



Anesthesia for Orthopedic Surgery in the Elderly: Facts to Think About

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The number of older patients undergoing sophisticated orthopedic procedures is steadily growing. The progress made in anesthesiology permits operating on more and more older and sicker patients. The concept of early and efficient rehabilitation is a new and widely accepted necessity for improving the success in orthopedics. Pain, central nervous dysfunction and fatigue are conditions which may hinder this concept. All measures to avoid their appearance should be undertaken. The control of postoperative pain and surgical stress seems to be essential in this clinical context. Despite lack of data, the application of a continuous regional analgesia (epidural, spinal, peripheral blockade) seems promising to improve surgical outcome and health-related quality of life and should be applied whenever possible.

Key words: Orthopedic surgery - Elderly - Regional Anesthesia

DISTINCTIVE FEATURES OF ORTHOPEDIC PATIENTS AND COMPLICATIONS

The attitude and expectations of the orthopedic patient are often different from most other surgical patients. With the exception of patients with massive trauma - most often young and healthy patients - the orthopedic patient, usually older, seldom has a life-threatening disease process. The goals in aged orthopedic patients are to reduce discomfort, increase mobility and improve function. They are frequently familiar with hospitals, surgery and pain. Some distinctive features related to orthopedics deserve to be mentioned.

Osteoarthritis

Osteoarthritis, the most common of the rheumatologic diseases, is the presenting disease process for the majority of some 100,000 total hip replacements and a nearly equal number of total knee replacements in the United States each year¹. General ageing of the population exposes an increasing number of people to osteoarthritis and fractures among other orthopedic disorders.

Rheumatoid arthritis

Although less common than osteoarthritis, rheumatoid

arthritis affects approximately 1% of adults in the United States, with an estimated 100/200 new cases each year. The disease affects women two to three times more often than men and increases in incidence with age². One has to be aware that instability of C1-C2 can occur asymptotically^{3,4}. Difficult airway and peri- and postoperative bleeding can be expected.

Hip fractures

Patients with fractures of the proximal femur and pelvis are among those with musculoskeletal disorders who most frequently require anesthesia. It is estimated that 1 in 50 patients over 60 years of age has suffered a fractured hip and that 80% of patients with hip fracture are more than 60 years old⁵. Any serious correctable disease should be treated as expeditiously as possible, since immobilisation, for even a short period of time, exponentially increases the incidence of pulmonary complications. Postoperative confusion is a well-recognised problem in the geriatric patient after such an operation. The incidence may reach up to 28-50%^{6,7}.

Fat embolism

Post-traumatic embolisation of fat has been a source of controversy, since first described in 1961. To date there is no agreement on its frequency, etiology and pathogenesis. However, fat embolism is not uncommon after pelvic and long bone fractures. Prosthesis implantation syndrome is a risk whenever for example a femoral prosthesis is inserted⁸. Surgical precautions, such as avoidance of excessive cement pressurisation, the use of low viscosity cement, cautious high-pressurised canal lavage and the use of a venting hole, are effective techniques to minimise in-

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tramedullary canal pressure^{9,10}.

Air embolism

Venous air embolism is a known complication during anesthesia for hip replacements, laparoscopies and operative procedures in which the operative site is above the level of the heart. Recently, such a complication during anesthesia for shoulder arthroscopy in a beach chair position has been reported¹¹. Patients at risk should be well hydrated - older patients are often dehydrated - and surgical hemostasis is essential at all times.

WHICH ANESTHETIC TECHNIQUE?

The concepts of modern orthopedics have rapidly evolved since Salter et al.^{12,13} demonstrated the beneficial effects of continuous passive motion, amongst which is the regeneration of chondroblasts. The beneficial effects of continuous passive motion are listed below:

- stimulating effect on healing of articular tissue;
- prevents adhesions and joint stiffness;
- does not interfere with healing of the incision over the moving joint;
- simulates regeneration of articular cartilage through neochondrogenesis.

These observations have led to the concept of early and efficient rehabilitation. To meet these requirements, the following conditions have to be fulfilled in the postoperative period:

- patient should be co-operative (no deep sedation);
- patient should be pain-free;
- fatigue should be minimised;
- muscular catabolic breakdown should be reduced as much as possible.

