

# Multimodalna analgezija

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# Uvod

- Jedna od najčešćih zabrinutosti pacijentima pre operacije je prisustvo postoperativnog bola
- adekvatna postoperativna analgezija se postiže kod manjine pacijenata
- Neodgovarajuća kontrola bola nije se značajno promenila u poslednjih nekoliko godina u grupi odraslih hirurških pacijenata u Ujedinjenim Države su otkrile da je 86% iskusilo bol nakon operacije, od kojih je 75% imalo umeren do jak bol u neposrednom postoperativnom periodu, i 74% doživeli su sličan nivo bola čak i nakon otpuštanja iz kuće
- [Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;9](#)

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- Akutni bol je normalan, predvidljiv fiziološki odgovor na mehaničku, hemijsku ili temperaturnu stimulaciju uzrokovane hirurškim zahvatom, povredom ili akutnom bolešću.
- Jake, trajne nociceptivne kaskade koji u veoma kratkom vremenskom periodu usled razvoja periferne i centralne senzibilizacije može dovesti do hroničnog bola.
- Bol osećaj pojedinca, osim senzornog, on će uticati na emocionalnu i kognitivnu komponentu.
- Efikasna prevencija i lečenje akutnog bola su etičke i humane procedure koje moraju biti uključene u program kvaliteta tretmana pacijenata

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# Bol - definicija

- Bol predstavlja individualno, subjektivno iskustvo povezano sa aktuelnim ili potencijalnim oštećenjem tkiva, čija je manifestacija rezultat složene interreakcije fizioloških i neurohemijskih efekata sa psihosocijalnim faktorima.

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# Akutni bol

- Akutni bol - bol u prvih 7 dana od operacije
- Hronični bol – bol koji traje duže od 3 meseca
  
- Akutni postoperativni bol – bol usled hirurške intervencije, kao i proceduralni bol (drenovi, sonde, kateteri).

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# Cilj lečenja bola

- Cilj je liječenja potpuno uklanjanje akutne boli multimodalnim pristupom te primjenom koncepta preventivne analgezije.

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# Zasto lečiti bol

- Osnovno ljudsko pravo !
  - ↓bol i patnja
  - ↓ komplikacije
  - ↓verovatnoću razvoja hroničnog bola
  - ↑ zadovoljstvo pacijenta
  - ↑brzina oporavka → ↓duzina boravka u bolnici ↓cena
  - ↑produktivnost i kvalitet zivota
  
- [Acute Pain Management: Scientific Evidence. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine 2005](#)

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# Neželjeni efekat slabe kontrole bola

- **KVS-IM** i disritmija
- **Respiratorni trakt**-atelektaza i pneumonija
- **GI-ileus**, popustanja anastamoza
- **Hiperkoagubilno stanje**-DVT i Plucna embolija
- **Oštećenje imune funkcije**-infekcije , kancer, zarastanje rane
- **Psihološke** - Aksioznost, Depresija, umor

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# Prediktori postoperativnog bola

- Preoperativni bol
- Mlađe životno doba
- Anksioznost
- Gojaznost
- Strah od intervencije
- Tip operacije (abdominalne, torakalne, ortopedske, dugog trajanja)

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# Posebne subpopulacije bolesnika kod kojih bol može biti neadekvatno tretiran:

- pedijatrijski bolesnici
- gerijatrijski bolesnici
- kritično oboleli
- bolesnici sa oštećenim kognitivnim funkcijama

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# Gde je problem ?

- Multifaktorijelni problem
- Bol se tretira samo na zahtev
- Slaba komunikacija sa bolesnikom
- Ne procenjuje se intenzitet bola
- Ne pridržavanje protokola
- Ne korišćenje regionalnih tehnika analgezije (epidural, nervni blokovi...)

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# Preentivna, preventivna, multimodalna analgezija

- Šta oni zaista znače?

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# Preentivna, preventivna, multimodalna analgezija

- Da bi se poboljšalo upravljanje postoperativnim bolom, postoji nekoliko pojmova koji su razvijeni.
- preemptivna analgezija,
- preventivna analgezija,
- i multimodalna analgezija.

