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Do Postoperative Pain Management Techniques Influence Postoperative Delirium?

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Abstract Postoperative delirium (POD) is a common postoperative complication in older patients and may increase morbidity and mortality. The etiology of POD is multifactorial and suggested to be the result of interactions between patient vulnerability (predisposing factors) and exposure to precipitating factors. Poorly controlled postoperative pain has been identified as a precipitating risk factor for POD. However, effective pain management strategies to reduce incidence of POD are still far from being elucidated. Postoperative pain management techniques in older patients have changed substantially in recent years; for example, peripheral nerve blocks and multimodal analgesia have become common adjunctive techniques. It is unclear; however, whether these pain control management techniques can change the incidence of POD. In this review, we will focus on the English-language literature published last 30 years investigating the association between pain management strategies and incidence of POD. We will review opioid analgesics which are the most commonly used postoperative pain medications for major surgery. In addition, we will highlight pain control techniques including intravenous patient-controlled analgesia, epidural analgesia, peripheral nerve blocks, multimodal analgesia, and structured pain management protocols in multi-component delirium intervention. Furthermore, pain control in cognitively impaired patients will be reviewed.

Keywords Postoperative delirium · Cognitive impairment · Pain management · Peripheral nerve block · Multimodal analgesia · Analgesics

This article is part of the Topical Collection on *Perioperative Delirium*.

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Introduction

Postoperative delirium (POD) is a common complication in older patients, characterized by a disturbance of consciousness with compromised ability to focus, sustain or shift attention, impairment of memory, and disorganized thinking. It occurs over a short period of time after surgery and tends to fluctuate over the course of the day [1]. POD is associated with prolonged hospital stays and other long-term consequences such as increased risk of post-discharge mortality, cognitive decline, and functional dependence [2–4]. In older patients, reported rates of POD vary from 15 to 53 % depending on the patient population, type of surgery, delirium assessment tools, diagnostic criteria, and other factors [5, 6].

The cause of delirium is still uncertain and the pathogenic pathway may vary among different medical scenarios. The development of delirium involves the complex interrelationship between patient vulnerability (predisposing factors) and exposure to precipitating factors such as drugs and surgical insults [7]. In the delirium predictive model developed by Inouye et al., five precipitating factors for delirium in hospitalized patients were identified; use of physical restraints, malnutrition, addition of more than three medication types during the period from 48 to 24 h

before the onset of delirium, use of a bladder catheter, and any iatrogenic event [7].

Benoit et al. reported that lower education, preoperative depression, greater use of preoperative psychoactive medication, and higher amounts of smoking were shown to be risk factors for POD in patients receiving elective abdominal aortic aneurysm surgery [8]. Brouquet et al. investigated the risk factors for POD after major abdominal surgery. They concluded that impaired mobility, ASA physical status of 3–4, and postoperative administration of tramadol were risk factors [9]. Other proposed risk factors for POD in other studies include preoperative administration of beta-blockers, higher age, creatinine >1.3 mg/dl, and history of hypertension and atrial fibrillation [10, 11].

The pathogenesis of POD remains poorly understood. Dominant hypotheses focus on the neurotransmission disruption and unbalanced inflammatory response caused by surgical stress in susceptible individuals [12]. Acetylcholine depletion has long been linked to the development of delirium [13, 14]. High levels of inflammatory biomarkers, C-reactive protein, interleukin (IL)-8, and IL-6 in cerebral spinal fluid were found in patients with delirium [15]. A dysfunctional interaction between the cholinergic and immune systems also may contribute to the pathogenesis of POD [16]. High levels of pain disrupt a normal neurotransmitters network, through stimulating the release of dopamine at the basal ganglion [17]. High intensity of pain is also capable of altering sleep-wake cycle and promoting neuroinflammation [12]. All these consequence might precipitate the development of POD. A number of clinical studies have shown that undertreated postoperative pain is associated with the development of POD [18, 19, 20•, 21, 22]. However, opioids, the most prevalent postoperative analgesics, might contribute to delirium by increasing dopamine levels and decreasing acetylcholine levels [23]. Since few therapeutic options are available, prevention strategies remain important to limit the development of POD.