GENERAL VERSUS REGIONAL ANESTHESIA

The surgical stress response is characterised by activation of the sympathetic system and the segmental responses, resulting in an increase in catabolic hormones, and a reduction in anabolic hormones and hypermetabolism^{14,15}. Negative consequences of surgical stress are pain, increased fatigue and prolonged recovery from surgical interventions, intestinal paralysis¹⁶, decreased splanchnic perfusion¹⁷, and immunosuppression¹⁸. Generally, geriatric patients have a decreased functional reserve of organ systems and thus become increasingly intolerant to surgical stress, which explains the higher incidence of perioperative complications and death^{19,20}.

A central neuraxial blockade reduces surgical stress by

blocking nociceptive afferent input signals from the traumatised site and prevents sympathetic as well as segmental efferent nerve activity. The application of regional anesthesia in elderly patients has been recommended. If we look at specific end-points, regional anesthesia has shown many advantages over general anesthesia. The term regional anesthesia in this section includes epidural and spinal procedures. Spinal is considered here in order to obviate the problem of technical difficulties, which may occur in older patients, due to anatomical deformities that could make the placement of a catheter more hazardous.

The increase of catabolically acting hormones, which result in hypermetabolism and release of substrates from peripheral stores, is a classic postoperative occurrence. Thus, postoperative endocrine metabolic responses, such as hypercortisolemia, hyperglycemia, altered insulin resistance and accelerated protein turnover and breakdown^{21,22}, may have severe deleterious consequences in older patients. Brandt et al.²³ observed that the mean cumulative 5 day nitrogen losses were significantly lower after either lumbar epidural or general anesthesia in patients undergoing hysterectomy. Carli et al.²⁴ report on the protein-sparing effects of thoracic epidural analgesia with local anesthetics in patients scheduled for colorectal surgery. Kapral et al.²⁵ observed that epidural anesthesia preserves splanchnic perfusion and metabolism in patients undergoing major abdominal surgery, and these observations have also been supported by experimental findings²⁶. A recent investigation²⁷ showed that epidural blockade alternated the hyperglycemic response to surgery through modifications of glucose production. This study confirms those reported after hip surgery, performed with intrathecal neuraxial blockade²⁸.

Modifications in post-operative immune function represent the body's general physiological response and are mainly dependent on the extent and duration of surgery, patient's age, health status, as well as other factors^{29,30}. It has been demonstrated that volatile and intravenous anesthetics contribute to the postoperative immunosuppression³¹. Thus, it is mandatory to use the least deleterious anesthetic technique on the immune system in the older population, whose immunity is naturally compromised. Epidural anesthesia was shown to attenuate the postoperative decrease of natural killer cells³², to improve the postoperatively impaired natural cell killer activity compared to general anesthesia³³ and to prevent, to a minor degree, alterations in lymphocyte subsets³⁴.

Postoperative pain is a major concern after orthopedic limb surgery. Moderate to severe at rest, it is exacerbated during movement and, particularly after hip and knee

surgery, by severe muscular spasms³⁵. This not only causes the patient discomfort, but also compromises early postoperative physical rehabilitation and ambulation³⁶. Patient-controlled analgesia with intravenous morphine has long been considered the “gold standard” in pain relief after major surgery³⁷. However, numerous studies have shown the superiority of the regional techniques to control postoperative pain³⁸⁻⁴¹. Mann et al.⁴¹ compared the efficacy of epidural to intravenous patient-controlled analgesia in the elderly after major abdominal surgery. The results showed that the epidural technique not only provides better pain relief and bowel activity, but also improves mental status.

Finally fatigue is a major drawback for early rehabilitation. Fatigue is proportional to the intensity of the stress induced by surgery⁴². Factors influencing postoperative fatigue include endocrine and inflammatory response, restricted mobilisation, impaired nutritional intake and pain⁴³, conditions susceptible to be better managed by the application of regional techniques for peri- and postoperative pain control. Carli et al.⁴⁴ compared the effects of epidural analgesia to intravenous patient-controlled opioid analgesia on well-defined functional outcomes after colonic surgery. It was shown that the superior quality of pain relief provided by epidural analgesia had a positive impact on out-of-bed mobilisation, bowel function and intake of food, with long-lasting effects on exercise capacity and health-related quality of life. Evidence would suggest application of regional anesthesia in elderly patients undergoing orthopedic surgery. However, available data remain controversial. On the other hand, a recent meta-analysis of all randomised trials with or without intraoperative neuraxial blockade⁴⁵ showed a reduction in mortality rates of approximately 30% in patients allocated to regional techniques. Other benefits of neuraxial blockade were a lower incidence of deep vein thrombosis, pulmonary embolism, and respiratory complications. Another study demonstrated on patients undergoing coronary artery bypass grafting⁴⁶, a decreased incidence of postoperative myocardial ischemia when thoracic epidural anesthesia was added to general anesthesia. In patients undergoing surgery for fractured hip, Juelsgaard et al.⁴⁷ demonstrated that the incidence of hypotension and myocardial ischemia was lowest in the group receiving incremental spinal anesthesia, compared to single-dose spinal or general anesthesia. On the other hand, several studies on elderly patients undergoing hip fracture repair failed to reveal advantages of regional anesthesia compared to general anesthesia^{48,49}. Urwin et al.⁵⁰ demonstrated a reduced 1-month mortality and incidence of deep vein thrombosis in the regional group in this clinical context. Bode et al.⁵¹

