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Chapter 4

Patient-Controlled Analgesia (PCA) in Acute Pain: Pharmacological and Clinical Aspects

Marcos Tadeu Parron Fernandes,
Fernanda Bortolanza Hernandes,
Thaís Natália de Almeida, Vitor Pinheiro Sobottka,
Regina Célia Poli-Frederico and
Karen Barros Parron Fernandes

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Abstract

Moderate or severe pain are important sources of complications as well as morbidity and mortality in the postoperative period after surgical procedures. Patient-controlled analgesia (PCA) is an effective strategy for postoperative analgesia, since it may provide suitable analgesic dose just after system activation, with reduced periods of pain and an increase in patients' satisfaction. Although intravenous and epidural routes are the typical approaches used for PCA, regional patient-controlled analgesia has been shown to be an effective alternative providing a higher standard of analgesia with lower incidence of adverse effects. New devices and routes of PCA administration (transdermal, sublingual, inhalation, and oral routes) have shown to be promising alternatives in clinical studies. Nowadays, there is still no consensus regarding which is the best route or drug used since clinical efficacy/safety depends on the complex comprehension of the drugs pharmacokinetic profile through different routes of administration. Additionally, pharmacoeconomic studies are needed to evaluate the cost-effectiveness of these approaches.

Keywords: patient-controlled analgesia, opioids, acute pain, analgesic medication, morphine

1. Introduction

The International Association for Study of Pain defines pain as an unpleasant experience, with or without tissue damage, which can be related to individual memories, life expectations and

emotions [1]. The painful experience involves interpretation of biological aspects of pain and its interaction with social and cultural characteristics [2].

In surgical procedures, moderate to severe pain can be observed in up to 40% of cases [3], representing an important source of complications as well as morbidity and mortality in the postoperative period [4]. Postoperative pain can limit mobility and respiratory function, increasing the incidence of atelectasis, pneumonia and thromboembolic events [5, 6].

Moreover, the lack of adequate pain control in acute situations can lead to chronic pain, with deleterious effects for the patient and health-related quality of life [7]. Despite these findings, between 50% to 75% of those submitted to major surgery do not receive enough analgesic medication, increasing the risk of complications and length of stay and costs for the health system [8].

Morphine was isolated by a German pharmacist Friedrich Wilhem Sertürner in 1806 and, after that, opioids have become widely used in clinical practice for pain control. Later in 1844, parenteral administration of morphine has started after the introduction of glass syringe [2].

In 1963, Roe demonstrated that administration of small doses of intravenous morphine allowed a better pain control compared to intramuscular injections [9]. Sechzer, in 1968, was the first to evaluate the quality of analgesia after administration of small doses of opioids *per* patient request, performing the first patient-controlled analgesia (PCA). Due to complex logistic to meet the requests of many patients, which would require numerous nursing staff, Sechzer and other doctors began to develop equipment prototypes for analgesic administration with reduced costs. The first PCA pump available for marketing was named "Cardiff Palliator" and it was developed in the Welsh National School of Medicine in 1973 [10, 11].

Since then, several drugs and routes of administration have been used in PCA, with differences in analgesic efficacy, tolerability profile, adverse effects, and procedure-related complications as well as patient satisfaction [12].

2. PCA: principles and pharmacological aspects

The principle of intravenous PCA was first described by Austin et al. in 1980, after he administrated small increasing doses of meperidine and measured the plasma levels, demonstrating the dose-related analgesic effect in patients [13].

Despite being associated with the idea of pump with intravenous opioids, there are several routes of administration, drugs, and equipment that can be used in this mode of analgesia. It is essential that, for the PCA recommendation, individual pain pattern and intensity be considered.

The patients must be previously and duly enlightened on the technical procedure and their consent should be obtained. As desirable characteristics of PCA, we can highlight the adequate pain relief according to individual requirements, the tolerance and safety profile of

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drugs administered, the high level of patients' satisfaction and minimal complications related to technological aspects [12].

In order to understand the effectiveness of PCA, we need to understand the concept of "minimal effective analgesic concentration (MEAC)." The MEAC is defined as the smallest concentration at which the pain is relieved [13].

Considering the existence of individuals' variability, the MEAC cannot be determined from the plasma levels of opioids. It is known that the plasma concentration is a function related to the dose, dosage intervals, gender and age of the patient. It can be calculated based on pharmacokinetic concepts such as volume of distribution and distribution and elimination rates. However, in clinical situations, the plasma levels are not able to predict the pattern of analgesic response [14]. Tamsen et al. showed that the MEAC has a direct correlation with preoperative concentrations of endogenous opioids and substance P in the cerebral spinal fluid. Obviously, the achievement of these measurements is restricted in clinical practice [15].

