"OVERVIEW"

Pain Relief Following Cardiac Surgery: A Review

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Introduction

Significant improvements in postoperative pain management have taken place over the last two decades. The contrasting personal experiences of two doctors demonstrates the altered outlook for patients undergoing cardiac surgery. In 1976 Ian Donald, a doctor who underwent heart valve replacement, reported that the pain following cardiac surgery "defies description"[1], while the opinion of a medical colleague following recent cardiac surgery was that this pain "has been conquered".

Improvements in pain control have taken place alongside substantial changes in the practice of cardiac surgery, anaesthesia, cardiology and critical care medicine[2-4]. Invasive cardiology and studies showing benefit from surgery in patients with advanced cardiac and systemic disease has led to a change in patient profile. Candidates for cardiac surgery now tend to be older, with advanced disease, and an increasing proportion require repeat operations or emergency procedures[5-11]. Those with chronic heart failure may have altered drug metabolism caused by hepatic congestion and renal impairment. Postoperative analgesia must therefore be tailored to the individual needs of each patient.

Effect of Pain

Pain is almost inevitable after surgery, and the degree of pain experienced depends to a great extent on the size and site of the operative incision, thoracic wounds being the most severe[12]. Good pain relief is one of the principal goals of postoperative care, and every effort is made to ensure that patients are comfortable in the postoperative period. While pain relief is important in relieving the patient's distress, it also helps to prevent haemodynamic upset.

Severe pain can cause significant increases in heart rate and blood pressure because of its stimulant effect on the sympathetic nervous system. This may have serious consequences for patients with cardiac disease, who are especially vulnerable in the immediate postoperative period. Tachycardia and hypertension adversely affect the balance between myocardial oxygen supply and demand and so may precipitate arrhythmias, acute ischaemia and heart failure.

Pain impairs the ability to cough and causes splinting of the diaphragm, which may result in atelectasis and pneumonia. Pain also reduces mobility, predisposing to deep venous thrombosis and its sequelae[13]. Pain control in the acute phase may prevent the development of chronic pain syndromes[14].

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Causes of Pain

There are many possible sources of pain following cardiac surgery. Wound pain is inevitable, and in addition to the sternotomy incision there may be an extensive leg wound following vein harvesting. Additional sources of pain and discomfort include mediastinal and pleural drains, tracheal tubes and urethral catheters. Physiotherapy, movement, and tracheal toilet (i.e. suctioning of secretions) add to the patient's distress. Acute pain from the incisions has usually become tolerable after the third day, but complications may arise leading to further pain. These include wound infection, haematoma formation, sternal dehiscence, pleural effusion, pneumonia and myocardial infarction (MI). Bacterial mediastinitis and pericarditis are occasional sources of severe pain, and patients who have sustained a recent MI may develop Dressler's syndrome. Retraction of the chest wall intraoperatively can cause trauma to the thoracic cage, leading to the development of costochondritis, musculoskeletal or myofascial pain postoperatively[14].

The Role of Sedation

Pain control must be optimised before sedative agents are used. Sedative agents should relieve anxiety without causing adverse haemodynamic or respiratory effects. Insufficient sedation leads to restlessness, agitation, tachycardia and hypertension, while oversedation is associated with hypotension, reduced respiratory effort, hypercarbia and gastric hypomotility. Oversedation may also mask intercurrent illness and prolong time spent in ICU[13].

Mechanical ventilation is usually required for several hours after cardiac surgery until patients are haemodynamically stable, normothermic, and the effects of depressant drugs have diminished. Patients are usually hypothermic in the immediate postoperative period having been cooled to circa 28°C during cardiopulmonary bypass (CPB). Severe shivering can double the body's oxygen requirement, placing an unacceptable demand on the post-CPB myocardium. Shivering may also interfere with haemodynamic monitoring[15-17]. Control of shivering may necessitate mechanical ventilatory support, and even on occasion muscle relaxation. Appropriate sedation is therefore indicated during this phase.

