

Practice Guidelines for the Prevention, Detection and Management of Respiratory Depression Associated with Neuraxial Opioid Administration: An Updated Report

American Society of Anesthesiologists

Bibliography by Section

I. Identification of patients at increased risk of respiratory depression

Reviewing medical records (patient condition).

Nonrandomized comparative studies (comparisons of patient condition or clinical status)

1. von Ungern-Sternberg BS, Regli A, Bucher E, Reber A, Schneider MC: Impact of spinal anaesthesia and obesity on maternal respiratory function during elective Caesarean section. *Anaesthesia* 2004; 59:743-749

Observational studies, case reports, or non-pertinent comparison groups

1. Brockway MS, Noble DW, Sharwood-Smith GH, McClure JH: Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; 64:243-245
2. Lamarche Y, Martin R, Reiher J, Blaise G: The sleep apnoea syndrome and epidural morphine. *Can Anaesth Soc J* 1986; 33:231-233
3. Ogawa K, Iranami H, Yoshiyama T, Maeda H, Hatano Y: Severe respiratory depression after epidural morphine in a patient with myotonic dystrophy. *Can J Anaesth* 1993; 40:968-970
4. Ostermeier AM, Roizen MF, Hautkappe M, Klock PA, Klawns JM: Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. *Anesth Analg* 1997; 85:452-460

Physical examination.

No entries

II. Prevention of respiratory depression

Positive pressure ventilation.

No entries

Drug selection.

Route of administration.

Single-injection epidural opioids vs parenteral opioids (IV, IM):

Randomized controlled trials: intravenous opioids

1. Camann WR, Loferski BL, Fanciullo GJ, Stone ML, Datta S: Does epidural administration of butorphanol offer any clinical advantage over the intravenous route? *Anesthesiology* 1992; 72:216-220
2. Cohen SE, Woods WA: The role of epidural morphine in the postcesarean patient: efficacy and effects on bonding. *Anesthesiology* 1983; 58:500-504
3. Klinck JR, Lindop MJ: Epidural morphine in the elderly. A controlled trial after upper abdominal surgery. *Anaesthesia* 1982; 37:907-912

4. Morisot R, Dessanges JF, Regnard J, Lockhart A: Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine and fentanyl. *Br J Anaesth* 1989; 63:97-102
5. Park W, Thompson J, Lee K: Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg* 2001; 234:560-571
6. Peyton PJ, Myles PS, Silbert BS, Rigg JA, Jamrozik K, Parsons R: Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. *Anesth Analg* 2003; 96:548-554
7. Rosseel PM, van den Broek WG, Boer EC, Prakash O: Epidural sufentanil for intra- and postoperative analgesia in thoracic surgery: a comparative study with intravenous sufentanil. *Acta Anaesthesiol Scand* 1988; 32:193-198
8. Sandler AN, Chovaz P, Whiting W: Respiratory depression following epidural morphine: a clinical study. *Can Anaesth Soc J* 1986; 33:542-549
9. Shulman M, Sandler AN, Bradley JW, Young PS, Brebner J: Postthoracotomy pain and pulmonary function following epidural and systemic morphine. *Anesthesiology* 1984; 61:569-575

Randomized controlled trials: intramuscular opioids

1. Asantila R, Rosenberg PH, Scheinin B: Comparison of different methods of postoperative pain analgesia after thoracotomy. *Acta Anaesth Scand* 1986; 30:421-425
2. Chauvin M, Salbaing J, Perrin D, Levron JC, Viars P: Clinical assessment and plasma pharmacokinetics associated with intramuscular or extradural alfentanil. *Br J Anaesth* 1985; 57:886-891
3. Daley MD, Sandler AN, Turner KE, Vosu H, Slavchenko P: A comparison of epidural and intramuscular morphine in patients following cesarean section. *Anesthesiology* 1990; 72:289-294
4. Donadoni R, Rolly G: Epidural sufentanil versus intramuscular buprenorphine for postoperative analgesia. A double-blind comparative trial. *Anaesthesia* 1987; 42:1171-1175
5. Gustafsson LL, Friberg-Nielsen S, Garle M, Mohall A, Rane A, Schildt B, Symreng T: Extradural and parenteral morphine: kinetics and effects in postoperative pain. A controlled clinical study. *Br J Anaesth* 1982; 54:1167-1174
6. Hasenbos M, Simon M, van Egmond J, Folgering H, van Hoorn P: Postoperative analgesia by nicomorphine intramuscularly versus high thoracic epidural administration. Effects on ventilatory and airway occlusion pressure responses to CO₂. *Acta Anaesth Scand* 1986; 30:426-430
7. Hasenbos M, van Egmond J, Gielen M, Crul JF: Post-operative analgesia by epidural versus intramuscular nicomorphine after thoracotomy. Part II. *Acta Anaesth Scand* 1985; 29:577-582
8. Hasenbos M, van Egmond J, Gielen M, Crul JF: Post-operative analgesia by high thoracic epidural versus intramuscular nicomorphine after thoracotomy. Part III. The effects of per- and post-operative analgesia on morbidity. *Acta Anaesth Scand* 1987; 31:608-615
9. Henderson SK, Matthew EB, Cohen H, Avram MJ: Epidural hydromorphone: a double-blind comparison with intramuscular hydromorphone for postcesarean section analgesia. *Anesthesiology* 1987; 66:825-830
10. Jacobson L, Phillips PD, Hull CJ, Conacher ID: Extradural versus intramuscular diamorphine. A controlled study of analgesic and adverse effects in the postoperative period. *Anaesthesia* 1983, 38:10-18

