6

Patient-controlled analgesia

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6.0 | Patient-controlled analgesia

Patient-controlled analgesia (PCA) refers to all methods of pain relief that allow a patient to self-administer small doses of an analgesic agent as required. Most often, the term PCA refers to programmable infusion pumps that deliver opioid medications IV. However, many other methods and routes of delivery using opioids as well as other analgesic agents have been described (SC, epidural, IT, SL, IN, oral, pulmonary, and TD). In addition to treating postoperative pain, PCA is used for pain following trauma and with cancer.

For epidural PCA see Section 5.6.3; for PCA use in labour see Section 9.1.3.1 and in children see Sections 10.5.2 to 10.5.4.

6.1 | Efficacy of intravenous PCA

6.1.1 | Analgesia, patient preference and outcomes

An updated Cochrane review is published (McNicol 2015 **Level I** [Cochrane], 49 RCTs, n=3,412); this includes only four RCTs since 2005, which may reflect the adoption of PCA into usual clinical practice. The meta-analysis compares IV PCA using full mu-opioids with intermittent full mu-opioids (usually IM morphine), and also includes the use of supplemental NSAIDs or paracetamol. The most frequently used opioid is morphine (33/49 RCTs); the most common bolus size is 1 mg and the most common lockout intervals are 5 to 10 min. There was a lack of head-to-head trials comparing different opioids via PCA so no comparison of opioids could be made. IV opioid by PCA for treatment of postoperative pain provides better analgesia than conventional (IM, SC) opioid regimens, although the magnitude of the difference in analgesia is small (MD 9.7/100; 95%CI 12.5 to 7 [0 to 48 h]). PCA use increases opioid consumption at 0 to 24 h (7 MME; 95%CI 1.4 to 13) and 25 to 48 h (5 MME; 95%CI 3 to 8). PCA improves number of patients satisfied (80% vs 61) (RR 1.32; 95%CI 1.12 to1.53) (11 RCTs, n= 547) and satisfaction scores (SMD 0.55; 95%CI 0.13 to 0.97) (7 RCTs, n=427). This benefit may relate to the increased autonomy that PCA confers. None of the studies measured 'readiness for discharge'. LOS does not differ (10 RCTs), but this outcome may have been dependent on other factors. Serious adverse event rates (including death, wound infections, atelectasis and adhesions) do not differ between the two groups (19 RCTs, n=1,284). However, as death is a rare event, larger patient numbers are required to reliably evaluate this outcome. Other adverse events occur similarly: sedation (15 vs 16%), respiratory depression (Sa02 ≤ 90% or RR <10/m or need for naloxone) (2.3 vs 2%) and nausea and/or vomiting (30 vs 32%), while pruritus was more frequent in the PCA group (15 vs 8%) (RR 1.8; 95%CI 1.1 to 2.8).

In an ED setting, IV PCA was as effective as nurse-administered IV bolus doses of opioid (Evans 2005 **Level II**, n=86, JS 3). In two other RCTs in the ED setting, PCA morphine provided more effective analgesia with more rapid onset and higher patient satisfaction than nurse-administered IV morphine (Rahman 2012 **Level II**, n=96, JS 3; Birnbaum 2012 **Level II**, n=211, JS 3).

Other information obtained from published RCTs as well as cohort studies, case-controlled studies and audit reports suggests that IV PCA may be appreciably more effective than intermittent IM opioid analgesia in a "real world" clinical setting; patients given IM opioid analgesia were more than twice as likely to experience moderate to severe pain and severe pain than those given PCA (Dolin 2002 **Level IV SR**, 165 studies, n≈20,000).

In settings where there are high nurse:patient ratios and where it might be easier to provide analgesia truly on-demand, conventional forms of opioid administration may be as effective as IV PCA. A comparison of PCA vs nurse-administered analgesia following cardiac surgery found no difference in analgesia at 24 h (a period when nursing attention is likely to be higher) but significantly better pain relief with PCA at 48 h (Bainbridge 2006 **Level I**, 10 RCTs, n=666).

The enormous variability in PCA parameters (bolus doses, lockout intervals and maximum permitted cumulative doses) used in many studies indicates uncertainty as to the ideal PCA program and may limit the flexibility, and thus the efficacy, of the technique. Individual PCA prescriptions may need to be adjusted if patients are to receive the maximal benefit (Macintyre 2015 **NR**; Macintyre 2008 **NR**; Macintyre 2005 **NR**).

A number of studies have shown that PCA provides less effective pain relief vs epidural analgesia. See Section 5.6.1.1 .

6.2 | Cost of PCA

The use of any analgesic technique, even if it is known to provide more effective pain relief, requires consideration of the cost involved. There is limited data on the economic assessment of PCA vs conventional opioid analgesic techniques; information that is available often does not include the full scope of costs (eg cost of adverse effects or failure of an analgesic technique, as well as the more obvious costs of pumps, disposables and nursing time). However, in general, PCA comes at a higher cost because of the equipment, consumables and medicine preparation; nursing time needed is much less (Chang 2004 **Level II**, n=125, JS 3; Choiniere 1998 **Level II**, n=126, JS 3; Rittenhouse 1999 **Level III-2**; Jacox 1997 **NR**). PCA was more cost-effective than epidural analgesia after major abdominal surgery (LOS and morbidity excluded) (Bartha 2006 **Level III-2**, n=644). In a subsequent assessment, PCA costs were estimated by analysis of a large administrative database covering 500 USA hospitals (Palmer 2014 **Level III-3**, n=11,805,513). The direct and indirect cost estimates (US$ in 2012) were assessed for the first 48 h after major surgery (TKA, THA and open abdominal procedures). The cost estimates range from US$196 to 243 per patient. Further estimates, adding in the costs of adverse effects of PCA programming errors, phlebitis and bacteraemia due to IV access, increased the costs to US$342 to 389 per patient. See also Section 3.3.

6.3 | Medicines used for parenteral PCA

6.3.1 | Opioids

In general, there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of adverse effects between morphine and other opioids commonly used in PCA, although the results of individual studies are inconsistent (for more details see 6.3.1.10 below). Most studies are not powered adequately to make conclusions about comparative safety, especially for respiratory depression.

On an individual patient basis, one opioid may be better tolerated than another and a change to an alternative opioid may be beneficial if the patient is experiencing intolerable adverse effects (Woodhouse 1999 **Level II**, n=82 [cross over], JS 4).

6.3.1.1 | Morphine

Morphine is still a commonly used opioid for IV PCA (Palmer 2014 **Level III-2**, n=11,805,513). Compared with other opioids, morphine has a long equilibration half-life between plasma and the CNS effect site (2 to 3 h) (Aubrun 2012 **NR**; Lötsch 2005 **NR**). Furthermore, morphine has an active metabolite, M6G, which has opioid effects, with an equilibration half-life of 7 h and a long elimination half-life (Lötsch 2005 **NR**). Simulated peak effect-site concentration for morphine occurs 8 to 24 h after the commencement of PCA (Sam 2011 **Level III-3 PK**, n=10). These pharmacokinetic features may make morphine less suitable for IV PCA use than other opioids. Limited clinical data suggest that morphine may have a higher incidence of sedation and respiratory depression than fentanyl (Hutchison 2006 **Level III-2**, n=241).

