



Managing Perioperative Analgesia in the Hyperalgesic Patient.

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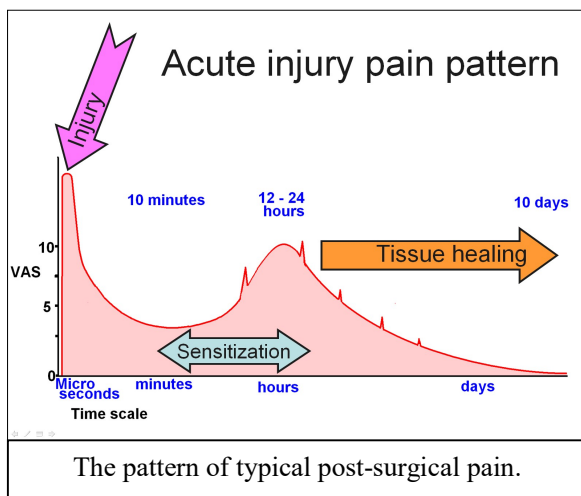
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Contents;

1. Introduction.
2. The purpose of pain in nature.
 - A. Natural analgesia.
 - B. Pain in nature, and its purpose
3. Pain physiology.
4. Hyperalgesia syndrome.
5. Pharmacology of pain, and treating hyperalgesia.
6. Spinal NMDA receptors.
7. Treating and preventing perioperative hyperalgesia.
8. A strategy how to manage perioperative hyperalgesia.
9. Illustrative cases.
10. Summary.

1. INTRODUCTION

Pain is a complication of surgery. Pain is unpleasant. For humane reasons it is always necessary to treat pain. Lack of pain treatment can induce complications affecting patient surgical outcome. For surgery, where pain is the part of the indication to operate, pain outcomes are even more critical. This applies in particular to orthopedic surgery, like arthroplasties. Severe preoperative pain *before* knee arthroplasty is the prime predictor of



chronic postoperative pain and development of complex regional pain syndromes at 6 months after surgery³.

Prevention of suffering is the primary outcome of treating pain. Preventing the physiological consequences and complications resulting from pain are the secondary outcomes. Absence of a secondary benefit is no reason not to treat pain. With analgesia improved surgical outcomes, if occurring, are bonus events.

Post-operative pain differs from cancer pain, and chronic pain. Post-operative pain is typically from fresh tissue damage and the pain

resolves rapidly as tissues heal. Pain is excruciating during surgery. After surgery pain diminishes in a fluctuating pattern to terminate with tissue healing. Only anesthesia can provide full analgesia during surgery.

Post surgical pain typically follows a pattern of;

- Diminishing briefly after tissue injury for a period of many minutes following the fresh tissue incisions. The injured cells released *primary algogenic substances dissipate*. This first phase may be concluded by the time the patient regains consciousness.
- Initial pain-worsening occurs over about the first 12 to 24 hours after surgery, as peripheral and central pain *sensitization* develops.
- Beyond the first 12 to 24 hours pain steadily resolves over days and weeks as *healing*

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occurs.

- Pain may persist beyond standard tissue healing time. That is regarded as **Chronic pain**. Some patients are predisposed to that phenomenon, and many risk factors for developing chronic pain are identifiable. The Perioperative analgesia plan can greatly influence this.
- Hyperalgesia may also exaggerate post-surgical pain and make it untreatable in the conscious patient.

Pain therapy has to be periodically down-graded in step wise fashion to adapt to the rapidly diminishing post-surgical pain over the early days. The major forms of analgesia are (1) local anesthetics, (2) sedative analgesics and (3) non-sedative analgesics. Sedative analgesics, typically opiates, have small therapeutic windows with high incidences of side effects such as pruritus, respiratory depression and nausea. Marijuana is a sedative with some analgesia too. Non-sedating analgesics are very safe but limited by lack of potency. Their potency ranges between 30% and 50% of that of opiates. Non-sedating analgesics are however additive to other forms of analgesia with no addition of side effects and are central to multimodal analgesia plans. The perioperative analgesia plan must also be flexible and included supplementary analgesia on an as-needed basis. As needed supplementary analgesia may be administered at the discretion of the nurse, or in the patients own control.

There must be a STEPDOWN ANALGESIA TRANSITION between three periods. The first step down is the transition from anesthesia to awake. A patient should recover from the end of regional or general anesthesia into established analgesia. The second transition is from opiate-based analgesia to opiate-free analgesia. When the second transition occurs, the patient can be discharged usually. Only very limited oral opiates should be sent home with the patient.

Some patients develop chronic pain syndromes after surgery. Predictive factors identify patients most likely to experience severe post-surgical pain and develop late chronic pain syndromes. Martinez showed patients with strong objective evidence of hyperalgesia before arthroplasty consumed more morphine after surgery than patients with less evidence of hyperalgesia pre-operative¹. He also saw bad movement-induced pain preoperatively correlated with increased morphine and higher pain score after arthroplasty. Patients with severe post-surgical pain are also more likely to develop chronic pain.

Kehlet summarized the factors predictive of patient developing a chronic pain syndrome after surgery². Preoperative factors for abnormal and chronic post-operative pain were (i) pain present for more than one month, (ii) Psychological “vulnerability”, (iii) preceding neurotoxic chemotherapy, (iv) intense immediate post surgical pain, and (v) operative nerve injury.

Preoperative depression, anxiety also predict from chronic pain and complex regional pain syndromes after arthroplasty, although this is not predictive after all types of surgery^{3,2}. Kehlet emphasized it was more the patient demonstrating poor ability to cope with challenges who was at risk for developing chronic pain.

The PREVENTION OF CHRONIC PAIN SYNDROMES AND HYPERALGESIA AFTER SURGERY needs a comprehensive, scientific and effective analgesia plan at the time of surgery³. The term “preventative analgesia” was promoted by Kissin and Reuben³. Preventive analgesia’s goal is to prevent peripheral and central pain sensitization. Kehlet in 1993 promoted analgesia that had many drugs each working at a different point in the pain signal transmission path and processing chain, and he called this multimodal analgesia⁴.

Classic pharmacology research is unimodal or single drug focused, and multimodal pain therapy regimens are harder to study and are under-researched.

Finally integrating the vast amount of complex basic science information on receptor systems and pain physiology into a comprehensible unifying pain mechanism theory and finally translating that into effective, rational, and practical clinical pain treatment practice in the perioperative period is very challenging.