Postoperative pain management in older patients can be a difficult task because of co-morbidities, concurrent medications, age-related pharmacodynamic and pharmacokinetic changes, or sometimes problems in the assessment of pain and effectiveness of pain management due to difficult communication. Among all the contributing factors associated with POD, postoperative pain and analgesic regimen are potentially modifiable. In addition, postoperative pain management techniques in older patients have changed substantially in recent years. Therefore, it is timely to assess the influence of different postoperative pain management regimens and techniques on the incidence of POD. In this review, we will focus on the English-language literature published last 30 years investigating the association of pain management strategies and POD after non-cardiac surgery.

Opioids

Although delirium can sometimes be a side effects of opioids, especially in older patients, opioid analgesics remain the most often used drugs for postoperative analgesia after major surgery. In older subjects, a reduced dose of opioids is usually recommended because of changes in pharmacodynamics and pharmacokinetics. After single intravenous (IV) injection of morphine, there is a 50 % reduction of apparent volume of distribution at steady state, and reduction of plasma clearance compared with young subjects [24]. For acute pain management, drug titration, especially IV opioid titration is encouraged to relieve acute postoperative pain because it quickly meets the needs of individual patients and limits the risk of overdose [25]. Among opioids analgesics, meperidine is known to be significantly associated with POD, if administered within 24 h of a delirious episode or at any time during postoperative days 1–3 for nondelirious subjects in both younger and older patients [26–28]. The anticholinergic property of its metabolite, normeperidine, might contribute to the deliriogenic effect of meperidine [29]. Some literature suggests that tramadol and oxycodone are responsible for cognitive changes [9, 30–32]. In contrast, a case-controlled study of total joint arthroplasty patients showed that the use of hydromorphone and morphine decreased the risk of delirium, but other opioid pain medications including tramadol and oxycodone did not affect the risk of delirium [33••]. According to the available data, which opioid analgesics increase the risk of POD, except for meperidine, is not conclusive.

Intravenous Patient-Controlled Analgesia (IV-PCA)

Theoretically, IV-PCA allows patients to self-administer small doses of opioids, allowing better doses of titration, reducing serum opioid level fluctuation. IV-PCA is an improved method of postoperative analgesia compared with as-needed intramuscular injections [34]. In addition, when using IV-PCA in the ward, the elderly required less opioid than young patients to achieve pain relief and satisfaction [34]. In the study by Keita et al., both the patient-controlled and subcutaneous injection of morphine did not affect cognitive function in older patients with normal preoperative mental status undergoing total hip arthroplasty (TPA) [35]. Leung et al. reported that oral opioid analgesics as the sole means of postoperative pain control is associated with a lower risk of developing delirium in comparison to IV-PCA [19].

IV-PCA is a sophisticated pain management tool; however, for those frail elderly or cognitively impaired patients, IV-PCA should be used with caution by

monitoring pain relief and opioid side effects. And also, the use of background infusion of morphine is generally not recommended in the older patients [36].

Epidural Analgesia

Epidural analgesia using a combination of local anesthetics with a low dose of opioid is widely used for postoperative analgesia for major non-cardiac surgeries, especially upper abdominal and thoracic surgeries. It offers the advantages of better pain relief and attenuation of surgical stress than parenteral opioid therapy [37–39]. Patient-controlled epidural analgesia (PCEA) allows each patient to self-administer medications to titrate to his/her comfort with or without background infusion. To date, only a few studies have compared epidural or PCEA with systemic opioid-based analgesia with respect to delirium. Eriksson-Mjoberg et al. found significantly better pain relief in patients receiving an epidural but with no concurrent improvement in the profile of delirium [40]. Williams-Russo et al. conducted a prospective randomized controlled trial to compare IV fentanyl with epidural fentanyl and bupivacaine in 51 patients undergoing total knee arthroplasty (TKA) [41]. In this report, pain scores were not significantly different between the two groups. Using "The Diagnostic and Statistical Manual for Mental Disorders" (DSM) criteria, the overall incidence of delirium was 41 %, with no significant difference between the epidural (38 %) and IV (44 %) groups. Mann et al. compared the effectiveness of pain control and safety of PCEA using a mixture of bupivacaine and sufentanil with those of IV-PCA using morphine after major abdominal surgery in patients older than 70 years old [42]. Abbreviated mental test (AMT) and criteria from DSM III were used to assess delirium. PCEA did not reduce the incidence of POD but improve the recovery of mental status assessed by AMT. Intrathecal morphine has been suggested to improve pain relief within the first postoperative day and reduce the overall morphine consumption compared with IV-PCA morphine alone. Nonetheless, it did not reduce the episodes of POD diagnosed with "The Confusion Assessment Method" (CAM) [43]. Therefore, despite better pain relief, there is still a lack of evidence to support that epidural analgesia is capable of decreasing the incidence of POD compared with IV-PCA. Further comprehensive clinical trials comparing epidural and IV analgesia are necessary.

