Rev Bras Anestesiol. 2016;66(5):505–512

REVISTA BRASILEIRA DE ANESTESIOLOGIA
Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

REVIEW ARTICLE

Postoperative persistent chronic pain: what do we know about prevention, risk factors, and treatment☆

Durval Campos Kraychete[a,b,c], **Rioko Kimiko Sakata**[d,*], **Leticia de Oliveira Carvalho Lannes**[e], **Igor Dórea Bandeira**[f,g], **Eduardo Jun Sadatsune**[h]

[a] *Departamento de Anestesiologia e Cirurgia, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil*
[b] *Sociedade Brasileira para o Estudo da Dor, São Paulo, SP, Brazil*
[c] *Ambulatório de Dor, Complexo Universitário Prof. Edgar Santos, Salvador, BA, Brazil*
[d] *Departamento de Anestesiologia, Dor e Terapia Intensiva, Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil*
[e] *Anestesiologia, Complexo Universitário Hospital Edgar Santos, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil*
[f] *Faculdade de Medicina, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil*
[g] *Liga Acadêmica para o Estudo da Dor, Salvador, BA, Brazil*
[h] *Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil*

Received 10 November 2014; accepted 11 December 2014
Available online 20 July 2016

KEYWORDS
Postoperative chronic pain;
Analgesia;
Prevention;
Treatment;
Risk factors

Abstract
Background and objectives: Postoperative persistent chronic pain (POCP) is a serious health problem, disabling, undermining the quality of life of affected patients. Although more studies and research have addressed the possible mechanisms of the evolution from acute pain to chronic postoperatively, there are still no consistent data about the risk factors and prevention. This article aims to bring what is in the panorama of the current literature available.
Content: This review describes the definition, risk factors, and mechanisms of POCD, its prevention and treatment. The main drugs and techniques are exposed comprehensively.
Conclusion: Postoperative persistent chronic pain is a complex and still unclear etiology entity, which interferes heavily in the life of the subject. Neuropathic pain resulting from surgical trauma is still the most common expression of this entity. Techniques to prevent nerve injury are recommended and should be used whenever possible. Despite efforts to understand and select risk patients, the management and prevention of this syndrome remain challenging and inappropriate.

☆ Instituição: Universidade Federal da Bahia, Salvador, BA, Brasil; Universidade Federal de São Paulo, São Paulo, SP, Brasil.
* Corresponding author.
E-mail: riokoks.dcir@epm.br (R.K. Sakata).

http://dx.doi.org/10.1016/j.bjane.2014.12.005

PALAVRAS-CHAVE
Dor crônica pós-operatória;
Analgesia;
Prevenção;
Tratamento;
Fatores de risco

Dor crônica persistente pós-operatória: o que sabemos sobre prevenção, fatores de risco e tratamento?

Resumo
Justificativa e objetivos: A dor crônica persistente pós-operatória (DCPO) constitui um grave problema de saúde, incapacitante, mina a qualidade de vida dos pacientes acometidos. Apesar de mais estudos e pesquisas terem sido desenvolvidos a respeito dos possíveis mecanismos da evolução da dor aguda para dor crônica pós-operatória, ainda não existem dados consistentes a respeito de seus fatores de risco e prevenção. Este artigo se propõe a trazer o que há no panorama da literatura atual disponível.
Conteúdo: Esta revisão descreve a definição, os fatores de risco e os mecanismos da DCPO, sua prevenção e seus tratamentos. Os principais medicamentos e técnicas são expostos de forma compreensiva.
Conclusão: A dor crônica persistente pós-operatória é uma entidade complexa e de etiologia ainda não esclarecida, que interfere intensamente na vida do sujeito. A dor neuropática decorrente do trauma cirúrgico ainda é a expressão mais comum dessa entidade. Técnicas que evitem a lesão de nervos estão recomendadas e devem ser usadas sempre que possível. Apesar dos esforços para entender e selecionar os pacientes de risco, o manuseio e a prevenção dessa síndrome continuam desafiantes e inapropriados.