A British Journal of Anesthesia editorial of February 2010 commenting on an opiate induced hyperalgesia study was unable to recommend a therapy plan and it could only speculate, express hope in future drugs, and say clinical research is now needed.

It is hoped this lecture will be practical.



Reference⁵.

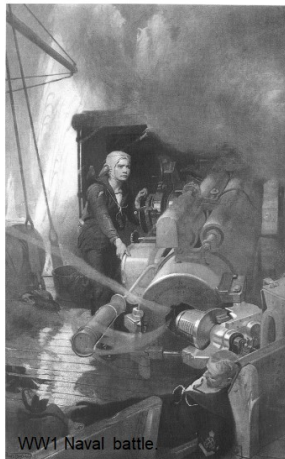
2. THE PURPOSE OF PAIN.

A. NATURAL ACUTE ANALGESIA

(Patrick Wall – *Pain the science of suffering*. Weidenfield and Nicolson publishers.) (Donald Price - *Psychological mechanism of pain and analgesia*. IASP press)

In nature there are only limited advantages to having acute analgesia. There is however much more natural advantage to experiencing pain from injury. Pain terminates in the longer term due to tissue healing. Natural acute analgesia is seen in two circumstances.

Natural analgesia requires two things to happen to be take effect. The first is distraction from the injury, and second transformation of the anticipated sensation from an unacceptable one to a more acceptable one in the subject's mind. Only humans can perform this "transformation". Superimposed hyperadrenalism multiplies the effect.



Pain can be totally inhibited by the body for modest periods.

- Some people feel little pain despite astoundingly severe acute injuries.



During World War 1 this 18-year-old sailor stood at his post and performed his task bravely, and as if unaware he had received shrapnel wounds that proved fatal ultimately. He was awarded a posthumous Victoria Cross for valor. His intense focus on his critical tasks and the extreme distraction by the noise of battle and roar of cannons strongly inhibited his experience of pain. Many soldiers in the heat of battle feel very little of their wounds

It was well described in the American civil war and in more recent wars how a soldier in the chaos of battle if totally focused upon executing a task, and having to concentrate hard to ignore surrounding auditory and visual sensory inputs, could experience total absence of the sensation of brutal injuries of limb amputation magnitude. This is part of the *fight-or-flight* reaction. Extreme focus, or extreme distraction from the injury, by attempting escaping or fighting under life threatening circumstances of hyperadrenalism can be associated with total analgesia. This is total distraction from the injury.

The second circumstance where natural analgesia may be observed is using hypnotic analgesia. This requires three steps to be taken by the subject about to experience pain. A second person may augment those steps by repeatedly reminding the subject of the steps. This is hypnosis. Step one is to consciously decide to

accept the noxious event, e.g. an injection. The second step is to repeatedly think of the impending noxious intervention as a *tolerable* sensation, e.g. as a "mosquito bite that burns" rather than "a sharp needle stab that pricks." This is *transformation of the anticipated sensation*. Thirdly the subject must dissociate from the procedure by imagining they are at another location that is appealing, e.g. being on the beach at sunset. We call this method *dissociation from location*. These techniques if used as a part of daily anesthesiology practice when inserting needles into conscious patients are very dramatic in their efficacy



It will be noted that all of these analgesia steps require consciousness and active participation of the subject.

An uncooperative reluctant fearful subject will not experience natural analgesia and pain will be maximal.

B. PAIN IN NATURE AND ITS PURPOSE.

There are many more physiological mechanisms devoted to amplifying pain intensity and extending the duration of the pain signals beyond the initial injury, than physiological mechanisms devoted to diminishing the pain. It is only after escaping the physical threat in nature, that pain should appear and serve its purpose.

Pain serves the following purposes;

(1) it immobilizes the animal for healing to occur, (ii) it induces learning to avoid similar physical injuries or threats in the future, and (iii) it grades the pain in proportion to the injury magnitude to induce the appropriate size response.

It will be seen that many natural mechanisms involving neurotransmitters and neural tract activity, that are initially analgesic in their role if remaining active swiftly convert to the opposite effect and become anti-analgesic. The analgesic mechanism thus becomes an algescic mechanism.

This is a common pattern in pain physiology

It is this natural phenomenon of sustaining and amplifying pain signals which when exaggerated that causes hyperalgesia.



Does pain serve any purpose in nature?

Run away!

INSTANT PAIN alerts that there is a problem.



Rest!

SUSTAINED PAIN encourages resting and licking = facilitate healing.



Promote healing!



PAIN SUFFERING alters behavior;

- Remember pain.
- Learn pain avoidance behaviors.

The instant pain from an acute injury serves many purposes. It alerts the animal to escape the source of injury. The subsequent sustained inflammation mediated pain encourages healing actions via resting and licking. Finally, there is learning involved for future injury avoidance. Learning is mediated by substance-P.

3. PAIN PHYSIOLOGY IN DETAIL

Tissue damage releases the primary algogenic substances (hydrogen ions, potassium and bradykinin) which trigger pain signals in nociceptors at nerve endings. That is pain signal TRANSDUCTION. That peripheral signal gets AMPLIFIED by sensitizing substances

such as prostaglandins, and leukotrienes in the damaged tissue.

That is PERIPHERAL

SENSITIZATION and the pain increases. Peripheral Sensitization

starts a few hours after first injury with mast cells in the injury area

manufacturing prostaglandins.

Inflammatory cells migrate from the circulation into the injured tissue

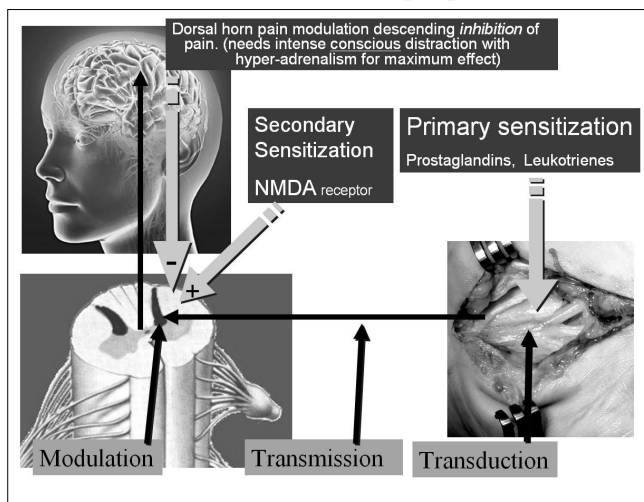
under influence of substance-P a few hours later and manufacture

leukotrienes. Leukotrienes further

increases peripheral sensitization.