Peripheral Nerve Block

Peripheral nerve blocks are a rapidly evolving area in anesthesia practice, especially after the introduction of nerve stimulator and/or ultrasound guidance. Peripheral nerve blocks may benefit postoperative cognitive function by providing superior analgesia, a reduced opioid requirement and lower opioid-related side effects. In a prospective nested cohort study on patients over 65 years of age who underwent unilateral TKA, continuous femoral nerve block combined with or without IV-PCA was shown to reduce the incidence of POD compared with IV-PCA only [44•] . The analgesic efficacy of each individual nerve block might contribute to the efficacy against delirium. The prevalence of delirium ranges between 5 and 61 % in older patients with hip fractures [21, 45, 46]. In a systemic review comparing the efficacy of different peripheral nerve blockades in hip fracture patients on POD, 3 in 1 block, fascia iliaca, and lumbar-sacral plexus blockade were compared. Among these, fascia iliac block was identified as the most effective block technique that had a statistically significant association with reduction in POD [47]. Mouzopoulos et al. conducted a randomized placebo-controlled study to assess the effectiveness of fascia iliaca block for prevention of perioperative delirium in hip fracture patients. They reported that fascia iliaca block was effective in preventing delirium in patients with intermediate risk for delirium [48]. In a prospective randomized controlled trial, patients undergoing TPA were randomized into three postoperative treatment groups: continuous lumbar plexus block with IV-PCA, continuous femoral block with IV-PCA, and IV-PCA alone. The use of IV-PCA with hydromorphone alone led to significantly more frequent serious delirium and/or confusion (defined as a complete loss of orientation to time and space) (10.7 %). Incidence of delirium was reduced dramatically when IV-PCA was combined with either a continuous lumbar plexus (0 %) or femoral nerve block (1.3 %) [49]. According to results from both clinical trials and systemic review, peripheral nerve blockade is effective in reducing POD [50]. More clinical trials to compare single-shot and continuous forms of each individual block with respect to delirium are needed.

Multimodal Analgesia

Multimodal analgesia is a technique combining different analgesics acting through different mechanisms or at different sites which have the additive or synergistic effects to achieve sufficient analgesia [51]. Multimodal analgesia has been proposed as a way to decrease opioid consumption and thus opioid-related adverse events [52].

Medications or techniques which may be beneficial alone or in combination in multimodal analgesia for postoperative acute pain include Nonsteroidal Anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors,

the N-methyl-D-aspartate antagonists, gabapentin, and local anesthetic injection through different routes, such as nerve block or surgical site infiltration [53–55]. Multimodal opioid-sparing analgesia together with a fast-track standard protocol driven therapy was associated with a lack of POD after elective THA and TKA in 220 cognitively intact patients older than 60 years [56••]. However, this study lacks a control comparison group. In contrast, two other cohort studies which utilized multimodal pain management strategies using a combination of tramadol plus acetaminophen [57] or morphine and acetaminophen [58] did not change the incidence of POD compared with standard care.

