



Subcutaneous or intravenous opioid administration by patient-controlled analgesia in cancer pain: a systematic literature review

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Received: 25 January 2018 / Accepted: 20 July 2018 / Published online: 28 July 2018

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Abstract

Context Opioids administered by various routes are a mainstay of tumour-related pain management. Subcutaneous or intravenous patient-controlled analgesia (PCA) with opioids is an appropriate and safe form of treatment for postoperative pain but studies on this form of administration are sparse in the setting of cancer pain despite widespread use.

Objective To evaluate the published studies on opioids administered by subcutaneous and intravenous patient-controlled analgesia for patients with cancer pain.

Methods Articles were identified from the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 7, 2016), PubMed (Medline; 1975 to 2016) and EMBASE (1974 to 2016). Additional reports were identified from the reference lists of retrieved papers. Studies based on original data with a focus on intravenous or subcutaneous PCA administration of opioids in patients suffering from cancer-related pain were selected. The language was restricted to Dutch, English or German. Predefined information was extracted depending on the topic.

Results Fifty studies published since 1980 met the inclusion criteria. A wide range of study designs, study quality and research objectives were observed. The studies indicated use of standard or by proxy PCA in the inpatient and outpatient setting were safe and useful while significant adverse effects were rarely observed.

Conclusion This systematic review of the current evidence suggests PCA can be appropriately used in a wide range of clinical situations.

Keywords Patient-controlled analgesia · Cancer · Pain · Opioid · Review

Introduction

Pain is a frequent and disturbing symptom of cancer. This is reflected in the rising prevalence of pain in patients with

cancer from 50% at the time of diagnosis to approximately 80% in patients with advanced cancer [1, 2].

The cornerstone of cancer-pain management is the administration of an opioid analgesic agent by various routes. Oral administration is the preferred and, often, the initial route as recommended by the World Health Organisation [2, 3], but there are circumstances that demand parenteral administration especially when patients require rapid-onset analgesia or for those who cannot tolerate oral agents.

There are several ways to achieve rapid-onset analgesia which includes the use of subcutaneous (sc) or intravenous (iv) patient-controlled analgesia (PCA) [2, 3] especially when there is a need for other parenteral medication(s) [4]. The PCA device can be programmed for both a background infusion rate and bolus dose, interval between doses, and hourly maximum dose with the two most common modes of administration being demand dosing or continuous infusion plus demand

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00520-018-4368-x>) contains supplementary material, which is available to authorized users.

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dosing. Therefore, PCA allows a continuous infusion of an opioid to be administered via a programmable pump providing a constant plasma concentration as well as enabling the patient to voluntarily control their pain by use of on-demand supplemental boluses [5]. PCA therapy is presumed to benefit a patient's pain management by avoiding delays in the administration of analgesia, making it easier to titrate the dose of medication and being more adaptable to the patients' need for analgesia [6]. These are the type of benefits that make PCA ideal for use in palliative care, outpatient care and breakthrough pain management in cancer patients while PCA by proxy allows these advantages to also be accessible to young or ill children and patients with cognitive or physical disability.

The safety and efficacy of PCA administered opioid has been thoroughly investigated for the management of postoperative pain and guidelines are well defined [7, 8]. Unfortunately the same cannot be said for PCA opioid administration in cancer pain despite the wide use of opioids in this setting [9]. The purpose of this systematic review is to evaluate the safety, efficacy and usefulness of parenteral PCA opioid administration in cancer pain directly related to the tumour.

Methods

An integrative evaluation concept was used to guide this review [10] allowing for selection of studies using a wide variety of study designs including non-randomised studies.

Search strategy

In July 2016, a systematic literature search of PubMed (Medline; 1975–2016), EMBASE (1974–2016) and the Cochrane Central Register of Controlled Trials (The Cochrane Library, issue 7) was performed for studies in Dutch, English or German language. A search strategy was developed with a librarian expert at Radboud University Nijmegen. The search strategy for PubMed is presented in Table 1 and was adapted for other databases (complete search strategy tabled as supplement S1, Appendix). A hand search of the reference lists of identified papers was also performed and identified articles loaded into Endnote X5, when duplicates were deleted.

