conditions, types of surgery, and previous experiences related to both acute and chronic pain management. Critical multimodal protocols must be designed based on surgical procedures and structural organization to warrant improved outcome including having minimum side effects related to the treatment and rapid returning to social life and daily activities (Fanelli, 2008).

Several multimodal approaches have been advocated based on different combinations of anti-inflammatory drugs, and regional anesthesia (epidural, peripheral nerve blocks, paravertebral blocks, and local injection/infusion of local anesthetics) (Buvanendran, 2010; Mathiesen, 2009). Although each of these drugs and/or techniques has been demonstrated as being effective in reducing the need for postoperative intravenous opioids alone, the evidence supporting specific combinations of drugs and/or regional techniques is still limited.

3.1 Multidisciplinary approach

Faster recovery, reduced hospital stay, and decreased length of convalescence can occur if multimodal analgesia is combined with a rehabilitation program that is multidisciplinary and multimodal (Gajraj&Joshi, 2005).

Treatment of postoperative pain requires good multi-disciplinary and multi-professional co-operation. Multidisciplinary team consists of the anesthesiologist himself has overall

responsibility, pain nurse and specialist surgeon, sometimes pharmacist. In the ward the patient's physician and nurse, physiotherapist when needed are responsible for all care, in partnership with the pain team. The nurse is responsible to report the patient's intensity of pain to the physician and to treat the pain within the defined rules of the local guidelines. Also should pay attention to the effects and side effects of the pain treatment. The pain team nurse is the first point of contact while the anesthesiologist and pharmacist are available to provide specialist advice (Rawal).

All staff involved in the treatment of postoperative pain require regularly updated training emphasising the importance of team-working and co-operation. In this training programme the main headings should be included as; a. Physiology and pathophysiology of pain, b. Pharmacology of analgesics, c. Locally available treatment methods d. Monitoring routines with regard to treatment of pain and e. Local document for treatment and assessment of pain (Rawal).

It is important to understand of the postoperative pain experience from a patient's perspective, if health care professionals are to identify ways to improve care. In Apfelbaum et al study (Apfelbaum et al, 2003); when asked about attitudes regarding pain and pain medications, 75% of patients believed that it was necessary to experience some pain after surgery, and 8% of patients had postponed surgery because they were worried about the possibility of experiencing pain. Although most patients claimed to receive preoperative education on postoperative pain management, that study's findings suggested that a patient's real concern is not adequately addressed.

The patient himself and family members are also to be undertaken as the members of the multidisciplinary team. Education is an important role in this point. Patients are unlikely to be aware of postoperative pain treatment techniques and as the success of pain relief is influenced by their knowledge and beliefs, it is helpful to give patients (and parents in case of cognitively impaired, severely emotionally disturbed, children) detailed information about postoperative pain and pain treatment. Adequate information gives the patient realistic expectations of the care that can be provided (pain relief, not a "pain free status"). Patients who do not speak the local language, and patients whose level of education or cultural background differs significantly from that of their health care team need special concern. A preoperative discussion with the patient and relatives can be helpful about an effective postoperative pain management (Rawal).

It is important to emphasize the need for collaboration between the various health care providers involved in the patient's perioperative care (eg, anesthesiologists, surgeons, nurses, and physiotherapists) to integrate improved perioperative pain management strategies with the recently described fast-track recovery paradigms (White, 2007). This type of multi-disciplinary approach has been documented to improve the quality of the recovery process and reduce the hospital stay and postoperative morbidity, leading to a shorter period of convalescence after surgery (White&Kehlet, 2010).

3.2 Pre-emptive – Preventive analgesia

The concept of pre-emptive analgesia has its origins in the idea that painful stimuli, if not prevented by administration of preoperative analgesic drugs, could lead to spinal sensitization and neuroplasticity processes, resulting in increased pain intensity and duration after surgery. Many authors have studied the effects of different timing of administration of single drugs (*e.g.*, pre-, intra- or postoperative) and have reported no differences in efficacy (Moiniche, 2002).

This approach does not seem to offer any clinically significant advantages over so-called preventative multimodal analgesic regimens when an effective pro-active approach to pain management is initiated in the early postoperative period and extended into the postdischarge period (Sun, 2008). Starting with intensive pain therapy at the beginning and analgesia must be continued, using step-down techniques that involve a change in drugs or route of administration (*i.e.*, from the epidural and intravenous routes to *per os* administration) (Fanelli, 2008).
The main goals of preventive analgesia are: to decrease pain after tissue injury, to prevent spinal sensitization and to reduce the incidence of inflammatory or chronic pain (Senturk, 2002).

4. Drugs in postoperative pain management

Multimodal (or balanced) analgesia represents an increasingly popular approach to preventing postoperative pain. The approach involves administering a combination of opioid and nonopioid analgesics (and adjuvant agents) that act at different sites within the central and peripheral nervous systems in an effort to improve pain control, with fewer opioid-related side effects mainly sedation, nausea, vomiting pruritis, constipation (Elvir Lazo&White, 2010; Vadivelu, 2010).
The development of newer agents available for postoperative pain control opens up possibilities for newer combinations in multimodal analgesia. Multi-pharmacological therapy based on synergistic effects of two or more drugs gives better results than a mono-pharmacologic approach (Vadivelu, 2010).

4.1 Opioids

Opioid analgesics continue to play an important role in the acute treatment of moderate-to-severe pain in the early postoperative period. The problem about these drugs is the variety of perioperative complications eg, drowsiness and sedation, PONV, pruritus, urinary retention, ileus, constipation, ventilatory depression of them. These opioid-related adverse effects inhibit rapid recovery and rehabilitation (Buvanendran&Kroin, 2009; Vadivelu, 2010).
Their effects can be summarized as hyperpolarization of first- and second-order sensory neurons, with inhibition of synaptic transmission. They act by binding to μ receptors, which initially results in increased G protein activity; this, in turn, leads to K+ efflux and inhibition of Ca2+ influx into the cell. Opioids also stimulate the supraspinal descending inhibitory system, which further increases the hyperpolarization of second-order neurons by releasing 5-HT and glycine. Opioid receptors have been demonstrated *in vitro* in peripheral nerve terminals, but they are unable to influence the inflammatory reaction, resulting lack of effectiveness on postoperative pain during movement (Christie, 2000).
Opioids can be used in different ways; i.e intravenous, intramuscular, subcutaneous, transmucosal, epidural, intrathecal, transdermal. The most common route of postoperative systemic opioid analgesic administration is intravenous. When the most important source of nociceptive stimuli is visceral pain, good results may be achieved by intrathecal administration of small doses of opioids (Rathmell, 2005).
Patient controlled analgesia (PCA) optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamics variability in individual patients. It can be programmed for several variables: demand (bolus) dose, lockout interval, continuous or basal infusion, and 4 h limit (Table 2). PCA provides superior postoperative analgesia and improves patient satisfaction when compared with traditional PRN analgesic regimens.