Introduction

Postoperative chronic pain (POCP) has been the focus of several investigations in recent years, contributing to solve uncertain questions on the subject, such as the possible evolutionary mechanisms of acute pain to POCP. However, there are few consistent data in the literature, so this article aims to draw a picture of the current literature available. Usually, the therapeutic options for the overall improvement of POCP are not yet defined, which facilitates the occurrence of disability and direct interference in the quality of life of affected patients. POCP has been described for a number of diseases of varied duration, mainly characterized by a lack of understanding of the factors that initiated or maintained its development. It is known that such factors involved in this process of chronicity may be biological, psychological, and social.[1]

Definition

Persistent postoperative chronic pain (POCP) is defined as pain lasting for two or more months after surgery, when other causes of pain are excluded, such as cancer or chronic infection.[2]

In the immediate postoperative period, direct activation of nociceptors, inflammation, and possible damage to nerve structures cause pain at rest or incident pain at the surgical site and nearby region. There is pain evoked by touching the wound, motion, breathing, coughing, or gastrointestinal activity. There may also be effective nerve damage, a neuropathic component may develop immediately after surgery and persist in the absence of peripheral nociceptive or inflammatory stimulus. Thereby defining neuropathic pain is essential to develop strategies for persistent chronic pain prevention and treatment. Generally, there are signs of nerve injury, especially after herniorrhaphy, mastectomy, thoracotomy, and mandibular osteotomies.[3] It is important to understand that POCP is initiated by an event and maintained regardless of what caused it. Persistent chronic pain after surgery has been the main factor interfering with the individual's return to daily life activities, which affects his/her capacity and productivity.[1]

Incidence

Although poorly documented in the literature, the incidence of POCP is very variable and occurs after both highly complex operations and minor surgeries. Between 5% and 80% of patients develop chronic pain after surgical procedures, particularly those that cause nerve damage.[4–6] The incidence of POCP is 30–81% after limb amputation, 11.5–47% after thoracotomy and inguinal hernia, 3–56% after cholecystectomy,[4] 10–50% after breast surgery,[7] 15% after vasectomy,[8] 6–18% after cesarean, and 4–10% after normal delivery.[9]

This wide variation in incidence may be associated with different definitions used for POCP in several studies.[10,11] In this study, we consider the definition by Macrae: the pain must develop after surgical procedure, with at least two months duration, and is not related to pre-existing pain and have no other defined etiologies.[12] Other causes for such variability are the evaluation and interpretation of pain syndrome types and the various study designs.[11]

Risk factors

Among the factors that may be linked to postoperative chronic persistent pain are age, sociocultural factors, obesity, genetic load, history of previous surgery, surgical technique used, muscle ischemia, nerve damage, type of analgesia, and presence of preoperative pain.[13–15] Preexisting painful conditions (irritable bowel syndrome, migraine, fibromyalgia, Raynaud's disease, among others) and psychological aspects, such as fear of the procedure, pain expectation, and pain catastrophizing are also associated.[12]

Younger patients undergoing thoracotomy had a higher incidence and severity of pain than older patients, but the pain was more easily controlled.[10] Contrary to what was believed, sex may not have much influence on the development of POCD, with conflicting findings in the literature.[15] By genetic character, the functional polymorphism of catecholamine-O-methyltransferase (COMT) is related to the change and exacerbation of pain sensitivity.[3]

In thoracotomy, posterolateral and subcostal incisions contribute to the occurrence of POCP,[1,16] are more painful than medians, and the use of rib retractors further increase this differentiation due to reduced electrical conduction of adjacent intercostal nerves.[3] In abdominal surgery, transverse and oblique access techniques cause less pain and impaired lung function than the midline approaches, particularly in the first 24 h, although there are no differences in perioperative and postoperative complications and recovery time.[17] The severity of immediate postoperative pain can also increase the occurrence of pain after cholecystectomy or limb/breast phantom pain.[3]

A study evaluating factors associated with postoperative pain in liver donor patients showed that anxiety and number of given analgesics were related to the chronicity of the painful process.[18] Psychosocial vulnerability, depression, stress, hospital stay, and delay to return to daily activities are important risks of psychic origin for persistent postoperative chronic pain.[19]