11. Lomessy A, Magnin C, Viale JP, Motin J, Cohen R: Clinical advantages of fentanyl given epidurally for post-operative analgesia. *Anesthesiology* 1984; 61:466-469
12. Perriss BW, Latham BV, Wilson IH: Analgesia following extradural and IM pethidine in post-cesarean section patients. *Br J Anaesth* 1990; 64:355-357
13. Rawal N, Sjostrand U, Christoffersson E, Dahlstrom B, Arvill A, Rydman H: Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function. *Anesth Analg* 1984; 63:583-592
14. Rybro L, Schurizek BA, Petersen TK, Wernberg M: Postoperative analgesia and lung function: a comparison of intramuscular with epidural morphine. *Acta Anaesth Scand* 1982; 26:514-518
15. Thind GS, Wells JC, Wilkes RG: The effects of continuous intravenous naloxone on epidural morphine analgesia. *Anaesthesia* 1986; 41:582-585

Single-injection spinal opioids vs parenteral opioids (i.e., IV, IM, intermittent IV, IV PCA):

Randomized controlled trials

1. Fournier R, Weber A, Gamulin Z: Intrathecal sufentanil is more potent than intravenous for postoperative analgesia after total-hip replacement. *Reg Anesth Pain Med* 2005; 30:249-254

Epidural opioids (single-injection or PCEA) vs IV PCA opioids:

Randomized controlled trials: single-injection vs IV opioids

1. Rosenberg PH, Heino A, Schein B: Comparison of intramuscular analgesia, intercostal block, epidural morphine, and on-demand-i.v.-fentanyl in the control of pain after upper abdominal surgery. *Acta Anaesth Scand* 1984; 28:603-607
2. Weller R, Rosenblum M, Conard P, Gross JB: Comparison of epidural and patient-controlled intravenous morphine following joint replacement surgery. *Can J Anaesth* 1991; 38:582-586

Randomized controlled trials: PCEA vs IV PCA opioids

1. Chauvin M, Hongnat JM, Mourgeon E, Lebrault C, Bellenfant P, Alfonsi P: Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. *Anesth Analg* 1993; 76:1251-1258
2. Glass PS, Estok P, Ginsberg B, Goldberg JS, Sladen RN: Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. *Anesth Analg* 1992; 74:345-351
3. Grant RP, Dolman JF, Harper JA, White SA, Parsons DG, Evans KG, Merrick CP: Patient-controlled lumbar epidural fentanyl compared with patient-controlled intravenous fentanyl for postthoracotomy pain. *Can J Anaesth* 1992; 39:214-219
4. Halpern SH, Muir H, Breen TW, Campbell DC, Barrett J, Liston R, Blanchard JW. A multicenter randomized controlled trial comparing patient-controlled epidural with intravenous analgesia for pain relief in labor. *Anesth Analg*. 2004; 99:1532-1538
5. Menigaux C, Guignard B, Fletcher D, Sessler DI, Levron JC, Chauvin M: More epidural than intravenous sufentanil is required to provide comparable postoperative pain relief. *Anesth Analg* 2001; 93:472-476

6. Parker RK, White PF: Epidural patient-controlled analgesia: an alternative to intravenous patient-controlled analgesia for pain relief after cesarean delivery. *Anesth Analg* 1992; 75:245-251

Nonrandomized comparative studies

1. Bromage PR, Camporesi E, Leslie J, Chestnut D: Epidural narcotics for postoperative analgesia. *Anesth Analg* 1990; 59:473-480
2. Cohen SE, Tan S, White PF: Sufentanil analgesia following cesarian section: epidural versus intravenous administration. *Anesthesiology* 1988; 68:129-134
3. Duarte LTD, Fernandes MCBC, Costa VV, Saraiva RA: The incidence of postoperative respiratory depression in patients undergoing intravenous or epidural analgesia with opioids. *Revista Brasileira de Anestesiologia* 2009; 59:409-420
4. Holland RB, Levitt MWD, Whitton LA, Shadbolt N: Carbon dioxide response after epidural morphine. *Anaesthesia* 1982; 37:753-757
5. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B: The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth* 2005; 17:537-542
6. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B: The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth* 2005; 17:537-542
7. Wheatley RG, Sommerville ID, Sapsford DJ, Jones JG: Postoperative hypoxaemia: comparison of extradural, IM and patient-controlled opioid analgesia. *Br J Anaesth* 1990; 64:267-275