General inflammation is

initiated and mediated by





substance-P released from injured nerve endings. Substance-P causes vasodilation and vascular endothelial cell separation which facilitates leukocytes escaping from capillaries. Substance-P's release can be inhibited by μ -opioid receptor stimulation on the preterminal nerve ending. Although systemic morphine does not affect wound inflammation, wound injection with morphine in high concentration to block substance-P causes very significant reduction in inflammation but very poor wound healing as well.

Post-surgical pain peaks at around 12 to 24 hours after surgery due to peripheral and central sensitization where after pain steadily resolves parallel to the healing process.

The peripheral pain signals travels via peripheral nerves to spinal cord where the signal's further transmission is either inhibited or enhanced. This is pain signal TRANSMISSION. The pain consciously experienced depends on the balance of facilitory or inhibitory influences at the spinal cord level. Inhibitory mechanisms are mediated via descending neural signals and stimulatory mechanisms are largely mediated by spinal cord cell functional changes (neuro-plasticity). See the Natural analgesia paragraph.

Sustained pain signal input at spinal cord level leads to CENTRAL SENSITIZATION where the pain experienced increases. Secondary neurons with NMDA receptors are strongly involved with central sensitization. GABA receptors are also involved but to lesser to a lesser degree. Substance-P at spinal level is also involved in pain signal amplification and it has special roles in the (i) *grading* of pain, (ii) *pain avoidance* learning behavior, and (iii) a mediating the psycho-emotional experience of *suffering*.

PATHOLOGICAL PAIN results when these pain processes are (i) unusually exaggerated or (ii) unusually persistent. Pathological pain includes phenomena of (1) allodynia (pain from tactile stimuli), (2) hyperalgesia (exaggerated pain for the stimulus), and (3) spontaneous pain (pain without an initiating peripheral stimulus).

Available perioperative pain therapy can be directed at many points in the physiological chain of pain signaling. A few examples are;

1. Block *transduction* of pain (no clinically approved drug presently).
2. Block *peripheral sensitization* (NSAIDS, opioids) (Lipoxygenase inhibitors?)
3. Block *peripheral transmission* (Local anesthetic nerve blocks).
4. Block *spinal sensitization* (gabapentin, pre-gabalin, COX3 inhibitors, NSAIDS).
5. *Reverse spinal sensitization* (ketamine, Magnesium)
5. *Block spinal substance-P* (initial opioid effect)
6. Block *brain pain perception* (opioid's main effect).

** The Underlined drugs above are the drugs of most proven and of most obvious benefit.

A few of these substances have dual and opposing effects on pain relief. For example, opiates simultaneously induce opioid tolerance that increase the dose of opiates need and extends the duration of severe pain needing opioid analgesia, and induce hyperalgesia that extend beyond healing resulting in chronic pain syndromes and delayed recovery. Opiates provide profound analgesia initially, but are best used as briefly as necessary due to their side effects and hyperalgesia effects associated with chronic pain syndromes.

4. HYPERALGESIA SYNDROME

This term is a clinical concept sometime used. It generally means a patient does not obtain pain relief from a standard dose of morphine.

Hyperalgesia syndrome overlaps with the entities of (i) chronic opioid induced tolerance, (ii) acute opioid induced tolerance, (iii) opioid induced hyperalgesia, (iv) Complex Regional Pain Syndromes {CPRS}, and (v) spontaneous pain, and (vi) paradoxical pain.

Allodynia which is pain induced by light touch to the skin, or deep tissue allodynia is commonly present or has been previously present. Paradoxical pain is pain that worsen after administration of opiates^{6,7,8,9}. Opiates can also cause muscle spasms associated with pain particularly in high doses⁹.



5. PHARMACOLOGY OF PAIN AND DRUGS CAUSING HYPERALGESIA

SECTION OUTLINE

1. Opiates and pain
2. Opiate induced hyperalgesia and opiate tolerance
3. Nicotine induced hyperalgesia
4. Marijuana and other drug induced hyperalgesia
5. Volatile anesthetic induced acute hyperalgesia

1. OPIATES AND PAIN

Opiates have been the mainstay of therapy for severe pain for over a hundred years. Despite their many side effects opiates have been the best analgesia options for severe pain for a long time. Opiates side effects include constipation, pruritis, nausea, sedation, respiratory depression, addiction tolerance and induction of tolerance and hyperalgesia.

Intermittent intramuscular bolus opiate administration has the problem that the patient fluctuates between too much and too little drug. Patient Control Analgesia (PCA) provides a better titration between peaks and troughs and most patients choose to tolerate slight pain in preference to inducing side effects specifically of nausea and sedation. The problems of opiate addiction, tolerance and hyperalgesia do not occur in typical post surgical patients because of how fast healing occurs with natural reduction in pain.

Long term opiates when used, are additionally associated with increased dose needs up to 10-fold over two years, and in many patients with (i) failure to relieve pain, (ii) addiction, (iii) abuse, (iv) hyperalgesia, and (v) extreme side effects. The hyperalgesia induced by opiates can become exaggerated upon opiate withdrawal. There is concept called “paradoxical pain” which refers to pain induced by opioids. It refers to the dualist nature of opioids that have an antinociceptive effect parallel to the nociceptive effect¹⁰.

INTRATHECAL (AND EPIDURAL) OPIATES AND HYPERALGESIA.

Spinal morphine and other opiates have been shown to acutely induce hyperalgesia¹¹. Clinically opiate induced acute hyperalgesia has not been readily recognized but experimentally it is can be clearly shown. The clinical patient will simply be seen as an undifferentiated “pain problem” not responding to standard doses of opiate.

A single dose of spinal morphine experimentally induces (i) immediate analgesia lasting 3 to 5 hours followed by (ii) a late onset (after 5 hours) hyperalgesia lasting 1 to 2 days. Ketamine given simultaneously did not alter the early morphine associated analgesia by nearly eliminated the late onset hyperalgesia¹².