6.3.1.2 | Fentanyl

In general, there is limited evidence to show a difference between morphine and fentanyl in terms of pain relief or the incidence of most adverse effects (Woodhouse 1996 **Level II**, n=50, JS 5; Howell 1995 **Level II**, n=37, JS 3); pruritus was more common with morphine (Woodhouse 1996 **Level II**, n=50, JS 5). A retrospective cohort study of patients having hip or knee surgery found those receiving PCA fentanyl, when compared with morphine or hydromorphone, had lower pain scores and fewer opioid-related adverse effects (PONV, sedation, pruritus or urinary retention) (Hutchison 2006 **Level III-2**, n=241). Fentanyl PCA vs morphine PCA after cardiac surgery had a lower incidence of nausea (32 vs 52%) (Gurbet 2004 **Level II**, n=75, JS 3).

6.3.1.3 | Tramadol

Tramadol by IV PCA has similar analgesic efficacy vs other opioids by IV PCA, mainly vs morphine (7 RCTs) (Murphy 2010 **Level I**, 12 RCTs, n=782). However, the adverse-effect profile is different with the tramadol group experiencing more PONV (OR 1.52; 95%CI 1.07 to 2.14) but less pruritus (OR 0.43; 95%CI 0.19 to 0.98). There was no difference in sedation or fatigue. Data were insufficient to assess safety**.** Tramadol also has a lower risk of respiratory depression and less effect on gastrointestinal motor function compared with other opioids. See also Section 4.1.1.2.

6.3.1.4 | Hydromorphone

There is limited data examining the use of hydromorphone when delivered by IV PCA. A survey of a large USA inpatient database found that hydromorphone was the second most commonly used opioid for PCA after morphine (Palmer 2014 **Level IV**, n=11,805,513). When compared with morphine in patients having general surgery, there was no difference in adverse effects, pain relief or satisfaction (Hong 2008 **Level II**, n=50, JS 4). Hydromorphone and morphine IV PCA had similar rates of opioid-induced adverse effects, with fentanyl having the lowest in a retrospective comparison of patients after hip or knee surgery (Hutchison 2006 **Level III-2**, n=254). In a comparison of IV PCA morphine with hydromorphone in patients having open abdominal surgery, analgesia was equivalent and there were similar adverse effects (Rapp 1996 **Level II**, n=61, JS 3). The morphine group had less cognitive impairment and the hydromorphone group had better mood. A study of patients having IV PCA for oral mucositis pain after bone marrow transplantation found that hydromorphone vs morphine was equally effective for analgesia but hydromorphone had more frequent adverse effects (Coda 1997 **Level II**, n=119, JS 4). Comparing PCA hydromorphone with PCA sufentanil in patients having surgery for colorectal cancer found that postoperative mood assessment differed, with 'anger' being lower in the hydromorphone

group (Yang 2018 **Level II**, n=80, JS 5). This may be due to differences in opioid receptor type affinity.

Safety issues have occurred due to confusion about the name of the medicine and its high potency (5 times that of morphine) (NSW Health 2011 **GL**) (See also Section 9.5.5).

6.3.1.5 | Oxycodone

Oxycodone, unlike morphine, has a rapid equilibration with the CNS which might make it more suited to PCA use (Sadiq 2013 **BS** & **PK** [rodent]). Oxycodone IV PCA vs morphine IV PCA resulted in similar pain relief and adverse effects during the first 24 h after surgery (breast or spinal) (Silvasti 1998 **Level II,** n=50, JS 3). The dose requirements were similar. After laparoscopic hysterectomy, IV PCA oxycodone dose requirements were lower than with morphine (Lenz 2009 **Level II**, n=91, JS 4) with less sedation in the oxycodone group; pain scores were lower but only in the first h after surgery and thereafter were similar. After maxillofacial surgery, IV PCA oxycodone vs IV PCA tramadol provided equivalent analgesia (Silvasti 1999 **Level II**, n=54, JS 3).

In patients having laparoscopic gynaecological surgery, IV PCA oxycodone and PCA fentanyl produced equivalent analgesia and satisfaction. Dizziness was more common in the oxycodone group, whilst nausea and vomiting were the same (Park 2015 **Level II**, n=74, JS 4). In laparoscopic hysterectomy patients (who received ketorolac and ramosetron), IV PCA oxycodone improved pain relief vs PCA fentanyl, but increased adverse effects of PONV, dizziness, and drowsiness (Kim 2017 **Level II**, n=130, JS 5).

Trials to date are not adequate in sample size to assess if IV PCA oxycodone confers superiority over other opioids.

6.3.1.6 | Pethidine

Compared with morphine, IV PCA pethidine (meperidine) may lead to less effective pain relief on movement (Plummer 1997 **Level II**, n=102, JS 4; Sinatra 1989b **Level II**, n=75, JS 4; Bahar 1985 **Level II**, n=48, JS 1), no difference in nausea and vomiting (Plummer 1997 **Level II**, n=102, JS 4; Woodhouse 1996 **Level II**, n=50, JS 5; Stanley 1996 **Level II**, n=40, JS 5; Bahar 1985 **Level II**, n=48, JS 1) and less sedation (Sinatra 1989a **Level II**, n=75, JS 4) and pruritus (Woodhouse 1996 **Level II**, n=50, JS 5; Sinatra 1989b **Level II**, n=75, JS 4). IV PCA pethidine may cause more cognitive impairment than morphine (Plummer 1997 **Level II**, n=102, JS 4). Pethidine has a neurotoxic metabolite (norpethidine) that can accumulate during PCA administration and can cause adverse effects (Simopoulos 2002 **Level IV**, n=355; Stone 1993 **Level IV**, n=3; McHugh 1999 **NR**).

6.3.1.7 | Methadone

Methadone by IV PCA, in comparison to morphine, provided more effective pain relief at rest and during movement for the first 24 h after surgery, with no difference in adverse effects (Neto 2014 **Level II,** n=34 [trial discontinued prematurely], JS 4). It should be noted, that the pharmacokinetics of methadone are complex (and are not suited to IV PCA use in acute pain management) (Weschules 2008 **NR**). (See also Section 4.3.1.2)

6.3.1.8 | Other opioids

Remifentanil IV PCA provided at least equivalent analgesia vs morphine or fentanyl PCA and may be associated with less nausea and vomiting (Kucukemre 2005 **Level II**, n=69, JS 4; Gurbet 2004 **Level II**, n=75, JS 3). See also Section 9.1.3.1 for discussion of use of IV PCA remifentanil during labour.

6.3.1.9 | Opioid combinations

The combination of two opioids in the PCA syringe has been investigated.

There was no difference in pain scores and adverse effects between fentanyl/morphine and fentanyl by PCA, apart from slightly less nausea with the combination (Friedman 2008 **Level II**, n=64, JS 5).