Mechanisms of persistent postoperative chronic pain

The mechanisms of postoperative chronic pain are complex and not fully understood. Different mechanisms are responsible for different pain syndromes, even in one type of surgery.[11]

The surgical stimulus and tissue trauma that results from incision cause postoperative inflammatory reaction which only terminates with the final healing process; thus, facilitating the process of neuroplasticity and consequent changes in neuronal membrane excitability. Furthermore, there is a possible reduction of the central inhibitory mechanisms and increased excitatory synaptic efficacy.[20,21]

Neuroplasticity can be divided into two interconnected types: peripheral and central. Peripheral neuroplasticity occurs from the release of inflammatory mediators (cytokines, prostaglandins, bradykinin, histamine, serotonin, H+ ions) by damaged tissues or inflammatory cells, with activation of intracellular cascades that culminate in reducing the excitatory threshold and may cause pain perception with a reduced stimulus (allodynia) or increased response to aggressive stimulus (hyperalgesia).[3]

Similarly, in central neuroplasticity there is also increased synaptic efficacy for pain transmission.[3] A peripheral nociceptive stimuli may cause the activation of intracellular pathway of protein kinases in the spinal cord dorsal horn and modify the expression of ion channels and receptor and neurotransmitter density which facilitate nerve hyperexcitability. There is increased activity and density of aminopropanoic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, subsequent production of nitric oxide (NO), activation of protein kinases (PKA and PKC) and other second messengers.[20,22] The NO stimulates the release of prostaglandin E2 and, as transcellular neuromediator, leaves the cell and amplifies the postsynaptic release of aspartate, glutamate, and substance P (SP), and activates even more specific receptors. Thus, the increase of glutamatergic synapses in the dorsal horn of the spinal cord, caused by the initial pain stimulus, reinforces the transmission of new nociceptive stimuli and recruits non-nociceptive stimuli to the pain pathway.[22] At the end of the central sensitization induction chain, the responsiveness of neurons increases and, even those that usually have an ineffective synapse to innocuous stimuli, start to activate the neuronal transmission of pain.[3]

The propagation mechanism of postoperative pain following direct peripheral nerve injury varies widely. The major injury of nerves that are located in the surgical field of most procedures is probably a prerequisite for the development of POCP.[3] In a study of thoracotomy with and without intercostal nerve protection, lower pain score was found in patients who had their intercostal nerve protected after 2–7 days postoperatively. However, this finding was not maintained in the evaluation one month after surgery.[23] In another article, the authors performed an electrophysiological study of patients undergoing thoracotomy and assessed intercostal nerve damage before and three months after the procedure; there was no association between intercostal nerve damage and pain or sensitivity change at the end of follow-up.[2]

Prevention

Early and late post-surgical pain prevention is a major challenge for anesthesiologists and surgeons because POCP treatment is difficult. In an attempt to improve patient management in the perioperative period and predict possible postoperative pain, more studies addressing this issue are being developed every day. It is necessary to educate the medical staff so that effective measures are taken and unnecessary and inappropriate operations are minimized.[13]

Human and experimental animal studies indicate that some of neuroplastic changes (spinal sensitization) after trauma can be prevented through aggressive treatment of acute pain. However, the hypothesis that preventive analgesia can promote clinically significant reduction of

post-operative pain severity or duration remains unanswered. Controlled clinical trial data were not favorable, although there are studies with positive results.

Multimodal analgesia with combined drugs having different mechanisms of action and additive or synergistic effects seems to interfere appropriately with the pain complexity transmission.[1] Drug combination, in addition to contemplate the various inhibitory targets of pain pathophysiology, also promotes significant reductions in adverse effects by decreasing the dosage required. In the case of opioids, there is a 20–40% decrease of unwanted effects, particularly nausea, vomiting, and sedation.[24] Multimodal regimens have focused on the use of opioids, α2-adrenergic agonists, COX antagonists, gabapentin, pregabalin, steroids, NMDA antagonists, and local anesthetics.[25]

POCP prevention must be done not only by the anesthesiologist, but also by the surgical team. Patients undergoing surgical procedures should be aware of the risk of POCP, given its high incidence. Each elective surgery should be evaluated carefully, with assessment of risks and benefits. The staff should know the different surgical techniques to which the patient can be subjected, choosing, when possible, the technique with the lowest risk of developing COPD.

