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Acute Postoperative Pain

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Abstract

One of the most important causes of postoperative morbidity and mortality is insufficiently treated pain. Postoperarive pain that could not be treated sufficiently leads to problems like reduction in vital capacity and alveolar ventilation, pneumonia, tachycardia, hypertension, myocardial ischemia and infarction, conversion to chronic pain, delay in wound healing and prolonged hospital stay. These problems may be prevented by successful management of postoperative pain. Acute postoperative pain management is a dynamic process. A detailed preoperative assessment should be done at the beginning and the most appropriate pain management should be provided by utilizing the newest drugs and techniques after estimation of risk- benefit status for each patient.

Keywords: Acute postoperative pain; Management; NSAIDs; Opioid; Analgesic; Patient controlled analgesia

Accurate management of pain is one of the most important challenges of health care providers. One of the most important concerns of the patients in postoperative period is postoperative pain. Effective relief of postoperative pain is one of the primary targets as postoperative pain also affects the clinical outcomes of the surgeons. Ineffectively treated and persistent postoperative pain may lead to anxiety, sleep disorders, demoralization, disturbances in mental activity and social relations [1-3]. Besides, postoperative pain may increase heart rate and blood pressure, suppress immune functions, decrease pulmonary functions, increase the probability of dangerous complications (myocardial ischemia, deep venous thrombosis, pulmonary embolism, hypoxia, pneumonia, stroke). In addition to these severe adverse effects, uncontrollable pain is related with gastrointestinal events like vomiting, emesis and ileus.

Uncontrollable acute pain may result in prolonged hospital stay and unplanned hospital admissions and increased hospitalizations besides psychologic and physiologic effects [4]. In a retrospective study, unplanned re-applications and admissions within postoperative 30 days was estimated as 38% [5]. Prolongation of acute pain treatment causes central and peripheric nervous system sensitization and may lead to chronic pain development of which treatment is hard and expenditure is high.

Pain was found as one of the three medical problems causing delay in discharge after ambulatory surgery. That an effective postoperative pain management cannot be achieved is a reality and unfortunately satisfaction is low both for the physicians and the paients. Even, in a study approximately 80% of the patients were reported to suffer from pain afer surgery [6]. Many patients still suffer from pain despite focusing on pain management programs and developing novel postoperative pain management programs.

Preventive Analgesia

Central sensitization and hyperexitability develop after surgical incision and this condition results in amplification of postoperative pain. Some short-term (reduction in postoperative pain and acceleration of recovery) and long- term (reduction in chronic pain development) benefits can be obtained in recovery period by preventing central sensitization through analgesic treatment. Preemptive analgesia concept is a pharmacologic strategy based on analgesic drug administration prior to surgical stimulation in order to prevent postoperative pain. Preemptive analgesia is an antinosiseptive treatment and prevents postoperative pain development by hindering afferent input formation. The purpose is to prevent or reduce any pain memory and thereby to reduce anlgesia requirement. Main characteristics of preemptive analgesia is beginning before surgery and preventing central sensitization related to surgical trauma or inflammatory events [7-11].

Multimodal Approaches

Controlling postoperative pain with unimodal approaches is almost impossible as it is a complex problem. Thus multimodal approach has been applied in clinical practice for last 15 years. It was determined that early mobilization, early oral intake, early returning of colon functions, early discharge and short duration of hospital stay, lower pain scores were obtained with a successful postoperative pain control and reduction in perioperative stress response was achieved with utilization of regional anesthetic techniques. Epidural anesthesia and analgesia is accepted as a complementary factor of multimodal approach due to phsiologic benefits and near-excellent postoperative analgesia.

Treatment Methods

Many options are available for postoperative pain treatment. These include systemic analgesics (eg, opioids, non-opioids) and regional analgesic techniques (neuroaxial and peripheral nerve blocks). Clinicians should take the prefer of the patient into consideration when evaluating individual risks and benefits of each treatment in order to apply the best postoperative pain regimen [12-14]. That there were genetic differences in pain susceptibility and genetic background affecting pharmacokinetics and pharmacodynamics of analgesic drugs would be the focus of postoperative pain management in the future [15].