Beneficial effects on pain relief and the incidence of pruritus in a comparison of morphine, nalbuphine and varying combinations of the two medicines were dependent on the ratio of medicines used (Yeh 2007 **Level II**, n=311, JS 5). The combination, when compared to morphine alone, provided improved analgesia and reduced nausea.

The combination of alfentanil/morphine IV PCA resulted in no differences in pain relief or adverse effects vs morphine alone, although patients who received alfentanil/morphine rated speed of onset and adequacy of analgesia as better (Ngan Kee 1999 **Level II**, n=80, JS 5). There was no improvement in pain-related sleep disturbance with this combination vs fentanyl alone but analgesia, both at rest and movement, was better in the first 24 h after surgery (Lee 2013 **Level II**, n=212, JS 5).

Compared with IV PCA tramadol alone, remifentanil added to tramadol improved pain relief but increased total opioid doses used (Unlugenc 2008 **Level II**, n=62, JS 4).

6.3.2 | Adverse effects of PCA opioids

As noted in Section 6.1.1 above, meta-analyses and individual studies have shown that, in general, the risk of adverse effects is similar for all opioids administered by PCA, regardless of the opioid used. However, individual patients may be intolerant of specific opioids but tolerant of others (Woodhouse 1999 **Level II**, n=82 [cross over], JS 4). In a network meta-analysis, adverse effects occur at differing frequencies for the various opioids at equianalgesic doses (Dinges 2019 **Level I** [NMA], 63 RCTs, n unspecified). Results were reported as a relative risk (morphine was the comparator);

- Nausea and vomiting, was most frequent with buprenorphine (RR 1.37; 95%CI 1.05 to 1.8) and least with fentanyl (RR 0.82; 95%CI 0.67 to 1.0). Other opioids were not different to morphine (39 RCTs, n=4,614);
- Pruritus was the most frequent with morphine, and the least frequent with methadone (RR 0.17; 95%CI 0.03 to 0.90) and pethidine (RR 0.47; 95%CI 0.25 to 0.87). Other opioids (including oxycodone, tramadol, fentanyl, hydromorphone and remifentanil) were not significantly different to morphine (39 RCTs, n=3,480);
- Sedation was least frequent with fentanyl, oxymorphone and pethidine. Other opioids were not different to morphine (31 RCTs, n=1,528);
- Satisfaction was highest with oxycodone, alfentanil, remifentanil, fentanyl, and pethidine. Tramadol had the least satisfaction. Other opioids were not different to morphine (17 RCTs, n=1,476).

OIVI is rare with 22 cases reported (n=2,452); sufentanil, alfentanil, remifentanil and morphine have the highest reported rates here.

Two reviews of published RCTs, cohort studies, case-controlled studies and audits reported the following incidences associated with IV PCA use: respiratory depression 1.2 to 11.5% (depending on whether respiratory rate or oxygen saturation were used as indicators), nausea 32%, vomiting 20.7% and pruritus 13.8% (Dolin 2005 **Level IV SR**, 183 studies [PONV] & 89 studies [sedation] & 166 studies [pruritus], n 100,000; Cashman 2004 **Level IV SR**, 165 studies, n 20,000). Excessive sedation was not used as an indicator of respiratory depression in any of the studies included in these reviews (see importance of sedation score in Section 4.3.1.4).

The incidence of respiratory depression (<10 breaths/min) with PCA morphine was 0.06% and no patient required naloxone (Cheung 2009 **Level IV**, n=5,137). The incidence of nausea was 47.4% and vomiting was 18.5%; these were most common in female patients and those having gynaecological surgery. The incidence of pruritus was 8%.

In 1.86% of patients who received PCA for postoperative pain relief, respiratory depression (defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2; defined as "asleep but easily roused") was identified; of these 13 patients all had respiratory rates of <10 breaths/min and 11 also had sedation scores of 2 (Shapiro 2005 **Level IV**, n=700).

Impact of adjuvants on IV PCA adverse effects

The combination of NSAIDs with IV PCA morphine reduces adverse effects vs IV PCA morphine alone:

- PONV is reduced by 30% (OR 0.70; 95%CI 0.53 to 0.88) (Maund 2011 **Level I**, 60 RCTs, n unspecified);
- Sedation is reduced by 29%, while respiratory depression, pruritus and urinary retention are not reduced (Marret 2005 **Level I**, 22 RCTs, n=2,307).

These benefits are most likely due to the opioid-sparing effect of concurrent NSAIDs, rather than a direct effect of NSAIDs themselves. Similar beneficial effects have also been found for the addition of IV ketamine via various regimens (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453; Wang 2016 **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap), gabapentin (Fabritius 2016 **Level I** [PRISMA], 132 RCTs, n=9,498), pregabalin (Fabritius 2017 **Level I** [PRISMA], 97 RCT, n=7,201), IV lidocaine (Weibel 2018 **Level I** [Cochrane], 68 RCTs, n=4,525) and the alpha-2 agonists clonidine (Sanchez Munoz 2017 **Level I** [PRISMA], 57 RCTs, n=14,790) and dexmedetomidine by various administration regimens (Wang 2018 **Level I** [PRISMA], 40 RCTs, n=2,401).

6.3.3 | Adjuvant medicines

Discussion of adjuvant medicines in this section will be confined to those added to the PCA opioid solution. For additional information see Chapter 4.

6.3.3.1 | Antiemetics

Droperidol added to the PCA morphine solution is effective in preventing nausea (NNT 2.7; 95%CI 1.8 to 5.2) and vomiting (NNT 3.1; 95%CI 2.3 to 4.8) with no apparent dose-responsiveness (Tramer 1999 **Level I**, 6 RCTs [droperidol], n=642). Adverse effects were not increased when the dose of droperidol was <4 mg/d. However, in a subsequent comparison of 0.5 mg, 1.5 mg and 5 mg droperidol added to 100 mg PCA morphine, the smallest dose had no significant antiemetic effect and the 1.5 mg dose was effective against nausea (NNT 6.3; 95%CI 3.3 to 100) but not vomiting (Culebras 2003 **Level II**, n=340, JS 4). The 5 mg dose significantly reduced both nausea and vomiting but at the cost of unacceptable sedation (NNH 6.4; 95%CI 4.1 to 15), which was not seen at the other doses. The 1.5 mg and 5 mg doses also reduced pruritus. There was no difference in dysphoric effects. In another RCT, droperidol 5 mg added to morphine 100 mg by PCA resulted in morphine-sparing and, in the first 24 h after surgery, reduced the frequency of PONV (Lo 2005 **Level II**, n=179, JS 5). While, droperidol given as a single dose at the end of surgery was as effective as adding droperidol to PCA morphine (Gan 1995 **Level II**, n=82, JS 3). The cost-benefit and risk-benefit of the routine addition of droperidol to PCA opioids must therefore be considered, because all patients receive the medication when not all will need it and some patients might receive inappropriately high doses of droperidol.