Drug *- Concentration	Bolus dose	Lockout interval (min)	Basal-Continuous infusion **
Morphine (1 mg/ml)	0.5-2 mg	5-10	0-2 mg/h
Fentanyl (0.01 mg/ml)	10-20 μg	5-10	0-60 μg/h
Alfentanil (0.1 mg/ml)	0.1-0.2 mg	5-8	
Sufentanil (0.002 mg/ml)	2-5 μg	4-10	0-8 μg/h
Meperidine (10 mg/ml)	5-25 mg	5-10	0-20 mg/h
Tramadol (4-5 mg/ml)	10-20 mg	6-10	0-20 mg/ml

* Individual patient requirements vary widely. Titrated loading doses can be used if necessary to establish initial analgesia.
** Continuous infusions are not initially recommended for opioid-naive adult patients

Table 2. Intravenous PCA Regimens

Opioid analgesics will likely remain the primary treatment option for patients who require rescue analgesic therapy in the postoperative period until more potent and rapid-acting nonopioid analgesics become available for routine clinical use.

4.1.1 Controlled-release opiods

Controlled-release opioids are not traditionally considered useful in the immediate postoperative period, but some studies have demonstrated that controlled-release oxycodone may be used for postoperative pain control when remifentanil is used for maintenance of anesthesia. Its preoperative administration leads to adequate plasma concentrations for postoperative analgesia and hyperalgesia treatment following short surgery (1-2 h) (Nishimori, 2006). In addition, controlled-release opioids are an optimal choice for step-down analgesia in the late postoperative and rehabilitation periods following orthopedic surgical procedures (de Beer J de, 2005).

4.1.2 Tramadol

Tramadol enhances inhibitory effects on pain transmission at the spinal level blocking nociceptive signal transduction both by opioid and monoaminergic mechanisms. Its opioid and nonopioid modes of action appear to act synergistically. The drug is available in formulations suitable for oral, rectal and parenteral administration. Tramadol has been shown to provide effective analgesia after intravenous and oral (in a few of newer clinical studies) administration for postoperative pain management. The main advantage of tramadol in postoperative analgesia is a relative lack of respiratory depression. The potential of abuse is also negligible.

4.2 Nonopioids

Opioid analgesics, once considered the standard approach to preventing acute postoperative pain, are being replaced by a combination of nonopioid analgesic drugs with diverse modes of action as part of a multimodal approach to preventing pain after ambulatory surgery.
Nonopioid analgesics are increasingly being used before, during, and after surgery to facilitate the recovery process especially after ambulatory surgery because of their anesthetic-and analgesic-sparing effects and their ability to reduce postoperative pain (with movement), opioid analgesic requirement, and side effects, thereby shortening the duration of the hospital

stay. Nonopioid analgesics will likely assume a greater role as preventive analgesics in the future as the number of minimally invasive (keyhole) surgery cases continues to expand.
Recent studies have confirmed that a rational combination of different nonopioid analgesics when given as part of multimodal analgesia reduces postoperative pain. The use of traditional NSAIDs, COX-2 inhibitors, acetaminophen, ketamine, dexmedetomidine, dextromethorphan, alpha2-agonists, gabapentin, pregabalin, and glucocorticoid steroids can provide beneficial effects when administered in appropriate doses as part of a multimodal analgesic regimen in the perioperative setting (Elvir Lazo&White, 2010).
Nonopioid drugs used in postoperative pain management can be classified as:

1. NSAIDs and COX-2 inhibitors
2. Acetaminophen
3. Paracetamol
4. Adjuvants
   a. Alpha-2 adrenergic agonists
      i. Clonidine
      ii. Dexmedetomidine
   b. N-methyl-D-aspartate antagonists (Antihyperalgesic drugs)
      i. Ketamine
      ii. Dextramethorphan
      iii. Magnesium
   c. Gabapentin-type drugs
      i. Gabapentin
      ii. Pregabalin
   d. Glucocorticoids
      i. Dexamethasone
   e. Newer drugs
      i. Capsaicin
      ii. Glyceryl trinitrate
      iii. Cholinergic drugs
         Nicotine
5. Local Anesthetics

4.2.1 NSAIDs and cyclooxygenase-2-selective inhibitors

NSAIDs are known to achieve pain relief by their effect on COX-1 and 2 with the various NSAIDs differing in the proportion to which they inhibit COX-1 and COX-2. They are acid compounds with analgesic, antipyretic and anti-inflammatory properties via inhibition of prostaglandin (PG) synthesis. Prostaglandins, including PG-E2, are responsible for reducing the pain threshold at the site of injury, resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue. The primary site of action of NSAIDs is believed to be in the periphery though recent research indicates that central inhibition of COX-2 may also play an important role in modulating nociception. NSAIDs inhibit the synthesis of prostaglandins both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after surgical trauma (Buvanendran&Kroin, 2009; Fanelli, 2008; McClane, 2010).
NSAIDs are administered orally, parenterally or by the rectal route.
NSAIDs are useful as the sole analgesic after minor surgical procedures. They provide moderate postoperative analgesia and thereby have a significant opioid-sparing effect of 20-

30% after major surgery (Power, 1999). This may be of clinical importance as NSAIDs may reduce the incidence of opioid-related side-effects (respiratory depression, sedation, nausea and vomiting, ileus, urinary bladder dysfunction and possibly sleep disturbances). Since the COX-2 enzyme, the primary target of NSAIDs, is inducible, it is not found in damaged tissues until a few hours following the onset of a noxious stimulus. This could explain the lack of efficacy of preemptive administration of these drugs (Ness, 2001).
NSAID use is not appropriate in all patients because of their age or renal or hematological status or because of previous dyspeptic symptoms (McClane, 2010). COX-2-selective inhibitors (celecoxib, etoricoxib, rofecoxib- is no longer in use due to adverse cardiovascular events-) have the advantage over NSAIDs in the perioperative setting of not increasing the risk of bleeding (Buvanendran&Kroin, 2009).
Many patients now receive a NSAID as a routine part of their postoperative analgesic management. Recent practice guidelines for acute pain management in the perioperative setting specifically state 'unless contraindicated, all patients should receive around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen' (Ashburn, et al, 2004).

4.2.2 Acetaminophen

Acetaminophen is antipyretic and analgesic but has little, if any, anti-inflammatory action. Its analgesic efficacy is not more than that of traditional analgesics; however, it has fewer side effects. Preparation of intravenous acetaminophen recently has been released in Europe. A 100 ml solution is presented as 10 mg/ml for administration over a period of 15 minutes. The onset of action is within five to 10 minutes, with the peak at one to two hours. Optimal analgesia for moderate to severe postoperative pain cannot be achieved using a single agent alone, but a balanced approach in combination with non-steroidal agents can result in up to a 40 to 50 percent reduction in opioid requirements (Vadivelu, 2010).

4.2.3 Paracetamol

Paracetamol has antipyretic and analgesic properties, but it is devoid of anti-inflammatory effects. It has an inhibitory action on central COX-2 and COX-3 enzymes, which would explain its antipyretic activity. The analgesic effect seems to be due to activation of descending serotonergic inhibitory pathways as well as inhibition of central NO synthases (Graham&Scott, 2005). Similar to other analgesic drugs, paracetamol shows differential properties in terms of pain control. Paracetamol may be more effective in treating episiotomy or abdominal pain rather than pain following orthopedic surgery or tooth extraction (Gray, et al, 2005; macario&Lipman, 2001). The different relative roles of peripheral COX enzymes in postoperative pain may explain these differing efficacies.
When paracetamol and NSAIDs are administered by an intravenous route, they show sparing effects on opioid consumption (about 25% and 30%, respectively); this effect begins 4 h after their first administration and is synergistic (Elia et al, 2005; Mirande, 2006).

