

The use of opioid adjuvants in perioperative multimodal analgesia

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Abstract

Postoperative analgesia plays a crucial role in day-case surgery. Patients expect effective pain relief after surgery, without side effects, and this may not always be possible when more complicated procedures are performed in ambulatory settings. Moreover, both surgeons and patients expect anaesthesiologists to provide an effective pain treatment service especially after ambulatory surgery, even in private practice settings.

The protocols based on intravenous opioids or central neuraxial blockade are no longer appropriate, when a short, uncomplicated postoperative course is anticipated. Multimodal analgesia, combining different groups of analgesics, both opioid and non-opioid, with different mechanisms of action, and targets in central and peripheral nervous systems with minimal side effects may be an answer. In this review, we present and discuss the current status of knowledge, with special reference to the role of adjuvants to opioids in acute postoperative pain.

Key words: analgesia, perioperative, adjuvants; analgesics, opioids

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Effective management of acute postoperative pain is ever present in discussions about the improvement of medical care quality, both at the university and everyday anaesthetic practice level. According to the available literature, 75-85% of patients find the postoperative pain therapy unsatisfactory [1, 2]. Similar opinions regarding the quality of pain control are expressed by physicians [3].

Recently, vast advances have been observed in the approach to pain, its key role in the assessment of patient's condition as the "fifth vital sign", in particular [4, 5]. Moreover, some progress is also noticeable in understanding of pain transmission pathways and plasticity of peripheral and central nervous system leading to prolonged acute pain sensations.

The difficulties in postoperative pain therapy result from the complexity of ambulatory and one-day surgical procedures; the expectations regarding postoperative management are increasingly high, amongst both patients and surgeons, who carry out some procedures (previously performed only in hospital settings) in private clinics. The effective treatment based on intravenous opioids or central blocks is no longer suitable to meet the major demand

for ensuring the short, uncomplicated postoperative period [6]. The adverse side effects of opioid analgesics, e.g. their sedative and the respiratory centre-depressive effects, are the pivotal problems in the therapy of acute postoperative pain, especially in one-day surgery. Any delays in pain control lead to delayed discharge and rehabilitation of patients, prolonged full recovery and return to work [7].

Multimodal analgesia, i.e. analgesic therapy combining simultaneous actions of various analgesics, is likely to fulfil the increasingly high expectations concerning the efficacy of pain therapy [8]. It was designed to improve analgesic management, reduce opioid doses and minimise their side effects. The method involves combined use of various analgesics, both opioid and non-opioid, of different mechanisms of action and sites of uptake in the central and peripheral nervous system, in order to achieve better analgesic efficacy and to limit the risk of potential adverse effects [9].

The major goals of ideal set of analgesic drugs include increased efficacy, minimal side effects, safety and, most importantly, the possible use of drugs by patients and

their caregivers outside the hospital, without impairing patients' abilities to drive or delaying their return to work [10]. The present paper discussed shortly the selected, basic non-opioid pharmaceutical agents and their combinations used in multimodal analgesia. The following groups of drugs were considered:

- non-opioid analgesics (paracetamol, metamizole)
- NLPZ (non-steroidal anti-inflammatory drugs and COX-2 inhibitors)
- α -2 receptor agonists (dexmedetomidine, clonidine)
- NMDA receptor antagonists (ketamine, magnesium)
- glucocorticosteroids (dexamethasone)
- antiepileptic drugs (gabapentin, pregabalin).