Evidence of benefit from the addition of $5HT_3$ antagonists to IV PCA is unclear. Ondansetron, given both as a bolus at the end of surgery and mixed with morphine in the PCA solution, reduced the incidence of nausea and the need for additional antiemetics but not the patients' perception of their overall satisfaction with care (Cherian 2001 **Level II**, n=81, JS 4). Adding ondansetron to PCA opioids reduces nausea and/or vomiting (NNT 2.9; 95%CI 2.1 to 4.7) (Tramer 1999 **Level I**, 2 RCTs [ondansetron], n=184). A later study showed that ondansetron given as an initial dose of 4 mg followed by 0.2 mg/1 mg morphine PCA morphine could reduce nausea and vomiting; although pain scores were higher (Boonmak 2007 **Level II**, n=160, JS4). The combination of ondansetron plus prochlorperazine to IV PCA morphine was more effective than ondansetron alone (Jellish 2009 **Level II**, n=150, JS 4).

Dexamethasone 8 mg given at the start of surgery reduced the incidence of severe nausea and vomiting only vs ondansetron at the end of surgery in patients receiving PCA fentanyl with added ondansetron (12 mg added to 2 mg fentanyl) (Song 2011 **Level II**, n=130, JS 4). The addition of midazolam to PCA morphine had a similar antiemetic effect to that of ondansetron but was associated with an increase in mild sedation (Huh 2010 **Level II**, n=90, JS 3).

6.3.3.2 | Ketamine

Two systematic reviews evaluated the effect of peri- and postoperative ketamine (sub-anaesthetic doses) coadministered as an adjuvant to PCA (morphine 15 RCTs and 1 RCT each in adults for tramadol & fentanyl and in adolescents for fentanyl & hydromorphone) (Assouline 2016 **Level I** [PRISMA], 19 RCTs, n=1,453) and to PCA morphine (33 RCTs, n=2,374) or PCA hydromorphone (3 RCTs, n= 128) (Wang 2016 **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap).

Adding ketamine to an opioid in the PCA pump in various ratios has benefits to pain scores at rest at 24 h (WMD 21.1/100; 98%CI 21.8 to 20.39) (9 RCTs, n=595) and opioid consumption (-28%) (7 RCTs, n=495) and PONV (-44%) (7 RCTs, n=435) (Assouline 2016 **Level I** [PRISMA], 19 RCTs, n=1,453). Respiratory depression (RR 0.31; 98%CI 0.06 to 1.51) (9 RCTs, n=871) and hallucinations (OR 1.16; 98%CI 0.47 to 2.79) (7 RCTs, n=690) are not increased. A parallel meta-analysis on ketamine added to morphine or hydromorphone PCA confirms these results (Wang 2016 **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap). There was no dose-response effect found and the optimum analgesic/sub-anaesthetic dose is uncertain.

IV Ketamine PCA vs hydromorphone PCA reduced supplemental analgesia and need for supplemental oxygenation, but was associated with more hallucinations (Takieddine 2018 **Level II**, n=20, JS 5).

The stability and compatibility of mixtures of tramadol with ketamine in polyolefin bags were satisfactory over a test period of 14 d at 4° and 25°C (Gu 2015 **BS**).

For more details see also Section 4.6.

6.3.3.3 | Naloxone

There was no analgesic benefit of adding naloxone to the PCA morphine solution (Cepeda 2004 **Level II**, n=265, JS 5; Sartain 2003 **Level II**, n=96, JS 5; Cepeda 2002 **Level II**, n=166, JS 5); with "ultra-low doses" only (naloxone 0.6 mcg per morphine 1 mg), the incidence of nausea and pruritus was decreased (Cepeda 2004 **Level II**, n=265, JS 5).

6.3.3.4 | Other adjuvants

Ketorolac added to morphine (Chen 2009 **Level II**, n=102, JS 5; Chen 2005b **Level II**, n=79, JS 5) or tramadol (Lepri 2006 **Level II**, n=60, JS 3) by PCA did not improve pain relief or alter the incidence

of adverse effects; however, it was opioid-sparing and led to an earlier return of bowel function after colorectal surgery (Chen 2009 **Level II**, n=102, JS 5).

The addition of lidocaine to morphine conferred no benefit in terms of pain relief or adverse effects (Cepeda 1996 **Level II**, n=195, JS 5).

The addition of clonidine to IV PCA morphine resulted in significantly better pain relief for the first 12 h only, and less nausea and vomiting vs morphine alone; there was no reduction in morphine requirements (Jeffs 2002 **Level II**, n=60, JS 5).

Dexmedetomidine/morphine by IV PCA resulted in better pain relief (at rest and movement), significant opioid-sparing (29%) and a lower incidence of nausea vs IV PCA morphine alone (Lin 2009 **Level II,** n=100, JS 5). Adverse cardiovascular effects, sedation or respiratory depression were not increased in the dexmedetomidine/morphine group. Dexmedetomidine/sufentanil IV PCA sufentanil IV PCA alone in patients having elective abdominal surgery (laparoscopic and open) improved pain relief at rest and with movement, nausea (25% vs 12.5%) and vomiting (18.2% vs 6.25%) (Gao 2018 **Level II**, n=210, JS 4).

Magnesium added to morphine was opioid-sparing and led to better pain relief (Unlugenc 2003 **Level II**, n=90, JS 3); added to tramadol, it was opioid-sparing but only provided better pain relief for the first 2 h (Unlugenc 2002 **Level II**, n=66, JS 4).

Midazolam/morphine IV PCA after spinal surgery reduced anxiety and provided a small reduction in the pattern of morphine consumption over time vs IV PCA morphine (Day 2014 **Level II,** n=29, JS 4). Sedation scores were not reported.

The addition of nalbuphine to PCA morphine resulted in reduced pruritus without affecting pain relief (Yeh 2008 **Level II**, n=311, JS 5).

6.4 | Program parameters for IV PCA

6.4.1 | Bolus dose

While the optimally sized bolus dose should provide good pain relief with minimal adverse effects, there are only limited data available concerning the effects of various dose sizes. In patients prescribed 0.5 mg, 1 mg and 2 mg bolus doses of morphine, most of those who were prescribed 0.5 mg were unable to achieve adequate analgesia, while a high incidence of respiratory depression was reported in those who received 2 mg (Owen 1989a **Level II**, n=21, JS 3). It was concluded that the optimal PCA bolus dose for morphine was therefore 1 mg.

Similarly, in patients prescribed 20, 40 or 60 mcg bolus doses of fentanyl, the larger dose was associated with an increased risk of respiratory depression and a conclusion was made that the optimal dose of fentanyl for use in PCA was 40 mcg (Camu 1998 **Level II**, n=150, JS 4). However in this study, each dose was infused over 10 min, which could alter the effect of that dose.

Four different demand doses of fentanyl (10, 20, 30 and 40 mcg) were assessed for the management of pain during changes of burns dressings. Pain relief was significantly better with the 30 mcg and 40 mcg doses; no patient became sedated or experienced nausea and vomiting (Prakash 2004 **Level II**, n=60, JS 2).

