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# Postoperative Pain Management After Hysterectomy – A Simple Approach

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## 1. Introduction

Surgery is often physically and psychologically stressful and in the postoperative period, many patients experience significant amounts of pain and discomfort. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage".

Although acute pain and associated responses can be unpleasant and often debilitating, they serve important adaptive purposes. They identify and localize noxious stimuli, initiate withdrawal responses that limit tissue injury, inhibit mobility thereby enhancing wound healing[1]. Nevertheless, intense and prolonged pain transmission[2], as well as analgesic undermedication, can increase surgical postsurgical / traumatic morbidity, delay recovery, and lead to development of chronic pain. Despite the obviously simple nature of surgical incision, however, perioperative and specifically postoperative pain remain underevaluated and poorly treated. Recent surveys suggest that 80% of patients experience pain after surgery[3], 11% having severe pain, and that pain delays recovery in 24% of patients undergoing ambulatory surgery[4].

## 2. Pathophisiology of acute pain

A number of theories have been formulated to explain noxious perception: The specificity theory by Descartes, the intensity theory by Sydenham, and recently the gate control theory by Melzack and Wall where they suggested that sensory fibers of differing specificity stimulate second-order spinal neurons fire at a different intensity.[5] Pain perception is dependent on the degree of noxious stimulation, local descending inhibition from CNS centers, and responses of second order transmissions cells. Woolf and coworkers have proposed a new theory to explain pain-processing, suggesting that primary and secondary hyperalgesia as well as qualitative differences among physiologic, inflammatory, and neuropathic pain reflect sensitization of both peripheral nociceptors and spinal neurons. Noxious perception is the result of several distinct processes that begin in the periphery, extended up the neuraxis, and terminate at supraspinal regions responsible for interpretation and reaction. [6]

Pain can only be experienced when nociceptive afference reaches the cortex. Most brain imaging studies report an activation of the sensory and affective brain structures following a nociceptive stimulus, demonstrating that pain perception is a complex experience with emotion, cognitive factors, and previous experience playing an important role in perceived pain. It can therefore be understood why the clinician should address pain from both the physical as well the emotional aspect.

Injured tissues will release various substances, such as potassium, prostaglandins, histamine, of bradykinins that are pronociceptive, and will also evoke an immune response. [7]These inflammatory and immune factors will sensitize the nociceptive receptors directly within the lesion and in the surrounding neurons. Primary hyperalgesia, which follows the release of these factors, may be measured as a lowered pain threshold in and around the lesion.

The most important fibers in the transmission of nociceptive stimulus are the A**δ** and C fibers. The first ones will rapidly transmit a brief and acute pinprick-like sensation, perceived to be precisely located at the point of stimulation. Following this activity, C fibers will transmit their information with a relatively long delay (100 millisenconds to a second, depending on the stimulus location). This second sensory input results in a more diffuse deep pain sensation. [8]

Secondary hyperalgesia is a phenomenon that refers to sensitization that occurs within the central nervous system[9]. Repeated recruitment of C-fibers following an injury will produce central sensitization by changing the respose properties of the membranes of secondary neurons. This will result in an increase of the firing rate, a phenomenon known as windup[10]. The high frequency recruitment of C fibers, either by increased repetitive stimuli or by a tonic stimulation[11], will induce an increase of the perceived pain, even if the intensity of the stimulation remains constant. The spinal sensitization can persist for minutes, but can also be present for hours and even days[12]. The prolonged activation of the NMDA receptors will induce the transcription of rapidly expressed genes (c-fos, c-jun), resulting in sensitization of nociceptors. This neuronal plasticity of the secondary neuron will result in a reduced threshold in the spinal cord, producing hyperalgesic and allodynic responses that may persist even after the healing of the injury. Considering the impact of sensitization, an aggressive and early treatment plan to reduce pain will help in preventing ongoing chronic pain[6].

After reviewing some of the above mentioned theories, we can conclude that pain is a dynamic phenomenon; all the nociceptive signals will be modulated at all levels from the periphery to the brain but we still have to take into account genetic and environmental factors that will influence the acute perception and the development of persistent pain. Understanding the neurophysiologic mechanisms involved in the development and maintenance of pain will help the clinician to devise a more effective treatment plan.