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# Preemptivna analgezija

- primena analgetske terapije pre bolnog stimulusa koja bi trebalo da smanji promene na sinapsama u zadnjim rogovima kičmene moždine itako prevenira centralnu senziciju posredovanu perifernim C vlaknima
- primena se nastavlja i postoperativno (uz osnovnu analgeziju)
- najači perioperativni triger nastaje intraoperativno
- preemtivni efekat prisutan neposredno postoperativno (kontrola bola, potrošnja analgetika)

- [Wall PD. The prevention of postoperative pain. Pain 1988;33: 289-290](#) [Katz J, Kavangagh BP, Sandler AN et al. Preemitive analgesia . Clinical evidence of neuroplsticity contributing to postoperative pain. Anesthesiology 1992;77:436-46](#)

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# Preventivna analgezija

- Za razliku od preentivne analgezije, koja uključuje davanje analgetika ranije hirurška intervencija, preventivna analgezija je a širi koncept.
- Cilj preventivne analgezije je da minimizira senzibilizaciju izazvanu štetnim podražaji koji se javljaju intraoperativno i postoperativno
- farmakološke supstance koje ne pripadaju grupi analgetika
- intraoperativna i postoperativna primena farmakoloških supstanci (postoperativni triger je najjači zbog reparatornih procesa i inflamacije)
- [Katz J, McCartney CJ. Current status of pre-emptive analgesia. Curr Opin Anaesthesiol. 2002;15: e analgesia. Curr Opin Anaesthesiol. 2002;15:435–441](#) [Vadivelu N,Mitra S,Schermer E et al.Preventive analgesia for postoperative pain gesia for postoperative pain-broader concept.Local broader concept.Local and Regional Anesthesia 2014; and Regional Anesthesia 2014;7:17-22](#)

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# Preventivna analgezija

- cilj je smanjiti potrošnju analgetika uz bolju kontrolu bola
  - prisustvo analgetskog efekta primenjene farmakološke supstance nakon 5,5 poluvremena eliminacije (kada direktni efekat nestane)
  - bolji kvalitet postoperativnog oporavka i kvalitet života nekoliko meseci posle operacije
  - ne postoji konsenzus o tačnom trenutku kada započeti primenu niti koliko dugo primenjivati preventivnu analgeziju
- [Dahl J, Kehlet H. Preventive analgesia. Curr Opin in Anesthesiology 2011;24:331 n Anesthesiology 2011;24:331-38](#)

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# Postoperative Pain Management – Good Clinical Practice

## Balansirana – multimodalna analgezija



General recommendations  
and principles for  
successful pain management



Produced in consultation with the  
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# Multimodalna analgezija

- Multimodalna analgezija je davanje dva ili više analgetika koji deluju kroz različite mehanizme
- kombinovana primena nefarmakoloških i farmakoloških postupaka
- kombinacija postupaka ističe sinergizam/aditivni efekat
- analgetici mogu biti primenjeni istim putem ili različitim putem
- smanjuje dozu svakog od njih analgetik pojedinačno i potencijalno neželjene događaje

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# Multimodalna analgezija

- Dakle, cilj multimodalna analgezija je da poboljša ublažavanje bola uz smanjenje opioidnih potreba i neželjenih efekata povezanih sa opioidima.
- literaturi zasnovane su na studijama koje koriste bimodalnu terapiju (kao što je a kombinacije ketorolaka i morfina) kao sredstvo kontrole bol.

Schug S,Palmer G,Scott D et al. Preventive and pre-emptive analgesia. In: Acute Pain Management:scientific Evidence.Australian and New Zealand College of Anaesthetists 4th Ed 2015;1:23-24

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# Multimodalna analgezija

## Analgetici

### Pharmacological options of pain management

Non-opioid analgesics	Paracetamol NSAIDs, including COX-2 inhibitors* Gabapentin, pregabalin <sup>2</sup>
Weak opioids	Codeine Tramadol Paracetamol combined with codeine or tramadol
Strong opioids	Morphine Diamorphine Pethidine Piritramide Oxycodone
Adjuvants**	Ketamine Clonidine

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# Paracetamol

## Paracetamol

Administration	(i) Intravenous: Start 30 min before the end of surgery. (ii) Oral administration as soon as possible. Duration: as long as required.
Dosage	4 x 1 g paracetamol/day (2 g propacetamol/day). Dose to be reduced (e.g. 3 x 1 g/day) in case of hepatic insufficiency.
Monitoring	Pain scores.
Comments	Should be combined with NSAID and/or opioids or loco-regional analgesia for moderate to severe pain.