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Systemic Analgesic Techniques

Opioids

Opioid analgesics are one of the mainstay of postoperative pain treatment. These agents usually acts upon μ-receptors in central and peripheric nervous sytem. A theorically important advantage of opioid analgesics is not having ceiling effect. Use of opioid analgesics are limited due to side effects like emesis-vomiting, sedation, respiratory depression. Opioids may be used in many formulas and in many different ways: subcutaneous, transcutaneous, transmucosal, intramuscular, intravenous, oral, intrathecal, epidural and intraarticular.

Opiod doses, serum concentrations and response to postoperative pain differ among individuals. For example, oral route is not prefered much in treament of moderate and severe postoperative pain as it shows a wide variability even in serum drug concentrations develops from intravenous or intramuscular route. Parenteral administrations provide faster and safer initial analgesic effect. Duration of parenteral opioid use may prolong especially in patients who cannot tolerate oral intake in postoperative period. Switching from parenteral use to oral use of opiods begins after the patients return to oral intake and if postoperative pain has been controlled with parenteral opiods. Continuously released oral opioids may provide a better analgesia compared to the ones when taken in case of requirement (currently paracetamole combined forms are available). Although passive form of transdermal fentanyl is not routinely used in postoperative pain treatment, a new version, patient actived electrically facilitated delivery of transdermal fentanyl is being used in hospitalized patients [16].

Iontophoretic transdermal fentanyl

Although effectiveness and patient satisfaction of paient controlled analgesia (PCA) have been shown, it limits intravenous administration due to risks like limitation of patient mobilization because of pump, lines and tubes and programming errors. Althogh the most widely used opioid for intravenous PCA is morphin, properties of fentanyl made it the most optimal candidate for iontrophic drug administration. Low molecular weight and high lipid solubility are among the ideal properties of a drug for transdermal administration [17]. Morphin has a lower molecular weight and higher lipophility compared to fentanyl (372 Da Fentanyl, 758 Da Morphin). Fentanyl is 100 fold stronger than morphin and passes into central nervous system 133 fold easier [18].

Patient controlled fentanyl hydrochlorid ionotrophic tarnsdermal system (fentanyl ITS) has been designed in order to eliminate aforementioned concerns. Fentanyl ITS is an innovator, non-invasive, needle-free, self-contained, pre-programmed drug system that iontrophic method is used for transdermal fentanyl administration by applying low density electrical power in a certain area. It provides a controlled analgesia without fluctuations. Conventional fentanyl patch that provides drug release in a constant velocity for 72 hours has been designed to use in chronic pain. Fentanyl ITS enables diffusion of 40 μg dose into blood circulation through intact skin in 10 min. 1. hour plasma concentrations of fentanyl ITS and intravenous fentanyl are different (0.1 and 0.7 ng/ml, respectively). This administration technology is much more superior to pacebo and it has been reported to be equal to patient controlled morphine analgesia [19,20].

In a study comparing morphine PCA and fentanyl ITS, the latter was reported to require 4% less staff (19). According to data obtained from controlled clinical trials, fentanyl ITS is a safe and effective method in postoperative pain management. Fentanyl ITS enables reducing pain to acceptable levels following loading dose of opiods by hindering analgesia spaces and first pass effect develop from other pain management modalities. Thereby fentanyl ITS may be a valuable option in postoperative pain management for both patients and health proffessionals that provides a safe and easy treatment and high patient satisfaction [22].

Tramadol

Tramadol should be discussed under a separate title. Tramadol is a synthetic analogue of codeine. Its analgesic effect is moderate. It is the only drug acts upon two different mechanisms. One of its metabolites has a poor affinity to μ-opioid receptor without affecting delta and kappa receptors. The second mechanism is reuptake inhibition of neurotransmitters norepinephrin and serotonin. Tramadol causes side effects like respiratory depression and sedation encountered with other opiods in postoperative pain treatment less. 100 mg tramadol given in peroral route at every 6 hours following hand surgey was found more effective than metamizole and paracetamole [22].