## 3. Risk factors for developing chronic pain

Three factors have been proposed to play a role in the chronicity of pain: personal predisposition, environmental factors, and psychologic factors.

It is also well known that chronic pain syndromes more frequently affect women than men; the reason for this predisposition is probably multifactorial, with sex hormones likely

playing an important role. The age is also a factor in this sort of patients; literature suggests that in the 50s it begins a reduction in endogenous pain control which contributes to the higher prevalence of chronic pain in the older population. Expectations of pain, which has not previously been experienced, may confound pain memory, especially when anxiety levels are high. Hysterectomy procedure is a high-risk surgery in terms of psychological and environmental ambience for most of the patients where the surgical team must be aware of these factors.

## 4. Physiology and anatomy of pain in hysterectomy

Uterine innervation stems from a variety of sources. Parasympathetic nerves stemming from S2 to S4 conglomerate into the cervical ganglion of Frankenhauser. Sympathetic nerves, the predominant influence in uterine innervation, descend from T7-T8 to the internal iliac plexi bilaterally to meet their parasympathetic counterparts. Together these nerves innervate not only the uterus, but also the bladder and upper vagina. Within the uterus nerves terminate both within muscle fibers and the endometrium itself. The perineum is innervated by the pudendal nerve, which also enters the spinal cord at the S2-S4 levels.

Although these systems are primarily responsible for the function of the uterus, the perception of pain stems from different sites. Visceral afferent fibers from the uterine corpus transmit pain signals to the brain by entering the spinal cord at the T11-T12 levels, whereas spinal cord levels S2-S4 receive signals from the cervis, vagina, and perineum. Recognition of this divergence is the key[13], because of the pain fibers' high entry point in the spinal cord the block of lower stems will be insufficient for relieving pain independently of the type of surgery (laparoscopic vs open procedure).

Recent advances in minimally invasive surgery have made procedures to be less traumatic however abdominal pain must be avoided because it can restrict ventilation and prevent ambulation; this statement is particularly important in the obese population.[14]

## 5. Mechanistic approach to pain treatment

The different types of pain may be divided into two categories: nociceptive and neurogenic. Acute postoperative pain relies in the nociceptive category where there is a transitory response to nociceptive stimuli that could be mechanical, thermal or chemical. Nociceptive pain plays an important protective role and is normally present for as long as the protection of the organism in necessary; however if not treated well it will persist even after healing of the initial injury.

Postoperative pain management is based on a number of principles. Pain prevention is preferable to, and more efficacious than, treatment of established pain[15]. Multimodal analgesia is a rational approach to pain management and is more effective. The aim of multimodal analgesia combinations is to reduce postoperative pain. Theoretically, multimodal analgesia is achieved by a combination of opioids, and regional blocks, which attenuate the pain-related signals in the central nervous system, and nonsteroidal anti-inflammatory drugs, which act mainly in the periphery to inhibit the initiation of pain signals.

Abdominal hysterectomy is refered among the most frequently procedures associated to pain in the gynecologic population.[16]

Whether is an open or laparoscopic procedure, abdominal or vaginal approach, the clinician has many options for providing multimodal analgesia: patient control analgesia, epidural analgesia, intratecal opioids, wound infiltration, nonsteroidal anti-inflammatory drugs and adjuvant drugs.

### 5.1 Nonselective nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, and acetaminophen

Nonsteroidal anti-inflammatory drugs (NSAIDs) form a heterogeneous group of organic acids that have analgesic, antipyretic, anti-inflammatory, and platelet inhibitory actions.

NSAIDs have long been used in the treatment of nonoperative pain syndromes; their mechanism of action is through the nonspecific inhibition of COX, which therefore blocks both the constitutive COX-1 isoform, responsible for gastric protection and platelet function, and the inducible proinflamatory isoform, COX-2. Thus, the actions of the NSAIDs result in both the desired analgesic effects and the unwanted adverse effects of the COX isoforms.