Haemodynamic instability is common in the early postoperative period since myocardial function and

peripheral vascular resistance are altered after cardiac surgery. Metabolic acidosis is a feature of this situation. Controlled ventilation helps prevent the development of hypoxia and hypercapnia which could further compromise myocardial function. In addition, if large doses of opioids are used as part of the anaesthetic technique, respiratory depression is likely and ventilatory support may be necessary.

Methods of Pain-Relief

Anaesthesia

Most anaesthetic techniques used for cardiac surgery provide an analgesic effect into the postoperative period. High-dose opioid anaesthesia is popular for cardiac surgery because it produces minimal haemodynamic upset. This technique is asssociated with profound analgesia and sedation postoperatively. Techniques which include spinal opioids or local anaesthetics also provide residual analgesia[2-4]. While the anaesthetic technique influences the level of sedation and analgesia in the immediate postoperative period, requirements for analgesia have also been shown to be affected by surgical and psychological factors[14].

Intravenous Analgesia and Sedation

Opioids

This group of drugs is the mainstay of early postoperative pain control in the ICU, and their beneficial effects include analgesia, sedation and euphoria[13,17,18] Opioids promote greater tolerance of tracheal intubation by suppression of tracheolaryngeal irritability. Serious adverse effects include respiratory depression, and nausea and vomiting. Hypotension may occur when high doses are used (due to histamine release), and also in conjunction with cardiovascular depressant drugs. Patients with cardiac disease are particularly susceptible. The duration of action of opioids is prolonged in the elderly, and in patients with hepatic and renal impairment[19,20].

Morphine is the gold standard and has been used extensively following cardiac surgery. It has a potent analgesic effect, with some sedation, and onset is rapid after intravenous (IV) administration. Pethidine is less potent and less popular than morphine. However it has certain useful properties: histamine release is less common than with morphine, so pethidine is a good alternative in patients prone to bronchospasm. Pethidine can also be used to control shivering[16] (in a dose of 0.25-0.5mg/kg).

Newer man-made opioids including fentanyl, sufentanil and alfentanil, are highly-lipophilic drugs with greater potency, more rapid onset and shorter duration of action than morphine. These drugs are expensive, and because of their short durations of action are administered by infusion. Their principal advantage is a sympatholytic effect resulting in decreased heart rate, and suppression of catecholamine release. They do not release histamine and have no vasodilatory effects. The elimination of both fentanyl and alfentanil is delayed after CPB, which may lead to prolonged respiratory depression post-operatively[19,21].

Benzodiazepines

The benzodiazepines have anxiolytic, sedative, and amnesic as well as anti-convulsant effects. They reduce analgesic requirements by potentiation of opioids. While effects on the cardiovascular system are minimal when used as the sole agent in healthy patients, the benzodiazepines may cause hypotension in those with cardiac disease. Respiratory depression may also occur, particularly with concomitant opioid administration, although they are generally safe when carefully titrated to effect.

Midazolam has become the reference drug for ICU sedation. It is more potent than diazepam, and being water soluble is non-irritant. Onset of action is rapid, duration of action and elimination half life are short, and there is little accumulation. Midazolam is readily administered by infusion. There is great individual variation in response to midazolam and emergence depends on many factors including age, dose given, duration of infusion, and liver and renal function. Elimination may be prolonged in critically ill patients, the elderly, and after major surgery[19,22,23]. Tolerance develops with prolonged administration.

Benzodiazepine-opioid combination

A combination of IV opioids and benzodiazepines is generally used in the initial postoperative phase. This combination of agents provides analgesia and amnesia, with a reduction in the dose requirement of each drug and therefore potentially fewer side effects, less accumulation, and a lower risk of tolerance developing. Respiratory depression is a possibility when large doses are given, but mild hypercarbia is now accepted as an accompaniment of good analgesia[24].