Data collection

The title and abstracts of identified studies were independently reviewed (LN and PS) for eligibility in a blinded and standardised manner using predefined inclusion criteria (Table 2). If more information was required to make a classification, then full-text articles were obtained and reviewed. All full-text articles were then read and rated independently (LN

Table 1 Used search terms

PUBMED
(“Analgesia, Patient-Controlled”[Mesh] OR “analgesia, patient-controlled” [tiab] OR “analgesia, patient controlled” [tiab] OR “Patient-Controlled Analgesia” [tiab] OR “Patient Controlled Analgesia” [tiab] OR “patient-controlled intravenous analgesia” [tiab] OR “patient controlled intravenous analgesia” [tiab] OR “patient-controlled subcutaneous analgesia” [tiab] OR “patient controlled subcutaneous analgesia” [tiab] OR “patient controlled administration” [tiab] OR “patient-controlled administration”[tiab])
AND
(“Neoplasms”[Mesh] OR “cancer” [tiab] OR “tumor” [tiab] OR “tumour” [tiab] OR “neoplasm” [tiab])
AND
(“Pain”[Mesh] OR “pain” [tiab])

and PS) with discrepant eligibility ratings discussed to see if a consensus could be achieved. If consensus could not be reached ($n = 19$), an independent expert in pain medicine (BZ or MF) was available to provide a blinded adjudicating decision.

In this review, we only included studies that reported on pain directly related to a tumour. We did not include studies on treatment-related pain.

Data analysis

All included studies were assessed and rated for quality (LN and PS) using assessment forms appropriate for the study type (see Table S3) and data extracted using predetermined data collection forms (see Table S2).

Results

Of the 1429 identified articles after the database search, 937 were found to be relevant with a further 10 references found after a search of the reference lists of these studies. Screening of these 947 abstracts resulted in 129 full-text articles being obtained for eligibility assessment. Inclusion criteria were met by 62 papers of which 12 were excluded after further discussion with an expert in pain medicine (BZ or MF).

The 50 studies identified included 6 randomised controlled trials (RCTs), 16 prospective observational studies, 11 case series and 17 descriptive studies, of which, 9 were case studies. All but one of the prospective studies [11] was performed before the year 2000.

The literature search is presented in Fig. 1.

Evidence for safety and efficacy with inpatients

In total, 20 articles ($n = 1369$ subjects) reported on safety and efficacy outcomes for inpatient PCA use in palliative and non-palliative cancer pain management [6, 9, 11–28].

Table 2 Eligibility criteria for review

Inclusion criteria (study characteristics)	
Type of patients	Primary patients suffering from cancer related pain
Type of intervention	Opioids with i.v. or s.c. administration via a patient-controlled analgesia device
Type of studies	Studies based on original data
Exclusion criteria (report characteristics)	
Type of patients	Other than cancer related pain, e.g. mucositis or postoperative pain
Type of intervention	Administration form other than i.v. or s.c. PCA or analgesia than other opioids
Type of studies	Studies not based on original data (e.g. reviews).
Language restrictions	Articles not published in English, Dutch or German
Unavailable full-text	No full-text availability by Subito or on author's request
Double reporting ^a	
Absence of reporting of exact statistics	

^a In case of multiple articles reporting on the same patient cohort, the article reporting on the largest sample will be considered for review

Four randomised (double-blind) crossover studies were described [16, 23, 27, 28]. Three compared PCA sc injection with continuous infusion of hydromorphone [16], epidural and sc continuous morphine administration [23] and continuous sc infusion of hydromorphone with and without PCA availability [27]. The last RCT compared the duration of analgesia produced by iv morphine and methadone [28]. Results of all four RCTs confirm that most patients had adequate