Some systematic reviews have concluded that there are no significant differences in the analgesic efficacy between different NSAIDs, but they do have different levels of toxicities, especially at high or increased doses[17]. The use of the NSAIDs in preemptive analgesic therapy has been debated and is still controversial with non measurable long-term advantage when compared with its postoperative use[18]

The postoperative use of NSAIDs has been evaluated in several types of surgical procedures and in several dosages forms either as a single therapy compared with other analgesics or placebo or in a multimodal approach in combination with different kinds of analgesics to determine their efficacy, opiate-sparing effects and safety. One example is the postoperative use of ketorolac in combination with tramadol in patients who underwent abdominal surgery; the use of this combination was found to be safe and effective with similar pain relief when compared to a higher dose of tramadol used as monotherapy[19]

In another study a group of patients with open gynecologic surgery, received a loading dose of parecoxib on day one and continued their analgesic regimen with morphine through a PCA. After day one they were separated in two groups: placebo vs parecoxib 20mg twice daily on days 2-5. The results were that in the parecoxib treatment group, 24-hour summed pain intensity scores were significantly lower than in the placebo treatment group on days 2 and 3 and consumed less rescue medication compared with the placebo-treated patients[20]

In an effort to minimize the risk of bleeding and the risk of gastrointestinal complications that have traditionally been associated with the use of the nonselective NSAIDs, the use of COX-2 inhibitors as non opioid adjuvants has become increasingly popular to reduce pain during the perioperative period[21]. They haven't shown increased analgesic potency in the treatment of postoperative pain; even more valdecoxib was not approved by the US FDA for the management of acute pain. Actually valdecoxib and rofecoxib were voluntarily withdrawn from the market because of concerns of increasing the risk of cardiovascular events.

Unless there is a major contraindication for the use of the NSAIDs, they are generally accepted for the management of mild to moderate postoperative pain and as adjuncts for use with other analgesics in moderate to severe postoperative pain (table 1). The concomitant inhibition of physiological COX-1 leads to renal toxicity, platelet dysfunction, and gastrointestinal toxicity.

| | COX Selectivity | COX-2:COX-1 ratio | Vd (l) | $T_{1/2\beta}$ (h) | Clearance ($l\ h^{-1}$) |
|---|---|---|---|---|---|
| Ibuprofen | None | 1:1 | 10 | 2.4 | 4.4 |
| Diclofenac | None | 1:1 | 30 | 2 | 15.6 |
| Ketorolac | None | 1:1 | 14 | 5.4 | 2.3 |
| Meloxicam | Moderate | 10-13:1 | 10-15 | 20-22 | 0.5 |
| Celecoxib | High | 375:1 | 400 | 11 | 30 |
| Rofecoxib | High | >800:1 | 86 | 17 | 7.2 |

Table 1. Preparing for the primary FRCA, Non-steroidal anti-inflammatory drugs, Sharpe P. and Thompson J.
Bulletin 6. The Royal College of Anaesthetists, March 2001

The group of patients who are at higher risk of adverse reactions when treated with NSAIDs are well known; they include the elderly, pregnant women (and their fetuses), neonates, patients with liver, kidney, or cardiac disorders, and those with hypertension, multiple myeloma, peptic disorders, or active rheumatoid arthritis.

The dosage of any NSAIDs must be according to specific recommendations and prescribing practices. It is well known that many of the medication errors in the hospital setting are due to analgesic overdose and misused[16].

### 5.2 Acetaminophen (paracetamol)

Acetaminophen was first used in 1883 but gained widespread acceptance only after 1948. It possesses a wide safety profile. The WHO has recommended it to be used as the first line medication for mild, moderate, or severe pain and to add opioids and other analgesics as the pain remains persistent or increases. This multimodal approach has been adopted in the European Union and has effectively resulted in a 33% decrease in opioids use and their adverse effects.

Although paracetamol is acceptably safe in usual dosages, there have been some reports that in patients with significant hepatic dysfunction or those taking substances that induce hepatic enzymes even common doses may aggravate liver dysfunction, sometimes to the point of causing hepatic failure. Stable mild chronic liver disease does not seem to be a contraindication.[22]

Paracetamol is one of the most commonly ingested medications in deliberate self-poisoning and accidental ingestion by children. The problem of overdosage is substantial. Fulminant hepatic failure occurs in 1-5% of cases of paracetamol overdosage 3-6 days after ingestion[23] with frequent deaths in people who take 20-25g. There is noly a narrow margin betwwn the normal maxium 24-hour dosage and that which can cause liver damage and acute hepatic failure.