NON-OPIOID ANALGESICS

PARACETAMOL

Despite its wide use, both due to medical recommendations and availability (over-the-counter – OTC), the mechanism of action of paracetamol is poorly known. The drug is likely to inhibit the central activity of COX-2 and COX-3 isoform [10]. According to the recent reports based on studies in animals and healthy volunteers, paracetamol affects the serotonergic antinociceptive system by stimulating the activity of serotonergic pathways (5-HT). This observation may be of some importance as the combination of paracetamol with antiemetic drugs from the group of 5-HT₃ receptor antagonists (ondansetron, tropisetron) can partially abolish its analgesic effects [11, 12]. It is well known that paracetamol reduces the doses of opioids needed. The administration of 1 g of i.v. paracetamol before surgery decreases the total opioid dose and accelerates the recovery of patients after laparoscopic hysterectomy and cholecystectomy [11, 13]. Oral premedication with 2 g of paracetamol and 200 mg of celecoxib improves the effectiveness of postoperative therapy in ENT procedures under local anaesthesia [14]. The combination of paracetamol and NSAIDs provides better effectiveness of therapy, compared to the use of any of the drugs individually. The meta-analysis comparing the combined effects of paracetamol and NSAIDs (e.g. ibuprofen – 6 studies; diclofenac – 8 studies; ketoprofen – 3 studies; ketorolac – 1 study, tenoxicam – 1 study) demonstrated the benefits of their combined use over each drug given alone [15].

METAMIZOLE

Metamizole is an analgesic and antipyretic drug from the phenylpyrazole group exerting effects on COX-3 yet with additional spasmolytic action by inhibiting the adenosine reuptake. The study on metamizole in multimodal analgesia showed that in minor orthopaedic procedures 3 g administered over 24 postoperative hours relieves the pain and consumption of opioids by 20% [16]. In laparoscopic abdominal surgery, the same intervention reduces the opioid demand by 67% [16].

After mammary procedures, the comparison of repeated doses of metamizole (4 g day⁻¹) with the equivalent dose of paracetamol (4 g day⁻¹) revealed comparable opioid consumption and similar satisfaction of patients [17].

According to the randomized, double blind, placebo-controlled study carried out in 196 patients, the efficacy of adjuvants during postoperative pain management was similar for paracetamol (1g every 6 h), metamizole (1g every 6 h) and parecoxib (40 mg every 12 h) compared to placebo. Importantly, the authors failed to demonstrate reduced consumption of opioids or alleviated adverse side effects, irrespective of the drug used [18].

The combination of metamizole and tramadol is readily used and effective; its analgesic effect is synergistic or additive depending on the proportions of doses applied [19]. The combined use of both drugs reduced opioid demands [20]. Metamizole is commonly used and available in many countries; yet no randomised, placebo-controlled studies assessing its spasmolytic component in abdominal surgeries are available and therefore clinical trials should be continued.

AGONISTS OF ADRENERGIC RECEPTORS

The activation α -2 receptors is an element of the CNS internal control; their marked density is found in the gelatinous substance of the spinal posterior horns. The activation of α -2 receptors in CNS leads to alleviation of pain sensations.

DEXMEDETOMIDINE

Dexmedetomidine is the drug selectively stimulating α -2 adrenergic receptors, which provides analgesic, sedative and anti-anxiety effects. The impact of higher doses on peripheral α -1 receptors can cause hypotension and bradycardia. The study conducted in the group of patients undergoing bariatric procedures under general anaesthesia demonstrated that patients receiving intraoperatively dexmedetomidine, 0.2, 0.4 or 0.8 μ kg⁻¹ h⁻¹, had lower fentanyl demands during the postoperative period, less frequent episodes of nausea and vomiting as compared to the placebo group [21].

The randomised study assessing the effects of i.v. morphine-dexmedetomidine combination used for hysterectomy revealed lower opioid requirements during the first 24 postoperative hours. The consumption of morphine administered in the form of patient-controlled analgesia (PCA) was 33 mg once used alone and 23 mg when combined with dexmedetomidine. The therapy-related bradycardia and hypotension were observed, yet their severity was low [22].

CLONIDINE

The intravenous administration of clonidine limits its side effects, which include bradycardia, hypotension or sedation; the subarachnoid or epidural route is preferred. Clonidine (1 μ g kg⁻¹) combined with subarachnoid morphine (4 μ g kg⁻¹) during prostatectomy under general anaesthesia reduced the intraoperative consumption of sufentanil. The postoperative observations also demonstrated lower pain scores and lower PCA morphine use in the group of patients receiving morphine (18 mg) and clonidine, compared to patients receiving only morphine (25 mg) or those without subarachnoid anaesthesia (66 mg). The

percentages of adverse side effects were comparable in each of these three groups [23].