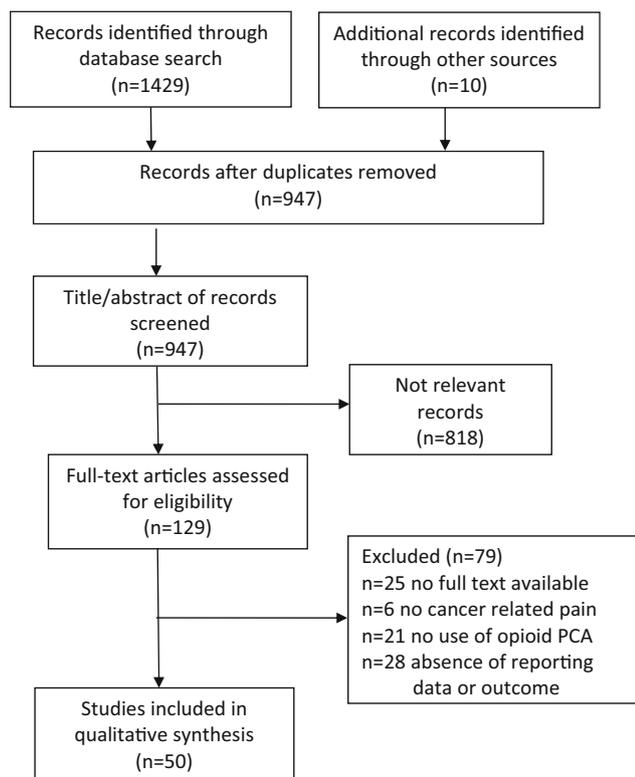
overall pain control due to PCA. None of the RCTs achieved a significant result.

There were eight observational prospective studies [11–13, 15, 18, 19, 21, 22] of which only two [11, 21] were of sufficient quality to inform this review. Enting et al. evaluated the efficacy of parenteral (iv or sc) opioids in 100 patients with cancer pain to show a significant decrease of mean pain intensity (0–10 scale) at rest and during movement [21]. Ruggiero et al. revealed a significant decline in pain intensity score (VAS, AFS) at 4 and 48 h of iv fentanyl PCA use in eight paediatric inpatients older than 6 years with moderate to severe cancer pain [11].

Among the six retrospective studies [6, 9, 12, 14, 17, 24], three used a validated tool (VAS or NRS) to describe relief from pain in subjects [9, 14, 17]. For example, Schiessl et al. reported a median pain score (NRS) of 1.0–4.0 at rest compared with 3.5–7.0 with movement among 141 cancer pain patients using a morphine PCA (iv and sc) [9].

In general, the identified articles report that PCA is an effective and safe method to reduce cancer-related pain for inpatients. The well-known adverse effects of opioids, such as sedation, nausea and constipation, were commonly reported, but only two studies identified major adverse effects. Bruera et al. (1988b) reported 6 of 108 adults with cancer experienced severe sedation, and 1 patient experienced respiratory depression [12]. Moulin et al. reported a respiratory complication in one subject ($n = 60$) during dose titration requiring naloxone reversal [29]. The only other adverse event reported was the risk of hypoglycaemia in the observational study of Flory et al. where methadone PCA ($n = 641$) at > 40 mg methadone oral equivalent a day was associated with an increased risk of hypoglycaemia [22].

Four studies specifically reported on the use of PCA for palliative care in paediatric inpatients [11, 14, 24, 26].

**Fig. 1** flowchart of literature search

Angheliescu et al. describe the pain scores and complications of 43 children with cancer using opioid PCA for pain control during the last 2 weeks of life. The mean daily equivalent dose of morphine (MED) and benzodiazepine requirement increased over this time in response to an increase in the mean pain score [14]. In all four paediatric studies, there were no documented severe respiratory complications (respiratory depression or apnoea) requiring naloxone administration or mechanical ventilation [11, 14, 24, 26].

Patient care studies generally indicate satisfaction and, even preference, for PCA compared with conventional modalities from patients and families [11–13, 17, 18, 23, 26]. However, this was not consequent with two studies [16, 27] indicating patient dissatisfaction with PCA. Vanier et al. reported the reason for this discontent as patients being afraid of making an error or self-administering too much medication [27].