investigated the cardiac outcome in patients undergoing peripheral vascular surgery with either general anesthesia, spinal or epidural anesthesia. The incidence of myocardial ischemia or cardiac failure was similar in the three groups. It would be too early to draw any definite conclusions from these studies. Several of them are retrospective, the outcome was not precisely defined, age was rarely a primary end-point, a continuous regional analgesia technique was not always provided. The latter seems in this context promising, since it has been consistently demonstrated that patient-controlled analgesia through a perineural catheter provides better pain control, lower incidence of side-effects and higher patient satisfaction during the first 2-3 postoperative days⁵²⁻⁵⁵.

Moreover, it has been shown that the surgical outcome in terms of rehabilitation is positively influenced by regional continuous analgesia^{56,57}. Unfortunately, data showing the specific outcome of regional anesthesia and analgesia in elderly patients undergoing orthopedic surgery are lacking. In this clinical context the real question is how much local anaesthetic do we need, and for how long postoperatively?

CENTRAL NERVOUS SYSTEM DYSFUNCTION

Central nervous system dysfunction (delirium, acute state of confusion) is a postoperative complication associated with increased mortality, more frequent complications, and prolonged hospital stay^{58,59}. This complication is common after major surgery in the elderly^{60,61}. Its occurrence would delay the beginning of the rehabilitation and could jeopardise surgical outcome.

Many factors have been implicated as possible causes. A large study⁶² has identified increasing age and duration of anesthesia, low education, a second operation, postoperative infection and respiratory complications, as risk factors for early postoperative cognitive dysfunction, but only age as a risk factor for late postoperative cognitive dysfunction. Hypoxemia and hypotension were not identified as risk factors at any time. Benzodiazepine application may be associated with cognitive dysfunction as well as sudden weaning⁶². Anticholinergic medication has also been associated with postoperative confusion⁶³. A significant higher incidence of mental complications after elective hip replacement surgery was found in patients anesthetised with thiopental-fentanyl-nitrous oxide than in patients operated on under epidural anesthesia/analgesia⁶⁴. On the other hand, the cognitive function was not different between the groups receiving either spinal or general anesthesia for transurethral prostatectomy in elderly men,

but postoperative analgesic regimen was similar in the two groups⁶⁵. Berggren et al.⁶⁶ observed no difference in the incidence of confusion in elderly patients undergoing repair of femoral neck fractures under halothane or epidural anesthesia. However, in the latter the epidural catheter was removed at the end of the surgical procedure! Lynch et al.⁶⁷ were able to demonstrate that higher pain scores at rest were associated with an increased risk of delirium over the first 3 postoperative days in patients older than 50 years. Pain with movement and maximal pain were not associated with delirium. The authors concluded in stressing the importance of a more effective control of postoperative pain. A recent investigation⁶⁸ identified an abnormal serum sodium and ASA physical status >II as risk factor for postoperative confusion in patients admitted for hip fracture repair.

OPIOID AND OTHER ANALGESICS

The composition of the body changes with ageing and can modify drug pharmacokinetics. The lean body mass and water content decreases in the elderly while the fat content increases⁶⁹. Ageing also changes the protein concentrations, albumin blood levels decrease, while those of alpha-1-acid glycoprotein⁷⁰ increases. Opioids, morphine in particular, are the mainstays of the treatment of postoperative pain. However, in addition to their beneficial pain-relieving effects, opioids are associated with collateral effects which can hamper early and efficient postoperative rehabilitation. Opioids are weak blockers of A-delta fibres, which are linked to pain during movement⁷¹. Sedation and alteration in sensorium are common occurrences⁷², which can negatively interfere with active rehabilitation. Opioids possess a number of adverse effects in the gastrointestinal tract which delay enteral feeding and lessen absorption^{73,74}. These effects have a negative impact on early rehabilitation.