The standard method of drug administration is by intermittent IV bolus which is simple, effective and inexpensive. Staffing on a one nurse per patient basis and the use of preloaded syringes allows the immediate administration of opioid or benzodiazepine as needed. Morphine is given in boluses of 2.5-5mg, and midazolam in doses of 1-2.5mg. Continuous infusion has recently become popular because of its smooth sustained effect. Both morphine and midazolam are generally given at a rate of 1-5mg/hr. Disadvantages of this technique include the need for infusion devices, increased drug costs, and the potential for accumulation, tolerance, and prolonged emergence to occur. Oversedation is a potential hazard.

Antagonists

Specific opioid and benzodiazepine antagonists are available, and have increased the safety with which these agents can be used.

Unfortunately these drugs have their own limitations. The opioid antagonist naloxone can cause tachycardia, hypertension and agitation with adverse effects in patients with ischaemic heart disease. Flumazenil the benzodiazepine antagonist has a short half-life, and sedation and respiratory depression may recur following a single dose: an infusion is usually required[25,26].

Propofol

This intravenous anaesthetic is an effective alternative to midazolam for sedating critically ill patients[27-31]. Its advantages include rapid onset, short duration of action and accurate titratable control of level of sedation when given by continuous infusion. Propofol suppresses tracheolaryngeal reflexes which is useful in intubated patients. Following cardiac surgery propofol produces a similar quality of sedation to that achieved with midazolam, with a reduction in duration of intubation and ventilation[27,31-34]. Redistribution, elimination and clearance are prolonged in cardiac surgical patients, probably as a result of CPB and moderate hypothermia[31]. Propofol has neither analgesic nor potent amnesic properties.

Adverse haemodynamic effects are more likely to occur in the critically ill, and include vasodilatation, hypotension, and a dose-dependent decrease in myocardial contractility[19,28,35,36]. Propofol may produce an imbalance in myocardial oxygen supply and demand in patients with severe ischaemic heart disease (IHD), and should be used with caution in patients with limited cardiovascular reserve, especially in the presence of hypovolaemia. However afterload reduction may be beneficial in patients with mitral and aortic insufficiency. In patients with IHD and good left ventricular function, propofol can be used for induction and maintenance of anaesthesia[35]. It may also be given as part of a technique to facilitate early extubation[2,4].

Regional Analgesia and Sedation

Intrathecal opioids

Following the discovery of opioid receptors in the spinal cord, morphine was shown to be effective by the intrathecal and epidural routes in patients with severe pain[37-40]. Intrathecal morphine (ITM) was first used for postoperative analgesia in patients undergoing cardiac surgery by Mathews and Abrams in 1980[41]. Since then spinal opioids have been given to over 10,000 patients undergoing cardiac surgery in this hospital. They remain popular because of excellent analgesia and patient well-being postoperatively. Although different opioids have been given by the intrathecal route, morphine is the most popular agent because of its long duration of action and predictable effect. A particular advantage of morphine is its ability to give pain relief in the thoracic area after lumbar injection. More lipid soluble agents (e.g. fentanyl) may be unable to exert a distal effect because of greater binding to the spinal cord at the site of administration. ITM provides superior analgesia and greater haemodynamic stability than intravenous morphine following cardiac surgery[42-44]. It is also associated with improved postoperative respiratory function after thoracotomy[45,46].

The intrathecal route provides prolonged analgesia with low dose requirements, and the technique of lumbar puncture is simple, reliable and inexpensive. A 25-26 gauge pencil-point needle is used, and morphine is administered as a preservative-free preparation. The side-effects seen with IV opioids may occur when the spinal route is used, but they are less common being dose-related. Delayed respiratory depression is a concern, particularly in elderly patients, and when concomitant systemic opioids or other respiratory depressants are used. Patients who receive intrathecal opioids for postoperative analgesia should be monitored in an ICU or High Dependency Unit (HDU) setting[47-49].

Epidural opioids

The epidural route provides excellent analgesia which may be continued for several days. Benefits such as reduced sedative requirement, better pain relief, early tracheal extubation, significantly improved perioperative pulmonary function, and attenuation of the stress response have made this technique a popular choice for postoperative patients in the general ICU[50]. Recent work has confirmed that these benefits also apply after cardiac surgery[51-53].