Observational studies, case reports, or non-pertinent comparison groups

1. Abouleish E: Apnoea associated with the intrathecal administration of morphine in obstetrics. *Br J Anaesth* 1988; 60:592-594
2. Abouleish F, Rawal N, Rashad MN: The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. *Reg Anesth* 1991; 16:137-140
3. Baker MN, Sarna MC: Respiratory arrest after a second dose of intrathecal sufentanil. *Anesthesiology* 1995; 83:231-232
4. Bernard JM, Hommeril JL, Legendre MP, Passuti N, Pinaud M: Spinal or systemic analgesia after extensive spinal surgery: comparison between intrathecal morphine and intravenous fentanyl plus clonidine. *J Clin Anesth* 1993; 5:231-236
5. Blackburn C: Respiratory arrest after epidural sufentanil. *Anaesth* 1987; 42:665-666
6. Brockway MS, Noble DW, Sharwood-Smith GH, McClure JH: Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; 64:243-245
7. Burstal R, Wegener F, Hayes C, Lantry G: Epidural analgesia: prospective audit of 1062 patients. *Anaesth Intens Care* 1998; 26:165-172
8. Christensen V: Respiratory depression after epidural morphine. *Br J Anaesth* 1980; 52:841
9. Cohen SE, Labaille T, Benhamou D, Levron JC: Respiratory effects of epidural sufentanil after cesarean section. *Anesth Analg* 1992; 74:677-682
10. Davies GK, Tolhurst-Cleaver CL, James TL: CNS depression from intrathecal morphine. *Anesthesiology* 1980; 52:280
11. Davies GK, Tolhurst-Cleaver CL, James TL: Respiratory depression after intrathecal narcotics. *Anaesthesia* 1980; 35:1080-1083
12. Ferouz F, Norris MC, Leighton BL: Risk of respiratory arrest after intrathecal sufentanil. *Anesth Analg* 1997; 85:1088-1090

13. Gjessing J, Tomlin PJ: Postoperative pain control with intrathecal morphine. *Anaesthesia* 1981; 36:268-276
14. Glass PSA: Respiratory depression following only 0.4 mg of intrathecal morphine. *Anesthesiology* 1984; 60:256-257
15. Glynn CJ, Mather LE, Cousins MJ, Wilson PR, Graham JR: Spinal narcotics and respiratory depression. *Lancet* 1979; 2:356-357
16. Greenhalgh CA: Respiratory arrest in a parturient following intrathecal injection of sufentanil and bupivacaine. *Anaesthesia* 1996; 51:173-175
17. Gustafsson LL, Schildt B, Jacobsen K: Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; 54:479-486
18. Gustafsson LL, Schildt B, Jacobsen K: Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; 54:479-486
19. Gwartz KH, Young JV, Byers RS, Alley C, Levin K, Walker SG, Stoelting RK: The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. *Anesth Analg* 1999; 88:599-604
20. Hansdottir V, Philip J, Olsen MF, Eduard C, Houltz E, Ricksten SE: Thoracic epidural versus intravenous patient-controlled analgesia after cardiac surgery: a randomized controlled trial on length of hospital stay and patient-perceived quality of recovery. *Anesthesiology* 2006; 104:142-151
21. Hays RL, Palmer CM: Respiratory depression after intrathecal sufentanil during labor. *Anesthesiology* 1994; 81:511-512
22. Hein A, Rösblad P, Gillis-Haegerstrand C, Schedvins K, Jakobsson J, Dahlgren G: Low dose intrathecal morphine effects on post-hysterectomy pain: a randomized placebo-controlled study. *Acta Anaesthesiol Scand* 2012; 56:102-109
23. Horlocker TT, Abel MD, Messick JM Jr, Schroeder DR: Small risk of serious neurologic complications related to lumbar epidural catheter placement in anesthetized patients. *Anesth Analg* 2003; 96:1547-1552
24. Jaffee JB, Drease GE, Kelly T, Newman LM: Severe respiratory depression in the obstetric patient after intrathecal meperidine or sufentanil. *Int J Obstet Anesth* 1997; 6:182-184
25. Karl HW, Tyler DC, Krane EJ: Respiratory depression after low-dose caudal morphine. *Can J Anaesth* 1996; 43:1065-1067
26. Krane EJ: Delayed respiratory depression in a child after caudal epidural morphine. *Anesth Analg* 1988; 67:79-82
27. Lamarche Y, Martin R, Reiher J, Blaise G: The sleep apnoea syndrome and epidural morphine. *Can Anaesth Soc J* 1986; 33:231-233
28. Madsen JV, Rybro L, Schurizek BA, Husegaard HC, Joensen F, Moller LV, Wernberg M: Respiratory depression following postoperative analgesia with epidural morphine. *Acta Anaesthesiol Scand* 1986; 30:417-420
29. Mann C1, Pouzeratte Y, Boccara G, Peccoux C, Vergne C, Brunat G, Domergue J, Millat B, Colson P: Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000; 92:433-441
30. Mehnert JH, Dupont TJ, Rose DH: Intermittent epidural morphine instillation for control of postoperative pain. *Am J Surg* 1983; 146:145-149
31. Moon RE, Clements FM: Accidental epidural overdose of hydromorphone: a case report. *Anesthesiology* 1985; 63:238-239
32. Ogawa K, Iranami H, Yoshiyama T, Maeda H, Hatano Y: Severe respiratory depression after epidural morphine in a patient with myotonic dystrophy. *Can J Anaesth* 1993; 40:968-970