REFERENCES

1. Mankin HJ, Brandt KD & Shulman LE. Workshop on etiopathogenesis of osteoarthritis. *J Rheumatol* 1986; 13:1127.
2. Harris ED Jr. Rheumatoid arthritis: Pathophysiology and implications of therapy. *N Engl J Med* 1990;322: 1277-1289.
3. Mathews JA. Atlanto-axial subluxation in rheumatoid arthritis: A 5-year follow-up study. *Ann Rheum Dis* 1974;33:526-631.
4. Crellin RQ, Maccabe JJ & Hamilton EB. Severe subluxation of the cervical spine in rheumatoid arthritis. *J Bone Joint Surg* 1970;52:244-251.
5. Sisk DT. Fractures of hip and pelvis. In Crenshaw AH (ed) *Campbell's Operative Orthopaedics*. St. Louis: CV Mosby, 1987, pp1719-1781.
6. Edlund A, Lundstrom M, Lundstrom G. Clinical profile of delirium in patients treated for femoral neck fractures. *Dementia and Geriatric Cognitive Disorders* 1999;10:325-329.
7. Marcantonio ER, Flacker JM, Wright RJ. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001;49:516-522.
8. Fallon KM, Fuller JG & Morley-Forster P. Fat embolization and fatal cardiac arrest during hip arthroplasty with methylmethacrylate. *Canadian Journal of Anesthesia* 2001;48:626-629.
9. Patterson BM, Healey JH, Cornell CN & Sharrock NE. Cardiac arrest during hip arthroplasty with a cemented long-stem component. A report of seven cases. *J Bone Joint Surg* 1991;73:271-277.
10. Byrick RJ, Bell RS, Kay JC. High-volume, high-pressure pulsatile lavage during cemented arthroplasty. *J Bone Joint Surg* 1989;71:1331-1336.
11. Hegde RT & Avatgere RN. Air embolism during anaesthesia for shoulder arthroscopy. *Br J Anaesth* 2000;85:926-927.
12. Salter RB, Simmonds DF, Malcolm BW. The biological effect of continuous passive motion on the healing of full-thickness defects in articular cartilage. An experimental investigation in the rabbit. *J Bone Joint Surg* 1980;62:1232-1251.
13. Salter RB. History of rest and motion and the scientific basis for early continuous passive motion. *Hand Clinics* 1996;12:1-11.
14. Riles TS, Fisher FS, Schaefer S. Plasma catecholamine concentrations during abdominal aortic aneurysm surgery: the link to perioperative myocardial ischemia. *Ann Vascular Surg* 1993;7:213-219.
15. Weissman C. The metabolic response to stress; an overview and update. *Anesthesiology* 1990;73:308-327.
16. Steinbrook RA. Epidural anesthesia and gastrointestinal motility. *Anesth Analg* 1998;86:837-844.
17. Boldt J, Papsdorf M, Piper S. Influence of dexmedetomidine hydrochloride on haemodynamics and regulators of circulation in patients undergoing major abdominal surgery. *Acta Anaesth Scand* 1998;42:941-947.
18. Ogawa K, Hirai M, Katsube T. Suppression of cellular immunity by surgical stress. *Surgery* 2000;127:329-336.