Careful dissection of the surgical field and less invasive techniques can be strategies to prevent pain while avoiding nerve damage and minimizing local inflammatory process.[26] For thoracotomy, preference should be given to the anterolateral approach and less invasive techniques.[3] In abdominal surgery, studies have found that the use of electrocautery may require less use of analgesics in the postoperative period, and that the use of diathermy initiated in periods shorter than the first 24 h after surgery significantly reduced pain.[16] In the specific example of inguinal hernia correction, procedure with a high rate of POCD, surgeons should avoid: (1) indiscriminate division of the subcutaneous tissue; (2) removal of the cremaster muscle fibers; (3) excessive dissection of the ilioinguinal nerve; (4) damaging the neural structures (stretching, bruising, cutting, grinding, cauterization, suturing); (5) overtighten the inguinal ring; (6) suturing the edge of the internal oblique muscle.[15]

A scale to assess the risk probability of developing POCP, including some predictors such as age, sex, preoperative pain, type of surgery, incision size, level of anxiety, among others, was developed and validated in outpatient and hospital patients, showed a good correlation with the development of postoperative acute pain.[27] Because acute postoperative pain is associated with the risk of developing chronic pain, identifying possible risk patients allow more and more preventive measures to be taken throughout the perioperative period in an attempt to block the development of POCP.

Effective prevention of POCP must follow a list of goals:

- Perioperative analgesia
- Surgery with less trauma
- Avoid nerve damage
- Avoid compression of structures
- Improve venous return
- Control diabetes mellitus
- Early mobilization

Anesthetic approaches for persistent postoperative chronic pain prevention

Pharmacological

Antidepressants

The use of antidepressants for treating postoperative chronic pain, particularly in cases of neuropathic pain, is well established in the literature.[28] However, the heterogeneity of this group of drugs and studies performed do not allow conclusions about its role in POCD prevention, although positive results have being reported from its perioperative use.[29] The main argument for its use is to reduce the central sensitization provided by these drugs mechanism of action. Its routine use is not indicated because there is no evidence of benefits that outweigh the possible adverse effects, such as increased perioperative bleeding and serotonin syndrome, among others.[30–32]

Gabapentin

Gabapentin mechanism of action is by reducing the hyperexcitability of spinal dorsal horn neurons induced by acute injury, responsible for central sensitization. This occurs via postsynaptic binding of gabapentin to voltage-gated calcium channel α2-δ subunits in spinal dorsal horn neurons, which reduces the entry of calcium into nerve endings and reduces the release of excitatory neurotransmitters.[33] Furthermore, gabapentin can act on NMDA receptors, sodium channels, monoaminergic pathways, and opioid system.[34–37]

In a multimodal analgesia study, which includes gabapentin and local anesthetic given by various routes to patients undergoing mastectomy, there was less consumption of analgesics, better control of acute pain, and persistent reduction of about 30% in this group, compared to control group. In a second randomized study[38] of patients undergoing thyroidectomy, previous use of gabapentin reduced the incidence of neuropathic pain up to 6 months postoperatively.[39]

In a review, the authors concluded that patients who received gabapentin (300–1800 mg day^{-1}) as a single dose 24 h before surgery, or those receiving it up to 10 days after surgery, required a lower dose of opioid and had lower pain scores postoperatively. Postoperative opioid consumption was lower in the single-dose gabapentin group in 14 of the 17 studies assessed. In the pre- and postoperative treatment group, opioid consumption was lower in seven studies. Late pain assessments were performed in four studies (after 30 days in two and after three months in two) and there was difference only in one of them. The authors concluded that to achieve improved pain symptoms, a single dose of gabapentin 1200 mg preoperatively seems to be sufficient. The use of higher doses and for longer periods increased the incidence of related side effects, such as sedation, dizziness, nausea and vomiting.[40]