Epidural analgesia has many specific advantages for patients with coronary artery disease and after CABG[51-56]. These include improved distribution of myocardial blood flow, decreased myocardial O_2 consumption, and a vasodilatory effect on stenosed coronary vessels during CABG. Thoracic epidural analgesia with sufentanil and bupivacaine is associated with greater haemodynamic stability than general anaesthesia during CABG[51-53].

Further advantages include a reduced ICU and hospital stay. There is a low incidence of systemic effects compared to conventional techniques, but as with ITM, delayed respiratory depression may occur, and patients need care in an ICU or HDU. The benefit-to-risk ratio is high for ICU patients, and the technique confers medical and economic benefits[50]. Potential problems include catheter migration, infection, and epidural haematoma formation (see below).

Spinal haematoma

The use of spinal opioids in patients who are heparinised intraoperatively is controversial because of the potential for haematoma formation and consequent neurological damage. There are conflicting reports as to the risks involved[57]. In this unit there have been no neurological sequelae attributable to haematoma in the fifteen years since spinal opioids were introduced to our practice. Lumbar puncture (LP) may cause neurological sequelae in patients who have not been heparinised, while epidural anaesthesia is well described for surgery with full heparinization without any permanent neurological complications[58-59].

Given the factors that might predispose to bleeding following LP, various recommendations have been devised[44,57]. These include: avoidance of LP in patients with a coagulopathy, and those receiving heparin infusions; stopping anticoagulant therapy 4 days and aspirin 10 days prior to surgery; the use of a fine bore needle (at least 25-26G); a careful atraumatic technique; postponement of surgery after a difficult or bloody tap; and maximising the interval between LP and heparinisation (at least one hour

is desirable). In some centres the epidural catheter is inserted on the day before surgery, so that the interval between insertion and heparinisation is more than 20 hours[56,60]. However, experience with epidural anaesthesia in cardiac surgery is relatively limited, compared to extensive experience with the intrathecal route.

Although these guidelines are useful in some respects, the practical interpretation is that the INR should be less than 1.4, and, given the efficacy of aspirin therapy, it is not discontinued until hospital admission. No case has been cancelled as a result of a traumatic tap in this unit. All patients should be monitored for neurological dysfunction in the postoperative period.

Analgesia and Sedation by Alternative Routes

Inhalational Analgesia and Sedation

Nitrous Oxide

Nitrous oxide (N_2O) is an effective analgesic and sedative agent with a rapidly reversible effect. Its usefulness postoperatively is limited by a number of adverse properties. These include a depressant effect on the myocardium, the risk of pulmonary hypertension, and the risk of enlarging any residual air bubbles in the circulation following CPB, the potential for bone marrow suppression with prolonged use and the unlikely but catastrophic effect of inadvertent administration of 100% N_2O. Postoperative cardiac patients are prone to hypoxaemia and may not tolerate the reduction in inspired oxygen necessitated by the use of N_2O. Entonox (a 50:50 mixture of O_2 and N_2O) is very useful for short painful procedures such as removal of chest drains and physiotherapy[1,18].

Isoflurane

This volatile anaesthetic agent has been used to sedate ICU patients[61,62]. It has a rapid onset, is readily reversibile, and has minimal haemodynamic effects. Elimination is independent of renal or hepatic function. However isoflurane may cause hypotension, and long term use may be associated with hallucinations and peripheral neuropathy. Environmental pollution is a hazard and appropriate equipment is needed to allow safe usage. Treatment which requires disconnection of the patient from the ventilator (e.g. physiotherapy, tracheal toilet) disrupts the supply of isoflurane, and may cause the patient to wake up. The high dose needed after this to re-sedate the patient increases the risk of adverse effects.

After Tracheal Extubation

Following tracheal extubation, sedative drugs are rarely used, although good analgesia is still required. Opioids are needed if pain is severe, and may also be given for short painful procedures such as the removal of chest drains.