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# Paracetamol

- Mehanizam dejstva - nedovoljno razjašnjen:
- Paracetamol (acetaminofen) se generalno smatra slabim inhibitorom sinteze prostaglandina (PG). Međutim, in vivo efekti paracetamola slični su efektima selektivnih inhibitora ciklooksigenaze-2 (COX-2)
- ↓COX3 (forma COX1 u CNSu)
- derivat je fenola (10-40% vezane forme), intenzivno prolazi HE barijeru
- AM404 (endogeni kanabinoid):deacetilacijom i konjugacijom sa arahidonskom kiselinom,, čime se ↑CB1 i TRPV1 ( CB1 i TRPV1 (↑endogenih, ↓COX)
- minimalan periferni efekat (visoko bezbedan)

- [Graham GG, Scot KF. Mechanism of action of paracetamol. Am J Ther 2005;12:46 mol. Am J Ther 2005;12:46-55](#)

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# Paracetamol

- preventivna analgezija 15mg/kg iv, 1 sat pre operacije
- ortopedska hirurgija ortopedska hirurgija – efekat u prvih 24 sata
- **Oprez: prva dva trimestra trudnoće (preeklampsija), pacijenti sa astmom, pacijenti sa insuficijentnom funkcijom jetre (proces oksidacije)**
- Toygar P, Akkaya T, Ozkan D, Ozel O, Uslu E, Gümüş H. Does IV paracetamol have H. Does IV paracetamol have preemptive analgesic ef preemptive analgesic effect on lumbar disc surgerie fect on lumbar disc surgeries? Agri 2008;20:

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# NSAIL i COX 2

- **Mehanizam dejstva:**
- Neselektivni NSAID i COX-2 specifični inhibitori igraju važnu ulogu u prevenciji periferne i centralne senzibilizacije.
- inhibitori COX 1(konstitutivna forma) i COX 2 (inducibilna forma)
- Inhibiraju lucenje PGE2
- aditivni efekat sa svim ostalim komponentama multiaditivni efekat sa svim ostalim komponentama multimodalnog pristupa
- **Farmakologija**
- slabe kiseline
- COX2 enzim većeg afiniteta za supstrate (posedovanje hidrofobnog lanca sa druga čijim konformacionim promenama)
- ↓ analgetski ↑ antiinflamatorno
  
- [Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. JAMA 2003;290:2411–8](#)

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# NSAIL i COX 2

- efikasni kod minimalno invazivnih operativnih procedura (VATS, laparoskopija)
- ortopedska hirurgija ortopedska hirurgija – Ketoprofen/Ketorolac (osim spinalne hirurgije)  
Ketoprofen/Ketorolac (osim spinalne hirurgije)
- neurohirurgija , ORL i MFH
- **Oprez kod NSAIL: ↓ bubreg, ulkusna bolest, kardiovaskularna bolest, stariji pacijenti, deca <5 godina, poslednji trimestar trudnoće (DAP)**

- [Tippana E, Bachmann M, Kalso E, Pere P. Effect of paracetamol and coxib with or without dexametasone after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2008;52:673-80](#)

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# Nesteroidni antiinflamatorni lekovi