2. OPIATE INDUCED HYPERALGESIA AND OPIATE TOLERANCE^{13, 14, 15, 16, 17}

Opioid tolerance is the reduction in their analgesic effect of opioids induced by ongoing opioid administration. Tolerance with long term opiate therapy is well known, but Acute Opiate Tolerance (AOT) is a more recently recognized phenomenon. Opioid Induced Hyperalgesia (OIH) is increased sensitivity to pain for given stimulus or a lowered threshold to pain for small stimulus⁷⁷. In animal research they can be clearly differentiated and have different mechanisms. In a patient after surgery the two appear similar in that a patient does not achieve pain relief from a morphine dose expected to produce pain relief. The development of



allodynia (skin sensitivity manifesting with pain to light touch) differentiates and diagnoses hyperalgesia. Absence of allodynia does not exclude hyperalgesia as a diagnosis as *deep tissue hyperalgesia* can also exist but deep tissue hyperalgesia is hard to recognize clinically. Clinically it is not critical to differentiate between OIH and AOT, as the problem looks the same and current available treatment options are similar¹⁸.

The phenomena of AOT and OIH develop fast and are observable in laboratory animals within 15 minutes, and even after a single dose of morphine¹⁹. The mechanisms for Acute OIH exist at peripheral, spinal and supraspinal levels. *Chronic* morphine increases the cytokine tissue responses to surgery, but acute morphine administered at the time of incision does not²⁰. This is a *peripheral mechanism* for increasing peripheral signaling of pain.

Non-opioid analgesia for chronic pain does not modulate long term pain (cause hyperalgesia), only opioids do²¹.

Remifentanyl induced acute opioid tolerance is consistently demonstrated in animal research. The NMDA receptor effects of Remifentanyl at clinical doses is seen as soon as after 36 minutes infusion and persist for the remifentanyl washout time and beyond that²². Remifentanyl in humans has been clearly associated with 30% increases in post surgical 24 morphine requirements after scoliosis surgery, and 50% morphine increased usage after colorectal surgery^{23, 24}. Remifentanyl induced opioid tolerance is however not shown after all human studies (e.g. surgery under two hours duration) possibly due to the same studies selecting surgery of insufficiently large size or insufficiently long duration.

Although greatest interest has been in remifentanyl induced acute opioid tolerance and opioid induced hyperalgesia, the same effects have been shown after use of anesthetic fentanyl and even morphine in the longer-term remifentanyl.

The two phenomena of opioid induced acute opioid tolerance and opioid induced hyperalgesia share a spinal cord dorsal horn NMDA receptor mechanism.

The mechanisms of how opiates induce opiate tolerance and hyperalgesia involves interactions with inflammatory cells within the nervous system²⁵. Opiates up regulate micro-glial cells and macrophages. Those cells are involved in inflammation. Inflammation is normal process that is part of defense against infection and in healing of injured tissues. The immune system and the central nervous system have extensive bidirectional influences on each other. Neuropathic pain results from damage and degeneration of the central nervous system that can result from an inflammatory injury. Neuropathic pain depends on activation of Schwann cells, microglial cells, and astrocytes.

3. NICOTINE INDUCED HYPERALGESIA

Chronic pain studies have shown that smokers have more events of pain in a life time than non-smokers. Chronic pain studies have also shown heavy smokers have more severe grades of pain than non-smokers.

It has been shown that Nicotine activates brain NMDA receptors associated with dopaminergic "satisfaction centers". Animal research clearly shows nicotine induces hyperalgesia via spinal cord NMDA receptor upregulating.

Human clinical studies using nicotine therapy perioperative have had variable results on pain. Some methodological questionable trial suggested nicotine therapy improved analgesia while one well performed trial showed no analgesia from nicotine therapy. Nicotine therapy has been studied as a means to block volatile induced hyperalgesia as nicotine receptor mechanisms are suspected there. Mostly nicotine therapy has been disappointing as an analgesic.

The practical summary here is that nicotine therapy has no role in perioperative analgesia. However, patients who are severe heavy nicotine addicts can be identified as likely hyperalgesia patients before surgery who will experience unusual severe pain after surgery. As the final mechanism of nicotine



hyperalgesia involves the NMDA receptor upgrading, NMDA receptor antagonists (magnesium, ketamine) will be beneficial analgesia supplements.

4. MARIJUANA AND OTHER DRUG INDUCED HYPERALGESIA

With the recent development of synthetic cannabinoids and also a cannabinoid receptor blockers it has become possible to study the effects of marijuana on pain in a blinded and scientific fashion. It is clear that marijuana only has a very mild analgesic effect in a very small dose range. Exceeding that dose range results in high incidences of side effects and psychotic reactions, and enhanced pain.

Regular marijuana causes hyperalgesia.

The prime animal laboratory researcher demonstrating this is Zeilhofer publishing in Science magazine. There are also publications in anesthesiology magazine, (Wallace 2007, Kraft 2008, Holdkraft 2006).

The dominant “benefit” marijuana users with pain get is the satisfaction of the pleasure centers in the brain, but pain in fact worsens. The patients do get feeling of relief from the pain suffering and strong feeling of not caring about the pain during the intoxication period with the marijuana. It has also been said that morphine similarly does not eliminate pain but does strongly makes the subject not care about the pain. A patient presenting for surgery with history of marijuana use can be expected to experience more than usual pain after surgery. Similarly, hyperalgesia has been observed in **heroin** and **cocaine** users.

Withdrawal from **alcohol**, especially after chronic use is associated with hyperalgesia^{26, 27, 28}. Even withdrawal of single dose of alcohol without even prior chronic use induces a period of hyperalgesia. Alcohol withdrawal hyperalgesia appears during a period of alcohol abstinence, but there is also hyperalgesia present during alcohol intoxication in subjects who are exposed to sustained regular alcohol consumption, such as alcoholics²⁹.

5. VOLATILE ANESTHETIC INDUCED ACUTE HYPERALGESIA

Research shows volatile anesthetics can cause acute hyperalgesia. It has been observed since 1960 that patients can manifest exaggerated pain in the immediate post volatile anesthetic period³⁰. Particularly isoflurane has been studied in this regard, but all volatiles are suspected of causing the problem. Isoflurane exhibits analgesia in high (anesthetic) concentrations (0.4 MAC upwards), but has anti-analgesic effects in low concentrations (0.1 to 0.2 MAC) as would be experienced during recovery from anesthesia^{31, 32}.