For the PCA effectiveness, the MEAC should be achieved by titration, which means that the drug is administered as a *bolus* of small doses until the establishment of an adequate analgesia pattern is obtained. Considering the acute postoperative pain, this can be done in the post-anesthetic recovery room, before patient discharge. From this reference dose, the equipment is regulated in order to maintain the plasma concentration of analgesic levels of MEAC or slightly above it, looking for adequate pain control with minimal adverse effects. The goal of this approach is to prevent the occurrence of sharp peaks and troughs in plasma concentrations in a standard that seeks the lowest level of oscillation of concentrations, ideally as close to a continuous infusion [16].

Regardless of the route or administered drug, the two main types of PCA are: the demand dosing (the fixed dose which is self-administered intermittently) and continuous infusion associated with demand dosing (the constant-rate fixed background infusion is supplemented by patient demand dosing), whereas the principles of a fixed infusion administration as well as principles of variation of the infusion rates managed by a period of time are considered [17].

Some basic principles and technical parameters are common to several modalities. They are initial loading dose, demand dose, interval lockout, and background infusion rate.

The initial dose usually is not administered by the patient, since the goal of first administration is to promote adequate pain control or prevent the early pain manifestation. This approach allows the establishment of the demand dose, also called PCA dose or *bolus* dose, which will be administered by the patient when he shoots the demand button.

The lockout interval is a set period in which the equipment does not perform a new infusion of demand. During the interval lockout, if the patient triggers the button, he/she will not receive the medication. Normally, the equipment has a sound signal connected to the drive, regardless of the infusion, so that the patient does not know whether his/her requests were effective. The lockout interval has the primary function of security by preventing the administration of an overdose of analgesic drugs. The background infusion rate is a given infusion rate in a continuous manner, independent of the patient's wish (also called continuous infusion). The

1-h and/or 4-h limits, depending on the equipment configuration, it has the function to limit the total cumulative dose in the period of 1 or 4 h in order to reduce the adverse effects and ensure the patient safety [11, 18].

Considering the advances in the development of drug delivery systems, the use of infusion pumps for patient-controlled analgesia (PCA) and analgesia epidural catheter with opioids are considered the most powerful strategies to control of postoperative pain. However, there are doubts about the advantages and limitations of these different forms of PCA.

The basal opioid administration doses may be administered concurrently with the administration of opioids by PCA techniques. However, the basal administration increases the risk of respiratory depression without providing necessarily an additional analgesia pattern [19].

PCA different modalities can minimize the occurrence of gaps in analgesic administration, supplying analgesic dosage immediately after the system activation, providing more uniform analgesia and eliminating painful waiting periods between the patient's request and drug administration.

3. PCA modalities

Electronic PCA pumps have several models in the market, including small portable devices nowadays. Since the first commercially available PCA pump (“Cardiff Palliator”), PCA devices have evolved enormously in technological sophistication, ease of use, flexibility and portability.

3.1. Intravenous PCA (IV-PCA)

Currently, IV-PCA is one of the most used techniques for acute pain control. Its use is suitable for virtually any patient undergoing surgery that are cursed with postoperative pain of moderate or severe intensity [18]. Many studies have demonstrated the efficacy, safety, and patient satisfaction with PCA intravenously. A meta-analysis involving 115 randomized clinical trials demonstrated that this technique provides greater efficacy when compared to intramuscular administration of analgesics [20]. Another study showed that, among patients who received IV-PCA, 36% experienced moderate to severe pain in the first 24 h after surgery when compared to 67% of important painful experience among patients who received intramuscular opioids [21]. Moreover, it was verified that the IV-PCA is associated with a higher rate of patient satisfaction [22].

Despite the possibility that IV-PCA may be combined to a basal opioids infusion, it was shown that the incidence of respiratory depression with IV-PCA was much smaller (0.19% versus 0.29%) when compared to the combination of this technique with systemic infusion of opioids (1.09–3% versus 8%) [23].

IV-PCA is associated with potential complications inherent in the technique, which are operator-dependent. Errors may occur in the drug administration, usually by programming failures

on infusion pump [24] and they may result in inadequate pain control, heavy sedation, respiratory depression, and, eventually, death of the patient [25]. Currently, many infusion pumps feature smart devices that are equipped with an integrated software library on dosing regimens of different drugs, thus avoiding underdosing or overdosing. In these models, the smart bombs are programmed to stop operation or to alert clinicians when doses exceed the limits [26].