Evidence for safety and efficacy with PCA by proxy

Seven articles ($n = 2104$) studied or described the safety and efficacy of PCA by proxy (e.g., nurse controlled analgesia (NCA) or parent-administered PCA) in patients with cancer pain [13, 30–35] with three reporting on this modality in outpatient care [31–33]. The majority described use in the paediatric population [30, 31, 33–35]. Three studies were not included in the analysis as they either did not specify outcomes for the use of PCA by proxy [32, 34] or had a mix of non-cancer and cancer-related conditions [33].

PCA by proxy was found to be a safe, effective method to reduce pain. However, only two studies used a validated pain measurement tool (VAS, FLACC-scale, NRS or Wong-Baker scale) [13, 31]. Bruera et al. was the only prospective study and described the experience of 20 subjects on nurse-controlled analgesia (NCA) compared with 25 subjects using standard PCA. Pain relief was not significantly different and satisfactory (NRS < 30) for both groups [13]. Angheliescu et al. in a retrospective study described 45 children with an accumulated use of 1110 PCA days, 154 days by parent proxy and although pain relief was reported as an outcome measure, pain scores for standard vs. proxy PCA were not specified [31].

PCA by proxy has been reported to result in an increased MED in NCA for adults [13] and parent proxy for children [31]. However, this did not result in an increase in adverse effects (no significance values provided) in both studies [13, 31]. Angheliescu et al. have conducted chart reviews of clinician and parent proxy PCA [30] and parent proxy PCA [13] for a total of 1894 patients, 11,123 PCA days of which respectively 936 were clinician proxy days and 2022 were parent proxy days. Both studies reported a significantly lower complication rate. Unfortunately, the details on adverse events was not specified other than naloxone being administered on one occasion in a clinician proxy PCA compared to twice in standard PCA use [30, 35].

PCA for palliative care at home

There were 19 articles ($n = 882$) on PCA use in outpatient care [4, 9, 12, 14, 15, 17, 24, 29, 31–33, 36–43] with 3 focussing on use at home in children with cancer [31, 33, 41]. Safety and efficacy was the main theme of 14 studies [2 prospective [36, 37], 10 retrospective [4, 12, 29, 31–33, 38–41] and 2 case reports [42, 43]] and only 2 retrospective chart reviews looked at use of PCA at the end of life for children with cancer pain [14, 41]. Both studies reported iv MED (mg/kg/day), pain intensity scores (VAS 0–10) and adverse events. Angheliescu et al.'s study of 44 inpatient children showed a MED of 19.0 mg/kg/day (SD 25.8) with a mean VAS of 4.6 (SD 3.3) on the last day of life [14]. Schiessl et al. provided an insight into the last day of life for 8 children in the outpatient setting by reporting a MED of 2.21 mg/kg/day (range 0.32–18.76) for a VAS value of 0 (range 0–5) [41]. Complication rate was not comparable, but no major adverse effects were reported. Furthermore, three single case reports described the use of PCA for palliative care in outpatients [44] or a palliative care unit [45, 46] but provided insufficient information to be presented. Table 3 summarises the outcome measures used in the studies [1–3, 47–49].

Using PCA for dose finding and opioid rotation

Nine studies ($n = 189$) report on dose finding and opioid rotation in patients with cancer pain [21, 25, 50–56] including five observational prospective studies [50, 53–56] and two case series [51, 52].

Three prospective studies [50, 55, 56] and one case series [51] ($n = 144$) provide information on iv fentanyl PCA use before and during the switching to a transdermal delivery system. The mean daily total dose of opioid consumption and the mean daily fentanyl plasma concentration (ng/ml) appear to be in a similar range during the switching period; however, a meta-analysis calculation was not completed to verify this perception. The effective dose, in all the studies, was identified within a week and a reduction in pain gained on day 1 of starting the PCA. Pain remained well controlled throughout the transition from iv to transdermal fentanyl with no significant increase in sedation or PCA administration. The reported complications were mainly minor side effects except in one study [55] where three subjects (6%) developed a respiratory rate below 8 breaths per minute during sleep. All patients remained haemodynamically stable throughout the conversion.

Furthermore, single studies were performed on the switch from iv morphine PCA to oral slow-release morphine [54], rotation from iv PCA fentanyl to PCA methadone [53] and switch from transdermal to iv PCA fentanyl [52]. Enting et al. prospectively evaluated opioid rotation, among other parameters, and possible effects on treatment outcome in cancer pain.