33. Ostermeier AM, Roizen MF, Hautkappe M, Klock PA, Klafta JM: Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. *Anesth Analg* 1997; 85:452-460
34. Palmer CM: Early respiratory depression following intrathecal fentanyl-morphine combination. *Anesthesiology* 1991; 74:1153-1155
35. Paulus DA, Paul WL, Munson ES: Neurologic depression after intrathecal morphine. *Anesthesiology* 1981; 54:517-518
36. Scott DB, McClure J: Selective epidural analgesia. *Lancet* 1979; 1:1410-1411
37. Sidi A, Davidson JT, Behar M, Olshwang D: Spinal narcotics and central nervous system depression. *Anaesthesia* 1981; 36:1044-1047
38. Sjogren P, Jakobsen S, Valentin N: Respiratory depression during epidural morphine treatment. *Acta Anaesth Scand* 1991; 35:553-555
39. Stenseth R, Sellevold O, Breivik H: Epidural morphine for postoperative pain: experience with 1085 patients. *Acta Anaesth Scand* 1985; 29:148-156
40. Yarnell RW, Polis T, Reid GN, Murphy IL, Penning JP: Patient-controlled analgesia with epidural meperidine after elective cesarean section. *Reg Anesth* 1992; 17:329-333
41. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T: Epidural anesthesia and analgesia in high-risk surgical patients. *Anesthesiology* 1987; 66:729-736

Extended-release epidural morphine vs parenteral morphine:

Randomized controlled trials

1. Hartrick CT, Martin G, Kantor G, Koncelik J, Manvelian G: Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. *J Bone Joint Surg Am* 2006; 88:273-281

Extended-release epidural morphine vs immediate release epidural morphine:

Randomized controlled trials

1. Carvalho B, Riley E, Cohen SE, Gambling D, Palmer C, Huffnagle HJ, Polley L, Muir H, Segal S, Lihou C, Manvelian G: Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. *Anesth Analg* 2005; 100:1150-1158
2. Carvalho B, Roland LM, Chu LF, Campitelli VA, 3d, Riley ET: Single-dose, extended-release epidural morphine (DeopDur) compared to conventional epidural morphine for post-cesarean pain. *Anesth Analg* 2007; 105:176-183
3. Gambling D, Hughes T, Martin G, Horton W, Manvelian G. A comparison of Depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. *Anesth Analg* 2005; 100:1065-1074

Nonrandomized comparative studies

1. Vanterpool S, Coombs R, Fecho K: Continuous epidural infusion of morphine versus single epidural injection of extended-release morphine for postoperative pain control after arthroplasty: a retrospective analysis. *Ther Clin Risk Manag* 2010; 6:271-277
2. Viscusi ER, Kopacz D, Hartrick C, Martin G, Manvelian G: Single-dose extended-release epidural morphine for pain following hip arthroplasty. *Am J Therapeutics* 2006; 13:423-431

Observational studies, case reports, or non-pertinent comparison groups

1. Gambling DR, Hughes TL, Manvelian GZ: Extended-release epidural morphine (DepoDur) following epidural bupivacaine in patients undergoing lower abdominal surgery: a randomized controlled pharmacokinetic study. *Reg Anesth Pain Medicine* 2009; 34:316-325
2. Kahl L, Parvizi J, Viscusi ER, Hozack WJ, Sharkey PF, Rothman RH: Lessons learned with extended-release epidural morphine after total hip arthroplasty. *Clin Orthop Relat Res* 2010; 468:1082-1087

Continuous infusion epidural opioids vs IV opioid infusion:

Randomized controlled trials

1. Backlund M, Lindgren L, Kajimoto Y, Rosenberg PH: Comparison of epidural morphine and oxycodone for pain after abdominal surgery. *J Clin Anesth* 1997; 9:30-35
2. Baxter AD, Laganieri S, Samson B, Stewart J, Hull K, Goernert L: A comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy analgesia. *Can J Anaesth* 1994; 41:184-191
3. Camu F, Debucquoy F: Alfentanil infusion for postoperative pain: a comparison of epidural and intravenous routes. *Anesthesiology* 1991; 75:171-178
4. El-Baz N, Goldin M: Continuous epidural infusion of morphine for pain relief after cardiac operations. *J Thorac Cardiovasc Surg* 1987; 93:878-883
5. Ellis DJ, Millar WL, Reisner LS: A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after cesarean section. *Anesthesiology* 1990; 72:981-986
6. Geller E, Chrubasik J, Graf R, Chrubasik S, Schulte-Monting J: A randomized double-blind comparison of epidural sufentanil versus intravenous sufentanil or epidural fentanyl analgesia after major abdominal surgery. *Anesth Analg* 1993; 76:1243-1250
7. Guinard JP, Mavrocordatos P, Chiolero R, Carpenter RL: A randomized comparison of intravenous versus lumbar and thoracic epidural fentanyl for analgesia after thoracotomy. *Anesthesiology* 1992; 77:1108-1115
8. Mackersie RC, Karagianes TG, Hoyt DB, Davis JW: Prospective evaluation of epidural and intravenous administration of fentanyl for pain control and restoration of ventilatory function following multiple rib fractures. *J Trauma* 1991; 31:443-451
9. Salomaki TE, Laitinen JO, Nuutinen LS: A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. *Anesthesiology* 1991; 75:790-795
10. Sandler AN, Stringer D, Panos L, Badner N, Friedlander M, Koren G, Katz J, Klein J: A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for postthoracotomy pain relief. Analgesic, pharmacokinetic, and respiratory effects. *Anesthesiology* 1992; 77:626-634
11. van Lersberghe C, Camu F, de Keersmaecker E, Sacre S: Continuous administration of fentanyl for postoperative pain: a comparison of the epidural, intravenous, and transdermal routes. *J Clin Anesth* 1994; 6:308-314