However, serious errors can still occur even with smart bombs. According to the Food and Drug Administration (FDA), 56,000 adverse events with these smart bombs during the period 2005–2009 have been reported [27].

Several complications may be observed from the IV-PCA, such as clogging or dislodgement of catheters, intervals between the administrations of opiates for maintenance of analgesic effect [28]. Still, this technique implies in risk for adverse effects related to opioids [29].

Furthermore, IV-PCA limits mobility and it reduces the comfort of the patient who is connected to the infusion pump, which can be minimized by using more modern compact equipment. Zafar et al. [30] reported that about 21% of patients who received IV-PCA complained of reduced mobility. It is worth noting, finally, the economic aspect, as a limitation of the technique, as well as the need of equipment (infusion pump) and the discarding of remaining solutions after the PCA use, causing unnecessary costs for health services [12, 30].

The major drugs used in this system are the opioid analgesics, such as morphine, hydromorphone, fentanyl, sufentanil and tramadol [31]. Meperidine is no longer considered a valid option for PCA as its toxic metabolite may be accumulated, especially in patients with abnormal kidney function [32]. Therefore, meperidine has not been recommended for acute pain [33].

3.1.1. Morphine

Morphine is the most common opioid used for IV-PCA and it is considered the gold standard for this procedure. Although many studies have demonstrated its clinical safety, adverse effects such as nausea, vomiting, itching, urinary retention, sedation and respiratory depression may occur. Its active metabolite morphine-6-glucuronide (M6G) have analgesic action but presents risk of adverse effects. As the M6G has renal elimination, the use of morphine should be done with caution in patients with impaired renal function and the elderly [34, 35]. The low therapeutic index of morphine in IV-PCA was shown in preclinical models, indicating that morphine cannot be the best option for all patients for pain relief in the postoperative period [31].

The usual morphine dose and the recommended parameters are: demand dose: 1–2 mg; lockout period: 6–10 min; continuous basal infusion dose: 0–2 mg/h [11].

3.1.2. Hydromorphone

Hydromorphone has been used in patients with impaired renal function or with a history of allergy to morphine. It is mainly metabolized by the liver and it is, approximately, five times more potent than morphine. Clinical effects of hydromorphone are dose-dependent and its adverse event profile is morphine-like [11, 36]. A systematic review of adverse events associated with the postoperatory use of six different opioids (buprenorphine, fentanyl, hydromorphone,

meperidine, morphine, and sufentanil) showed that after meperidine (proscribed, 67.9%), the opioid with the highest incidence of central nervous system side effects was hydromorphone (42.7%). Furthermore, at higher doses, hydromorphone can cause excitation [37].

Due to the similarity between morphine and hydromorphone, errors have been reported in programming the IV-PCA pump. Considering that these agents have significant differences in their clinical potency, inadvertent hydromorphone administration can result in serious complications [38].

Doses and recommended parameters are: demand dose: 0.2–0.4 mg; lockout period: 6–10 min; continuous basal infusion dose: 0–0.4 mg/h [11].

3.1.3. Fentanyl

Fentanyl is 80–100 times more potent than morphine and it may cause less respiratory depression when compared with morphine. It has no active metabolites, and it has a wider therapeutic index than morphine in preclinical models [39].

In a retrospective cohort study of 8955 patients who received one of the three opioids for postoperative pain (morphine, fentanyl or meperidine), the incidence of respiratory depression was 0.6% in the group of patients who received fentanyl, compared to 2.8% among patients who received morphine [40]. Although apparently it may be associated with smaller risk of respiratory depression when compared to morphine, fentanyl can be associated with more device programming errors, since this drug is dosed in micrograms [40, 41].

Because of its high lipid solubility, fentanyl has a pharmacokinetic profile characterized by a rapid onset and short action. Therefore, some patients may need doses too frequently or require a basal infusion rate, which greatly increases the risk of respiratory depression. Due to its high volume of distribution, prolonged administration may result in a significant increase in drug half-life, with consequent raise in the incidence of adverse effects [42]. Given these pharmacokinetic characteristics, there are complaint reports of patients after fentanyl administration in IV-PCA [43].

Doses and recommended parameters: demand dose: 20–50 μg; lockout: 5–10 min; Basal continuous: 0–60 μg/h [11].