Table 3 Possible outcome measures in studies on PCA safety and efficacy

Outcome measures		Example	Reference
Safety	Minor side effects, i.e. nausea, vomiting, constipation	Overall: VAS (0–100), %, % with benzodiazepine (children)	[13, 16, 17] Benzodiazepine [14]
	Major side effects	Respiratory depression: respiratory rate, naloxone administration, mechanical ventilation	[12, 15, 19, 24, 27, 29, 31, 35, 37]
		Haemodynamic: systolic blood pressure, heart rate	[19, 35]
		Sedation: RDI, RASS, 4 or 5-point sedation scale	[15, 18, 19]
	Mechanical complications		[37, 38, 29, 32, 40, 17, 33]
Efficacy	Pain relief: assessment before and after PCA start	Adults: VAS or NRS (0–10) Children: FLACC-scale, AFS, NRS or Wong-Baker (0–10)	[11, 31, 35]
	Satisfaction with PCA	Patients	[4, 11–13, 16, 18, 23, 27, 32]
		Relatives	[17, 29]

At a median of 6 days after initiation of PCA, pain was controlled in 70% of the group receiving the same opioid by PCA versus 72% (OR 1; 95%CI 0.4–2.7) of subjects starting on PCA with a different opioid [21]. Sabatowski et al. report a case of opioid rotation using L-methadone by PCA for intractable cancer pain and opioid-related side effects in an 8-year-old boy. The conversion ratio of 20:1 (morphine: L-methadone) was used to achieve adequate analgesia and reduction in opioid-related adverse effects, such as generalised myoclonus, hallucinations and cutaneous hyperalgesia [25].

PCA opioid consumption as a primary outcome measure

Twenty-one articles ($n = 1221$) reported on opioid consumption as a primary outcome in patients with cancer pain. Four articles were RCTs [16, 27, 57, 58], 5 used a prospective observational design [11, 18, 19, 21, 36] and 12 were retrospective studies [4, 9, 12, 14, 17, 31–33, 40, 41, 59, 60].

RCTs have assessed daily opioid consumption to ascertain the dose required to achieve pain relief [27, 58], the opioid sparing effect of a NSAID [57] and the distribution of analgesics delivered by PCA during the day [16]. For example, Björkman et al. investigated whether diclofenac has a morphine sparing effect and improves pain relief when added to parenteral PCA of morphine in patients with severe cancer pain. They reported a significant reduction in daily morphine consumption during treatment with diclofenac (daily i.v. morphine consumption 82.8 mg/day (SD12.1) vs. 95.0 mg/day (SD 12.7) $p = 0.001$) [57]. In another study, Vanier et al. [27] compared the use of a continual opioid infusion to a PCA mode and found no significant difference in pain scores or opioid consumption. Additionally, Kalso et al. [58] demonstrated that morphine and oxycodone can both be effectively

titrated with a PCA and then subsequently transitioned to an oral route; however, mean intravenous/oral dose ratios differed for each medication (morphine 0.29, range 0.16–0.35; oxycodone 0.51; range 0.38–0.65).

Opioid consumption was further analysed through prospective studies. For example, the study by Enting et al. [21] investigated the trend of opioid consumption and pain scores after switching from conventional oral opioid therapy to an i.v. PCA treatment. Pain scores decreased and median intravenous morphine equivalent doses increased from 80 mg/day (range 5–640 mg/d) to 135 mg/day (range 14–3600 mg/day) after 24–48 h and to 201 mg/day (range 14–4080 mg/d) after 6 days. No differences in pain scores or total opioid consumption were reported in the two conditions, opioid rotation plus change of route (oral to i.v.) or change of route (oral to i.v.) only.

Circadian rhythm of opioid requirement

Four articles were identified as looking at the circadian variation of opioid requirement [9, 19, 59, 60]. Three studies, two observational [19, 59] and one case series [9], concluded a pattern of less self-administered opioid at night although the intervals were not identical.