Nonrandomized comparative studies

1. Flisberg P, Rudin A, Linner R, Lundberg CJ: Pain relief and safety after major surgery: a prospective study of epidural and intravenous analgesia in 2696 patients. *Acta Anaesth Scand* 2003; 47:457-465

2. McNeely JK, Farber NE, Rusy LM, Hoffman GM: Epidural analgesia improves outcome following pediatric fundoplication: a retrospective analysis. *Reg Anesth* 1997; 22:16-23
3. Singelyn FJ, Bouverneur JM: Postoperative analgesia after total hip arthroplasty: IV PCA with morphine, patient-controlled epidural analgesia, or continuous "3-in-1" block?: A prospective evaluation by our acute pain service in more than 1,300 patients. *J Clin Anesth* 1999; 11:550-554
4. Teng YH, Hu JS, Tsai SK, Liew C, Lui PW: Efficacy and adverse effects of patient-controlled epidural or intravenous analgesia after major surgery. *Chang Gung Med J* 2004; 27:877-886

Continuous infusion epidural opioids vs IV PCA opioids:

Randomized controlled trials

1. Benzon HT, Wong HY, Belavic AM, Goodman I, Mitchell D, Lefheit T, Locicero J: A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. *Anesth Analg* 1993; 76:316-322
2. Boylan JF, Katz J, Kavanagh BP, Klinck JR, Cheng DC, DeMajo WC, Walker PM, Johnston KW, Sandler AN: Epidural bupivacaine-morphine analgesia versus patient-controlled analgesia following abdominal aortic surgery: analgesic, respiratory, and myocardial effects. *Anesthesiology* 1998; 89:585-593
3. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F: Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; 91:8-15
4. George KA, Wright PMC, Chisakuta AM, Rao NVS: Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. *Acta Anaesth Scand* 1994; 38:808-812
5. Ismail MT, Hassanin MZ: Neuraxial analgesia versus intravenous remifentanyl for pain relief in early labor in nulliparous women. *Arch Gynecol Obstet* 2012; 286:1375-1381
6. Royse C, Royse A, Soeding P, Blake D, Pang J: Prospective randomized trial of high thoracic epidural analgesia for coronary artery bypass surgery. *Ann Thorac Surg* 2003; 75:93-100

Observational studies, case reports, or non-pertinent comparison groups

1. Badner NH, Sandler AN, Koren G, Lawson SL, Klean J, Einarson TR: Lumbar epidural fentanyl infusions for post-thoracotomy patients: analgesia, respiratory, and pharmacokinetic effects. *J Cardiothorac Anesth* 1990; 4:543-551
2. Renaud B, Brichant JF, Clergue F, Chauvin M, Levron JC, Viars P: Ventilatory effects of continuous epidural infusion of fentanyl. *Anesth Analg* 1988; 67:971-975
3. Welch EA, Thornton JA: Continuous thoracic epidural fentanyl. A comparison of epidural fentanyl with intramuscular papaveretum for postoperative pain. *Anaesthesia* 1982; 37:309-316
4. Wood CE, Goresky GV, Klassen KA, Kuwahara B, Neil SG: Complications of continuous epidural infusions for postoperative analgesia in children. *Can J Anaesth* 1994; 41:613-620

Type of drug

Single-injection epidural hydrophilic opioids (e.g., morphine, hydromorphone) vs lipophilic opioids (e.g., fentanyl/sufentanil):

Randomized controlled trials

1. Rosseel PM, van den Broek WG, Boer EC, Prakash O: Epidural sufentanil for intra- and postoperative analgesia in thoracic surgery: a comparative study with intravenous sufentanil. *Acta Anaesthesiol Scand* 1988; 32:193-198
2. Sinatra RS, Sevarino FB, Chung JH, Graf G, Paige D, Takla V, Silverman DG: Comparison of epidurally administered sufentanil, morphine, and sufentanil-morphine combination for postoperative analgesia. *Anesth Analg* 1991; 72:522-527
3. Van der Auwera A, Venborgh C, Camu F: Analgesic and cardiorespiratory effects of epidural sufentanil and morphine. *Anesth Analg* 1987; 66:999-1003

Nonrandomized comparative studies

1. Torda TA, Pybus DA: Comparison of four narcotic analgesics for extradural analgesia. *Br J Anaesth* 1982; 54:291-295

Observational studies, case reports, or non-pertinent comparison groups

1. Yu PY, Gambling DR: A comparative study of patient-controlled epidural fentanyl and single dose epidural morphine for post-caesarean analgesia. *Can J Anaesth* 1993; 40:416-420