NSAIDs <sup>1</sup>	
Administration	(i) Intravenous: administration should start at least 30-60 min before end of surgery. (ii) Oral administration should start as soon as possible. Duration: 3-5 days.
Dosage examples	(i) <i>Conventional NSAIDs include:</i> ketorolac: 3 x 30-40 mg/day (only IV form) diclofenac: 2 x 75 mg/day ketoprofen: 4 x 50 mg/day (ii) <i>Selective NSAIDs include:</i> meloxicam 15 mg once daily COX-2 inhibitors are now licensed for postoperative pain management. They are as efficient as ketorolac but reduce GI side effects. Examples include: parecoxib: 40 mg followed by 1-2 x 40 mg/day (IV form) or celecoxib: 200 mg/day. However, there is some debate due to cardiovascular risks in patients with arteriosclerosis. *See note below Table 2, page 17
Monitoring	Pain scores. Renal function in patients with renal or cardiac disease, elderly patients, or patients with episodes of severe hypotension. Gastrointestinal side effects. Non-selective NSAIDs would be combined with proton inhibitors (i.e. omeprazol) in patients at risk of gastrointestinal side effects.
Comments	Can be added to the pre-medication. Can be used in association with paracetamol and/or opioids or local regional analgesia for moderate to severe pain.

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# Kortikosteroidi (Dexason)

- **Mehanizam dejstva**
- Periferni mehanizam
- ↓ funkciju leukotriena i citokina
- ↓ edem tkiva
- ↓ stimulacija nociceptivnih vlakana

## Centralni mehanizam

- ↓ sinteze prostaglandina
- ↑ ekspresiju Ser receptora na membrani
- menja propustljivost HE barijere za proteine
- 

Waldron NH, Jones CA, Gan TJ et al. Impact of perioperative dexamethasone on postoperative analgesia and side and side-effects: systematic review c review and meta and meta-analysis. Br J Anaesth 2013;110: 191 analysis. Br J Anaesth 2013;110: 191–200

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# Kortikosteroidi (Dexason) - primena

- preoperativna primena, isključivo
- doza:0,1-0,2mg/kg iv,
- jednokratno pozitivan efekat u ORL i MFH, abdominalnoj i ortopedskoj hirurgiji
- prevencija PONV, kraće vreme za uspostavljanje peristaltike
- Waldron meta analisis ↓ opioida ↓ boravak u UCI
- **Oprez kod primene Kortikosteroida:infekcije,usporava zarastanje rane, ulcus , hiperglikmija , avaskularna nekroza**
  
- Koh IJ, Chang CB, Lee JH et al. Preemptive low-dose dexamethasone reduces postoperative emesis and pain after TKA: a randomized controlled study. Clin Orthop Relat Res 2013;471: 3010–20

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# Opijati i opiodidi

- **Mehanizam dejstva**
  - Centralni efekat na m,k,d receptore preko G –proteinskih receptora
  - Inhibicija voltažno zavisnih Ca +2 kanala
  - Povećava provođenje K+ i dovodi do hiper polarizacije
  - Inhibicija adenilciklaze
- 
- [rosu, I. & Kock, M. \(2011\). New concepts in acute pain management: Strategies to prevent chronic postsurgical pain, opioid-induced hyperalgesia, and outcome measures. Anesthesiology Clinics ,29\(2\)\). 311-327](#)

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# Opioidi klasifikacija

- **Prirodni** –morfin i kodein
- **Polusintetski** –heroin , buprenofin , oxycodoin
- **Sintetski** :
  - 4 fenilpiperidin: fentanil i meperidin
  - Difenilpipelamin:loperamid i methadon
  - Benzomorfani :Pentaazocin
- **Endogeni** :enkefalini, dodorfini , dinorfini
- **Ostali** : tramadol

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# Morfijum

Morphine	
Administration	<ul style="list-style-type: none"> <li>(i) Intravenous.</li> <li>(ii) Subcutaneous by continuous infusion or intermittent boluses via indwelling cannula.</li> <li>(iii) Intramuscular (not recommended due to incidence of pain. 5-10 mg 3-4 hourly).</li> </ul>
Dosage: IV PCA  Subcutaneous	Bolus: 1-2 mg, lockout: 5-15 min (usually 7-8 min), no background infusion. 0.1-0.15 mg/kg 4-6 hourly, adapted in relation to pain score, sedation and respiratory rate.
Monitoring	Pain score, sedation, respiratory rate, side effects.
Comments	Side effects such as nausea, vomiting, sedation and apnoea. No other opioid or sedative drug should be administered.