Discussion

The technique of PCA can be considered a “fourth step” (high technology resource) of the analgesic ladder to mitigate cancer pain [3] with this concept having been affirmed by Vargas-Schaffer et al. [61] in their study on the validity of the WHO analgesic ladder. To our knowledge, this systematic review is the first to summarise the literature on the characteristics of

subcutaneous and intravenous PCA in adults and children with cancer pain. Fifty articles of varying quality and using a wide range of study designs and research objectives were eligible for analysis. The main topics identified were safety and efficacy of PCA for inpatient and outpatient care and PCA by proxy, outpatient use of PCA in palliative care and use of the PCA for dose optimisation, opioid rotation and as an outcome measure for opioid consumption.

Evidence for safety and efficacy of PCA use in cancer pain

The conclusion of studies identified was PCA opioid use was safe and useful in cancer pain management although the studies were assessed to be of low quality. Major side effects, such as severe sedation and respiratory depression, were rare. More common side effects, such as nausea, constipation and sedation, were directly related to the total amount of daily opioid consumption although the effect of multiple drugs was not evaluated [6].

Regarding the efficacy, the overall pain relief achieved with opioids delivered by PCA for cancer pain seems to be satisfactory ($n = 586$). An interesting finding was that most patients in research studies [16, 27] did not feel comfortable with PCA use compared to a high level of satisfaction with PCA in studies on patient care. A possible explanation could be patients' familiarity and comfort with technological resources over time as the research studies were older in contrast to the patient care studies. Furthermore, the study of Bruera et al. [16] comparing portable PCA bolus doses of s.c. hydromorphone only with continuous infusion may suggest that subjects found bolus administration alone caused more toxicity compared to a continuous background infusion.

Evidence for safety and efficacy with PCA by proxy

A small number of limited quality articles reported on the use of PCA by proxy in cancer pain [13, 30, 31, 35]. The major finding in the mainly paediatric focussed studies was PCA by proxy was safe and effective.

There was concern about the safety of by proxy PCA use in children because of the limited understanding of the pharmacokinetics and pharmacodynamics of opioids in children. Franson et al. [62] reviewed mainly postoperative PCA use in the paediatric population with special attention paid to PCA by proxy. This study made recommendations to decrease the incidence of complications. These included continuous monitoring to quickly detect and treat adverse outcomes, dosing to be individualised and education of parents in recognition that their involvement was frequently associated with positive outcomes and the use of reliable subjective and objective tools to assess pain. However, the included articles reported a reduced complication rate for PCA by proxy use compared with

standard PCA [30, 31, 35]. Angheliescu et al. [35] suggests the reduced incidence of serious side effects in the PCA by proxy group (0.87%) in comparison to standard PCA (1.48%) may be due to the characteristics of the patients and families attending their hospital. Families who lived nearby were often extremely involved in their child's care and skilled at assessing their child's status and symptoms [35]. Additionally, the children were often not opioid-naïve. These factors may potentially influence the generalisability of the findings to other populations. Parent and child satisfaction were not measured in the articles although a high level of satisfaction had been reported in children undergoing cleft palate surgery [48].

PCA for palliative care at home

PCA is widely used for palliative care for both inpatients and outpatients with cancer pain. The safety and efficacy in this situation did not differ from inpatients with cancer pain that were not palliative, and no major neurological or respiratory complications were reported in the outpatient setting.

Special attention should be paid to children and young adults with cancer at the end of life. Pain is prevalent and distressing in this patient population [63–67], and there is often a high opioid requirement. The last 2 weeks of life, in particular, have been reported to be associated with a significant increase in pain and need for opioid therapy with the highest mean pain score found on the day prior to death [14, 41]. Two studies [14, 41] suggest children dying at home can have better pain control and less opioid requirement with opioid delivered by PCA. This can be done safely; inpatients have a 3.68-fold increased risk (95% CI 1.36–9.95) of having complications [30, 35, 68] compared to outpatients [31]. However, the complication rates in these studies were relatively low compared with other literature [31, 35, 69, 70]. Further studies on PCA use at the end of life in children with cancer are recommended to better identify those who could benefit from outpatient care.