4.2.4 Adjuvants

Adjuvant drugs are defined as substances that may improve pain treatment and pain control, but they are not commonly defined as analgesics. Adjuvants are compounds, which by themselves have undesirable side effects or low potency but in combination with opioids allow a reduction of narcotic dosing for postoperative pain control. Thus they can provide beneficial effects when administered in appropriate doses as part of a multimodal analgesic regimen in the perioperative setting (Fanelli et al, 2008; Vadivelu et al, 2010).

Multimodal analgesia incorporates the use of analgesic adjuncts with different mechanisms of action to enhance postoperative pain management. Adjuvants are important in postoperative pain management due to side effects of opioid analgesics, which hinder recovery, especially in the increasingly utilized ambulatory surgical procedures (Buvanendran&Kroin, 2007). Multiple adjuvants recently have been developed for the control of pain.

4.2.4.1 Alpha-2 adrenergic agonists

Alpha-2 adrenergic activation represents an intrinsic pain control network of the central nervous system. The alpha-2 adrenergic receptor has high density in the substantia gelatinosa of the dorsal horn in humans and that is believed to be the primary site of action by which alpha-2 adrenergic agonists can reduce pain (Buvanendran&Kroin, 2007).

4.2.4.1.1 Clonidine

Clonidine is originally classified as an anti-hypertensive drug with negative chronotropic activity, but has antinociceptive properties as well. In the spinal cord, clonidine acts at alpha-2 adrenergic receptors to stimulate acetylcholine release, which acts at both muscarinic and nicotinic receptor subtypes with analgesic effects (Fanelli et al, 2008).
Clonidine can be administered orally, intravenously, neuraxially or perineurally in combination with local anesthetics. However, the side effects could be significant. The most important ones are hypotension, bradycardia and sedation (Rawal). Data about the systemic administration of clonidine could support the usefulness of low-dose IV administration. Nonetheless due to the many side effects of systemic clonidine administration, the spinal route is preferred.
Low doses of clonidine proved to be a useful adjunct analgesic when given neuraxially and in combination with peripheral nerve blocks (Habib et al, 2005). Significant results in terms of block duration were obtained when clonidine was added to local anesthetics for epidural or perineural analgesia. At low doses (2 μg/kg), it was shown to increase the duration of perineural blockade. Animal studies suggest that the mechanism of clonidine's potentiation of lidocaine nerve block is inhibition of the hyperpolarization-activated cation current, not via its binding to alpha-2 adrenergic receptors (Jurna, 1995).

4.2.4.1.2 Dexmedetomidine

Dexmedetomidine is a relatively new, highly selective central alpha-2 agonist. Dexmedetomidine, when used as an adjunct, can reduce postoperative morphine consumption in various surgical settings using various routes such as intravenous (Dholakia et al, 2007; Gurbet et al, 2006; Lin et al, 2009). In a recent study the authors found that; the addition of dexmedetomidine to intravenous PCA morphine resulted in superior analgesia, significant morphine sparing, and less morphine-induced nausea,while it was devoid of additional sedation and untoward hemodynamic changes (Dholakia et al, 2007).

4.2.4.2 N-methyl-D-aspartate antagonists (Antihyperalgesic drugs)

With the discovery of the N-methyl-D-aspartate (NMDA) receptor and its links to nociceptive pain transmission and central sensitization, there has been renewed interest in utilizing noncompetitive NMDA receptor antagonists, such as ketamine, dextromethorphan, magnesium ions as potential antihyperalgesic agents.

4.2.4.2.1 Ketamine

Ketamine has been a well known general anesthetic and analgesic for the past 3 decades. There is evidence that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to opioids, local anesthetics, and other analgesic agents.

Ketamine, is the most commonly used antihyperalgesic drug. There is a definite role of ketamine in preventing opioid-induced hyperalgesia in patients receiving high doses of opioid for their postoperative pain relief (Mitra, 2008). It acts as an antagonist of NMDA receptors and may reduce the intensity of hyperalgesia following rapid μ opioid receptor stimulation by short-acting agonists such as remifentanil and, to a lesser extent, sufentanil and fentanyl. Perioperative administration of 2-10 μg/kg/min following a loading dose of 0.5 mg/kg decreases hyperalgesia and allodynia after thoracic and abdominal surgery (Bilgin et al, 2005; Joly et al, 2005), although doses may vary depending on the overall duration and amount of exposure to short-acting opioids.

Routes of administration include oral, intravenous,intramuscular, subcutaneous, epidural, transdermal, and intra-articular.

Clinical use of ketamine can be limited due to psychotomimetic adverse effects such as hallucinations, excessive sedation and bad dreams. Other common adverse effects are dizziness, blurred vision, and nausea and vomiting (Bell et al, 2006). Although high doses of ketamine have been implicated in causing psychomimetic effects, subanesthetic or low doses of ketamine have demonstrated significant analgesic efficacy without these side effects (Buvanendran&Kroin, 2009). It can be used in sub-anesthetic doses as an adjunct to provide postoperative pain relief in opioid-dependent patients (Mitra et al, 2004).

4.2.4.2.2 Dextramethorphan

Dextromethorphan has a similar mechanism of action with a lower affinity for the NMDA receptor. Following oral administration, it is rapidly absorbed from the gut and crosses the blood-brain barrier. A systematic review of perioperative dextromethorphan treatment for acute post-surgical pain concluded that the drug was a safe potential adjunct to classical opioid-based analgesia, but the results were inconsistent (Duedahl et al, 2006).

4.2.4.2.3 Magnesium

The magnesium ion was the first agent discovered to be an NMDA channel blocker. Similarly to ketamine and dextromethorphan, magnesium ions act by blocking the NMDA receptor pore. Since magnesium crosses the blood-brain barrier with difficulty in humans, it is not clear whether its therapeutic effects are related to NMDA antagonism in the central nervous system.

Several clinical studies have shown that magnesium increases postoperative analgesia, but the best dosage regimen remains to be determined (Lysakowski et al, 2007). At very high doses, perioperative intravenous magnesium sulfate has been reported to reduce postoperative morphine consumption but not postoperative pain scores (Koinig et al, 1998; Tramer et al, 1996).

4.2.4.3 Gabapentin-type drugs

Pregabalin and gabapentin bind to voltage-gated calcium channels in the spinal cord and brain. Both drugs are used for seizures and neuropathic pain. One advantage of pregabalin in clinical use is that it has higher bioavailability than gabapentin and linear

pharmacokinetics. The gabapentinoid compounds have been used as part of multimodal analgesic in the postoperative period. Earlier clinical trials with gabapentin for early postsurgical pain have recently been reviewed (Buvanendran&Kroin, 2009).