Patient-controlled analgesia (PCA)

PCA opioid infusions are very effective in the management of acute postoperative pain and may be continued on the ward following discharge from ICU. Benefits include a rapid effect, and reductions in anxiety and total analgesic use. Nursing time is optimised, and the patient has the advantage of being in control[63].

Non steroidal anti-inflammatory agents (NSAIDs)

NSAIDs are now commonly used in the cardiac surgery ICU[13]. These drugs are effective against musculoskeletal pain, and are synergistic with opioids. They are not generally appropriate until the second or third postoperative days, when they may be the sole agents required. NSAIDs act by inhibition of the cyclo-oxygenase enzyme system, and have multiple effects. Antiplatelet functions may be advantageous in patients with coronary ischaemia, but are contraindicated in patients with a history of peptic ulcer disease, active bleeding, or coagulopathy. Renal blood flow depends on vasodilatory prostaglandins in pre-renal states, so NSAIDs should be avoided in patients with pre-renal oliguria.

Muscle Relaxants

With the evolution of proper pain relief, titrated anxiolysis and patient-sensitive ventilators, the need for paralysis 'to settle the patient on the ventilator' is now largely historical[18]. Hazards of muscle relaxants include the possibility of awake painful paralysis and the greater likelihood of an adverse outcome after inadvertent ventilator disconnection[13,18].

Special Cases

Some patients are difficult to manage in the postoperative period. These include patients who have developed encephalopathy, and those with a history of drug or alcohol addiction. Encephalopathy which is characterised by reversible confusion and coma may occur after CPB, particularly when a cerebral ischaemic event has occurred. Sepsis is an aggravating factor. Patients with alcohol dependence may suffer acute withdrawal and encephalopathy following CPB. Many will need prolonged ventilation: suitable sedatives include chlorpromazine and chlordiazepoxide[64]. Clonidine may be useful in more difficult cases although its use is often limited by hypotension and bradycardia[65].

Current Trends

There is a renewal of interest in early tracheal extubation of cardiac patients and postoperative transfer to a special cardiac surgery recovery area (CSRA) rather than an ICU. This has been shown to be both safe and cost-effective in selected patients[2-4,66-68]. A parallel surgical trend is towards performing CPB without hypothermia, thus reducing the need for postoperative ventilation to allow rewarming. Early extubation reduces patient discomfort postoperatively without adverse effects on haemodynamic or respiratory performance, overall morbidity or mortality. High risk patients and those in whom deep hypothermic circulatory arrest is performed are unsuitable for early extubation and continue to need ICU care[2-4].

Conclusion

Advances since Dr. Donald's unpleasant experience twenty years ago[1] include recognition of pain relief as the primary approach to postoperative agitation, and the ready use of IV opioids with acceptance of related mild

hypercarbia. The use of neuraxial analgesic techniques, although controversial, ensures superior analgesia. The introduction of NSAIDs providing analgesia without sedation is a further benefit. Early tracheal extubation is a new trend which appears to improve patient comfort.