NMDA RECEPTOR ANTAGONISTS

The discovery of N-methyl-D-aspartate (NMDA) receptors and their relationship with pain transmission and central sensitisation drew attention to therapeutic possibilities using non-competitive NMDA receptor antagonists, mainly ketamine to counteract hyperalgesia.

KETAMINE

Ketamine used for general anaesthesia for many years is the drug of recognised analgesic potential. The safety margin between minimal analgesic doses and high doses inducing adverse side effects is crucial. High doses of the drug are responsible for psychotomimetic effects (sedation, cognitive disturbances, hallucinations, nightmares). On the other hand, low, sub-anaesthetic doses of ketamine provide effective analgesia without the above-mentioned CNS adverse effects, do not affect the respiratory or cardiovascular system, and do not cause nausea, vomiting or postoperative paralytic ileus and constipation.

The perioperative use of ketamine (intraoperative loading dose of $0.5 \mu\text{g kg}^{-1}$ followed by intravenous infusions of $2 \mu\text{g kg}^{-1} \text{min}^{-1}$ continued after the procedure) enables to reduce the dose of morphine (27 mg) in the postoperative period, as compared to the management protocol in which ketamine is only used for postoperative analgesia (48 mg) or abandoned (50 mg) [24].

In the study, which did not prove the reduced opioid consumption after ketamine, the drug saturating dose was $0.5 \mu\text{g kg}^{-1}$ during surgery and only $0.2 \mu\text{g kg}^{-1} \text{min}^{-1}$ of it was given after its completion. The ketamine use only during surgery limits its positive impact enhancing the opioid effects. The key to success appears to be related to its dose and time of administration, i.e. up to 48 h after surgery [25]. The meta-analysis undertaken revealed that the combination of ketamine with morphine (PCA) reduced the opioid consumption, improved the analgesic effect and decreased the percentage of opioid-related postoperative reductions in saturation [26].

MAGNESIUM

The discovery of magnesium effects blocking the NMDA channels provided new possibilities for its use in pain management. However, due to its poor permeability through the blood-brain barrier the mechanisms of magnesium effects on NMDA receptors are not easy to be determined. The magnesium sulphate at a dose of 50 mg kg^{-1} , followed by its infusion, $15 \text{ mg kg}^{-1} \text{min}^{-1}$, in patients undergoing hysterectomy reduces the opioid demands within 48 postoperative hours, decreases the pain scores and limits the episodes of nausea and vomiting [27].

GLUCOCORTICOSTEROIDS

Corticosteroids have been recognised for cancer pain management; they show anti-oedematous and anti-inflammatory effects. Their adjuvant action can also

result from direct blockage of electrical stimuli within the nervous fibres damaged during surgery or trauma. The use of corticosteroids as co-analgesics for acute pain treatment, including the postoperative pain, have been well documented [28].

DEXAMETHASONE

Dexamethasone (8 mg) administered in a bolus 90 min before laparoscopic cholecystectomy reduces the percentage of nausea and vomiting episodes and decreases the pain intensity after surgery. Additionally, it reduces the visceral pain experienced during the first postoperative week compared to placebo [29]. Another relevant observation is lack of effects of i.v. dexamethasone dose of 4 mg on postoperative wound infections [30].

ANTIPILEPTIC DRUGS

Many investigations focusing on the pathomechanism of acute and chronic pain carried out during the last decade emphasise that acute pain is likely to convert into neuropathic pain, especially after surgical procedures. This phenomenon can be associated with central sensitization of nociceptive neurons within the posterior horns of the spinal cord. Pregabalin and gabapentin bind the subunit $\alpha_2\delta$ of the voltage-gated calcium channel in the spinal cord and brain.