Single-injection intrathecal hydrophilic opioids vs lipophilic opioids:

Randomized controlled trials

1. Cowan CM, Kendall JB, Barclay PM, Wilkes RG: Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; 89:452-458
2. Karaman S, Kocabas S, Uyar M, Hayzaran S, Firat V: The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. *Eur J Anaesthesiol* 2006; 23:285-291

Continuous infusion epidural hydrophilic opioids vs lipophilic opioids:

Randomized controlled trials: CIE hydrophilic opioids vs CIE lipophilic opioids

1. Dyer RA, Anderson BJ, Michell WL, Hall JM: Postoperative pain control with a continuous infusion of epidural sufentanil in the intensive care unit: a comparison with epidural morphine. *Anesth Analg* 1990; 71:130-136
2. Gedney JA, Liu EH: Side-effects of epidural infusions of opioid bupivacaine mixtures. *Anaesthesia* 1998; 53:1148-1155
3. Goodarzi M: Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. *Paediatr Anaesth* 1999; 9:419-422
4. White MJ, Berghausen EJ, Dumont SW, Tsueda K, Schroeder JA, Vogel RL, Heine MF, Huang KC: Side effects during continuous epidural infusion of morphine and fentanyl. *Can J Anaesth* 1992; 39:576-582

Randomized controlled trials: CIE hydrophilic opioids+bupivacaine vs CIE lipophilic opioids+bupivacaine

1. Berti M, Fanelli G, Casati A, Lugani D, Aldegheri G, Torri G: Comparison between epidural infusion of fentanyl/bupivacaine and morphine/bupivacaine after orthopaedic surgery. *Can J Anaesth* 1998; 45:545-550
2. Coppe E, Willaert J: Postoperative analgesia for major abdominal surgery with continuous thoracic epidural infusion of bupivacaine with sufentanil, versus bupivacaine with morphine. A randomized double blind study. *Acta Anaesthesiol Belg* 1992; 43:131-137
3. Saito Y, Uchida H, Kaneko M, Nakatani T, Kosaka Y: Comparison of continuous epidural infusion of morphine/bupivacaine with fentanyl/bupivacaine for postoperative pain relief. *Acta Anaesthesiol Scand* 1994; 38:398-401

Nonrandomized comparative studies

1. Hasenbos MA, Eckhaus MN, Slappendel R, Gielen MJ: Continuous high thoracic epidural administration of bupivacaine with sufentanil or nicomorphine for postoperative pain relief after thoracic surgery. *Reg Anesth* 1989; 14:212-218

Dose selection

High vs low doses of single-injection/single-dose epidural opioids (i.e., morphine, hydromorphone, fentanyl, or sufentanil):

Randomized controlled trials

2. Allen PD, Walman T, Concepcion M, Sheskey M, Patterson MK, Cullen D, Covino BG: Epidural morphine provides postoperative pain relief in peripheral vascular and orthopedic surgical patients: a dose-response study. *Anesth Analg* 1986; 65:165-170
3. Carvalho B, Riley E, Cohen SE, Gambling D, Palmer C, Huffnagle HJ, Polley L, Muir H, Segal S, Lihou C, Manvelian G: Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. *Anesth Analg* 2005; 100:1150-1158
4. Chauvin M, Salbaing J, Perrin D, Levron JC, Viars P: Clinical assessment and plasma pharmacokinetics associated with intramuscular or extradural alfentanil. *Br J Anaesth* 1985; 57:886-891
5. Krane EJ, Tyler DC, Jacobson LE: The dose response of caudal morphine in children. *Anesthesiology* 1989; 71:48-52
6. Reynvoet M, Dionys J, Vermaut G, Van Aken H: Surgical analgesia for knee arthroscopy with epidural lignocaine and sufentanil--effect of varying sufentanil doses. *Acta Anaesthesiol Belg* 1990; 41:319-325
7. Welch EA: The optimum concentration of epidural fentanyl. *Anaesth* 1983; 38:1037-1041
8. Whiting WC, Sandler AN, Lau LC, Chovaz PM, Slavchenko P, Daley D, Koren G: Analgesic and respiratory effects of epidural sufentanil in patients following thoracotomy. *Anesthesiology* 1988; 69:36-43
9. Yamaguchi H, Watanabe S, Harukuni I, Hamaya Y: Effective doses of epidural morphine for relief of postcholecystectomy pain. *Anesth Analg* 1991; 72:80-83

Nonrandomized comparative studies

1. Asantila R, Rosenberg PH, Scheinin B: Comparison of different methods of postoperative pain analgesia after thoracotomy. *Acta Anaesth Scand* 1986; 30:421-425
2. Viscusi ER, Kopacz D, Hartrick C, Martin G, Manvelian G: Single-dose extended-release epidural morphine for pain following hip arthroplasty. *Am J Therapeutics* 2006; 13:423-431

High vs low doses of extended-release epidural opioids (i.e., morphine, hydromorphone, fentanyl, or sufentanil):

Randomized controlled trials

1. Gambling D, Hughes T, Martin G, Horton W, Manvelian G. A comparison of Depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. *Anesth Analg* 2005; 100:1065-1074
2. Viscusi ER, Martin G, Hartrick CT, Singla N, Manvelian G; EREM Study Group. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* 2005; 102:1014-1022