The mechanism seems to be that at low concentration volatiles (0.1 MAC) inhibit spinal nicotinic receptors, which in turn diminishes nor-adrenaline release, with subsequent loss of nor-adrenaline mediated analgesia^{33, 34, 32}. Nicotine mechanism are associated with pain, and smokers are more likely to experience pain in life generally than non-smokers, and heavy smokers experience more severe pain than average smokers^{35, 36}. Nicotine nasal sprays therapy before and after surgery with have had variable results on postoperative pain, but nicotine patches significantly reduced early pain scores on non-smokers after surgery, but 24-hour morphine consumption remained unchanged^{37, 38}. Evidence suggests that volatile induced acute hyperalgesia only manifest it self in more painful surgeries especially if associated with pain prior to surgery, and also that the hyperalgesic effect is only observed in the first hour but not in the remainder of the day. The variable nicotine results in different trials may be due to the different surgery types studied and the different periods studied.

Propofol does not inhibit nicotinic receptors nor cause anesthetic induced hyperalgesia³⁹. One trial has shown a significant trend to patients experiencing less post-surgical pain in propofol anesthetized patients than in volatile anaesthetized patients⁴⁰.

Some chronic pain patients despite total peripheral nerve blockade after surgery, can have *spontaneous pain* for an hour or more after anesthesia. See case 3



earlier. Spinal cord neuron spontaneous signaling of pain may be worsened by (i) prior sleep disturbances, (ii) prior morphine administration, and (iii) spinal Nitric Oxide reduction. Spontaneous pain induced by morphine is reduced by the administration of substance-P^{41, 42, 43}. Spinal cord dorsal horn cells associated with spontaneous pain have redistributed membrane bound sodium channels, ectopic cell activity and nerve terminals that have grown extra terminal sprouts to reach neurons not normally reached⁴⁴. Spontaneous pain seems to be part of continuum of neuropathic disorders called "*hypersensitivity pain disorder*" which in turn is overlaps with other chronic pain groups⁴⁵. It would be no surprise that overlapping mechanisms for these pain conditions exist and that anesthesia may at time inhibit or dis-inhibit the manifestation of any of them.

It is probable that volatile anesthetics inhibit nicotine receptors which upon withdrawal of the volatile anesthetic have rebound nicotine receptor overactivity causing the brief period of hyperalgesia associated with volatile anesthetic withdrawal.

SUMMARY:

Volatile (anesthetic) Induced Hyperalgesia (VIH) is an entity suspected to exist since 1960 and recently proven to exist. The hyperalgesic effect is only of about an hour's duration. It has little clinical relevance in the average patient but may be additive with preexisting chronic pain syndromes and opioid induced hyperalgesia. In patients whose post-surgical pain control is predicted to be challenging it seems rational to avoid a volatile anesthetic, and use other special analgesia drugs such as ketamine with a propofol technique.

6. THE SPINAL N.M.D.A. RECEPTOR

This receptor has a central role in much of this lecture. It is a widely found calcium channel receptor with complex control. It is mainly the dorsal horn spinal NMDA receptors that are of interest in peri-operative pain. Once activated it allows inflow of Cations, in particular large amounts of sodium and small amounts of calcium, and outflow of potassium. The calcium inflow is a major factor in regulating synaptic plasticity involved in *learning* and *memory*. This would include pain avoidance behavior and memory of pain. The NMDA receptor is a very unusual receptor being gated by both ligands and voltage.

The ligands are glutamate mainly but also aspartate. Glycine mainly but also serine are co-agonists that facilitate the widening of receptor opening stimulated by glutamate. In order to open under glutamate stimulation, the cell membrane also needs to be *simultaneously depolarized*. Magnesium ions occlude the ion channel from the outside and their physiology influences NMDA receptor function. It is thought that this unusual requirement that the NMDA receptor be simultaneously depolarized and activated by a ligand for opening to occur is the underlying mechanism upon which learning is based. This is called coincidence detection. NMDA activation requires BOTH pre and post-synaptic cells to be activated in order to be activated itself.

NMDA antagonists have hallucinatory effects, analgesic effects, anesthetic effects and brain damaging effects. Antagonists include are ethanol, ketamine, tramadol, and N₂O. Others are dextromethorphan, memantine, methadone, phencyclidine and dextropropofol. The NMDA receptor effectively converts electrical signal into a biochemical signal to modify cell behavior (synaptic-plasticity), under appropriate circumstances. This plasticity allows a typical synaptic activity of milliseconds to have consequences lasting much longer periods in time (minutes, hours, days, months). Ketamine is non-competitive



NMDA receptor antagonist that has NMDA receptor effects (anti-hyperalgesia effects) far longer lasting than ketamine's anesthesia and anti-nociceptive (analgesia) effects at other receptors where it has competitive receptor effects. Substance-P at spinal level facilitates grading of pain, learning of pain avoidance behavior and the experience of suffering. Dr. Alan Basbaum has in presentation demonstrated how substance-P deficient mice when administered pain stimuli, jump moderately when a standardized pain is delivered, repeatedly meander into the danger zone to feel pain in their cages and keep on normal eating and breeding activities. Mice with normal substance-P demonstrate the serial pain stimuli by jumping very higher and higher over time. They learn to avoid the "danger" side of their cage where pain stimuli are delivered, and if prevented from pain avoidance the demonstrate stress and suffering by ceasing breeding and eating behaviors. Substance-P has an interplay with NMDA receptors. Spinal Neurons of the dorsal horn (lamina I) that express NMDA receptors also share expression of Substance-P receptors⁴⁶. NMDA receptor activation facilitates Substance-P (S-P) release^{47, 48}. Substance-P increases primary afferent c-fibre activity

NMDA receptors at spinal level are found with nicotine receptors on the same nor-adrenergic neurons. NMDA receptors and Nicotine receptors influence each other's activation consequences. It seems preceding depolarization of adjacent neuron membrane by Nicotinic receptor activation (with sodium inflows) facilitates NMDA receptor activation⁴⁹. Nicotine administration has also been associated with NMDA receptor up-regulation and this NMDA receptor change is associated with Nicotine addiction via brain reward system stimulation⁵⁰. NMDA receptor blockade diminishes nicotine receptor up-regulation and reduces nicotine addiction in tobacco smoke exposure^{51, 52, 53}. Nicotine's addictive affects based on nicotine induced dopamine release is diminished by NMDA antagonism⁵⁴.

7. TREATING AND PREVENTING ACUTE PERIOPERATIVE HYPERALGESIA

This is summary of strategies that have been investigated, some with success and some without success.