4.2.4.3.1 Gabapentin

Gabapentin, a third-generation anti-epileptic drug, is a structural analogue of Gaba Aminobutyric Acid (GABA), an important neurotransmitter in the central nervous system. Its main action, however, is to inhibit the alpha2δ subunit of Ca2+ channels with a resultant decrease in neuronal hyperexcitability. During the immediate postoperative period, however, its activation of descending inhibitory pathways may be more relevant and might explain its synergistic effect with opioids (Hurley et al, 2006).
Most of the reviews and meta-analyses concur that perioperative gabapentin helps to produce a significant opioid-sparing effect and probably also improves postoperative pain score relative to the control group (Hartrick et al, 2009; Tiipana et al, 2007).

4.2.4.3.2 Pregabalin

Pregabalin a structural analog of GABA and a derivative of gabapentin (S+ 3-isobutyl GABA). It is a novel drug with a heightened research interest in the analgesic, sedative, anxiolytic, and opioid-sparing effects, in various pain settings, including postoperative pain.
Its main advantages may be faster onset and reduced adverse side effects. Some studies suggest pregabalin to have effective sedative and opioid-sparing effects (Hartrick et al, 2009; Mathiesen et al, 2008), useful characteristics for the control of acute pain. Research on its established role as an analgesic adjuvant as a part of multimodal analgesia for acute pain control is ongoing.

4.2.4.4 Glucocorticoids

Glucocorticoids, including dexamethasone, have been used to reduce inflammation and postoperative pain in surgical procedures (Salerno et al, 2006). Glucocorticoid steroids can provide beneficial effects when administered in appropriate doses as part of a multimodal analgesic regimen in the perioperative setting (White, 2005, 2007).

4.2.4.4.1 Dexamethasone

Dexamethasone is a synthetic glucocorticoid with high potency and a long duration of action (half-life: 2 days), and has low mineralocorticoid activity. Although dexamethasone reduces PG synthesis, its possible analgesic effects have not yet been demonstrated.
In patients undergoing total hip arthroplasty under spinal anesthesia with propofol sedation a single preoperative intravenous dose of dexamethasone decreased the pain upon standing at 24 h compared to placebo (Kardash et al, 2008). In a recent study, it did not reduce postoperative pain scores and analgesic requirements after laparoscopic cholecystectomy. The main advantage of postoperative dexamethasone is its ability to reduce postoperative nausea and vomiting (Feo et al, 2006).

4.2.4.5 Newer drugs

4.2.4.5.1 Capcaisin

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a non narcotic and acts peripherally. It can be used as a cream and also as an injectable analgesic.

Capsaicin cream is usually combined with narcotic analgesics and NSAIDs to relieve a variety of painful ailments such as back pain, arthritic joint pains, and strains and sprains. Injectable capsaicin is used for the control of post operative pain, such as after total knee replacement, total hip replacement, hernia repair, shoulder arthroscopy, and bunionectomy (Aasvang et al, 2008). Pre-administration of neural blockade before injection of capsaicin may greatly decrease the burning discomfort.
Capsaicin appears to be a relatively safe drug. In the elderly who are sensitive to respiratory depression that can occur with opioids, capsaicin can be particularly beneficial as an adjuvant. The only absolute contraindication being patient hypersensitivity. Relative contraindications include age less than 2 years, patients with elevated liver enzymes, patients on ACE inhibitors, and patients showing signs of septic arthritis and joint infections (Vadivelu et al, 2010).

4.2.4.5.2 Glyceryl trinitrate

The organic nitrates, such as glyceryl trinitrate (GTN), act as nitric oxide donors.
High dose nitroglyserin patches, such as 30 mg daily, are hyperalgesic, whereas doses less than 6 mg per day are analgesic under different circumstances. Previously it has been observed that patients with past histories of angina who had spinal block, in which the nitroglycerin transdermal patch was applied prophylactically, required fewer analgesic after operation (Lauretti et al, 1999).

4.2.4.5.3 Cholinergic drugs

Acetylcholine may cause analgesia through direct action on spinal cholinergic muscarinic receptors M1 and M3 and nicotinic receptors subtypes.

4.2.4.5.3.1 Nicotine

In a study in nonsmoker patients having radical retropubic prostatectomy under general anesthesia, the application of a 7 mg nicotine patch 30–60 min before surgery for postoperative 24 hrs, resulted with lower cumulative PCA morphine consumption versus placebo group. But the intensity of nausea was greater in the nicotine group (Habib et al, 2008).
Table 3 summarizes the doses and routes of administration of frequently used drugs.

	Administration	**Dosage**
OPIOIDS		
Morphine	(i) Intravenous. (ii) Subcutaneous by continuous infusion or intermittent boluses via indwelling cannula. (iii) Intramuscular (not recommended due to incidence of pain. 5-10 mg 3-4 hourly).	IV PCA Bolus: 1-2 mg, lockout: 5-15 min (usually 7-8 min), no background infusion. Subcutaneous 0.1-0.15 mg/kg 4-6 hourly, adapted in relation to pain score, sedation and respiratory rate.
Codeine	Oral	3 mg/kg/day combined with paracetamol. A minimum of 30 mg codeine/tablet is required

	Administration	Dosage
OPIOIDS		
Tramadol	(i) Intravenous: inject slowly (risk of high incidence of nausea and vomiting). (ii) Intramuscular. (iii) Oral administration as soon as possible.	0.75-1.0 mg/kg 50-100 mg 6 hourly.
NONOPIOIDS		
Paracetamol	Oral	4 x 1 g paracetamol/day (2 g propacetamol/day). Dose to be reduced (e.g. 3 x 1 g/day) in case of hepatic insufficiency.
Combination of paracetamol and codeine	Oral	Paracetamol 500 mg + codeine 30 mg. 4 x 1 g paracetamol/day.
NSAIDs	(i) Intravenous administration should start at least 30-60 min before end of surgery. (ii) Oral administration should start as soon as possible. Duration: 3-5 days. (iii) Rectal	Ketorolac: 3 x 30-40 mg/day (only IV form) Diclofenac: 2 x 75 mg/day Ketoprofen: 4 x 50 mg/day (ii) Selective NSAIDs include: Meloxicam 15 mg once daily Celecoxib: 200 mg/day.
Acetaminophen	Intravenous	100 ml solution (10 mg/ml) administration over a period of 15 minutes.
ADJUVANTS		
Clonidine	(i) Oral (ii) Intravenous (iii) Combined with local anesthetics-neuraxially or perineurally	3- 5 μg/kg (oral) 1 μg/kg (intravenous) 1-2 μg/kg (epidural) or 75-100 μg (intrathecal)
Ketamine	Intravenous	Loading dose of 0.5 mg/kg followed by 2-10 μg/kg/min

* The doses and routes of administration of drugs described above are general examples and each patient should be assessed individually before prescribing

Table 3. The doses and routes of administration of frequently used drugs * (modified table by permission from Publisher AstraZeneca)

4.2.5 Local anesthetics

Sodium channel blocking drugs are usually used in the management of both acute and chronic pain. When dealing with postoperative pain, local anesthetics such as lidocaine and bupivacaine mostly preferred (McCleane, 2010).