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References

1. Donald, I. At the receiving end: a doctor's personal recollections of second-time cardiac valve replacement. Scot. Med. J. 1976; 21: 49-57.
2. Chong, J. L., Pillai, R., Fisher, A., Grebenik, C., Sinclair, M., Westaby, S. Cardiac surgery: moving away from intensive care. Br. Heart J. 1992; 68: 430-3.
3. Jindani, A., Aps, C., Neville, E., Sonmez, B., Tun, K., Williams, B. T. Postoperative cardiac surgical care: an alternative approach. Br. Heart J. 1992; 69: 59-64.
4. Chong, J. L., Grebenik, C., Sinclair, M., Fisher, A., Pillai, R., Westaby, S. The effect of a cardiac surgical recovery area on the timing of extubation. J. Cardiothor. Vasc. Anesth. 1993; 7: 137-41.
5. Mangano, D. T., Siliciano, D., Hollenburg, M. et al. Postoperative myocardial ischemia. Therapeutic trials using intensive analgesia after surgery. Anesthesiology 1992; 76: 342-53.
6. CASS (Coronary Artery Surgery Study). A randomised study of coronary artery bypass surgery. Survival data. Circulation 1983; 68: 939-50.
7. CASS (Coronary Artery Surgery Study). A randomised study of coronary artery bypass surgery. Quality of life in patients randomly assigned to treatment groups. Circulation 1983; 68: 951-60.
8. Takaro, T., Hultgren, H. L., Lipton, M. J. et al. The Veterans Administration co-operative randomised study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation 1976; 54 [Suppl. III]: 107-16.
9. Kaiser, G. C., Davis, K. B., Fisher, L. D. et al. Survival following coronary artery bypass grafting in patients with severe angina pectoris (CASS): An observational study. J. Thor. Cardiovasc. Surg. 1985; 89: 513-24.
10. Passamani, E., Davis, K. B., Gillespie, M. J., Killip, P. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. N. Engl. J. Med. 1985; 312: 1665-71.
11. Mock, M. B., Fisher, L. D., Holmes, D. R. et al. Comparison of effects of medical and surgical therapy on survival in severe angina pectoris and two vessel coronary artery disease with and without left ventricular dysfunction: a coronary artery surgery study registry study. Am. J. Cardiol. 1988; 61: 1198-1203.
12. Loan, W. B., Morrison, J. D. The incidence and severity of postoperative pain. Br. J. Anaesth. 1967; 39: 695.
13. Wheeler, A. P. Sedation, analgesia, and paralysis in the intensive care unit. Chest 1993; 104: 566-77.
14. Raj, P. P., Brannon, J. E. Analgesic considerations for the median sternotomy. In: Gravlee, G. P., Rauck, R. L. (eds). Pain management in cardiothoracic surgery. pp 101-24. J.B. Lippincott Co, Philadelphia, 1993.
15. Kaplan, J. A., Guffin, A. V. Shivering and changes in mixed venous oxygen saturation after cardiac surgery. Anesth. Analg. 1985; 64: 235.
16. MacIntyre, P. E., Pavlin, E. G., Dwersteg, J. F. Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in post-anesthesia shivering. Anesth. Analg. 1987; 66: 751-5.
17. Sun, X., Quinn, T., Weissman, C. Patterns of sedation and analgesia in the postoperative ICU patient. Chest 1992; 101: 1625-32.