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# Tramadol

<b>Tramadol</b>	
Administration	(i) Intravenous: inject slowly (risk of high incidence of NV). (ii) Intramuscular. (iii) Oral administration as soon as possible.
Dosage	50-100 mg 6 hourly.
Monitoring	Pain score, sedation, respiratory rate, side effects.
Comments	Tramadol reduces serotonin and norepinephrine reuptake and is a weak opioid agonist. In analgesic efficiency, 100 mg tramadol is equivalent to 5-15 mg morphine. Sedative drugs can have an additive effect.

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# Ketamin

- Antagonisti NMDA receptora
- hidrosolubilan, ↑Vd, norketamin (aktivan metabolit)
- ekskrecija putem urina
- simpatikomimetik (stabilnost KVS)

**oprez:** kod povećanog ICP, IOP, neregulisane hipertenzije, oprezno kod pacijenata sa srčanom slabošću i koronarnom bolešću

## mehanizam dejstva:

- fenilciklidinsko mesto vezivanja na receptoru
- voltažno zavistan modulator bola (otvoren jonski kanal Ca strujom)
- interakcija i sa drugim reakcijama i sa drugim tipovima receptora

[Hirota K, Lambert G. Ketamine its mechanism of action and unusual clinical uses. BJA 1996;22\(4\):441 ;22\(4\):441-443](#)

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# Magnezijum-Antagonisti NMDA receptora

- **Mehanizam dejstva:** • MMP: Mg blokira jonski kanal NMDA

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# Agonisti $\alpha_2$ receptora

- **Klonidin i dexmedetomidin**
  - $\alpha_2$ - $\delta$  subjedinica L subjedinica L- tipa voltažno zavisnih Ca tipa voltažno zavisnih Ca kanala (locirani u ZRKM)
  - selektivni antagonizam ove subjedinice inhibira influks jona Ca
    - inhibicija oslobađanja glutamata, NOR, , serotonin, supstance P postsinapsno
    - sedativni efekat (CNS)
  - Smanjuje postoperativnu koncentraciju opioda, kao i multimodalni regionalne infuzije anestetika
- 
- [Rockemann M, Seeling W, Brinkmann A et al. Analgesic and hemodynamic effects of epidural clonidine, clonidine/morphine and morphine/morphine and morphine after pancreatic surgery. Anesth Analg 1995;80:896 after pancreatic surgery. Anesth Analg 1995;80:896-74](#)

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# Antikonvulzivi Antikonvulzivi- značaj $\alpha 2$ - $\delta$ subjedinice

- $\alpha 2$ - $\delta$  podjedinice napon-zavisnih presinaptičkih  $Ca^{2+}$  kanala
- Gabapentin i pregabalin su GABA analozi koji smanjuju postoperativne potrebe opijata i smanjuju i akutni i hronični postoperativni bol kada se koriste u multimodalnoj analgeziji.
- Gabapentin smanjuje potrebe za opioidima i smanjuje i akutni i hronični postoperativni bol. smanjuju PONV, mada bez smanjenja postoperativnog bola.
- **Oprez:** ne primenjivati kod starije populacije, kod trudnica i porodilja, kod HBI zavisne od HD, sleep apnea
- [Clarke H, Bonin R, Beverly O et al. The Prevention of Chronic Postsurgical Pain Using Gabapentin and Pregabalin: A Combined Systematic Review and Meta Systematic Review and Meta-Analysis. Anesthes Analg 2012;115:428-42](#)

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# Kapsaicin (agonist vaniloidnog receptora 1 )

- Kapsaicin je ne-narkotičko sredstvo sa agonističkom aktivnošću na perifernim TRPV1 receptorima. On selektivno stimuliše neimelinizovane aferentne neurone C-vlakna, supstance P.
  - rane rehabilitacije i funkcionalnog oporavka nakon bolnih operacija
- 
- *Partrick CT, Pestano C, Carlson N, Hartrick S. Capsaicin instillation for postoperative pain following total knee arthroplasty: a preliminary report of a randomized, double-blind, parallel-group, placebo-controlled, multicentre trial. Clin Drug Investig 2011; 31: 877-82.*