Local anesthetics block sodium channels, thereby, preventing transmission of nerve impulse along the axonal fibre. This is a local effect at the site of injection. Tissue anesthesia occurs after the injection of the local anesthetics into tissue at appropriate concentration, but it lasts after the duration of the drug ended. However, local anesthetics are also absorbed into the systemic circulation from the site of injection and, depending on the dose and rate of absorption, may have systemic analgesic effects (Gupta,2010; McCleane, 2010).

Local anesthetic solutions delivered through an epidural or perineural route are the most important treatments for decreasing incident pain, hormonal stress and sympathetic responses during and after surgery (Chelly, 2001; Liu, 2007). Generally, higher doses are used intraoperatively and then reduced to reach differential motor-sensory block in the postoperative period. The best results are achieved when local anesthetic solutions are infused neuraxially with lipophilic opioids, such as sufentanil and fentanyl at adequate concentrations (George, 2006; de-Leon-Casaola&Lema, 1996).

In some studies the effectiveness of the intravenous infusion of lidocaine in reducing postoperative pain and facilitating the recovery process have been demonstrated (Kaba et al, 2007; Lauwick et al, 2008). Yardeni and colleagues (Yardeni et al, 2009) suggested that, perioperative administration of intravenous lidocaine could improve early postoperative pain control and reduce surgery-induced immune alterations. The injection of local anesthetic around wound edges has been proven to reduce postoperative pain, but only for the duration of that local anesthetic (Moinichi et al, 1998). Several concerns about these drugs have been expressed in the literature including the risk of infection, chondrolysis and systemic local anesthetics toxicity when they used locally.

The maximum doses for local anesthetics are summarized in Table 4.

Local anesthetic	**Maximum total dosage**
Prokain	400 mg
Chlorprocaine	800 mg
Lidocaine	4 mg/kg (without epinephrine) 7 mg/kg(with epinephrine) **or** 300 mg
Prilocaine	6 mg/kg (without epinephrine) 9 mg/kg(with epinephrine) **or** 500 mg
Bupivacaine	2 mg/kg (without epinephrine) 2.5 mg/kg(with epinephrine) **or** 150 mg
Levobupivacaine	2.5-3 mg/kg (insufficient data) **or** 150 mg
Ropivacaine	3-4 mg/kg (without or with epinephrine)

Table 4. Maximum doses of frequently used local anesthetics

5. Techniques in postoperative pain management

One approach for multimodal analgesia is the use of regional anesthesia and analgesia to inhibit the neural conduction from the surgical site to the spinal cord and decrease spinal cord sensitization (Buvanendran&Kroin, 2009). A variety of neuraxial and peripheral regional analgesic techniques can provide analgesia superior to that with systemic opioids and may even result in improvement in various outcomes. However, there are some risks associated with the use of such techniques. The clinician should evaluate the risks and benefits of these techniques on an individual basis in determining the appropriateness of neuraxial or

peripheral regional techniques for each patient, especially in light of some of the controversies about the use of these techniques in the presence of various anticoagulants.
Neuraxial (primarily epidural) and peripheral regional analgesic techniques (e.g., brachial plexus, lumbar plexus, femoral, sciatic-popliteal, and scalp nerve blocks), also a variety of wound infiltration techniques may be used for the effective treatment of postoperative pain. In general, the analgesia provided by epidural and peripheral techniques (particularly when local anesthetics are used) is superior to that with systemic opioids, (i.e., superior analgesia and decreased opioid-related side effects) and use of these techniques may even reduce morbidity and mortality (Wu&Fleisher 2000).
Techniques used in postopetaive pain management are:

1. Neuraxial Techniques
2. Peripheral Regional Analgesia Techniques
3. Infiltration Techniques
    a. Wound Infiltration
    b. Topical Application
    c. Local Infiltration Analgesia
4. Other – Nonpharmacological Techniques

5.1 Neuraxial techniques

Spinal or epidural analgesia techniques in single or continuous forms can be used in postoperative pain management. The use of epidural anesthesia and analgesia is an integral part of the multimodal approach because of the superior analgesia and physiologic benefits conferred by epidural analgesia.
Among the most commonly used pain-relieving techniques, there is evidence that the epidural local anesthetic or local anesthetic-opioid techniques are the most effective on providing dynamic pain relief after major surgical procedures (Kehlet et al, 1999). Epidural local anesthetic application comes in as the major component of multimodal analgesia.
Postoperative epidural analgesia is usually accomplished with a combination of a long-acting local anesthetic and an opioid, in dilute concentrations (Table 5). Long-acting local anesthetics are preferred because they are associated with less tachyphylaxis. Thoracic epidural analgesia with local anesthetics and opioids for abdominal, thoracic and vascular surgery improves bowel recovery times while decreasing the risks of cardiovascular adverse events and of developing persistent pain (Liu, 2004; Nishimori et al, 2006;). In an unpublished study of ours (Sivrikaya et al, 2000), preemptive analgesia with epidural tramadol has supressed the peroperative stress response and also reduced the pain intensity in the early postoperative period in patients had abdominal hysterectomy under general anesthesia.
Maintenance techniques in epidural analgesia include:
Continuous Infusion: An easy technique that requires little intervention. The cumulative dose of local anesthetic is likely to be higher and side effects are more likely than with the other two techniques.
Intermittent Top-up: Results in benefits due to frequent patient/staff contact but can produce a high staff workload and patients may have to wait for treatment.
Patient-Controlled Epidural Analgesia (PCEA): This technique produces high patient satisfaction and reduced dose requirements compared with continuous infusion. However, sophisticated pumps are required and accurate catheter position is important for optimal efficacy (Rawal).

Local anesthetics / opioids	Ropivacaine 2% (2 mg/ml) **or** Levobupivacaine **or** Bupivacaine 0.1-0.2% (1-2 mg/ml)	Sufentanil 0.5-1 µg/ml **or** Fentanyl 2-4 µg/ml **or** Morphine 0.05-0.1 mg/ml **or** Clonidine 5-20 µg/ml (clinical application is limited by its side effects) **or** Epinephrine 2- 5 µg/ml
Dosage for continuous infusion (thoracic or lumbar level)	6-12 ml/h	
Dosage for patient controlled infusion (thorasic or lumbar level) **	Background: 4-6 ml/h Bolus dose: 2 ml (2-4 ml) Minimum lockout interval 10 min (10-30 min) Recommended maximum hourly dose (bolus + background): 12 ml	

* The tip of the catheter should be placed as close as possible to the surgical dermatomes: T_6-T_{10} for major intra-abdominal surgery, and L_2-L_4 for lower limb surgery.
** There are many possible variations in local anesthetic/opioid concentration yielding good results, the examples given here should be taken as a guideline; higher concentrations than the ones mentioned here are sometimes required but cannot be recommended as a routine for postoperative pain relief.

Table 5. Examples of local anesthetics and opioids and doses in epidural analgesia *
(by permission from Publisher AstraZeneca)

Continuous central neuraxial blockade is one of the most effective forms of postoperative analgesia, but it is also one of the most invasive. However, this technique remains the first choice for a number of indications, such as abdominal, thoracic, and major orthopedic surgery, where adequate pain relief cannot be achieved with other analgesia techniques alone. Continuous central neuraxial blockade can be achieved via two routes: Continuous epidural analgesia - the recommended first choice and continuous spinal analgesia - should be limited to selected cases only, as there is less experience with this technique.