19. Hall WJ. Update in geriatrics. *Ann Inter Med* 1997; 127:557-564.
20. Auroy Y, Laxenaire MC, Clergue F. Anesthésies selon les caractéristiques des patients, des établissements et de la procédure associée. *Ann Françaises d'Anesthésie-Réanimation* 1998;17:1311-1316.
21. Carli F, Webster J, Ramachandra V. Aspects of protein metabolism after elective surgery in patients receiving constant nutritional support. *Clin Sci* 1990;78:621-628.
22. Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In Cousins MJ & Bridenbough PO (eds) *Neural Blockade in Clinical Anesthesia and Management of Pain*, pp129-175. Philadelphia, PA: Lippincott-Raven 1998.
23. Brandt MR, Fernandes A, Mordhorst R & Kehlet H. Epidural analgesia improves postoperative nitrogen balance. *Br Med J* 1978;1:1106-1108.
24. Carli F, Webster J, Pearson M. Protein metabolism after abdominal surgery: effect of 24-h extradural block with local anaesthetic. *Br J Anaesth* 1991;67: 729-734.
25. Kapral S, Gollmann G, Bachmann D. The effects of thoracic epidural anesthesia on intraoperative visceral perfusion and metabolism. *Anesth Analg* 1999;88: 402-406.
26. Sielenkamper AW, Eicker K, Van Aken H. Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats. *Anesthesiology* 2000;93:844-851.
27. Lattermann R, Carli F, Wykes L & Schricker T. Epidural blockade modifies perioperative glucose production without affecting protein catabolism. *Anesthesiology* 2002;97:374-381.
28. Halter JB, Pflug AE. Effect of sympathetic blockade by spinal anesthesia on pancreatic islet function in man. *Am J Physiol* 1980;239:150-155.
29. Abraham E. Physiologic stress and cellular ischemia: relationship to immunosuppression and susceptibility to sepsis. *Crit Care Med* 1991;19:613-618.
30. Kurz A, Sessler DI & Lenhardt R. Perioperative normothermia to reduce the incidence of surgical wound infection and shorten hospitalization. Study of wound infection and temperature group. *New Engl J Med* 1996;334:1209-1215.
31. Salo M & Nissila M. Cell-mediated and humoral immune responses to total hip replacement under spinal or general anaesthesia. *Acta Anaesth Scand* 1990; 34:241-248.
32. Tonnesen E & Wahlgren C. Influence of extradural and general anaesthesia on natural killer cell activity and lymphocyte subpopulations in patients undergoing hysterectomy. *Br J Anaesth* 1988;60:500-507.
33. Koltun WA, Bloomer MM, Tilberg AF. Awake epidural anesthesia is associated with improved natural killer cell cytotoxicity and a reduced stress response. *Am J Surg* 1996;171:68-72.
34. Hashimoto T, Hashimoto S, Hori Y. Epidural anaesthesia blocks changes in peripheral lymphocytes subpopulation during gastrectomy for stomach cancer. *Acta Anaesth Scand* 1995;39:294-298.
35. Bonica JJ. Postoperative pain. In Bonica JJ (ed) *The Management of Pain*. 2nd edn, Philadelphia: Lea & Febiger, 1990, pp461-480.
36. Ryu J., Saito S, Yamamoto K & Sano S. Factors influencing the postoperative range of motion in total knee arthroplasty. *Bull Hosp Joint Dis* 1993;53:35-40.
37. Egbert AM, Parks LH, Short LM & Burnett ML. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. *Arch Intern Med* 1990;150:897-1903.
38. Shir Y, Raja SN & Frank SM. The effect of epidural versus general anesthesia on postoperative pain and analgesic requirements in patients undergoing radical prostatectomy. *Anesthesiology* 1994;80:49-56.
39. Rundshagen I, Kochs E, Standl T. Subarachnoid and intravenous PCA versus bolus administration for postoperative pain relief in orthopaedic patients. *Acta Anaesth Scand* 1998;42:1215-1221.
40. Wulf H, Biscopin J, Beland B. Ropivacaine epidural anesthesia and analgesia versus general anesthesia and intravenous patient-controlled analgesia with morphine in the perioperative management of hip replacement. *Anesth Analg* 1999;89:111-116.
41. Mann C, Pouzeratte Y, Boccara G. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000;92:433-441.
42. Watters JM, Clancey SM, Moulton SB. Impaired recovery of strength in older patients after abdominal surgery. *Ann Surg* 1993;218:380-393.
43. Christensen T & Kehlet H. Postoperative fatigue. *World J Surg* 1993;17:220-225.
44. Carli F, Mayo N, Klubien K. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery. *Anesthesiology* 2002;97:540-549.
45. Rodgers A, Walker N, Schug S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia; results from overview of randomised trials. *Br Med J* 2000;16:1493.