High vs low doses of single-injection/single-dose intrathecal opioids:

Randomized controlled trials

1. Abboud TK, Dror A, Mosaad P, Zhu J, Mantilla M, Swart F, Gangolly J, Silao P, Makar A, Moore J, Davis H, Lee J: Mini-dose intrathecal morphine for the relief of post-cesarean section pain. *Anesth Analg* 1988; 66:137-143
2. Belzarena SD: Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. *Anesth Analg* 1992; 74:653-657
3. Boezaart AP, Eksteen JA, Spuy GV, Rossouw P, Knipe M: Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. *Spine* 1999; 24:1131-1137
4. Bowrey S, Hamer J, Bowler I, Symonds C, Hall JE: A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. *Anaesthesia* 2005; 60:449-452
5. Jacobson L, Chabal C, Brody MC: A dose-response study of intrathecal morphine: efficacy, duration, optimal dose, and side effects. *Anesth Analg* 1988; 67:1082-1088
6. Murphy PM, Stack D, Kinirons B, Laffey JG: Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. *Anesth Analg* 2003; 97:1709-1715
7. Norris MC, Fogel ST, Holtmann B: Intrathecal sufentanil (5 vs. 10 microg) for labor analgesia: efficacy and side effects. *Reg Anesth Pain Med* 1998; 23:252-257
8. Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA: Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. *Anesth Analg* 2003; 97:1452-1457
9. Samii K, Chauvin M, Viars P: Postoperative spinal analgesia with morphine. *Br J Anaesth* 1981; 53:817-820
10. Sarma VJ, Bostrom UV: Intrathecal morphine for the relief of post-hysterectomy pain--a double-blind, dose-response study. *Acta Anaesthesiol Scand* 1993; 37:223-227
11. Varrassi G, Celleno D, Capogna G, Costantino P, Emanuelli M, Sebastiani M, Pesce AF, Niv D: Ventilatory effects of subarachnoid fentanyl in the elderly. *Anaesthesia* 1992; 47:558-562

Nonrandomized comparative studies

1. Baraka A, Noueihid R, Hajj S: Intrathecal injection of morphine for obstetric analgesia. *Anesthesiology* 1981; 54:136-140
2. Clergue F, Montembault C, Despierres O, Ghesquiere F, Harari A, Viars P: Respiratory effects of intrathecal morphine after upper abdominal surgery. *Anesthesiology* 1984; 61:677-685

High vs low doses of continuous infusion epidural (CIE) opioids:

Randomized controlled trials

1. Sjoström S, Blass J: Postoperative analgesia with epidural bupivacaine and low-dose fentanyl—a comparison of two concentrations. *Acta Anaesthesiol Scand* 1998; 42:776-782
2. Thomson CA, Becker DR, Messick JM, de-Castro MA, Pairolero PC, Trastek VF, Murray MJ, Schulte NK, Offord KP, Ferguson JA: Analgesia after thoracotomy: effects of epidural fentanyl concentration/infusion rate. *Anesth Analg* 1995; 81:973-981

Nonrandomized comparative studies

1. Scott DA, Beilby DS, McClymont C: Postoperative analgesia using epidural infusions of fentanyl with bupivacaine: a prospective analysis of 1,014 patients. *Anesthesiology* 1995; 83:727-737

Dose reduction vs cessation of opioids (to improve respiratory rate and reduce adverse outcomes related to respiratory depression):

No entries

Drug combinations

Neuraxial opioids with versus without parenteral opioids, hypnotics or dissociative anesthetics (e.g., ketamine):

Randomized controlled trials

No entries

Nonrandomized comparative studies

1. Ahuja BR, Strunin L: Respiratory effects of epidural fentanyl: changes in end-tidal and respiratory rate following single-doses and continuous infusion *Anaesth* 1985; 40:949-955

III. Monitoring for respiratory depression

Detection of respiratory depression.

Pulse oximetry monitoring versus no pulse oximetry monitoring.

Randomized controlled trials

1. Bierman MI, Stein KL, Snyder JV: Pulse oximetry in the postoperative care of cardiac surgical patients: a randomized controlled trial. *Chest* 1992; 102:1367-1370

2. Cote CJ, Goldstein EA, Cote MA, Hoaglin DC, Ryan JF: A single-blinded study of pulse oximetry in children. *Anesthesiology* 1988; 68:184-188
3. Moller JT, Jensen PF, Johannessen NW, Espersen K: Hypoxaemia is reduced by pulse oximetry monitoring in the operating theatre and in the recovery room. *Br J Anaesth* 1992; 68:146-150
4. Moller JT, Johannessen NW, Espersen K, Ravio O, Pedersen BD, Jensen PF, Rasmussen NH, Rasmussen LS, Pedersen T, Cooper JB, Gravenstein JS, Chraemmer-Jorgensen B, Djernes M, Wiberg-Jorgensen F, Heslet L, Johansen SH: Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. *Anesthesiology* 1993; 78:445-453
5. Moller JT, Sennild I, Johannessen NW, Jensen PF, Espersen K, Gravenstein JS, Cooper JB, Djernes M, Johansen SH: Perioperative monitoring with pulse oximetry and late postoperative cognitive dysfunction. *Br J Anaesth* 1993; 71:340-347