Gabapentin was first introduced as an adjuvant anticonvulsant drug and subsequently shown to be effective for treatment of chronic pain. More recently, it has been extended into management of postoperative pain [55]. The effect of gabapentin on the incidence of POD is still under debate. Leung et al. investigated the effect of gabapentin on reducing the incidence of postoperative delirium in 21 patients having spinal surgery, who were randomized to receive either gabapentin in the dose of 900 mg started 1–2 h before surgery and continued for the first 3 postoperative days or placebo as an add-on to PCA hydromorphone [59]. POD detected with CAM occurred in 5/12 patients (42 %) who received placebo versus 0/9 patients who received gabapentin ($P = 0.045$). In contrary, in a double-blind randomized placebo-controlled trial and its post hoc analysis in patients underwent TKA, patients received gapapentin 600 mg or placebo before surgery. In addition, placebo or gabapentin 200 mg tid was given for 4 days after surgery. There was no difference in the incidence or duration of POD between the placebo and gabapentin groups [60]. Larger studies in higher risk patients are still needed to clarify the role of gabapentin in POD.

Ketamine has been in use as an anesthetic agent for more than 50 years. Using higher doses of ketamine has become less popular owing to its side effects including hallucinations and the emergence of delirium [61, 62]. Recent evidence suggest that the perioperative subanaesthetic doses of ketamine have the beneficial effect of reducing rescue analgesic requirements and pain intensity with mild or absent adverse effects [63]. Administration of low-dose ketamine (0.5 mg/kg) on induction of anesthesia significantly reduced POD within 5 days and postoperative cognitive dysfunction 1 week after major cardiac surgery [64, 65]. Nonetheless, despite the anti-inflammatory action of ketamine which renders it to be a possible preventive drug for delirium [66] as an adjuvant of postoperative pain management, ketamine has not been shown to have cognitive benefit in non-cardiac surgical patients. As one of the medications in multimodal analgesia, small doses of ketamine combined with IV-PCA morphine resulted in less favorable cognitive outcomes (as measured by trail-making test B) compared with IV-PCA morphine only in patients after major abdominal surgeries [67]. It is still unclear whether ketamine is associated with incidence of POD as a multimodal postoperative analgesic.

Structured Pain Management Protocol in Multicomponent Delirium Intervention

Because the etiology of delirium is multifactorial, multicomponent intervention that combines both pharmacological and non-pharmacological strategies represent the most effective and clinically relevant way of prophylaxis [68, 69]. A systemic review showed that multifactorial intervention was effective in preventing delirium (pooled RR = 0.71, 95 % CI 0.58–0.86, $P = 0.000$) [70]. Postoperative multimodal aggressive pain control management is a key element in multi-component therapy. In addition, a prospective, randomized, blinded study suggested that proactive geriatrics consultation reduced delirium by over one-third, and reduced severe delirium by over one-half [71]. In this study, the pain control strategy included around-the-clock acetaminophen, early stage breakthrough pain treatment with low dose subcutaneous morphine and late-stage breakthrough pain treatment with oxycodone as needed In an optimized hip fracture program which deceased the incidence of delirium (9.2 % in intervention group vs. 2.8 % in conventional group, $P = 0.006$), pain treatment consisted of continuous femoral nerve block with bupivacaine, and supplementary pain treatment with acetaminophen or tablet ibuprofen [72]. Although multi-component therapies comprising structured protocol driven pain control have showed promising results, we were not able to confirm the prophylactic effect of delirium on any pain management protocols.

Pain Control and Delirium in Cognitively Impaired Patients

Most of the clinical trials on POD excluded patients with preoperative cognitive impairment in whom delirium is most likely to occur and hardest to detect. However, these patients are particularly at risk because their pain is not well assessed and, therefore, often undertreated. Unrelieved pain is a risk factor for the development or aggravated delirium. Effective pain management requires accurate assessment and appropriate interventions. In older persons receiving hip fracture surgery, patients with cognitive decline or with delirium received only 53 and 34 %, respectively, of the amount of morphine equianalgesic dose that was administered to