3.1.4. Sufentanil

Sufentanil is a fentanyl analog, being about 5–10 times more potent than Fentanyl itself. It represents the opioid with greater therapeutic index (25,000) used for postoperative pain in preclinical studies [39]. The high therapeutic index is clinically relevant for evoking a decreased risk of incidence of respiratory depression compared to morphine, fentanyl, and alfentanil [44]. In a randomized clinical trial with 30 volunteers, it was noted that sufentanil provided more effective analgesia and less respiratory depression when compared with fentanyl [44].

Sufentanil is highly lipophilic (twice more lipophilic than fentanyl) and it provides rapid onset of action and shorter effect duration when administered intravenously to PCA, justifying its

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rare use in this route. However, unlike fentanyl, its half-life of elimination does not increase with infusion time and it shows paradoxical increase in their concentration during the elimination phase [39]. A randomized clinical trial that compared plasma levels of sufentanil and fentanyl in 41 patients undergoing coronary artery bypass surgery, demonstrated the occurrence of peak plasma concentration (increase of 29–49%) from 4 to 15 h after administration *bolus* of fentanyl. On the other hand, only one patient had sufentanil treated with this paradoxical effect (43% increase). This peak in plasma concentration explains the occurrence of late respiratory depression in patients treated with fentanyl [45]. Therefore, considering their high therapeutic index and predictable pharmacokinetic profile, sufentanil represents a promising example of opioid that could be used to PCA cases requiring short duration of effect and availability intravenously.

The doses and the usual parameters are: demand dose: 4–6 μg; lockout: 5–10 min; continuous baseline: 0–8 μg/h [11].

3.1.5. Tramadol

Tramadol acts on opioid receptors with higher affinity for κ receptors than δ and μ receptors. It has an active metabolite, mono-O-desmethyl (M1), which has analgesic effect. In addition to the opioid agonist activity, tramadol analgesia is also promoted by inhibiting the central norepinephrine and serotonin reuptake. Tramadol potency compared to morphine is approximately 0.1. Several studies have shown that tramadol is a safe and an effective option for PCA, but with a higher incidence of nausea and vomiting [46, 47]. The recommended doses are: demand dose: 10–20 mg; lockout: 6–10 min; continuous baseline: 0–20 mg/h [11].

3.1.6. Oxycodone

Oxycodone is an opioid μ receptor agonist indicated for the treatment of moderate to severe pain. Despite being most frequently used orally, in recent years, its intravenous use has increased. Its potency is about 1/75 of fentanyl, and in some studies has shown great potency up to 1/60 [48, 49].

A randomized clinical trial with 82 patients compared IV-PCA with oxycodone and fentanyl. In this study, oxycodone demonstrated potency of 1/55 of fentanyl for the same levels of analgesia, being equally safe and the same incidence of adverse effects such as nausea, vomiting and sedation [45]. It is a drug with good efficacy and a promising role in the practice of PCA. Its use must be made on demand associated with basal infusion. The recommended doses are: demand bolus: 1 mg; lockout: 15 min; background infusion rate: 1 mg/h [50].

3.1.7. Other drugs

Other opioids have been less used in IV-PCA. The alfentanil, probably due to their pharmacokinetic characteristics, did not show good results and a demand dose was not established to present a satisfactory analgesia [51]. The remifentanil, because of their ultrashort half-life, does not have a favorable profile for PCA with some indication for analgesia for a short period such as during labor [52].

Other drugs have been used by some authors that are normally associated with morphine. Ketamine, which is an agonist of the NMDA receptor, and naloxone, which is an antagonist of opioid receptors, have shown conflicting results regarding the safety or quality of analgesia, and more studies are needed so that they can get their recommended use [18].

3.2. Epidural PCA

Epidural patient-controlled analgesia (EPCA) is the second most significant method used and studied within the PCA approach. Its use is mainly for control of acute postoperative pain, commonly in patients undergoing orthopedic, abdominal and thoracic surgery [12]. EPCA allows the use of opioids, local anesthetics, or a combination of both. Opioids epidural administered provide greater analgesic potency when compared to equivalent doses of opioid administered intravenously [53].

Although both opioids and local anesthetics represent feasible options, local anesthetics are the most appropriate strategies for patients sensitive to the opioids adverse effects, even though it is associated with a higher incidence of hypotension, motor block and urinary retention compared with the use of opioids [53]. Similarly to the PCA intravenous technique, EPCA allows patients to administer the medication in accordance with analgesic requirements. There is large evidence indicating that the EPCA represents a safe and effective method [46, 54]. A meta-analysis concluded that, regardless of the drug chosen, epidural provides a better analgesia pattern when compared to intravenous PCA technique [55].