Rigid adherence to an "optimal" dose may not, however, lead to the best pain relief for all patients. If the prescribed dose is not "optimal" and not too small, the patient will be able to compensate to some degree by changing their demand rate. However, they will only compensate to a certain degree. Even if uncomfortable, patients may only average four demands/h, even though they could press the PCA button more frequently (Owen 1989a **Level II**, n=21, JS 3).

Initial orders for bolus doses should take into account factors such as a history of prior opioid use (see Section 9.7) and patient age (Macintyre 2015 **NR**; Macintyre 2008 **NR**). PCA morphine requirements are known to decrease as patient age increases (Gagliese 2008 **Level IV**, n=246; Macintyre 1996 **Level IV**, n=1,010) (see also Section 9.2.4.2). Subsequent bolus doses may require adjustment according to patient pain reports or the onset of any adverse effects.

The number of demands a patient makes, including the number of "unsuccessful" demands, is often used as an indication that the patient is in pain and as a guide to adjusting the size of the bolus dose. However, there may be a number of reasons for a high demand rate other than pain. For example, excessive PCA demands may correlate with anxiety, poor perioperative adaptation to surgery involving avoidance behaviour and intrusive thoughts, as well as high pain scores (Katz 2008 **Level IV**, n=117). See also Section 1.2.2 for additional information on the relationship between pain relief and psychological factors in PCA.

6.4.2 | Lockout interval

The lockout interval is a safety mechanism that limits the frequency of doses delivered to the patient. For maximum safety, it should be long enough to allow the patient to feel the full effect of one opioid dose before another dose can be delivered. However, if it is too long the effectiveness of PCA could be reduced. There were no differences in pain relief, adverse effects or anxiety when lockout intervals of 7 or 11 min for morphine and 5 or 8 min for fentanyl were used (Ginsberg 1995 **Level II**, n=78, JS 4).

6.4.3 | Concurrent background (continuous) infusions

When a background infusion is used, opioid will continue to be delivered regardless of the patient's sedation level or respiratory status. The addition of a continuous background infusion significantly increases the risk of respiratory depression (OR 4.68; 95%CI 1.20 to 18.21) (George 2010 **Level I** [Cochrane], 14 RCTs, n=769); in 12 of the 14 RCTs, morphine was used. The risk was increased in adults in comparison to children (OR 10.2; 95%CI 3 to 35) (11 adult, 1 mixed, 2 paediatric). The definition of respiratory depression in this meta-analysis was either respiratory rate ≤10, saturation ≤90% or $PaCO_2$ ≥50.

There is no good evidence to show that the addition of a background infusion to IV PCA improves pain relief or sleep or reduces the number of demands (Dal 2003 **Level II**, n=35, JS 3; Parker 1992 **Level II**, n=156, JS 2; Parker 1991 **Level II**, n=230, JS 3; Owen 1989b **Level II**, n=22, JS 2). In adults, the routine use of a background infusion is therefore cautioned against, although it may be useful in opioid-tolerant patients (see Section 9.7).

Limited data found that the use of time-scheduled decremental continuous infusion of opioid added to the PCA program provided better pain relief than bolus only PCA in women having laparoscopic gynaecological surgery (Zhu 2019 **Level II**, n=90, JS 5; Kim 2013 **Level II**, n=99, JS 4). The use of PCA with a variable rate feedback background infusion in patients having spinal fusion surgery showed equivalent analgesia, and less total opioid dose than PCA with a constant rate background infusion (Lee 2019 **Level II**, n=78, JS 5). Estimating the risk of respiratory depression with these techniques from small studies is not possible.

6.4.4 | Dose limits

Limits to the maximum amount of opioid that can be delivered over a certain period (commonly 1 or 4 h) can be programmed into most PCA machines. There is no good evidence of any benefit that can be attributed to these limits (Macintyre 2015 **NR**).

6.4.5 | Loading dose

There is enormous variation in the amount of opioid a patient may need as a "loading dose", and there is no good evidence of any benefit that can be attributed to the use of the loading dose feature that can be programmed into PCA machines. PCA is essentially a maintenance therapy; therefore adequate pain relief should be established before PCA is started by administration of individually titrated loading doses (Macintyre 2015 **NR**; Macintyre 2008 **NR**). IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy in the treatment of acute sickle cell pain (Rees 2003 **GL**).

When administering IV loading doses of opioids, lipophilic medicines such as fentanyl are more appropriate than morphine for titrating analgesia because they equilibrate more quickly with the brain. While plasma and CNS fentanyl levels equilibrate within minutes, morphine takes many hours, which can lead to OIVI occurring well after a patient has been deemed "comfortable" and discharged from a high acuity area to a lower level area (eg PACU or ED to the ward) (Aubrun 2012 **NR**; Lötsch 2005 **NR**).

6.5 | Efficacy of PCA using other systemic routes of administration

6.5.1 | Subcutaneous PCA

Data on the effectiveness of SC PCA vs IV PCA are variable and inconsistent. Both similar (Bell 2007 **Level II**, n=130, JS 3; Munro 1998 **Level II**, n=80, JS 3; White 1990 **Level II**, n=24, JS 5; Urquhart 1988 **Level II**, n=30, JS 1) and significantly better (Keita 2003 **Level II**, n=40, JS 3; Dawson 1999 **Level II**, n=100, JS 2) pain relief has been reported, as well as the same (Keita 2003 **Level II**, n=40, JS 3; Dawson 1999 **Level II**, n=100, JS 2; Munro 1998 **Level II**, n=80, JS 3; Urquhart 1988 **Level II**, n=30, JS 1) or higher incidence of nausea and vomiting (White 1990 **Level II**, n=24, JS 5) or pruritus (Bell 2007 **Level II**, n=130, JS 3). SC PCA vs IV PCA may result in higher opioid use (Bell 2007 **Level II**, n=130, JS 3; Dawson 1999 **Level II**, n=100, JS 2; White 1990 **Level II**, n=24, JS 5; Urquhart 1988 **Level II**, n=30, JS 1) or may not (Munro 1998 **Level II**, n=80, JS 3).

6.5.2 | Oral PCA

Oral PCA, using a modified IV PCA system, is as effective as IV PCA (Striebel 1998 **Level II**, n=64, JS 2). An oral PCA device has been developed that uses radiofrequency identification (RFID) technology to allow patients in an oncology ward access (subject to a lockout interval) to a medication-dispensing system at the bedside (Rosati 2007 **Level IV**, n=20).

The use of a computer-controlled oral PCA dispensing device (the PCoA® Acute Device) was compared to conventional nurse-administered on-request oral opioid analgesia in patients having a variety of elective surgical procedures (Wirz 2017 **Level II**, n=70, JS 3). This device allowed secure patient access to bedside oral opioid analgesia (oxycodone or morphine) via RFID technology with higher use of opioid analgesia.