Available in oral, rectal and intravenous administration (most of the countries)

### 5.3 Opioids

Opioids represent a class of analgesics that provide powerful dose-dependent pain relief for patients suffering moderate to severe pain. This class of drug includes a large number of compounds with variable pharmacokinetics and pharmacodynamics and a dosing versatility for its administration.

Opioids interact with specific transmembrane G-protein coupled binding sites termed opiate or opioid receptors. These receptors are located primarily in the spinal dorsal horn, central gray, medial thalamus, amygdala, limbic cortex, and other regions of the central nervous system that process affective and suffering aspects of pain perception[24]. Opioid receptors serve as binding sites for endogenous ligands, including endorphins and the enkephalins, which naturally modulate pain transmission and perception. Opiates ad synthetic opioids have structural/chemical similarities that enable them to bind and activate opioid receptors resulting in powerful, dose-dependent analgesia[25]

Three principal opioid receptor subtypes, designated as μ, κ and δ have been isolated and characterized. μ receptor (also known as OPR1) is the main responsible for the analgesic and side effects of opiates; its primary agonist includes β-endorphin and morphine.[26]

According to their binging affinities and intrinsic activity at receptor subtypes, opioids are classified as agonists, partial agonists, mixed agonist-antagonists, and complete antagonists[17,18]. (tables 2 and 3)

| Opiates | | | |
|---|---|---|---|
| Agonists | Partial Agonist | Agonist/Antagonist | Antagonist |
| Morphine and derivates<br>Codeine<br>Fentanyl<br>Sulfentanil<br>Alfentanil<br>Remifentanil<br>Meperidine | Buprenorphine | Nalbuphine<br>Butorphanol<br>Pentazocine | Naloxone<br>Naltrexone |

Table 2.

In acute pain scenarios, most opioid-related adverse events are transient and tend to resolve with ongoing treatment. The common adverse events are nausea, vomiting, sedation, pruritus, and constipation. Patients recovery from abdominal and gynecological surgery are generally at risk for opioid-induced bowel dysfunction and ileus with recommendation that such therapy may be supplemented with stool softeners, bulk laxatives, and occasional enemas[27].

When using opioids for acute pain management it is recommended to have safety rules that must be applied mainly in high risk patients. Neonates, infants, and children are at risk of adverse effects of opioids, owing to pharmacokinetic and pharmacodynamic changes. Routine use of pulse oximetry is recommended in all children receiving opioids[28].

Elderly patients are particularly at risk, as a number of other susceptibility factors can co-exist. Renal insufficiency can result in clinically significant accumulation of

| Opiates | |
|---|---|
| Morphine | Standard of comparison of all opioid analgesics<br>Moderate analgesic potency<br>Slow onset to peak effect<br>Intermediate duration of activity<br>Dose dependent adverse effects<br>Release of histamine which may precipitate hypotension and bronchospasm<br>Increases smooth muscle tone which exacerbate biliary, tubular, and ureteral colic |
| Oxycodone | Semisynthetic mu receptor agonist<br>High oral bioavailability<br>Less sedation than equivalent doses of morphine |
| Hydromorphone | Semysinthetic mu selective opioid agonist<br>Analgesic potency 5-6 times greater than morphine with a greater ability to penetrate the blood brain barrier<br>Less histamine release |
| Fentanyl | Mu-specific opioid agonist related to meperidine<br>Analgesic potency 35-60 times greater than morphine<br>Rapid onset and variable dose-dependent duration of effect<br>Rapidly penetrate blood brain barrier and bind opioid receptors in central nervous system<br>Provide hemodynamic stability<br>Major adverse effects include rapid and profound respiratory depression and chest wall rigidity |
| Methadone | Opioid agonist<br>Analgesic potency 1.5-2 times greater than morphine<br>Oral bioavailability greater than 80%<br>Accumulates in tissues so analgesic duration and risk of overdosing may increase with doses<br>Prolongation of QTc interval and may initiate or exacerbate torsades de pointes and Wolff-Parkinson-White syndrome<br>Good choice for patients with highly opioid dependent disorders |
| Meperidine | Opioid agonist<br>Analgesic potency one tenth that of morphine<br>Produces smooth muscle relaxing effect |
| Codeine | Opiate-derived analgesic<br>Analgesic potency one-third to one-fourth as potent as morphine<br>High incidence of nausea and vomiting |
| Tramadol | Weak mu-receptor opioid agonist<br>Also inhibits re-uptake of both 5-HT and noradrenaline and stimulates the presynaptic release of 5-HT<br>Analgesic potency similar to codeine<br>Not recommended for severe acute pain |
| Sufentanil | Synthetic mu-specific opioid agonist related to fentanyl<br>Analgesic potency 500-700 times greater than morphine<br>Rapid onset and dose dependent duration of effect |
| Buprenorphine | Partial agonist-type opioid<br>Available in a sublingual formulation |