cognitively intact patients [73]. In contrast, a study examining the older surgical cohort showed that although the patients with POD received larger doses of postoperative opioid analgesics, they still suffered from high intensity of pain [74]. All of these results suggest suboptimal pain management in this patient population. Inappropriate pain assessment and management in the preoperative cognitively impaired patients might contribute to their high risk of delirium. Adequate assessment of pain levels in cognitively impaired older patients requires the use of specific tools. The "Verbal Rating Scale" (VRS) appears to be a useful pain measurement tool in older patients with cognitive impairment (MMSE <17) compared with "The Visual Analogue Scale" (VAS), the Red Wedge Scale (RWS), or the faces pain scale (FPS). Elderly cognitively impaired patients may prefer the VRS because it is easy to understand and they are more comfortable with using words than numbers to rate pain [75, 76]. Although there are a certain number of studies on the appropriate pain assessment instrument in this population, few studies examining the most effective pain management protocol against POD in patients with cognitive impairment. The adoption of a suitable pain assessment instrument and standardized multimodal protocol for pain control may help improve the ability of clinicians to make better therapeutic decisions.

Conclusions

Heterogeneity in delirium assessment instruments and the small size of available studies precluded direct conclusions as to what type of pain management strategies are likely to prevent POD. Limited data suggest successful multimodal analgesia strategies that minimize the use of opioids postoperatively have a beneficial effect on POD especially when a peripheral nerve blockade is included. Concern for side effects of opioids should not prevent the use of opioid analgesic therapy sufficient to achieve an optimal acute pain control and accepted level of comfort in older patients.

Compliance with Ethics Guidelines

Conflict of Interest Xiaoguang Zhang and Sakura Kinjo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. O'Keeffe ST, Ni Chonchubhair A. Postoperative delirium in the elderly. Br J Anaesth. 1994;73(5):673–87.
2. Witlox J, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304(4):443–51.
3. Inouye SK, et al. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med. 1998;13(4):234–42.
4. Bellelli G, et al. Duration of postoperative delirium is an independent predictor of 6-month mortality in older adults after hip fracture. J Am Geriatr Soc. 2014;62(7):1335–40.
5. Zywiel MG, et al. The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. Clin Orthop Relat Res. 2014;472(5):1453–66.
6. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354(11):1157–65.
7. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996;275(11):852–7.
8. Benoit AG, et al. Risk factors and prevalence of perioperative cognitive dysfunction in abdominal aneurysm patients. J Vasc Surg. 2005;42(5):884–90.
9. Brouquet A, et al. Impaired mobility, ASA status and administration of tramadol are risk factors for postoperative delirium in patients aged 75 years or more after major abdominal surgery. Ann Surg. 2010;251(4):759–65.
10. Katznelson R, et al. Delirium following vascular surgery: increased incidence with preoperative beta-blocker administration. Can J Anaesth. 2009;56(11):793–801.
11. Miyazaki S, et al. Risk factors of stroke and delirium after off-pump coronary artery bypass surgery. Interact CardioVasc Thorac Surg. 2011;12(3):379–83.
12. McDaniel M, Brudney C. Postoperative delirium: etiology and management. Curr Opin Crit Care. 2012;18(4):372–6.
13. Roche V. Southwestern internal medicine conference. Etiology and management of delirium. Am J Med Sci. 2003;325(1):20–30.
14. Han L, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med. 2001;161(8):1099–105.
15. MacLullich AM, et al. Cerebrospinal fluid interleukin-8 levels are higher in people with hip fracture with perioperative delirium than in controls. J Am Geriatr Soc. 2011;59(6):1151–3.
16. Cerejeira J, et al. The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc. 2012;60(4):669–75.
17. Wood PB, et al. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci. 2007;25(12):3576–82.
18. Lynch EP, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg. 1998;86(4):781–5.
19. Vaurio LE, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006;102(4):1267–73.
20. • Nie H, et al. Pain and cognitive dysfunction are the risk factors of delirium in elderly hip fracture Chinese patients. Arch Gerontol Geriatr. 2012;54(2):e172–4. *Pain intensity and preoperative cognitve dysfunction are the risk factors of postoperative delirium in elderly Chinese hip fracture patients.*
21. Morrison RS, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003;58(1):76–81.
22. Morrison RS, et al. The impact of post-operative pain on outcomes following hip fracture. Pain. 2003;103(3):303–11.