Tramadol /paracetamol 37.5 mg/ 325 mg oral preparations may be a beneficial option for multimodal analgesia in treatment of postoperative pain [23]. In a study comparing oral tramadol use and oral naproxen use in postoperative pain treatment after caesarean section, both drugs were reported to have similar analgesic effect an deven oral naproxen was reported to be preferred more by the mothers together with less side effects [24]. Tramadol and tapentadol were reported to be approved by FDA [25]. 1-2 mg/kg intravenous tramadol was shown to be an appropriate alternative to intravenous morphin in patients who underwent tonsillectomy [26]. The most bothersome side effects of tramadol are postoperative emesis and vomiting (9-10%), itching (7%) and rash (4%). These side effects' occuring during postoperative oral use is probable. Ondansetron used for treatment of postoperative emesis and vomiting was reported to lead to inhibition of tramadol analgesia due to causing reduction of binding 5-HT_3 receptors at spinal level [27]. Availability of injectable, drop and suppository forms besides preparations combined with paracetamole enables more flexibility for using this drug in postoperative period. Tramadol is the best analgesic that may be used for mild and moderate postoperative pain due to its opiod sparing effect and low incidence side effects.

Intravenous patient-controlled analgesia

Postoperative pain frequently resulted in inadequate analgesia due to delay in administration of the analgesic agent, especially intramuscular injection when needed conventionally based on the demand of the patient.

Great changes occur in plasma drug concentration profile develops following opioid administration via intramuscular or infusion route for postoperative pain treatment. For example; differences reaching 2-5 fold may be observed in maximum plasma concentration of the drug during intramuscular pethidine use. This variability leads to inadequate effectiveness of intramuscular administrations of opioids for postoperative pain treatment. On the other hand, physicians' using analgesics by not taking drug pharmacokinetics into consideration, nurses' acting conservatively due to abstaining from side effects that may develop during narcotic use have led to seeking safer and more effective methods for postoperative analgesia.

PCA is a closed circuit conrol system that the individual plays an active role in pain control. The method is based on an infusion technique that a special pump is used and a preconditioned analgesic drug is used in a specified way, by patient's pressing a button and that may be programmed in many different ways and doses. A timer in the

pump prevents application of an additional dose before a certain time. So excessive sedation and respiratory depression may be prevented. It is accepted that the treatment should be individualized in order to activate postoperative pain treatment. PCA is a method that may comprise wide analgesic need encountered in postoperative period.

However user and operator related errors are frequently seen besides material and equipment related faults [28,29]. In conclusion, intravenous PCA provides a superior anlagesia and a good patient satisfaction compared to conventional PRN analgesia regimen. Recommended opiods, doses and programs are given in Table 1.

Nonsteroidal antiinflammatory drugs

Nonsteroidal antiinflammatory drugs are still superfluous popular drugs. They have a wide use area in musculosceletal and chronic pain. Showing local effect without causing side effects and cognitive disturbances are the advantages of these drugs. Although their side effects have been defined well some side effects were neglected and underestimated. Opiophobia of both physicians and the patients, commercial concerns of drug companies make NSAIDs remain still popular.

They are composed of a heterogenous group with different chemical structures, pharmacologic and therapeutic effects. These group of drugs are also called as peripherally effective drugs as they develop analgesia with effects on peripheral regions that the pain arises. These agents that have varying degrees of analgesic, antipyretic and antiinflammatory effects do not lead to addiction and tolerance differently from opioids. This group of drugs are used either alone in mild or moderate pain or in treatment of severe postoperative pain together with adjuvants or in combination with opioids (Table 2).

NSAIDs that are also called as nonopioid analgesics show their analgesic and antiinflammatory effects by inhibiting prostaglandin synthesis as the result of cyclooxygenase enzyme inhibition. Cyclooxygenase has two forms named as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) . Most of NSAIDs inhibit COX-1 and COX-2 isoform in a non-selective way or have a small degree of selectivity for COX-1. They consequently block inflammatory cascade and cyclooxygenase by inhibiting prostaglandin and tromboxane and lead to reduction in pain, fever, platelet aggregation and inflammatory response [30]. On the other hand, some novel antiinflammatory drugs like nabumeton and meloxicam specificly inhibit COX-2. Ulcerogenic side effect incidence of COX-2 selective NSAIDs are lower.