In a population-based study of 2276 surgical patients, Kim et al. [56] discloses that ropivacaine with fentanyl was able to provide good quality analgesia for up to 48 h after the several surgical procedures, with limited side effects [56].

Unlike IV-PCA, the use of continuous infusion, coupled with the demand dose, have shown excellent results with minimal complications. Small doses of local anesthetics of long action combined with low doses of opioids (i.e., fentanyl or sufentanil) with continuous infusion rate associated with increments *bolus* may be combined [57, 58]. The following concentrations are recommended: bupivacaine: 0.05–0.125%; levobupivacaine: 0.05–0.125%; ropivacaine: 0.1–0.2%. Additionally, the following doses are recommended: demand dose: 2–4 ml; lockout: 10–20 min; continuous basal infusion: 4–10 ml/h [11].

Despite many advantages, EPCA also has limitations, especially considering the complexity of the procedure and technical staff training. In addition, there are reports of catheter migration which may lead to failure in the procedure in 17% of cases. It has been suggested that this technique has great effectiveness but it should be used with caution considering individual factors, in order to ensure patient safety [56].

3.3. Patient-controlled regional analgesia

There are several techniques that use catheters for the purpose of providing postoperative analgesia with little or no opioid use. In this model of patient-controlled regional analgesia, local anesthetics (ropivacaine, bupivacaine or levobupivacaine) are normally administered

through a catheter located in perineural site, intraarticular region or surgical incision site. Eventually, a combination of local anesthetics and opioids can be administered by the infusion pump [12].

Several studies have addressed the effectiveness of this method for postoperative analgesia [59]. Vintar et al. [60] noted that about 80% of patients who received bupivacaine and ropivacaine at the incision site were satisfied with the outcome of the procedure and said they would use this treatment again.

Studies emphasizing the intraarticular administration of opioids and/or local anesthetics are rare. Vintar et al. [60], in a controlled clinical trial, describes that the group which received the combination of ropivacaine/morphine/ketorolac required less use of rescue analgesics in relation to other groups.

It is estimated that, during orthopedic surgery, drug administration by intraarticular can provide 12–15 h of analgesia [61]. In this context, the most efficient strategy would be the infusion of local anesthetics via epidural. Additionally, the brachial plexus, lumbar plexus and femoral nerve and sciatic nerve are examples of sites for drugs infusion. In a clinical trial, the PCRA ropivacaine 0.2% in the brachial plexus region was effective in shoulder orthopedic surgery regarding pain intensity, opioids' use as rescue medication, and less sleep disorders [61].

In a multicenter study involving orthopedic surgeries, the perineural ropivacaine administration by continuous infusion or PCRA was compared to intravenous morphine. Patients receiving morphine showed higher levels of postoperative pain and required higher consumption of analgesic as rescue medication, significantly increasing the side effects such as nausea, vomiting, dizziness and sleep disturbances [62].

3.4. Other modalities of patient-controlled analgesia

3.4.1. Transdermal

The iontophoretic fentanyl system (IONSYS; Ortho-McNeil, Raritan, NJ, USA) is a preprogrammed noninvasive method of PCA, which does not require venous access for drug administration. By adhesively secured to the outside of the arm or chest of the patient, fentanyl is transferred iontophoretically through intact skin. The system allows the transdermal administration of the drug for 10 min and a 10 min lockout interval between administrations [39].

However, the fentanyl dose administered over time is not constant. Whereas the target dose for the desired effect of fentanyl is 40 μg, it is estimated that the average dose is 16 μg after the initial application. Therefore, it would take a long period of time until the optimal dose is reached. Many patients do not receive adequate analgesia for up to 10 h after the start of the application [39].

Although clinical studies have suggested that the use of transdermal fentanyl could show similar efficacy to morphine in PCA intravenously in relation to the overall control of pain [12], there was a need for additional analgesia in 40% of patients involved in the first 3 h of treatment. Moreover, there were local side effects such as skin redness in about 60% of cases. This system

was not marketed in the U.S. and it was withdrawn from the European market by the manufacturer due to a manufacturing error in some units [38].

3.4.2. Sublingual

A new sublingual administration system using sufentanil (AcelRx Pharmaceuticals, Redwood City, CA, USA) is designed as a microtablet coupled to a preprogrammed portable device with locking features and radio frequency identification to enable the characterization of a single user. Although intravenous sufentanil present a short half-life context-dependent due to its rapid redistribution, pharmacokinetic studies in healthy subjects showed that after sublingual administration, sufentanil has adequate profile for the postoperative analgesia [39].