5.2 Peripheral regional analgesia techniques

It is clear that local anesthetic techniques, particularly peripheral nerve blockade, will be one of the cornerstones of postoperative pain management. A variety of peripheral regional analgesic techniques (e.g. brachial plexus, lumbar plexus, femoral, paravertebral nerve blocks) as a single injection or continuous infusion can be used to enhance postoperative analgesia. Peripheral regional techniques may have several advantages over systemic opioids (i.e., superior analgesia and decreased opioid-related side effects). Also

the side effects associated with central neuraxial blockade, such as hypotension and wide motor blockade with reduced mobility and proprioception, and complications such as epidural Hematoma, epidural abscess and paraparesis can be avoided (Liu&Salinas, 2003).

Continuous peripheral nerve blocks are being increasingly used since they may provide more selective but still excellent postoperative analgesia with reduced need for opioids over an extended period (Table 6). The vailability of disposable local anesthetic infusion systems and the encouraging results from these early studies have led to the increasing popularity of these techniques for pain control in the postdischarge period (Elvir Lazo&White, 2010). This technique has become increasingly popular due to its ability to control moderate to severe pain and accelerate recovery especially after orthopedic surgery procedures (Capdevila et al, 2005; Ilfeld&Enneking, 2005; White, 2003).

Patient controlled regional analgesia (PCRA) can also be used to maintain peripheral nerve block. A low basal infusion rate (e.g. 3-5 ml/h) associated with small PCA boluses (e.g. 2.5-5 ml - lockout: 30-60 min) is the preferred technique (Rawal).

Site of catheter	**Local anesthetics and dosage***
	Ropivacaine 0.2%-0.375% Bupivacaine 0.1-0.125% Levobupivacaine 0.1-0.2%
Interscalene	5-9 ml/h
Infraclavicular	5-9 ml/h
Axillary	5-10 ml/h
Femoral	7-10 ml/h
Popliteal	3-7 ml/h
Patient controlled regional analgesia	Background: 3-5 ml/h Bolus dose: 2,5-5 ml Lockout interval: 30-60 min

*Sometimes, higher concentrations are required in individual patients. As a standard, starting with a low concentration/dose is recommended to avoid sensory loss or motor block.

Table 6. Examples of local anesthetics and doses in continuous peripheral nerve analgesia and PCA (modified table after using by permission from Publisher AstraZeneca)

5.2.1 Paravertebral blocks

The evidence suggests that the use of paravertebral blocks provide effective postoperative pain control following breast and thoracic surgery as well as for inguinal hernia repair (Greengrass et al, 1996; Karmakar, 2011; Pusch et al, 1999). On their own, paravertebral blocks have been demonstrated to provide effective postoperative analgesia lasting up to 24 hrs (Chelly et al, 2011).

Chelly et al showed in their study that; a multimodal approach, including paravertebral blocks (prior to surgery), celecoxib (pre and post surgey), and ketamine (immediately prior to surgery), provides better postoperative pain control than PCA morphine alone in patients

undergoing open radical retropubic prostatectomy. This approach also allows a reduction in the postoperative need for opioids, lessens the related side effects (e.g., PONV, constipation, and bladder spasm), and facilitates earlier patient recovery which can be connoted that it fascilitates the patient's early recovery (Chelly et al, 2011).

5.3 Infiltration techniques

Local anesthetics can be administered for perioperative pain management via different routes (Table 7). It is crucial for improving the perioperative outcomes especially after day-case surgery (White&Kehlet, 2010).

	Local anesthetic	Volume	Additives
Intraarticular instillation			
Knee arthroscopy	0.75% Ropivacaine	20 ml	Morphine 1-2 mg
	0.5% Bupivacaine	20 ml	Morphine 1-2 mg
Shoulder arthroscopy	0.75% Ropivacaine	10-20 ml	
Intraperitoneal instillation			
Gynecological	0.75% Ropivacaine	20 ml	
Cholecystectomy	0.25% Ropivacaine	40-60 ml	
Wound infiltration			
Inguinal hernia Perianal surgery	0.25-0.5% Ropivacaine	30-40 ml	
	0.25-0.5% Levobupivacaine	30-40 ml	
	0.25-0.5% Bupivacaine	Up to 30 ml	
Thyroid surgery	0.25-0.5% Ropivacaine	10-20 ml	
	0.25-0.5% Levobupivacaine	10-20 ml	
	0.25-0.5% Bupivacaine	Up to 20 ml	

Table 7. Local anesthetic infiltration (by permission from Publisher AstraZeneca)

There are a few techniques for the delivery of the drugs locally into the tissues: intermittent injection, continuous infusion or a combination of two: Intermittent injections (also sometimes referred to as patient-controlled regional analgesia) have the advantage that pain relief can be timed in order to achieve maximal effect during the painful periods such as during mobilization. However, the disadvantage is that sleep quality may be disturbed, as patients sometimes wake up at night due to severe pain, which may be annoying and can also be a cause of patient dissatisfaction. Continuous local anesthetic administration has its advantage in that the patient has adequate pain relief most of the time. However, during periods of activity, the pain could be more severe, which may hamper mobilization. Methods using pumps that have a dual function with low-dose continuous infusion combined with self-administered bolus doses during mobilization are ideal. Several such

pumps are available in the market today, including mechanical (elastometric) and electronic (Gupta, 2010).

5.3.1 Wound infiltration

Infiltrating local anesthetics into the skin and subcutaneous tissue prior to making an incision may be the simplest approach to analgesia. It is a safe procedure with few side effects and low risk for toxicity. Particularly, local anesthetic toxicity, wound infection and healing do not appear to be major problems (Buvanendran&Kroin, 2009).

Although the benefit of local wound infiltration has been documented (Barr-Dayan et al, 2004; Legeby et al, 2009; Park et al, 2002), controversy exists as to the appropriate timing of administering local anesthesia for surgery. A single injection of local anesthetics into the wound is unlikely to have long-lasting effects. Therefore, new techniques for wound infiltration have evolved during the last 10 years and several of them are today used routinely during ambulatory surgery and even in the inpatient setting. One such technique is the use of catheters inserted into incision, fascia, intra-articularly and intraabdominally for the intermittent injection or continuous infusion of local anesthetics and adjuvants for pain management (Gupta, 2010).

Continuous wound infusion of local anesthetics, which is mainly used in general surgery and orthopedics, is an interesting technique in postoperative pain therapy. Continuous wound infusion of local anesthetics is able to reduce postoperative opioid requirements and results in decreased pain scores (Gupta et al, 2004; Rasmussen et al, 2004). Recent studies indicate that rehabilitation seems to be enhanced and postoperative hospital stay may be shorter. Continuous wound infusion is an effective analgesic technique, which is simple to perform. Comparisons with other analgesic techniques, such as peripheral nerve blocks, epidural analgesia and other multimodal analgesic concepts are still required.