1. **Pre-anesthetic morphine.** In scoliosis surgery performed under propofol and remifentanyl infusion, prior doses of morphine did **not** alter the 24-hour morphine needs after surgery. That is prior morphine did not prevent remifentanyl induced hyperalgesia⁵⁵. Pre-anesthetic morphine is not recommended treatment to prevent acute OIH from remifentanyl.
2. **Magnesium.** Magnesium has effects on the NMDA receptors that in nearly all studies reduces pain, improves neuropathic pain, prevents OIH, and reduces opioid consumption after surgery for 24 hours. Magnesium acts as a NMDA receptor antagonist. This has been very uniformly shown to reduce pain and morphine requirements after cardiac surgery, thoracic surgery, major abdominal surgery, laparoscopic cholecystectomy, and orthopedic surgery except in trial after caesarean section^{56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66}. Perioperative Magnesium therapy did not however reduce pain beyond the days in hospital and has no long-term effect. In some studies magnesium was administered as a single bolus of 40 to 50 mg/kg and in some studies a post operative infusion was used too. Magnesium deficient individuals are however very prone to chronic pain syndromes⁶⁷. Magnesium suppresses neuropathic pains^{68, 69, 70}. In practice perioperative analgesia magnesium should be avoided together with ketamine as anecdote suggests excess synergism for sedation. Consider small dose



magnesium therapy for documented magnesium deficiency, e.g. 2 g dose administered once over 60 minutes. Magnesium although somewhat successful is of much shorter in benefit than ketamine which binds the NMDA receptor irreversibly and achieves over 24 hours of benefit.

3. **Ketamine** has clearly been shown to dramatically prevent opioid induced hyperalgesia in laboratory research⁷¹. The doses that have these effects are *much lower* than what were its previous “analgesia doses”⁷². Ketamine as a spinal cord NMDA receptor antagonist has been shown in small dose (0.15 mg/kg plus 2 microgram/kg/min infusion) to significantly **reduced** post-operative opioid needs^{73, 76, 60, 62}. In volunteer studies where there are limitations on usable pain stimuli ketamine has been shown to have useful additive analgesia effect, a respiratory stimulating effect opposing opioid induced respiratory depression, but to not prevent remifentanyl induced hyperalgesia with all pain stimuli types⁷⁴. In an animal bone fracture model designed to replicate orthopedic patient’s ketamine had similar effects against opioid induced hyperalgesia⁷⁵. Ketamine in low doses (0.5 mg/kg) is highly recommended.
4. **Lornoxicam** (a NSAID). Benefit (reduced morphine needs) has been shown but no direct effect was proposed, and this possibly simply is part of the benefits of multimodal analgesia⁷⁶. Not recommended.
5. **Pre-surgical naloxone**. In rat research administering naloxone for day before a surgical cut and stopping it prior to surgery resulted in less pain than in untreated animals⁷⁷. This has not been tried in humans and could only be done if they were pain free before surgery anyway. Not recommended.
6. **Alpha-2 agonists (clonidine)**. These drugs are relatively well researched but have been limited in winning wide popularity because of their analgesia doses are limited by hypotensive effects, sedative effects, and short durations of benefits. Their results in peripheral nerve blocks is very variable in research results, except with Bier blocks. Alpha-2 receptors have been shown in the substantia gelatinosa of the spinal cord and their activation inhibits NMDA receptors⁷⁸. This implies alpha-2 agonist drugs could clinically diminish opioid induced hyperalgesia and acute opioid tolerance. The analgesia effects of alpha2-agonists are well known, but whether they are additive or synergistic with acute opioid administration analgesia effects is less clear. Alpha2-agonists however don’t seem to have any effects on peripheral pain sensitization^{79, 80}. Alpha2-agonists do however have opposite cortical effects in morphine tolerate rats than in normal rats that could translate to enhanced central effect analgesia with addition of clonidine in opioid tolerance⁸¹. Alpha-2 agonists do not cause hyperalgesia upon termination of treatment or infusion⁸². They are not recommended for perioperative analgesia.
7. **Gabapentin** administered preoperatively in a rat study showed it did not augment fentanyl analgesia but did in dose dependant fashion prevent fentanyl induced hyperalgesia⁸³. Their main effect is to inhibit release of nociceptive neurotransmitters like glutamate centrally. Consider using this in cases of anticipated severe post-operative hyperalgesia.
8. **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**. Some research has suggested NSAIDs may enhance development of opioid induced hyperalgesia, or have no anti-opiate induced-hyperalgesia effects^{84, 85, 86}. NSAIDs are however proven analgesics whose benefits may simply be *additive* analgesia at the time of administration. Also, NSAIDs have a proven morphine sparing effective of 30 to 50%. A NSAID –opiate *synergistic* effect would likely result if they had had a beneficial effect on AOT and OIH. It is suggested NSAIDs have a greater spinal benefit than a peripheral benefit. Regardless NSAIDs are recommended as part of a multimodal analgesia plan when treating all grades of pain. Neuraxial administration is not recommended at this point. The longer half-life oral COX-2 inhibitors seem the ideal perioperative drug especially as they “preserve” platelet function and celecoxib has escaped incrimination of cardiac detrimental effects in short duration therapy (5 days). It is however prudent to still avoid it in patients



with multiple severe coronary artery disease risk factors. Use NDSAIDS for perioperative analgesia when ever no contraindication exists.

9. **Topical wound opioids.** Opioids inhibit release of substance-P from nerve endings into the injured tissues. This diminishes vascularity, inflammatory cell infiltration and leukotriene release. This may be a minor part of systemic opioid analgesia benefit via reducing peripheral sensitization. Direct topical application of morphine however results in excess loss of inflammation with resultant poor wound healing and persistence of inflamed hypertrophic collagen poor scar⁸⁷. This modality of therapy is not recommended.
11. **Nerves blocks** are highly recommended. They are well shown to reduce long term pain and prevent phantom limb pain etcetera.

8. A STRATEGY HOW TO MANAGE PATIENTS WITH PERI-OPERATIVE HYPERALGESIA

It is very hard to treat hyperalgesia after surgery. The patient at risk for perioperative hyperalgesia is best identified *before* surgery for giving preventive therapies. The syndrome is very easily prevented.

Identify risk patient for severe post-surgical pain;

- Large mutilating operations
- Acute severe injury
- Indication for surgery is pain (e.g. for an arthroplasty)
- Abnormal psychological profile (poor coping mechanisms, depression, agitation)
- Chronic oral opioids usage
- Previous symptoms of hyperalgesia or allodynia.
- Remifentanyl anesthetic
- Volatile anesthetic
- Heavy smoking habit.
- Prior use if of marijuana, cocaine or heroin.