Table 3.

pharmacologically active opioid metabolites and prolonged narcosis; such patients must be monitored for signs of toxicity. To date, this effect has only been reported with codeine, morphine, and pethidine. Dextropropoxyphene is not recommended in renal insufficiency.[29]

The use of oxygen supply, highly trained nurses, monitoring to avoid respiratory and cardiovascular adverse events is highly recommended.

### 5.4 Patient control analgesia

Patient control analgesia (PCA) is the standard technique for the management of moderate or severe postoperative pain. The concept of intravenous PCA is described as a technique that allows patients to self-administer intravenous opioids as required and dates back to the mid-1960s. Nowadays the drugs used in this kind of devices vary according to hospital facilities and clinician preferences. Opioids are the first line drugs used in PCA, however in many hospitals a combination of opioids and NSAIDs for background infusions with a extra shot at patient request are now used. Regular paracetamol and NSAIDs can be used simultaneously. Supplementary oxygen should be considered, particularly on the first and second postoperative nights.

Over the years, further improvements were made to the design of PCA devices. These have resulted in increases in security and data output capacity, introduction of error reduction programs, and a choice of mains in battery power. In addition, a variety of disposable delivery systems are now available. Before PCA can be used safely and effectively it is mandatory to educate the patients, all medical and nursing staff involved in its utilization.

### 5.5 Intravenous PCA

Most authors use morphine as the opioid of choice beginning with a small dose (1mg of morphine) at patient request, with a lockout period (5 minutes) to prevent overdosing. However there are many side effects of morphine that has lead a vary of studies searching for the optimal opioid for PCA analgesia. Lenz et al. showed in their study that oxycodone was more potent than morphine for visceral pain relief but not for sedation in patients after laparoscopic hysterectomy[30].

For abdominal hysterectomies in a teaching hospital in Mexico City a combination of fentanyl (1mg) plus ketorolac (90-120mg of ketorolac) in a mix of 100cc of total volume is given to the patients at a rate of 0.4mcg/kg/hr of fentanyl with the same dose for patient request with a lockout of 30minutes[16].

### 5.6 Epidural analgesia

Epidural analgesia provides excellent pain management after major surgery. It is only safe to use on wards with trained staff under pain service supervision. Usually, a combined local anesthetic and opiate infusion is used. These drugs act synergistically, but can be given separately. The level and density of block must be regularly assessed. Ideally, the local anesthetic will provide blockade of small nerve fibers (pain and temperature) but maintain fine sensation and motor power. The opiates augment the analgesic effect at spinal level.

The sympathetic blockade associated with local anesthetics can result in vasodilation and subsequent hypotension. The location of the epidural catheter placement affects the efficacy of epidural analgesia and influences patient outcomes. Epidural catheters should be inserted in a location congruent to the incisional dermatome. Discrepancy between epidural catheter insertion level and incision site may lead to an increased rate of side effects secondary to an increased infusion rate and increased volumes of local anesthetics used. Inadequate pain relief can lead to early termination of epidural analgesia and masking the potential beneficial effects of epidural analgesia[31]

Side effects of epidural opiates include pruritus, nausea and vomiting, urinary retention, and respiratory depression. Continuous supplementary oxygen should be used.

The choice of analgesic agents administered in the epidural space play a significant role in the achievement of optimal analgesia. The most common agents used are opioids and local anesthetics. Other agents include clonidine, neostigmine, adenosine, ketamine.

Removal of epidural catheters may need to be timed to match a therapeutic trough after prophylactic heparin or low molecular weight heparin is given.