6.5.3 | Sublingual PCA

A sublingual sufentanil tablet system (SSTS) has been trialled in both postsurgical and other acute pain settings. When compared to IV morphine PCA for analgesia after major abdominal or arthroplasty surgeries, SSTS 15 mcg provided analgesia that was noninferior to IV PCA with a similar rate of adverse effects and superior satisfaction ratings from patients and nursing staff (Melson 2014 **Level II**, n=357, JS 2). Specifically for postarthroplasty pain management, SSTS 15 mcg was found to be superior to placebo but with a higher rate of nausea and vomiting (Jove 2015 **Level II**, n=419, JS 5). For abdominal surgeries, the analgesia from SSTS was superior to placebo with similar adverse events profiles for 15 mcg (Ringold 2015 **Level II**, n=172, JS 5) and 30 mcg, with rapid onset of reported analgesic effect within 15 min of administration (Minkowitz 2017 **Level II**, n=161, JS 5). SSTS 30 mcg was also trialled for acute pain management in the ED setting (Miner 2018 **Level III-3**, n=76). See also Section 6.7.2.2 below.

6.5.4 | Intranasal PCA

IN PCA fentanyl can be as effective as IV PCA (Paech 2003 **Level II**, n=24, JS 3; Manjushree 2002 **Level II**, n=40, JS 4; Toussaint 2000 **Level II**, n=57, JS 3; Striebel 1996 **Level II**, n=50, JS 2), as is IN PCA butorphanol (Abboud 1991 **Level II**, n=186, JS 2). As would be expected from the data on IN bioavailability of opioids (see Section 5.5.2), higher doses are needed via the IN route (Manjushree 2002 **Level II**, n=40, JS 4; Striebel 1996 **Level II**, n=50, JS 2). IN PCA pethidine is as effective as IV PCA pethidine, although larger doses are needed (Striebel 1993 **Level II**, n=112, JS 3), and more effective than SC injections of pethidine (Striebel 1995 **Level II**, n=44, JS 2).

Diamorphine IN PCA (bolus doses of 0.5 mg) is less effective than IV PCA morphine (non-equivalent higher bolus doses of 1 mg were used) after joint arthroplasty surgery (Ward 2002 **Level II**, n=52, JS 2). It provided better pain relief in doses of 0.1 mg/kg vs 0.2 mg/kg IM morphine in children with fractures (Kendall 2003 **NR**). See also Section 6.7.2.3 below.

6.5.5 | Transdermal PCA

Iontophoretic TD fentanyl PCA provided analgesia superior to placebo but significantly more patients in the TD group withdrew because of inadequate analgesia vs IV PCA morphine (Poon 2009 **Level I** [QUOROM], 6 RCTs, n=2,866). There was no difference in patient global assessment.

Maximum blood concentrations of fentanyl were the same if the fentanyl patient-controlled TD patch was placed on the chest or upper outer arm, but less if placed on the lower inner arm; the pharmacokinetics were not affected by gender, ethnicity, age or weight (Gupta 2005 **Level IV PK**). See also Section 6.7.2.4 below.

6.6 | Safety and complications related to PCA

Complications related to the use of PCA can be divided into operator or patient-related errors, and problems due to the equipment, practice environment or opioid used.

A large case series of PCA use (by IV, epidural and regional routes) including various device types (elastomeric, CO2 driven, semiprogammable disposable and programmable electronic) reported an incidence of adverse events related to with human error (0.74%), and device-related errors (0.19%) (Son 2019 **Level IV**, n=82,685). Human error in this study included the process of PCA solutions prepared by clinical staff rather than prepared commercially. The highest device error-rates occurred in the programmable electronic device group. Adverse events were associated with 63% of the errors and two patients had severe respiratory depression requiring ICU admission; there was no PCA-related death.

An early prospective study of patients given PCA postoperatively found nine cases of respiratory depression (Looi-Lyons 1996 **Level IV**, n=4,000). These were associated with drug interactions, continuous (background) infusions, nurse- or physician-controlled analgesia, and inappropriate use of PCA by patients. A similar sized prospective study showed that use of PCA was associated with 14 critical events: 8 programming errors (all associated with the setting of a continuous infusion); 3 family members activating PCA; 1 patient tampering; and 3 errors in clinical judgment (Ashburn 1994 **Level IV**, n=3,785).

Analysis of data from the USA FDA's Manufacturer and User Facility Device Experience (MAUDE) database shows that 76.4% of adverse effects related to IV PCA were attributed to technical problems with devices (eg frayed wires or cracks in syringes/ cartridges) and 6.5% were caused by operator error (Schein 2009 **Level** IV, n=2,009 [events]). Of these operator errors (n=131 events), most (81%) related to pump misprogramming and 48% were associated with patient harm. In contrast, only 0.5% of technical device problems resulted in patient harm.

A later retrospective analysis (from July 2000 to June 2005) reported to a national voluntary medication error-reporting database (MEDMARX), showed that PCA-related medication errors continue where 9,571 (1%) were related to PCA use (Hicks 2008 **Level IV**, n= 919,241 [errors]). Of these, 624 (6.5%) were associated with patient harm. By comparison, only 1.5% of medication error reports in general led to harm. The majority of PCA errors occurred during the administration of the medication. Of these, 38% were errors in dose or quantity, 17.4% involved an omission and 17.3% were related to an unauthorised or wrong medicine; human

factors were the main cause of errors; distractions (37.8%) and inexperienced staff (26.3%) were the leading contributing factors. Overall, human factors were the leading cause of PCA errors. A postmarketing surveillance program (2011 to 2016) by the FDA identified 1,430 events with use of IV PCA, of which 11% were associated with an unfavorable clinical outcome; device related issues, which were mostly identified as preventable, occurred in 87% of these (Lawal 2018 **Level IV**, n=1,430 [events]). The authors suggest that education, training and development of improved safety features for PCA devices are needed to improve the overall safety of PCA use.

The implementation of "smart pump" technologies may reduce the incidence and severity of PCA pump programming errors (Ohashi 2014 **Level IV SR** [PRISMA], 22 studies, n unspecified; Mai 2012 **Level III-3**). These technologies include the adoption of standardised and preselected medicine concentrations and dosages. Additionally, the extent of dose sizes is limited to safe ranges through the use of "soft" and "hard" limits.

The safety of PCA can be improved by the use of a hospital-wide safety improvement program (Paul 2010 **Level III-3**, n=25,198). A large prospective survey initially found that the incidence of errors with the use of PCA was 0.25%. Following the introduction of a safety improvement initiative, the incidence of PCA errors was reduced to 0.09% (OR 0.28; 95%CI 0.14 to 0.53).

The costs and rates of errors due to the use of IV PCA were estimated from two large safety-reporting databases in the USA (Meissner 2009 **Level IV**). The datasets included medication errors and device errors. The estimated average cost of a PCA adverse effect in the medication error dataset was US$733, whereas the cost related to a pump error was US$552. An error which lead to patient harm cost 120–250 times more than a non-harmful error. The estimated annual error rates per 10,000 patients in the USA using PCA were 407 for PCA drug errors and 17 for PCA device errors.

The safety of PCA prescribing and patient observation may be improved by the adoption of a common and standardised form and process that incorporates human factors and safety triggers (Agency for Clinical Innovation 2014 **GL**).