The role of anti-epileptic drugs in the treatment of neuropathic pain has been well established for many years. However, their use for chronic neuropathic pain after surgical procedures is still widely analysed in terms of their effectiveness and safe doses, which is of great importance in this group of drugs.

GABAPENTIN

Gabapentin as an element of multimodal analgesia was evaluated in various studies concerning postoperative pain. The findings document its potential to reduce morphine demands in the immediate postoperative period after lower gastrointestinal and spinal surgeries yet do not show lower incidence rates of adverse side effects caused by opioids. Gabapentin appears to be an effective adjuvant in the therapy of children and young patients after spinal surgeries [31, 32].

PREGABALIN

Pregabalin is used to treat seizures and neuropathic pain. Compared to gabapentin, its advantage is bigger bioavailability and linear pharmacokinetics. The meta-analysis based on the reports published in the years 1966-2010 demonstrates that the severity of postoperative pain does not decrease after gabapentin. However, the cumulative consumption of opioids is found to be lower and opioid-related adverse effects are limited (vomiting – RR 0.73; 95% CI 0.56-0.95). Otherwise, the incidence of visual disturbances is markedly higher (RR 3.29; 95% CI 1.95-5.57) [33].

It seems that gabapentin and pregabalin are useful for prevention of sensitization of CNS nociceptive neurons, including the posterior horns of the spinal cord, which

intensifies postoperative pain sensations and the conversion of acute pain into neuropathic pain. This phenomenon concerns 10-15% of surgical patients, may last even several months and is often responsible for markedly worsened quality of life of patients [34].

Oral premedication with pregabalin, 300 mg, significantly relieves the resting pain and reduces morphine demands in patients after gynaecological procedures [35]. Used before surgery and then for 14 postoperative days at a dose of 300 mg, pregabalin decreases the percentage of episodes of chronic neuropathic pain after knee replacements [37]. The relevant problems of pregabalin therapy involve confusion and excessive sedation in the postoperative period [38]. The combination of three drugs – pregabalin 150 mg, paracetamol 975 mg and celecoxib 400 mg administered orally reduces the opioid consumption during and after radical prostatectomy [39].

CONCLUSIONS

The methods of multimodal analgesia with several available adjuvants provide patients with many benefits and improve the pain management, especially in one-day surgery settings. The modern approach to analgesic therapy oriented at the use of pharmacological and non-pharmacological methods reducing the severity of pain, is to limit opioid consumption and intensity of opioid-related side effects (nausea and vomiting), to shorten hospitalization and to reduce the treatment costs. Balanced, and multimodal analgesia is the optimal measure for perioperative pain management.

The majority of studies on postoperative pain involves the period of hospital stay without the analysis of the treatment course after discharge. The treatment of acute postoperative pain should be followed up to 2 weeks after surgery. Irrespective of type of surgery, this period can be divided into three stages during which the analgesic therapy is carried out by different individuals. Immediately after surgery (in one-day surgery – 6 h, in hospitalized patients – 24 h), the pain treatment is provided mainly by anaesthesiologists. During the second stage (until discharge), the therapy provided by the surgical team. The third stage after discharge is based on surgeon's orders, GP recommendations, patients' experiences and home first-aid kit stocks. The division of the postoperative period into the above-mentioned stages shows that the complex provision of analgesic management should be based on cooperation of many therapeutic groups, including physicians, nurses and physiotherapists. In each stage, the sets of drugs, their sequence without adjuvants and beneficial combinations of various analgesics can differ markedly. Noteworthy, the concept of multimodal analgesia or use of adjuvants is poorly popularized, except for anaesthetic circles, which results in therapeutic failures leading to conversion of acute postoperative pain in to chronic pain.