Acetaminophen and other antipyretics effect as reducing pain and fever with primary central mechanism. Acetaminophen is antipyretic and analgesic however has a very little anitinflammatory effect. Its analgesic effect is no more than conventional analgesics and has less side effects. Its mechanism of action was discussed and it was seen to cause COX-3 inhibition. Intravenous form of acetaminophen was produced and begun to use in recent years. 10 mg/mL paracetamol in 100 ml solution is used as infusion in 15 min or longer. Its effect begins within 5-20 min, reaches peak level in 1-2 hours and its duration of effect is 4-6 hours. IV paracetamol is the pro-drug of acetaminophen. Analgesic effect of paracetamol is accepted to be related with blood concentration of the drug. 1 gr of IV paracetamol is hydrolized to 0.5 gram acetaminophen and thus 15 mg/kg of acetaminophen is equal to 30 mg/kg of paracetamol. Recomended dose is 15 mg/kg. It cannot control moderate and severe postoperative pain alone however decreases opioid requirement 40-50% in its combination with NSAIDs [31-33]. Intravenous acetaminophen should be considered to use in mild or moderate postoperative pain [34,35]. Primary goal of developing selective COX-2 inhibitors (Coxibs) is to reduce gastrointestinal bleeding and risks. Coxibs may be an interesting option in management of postoperative pain. This explains why they should be theorically discriminated from conventional NSAIDs due to their less harmful effect on platelet functions and hemostasis. An opinion about generalization of Coxib use can be made only after determination of risk-benefit ratios of all NSAIDs. Whether Coxibs have specific properties in certain conditions should be determined through studies. However their increased costs are more than their benefits. They were reported to be able to be a part of multimodal approach in management of postoperative pain [36-38].

	Bolus	Lockout interval (min)	Continuous rate
Morphine (1 mg/mL)	0.5-2.5 mg	5-10	0.01-0.03 mg/kg/h
Fentanyl (10 µg/mL)	10-20 µg	4-10	0.5-1 µg/kg/h
Alfentanyl (0.1 mg/mL)	0.1-0.2 mg	5-8	-
Sufentanyl (0.002 mg/mL)	2-5 µg	5-10	0-8 µg/kg/h
Meperidine (10 mg/mL)	5-25 mg	5-10	10 mg/h
Tramadol (10 mg/mL)	10-20 mg	5-10	10-20 mg/h

All doses are for adult patients

Table 1: Opiods and recommended programs used in intravenous PCA.

Drug*	Mean NNT†	95% CI
Diclofenac (100 mg PO)	1.9	1.6 - 2.2
Rofecoxib (50 mg PO)	1.9	1.8 - 2.1
Codein (60 mg) + acetaminophen (1000 mg PO)	2.2	1.7 – 2.9
Diclofenac (50 mg PO)	2.3	2.0 – 2.7
Ibuprofen (600 mg PO)	2.4	1.9 – 3.3
Oxycodone (15 mg PO)	2.4	1.5 – 4.9
Oxycodone (5 mg) + acetaminophen (325 mg PO)	2.5	2.0 – 3.2
Ketorolac (10 mg PO)	2.6	2.3 – 3.2
Meperidine (100 mg IM)	2.9	2.6 – 3.6
Morphine (10 mg IM)	2.9	2.6 – 3.6
Ketorolac (30 mg IM)	3.4	2.5 – 4.9
Acetaminophen (1000 mg PO)	3.8	3.4 – 4.4
Aspirin (1000 mg PO)	4.0	3.2 – 5.4
Codeine (60 mg) + acetaminophen (600 to 650 mg PO)	4.2	3.4 – 5.3
Aspirin (600 to 650 mg PO)	4.4	4.0 – 4.9
Dextropropoxyphene (65 mg) + acetaminophen (650 mg PO)	4.4	3.5 – 5.6
Acetaminophen (600 to 650 mg PO)	4.6	3.9 – 5.5
Tramadol (100 mg PO) Dextropropoxyphene (65 mg PO)	4.8 7.7	3.8 – 6.1 4.6 – 22
Dihydrocodeine (30 mg PO) Codeine (60 mg PO)	8.1 16.7	4.1 – 540 11.0 – 48.0

CI, confidence interval; IM, intramuscular; NNT, number needed to treat; PO, oral route.
†NNT in this case refers to the number of patients who must be treated to obtain greater than 50% relief of moderate to severe postoperative pain.