PCA safety can be addressed through a variety of strategies including the adoption of new and emerging technologies such as bar-code scanning of prefilled syringes, computer provider order entry (electronic medication management), and feedback using continuous capnography in combination with pulse oximetry (Ocay 2018 **NR**).

For more detail on adverse effects due to the opioid administered, equipment used or operator and patient-related factors, see Sections 6.3, 6.7 and 6.8 respectively.

6.7 | Equipment

Both programmable PCA pumps and disposable PCA devices are available.

6.7.1 | Programmable PCA pumps

These types of pumps allow significant flexibility of use. Adjustments can be made to the dose delivered and lockout intervals, background infusions can be added and accurate assessments can be made of the total dose of medicine delivered. In addition, access to the syringe (or other medicine reservoir) and the microprocessor program is only possible using a key or access code.

All require disposable items eg generic or dedicated syringes or cartridges, antisiphon valves (to prevent siphoning of medicine from the medicine reservoir) and anti-reflux valves (to prevent backflow of medicine into the IV infusion line). See Section 6.7.3 below.

6.7.2 | Disposable PCA devices

6.7.2.1 | Parenteral PCA devices

Disposable PCA devices are often based on the same physical principle; the volume of pressurised fluid delivered (dependent upon spring or elastomer technology) is determined by mechanical restrictions within the flow path and the speed of filling of the bolus dose reservoir determines the lockout interval (Skryabina 2006 **NR**). Advantages include small size and weight, freedom from an external power source, elimination of programming errors and simplicity of use. Disadvantages include an inability to alter the volume of the bolus dose delivered or add a background infusion, difficulties accurately determining the amount of medicine the patient has received, the possibility of inaccurate flow rates, and long-term costs (Skryabina 2006 **NR**). There may also be security issues as the medicine reservoirs for these devices are more readily accessible.

6.7.2.2 | Sublingual PCA devices

A sublingual sufentanil tablet system (SSTS) has been developed commercially and incorporates a hand-held computerised dispenser which is activated by an RFID tag linked to an individual patient, and dispenses SL sufentanil 15 to 30 mcg tablets in a patient-controlled manner with a 20 min lockout (Frampton 2016 **NR**).

6.7.2.3 | Intranasal PCA devices

Metered-dose PCINA devices are available. The medicines must be administered in small volumes to avoid significant run-off into the pharynx.

Initial PCINA devices delivered sprays of a reasonable dose but a large volume (eg 25 mcg fentanyl/0.5 mL) (Striebel 1996 **Level II**, n=50, JS 2; Striebel 1993 **Level II**, n=112, JS 3) or smaller volume but with smaller doses than commonly used with IV PCA (eg 9 mcg fentanyl/0.180 mL) (O'Neil 1997 **Level IV**, n=10). A specially formulated solution of 300 mcg/mL fentanyl has been used in a device that enables fentanyl doses of 54 mcg to be delivered in just 0.18 mL (Paech 2003 **Level III-1**, n=21).

6.7.2.4 | Transdermal PCA devices

The iontophoretic TD PCA fentanyl system uses a low-intensity electric current to drive the medicine from the reservoir through the skin and into the systemic circulation (Scott 2016 **NR**). The IONSYS device, which is applied to the chest or upper outer arm, delivers a fixed dose of 40 mcg fentanyl over a 10-min period following a patient demand and allows delivery of up to 6 doses/h, up to a maximum of 80 doses in 24 h (Power 2008 **NR**). This device must be replaced every 24 h and is designed for in-hospital use only.

After initial technical difficulties related to corrosion, the device was reapproved by the FDA for short-term use in hospitalised patients in 2015; however, the manufacturer discontinued sale and distribution for business reasons in June 2017 (The Medicines Company 2017).

6.7.3 | Equipment-related complications

In general, modern PCA pumps have a high degree of reliability. However, problems continue to be reported as well as problems related to the disposable items required. Information regarding complications due to equipment problems is mainly case-series or report-based.

While the number of reports of "run-away" pumps, where the PCA pump unexpectedly delivers an unprescribed dose of medication (Notcutt 1990 **Level IV**, n=1,000), has decreased following changes made to pump design, they continue to occur, including a report of spontaneous triggering (Christie 1998 **CR**) and of a frayed wire in the demand apparatus leading to triggering as a result of an electrical short circuit (Doyle 2001 **CR**).

Uncontrolled siphoning of syringe contents when the PCA machine was above patient level has been reported following cracked glass PCA syringes (ECRI 1996 **CR**; Thomas 1988 **CR**), failure of a damaged drive mechanism to retain the syringe plunger (Kwan 1995 **CR**), improperly secured PCA cassettes (ECRI 1995 **CR**) and broken medication cartridge syringe (Doyle 2008 **CR**). To minimise the risk of siphoning, the use of antisiphon valves is recommended (ECRI 1996 **CR**).

Antireflux valves are essential if the PCA infusion is not connected to a dedicated IV line. The non-PCA infusion tubing should have an antireflux (one-way) valve upstream from the connection with the PCA line to prevent back-flow up the non-PCA line should distal obstruction occur; otherwise, inappropriate dosing can occur (Rutherford 2004 **CR**; Paterson 1998 **CR**)

In response to concern about problems with infusion pumps, including PCA pumps, in 2010 the FDA commenced the Infusion Pump Improvement Initiative. Areas for improvement included software, design of user interface, and mechanical and electrical defects (FDA 2010 **GL**). Device-related errors occurred in 0.19% of patients in a large series (Son 2019 **Level IV**, n=82,685). The highest device error-rates occurred in the programmable electronic device group. See also Section 6.6 above.

6.8 | Patient and staff factors

6.8.1 | Patient factors

Patient factors play a role in the effectiveness of PCA as well as complications that can arise from its use; as for equipment issues, much of the information regarding complications due to patient factors is case-based. Psychological factors that may affect PCA use and efficacy are discussed in Section 1.2.2.

6.8.1.1 | Education

Few controlled studies have evaluated the influence of information provision on PCA use. Of patients surveyed who used PCA, approximately 20% were worried that they may become addicted, 20% felt that the machine could give them too much medicine and 30% that they could self-administer too much opioid (Chumbley 1998 **Level IV**, n=200). In a follow-up study, the same group conducted focus groups with previous PCA users, developed a new information leaflet and then undertook a randomised study comparing the old and new leaflet. They found that patients wanted more information on the medication in the PCA, the possible adverse effects and assurance that they would not become addicted (Chumbley 2002 **Level IV**, n=100).

Comparisons have been made between different forms of education given to patients about PCA and results are inconsistent. In an assessment of patient information delivered using structured preoperative interviews or leaflets vs routine preoperative education, patients given leaflets were better informed and less confused about PCA and became familiar with using PCA more quickly but there were no effects on pain relief, worries about addiction and safety or knowledge of adverse effects; the structured preoperative interview resulted in no benefits (Chumbley 2004 **Level III-2**, n=225). Another comparison of structured education vs routine information showed that overall analgesic efficacy, adverse effects and recovery times were not affected by the education program (Lam 2001 **Level II**, n=60, JS 2). Patients who were shown a video on PCA prior to surgery had better knowledge about the technique and reported better pain control after surgery (Chen 2005a **Level III-2**, n=60; Knoerl 1999 **Level III-2**).