Observational studies, case reports, or non-pertinent comparison groups

1. Isono S, Suzukawa M, Sho Y, Ohmura A, Kudo Y, Misawa K, Inaba S, Nishino T: Preoperative nocturnal desaturations as a risk factor for late postoperative nocturnal desaturations. *Br J Anaesth* 1998; 80:602-605
2. Reeder MK, Goldman MD, Loh L, Muir AD, Casey KR, Lehane JR: Late postoperative nocturnal dips in oxygen saturation in patients undergoing major abdominal vascular surgery: predictive value of pre-operative overnight pulse oximetry. *Anaesthesia* 1992; 47:110-115
3. Rheineck-Leyssius AT, Kalkman CJ: Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room. *Br J Anaesth* 1997; 79:460-464
4. Stausholm K, Rosenberg-Adamsen S, Evaridsen L, Kehlet H, Rosenberg J: Validation of pulse oximetry for monitoring of hypoxaemic episodes in the late postoperative period. *Br J Anaesth* 1997; 78:86-87
5. Tinker JH, Dull DL, Caplan RA, Ward RJ, Cheney FW: Role of monitoring devices in prevention of anesthetic mishaps: a closed-claims analysis. *Anesthesiology* 1989; 71:541-546

End-tidal CO₂ monitoring vs no end-tidal CO₂ monitoring.

No entries

Monitoring level of sedation monitoring vs not monitoring level of sedation.

No entries

Timing and duration of monitoring.

Continuous vs intermittent monitoring (to improve detection of respiratory depression)

No entries

IV. Management of respiratory depression

Supplemental oxygen.

Randomized controlled trials

1. Fu ES, Downs JB, Schweiger JW, Miguel RV, Smith RA: Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. *Chest* 2004; 126:1552-1558

Nonrandomized comparative studies

1. Smith DC, Canning JJ, Crul JF: Pulse oximetry in the recovery room. *Anaesthesia* 44:345-348, 1989

Naloxone vs no naloxone.

Randomized controlled trials

1. Gueneron JP, Ecoffey C, Carli P, Benhamou D, Gross JB: Effect of naloxone infusion on analgesia and respiratory depression after epidural fentanyl. *Anesth Analg* 1988; 67:35-38
2. Rawal N, Schott U, Dahlstrom B, Inturrisi CE, Tandon B, Sjostrand U, Wennhager M: Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. *Anesthesiology* 1986; 64:194-201

Observational studies, case reports, or non-pertinent comparison groups

1. Baker MN, Sarna MC: Respiratory arrest after a second dose of intrathecal sufentanil. *Anesthesiology* 1995; 83:231-232
2. Blackburn C: Respiratory arrest after epidural sufentanil. *Anaesth* 1987; 42:665-666
3. Brockway MS, Noble DW, Sharwood-Smith GH, McClure JH: Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; 64:243-245
4. Christensen V: Respiratory depression after epidural morphine. *Br J Anaesth* 1980; 52:841
5. Davies GK, Tolhurst-Cleaver CL, James TL: Respiratory depression after intrathecal narcotics. *Anaesthesia* 1980; 35:1080-1083
6. Glynn CJ, Mather LE, Cousins MJ, Wilson PR, Graham JR: Spinal narcotics and respiratory depression. *Lancet* 1979; 2:356-357
7. Greenhalgh CA: Respiratory arrest in a parturient following intrathecal injection of sufentanil and bupivacaine. *Anaesthesia* 1996; 51:173-175
8. Krane EJ: Delayed respiratory depression in a child after caudal epidural morphine. *Anesth Analg* 1988; 67:79-82
9. Palmer CM: Early respiratory depression following intrathecal fentanyl-morphine combination. *Anesthesiology* 1991; 74:1153-1155
10. Sjogren P, Jakobsen S, Valentin N: Respiratory depression during epidural morphine treatment. *Acta Anaesth Scand* 1991; 35:553-555
11. Stenseth R, Sellevold O, Breivik H: Epidural morphine for postoperative pain: experience with 1085 patients. *Acta Anaesth Scand* 1985; 29:148-156

Naltrexone vs no naltrexone.

Randomized controlled trials

1. Abboud TK, Afrasiabi A, Davidson J, Zhu J, Reyes A, Khoo N, Steffens Z: Prophylactic oral naltrexone with epidural morphine: effect on adverse reactions and ventilating responses to carbon dioxide. *Anesthesiology* 1990; 72:233-237
2. Abboud TK, Lee K, Zhu J, Reyes A, Afrasiabi A, Mantilla M, Steffens Z, Chai M: Prophylactic oral naltrexone with intrathecal morphine for cesarean section: effects on adverse reactions and analgesia. *Anesth Analg* 1990; 71:367-370
3. Wittels B, Glosten B, Faure EA, Moawad AH, Ismail M, Hibbard J, Amundsen L, Binstock W, Senal JA, Cox SM: Opioid antagonist adjuncts to epidural morphine for postcesarean analgesia: maternal outcomes. *Anesth Analg* 1993; 77:925-932