### 5.7 Epidural PCA

Two meta-analysis have concluded that IV PCA is less effective than continuous epidural and PCA-epidural analgesia.[32], [33]

Local anesthetics are not widely used as the sole agent in postoperative epidural analgesia. To achieve effective analgesia using local anesthetics alone, patients will require higher concentrations of the drugs that could result in hypotension and motor block. Nevertheless, epidural of local anesthetics alone may be warranted in situations in which the side effects of opioids are troublesome to the patient.

The most commonly used local anesthetics in epidural analgesic preparations are bupivacaine, ropivacaine and levobupivacaine. Nowadays for many clinicians ropivacaine is the local anesthetic of choice for background infusions because of their unique property of minimum motor blockade. Most authors recommend an infusion with a 1-2% concentration of ropivacaine at a 4-6ml/hr. An additional opioid could be used in the same mixture.

### 5.8 Other pain management techniques

This includes the use of non-opiate drugs such as clonidine or tramadol, continuous nerve blocks, and novel drugs used epidurally. The management of a surgical patient with coexisting substance abuse issues or chronic pain problems of any cause is complex and requires the early involvement of a pain specialist.

### 5.9 Glucocorticoids for pain management

Glucocorticoids have a number of beneficial properties in a surgical setting. In addition to being antiemetic, they are antiinflammatory, analgesic, antipyretic, and antiallergic[34]. Glucocorticoids exert their effects by binding to a glucocorticoid receptor (GR) localized in the cytoplasm of target cells. There is a single class of GR that binds glucocorticoids, with no evidence for subtypes of differing affinity in different tissues[35].

Glucocorticoids may control inflammation by inhibiting many aspects of the inflammatory process through increasing the transcription of anti-inflammatory genes and decreasing the transcription of inflammatory genes.

Glucocorticoids inhibit the transcription of several cytokines that are relevant in inflammatory diseases, including IL-1b, IL-2, IL-3, IL-6, IL-11, TNF-a, GM-CSF and chemokines that attract inflammatory cells to the site of inflammation, including IL8, RANTES, MCP-1, MCP-3, MCP-4, MIP-1a and eotaxin.

The analgesic effect of glucocorticoids was first shown with betamethasone in patients undergoing third molar extraction[36]. A group of doctors from the Helsinki University Hospital chose to investigate the analgesic potency of different doses of dexamethasone for postoperative pain management of patients who underwent laparoscopic hysterectomy[37]. IV dexamethasone 15 mg before induction of anesthesia decreases the oxycodone consumption during the first 24 h after laparoscopic hysterectomy. During first 2 h after surgery, dexamethasone 10 mg reduces the oxycodone consumption as effectively as the 15 mg dose. The opioid-sparing potency of dexamethasone is dose dependent. The effect of the 5 mg dose on postoperative oxycodone consumption was negligible, whereas the 10 and 15 mg doses reduced oxycodone consumption during the first 2 h after surgery.

There is also some studies that presumed the prolonged analgesic effect of non steroidal anti-inflammatory drugs with dexamethasone; a group of experts from Scandinavia, have demonstrated that the association of 16 mg of dexamethasone with rofecoxib has prolonged its analgesic effect[38]. It is also worth mentioning a cost related benefit of the use of dexamethasone. Compared to costs of multiple doses of non-steroidal antiinflammatory drugs used during and after this procedure sounds reasonable to use a single dose of dexamethasone in order to reduce consumption of analgesics.

### 5.10 Adjuvants in anesthesia and postoperative pain

A number of adjuvants have been added to the intrathecal local anaesthetics for supplementation of intraoperative anaesthesia and postoperative analgesia. They have advantages as they reduce the dose of local anaesthetic; provide long lasting postoperative analgesia with reduced incidence of central nervous system depression, motor effects or hypotension.

Ketamine is an intravenous (IV) anesthetic with analgesic properties in subanesthetic doses, secondary to its action on the NMDA receptor. Several trials are investigating the use of low-dose ketamine for managing postoperative pain. The effect of adding ketamine to morphine for postoperative patient-controlled analgesia (PCA), compared with using morphine alone was investigated in six trials involving 330 patients. Only one trial in patients undergoing lumbar microdiscectomy[39] showed a beneficial effect of adding ketamine. There were no analgesic effects of ketamine in the other five studies in patients undergoing abdominal surgery [41]. Adverse effects including vivid dreams, hallucinations, dysphoria, and disorientation were increased in ketamine-treated patients in two studies.