18. Aitkenhead, A. R. Analgesia and sedation in intensive care. Br. J. Anaesthesiol. 1989; 63: 196-206.
19. Wood, M. Pharmacokinetics and principles of drug infusions in cardiac patients. In: Kaplan, J. A. (ed). Cardiac Anesthesia, pp 557-84. W.B. Saunders Co. Philadelphia, 1993.
20. Bovill, J. G. Opioids in cardiac anesthesia. In: Kaplan, J. A. (ed). Cardiac Anesthesia, pp 467-511. W.B. Saunders Co, Philadelphia, 1993.
21. Holley, F. O., Ponganis, K. V., Stanski, D. R. Effect of cardiopulmonary bypass on the pharmacokinetics of drugs. Clin. Pharmacokinet. 1982; 7: 234-51.
22. Malacrida, R., Fritz, M. E., Suter, P. M., Crevoisier, C. Pharmacokinetics of midazolam administered by continuous intravenous infusion to intensive care patients. Crit. Care Med. 1992; 20: 1123-6.
23. Harper, K. W., Collier, P. S., Dundee, J. W., Elliott, P., Halliday, M. J., Lowry, K. G. Age and nature of operation influence the pharmacokinetics of midazolam. Br. J. Anaesth. 1985; 57: 866-71.
24. Pandit, S. K., Galway, J. E., Dundee, J. W. Acidosis following thoracic surgery. Br. J. Anaesth. 1973; 45: 79-85.
25. Bodenham, A., Park, G. R. Reversal of prolonged sedation using flumazenil in critically ill patients. Anaesthesia 1989; 44: 603-5.
26. Bodenham, A., Brownlie, G., Dixon, J. S., Park, G. R. Reversal of sedation by prolonged infusion of flumazenil. Anaesthesia 1988; 43: 376-8.
27. Chaudhri, S., Kenny, G. Sedation after cardiac bypass surgery. Br. J. Anaesth. 1992; 68: 98-99.
28. Newman, L. H. McDonald, J. C. Wallace, P. G. M., Ledingham, I. McA. Propofol infusion for sedation in intensive care. Anaesthesia 1987; 42: 929-37.
29. Grounds, R. M., Lalor, J. M. Lumley, J., Royston, D., Morgan, M. Propofol infusion for sedation in the intensive care unit: preliminary report. Br Med. J. 1987; 294: 397-400.
30. Harris, C. E., Grounds, R. M., Murray, A. M., Lumley, J., Royston, D., Morgan, M. Propofol for long term sedation in the intensive care unit. A comparison with papaveretum and midazolam. Anaesthesia 1990; 45: 366-72.
31. McMurray, T. J. Collier, P. S., Carson, I. W., Lyons, S. M., Elliott, P. Propofol sedation after open heart surgery. A clinical and pharmacokinetic study. Anaesthesia 1990; 45: 322-6.
32. Ewart, M. C., Yau, K. W., Morgan, M. 2% propofol for sedation in the intensive care unit. Anaesthesia 1992; 47: 146-8.
33. Snellen, F., Lauwers, P., Demeyere, F., Byttebier, G., Van Aken, H. The use of midazolam versus propofol for short term sedation following coronary artery bypass grafting. Intens. Care Med. 1990; 16: 312-6.
34. Roekaerts, P., Huygen, F., de Lange, S. Infusion of propofol versus midazolam for sedation in the intensive care unit following coronary artery surgery. J. Cardiothor. Vasc. Anesth. 1993; 7: 142-7.
35. Reves, J. G., Berkowitz, D. E. Pharmacology of intravenous anesthetic induction drugs. In: Kaplan, J. A. (ed). Cardiac Anaesthesia, pp 512-34. W.B. Saunders Co, Philadelphia, 1993.