Pregabalin

With a mechanism of action similar to gabapentin, but with superior pharmacokinetic effect,[41] pregabalin is an effective drug known for treating various pain syndromes. It has remarkable ability to enhance the analgesic potency of opioids and reduce respiratory depression, in addition to having no deleterious effects on gastrointestinal mucosa and kidney function, as well as being easier to dose.[42]

Ketamine

Ketamine action is quite complex, as its molecule interacts with various types of receptors present in several binding sites—such as GABAergic receptors; opioids; monoaminergics; cholinergics; glutamatergics; and ion, calcium, sodium, and potassium channels.[43] Its main analgesic activity occurs through antagonism in N-methyl-D-aspartate (NMDA) receptor, as it plays an important role in the processing of pain stimuli by prolonging and amplifying the nociceptive responses.[44]

NMDA receptors are inactivated by ketamine through a non-competitive blockade by binding to the phencyclidinic site within the receiver channel, partially coating the magnesium binding site, and changing the channel open time. Ketamine affinity S(+) for this binding site is three to four times higher than that of its R(-) isomer and, hence, its analgesic and anesthetic strength when isolated is twice that of the racemic mixture, explained by the hypothesis that NMDA receptor blockade is this drug's main mechanism of action.[44]

The analgesic properties of ketamine are also expressed by other secondary mechanisms: activation of the descending inhibitory monoaminergic system, which is involved in the modulation of nociceptive processes and is generally activated by systemic opioids; activation of other receptor systems, such as opioid and cholinergic; blockade of sodium channels, in an action similar to that of local anesthetics.[45]

Ketamine can be used to prevent chronic persistent pain with good results by multimodal and balanced analgesic regimens. In a study of patients who underwent colon resection, the use of intravenous ketamine during surgery associated with epidural anesthesia significantly reduced pain levels by up to six months after the procedure.[45]

Clonidine

Clonidine provides analgesia by selective postsynaptic action in α2-agonist receptors of spinal dorsal horn, mimicking the action of norepinephrine. It also interacts with the cholinergic pathways, as intrathecal clonidine increases the concentration of acetylcholine in sheep and humans. There is inhibition of adenylate cyclase and voltage-dependent calcium channels and increased potassium channel opening time. This leads to the release suppression of excitatory neurotransmitters and, consequently, of neuronal excitation in the central nervous system areas associated with pain perception.[46]

An experiment with patients undergoing colon surgery demonstrated that the use of subarachnoid clonidine at a dose of 300 μg reduced the postoperative incidence of chronic pain after six and 12 months of surgery, compared with the use of bupivacaine alone by the same route.[47] One should bear in mind the effects of sedation, hypotension, bradycardia, and prolonged nerve block that can accompany the use of this drug.[48]

Other drugs

Further studies are necessary for the emergence of new drugs with preventive analgesic effects and determination of doses and appropriate duration of treatment required to reduce the central and peripheral sensitization. Several drugs have been studied, such as minocycline that modulates glia and inhibits apoptosis of dorsal root ganglion cells;[49] antagonists of excitatory receptors in glial cells; sodium channel blockers ($Na_v1.7$, $Na_v1.8$, $Na_v1.3$); agents that facilitate potassium channel opening, hyperpolarize the membrane; calcium channel inhibitors; high concentration capsaicin; cannabinoid receptor agonists; among other possibilities.[50]

Another area for clinical research focuses on the development of protocols to identify the variation between individuals in the response to pain to the same surgical stimulus. Genetic testing should enhance the ability of clinicians to differentiate patients who respond with mild or severe pain to the same nociceptive stimuli. Pharmacogenetics can also help identify the genetic polymorphism of receptors for drugs that may influence the need or response to certain analgesics.[51]

Regional anesthesia

Local anesthetics have always been used in regional anesthesia and analgesia. By blocking sodium channels in nerve membranes, these agents interrupt the conduction of nociceptive stimulus from injury site to central nervous system and prevent the onset of its sensitization cascade.[52]