6.8.1.2 | Inappropriate use of PCA

The safety of PCA depends on an adequate understanding of the technique by the patient and the fact that unauthorised persons do not press the demand button.

Oversedation with PCA has followed the patient mistaking the PCA handset for the nurse-call button, and family or unauthorised nurse-activated demands ("*PCA by proxy*") (Tsui 1997 **Level IV**, n=2,509; Sidebotham 1997 **Level IV**, n=6,035; Ashburn 1994 **Level IV**, n=3,785; Fleming 1992 **Level IV**, n=1,122; Chisakuta 1993 **CR**; Wakerlin 1990 **CR**).

There have been case reports expressing concerns that patients can use PCA to treat increasing pain and therefore mask problems such as compartment syndrome (Richards 2004 **Level IV**, n=4; Harrington 2000 **CR**), urinary retention (Hodsman 1988 **CR**), pulmonary embolism (Meyer 1992 **CR**) and myocardial infarction (Finger 1995 **CR**). However, appropriate routine patient monitoring should detect changes in pain scores and analgesic consumption enabling identification of such complications.

6.8.2 | Nursing and medical staff

The information regarding complications due to nursing and medical staff factors is also case-based.

Of 9,571 PCA-related adverse effects, 69.8% were related to human factors (Schein 2009 **Level IV**). Improper dose and quantity was the most common factor in 38.9%.

As noted above, operator error is a common safety problem related to PCA use (Looi-Lyons 1996 **Level IV**, n=4,000; Ashburn 1994 **Level IV**, n=3,785). Misprogramming of PCA pumps is thought to account for around 30% of PCA errors, be twice as likely to result in injury or death than errors involving general-purpose infusion pumps and lead to more harm than errors in other types of medication administration (ECRI 2006 **NR**). Mortality from programming errors has been estimated to range from 1 in 33,000 to 1 in 338,800 patients prescribed PCA (Vicente 2003 **NR**).

A number of reports involve the programming of medication concentrations that were lower than the concentration used, with the resultant delivery of an excessive amount of opioid leading to respiratory depression and sometimes death (ECRI 2002 **Level IV**; ECRI 1997 **Level IV**). The use of an incorrect prefilled "standard syringe" for PCA (morphine 5 mg/mL instead of the prescribed 1 mg/mL) also had a fatal outcome (Vicente 2003 **CR**). It has been suggested that medicine concentrations should be standardised within institutions to reduce the chance of administration and programming errors (ECRI 2002 **Level IV**).

PCA pumps using "smart pump" technology now incorporate dose error reduction systems described in Section 6.2 above.

Inappropriate prescriptions of supplementary opioids (by other routes) and sedative medicines (including some antihistamines) can lead to oversedation and respiratory depression (Tsui 1997 **Level IV**, n=2,509; Ashburn 1994 **Level IV**, n=3,785; Lotsch 2002 **NR**).

Human error occurred in 0.74% of patients in a large series, including mistakes with the preparation of PCA solutions by clinical staff rather than prepared commercially (Son 2019 **Level IV**, n=82,685). Documentation of the management of patient care during PCA use can be significantly improved with the PCA smart pump transmitting data directly into the electronic medical record. This automated integration resulted in an increased rate of fully completed PCA charts from 38% to 91% (Suess 2019 **Level III-3**, n=113).

6.9 | PCA in specific patient groups

For PCA use in the paediatric patient see Section 10.5.2, the obstetric patient Section 9.1.3.1,, the elderly patient Section 9.2, the patient with sleep disordered breathing Section 9.4, and the opioid-tolerant patient Section 9.7 respectively.

KEY MESSAGES

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane Review]).
2. Opioid administration by IV PCA leads to higher opioid consumption, a higher incidence of pruritus, but no difference in other opioid-related adverse effects, or hospital stay compared with traditional methods of intermittent parenteral opioid administration (**S**) (**Level I** [Cochrane Review]).

3. Patient satisfaction with intravenous PCA is higher when compared with conventional regimens (**S**) (**Level I** [Cochrane Review]).
4. The adjuvant use of ketamine with PCA opioid (in varying ratios) improves pain relief and reduces opioid consumption along with nausea and vomiting, with no increase in neurocognitive effects including hallucinations (**N**) (**Level I** [PRISMA]).
5. Iontophoretic transdermal fentanyl PCA is not as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**U**) (**Level I** [QUOROM]).
6. In settings where there are high nurse to patient ratios, there may be no difference in the effectiveness of PCA and conventional parenteral opioid regimens (**U**) (**Level I**).
7. Tramadol via intravenous PCA provides effective analgesia comparable to morphine by intravenous PCA (**U**) (**Level I**).
8. The addition of a background infusion to intravenous PCA morphine in adults increases the incidence of respiratory depression (**U**) (**Level I**) and does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
9. Different opioids by intravenous PCA show different rates of adverse effects; fentanyl PCA has the least rates of sedation, nausea and vomiting while pruritus is most frequent with morphine PCA (**N**) (**Level I** [NMA]). Furthermore, on an individual patient basis, one opioid may be better tolerated than another (**U**) (**Level II**).
10. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however, the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
11. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
12. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
13. In the emergency department, PCA morphine compared with IV morphine administered by nursing staff, provides more effective analgesia with more rapid onset and with higher patient satisfaction (**U**) (**Level II**).
14. The safety of PCA use can be significantly improved by hospital-wide safety initiatives (equipment, guidelines, education, monitoring) (**U**) (**Level III-3**).
15. The adoption of “smart pump” technologies in PCA design can improve documentation of patient care (**N**) (**Level III-3**), reduce programming errors and improve safety (**N**) (**Level IV SR**).
16. Operator-error, in particular programming error, remains a common safety problem with PCA useoften leading to patient harm (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ There is insufficient data to compare the risk of rare but serious adverse events with PCA opioid use to conventionally administered opioid analgesia (**N**).

☑ Adequate analgesia needs to be attained prior to commencement of PCA. Initial orders for bolus doses should consider individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted (**U**).

- ☑ The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration (**U**).
- ☑ PCA infusion systems must incorporate anti-siphon valves and, in non-dedicated lines, antireflux valves (**U**).
- ☑ Drug concentrations, prescription and observation forms should be standardised to improve patient safety (**U**).
- ☑ The pharmacokinetics of morphine (long equilibration half-time and active metabolites) may make it less suitable for PCA use than other opioids (**U**).
- ☑ Pethidine, when used in PCA, may cause central nervous system toxicity due to the accumulation of norpethidine (**U**).
- ☑ Improved methods of patient monitoring (eg continuous pulse oximetry, continuous capnography) may offer opportunities to improve safety in at-risk patient groups (**N**).

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