46. Loick HM, Schmidt C, Van Aken H. High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympathicolysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. *Anesth Analg* 1999;88:701-709.
47. Juelsgaard P, Sand NP, Felsby S. Perioperative myocardial ischaemia in patients undergoing surgery for fractured hip randomized to incremental spinal, single-dose spinal or general anaesthesia. *Eur J Anaesth* 1998; 15:656-633.
48. O'Hara DA, Duff A, Berlin JA. The effect of anesthetic technique on postoperative outcomes of hip fracture repair. *Anesthesiology* 2000;92:947-957.
49. Gilbert TB, Hawkes WG, Hebel JR. Spinal anesthesia versus general anesthesia for hip fracture repair: a longitudinal observation of 741 elderly patients during 2-year follow-up. *Am J Orthopedics* 2000;29:25-35.
50. Urwin SC, Parker MJ & Griffiths R. General versus regional anaesthesia for hip-fracture surgery: Meta-analysis of randomized trials. *Br J Anaesth* 2000;84: 450-455.
51. Bode RH Jr, Lewis KP, Zarich SW. Cardiac outcome after peripheral vascular surgery. Comparison of general and regional anesthesia. *Anesthesiology* 1996;84: 3-13.
52. Borgeat A, Sch?ppi B, Biasca N & Gerber C. Patient-controlled analgesia after major shoulder surgery. *Anesthesiology* 1997;87:1343-1347.
53. Borgeat A, Tewes E, Biasca N & Gerber C. Patient-controlled interscalene analgesia with ropivacaine after major shoulder surgery PCIA vs PCA. *Br J Anaesth* 1998;81:603-605.
54. Singelyn F, Seguy S & Gouverneur JM. Interscalene brachial plexus analgesia after open shoulder surgery; continuous versus patient-controlled infusion. *Anesth Analg* 1999;89:1216-1220.
55. Borgeat A, Perschak H, Bird P. Patient-controlled interscalene analgesia with ropivacaine 0.2% versus patient-controlled intravenous analgesia after major shoulder surgery: effects on diaphragmatic and respiratory function. *Anesthesiology* 2000;92:102-108.
56. Capdevila X, Barthelet Y, Biboulet P. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999;91:8-15.
57. Singelyn FJ, Deyaert M, Joris D. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg* 1998;87:88-92.
58. Marcantonio ER, Goldman L, Mangione CM. A clinical prediction rule for delirium after elective noncardiac surgery. *J Am Med Assoc* 1994;27:134-139.
59. Francis J, Martin D & Kappor WN. A prospective study of delirium in hospitalized elderly. *J Am Med Assoc* 1990;263:1097-1101.
60. Gustafson Y, Berggren D, Br?nnstr?m B. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc* 1988;36:525-530.
61. O'Keeffe ST & Ni Chonchubhair A. Postoperative delirium in the elderly. *Br J Anaesth* 1994;73:673-687.
62. Moller JT, Cluitmans P, Rasmussen LS. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet* 1998;351:857-861.
63. Tune LE, Damlovji NF, Holland A. Association of postoperative delirium with raised serum levels of anticholinergic drugs. *Lancet* 1981;26:651-653.
64. Hole A, Terjesen T & Breivik H. Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. *Acta Anaesth Scand* 1980;24:279-287.
65. Haan J, van Kleef J, Bloem BR. Cognitive function after spinal or general anesthesia for transurethral prostatectomy in elderly men. *J Am Geriatr Soc*, 1991; 39:596-600.
66. Berggren D, Gustafson Y, Eriksson B. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesth Analg* 1987;66:497-504.
67. Lynch EP, Lazor MA, Gellis JE. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* 1998;86:781-785.
68. Zakriya KJ, Christmas C, Wenz JF. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. *Anesth Analg* 2002;94:1628-1632.
69. Novak LP. Aging, total body potassium, fat-free mass, and cell mass in males and females between ages 18 and 85 years. *J Gerontol* 1972;72:438-443.
70. Abernethy DR, Kerzner L. Age effects on alpha-1-acid glycoprotein concentration and imipramine plasma protein binding. *J Am Geriatr Soc* 1984;32:705-708.
71. Pirec V, Laurito CE, Lu Y & Yeomans DC. The combined effects of N-type calcium channel blockers and morphine on A δ versus C fiber mediated nociception. *Anesth Analg* 2001;92:239-243.
72. Benedetti C. Acute Pain: A review of its effects and therapy with systemic opioids. In Benedetti C, Chapman CR & Giron G (eds) *Opioid Analgesia: Recent Ad-*

- vances in Systemic Administration. New York: Raven Press, 1990, pp367-424.
73. Jaffe JH & Martin WR. Opioid analgesics and antagonists. In Gilman AG, Goodman LS & Rall TW (eds) The Pharmacological Basis of Therapeutics. 7th edn, New York: Macmillan, 1985, pp491-531.
74. Aitkenhead AR. Analgesia and sedation in intensive care. Br J Anaesth 1989;63:196-206.