23. Robertson BD, Robertson TJ. Postoperative delirium after hip fracture. J Bone Joint Surg Am. 2006;88(9):2060–8.
24. Owen JA, et al. Age-related morphine kinetics. Clin Pharmacol Ther. 1983;34(3):364–8.
25. Aubrun F, Mazoit JX, Riou B. Postoperative intravenous morphine titration. Br J Anaesth. 2012;108(2):193–201.
26. Adunsky A, et al. Meperidine analgesia and delirium in aged hip fracture patients. Arch Gerontol Geriatr. 2002;35(3):253–9.
27. Eisendrath SJ, et al. Meperidine-induced delirium. Am J Psychiatry. 1987;144(8):1062–5.
28. Marcantonio ER, et al. The relationship of postoperative delirium with psychoactive medications. JAMA. 1994;272(19):1518–22.
29. Stone PA, Macintyre PE, Jarvis DA. Norpethidine toxicity and patient controlled analgesia. Br J Anaesth. 1993;71(5):738–40.
30. Agrawal A, Diwan SK, Mahajan R. Severe delirium following single dose of tramadol. Indian J Med Sci. 2009;63(2):80–1.
31. Crane JH, Suda KJ. Oxycodone induced delirium and agitation in an elderly patient following total right knee arthroplasty. Int J Clin Pharm. 2011;33(5):733–6.
32. Kunig G, et al. Unrecognised long-lasting tramadol-induced delirium in two elderly patients. A case report. Pharmacopsychiatry. 2006;39(5):194–9.
33. •• Nandi S, et al. Pharmacologic risk factors for post-operative delirium in total joint arthroplasty patients: a case-control study. J Arthroplasty 2014;29(2):268–71. *The use of hydromorphone and morphine decreases the risk of delirium and other opiate pain medications including tramadol and oxycodone do not affect the delirium risk in total joint arthroplasty patients.*
34. Egbert AM, et al. Randomized trial of postoperative patient-controlled analgesia versus intramuscular narcotics in frail elderly men. Arch Intern Med. 1990;150(9):1897–903.
35. Keita H, et al. Comparison between patient-controlled analgesia and subcutaneous morphine in elderly patients after total hip replacement. Br J Anaesth. 2003;90(1):53–7.
36. Aubrun F, Marmion F. The elderly patient and postoperative pain treatment. Best Pract Res Clin Anaesthesiol. 2007;21(1):109–27.
37. Block BM, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290(18):2455–63.
38. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology. 1995;82(6):1474–506.
39. Flisberg P, et al. Pain relief and safety after major surgery. A prospective study of epidural and intravenous analgesia in 2696 patients. Acta Anaesthesiol Scand. 2003;47(4):457–65.
40. Eriksson-Mjoberg M, et al. Extradural morphine gives better pain relief than patient-controlled i.v. morphine after hysterectomy. Br J Anaesth. 1997;78(1):10–6.
41. Williams-Russo P, et al. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc. 1992;40(8):759–67.
42. Mann C, et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. Anesthesiology. 2000;92(2):433–41.
43. Beaussier M, et al. Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. Reg Anesth Pain Med. 2006;31(6):531–8.
44. • Kinjo S, et al. Does using a femoral nerve block for total knee replacement decrease postoperative delirium? BMC Anesthesiol. 2012;12:4. *Continous femoral nerve block reduces the incidence of postoperative delirium compared with IV PCA.*
45. Marcantonio ER, et al. Delirium is independently associated with poor functional recovery after hip fracture. J Am Geriatr Soc. 2000;48(6):618–24.
46. Duppils GS, Wikblad K. Cognitive function and health-related quality of life after delirium in connection with hip surgery. A six-month follow-up. Orthop Nurs. 2004;23(3):195–203.
47. Rashiq S, et al. Efficacy of supplemental peripheral nerve blockade for hip fracture surgery: multiple treatment comparison. Can J Anaesth. 2013;60(3):230–43.
48. Mouzopoulos G, et al. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. J Orthop Traumatol. 2009;10(3):127–33.
49. Marino J, et al. Continuous lumbar plexus block for postoperative pain control after total hip arthroplasty. A randomized controlled trial. J Bone Joint Surg Am. 2009;91(1):29–37.