Local infiltration

Local infiltration of skin and subcutaneous tissue before the incision is a simple, safe, and easy to use method, with few adverse events and low risk of toxicity. Its inhibitory effects on local inflammation, together with the blockade of nociceptive fibers, contribute to reduce the neuronal sensitization.[53,54] Although some authors have shown that the administration of local anesthetic before incision reduces consumption and increases the time to request analgesics, others found no differences between those who underwent infiltration at the end of surgery.[55]

A review of inguinal hernia repair showed significant reductions in the scale of the immediate post-operative pain and additional analgesia consumption up to 50% lower in patients undergoing local anesthetic infiltration.[56] In hysterectomy, the use of bupivacaine in the wound allowed lower consumption of analgesics for up to three days after the procedure, although there were no differences between pain measurements in the visual scale.[57] It is also unclear whether this method prevents chronic pain, as most studies assess pain within 24–48 h.

Intra-articular infusion of local anesthetic (arthroplasty and other knee surgeries) can reduce pain, postoperative bleeding, opioid consumption, and allow a more comfortable rehabilitation.[58] Furthermore, in removal of iliac crest bone graft, this technique can avoid the incidence of iliac bone chronic pain in 4-year follow up.[59] It is important to remember that local anesthetic infusion in small joints, such as hands, can cause chondrotoxicity and infection.[60]

Peripheral nerve block

The use of nerve block is associated with improved recovery and reduced rate of hospital readmission of the patient when compared to general anesthesia.[61] A continuous infusion of local anesthetic causes better analgesia reduces the consumption of opioids and adverse effects (nausea, vomiting, sedation, and pruritus). The technical skill and the necessary infrastructure for managing catheters, however, are factors that still hinder the applicability of this method. Although there is no evidence for prevention of chronic pain, continuous peripheral nerve block provides better control of postoperative pain than systemic analgesia,[61] reduces hospital stay with improved recovery and sleep quality.[62–64]

Neuraxial block

Neuraxial blocks can inhibit the response to trauma, prevent peripheral transmission of nociceptive stimuli to central nervous system and, thus, reduce neuronal remodeling and the possibility of developing POCD. There are also other benefits, such as reduced mortality, deep venous thrombosis, pulmonary embolism, respiratory complications, and other morbidities.[65]

The incidence of persistent chronic pain six months after thoracotomy can be reduced about 34% using thoracic epidural analgesia with local anesthetic at the beginning of surgery and postoperative maintenance.[66] In orthopedic surgery, epidural block can minimize the risk of developing regional complex syndrome postoperatively, while some authors suggest that it may also reduce the incidence of phantom pain in amputees.[4] Although theoretically favorable, the findings of current literature on the use of intrathecal and caudal blockades to prevent POCD are inconsistent.[55]

Conclusion

Persistent postoperative chronic pain is a complex entity whose etiology is not fully elucidated, which affects the quality of life of individuals. Neuropathic pain resulting from surgical trauma is still the most common expression of this entity. For its prevention, appropriate perioperative analgesia is essential and techniques that avoid nerve damage are recommended and should be used whenever possible. Despite the efforts of investigators to understand and select patients at risk, the management and prevention of this syndrome are still inappropriate.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin N Am. 2005;23:21–36.
2. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011;377:2215–25.
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618–25.
4. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology. 2000;93:1123–33.
5. Keller SM, Carp NZ, Levy MN, et al. Chronic post thoracotomy pain. J Cardiovasc Surg (Torino). 1994;35 6 Suppl. 1:161–4.
6. Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. Br J Surg. 1999;86:1528–31.
7. Fecho K, Miller NR, Merritt SA, et al. Acute and persistent postoperative pain after breast surgery. Pain Med. 2009;10:708–15.
8. Leslie TA, Illing RO, Cranston DW, et al. The incidence of chronic scrotal pain after vasectomy: a prospective audit. BJU Int. 2007;100:1330–3.
9. Vermelis JM, Wassen MM, Fiddelers AA, et al. Prevalence and predictors of chronic pain after labor and delivery. Curr Opin Anaesthesiol. 2010;23:295–9.
10. Gerbershagen HJ, Ozgür E, Dagtekin O, et al. Preoperative pain as a risk factor for chronic post-surgical pain – six month follow-up after radical prostatectomy. Eur J Pain. 2009;13:1054–61.
11. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101:77–86.
12. Macrae WA. Chronic pain after surgery. Br J Anaesth. 2001;87:88–98.
13. Sakakura N, Usami N, Taniguchi T, et al. Assessment of long-term postoperative pain in open thoracotomy patients: pain reduction by the edge closure technique. Ann Thorac Surg. 2010;89:1064–70.
14. Sommer M, de Rijke JM, van Kleef M, et al. Predictors of acute postoperative pain after elective surgery. Clin J Pain. 2010;26:87–94.
15. Ip HY, Abrishami A, Peng PW, et al. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology. 2009;111:657–77.
16. Inaba T, Okinaga K, Fukushima R, et al. Prospective randomized study of two laparotomy incisions for gastrectomy: midline incision versus transverse incision. Gastric Cancer. 2004;7:167–71.
17. Brown SR, Goodfellow PB. Transverse verses midline incisions for abdominal surgery. Cochrane Database Syst Rev. 2005:CD005199.
18. Lee SH, Lim KC, Jeon MK, et al. Postoperative pain and influencing factors among living liver donors. Transplant Proc. 2012;44:363–5.
19. Niraj G, Rowbotham DJ. Persistent postoperative pain: where are we now? Br J Anaesth. 2011;107:25–9.
20. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10:895–926.
21. Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull. 2004;71:13–27.