Furthermore, greater emphasis should be placed on education of patients and their families, started already during preoperative anaesthetic visits. During such visits, the plan of analgesic treatment and benefits of

multimodal analgesia should be presented by explaining in an accessible way the mechanisms of drug actions and principles of combinations or otherwise of various groups of pharmaceutical agents. Moreover, maximal doses and, more importantly, their side effects should be discussed. Such an approach, although time-consuming, should also concern the teams of pain therapy. Only then, the concept of multimodal analgesia with adjuvants will leave the hospital settings and bring benefits to patients.

REFERENCES:

1. Dolin SJ, Cashman JN, Bland JM: Effectiveness of acute postoperative pain management. Evidence from published data. *Br J Anaesth* 2002; 98: 409-423.
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003; 97: 534-540.
3. Kinstner C, Likar R, Sandner-Kiesling A, Hutschala D, Pipam W, Gustorff B: Quality of postoperative pain therapy in Austria: national survey of all departments of anesthesiology. *Anaesthesist* 2011; 60: 827-34.
4. Schiavenato M, Craig KD: Pain assessment as a social transaction: beyond the "gold standard". *Clin J Pain* 2010; 26: 667-676.
5. Lynch M: Pain as the fifth vital sign. *J Intraven Nurs* 2001; 24: 85-94.
6. Elvir-Lazo OL, White PF: Postoperative pain management after ambulatory surgery: role of multimodal analgesia. *Anesthesiol Clin* 2010; 28: 217-224.
7. Elvir-Lazo OL, White PF: The role of multimodal analgesia in pain management after ambulatory surgery. *Curr Opin Anesthesiol* 2010; 23: 697-703.
8. Dobrogowski J, Przeklasa-Muszyńska A, Woron J, Wordliczek J: Zasady kojarzenia leków w terapii bólu. *Medycyna Paliatywna w Praktyce* 2007; 1: 6-15.
9. Szkutnik-Fiedler D, Szalek E, Grześkowiak E: Zasady leczenia bólu pooperacyjnego. Management of postoperative pain. *Farmacja Współczesna* 2010; 3: 21-29.
10. Wordliczek J, Dobrogowski J: Leczenie bólu. *PZWL*; 2007.
11. Jokela R, Ahonen J, Seitsonen E: The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy. *Clin Pharmacol Ther* 2010; 87:672-678.
12. Pickering G, Faure M, Commun F, de Boissy EC, Roche G i wsp: Tropisetron and paracetamol association in post-operative patients. *Fundam Clin Pharmacol* 2011; 25: 14.
13. Salihoglu Z, Yildirim M, Demiroglu S: Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystectomy. *Surg Laparosc Endosc Percutan Tech* 2009; 19:321-323.
14. Issioui T, Klein KW, White PF, Watcha M, Coloma M, Skrivanek G, Jones S, Thornton K, Marple B: The efficacy of premedication with celecoxib and acetaminophen in preventing pain after otolaryngologic surgery. *Anesth Analg* 2002; 94:1188-1193.
15. Ong CK, Seymour RA, Lirk P, Merry AF: Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review