Table 2: Effect of single dose analgesics in controlling moderate and severe pain more than 50%.

Analgesic adjuvants

Dexmedetomidine: Dexmedetomidine is a highly selective α2 adrenergic agonist. It has 8 fold greater receptor affinity compared to clonidine. It extremely reduces analgesic and anesthetic requirement due to their analgesic properties and increasing the effect of local anesthetics by changing ion transport and membrane potential in

locus ceruleus region of pons. It provides a stable hemodynamics and reduces oxygen need due to improving sympathoadrenal stability. It also reduces opiod related muscle rigidity and postoperative rigidity however it may lead to minimal respiratory depression. It may decrease morphin consumption when used as an adjuvant agent. Analgesic effect of dexmedetomidine was shown in postoperative pain [39,40].

Capsaicin: Capsaicin ise producced from hot chili peppers from the genus Capsium and has along background of use in medical practice [41]. It is a nonopioid and acts peripherally as a Transient receptor potential vanilloid 1 (TRPV-1) agonist [42]. TRPV-1 receptors are prominent in inflammatory conditions and unmyelinated C fiber ends [43].

TRPV receptors are activated as the result of highly intensive stimuli and substance P is released. Constant release of substance P leads to capsaicin depletion in presence of capsaicin and afterwards it leads to reduction of pain by decreasing C fiber activation. Capsaicin does not have a significant effect on A delta and A alpha fibers. It also does not affect sense of hot and touch.

Both topical and injectable forms of capsaicin are used in management of postoperative pain, arthritis, musculosceletal pain and neuropathic pain. Capsaicin cream is usually combined with opioid and NSAID and thereby it may be used in painful conditions lke low back pain, cervical pain, many forms of arthritis, muscle spasms and ligament stretching. They may be used in high concentrations in postherpetic neuralgia and may hinder respiratory depression effect caused by opioid use in the elderly by benefiting from opioid sparing effect [44]. The most important side effect is severe burning in application area and degree of burning is directly proportipnal with drug concentration.

Ketamine: NMDA receptor is a glutamate receptor characterized with N-methyl-D-aspartate affinity. Excitation of NMDA receptor in dorsal root plays an important role in sensitization process [45]. Recently, NMDA receptors were shown to be located in periphery of unmyelinated axons and thus excitator aminoacids could play a role in primary nosiseption in periphery in addition to their roles in central nervous system.

Use of ketamine in treatment of pain was mentioned in publications in 1996 [46]. It is the best anesthetic known for 30 years and it was shown to have an interaction with many receptor systems like NMDA receptor system, opioid, monoaminergic receptor and muscarinic receptor [47,48]. It may lead to selective non-competative NMDA blockadge in subanesthetic doses. In some studies carried out with low dose ketamine, it was shown to be effective in postoperative analgesia. Vast majority of the studies are focused on use of ketamine as an preemptive analgesic [11] and some studies suggest its postoperative use [49].

Ketamin is reported to cause psychomimetic side effects in postoperative period even with low doses [11]. Ketamine may be developed in various surgical procedures and anesthesia techniques by using intraoperatively and postoperatively for postoperative pain treatment. It may be used to reduce postoperative pain especially in intraoperative subanesthetic dose under general anesthesia.

Gabapentin: Gabapentin was initially an antiepileptic drug and a structural analogue of gamma-aminobutyricacid (GABA). It binds to α2-δ protein subunit of voltage-dependent calcium channels that are widely available in central and peripheral nervous system. This inhibits influx of calcium and decreases excitator neurotarnsmitter release in pain pathways [50].

Analgesic effect of gabapentin was widely investigated in surgical environments. As the result of these studies, it was reported to have an analgesic effect in postoperative pain [51-54].