36. Bailie, G. R., Cockshott, I. D., Douglas, E. J., Bowles, B. J. M. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. Br. J. Anaesth. 1992; 68: 486-91.
37. Yaksh, T. L., Rudy, T. A. Analgesia mediated by a direct spinal action of narcotics. Science 1976; 192: 1357-8.
38. Wang, J. K., Nauss, L. A. Thomas, J. E. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979; 50: 149-51.
39. Behar, M., Olshwang, D., Magora, F., Davidson, J. T. Epidural morphine in treatment of pain. Lancet 1979; i: 527-9.
40. Samii, K., Feret, J., Harari, A. Viars, P. Selective spinal analgesia. Lancet 1979; i: 1142.
41. Mathews, E. T., Abrams, L. D. Intrathecal morphine in open heart surgery. Lancet 1980; ii: 543.
42. Vincenty, C., Malone, B., Mathru, M., Venus, B. Comparison of intrathecal and intravenous morphine in post coronary bypass surgery. Crit. Care Med. 1985; 13 [Suppl]: 308.
43. Fitzpatrick, G. J., Moriarty, D. C. Intrathecal Morphine in the management of pain following cardiac surgery. Br. J. Anaesth. 1988; 60: 639-44.
44. Vanstrum, G. S., Bjornson, K. M., Ilko, R. Postoperative effects of intrathecal morphine in coronary artery bypass surgery. Anesth. Analg. 1988; 67: 261-7.
45. Gray, J. R., Fromme, G. A., Nauss, L. A. Wang, J. K., Ilstrup, D. M. Intrathecal morphine for post-thoracotomy pain. Anesth. Analg. 1986; 65: 873-6.
46. Neustein, S. M., Cohen, E. Intrathecal morphine during thoracotomy, Part II: Effect on postoperative meperidine requirements and pulmonary function tests. J. Cardiothor. Vasc. Anesth. 1993; 7: 157-9.
47. Cousins, M. J., Mather, L. E. Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61: 276-310.
48. Gjessing, J., Tomlin, P. Postoperative pain control with intrathecal morphine. Anaesthesia 1981, 36: 268-76. 49. Stoelting, R. K. Intrathecal Morphine - an underused combination for postoperative pain management. Anesth. Analg. 1989; 68: 707-9.
50. Crews, J C. Epidural opioid analgesia. Crit. Care Clin. 1990; 6: 315-42.
51. Leim, T., Booij, L., Hasenbos, M., Gielen, M. Coronary artery bypass grafting using two different anesthetic techniques: Part 1: Hemodynamic results. J. Cardiothorac. Vasc. Anesth. 1992; 6: 148-55.
52. Leim, T., Hasenbos, M., Booij, L., Gielen, M. Coronary artery bypass grafting using two different anesthetic techniques: Part 2: Postoperative outcome. J. Cardiothorac. Vasc. Anesth. 1992; 6: 156-61.
53. Leim, T., Booij, L., Gielen, M., Hasenbos, M., van Egmond, J. Coronary artery bypass grafting using two different anesthetic techniques: Part 3: Adrenergic responses. J. Cardiothorac. Vasc. Anesth. 1992; 6: 162-70.
54. Blomberg, S., Emanuelsson, H., Ricksten, S. E. Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth. Analg. 1989; 69: 558-62.
55. Kock, M., Blomberg, S., Emanuelsson, H. et al. Thoracic epidural anesthesia improves global and regional left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease. Anesth. Analg. 1990; 71: 625-30.
56. Reiz, S., Nath, S., Rais, O. The effects of thoracic epidural block and prenalterol on coronary vascular resistance and myocardial metabolism in patients with coronary artery disease. Acta Anaesthesiolog. Scand. 1980; 24: 11-16.
57. Owens, E. L., Kasten, H. W., Hessel, E. A. Spinal subarachnoid hematoma after lumbar puncture and heparinization. Anesth. Analg. 1986; 65: 1201-1207.
58. Rao, T. L. K., El-Etr, A. A. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. Anesthesiology 1981; 55: 618-20.
59. Odoom, J. A., Sih, I. L. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. Anaesthesia 1983; 38: 254-9.
60. Joachimsson, P. O., Nystrom, S. O., Tyden, H. Early extubation after coronary artery surgery in efficiently rewarmed patients. J. Cardiothor. Anesth. 1989; 3: 444-54.
61. Kong, K., Willatts, S., Prys-Roberts, C. Isoflurane compared with midazolam for sedation in the intensive care unit. Br. Med. J. 1989; 298: 1277-80.
62. Millane, T. A., Bennett, E. D., Grounds, R. M. Isoflurane and propofol for long-term sedation in the intensive care unit. A crossover study. Anaesthesia 1992; 47: 768-74.
63. Wolman, R. L. Patient-controlled analgesia following thoracic surgery. In: Gravlee, G. P., Rauck, R. L. (eds). Pain management in cardiothoracic surgery. pp 57-100. J.B. Lippincott Co., Philadelphia, 1993.
64. Crippen, D. W. The role of sedation in the ICU patient with pain and agitation. Crit. Care Clin. 1990; 6: 369-92. Br. Heart J. 1985; 54: 91-5.
65. IpYam, P. C., Forbes, A., Cox, W. J. Clonidine in the treatment of alcohol withdrawal in the intensive care unit. Br. J. Anaesth. 1992; 68: 106-8.
66. Shapiro, B. A., Lichtenthal, P. R. Inhalation-based anesthetic techniques are the key to early extubation of the cardiac surgical patient. J. Cardiothor. Vasc. Anesth. 1993; 7: 135-6.
67. Quasha, A. L., Loeber, N., Feeley, T. W., Ullyot, D. J., Roizen, M. F. Postoperative respiratory care: a controlled trial of early and late extubation following coronary artery bypass grafting. Anesthesiology 1980; 52: 135-41.
68. Foster, G. H., Conway, W. A., Pamulkov, N. et al. Early extubation after coronary artery bypass: brief report. Crit. Care Med. 1984; 12: 994-6.