50. Abou-Setta AM, et al. Comparative effectiveness of pain management interventions for hip fracture: a systematic review. Ann Intern Med. 2011;155(4):234–45.
51. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: what do they really mean? Plast Reconstr Surg. 2014;134(4 Suppl 2):85S–93S.
52. Halaszynski TM. Pain management in the elderly and cognitively impaired patient: the role of regional anesthesia and analgesia. Curr Opin Anaesthesiol. 2009;22(5):594–9.
53. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol. 2009;22(5):588–93.
54. Costantini R, et al. Controlling pain in the post-operative setting. Int J Clin Pharmacol Ther. 2011;49(2):116–27.
55. Kong VK, Irwin MG. Gabapentin: a multimodal perioperative drug? Br J Anaesth. 2007;99(6):775–86.
56. •• Krenk, L, et al. Delirium after fast-track hip and knee arthroplasty. Br J Anaesth. 2012;108(4):607–11. *A fast-track set-up with standardized multimodal opioid-sparing pain management decreases the incidence of postoperative delirium to zero in elderly patients undergoing elective total hip arthroplasty and total knee arthroplasty.*
57. Milisen K, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc. 2001;49(5):523–32.
58. Ogilvie-Harris DJ, Botsford DJ, Hawker RW. Elderly patients with hip fractures: improved outcome with the use of care maps with high-quality medical and nursing protocols. J Orthop Trauma. 1993;7(5):428–37.
59. Leung JM, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology. 2006;67(7):1251–3.
60. Dighe K, et al. Perioperative gabapentin and delirium following total knee arthroplasty: a post hoc analysis of a double-blind randomized placebo-controlled trial. Can J Anaesth. 2014. doi:10.1007/s12630-014-0235-5.
61. Fine J, Finestone SC. Sensory disturbances following ketamine anesthesia: recurrent hallucinations. Anesth Analg. 1973;52(3):428–30.
62. Lilburn JK, et al. Ketamine sequelae. Evaluation of the ability of various premedicants to attenuate its psychic actions. Anaesthesia. 1978;33(4):307–11.
63. Bell RF, et al. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603. doi:10.1002/14651858.CD004603.pub2.
64. Hudetz JA, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2009;23(5):651–7.
65. Hudetz JA, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand. 2009;53(7):864–72.
66. Bartoc C, et al. A randomized, double-blind, placebo-controlled study assessing the anti-inflammatory effects of ketamine in cardiac surgical patients. J Cardiothorac Vasc Anesth. 2006;20(2):217–22.
67. Reeves M, et al. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. Anesth Analg. 2001;93(1):116–20.

68. Patel J, et al. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia. 2014;69(6):540–9.
69. Pitkala KH, et al. Multicomponent geriatric intervention for elderly inpatients with delirium: effects on costs and health-related quality of life. J Gerontol A Biol Sci Med Sci. 2008;63(1):56–61.
70. Zhang H, et al. Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. Crit Care. 2013;17(2):R47.
71. Marcantonio ER, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc. 2001;49(5):516–22.
72. Pedersen SJ, et al. A comprehensive hip fracture program reduces complication rates and mortality. J Am Geriatr Soc. 2008;56(10):1831–8.
73. Adunsky A, et al. Exposure to opioid analgesia in cognitively impaired and delirious elderly hip fracture patients. Arch Gerontol Geriatr. 2002;35(3):245–51.
74. Leung JM, et al. Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? Am J Geriatr Psychiatry. 2013;21(10):946–56.
75. Pesonen A, et al. Evaluation of easily applicable pain measurement tools for the assessment of pain in demented patients. Acta Anaesthesiol Scand. 2009;53(5):657–64.
76. Clark ME, Gironda RJ, Young RW. Development and validation of the pain outcomes Questionnaire-VA. J Rehabil Res Dev. 2003;40(5):381–95.