Hollmann and Durieux (Hollmann&Durieux, 2000) found that there was a reduction in ileus and hospital stay when lidocaine was given intravenously following major abdominal surgery. Therefore, when administered in larger doses during wound infiltration analgesia, it is possible that some of the analgesic effect seen is via systemic absorption and anti-inflammation.

Wound infiltration with local anesthetics is a simple, effective and inexpensive way of regimen which can be used in a multimodal analgesic regime without major complications. Nonetheless this technique still open some questions to be answered as; to the site of catheter placement, catheter type to be placed, the drugs and concentrations recommended, the technique of administration and side-effects of the technique, including toxicity of local anesthetics. Also it remains unclear as to whether this technique is useful in all types of surgery or should preferably be used for specific operations (Gupta, 2000).

5.3.2 Topical application

5.3.2.1 Local anesthetics

Lidocaine patches were applied to the wound area in the next two studies, and the evidence shows that these are particularly effective for wound pain when the patient coughes and they reduce the postoperative pain score at discharge (Habib et al, 2009; Saber et al, 2009). To place lidocaine patches over or at least close to the wound is suggested as a safe and promising modality to consider in the management of postoperative pain control.

5.3.2.2 Clonidine

Clonidine is an alpha adrenoreceptor agonist and these receptors are known to be located centrally. In a volunteer study (Pratab et al, 2007) clonidine had a significant peripheral action in enhancing duration of local anesthesia on superficial co-infiltration with lidocaine. Hence an opportunity with this co-administration to prolong the duration of pain relief apparent after postoperative wound infiltration could be possible.

5.3.2.3 Nonsteroidal anti-inflammatory drugs

The topical application of NSAIDs could produce significant pain relief as the systemic levels achieved by transdermal application. Topically use of NSAIDs has become popular in the ophthalmic field, in which it has been shown that topically applied NSAIDs can reduce postoperative pain and inflammation (Cho, 2009; Jones&Francis, 2009). In a study, the use of a topical diclofenac patch resulted with reduced wound pain and analgesic requirement in patients who have undergone laparoscopic gynecologic surgery (Alessandri et al, 2006). As a result NSAID patch formulations, to be placed directly over the wound, would have a useful pain-relieving effect. But there is still some studies needed to compare this application with systemic administration of the same drug and what the side effect frequency might be with such application (McCleane, 2010).

5.3.2.4 Glyceryl trinitrate

Experimental data suggest that the production of endogenous nitric oxide is necessary for tonic cholinergic inhibition of spinal pain transmission. In a study; transdermal nitroglycerin and the central cholinergic agent neostigmine have enhanced each other's antinociceptive effects at the dose studied (Lauretti et al, 2010). In two recent more studies transdermal nitroglycerin enhanced the analgesic effect of intrathecal neostigmine following abdominal hysterectomy (Ahmed et al, 2010) and intrathecal fentanyl with bupivacaine following gynecological surgery (Gang et al, 2010).

5.3.3 Local infiltration analgesia

The administration of large volumes of local anesthetics with or without adjuvants into different tissue planes perioperatively is called local infiltration analgesia (LIA) (Gupta, 2010).

It is a multimodal technique developed by Kerr et al. (Kerr at al, 2008) for the control of pain following knee and hip surgery. In their study it was based on systematic infiltration of a mixture of a long acting local anesthetics (ropivacaine), a NSAID (ketorolac), and adrenaline into the tissues around the surgical field (periarticularly intraoperatively and via an intra-articular catheter postoperatively) to achieve satisfactory pain control with little physiological disturbance. The technique allows virtually immediate mobilization and earlier discharge from hospital. A recent study by Essving et al (Essving et al, 2009) on unicompartmental knee arthroplasty performed with minimal invasive technique, using the LIA technique found significantly shorter hospital stay, lower morphine consumption and pain intensity compared with placebo.

5.4 Other – Nonpharmacological techniques

A number of non-pharmacological methods of pain management may be used in conjunction with pharmacological methods in the postoperative setting. These

nonpharmacologic techniques, such as transcutaneous electrical nerve stimulation, acupuncture, psychological approaches (cold) and relaxing therapy and distraction, can be used in an attempt to alleviate postoperative pain.

5.4.1 Transcutaneous electrical nerve stimulation (TENS)

The use of TENS at paravertebral dermatomes corresponding to the surgical incision and/or acupoints has also been reported to improve postoperative pain management (Chen et al, 1998). Because this technique cause few if any adverse effects, its use as an adjunct to conventional pharmaceutical approaches should be considered as part of multimodal analgesic regimens in the future, particularly for patients in whom conventional analgesic techniques fail and/or are accompanied by severe medication-related adverse events (Chen et al, 1998; Usichenko, 2007; Wang et al, 1997).

5.4.2 Acupuncture

The term acupuncture describes a family of procedures involving the stimulation of anatomical points on the body using a variety of techniques. Acupuncture theory is based on two conditions: "yin," which is considered feminine, passive, dark, and cold, and "yang," which is masculine, aggressive, bright, and hot, as well as "qi," which is considered the vital energy that flows and cycles throughout the body. The acupuncture theory is to harmonize any imbalance in yin-yang and qi in a human body to restore the body to a healthy condition. Acupuncture is thought to unblock any obstruction to the flow of qi and, thereby, relieves pain.

Usichenko et al. (Usichenko, 2008) focused on randomized controlled trials of only auricular acupuncture (a popular method in which needles are placed in various parts of the earlobe) for postoperative pain control. They identified nine studies of acceptable quality (though none of the best quality), and concluded that the evidence that auricular acupuncture controls postoperative pain is promising but not compelling. Sun et al. (Sun et al, 2008) conducted a systematic review to quantitatively evaluate the efficacy of acupuncture and related techniques as adjunct analgesics for acute postoperative pain management. The authors concluded that perioperative acupuncture might be a useful adjunct for acute postoperative pain management. However, there are issues with applicability and generalizability of the procedure (Lee&Chan, 2006).

5.4.3 Cold

Iced-water or continuous flow cold therapy is used in orthopedic surgery after knee-surgery (Barber et al, 2000). It can be used both at hospital and at home. There are commercial systems, which are easy to use. The use of iced-water in other kinds of surgery needs further investigation.

5.4.4 Relaxing therapy and distraction

Music, or imagery, or hypnosis may have a positive effect in individual cases. There are commercial music CDs available for relaxation (Rawal).

6 Special aspects

6.1 Ambulatory procedures

The percentage of surgical procedures being performed on an outpatient basis continues to rise. Many more complex and potentially painful procedures in comorbid conditions of the

surgical outpatients are being routinely performed in the ambulatory setting (White & Kehlet, 2010).

Postoperative pain management have some disadvantages in this population; a. pain after minor surgery or in ambulatory patients is more difficult to treat because many of the aforementioned techniques are not available or are too risky. b. The increasing number and complexity of elective operations that are being performed on an ambulatory (or short-stay) basis in which the use of conventional opioid-based intravenous patient controlled analgesia and central neuraxial (spinal and epidural) analgesia techniques are simply not practical for acute pain management. c. The pressure to discharge patients after surgery could limit the pain medications health care professionals are willing to prescribe and it may explain the inadequate management of acute pain after surgery.