Pregabalin: Pregabalin is a lipophilic GABA analogue that has analgesic, anticonvulsant, anxiolytic, sleep modulation and opioid sparing effects. It was stated to be effective in many neuropathic pain models [55,56], incisional injury [57] and inflammatory conditions [59] as the successor of gabapentin. Pregabalin used in varying degrees of neuropathic pain like postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain and fibromyalgia. In the studies in recent years, there is an increasing interest that it is a part of multimodal analgesia in pain control. It is quite helpful in controlling postoperative pain through its opioid sparing and sedative effects although it was shown to have a significant analgesic effectiveness in acute conditions [59]. Although its mechanism is similar to gabapentin its pharmacologic profile is more superior.

Its reducing opioid requirement, preventing and decreasing opioid tolerence, increasing the quality of opioid analgesia, reducing respiratory depression, improving anxiety and gastric sparing effects make this agent attractive for management of postoperative pain.

Tapentadol: Tapentadol acts via central way with norepinephrin reutake inhibition and μ receptor agonist effect [60-62]. In humans, while it has 18 fold greater affinity to μ opioid receptors, it is 2-3 fold less effective than morphin. It was developed as the result of tolerance lowering studies . tapentadol is a novel analgesic with central effect and side effect incidence is lower than opioids. It was initially formulated as immediate- release preparation. Tapentadol was approved as potent Schedule II analgesic by US Food and Drug Administration (FDA). It is also the first analgesic developed in recent 25 yars for management of moderate and severe pain [63].

Tapentadol has two different forms. The first is immediate release 50, 75 and 100 mg tablets and it provides analgesia for 4-6 hours. Tapentadol was accepted to have equal analgesic potency with hydrocodone and oxycodone between tramadol and morphin. Tapentadol was seen to provide similar analgesic effectiveness compared to immediate release oxycodone [61]. It was also reported to be as effective as oxycodone in patients suffering from osteoartrit-related and chronic low back pain [64]. Its analgesic effect was shown in inflammatory, somatic and neuropathic pain and it was shown to have a better gastrointestinal tolerability (in terms of emesis, vomiting, constipation) compared to opioids [65].

The second form, tapentadol extended release (ER) is a constantly released form that may be effective for 12 hours for patients 18 years and above suffering from moderate and severe pain. It is used twice a day. Beginning of tolerance is low in chronic use and it significantly delays beginning of tolerence compared to morphin [66]. Its use is contrandicated in patients with severe bronchial asthma, paralytic ileus and using monoamine oxidase inhibitors.

Regional Analgesic Techniques

Neuroaxial and peripheric analgesic techniques may be used for effective treatment of pain. Analgesia provided by epidural and peripheric analgesic techniques is superior to systemic opioids [67] and morbidity and mortality decrease as the result of using these techniques [68,69]. Still, these techniques have some risks and the clinicans determine the appropriateness of neuroaxial and peripheric regional techniques by evaluating the individual risks and benefits of them.

Single dose neuroaxial opioids

Opiods are administered intrathecally or epidurally as single agent or adjvant. One of the most important factors for determination of clinical pharmacology of any opioid is the degree of lipophility or hydophility. Hyrdophilic opioids like morphin tend to stay in cerebrospinal fluid when they reached cerebrospinal fluid once through gradual migration from epidural space or directly intrathecal injection. The effect begins late and takes long. Ratio of side effects is high due to supraspnal and cephalic invasion.

Neuroaxial application of lipophilic opioids like fentanyl limits formation of some side effects like delayed respiratory depression due to rapid onset of analgesia and clearance from CSF. When studies reporting that there is not a difference between intravenous or epidural use of lipophilic agents in terms of dose and effect are taken into consideration, the most appropriate agent for single use seems to be morphin among opioids administered via neuroaxial route for postoperative analgesia. In the study carried out in 17 European countries, the most commonly preferred agents were seen to be morphin and fentanyl (Table 3) [70].