The patient with most risk factors will have the most severe pain after surgery.

Pre-anesthetic management of a patient predicted to have severe pain after surgery.

Place nerve blocks before surgery. Use pain modifying non-sedating analgesic premedication, such as Non-Steroidal anti-inflammatory drugs, and Gabapentin (600 to 900 mg oral) with premedication.

Intra-anesthetic management of a patient predicted to have severe pain after surgery.

In the high-risk patient consider using Propofol total intravenous anesthesia and avoid intra-operative short acting opioids completely. Administer ketamine at start of the anesthetic in a dose of 0.5 mg/kg and repeated once after an hour or two for longer surgeries. Give IV anti inflammatory drugs if not already given. Use morphine in doses of about 0.05 to 0.1 mg/kg lean body mass given between 30 and 45 minutes from end of surgery. As much morphine may used after awakening, as is needed.

Post-anesthetic management of a patient predicted to have severe pain after surgery.



Use a continuous regional anesthetic for analgesia. At this time use as much morphine as is required. Up to this time all therapies are aimed at avoiding opiates, but at this time opiates will be found to be effective and beneficial is used for a day or so. Transition from opiates to non-opiate analgesia as soon as it is achievable. Continue with multimodal analgesia using paracetamol, and non-steroidal anti-inflammatory drugs. Continue with GABAPENTIN in severe cases for 3 to 5 days. Use ketamine 0.5 mg/kg to rescue the patient still with severe pain.

Lastly consider any unusual pain is a sign of a surgical complications and reassesses the patient clinically fully. Pain is not a diagnosis, it is a symptom. Any observed unusual pain will rarely have an unexpected cause needing urgent reoperation.

9. ILLUSTRATIVE CASES

Case 1. A man of 57 has a 3rd time repeat knee arthroplasty. He was a heavy smoker with nicotine stained fingers, uses chronic oral opioids (hydrocodone), and had an agitated personality. He experienced marked pain on knee examination. He had at a time felt his clothing hurt the knee when it touched the skin (allodynia) and at times the knee felt burning deep inside without movement. He said pain after his previous surgery was terrible for long time. In addition, he had cardiomegaly, previous myocardial infarctions, and poor exercise tolerance,

He received a continuous femoral nerve block and a general anesthetic for the surgery, with remifentanyl infusion and desflurane anesthesia. He was administered 5 mg morphine before the end of surgery. Upon awakening he experienced severe pain and received additional morphine for a total of 20 mg. He still had severe pain and was vociferous and agitated. An additional obturator and sciatic nerve block are added. Skin testing with ice and muscle strength testing showed all nerve blocks were functional.

He then became restful and lay still with closed eyes but still stated his pain was 9/10 on a verbal rating score (VRS). He is discharged to the general ward where he continued to consume a lot of morphine over the next 48 hours and finally he was discharged on oral opioids.

Key points:

1. Some patients have *chronic pain preceding surgery* with potential for (i) hyperalgesia, (ii) complex regional pain syndromes, (iii) opioid tolerance, (iv) opioid induced hyperalgesia, and (v) opioid addiction.
2. There is an association between *severe nicotine addiction* and severe pain.
3. Remifentanyl and volatile anesthetics can cause *acute post anesthesia hyperalgesia*.
4. Remifentanyl is associated with *acute opioid tolerance*. The extreme form of hyperalgesia is associated with spontaneous pain signaled from spinal cord level nerves. Spontaneous pain can only be recognized when appropriate peripheral nerve blocks fail in the face of severe pain with evidence of prior allodynia.

This patient would have benefited from a different anesthetic and multimodal analgesia plan. The nerve blocks were appropriate

Case 2. A man of 42 years age had a tibial plateau fracture after slipping and falling on a frozen sidewalk. He has waited 3 days for surgery. He was on a PCA morphine IV infusion and had used a large amount of morphine. The night before surgery he was sleepy and complained a lot about his leg fracture pain. He was also experiencing spontaneous spasm of pain in the leg unrelated to movement or touching. The morning of surgery he was alert and very tender on the fracture leg. The foot demonstrated severe allodynia and even touching the skin on the toes lightly was sufficient to elicit loud vocal protestation. The surgeons



considered the possibility a compartment syndrome existed but the calf muscle was soft. He was not sleepy before the anesthetic.

A nerve block was prohibited by the surgeons due to concern for concealment of compartment syndrome. The problem was this patient (i) had opioid tolerance already, (ii) signs of hyperalgesia, and (iii) still had to undergo surgery. Uncontrollable post-surgical pain was expected. What analgesia plan could be made for this patient for after surgery?

He was given 600mg Gabapentin before surgery, general anesthesia was with propofol and N₂O. Volatile anesthetics and intra-operative opiates were totally avoided. Ketamine 0.5 mg per kg was given as well as ketorolac. Thirty minutes from the end of surgery 10 morphine was given. The patient awoke in comfort. He was able to smile within 10 minutes. This anesthetic and analgesia plan worked well.



Burns patients⁸⁸

These patients have exceptionally severe pain from the moment of primary injury. The pain is sustained due to multiplicity of hurtful interventions relating to skin grafting, wound cleaning with debridement, and dressing changes. Opiates are dominant and central in treating pain here. Measures however should still be taken to moderate opiate usage as much as possible. NSAIDs and acetaminophen have benefit even if only modest. Many of the interventions such as a dressing changes can be done with less than full anesthesia, but that still require dangerous amounts of sedatives and opiates requiring administration by dedicated trained personal. Ketamine is exceedingly useful for both its profound acute analgesia and its long-term anti-hyperalgesia effects. The hallucinations need prevention with benzodiazepines.

Regional anesthesia is limited in use due to the risk of catheter related infections. Topical regional anesthesia is limited due to the vast areas needing treatment and the then risk of local anesthetic toxicity. Patient self-administered 50% Nitrous Oxide (N₂O) (Entenox) is very effective during wound dressing changes. N₂O has NMDA blocking effects. All the centrally acting non-opiate analgesic agents have useful analgesia roles in burns patients too.

10. Summary

There is no reason to alter one's standard anesthesia care for regular patients undergoing common surgeries. Volatile induced hyperalgesia and opiate induced hyperalgesia are not common problems due to the swiftness and reliability with which tissues heal and terminate pain signaling.

However, for the patient with multiple pre-surgical risk factors for severe post-surgical pain and it may be worthwhile modifying the anesthesia plan as suggested above.