22. Burke S, Shorten GD. When pain after surgery doesn't go away. Biochem Soc Trans. 2009;37 Pt 1:318–22.
23. Yan S, Wu N, Xiong HC, et al. Effect of bilateral intercostal nerve protection on post-thoracotomy pain relief: a prospective single-blinded randomized study. Zhonghua Yi Xue Za Zhi. 2008;88:597–601.
24. Hakeem A, Shanmugam V. Inguinodynia following Lichtenstein tension-free hernia repair: a review. World J Gastroenterol. 2011;17:1791–6.
25. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9:723–44.
26. Sadatsune EJ, Leal PC, Clivatti J, et al. Dor crônica pós-operatória: fisiopatologia, fatores de risco e prevenção. Rev Dor. 2011;12:58–63.
27. Janssen KJ, Kalkman CJ, Grobbee DE, et al. The risk of severe postoperative pain: modification and validation of a clinical prediction rule. Anesth Analg. 2008;107:1330–9.
28. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010;150:573–81.
29. Wong K, Phelan R, Kalso E, et al. Antidepressant drugs for prevention of acute and chronic postsurgical pain: early evidence and recommended future directions. Anesthesiology. 2014;121:591–608.
30. Auerbach AD, Vittinghoff E, Maselli J, et al. Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery. JAMA Intern Med. 2013;173:1075–81.
31. Seitz DP, Bell CM, Gill SS, et al. Risk of perioperative blood transfusions and postoperative complications associated with serotonergic antidepressants in older adults undergoing hip fracture surgery. J Clin Psychopharmacol. 2013;33:790–8.
32. Weinrieb RM, Auriacombe M, Lynch KG, et al. Selective serotonin re-uptake inhibitors and the risk of bleeding. Expert Opin Drug Saf. 2005;4:337–44.
33. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6:108–13.
34. Gidal BE. New and emerging treatment options for neuropathic pain. Am J Manag Care. 2006;12 9 Suppl.:S269–78.
35. Taylor CP, Gee NS, Su TZ, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res. 1998;29:233–49.
36. Dahl JB, Mathiesen O, Møiniche S. ''Protective premedication'': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. Acta Anaesthesiol Scand. 2004;48:1130–6.
37. Sills GJ. Not another gabapentin mechanism! Epilepsy Curr. 2005;5:75–7.
38. Fassoulaki A, Triga A, Melemeni A, et al. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anesth Analg. 2005;101:1427–32.
39. Brogly N, Wattier JM, Andrieu G, et al. Gabapentin attenuates late but not early postoperative pain after thyroidectomy with superficial cervical plexus block. Anesth Analg. 2008;107:1720–5.
40. Clivatti J, Sakata RK, Issy AM. Review of the use of gabapentin in the control of postoperative pain. Rev Bras Anestesiol. 2009;59:87–98.
41. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia. 2004;45 Suppl. 6:13–8.
42. Rowbotham DJ. Gabapentin: a new drug for postoperative pain? Br J Anaesth. 2006;96:152–5.
43. Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth. 1996;77:441–4.
44. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol. 2008;182:313–33.
45. De Kock M, Lavand'homme P, Waterloos H. ''Balanced analgesia'' in the perioperative period: is there a place for ketamine? Pain. 2001;92:373–80.