- of analgesic efficacy for acute postoperative pain. *Anesth Analg* 2010; 110: 1170-1179.
16. Steffen P, Schumacher I, Weichel T: Differential administration of non-opioids in postoperative analgesia, I. Quantification of the analgesic effect of metamizole using patient-controlled analgesia. *Anaesthesiologie Intensivmedizin Notfallmedizin Schmerztherapie* 1996; 31: 143-147.
 17. Kampe S, Warm M, Landwehr S, Dagtekin O, Haussmann S, Paul M, Pilgram B, Kiencke P: Clinical equivalence of iv paracetamol compared to iv dipyron for postoperative analgesia after surgery for breast cancer. *Curr Med Res Opin* 2006; 22: 1949-1954.
 18. Brodner G, Gogarten W, Van Aken H, Hahnenkampk, Wempe C, Freise H, Cosanne I: Efficacy of intravenous paracetamol compared to dipyron and parecoxib for postoperative pain management after minor-to-intermediate surgery: a randomised double-blind trial. *Eur J Anaesthesiol* 2011; 28: 125-132.
 19. Rodríguez-Silverio, J, Arrieta, J, Flores-Murrieta, FJ: Synergistic interaction between tramadol and dipyron in thermal paw stimulation model in the rat. *Drug Dev Res* 2009; 70: 450-454.
 20. Keskinbora, K: Comparison of tramadol and tramadol plus metamizol for postoperative pain following abdominal surgery: 214; *Reg Anesth Pain Med* 2003; 28: 15.
 21. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, Skrivanek G, Macaluso A, Shah M, Provost D: Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. *Anesth Analg* 2008; 106: 1741-1748.
 22. Lin TF, Yeh YC, Lin FS, Wang Y, Lin C, Sun WZ, Fan SZ: Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* 2009; 102: 117-122.
 23. Andrieu G, Roth B, Ousmane L, Castaner M, Petillot P, Vallet B, Villers A, Lebuffe G: The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. *Anesth Analg* 2009; 108: 1954-1957.
 24. Zakine J, Samarcq D, Lorne E, Moubarak M, Montravers P, Beloucif S, Dupont H: Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. *Anesth Analg* 2008; 106: 1856-1861.
 25. Subramaniam K, Akhouri V, Glazer PA, Rachlin J, Kunze L, Cronin M, Desilva D, Asdourian CP, Steinbrook RA: Intra- and postoperative very low dose intravenous ketamine infusion does not increase pain relief after major spine surgery in patients with preoperative narcotic analgesic intake. *Pain Med* 2011; 12: 1276-1283.
 26. Carstensen M, Møller AM: The combination allows a significant reduction in pain score, cumulative morphine consumption, and postoperative desaturation. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. *Br J Anaesth* 2010; 104: 401-406.
 27. Ryu JH, Kang MH, Park KS, Do SH: Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. *Br J Anaesth* 2008; 100: 397-403.
 28. White PF: The changing role of nonopioid analgesic techniques in the management of postoperative pain. *Anesth Analg* 2005; 101: S5-S22.
 29. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J: Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. *Ann Surg* 2003; 238: 651-660.
 30. Coloma M, Duffy LL, White PF: Dexamethasone facilitates discharge after outpatient anorectal surgery. *Anesth Analg* 2001; 92: 85-88.
 31. Gilron I, Orr E, Tu D: A randomized, double-blind, controlled trial of perioperative administration of gabapentin, meloxicam and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 2009; 108: 623-630.
 32. Srivastava U, Kumar A, Saxena S, Mischira AR, Saraswat N, Mishura S: Effect of preoperative gabapentin on postoperative pain and tramadol consumption after minilap open cholecystectomy: a randomized double-blind, placebo-controlled trial. *Eur J Anaesthesiol* 2010; 27: 331-335.
 33. Zhang J, Ho KY, Wang Y: Efficacy of pregabalin in acute postoperative pain: a meta-analysis *Br J Anaesth*. 2011; 106: 454-462.
 34. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; 367: 1618-1625.
 35. Przesmycki K, Wiater-Kozioł E, Kotarski J, Czuczwar M, Jaskowiak R, Ząbek M, Kołacz A, Fijałkowska M, Kotus M: Wpływ premedykacji pregabaliną na intensywność bólu oraz zapotrzebowanie na morfinę po histerektomiach - doniesienie wstępne. *Anestezjol Intens Terap* 2011; 43: 14-17.
 36. Agarwal A, Gautam S, Gupta D, Agrawal S, Singh PK, Singh U: Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. *Br J Anaesth* 2008; 101:700-704.
 37. Buvanendran A, Kroin JS, Della Valle CJ: Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010; 110:199-207.
 38. White PF, Tufanogullari B, Taylor J, Kleink: The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. *Anesth Analg* 2009; 108:1140-1145.
 39. Trabulsi EJ, Patel J, Viscusi ER, Gomella LG, Lallas CD: Preemptive multimodal pain regimen reduces opioid analgesia for patients undergoing robotic-assisted laparoscopic radical prostatectomy. *Urology* 2010; 76: 1122-1124.

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