Sufentanil NanoTabs® shows high bioavailability and plasma half-life and it is safer than the administration of the drug intravenously to avoid the need for frequent administrations of the lipophilic opioids commonly used for this procedure. Several clinical trials have demonstrated its efficacy in pain relief in different types of orthopedic and abdominal surgery, having been described few side effects to this method [38].

3.4.3. Inhalation

Several products using the inhalation of PCA to opioid administration are described in the literature. Thipphawong et al. [63] tested a morphine inhalation system (System AERx Pain Management; Aradigma Corporation, Hayward, CA, USA), which had desirable characteristics of a drug for PCA (possibility of multiple dosing with lock time between them and observed similar efficacy to morphine IV-PCA).

Similarly, fentanyl (AeroLEF, YM Biosciences, Mississauga, ON, Canada) also had proven to control postoperative pain following orthopedic surgery. However, further studies are needed to confirm the effectiveness of opioids in this route, especially clinical trials phase III and IV.

3.4.4. Intranasal

The intranasal opioid administration is possible, since the nasal mucosa has an extensive vascularization, providing rapid drug absorption and distribution [12].

The presentation of intranasal morphine (Rylomine®, Javelin Pharmaceuticals Inc., Cambridge, MA, USA) was effective for the control of postoperative pain in orthopedic surgery [64]. However, the single dose after a nasal administration does not have the desirable safety features of PCA models, such as the possibility of multiple dosages and lock scheduled time between applications. Other opioids have been tested for intranasal administration but similar to morphine, these devices also did not have the desirable features of a PCA device. In this context, Toussaint et al. [65] noted that intranasal fentanyl administration showed similar efficacy compared to IV-PCA fentanyl. Intranasal sufentanil was also successfully used both in adults and pediatric patients [64].

However, this route may have local adverse effects: nasal irritation, nasal congestion, upper respiratory tract infections, sinusitis, rhinitis, pharyngitis, or epistaxis, which may be a limitation of its clinical use [66].

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3.4.5. Oral

Oral PCA device (Avancen, Mount Pleasant, SC, USA) is a drug unit coupled to a bracelet programmed to keep out of the drug for a predetermined time interval. After this lockout period, a green light indicates the possibility of new management. The equipment is compact and allows the patient to make the registration of pain on a scale of 0–10, providing feedback to the health team.

In a study of this device with hydromorphone administration, oxycodone and morphine, it was reported better control of pain in 95% of patients who used these devices when compared to the control group. Furthermore, it highlighted the ease of programming of this device by the health team [38].

Although this oral device for PCA is a good alternative, there are few studies regarding its safety. It is noteworthy of some shortcomings: lack of clinical efficacy in cases of moderate to severe pain, management failure in patients in whom oral administration is not available and uncertain absorption in the immediate postoperative period.

4. Conclusion

Patient-controlled analgesia (PCA) is a great option for acute pain control. Several advantages of this technique can be highlighted, such as higher analgesic standard with patient's satisfaction, and also minor side effects. However, there is still no consensus regarding which is the best route or drug used since clinical efficacy/safety depends on the complex comprehension of the pharmacokinetic drugs profile through different routes of administration. Additionally, pharmacoeconomic studies are needed to evaluate the cost-effectiveness of these approaches.

Author details

Marcos Tadeu Parron Fernandes[1,2], Fernanda Bortolanza Hernandes[3], Thaís Natália de Almeida[3], Vitor Pinheiro Sobottka[2], Regina Célia Poli-Frederico[4] and Karen Barros Parron Fernandes[4, 5]*

*Address all correspondence to: karenparron@gmail.com

1 Department of Anesthesiology, Irmandade da Santa Casa de Londrina Hospital (ISCAL), Londrina-PR, Brazil

2 Associate Professor, Department of Anesthesiology and Surgery, School of Medicine, Pontifical Catholic University of Parana (PUCPR), Londrina-PR, Brazil

3 School of Medicine, Pontifical Catholic University of Parana (PUCPR), Londrina-PR, Brazil

4 Associate Professor, Doctoral Program of Rehabilitation Sciences, University of Northern Parana (UNOPAR), Londrina-PR, Brazil

5 Institute of Education, Research and Innovation, Irmandade da Santa Casa de Londrina (ISCAL), Londrina-PR, Brazil

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