PCA in the outpatient setting can be helpful in the last phase of life as patients gain a sense of autonomy, independence, mobility and quality of life by playing an active role in their pain relief [32]. It has also been reported that such participation reduces the physical and psychological suffering for all involved in their care [32]. The question arising is where should PCA be started, in the hospital or at home, especially as many patients require dose increases during their first 2 weeks of PCA therapy [38]. A consideration for initiation PCA in the hospital is the increased opportunity to educate patients and relatives on the use of PCA while an indication for avoiding hospital admission was the finding that patients discharged from hospital on PCA had a significantly higher iv MED (mg/kg/day) (4.04) compared to PCA started as an outpatient (1.67) [31].

PCA opioid consumption as a primary outcome measure

Opioid consumption, mainly expressed as total daily opioid dose or iv morphine equivalent dose, was the main outcome measure used in both research and patient care studies. Nevertheless, there is a wide range of aims for which opioid consumption was chosen as a (primary) outcome measurement in the identified articles. It was used for comparison between two interventions in research studies while the amount of opioid needed was used to identify the trend for consumption in patient care studies.

PCA analgesimetry is based on the assumption that there is a strong and direct relationship between pain intensity and the dose of an opioid to provide pain relief. However, a relatively weak relationship in postoperative patients has been reported [48]. This being explained by interindividual variability of opioid response and pain tolerance without PCA and inpatient variability exemplified by the need for a constant opioid concentration for 32–48 h after surgery despite rapidly declining pain intensity [49]. For example, Schiessl et al. assumed the amount of iv morphine delivered by PCA was an accurate reflection of need as the patient controlled the amount delivered and the number of median undelivered bolus requests was zero on all treatment days [60]. These factors can be minimised by having increased numbers of patients in the treatment and control arms of the study.

Circadian rhythm of opioid requirement

Only two articles reported on the circadian distribution of analgesic consumption for cancer pain as a primary outcome [9, 59], with two other studies having this as a secondary outcome [19, 60]. All suggest reduced nocturnal opioid requirement. This was consistent with reports for short-term-studies (one or 2 day's duration) for postoperative pain [71–73]. An explanation for this phenomenon includes an increased pain threshold at night [74, 75], greater effect of opioids during evening/night [75–77] and circadian variability of physiologic processes impacting on opioid pharmacokinetics [76].

Limitations and future directions

The current systematic review was restricted to a qualitative analysis as the identified studies were of limited quality with considerable heterogeneity in study design, population and outcome measures used. Likewise, the paediatric studies were not only of limited quality but few in number. PCA devices have gone through a considerable amount of change over the years which have improved their reliability and sophistication. Unfortunately, all of the (randomised) controlled trials were performed before 1997 which makes the devices obsolete to those now in use. The designs of the studies are very

heterogeneous, making a global analysis impossible and representing a major limitation of this review. Comparisons across studies were also hindered by inconsistencies in the definitions and reporting used which was best seen in reviewing complications and adverse event rates.

Another concerning limitation was publication bias which limited the generalisability of the literature. Articles largely originated from Germany [9, 32, 41, 44, 55, 56, 60], Canada [12, 13, 17, 46, 59] and the USA [14, 18, 19, 30, 31, 35, 51, 52, 68] with this being more pronounced in reports on use in children [4, 9, 14, 30, 31, 35, 41, 60, 68].

The quality and comparability issues impact on the safety and efficacy of PCA therapy in cancer patients as it is difficult to ascertain optimal criteria for patient selection, PCA administration schedules, drug selection and dosing and optimal route of administration. Nevertheless, such limitations should not lead to avoidance of the modality in clinical practice for adults and children with cancer pain. Instead, it should be a motivation for quantitative analysis preferably through large, multicentre controlled trials to help influence future guidelines to improve such things as patient care safety.

Conclusion

PCA is a safe and convenient method of delivering opioid analgesia to patients with cancer pain. This review addressed the positive outcomes for the use of an opioid PCA in cancer pain in the clinical and research setting. Prospective studies are required to ensure robust guideline development particularly to further evaluate the safety and efficacy of this pain management strategy for patients with cancer pain.

Acknowledgements This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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