46. Detweiler DJ, Eisenach JC, Tong C, et al. A cholinergic interaction in alpha 2 adrenoceptor-mediated antinociception in sheep. J Pharmacol Exp Ther. 1993;265:536–42.
47. Bonnet F, Buisson VB, Francois Y, et al. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth. 1990;15:211–4.
48. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984–1995). Anesthesiology. 1996;85:655–74.
49. Watkins LR, Maier SF. Glia: a novel drug discovery target for clinical pain. Nat Rev Drug Discov. 2003;2:973–85.
50. Reuben SS. Preventing the development of complex regional pain syndrome after surgery. Anesthesiology. 2004;101:1215–24.
51. Chidambaran V, Ngamprasertwong P, Vinks AA, et al. Pharmacogenetics and anesthetic drugs. Curr Clin Pharmacol. 2012;7:78–101.
52. Yanagidate F, Strichartz GR. Local anesthetics. Handb Exp Pharmacol. 2007:95–127.
53. Sinclair R, Eriksson AS, Gretzer C, et al. Inhibitory effects of amide local anaesthetics on stimulus-induced human leukocyte metabolic activation LTB4 release and IL-1 secretion in vitro. Acta Anaesthesiol Scand. 1993;37:159–65.
54. Goldstein IM, Lind S, Hoffstein S, et al. Influence of local anesthetics upon human polymorphonuclear leukocyte function in vitro. Reduction of lysosomal enzyme release and superoxide anion production. J Exp Med. 1977;146:483–94.
55. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002;96:725–41.
56. Møiniche S, Mikkelsen S, Wetterslev J, et al. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. Br J Anaesth. 1998;81:377–83.
57. Hannibal K, Galatius H, Hansen A, et al. Preoperative wound infiltration with bupivacaine reduces early and late opioid requirement after hysterectomy. Anesth Analg. 1996;83:376–81.
58. Lombardi AV Jr, Berend KR, Mallory TH, et al. Soft tissue and intra-articular injection of bupivacaine, epinephrine, and morphine has a beneficial effect after total knee arthroplasty. Clin Orthop Relat Res. 2004:125–30.
59. Singh K, Phillips FM, Kuo E, et al. A prospective, randomized, double-blind study of the efficacy of postoperative continuous local anesthetic infusion at the iliac crest bone graft site after posterior spinal arthrodesis: a minimum of 4-year follow-up. Spine (Phila Pa 1976). 2007;32:2790–6.
60. Ballieul RJ, Jacobs TF, Herregods S, et al. The peri-operative use of intra-articular local anesthetics: a review. Acta Anaesthesiol Belg. 2009;60:101–8.
61. Shum CF, Lo NN, Yeo SJ, et al. Continuous femoral nerve block in total knee arthroplasty: immediate and two-year outcomes. J Arthroplasty. 2009;24:204–9.
62. Klein SM. Beyond the hospital: continuous peripheral nerve blocks at home. Anesthesiology. 2002;96:1283–5.
63. Klein SM, Pietrobon R, Nielsen KC, et al. Peripheral nerve blockade with long-acting local anesthetics: a survey of the Society for Ambulatory Anesthesia. Anesth Analg. 2002;94:71–6.

64. Klein SM, Evans H, Nielsen KC, et al. Peripheral nerve block techniques for ambulatory surgery. Anesth Analg. 2005;101:1663–76.
65. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000;321:1493.
66. Obata H, Saito S, Fujita N, et al. Epidural block with mepivacaine before surgery reduces long-term post-thoracotomy pain. Can J Anaesth. 1999;46:1127–32.