Concentration of fentanyl in systemic circulation rapidly increases after given into epidural space as it is a highly lipophilic opioid and it may reach systemic analgesic doses. Sometimes arguments occured that highly lipophilic opioids did not have a difference between systemic or epidural efficiency in terms of analgesia. However epidural fentanyl was shown to have an analgesic effect even when the amount of epidural fentanyl in systemic circulation is below analgesic level [71]. Required dose of intravenous fentanyl for analgesia in the same time and quality is 2-3 fold of epidural fentanyl dose. Blood level may reach sstemic analgesic dose when infusion is made. It shows a rapid analgesic effectiveness in intrathecal injection due to its rapid transport to arterial circulation and rapid diffusion to medulla spinalis and receptor affinity.

The most commonly used opioid for epidural analgesia is morphin. Quality of analgesia in postoperative period was found superior to systemic application in many studies. It was observed to show analgesic efficiency even in very low blood concentrations after epidural injection [72]. Intravenous morphin dose required for analgesia for the same time and quality is approximately 10 fold greater than epidural morphin dose. It accumulates in CSF due to its highly hydrophility and it shows a wide dermatomal invasion. Low doses should be initiated in the elderly patients and in epidural injections made from high levels like thracal cervical. Morphin concentration in CSF after intrathecal morphin injection is very high. It slowly passes from CSF towards opioid receptors in medulla spinalis due to its low lipid solubility. 0.1-0.3 mg is sufficient for postopertaive analgesia.

Epidural or intrathecal opioids may be given as intermittent injections and constant infusion. Ideal way for administration of morphin is intermittent injections as neuroaxial use of morphin may provide analgesia for long periods that may exceed even 24 hours. Duration of effect is shorter for agents with high lipid solubility and it may require frequent injections. Thus continuous infusion technique may provide an advantage with providing continuous analgesia and ease of application. However technologic need is more in this way. It may be remembered that side effect incidence due to drug accumulation may increase and the lowest possible doses should be used in continuous infusion techniques. Nurses' monitoring the patients being well educated is also an important factor for choosing the technique.

Drug	Single dose (mg)	Analgesia onset time (min)	Effect time (h)
Epidural			
Morfin	1-6	30	6-24
Extended release morphine	5-15		
Fentanil	0.025-0.1	5	2-4
İntratekal			
Morfin	0.1-0.3	15	8-24
Fentanil	0.005-0.025	5	3-6

Table 3: Intrathecal and epidural doses and duration of effect of the most comonly used opioids.

Extended Release Epidural Morphine (EREM)

This new drug that may be applied as a single dose seems close to our analgesic targets. A duration of effect that may prolong to 48 hours may be seen when EREM is used [73-77]. Side effects may also be avoided in case of opioids' cannot reach systemic concentrations besides better patient activity.

EREM was formulated so as to be administered epidurally at lumbar level. It was shown in a few studies to provide long lasting analgesia.

Side effects of EREM was treated with opioid antagonists. Opioid antagonists were needed in 10-12.5% of EREM administered patients [73-78]. Elderly are susceptible to the effect of EREM and close perioperative monitorization is required. 15 mg applied to the elderly patients and 20 mg EREM applied to the young patients were shown to be equal [78]. A careful perioperative monitorization is required for the elderly patients.

Patient controlled epidural analgesia

Intravenous patient controlled analgesia is a frequently used analgesia technique that is widely accepted. Epidural use of it may provide some benefits like reducing dependence on health personnel, determining minimal effective dose easier and individually. However these advantages may also lead to potential risks. Possible risks due to the patient's using more than needed opioid or local anesthetic are some of them. They do not have accepted ideal bolus or infusion doses, deadlock time. Highy lipophilic agents may be used in bolus mode due to short time for beginning of the effect. In case of using opioid local anesthetic combinations, it may be considered to give one of the agents as continuous infusion and the other as patient controlled boluses. Our patient controlled analgesia methods are presented in the table (Table 4).