Most common medical causes of delayed discharge after ambulatory surgery are; pain, drowsiness and nausea/vomiting (Vadivelu et al, 2010). Although many factors, in addition to pain, must be carefully controlled to minimize postoperative morbidity and facilitate the recovery process after elective surgery, the adequacy of pain control should remain a major focus of health care providers, caring for patients undergoing ambulatory surgical procedures (Elvir Lazo&White, 2010). Many patients undergoing ambulatory surgery continue to experience unacceptably high levels of pain after their operation. A survey by McGrath et al. showed that 30% of patients suffer moderate-to-severe pain following minor surgical procedures (McGrath et al, 2004).

To have a qualified postoperative pain control after ambulatory surgery, it is required that patient discharge is not delayed and that pain control remains effective once the patient is at home. It is important to avoid to use of long acting analgesics and to use regional anesthesia techniques for the anesthesia. Regional analgesia techniques offer a number of advantages for day case surgery patients such as: flexible duration of analgesia (with single shot techniques and/or with catheter infusions), flexible intensity of blockade (according to the type, concentration and volume of local anesthetic) and reduced need for opioids. Wound infiltration, intraperitoneal instillation, peripheral nerve blocks e.g. brachial plexus, paravertebral, femoral nerve blocks can be used in ambulatory surgery patients.

The adaptation of multimodal (or balanced) analgesic techniques as the standard approach for the prevention of pain in the ambulatory setting is one of the keys to improving the recovery process after day-case surgery (McGrath et al, 2004; White, 2007). Early studies evaluating approaches to facilitating the recovery process have demonstrated that the use of multimodal analgesic techniques can improve early recovery as well as other clinically meaningful outcomes after ambulatory surgery. These benefits have been confirmed in more recent studies (Elvir Lazo&White, 2010).

An aggressive multimodal perioperative analgesic regimen that provides effective pain relief, has minimal side-effects, is intrinsically safe, and can be managed by the patient and their family members away from a hospital or surgical center is the ideal one. Current evidence suggests that these improvements in patient outcome related to pain control can best be achieved by using a combination of preventive analgesic techniques involving both centrally and peripherally acting analgesic drugs, as well as novel approaches to administering drugs in locations remote from the hospital setting (White&Kehlet, 2010).

Nonopioid analgesics are increasingly being used as adjuvant before, during, and after surgery to facilitate the recovery process after ambulatory surgery because of their anesthetic and analgesic-sparing effects, their ability to reduce postoperative pain (with movement), and their opioid related side-effects (e.g., gastrointestinal and bladder dysfunction), thereby shortening the duration of the hospital stay and the convalescence period (White&Kehlet, 2010).

Patient-controlled regional analgesia (PCRA) encompasses a variety of techniques that provide effective postoperative pain relief without systemic exposure to opioids. Using PCRA, patients control the application of pre-programmed doses of local anesthetics, most frequently ropivacaine or bupivacaine (occasionally in combination with an opioid), via an indwelling catheter, which can be placed in different regions of the body depending upon the type of surgery. It is important to use suitable local anesthetics in low concentration and to inform patient adequately to avoid the risk of local anesthetic toxicity (Rawal, Vadivelu et al, 2010).

6.2 Stress response

Many detrimental pathophysiologic effects occur in the perioperative period and are associated with activation of nociceptors and the stress response. Uncontrolled pain may result in activation of the sympathetic nervous system, which can cause a variety of potentially harmful physiologic responses that may adversely influence the extent of morbidity and mortality (Vadivelu et al, 2010).

As afferent neural stimuli and activation of the autonomic nervous system and other reflexes by pain may serve as a major release mechanism of the endocrine metabolic responses and thus contribute to various organ dysfunctions, pain relief may be a powerful technique to modify surgical stress responses.

Systemic opioids (PCA or intermittent), NSAID, epidural opiod, lumbar and thorasic epidural local anesthetics are analgesic techniques are mostly used to supress the postoperative surgical stress responces but there is a pronounced differential effect of these various techniques on surgical stress responses (Kehlet&Holte, 2001). Any treatment with opioids, being epidural or PCA opioids, has very little effect on surgical stress responses and organ dysfunctions. Same applies to clonidine and also NSAIDs. Epidural anesthesia has the most profound inhibitory effect on surgical stress responses.

Several studies investigating lower extremity surgery have shown continuous lumbar epidural local anesthetic techniques to be most effective, probably because of a more effective afferent blockade. In abdominal procedures, there is a somewhat smaller efficacy of thoracic epidural local anesthetic techniques in modulating endocrine-metabolic responses, probably due to insufficient afferent blockade as well as the presence of other release mechanisms in eliciting the surgical stress response.

The neuraxial application of local anesthetics and opioids combined to general anesthesia (especially in patients undergoing major abdominal or thoracic procedures) as a multimodal strategy can provide superior pain relief, reduced hormonal and metabolic stress, enhanced normalization of gastrointestinal function, and thus a shortened postoperative recovery time, facilitating mobilization and physiotherapy (Schug&Chong, 2009). In a study by Sivrikaya et al (Sivrikaya et al, 2008) general anesthesia combined lumbar epidural analgesia can only partially attenuate the peroperative stress response and has some limited effects on

recovery of gastrointestinal functions, nevertheless provided a better postoperative analgesia compared to general anesthesia alone. Epidural opioid techniques are less effective on the stress response, and are comparable with systemic opioid techniques and the use of NSAIDs. More data on the use of multimodal analgesic techniques with combinations of different analgesics are needed on this issue.

7. Conclusion

Postoperative pain is a complication of surgery, which, in turn, complicates recovery with functional impairment and drug-related adverse effects. Despite an increased focus on pain management programs and the development of new standards for pain management, many patients continue to experience intense pain after surgery.

Many factors must be considered before deciding on the type of pain therapy to be provided to the surgical patient. These include the patients' co-morbid conditions, psychological status, exposure to analgesic therapies, and the type of surgical procedure.

The multimodal approach may potentially decrease perioperative morbidity, reduce the length of hospital stay, and improve patient satisfaction without compromising safety. However, widespread implementation of these programs requires multidisciplinary collaboration, change in the traditional principles of postoperative care, additional resources, and expansion of the traditional acute pain service. Although a multi-pharmacologic approach may be universally recommended, drugs and their route of administration must be changed according to the type of surgery and hospital resources, and of course to the patient needs.

8. References

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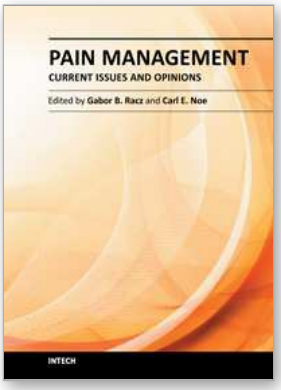

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Pain Management - Current Issues and Opinions is written by international experts who cover a number of topics about current pain management problems, and gives the reader a glimpse into the future of pain treatment. Several chapters report original research, while others summarize clinical information with specific treatment options. The international mix of authors reflects the "casting of a broad net" to recruit authors on the cutting edge of their area of interest. Pain Management - Current Issues and Opinions is a must read for the up-to-date pain clinician.

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