Dextromethorphan is a weak, noncompetitive NMDA antagonist that has been used as an antitussive agent. It has been shown to inhibit development of cutaneous secondary hyperalgesia in people after peripheral burn injury and to reduce temporal summation of pain[40]. Several studies investigated the effect of the perioperative administration of

dextromethorphan on acute postoperative pain. Opiate-related adverse effects were similar between patients who received dextromethorphan and control patients. Postoperative administration of IM dextromethorphan at a dose of 40 mg and oral dextromethorphan (200 mg every 8 hours) also were associated with a significant reduction in postoperative opioid consumption[41].

Analgesic effect of intrathecal neostigmine is secondary to acetylcholine release in the spinal cord tissue[42]. During surgical stimuli, a pre-existent spinal cholinergic tonus is activated. Neostigmine, an anticholinsterase drug increases the concentration of acetylcholine in the cerebrospinal fluid and acetylcholine bioavailability at the cholinergic nerves within the spinal cord. The existence of a cholinergic system in the spinal dorsal horn involved in sensory transmission and modulation is supported by anatomical, pharmacological and electrophysiological studies. Electrophysiological studies have demonstrated that cholinergic receptor agonists produce inhibitory effects on spinal dorsal horn neurons, including spinothalamic tract neurons[43]. This suggests that a spinal cholinergic system plays an important inhibitory role in the modulation of nociceptive transmission.

Nitric oxide (NO) was shown to be a central neurotransmitter and to act as a second messenger in the central nervous system. There are several reports of the relationship between NO and pain processing in the brain and the spinal cord. Acetylcholine and morphine induce analgesia via activation of the arginine-NO-cGMP pathway. Guanylate cyclase activity in the brain is markedly stimulated by NO, generated from L-arginine or provided through an exogenous source. The transdermal nitroglycerine patch has been related to NO formation during degradation of organic nitrates.

There is a significant increase in postoperative analgesia when neostigmine is added to intrathecal bupivacaine in patients undergoing total abdominal hysterectomy. A combination of 5 mg/day transdermal nitroglycerine patch and intrathecal low dose neostigmine (5 mcg) resulted in an average of 10 hours of postoperative analgesia after total abdominal hysterectomy during bupivacaine spinal block, compared to 3.5 hours in the control group. Also the use of intrathecal neostigmine and transdermal nitroglycerine delays the first requirement of rescue analgesia by 6.5 hours. Transdermal nitroglycerine has been shown to increase the postoperative analgesia of intrathecal opioids[44].

## 6. Conclusions

Recent developments in our understanding of incisional pain have highlighted the complexity of perioperative pain and the need for optimal management not only to provide rapid recovery but also to prevent long-term consequences.

More than 100 NSAIDs are marketed or at an advance stage of development worldwide. There is no a single compound with proven efficacy better than other in the treatment of postoperative pain. The search for more efficacious and better-tolerated compounds is still being persued.

Principles of safe IV treatment:

- Acetaminophen or pure NSAIDs alone
- Acetaminophen + NSAIDs
- Weak opioid + acetaminophen or
- Weak opioid + NSAIDs

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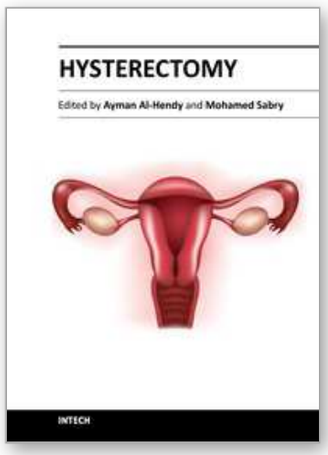


**Hysterectomy**

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This book is intended for the general and family practitioners, as well as for gynecologists, specialists in gynecological surgery, general surgeons, urologists and all other surgical specialists that perform procedures in or around the female pelvis, in addition to intensives and all other specialities and health care professionals who care for women before, during or after hysterectomy. The aim of this book is to review the recent achievements of the research community regarding the field of gynecologic surgery and hysterectomy as well as highlight future directions and where this field is heading. While no single volume can adequately cover the diversity of issues and facets in relation to such a common and important procedure such as hysterectomy, this book will attempt to address the pivotal topics especially in regards to safety, risk management as well as pre- and post-operative care.



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