Avoidance of opiates intra-operatively for all patients helps make post-operative opiates more effective and at lower doses.



References and studies;

Study 1

Intra-operative Magnesium and pain after laparoscopic cholecystectomy.

Mentes. Acta Scan Anes 2008

- Historically patients with pain after laparoscopic Cholecystectomy
 - 41% have severe pain.
 - 13% still have severe pain on day 7.
 - Pain limits same day discharge from hospital
- Two groups were formed for this study, and they respectively recieved
 - (i) 50mg Mg / kg.
 - (ii) saline. (blinded control)
- The Anesthetic technique included;
 - Induction ; Propofol, fentanyl, cis-atracurium
 - Maintenance; alfentanil, sevoflurane, N2O
- Post operative analgesia was with PCA Tramadol: 20 mg bolus, 5 mg/h infusion
- **RESULTS:** The Magnesium group significantly
 - Had less pain,
 - Used less tramadol,
 - Than the control group who got saline in stead of magnesium

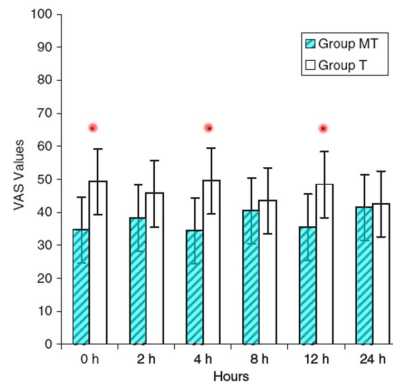


Fig. 2. Visual analogue scale (VAS) pain scores at rest. Values are mean \pm SD. (* $P < 0.05$ as compared between Group MT and Group T).

Study 2

Anesthesia matters: Patients anesthetized with Propofol have less post-operative pain than those anesthetized with Isoflurane.

Cheng. Anes. Anal. 2008.

- 80 woman undergoing uterine surgery were divided into 4 groups receiving combinations of nicotine or saline (placebo), and isoflurane or propofol maintenance (IN, IS, PN, PS).
- Anesthesia maintenance;
 - 2 groups with isoflurane maintenance, (I)
 - 2 groups with propofol maintenance, (P)
- Nasal spray at end of surgery.
 - 2 groups with 3mg nicotine (N).
 - 2 groups with saline (S).
- **RESULTS:** Propofol patients had significantly less pain and used less morphine in the first 2 hours after surgery.
- Nicotine spray had no influence on pain nor morphine use.
- **CONCLUSION:** This evidence supports the theory that volatile anesthetics induce hyperalgesia during the early post anesthetic period.

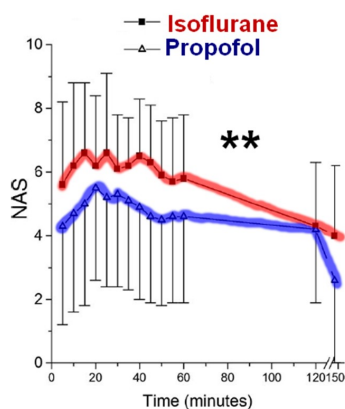


Figure 1. Numerical analog scores (NAS)

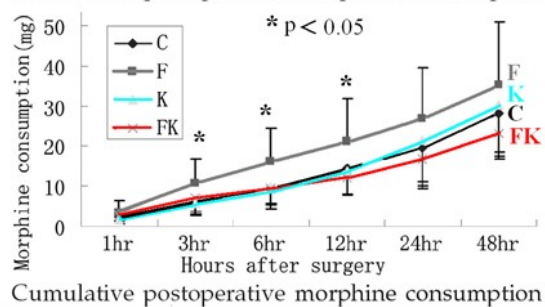
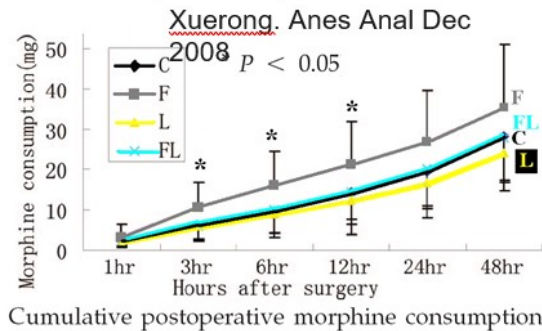
** $P < 0.01$, $n = 80$)

**Study 3****Ketamine and lornoxicam for preventing a fentanyl-induced increase in post-operative morphine requirement.**

- 90 women undergoing hysterectomy were divided into 6 groups receiving intra-operative analgesia supplements as follows;

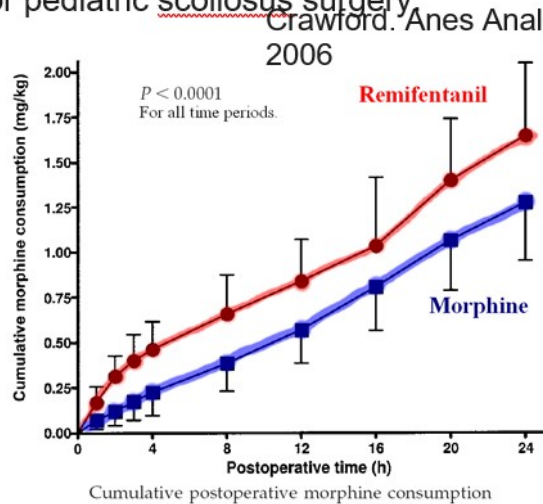
- **C** – Control (no analgesia)
- **F** - Fentanyl (1 µg/kg x 3 doses)
- **L** - Lornoxicam, (a NSAID)
- **FL** - Fentanyl + lornoxicam.
- **K** - Ketamine 15µg/kg/min (50 mg/h)
- **FK** – fentanyl + ketamine.

- All got spinal anesthesia 10 mg bupivacaine.

**Study 4****Development of acute opioid tolerance during infusion of remifentanyl for pediatric scoliosis surgery.**

- 30 teenagers underwent scoliosis surgery of 7.5 hours average duration.
- The patients were randomized into 2 groups;
 - Remifentanyl infusion (100µg/kg/min)
 - Morphine 0.1 mg/kg + boluses 0.05 mg/kg

- All were maintained with propofol anesthesia and O₂. and Air .



CONCLUSION; Intra-operative Remifentanyl administration induced an added hyperalgesia lasting 4 hours after surgery.



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