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# Beta-blokatori

- esmolol, smanjuju i intraoperativne i postoperativne potrebe opijata zbog njihovih anti-nociceptivnih efekata.
- intraoperativna kontinuirana infuzija esmolola umesto intraoperativnih opioda (uspešno je korišćena u ambulantnoj laparoskopskoj holecistektomiji, što je rezultiralo smanjenim PONV, smanjenim postoperativnim bolom.
- *Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanyl during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. Anesth Analg 2001; 92: 352-7.*

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# Multimodalne tehnike za postoperativnu analgeziju

**Neuroaxialno:** morfin + LA  
sufentanil + LA

**Sistemska:** opioidi (Mo, fentanil, sufentanil, tramadol)

+

NSAIDs  
COX NSAIDs  
Pregabalin  
Gabapentin

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# Treatment options in relation to magnitude of postoperative pain expected following different types of surgery<sup>1</sup>



## Mild intensity pain

*For example:*  
Inguinal hernia  
Varices  
Laparoscopy

## Moderate intensity pain

*For example:*  
Hip replacement  
Hysterectomy  
Jaw surgery

## Severe intensity pain

*For example:*  
Thoracotomy  
Upper abdominal surgery  
Aortic surgery  
Knee replacement

- (i) Paracetamol and wound infiltration with local anaesthetic
- (ii) NSAIDs (unless contraindicated) and
- (iii) Epidural local analgesia or major peripheral nerve or plexus block or opioid injection (IV PCA)

- (i) Paracetamol and wound infiltration with local anaesthetic
- (ii) NSAIDs (unless contraindicated) and
- (iii) Peripheral nerve block (single shot or continuous infusion) or opioid injection (IV PCA)

- (i) Paracetamol and wound infiltration with local anaesthetic
- (ii) NSAIDs (unless contraindicated) and
- (iii) Regional block analgesia  
Add weak opioid or rescue analgesia with small increments of intravenous strong opioid if necessary



# Analgetici

Analgetik	Način primene	Doza	Vremenski interval
Morfin	i.v.	1-2 mg	
Petidin (Meperidin)	i.v., i.m.	0.5-1.5 mg/kg	na 4-6 h
Tramadol	i.v., i.m., s.c.	50-100 mg	na 6 h
Paracetamol	i.v.	1 g	na 6 h
<b>NSAIL-neselektivni COX inhibitori</b>			
Ketorolak	i.v.	30-40 mg	na 6 h
Diklofenak	i.v.	75 mg	na 12 h
Ketoprofen	i.v.	50 mg	na 6 h
<b>NSAIL-selektivni COX-2 inhibitori</b>			
Celecoxib	Per os	200 mg	jednom dnevno
Meloxicam	Per os	15 mg	jednom dnevno
Parecoxib	i.v.	40 mg	1-2 puta dnevno

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# PCA – i.v.

<b>Koncentracija leka</b>	<b>Bolus</b>	<b>Sigurnosni interval</b>	<b>Kontinuirana infuzija</b>
<b>Morfin (1 mg/ml)</b>	0.5-2.5 mg	5-10 minuta	0.01-0.03 mg/kg/h
<b>Fentanil (0.01 mg/ml)</b>	10-20 µg	5-10 minuta	0.05-0.1 µg/kg/h

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# PCEA

Lek	Potrebna doza	Sigurnosni interval	Kontinuirana infuzija
Morfin	100–200 µg	10–15 minuta	300–600 µg/h
Fentanil	10–15 µg	6 minuta	80–120 µg/h
Bupivacain 0.125% + fentanil 4µg /ml	2 ml	10 minuta	4 ml/h
Ropivacain 0.2% + fentanil 5 µg /ml	2 ml	20 minuta	5 ml/h

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# Nefarmakoloske tehnike

- Akupunktura
- Muzikoterapija
- TENS
- Hipnoza
- TENS
- Ice terapija

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# Zaključak

- Izbor i dozu analgetika prilagoditi bolesniku, operativnom zahvatu, prisustvu drugih oboljenja ili bolnih sindroma
- Procena bola
- Dokumentovanje
- Multimodalna analgezija
- Protokol za analgeziju

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