Continuous peripheric nerve block

Continuous peripheric nerve block reduces possible adverse events compared to central nerve blocks that may lead to severe complications

	Demand dose (mL)	Continuous rate (mL/h)	Lockout interval (min)
0.05% levobupivacaine + 4 µg/mL fentanyl	2	4	10
0.0625% levobupivacaine + 5 µg/mL fentanyl	3-4	4-6	10-15
0.1% levobupivacaine + 5 µg/mL fentanyl	2	6	10-15
0.2 % ropivacaine + 5 µg/mL fentanyl	2	5	20

Table 4: Recomendations for use in epidural PCA.

like hematoma and epidural abscess. This procedure had obvious benefits for the patients and adverse events developed minimally were shown in many randomized studies [79]. Commonly used continuous peripheric nerve block analgesia regimens are shown in Table 5. In clinical trials including these analgesia regimens, it was stated that continuous peripheric nerve blocks were as effective as continuous epidural block following orthopedic surgery concerning lower and upper extremities. Both blocks were found much more effective than intravenous opioids [79]. Additionally, regional analgesia needs to be used in critically ill patients in order to reduce sedative and opioid drug use.

Chronicity of postoperative pain

Chronic pain developing following surgery was a condition that was not taken into account. However in recent years, it has begun to explicated significantly as a clinical and even a social roblem. Because postoperative chronic pain was detected to be seen not only after major surgery but also after minor surgery like inguinal hernia and vasectomy. Incidence of postoperative chronic pain was estimated as 1.8-6.7% in USA and 0.5-14% in Great Britain. Young age, presence of preoperative pain, malignity, infection, repeated surgical operations, type and duration of surgery, incision site, experience of the surgeon and genetic predisposition form preoperative risk factors [80,81]. Intraoperative nerve ınjury, complex surgical approaches or severe pain that was not treated in postoperative period, radiotherapy and chemotherapy, anxiety, depression form intraoperative and postoperative predictive factors.

All surgical procedures occur after an incision. Pain does not become chronic after every incision. In a study, it was adduced that more than half of acute postoperative neuropathic pain would convert to chronic neuropathic pain [82]. However conditions like intercostal nerve injury during thoracotomy, nerve injuries developing after traction, positioning or direct trauma in orthopedic operations or brachial plexus injury in axillary dissection in breast surgery are not rare and ratio of chronicity of the pain is high in these conditions (Table 6) [58,83].

According to many studies about chronic pain, postoperative pain was shown to be treated inadequately in acute period. These include conditions like breast surgery, hernia repair and thoracotomy [84-86]. The most important dilemma is probably about drugs and methods. Preemptive drugs are known to limit and better control acute postoperative pain. However epidural anesthesia applied during the surgery is known to prevent central sensitization and thus is a very important method that may prevent chronicity of postoperative pain.

Site of catheter's insertion	Common local anesthetics and consentration	Continuous infu-sion	Blos dose
Interscalene brachial plexus	Bupivacaine 0.1% and 0.125%	5-9 mL/h	3-5 mL
İnfraclavicular bra-chial plexus	Levobupivacaine 0.1% and 0.2%	5-9 mL/h	3-5 mL
Paravertebral		5-10 mL/h	3-5 mL
Lumbar plexus		8-10 mL/h	5-7 mL
Femoral nevre		7-10 mL/h	5-7 mL
Sciatic nevre		7-10 mL/h	5-7 mL
Popliteal sciatic nerve		5-7 mL/h	3-5 mL

Table 5: Common infusion modalities for continuous peripheral nevre block analgesia.

Type of operation	The insidence of chronic (%)
Amputasyon	50-85
Thoracotomy	30-50
Coronary artery bypass surgery	30-50
Mastectomy	20-50
Hernia repair	5-35
Hysterectomy	32
Hip arthroplasty	28
Colectomy	28
Cholecystectomy	26
Vasectomy	5-18
Caesarean section	6-10
Cataract	<1

Table 6: Chronicity rates of postoperative pain after some surgical procedures.

In conclusion, different opinions should be put forward about this issue.

Chronic pain that has become a significant public health problem as it affects many people brings severe economic outcomes together besides significantly affecting quality of life.

Conclusion

Acute postoperative pain is a clinical condition that should be treated accurately and completely. Each patient should be evaluated individually in preoperative period and the method should be determined according to the severity of the pain. This method should be a noninvasive method that may control postoperative pain. Management of postoperative pain, a very diffcult process, should begin in preoperative period, multimodal approach formed by newly developed drugs and regional techniques, preemptive analgesia methods may convert the difficult to easy. So we may also join to 'Hospitals Without Pain' of SIAARTI Study Group[87].

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