

A preliminary assessment of vital-signs-integrated patient-assisted intravenous opioid analgesia (VPIA) for postsurgical pain: a case series

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Ban Leong SNG
KK Women's and Children's Hospital

 sng.ban.leong@singhealth.com.sg *Corresponding Author*
ORCID: <https://orcid.org/0000-0001-5374-4271>

Daryl Jian'an Tan
KK Women's and Children's Hospital

Chin Wen TAN
KK Women's and Children's Hospital

Nian-Lin Reena HAN
KK Women's and Children's Hospital

Rehena SULTANA
Duke-NUS Medical School

Alex Tiong Heng SIA
KK Women's and Children's Hospital

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infusion pump, postoperative pain, vital sign monitoring, oxygen desaturation

Abstract

Background

We developed a Vital-signs-integrated Patient-assisted Intravenous opioid Analgesia (VPIA) analgesic infusion pump, a closed-loop vital signs monitoring and drug delivery system which embodies in a novel algorithm that takes into account patients' vital signs (oxygen saturation, heart rate). The system aims to allow responsive titration of personalized pain relief to optimise pain relief and reduce the risk of respiratory depression. Moreover, the system will be important to enable continuous monitoring of patients during delivery of opioid analgesia.

Methods

Nineteen patients who underwent elective gynecological surgery with postoperative patient controlled analgesia (PCA) with morphine were recruited. The subjects were followed up from their admission to the recovery room/ ward for up to 24 hours until assessment of patient satisfaction on the VPIA analgesic infusion pump.

Results

The primary outcome measure of incidence of oxygen desaturation showed all patients had at least one episode of oxygen desaturation (<95%) during the study period. Only 6 (31.6%) patients had oxygen desaturation that persisted for more than 5 minutes. The average percentage time during treatment that oxygen saturation fell below 95% was 4.6%. Fourteen (73.7%) out of 19 patients encountered safety pause, due to transient oxygen desaturation or bradycardia. The patients' median IQR pain scores at rest and at movement after post-op 24 hours were 0.0 2.0 and 3.0 2.0 respectively. The average \pm SD morphine consumption in the first 24 hours was 12.5 ± 7.1 mg. Majority of patients were satisfied with their experience with the VPIA analgesic infusion pump.

Conclusions

We have demonstrated the potential of VPIA analgesic infusion pump to increase the safety and patient satisfaction by incorporating vital signs monitoring to intravenous opioid analgesia.

Background

More than 230 million major surgeries are performed annually in the world that sometimes result in

moderate to severe post-surgical pain which is often poorly managed [1]. To treat pain, patient-controlled analgesia (PCA) with an opioid pump is often the preferred technique because patients are able to individualize their own analgesic therapy, potentially leading to greater pain relief efficacy and improved satisfaction [2]. To effect analgesia, the patient presses on a button to self-administer pre-set doses of opioid pain relief, through an intravenous line by using a PCA pump. A lockout time between each dose and a predetermined maximum hourly cumulative dose are usually set for safety purposes. The use of the PCA pumps allows patients to have greater autonomy in managing pain; this often leads to an overall reduced need for analgesics when compared with a fixed schedule dosing [3-4].

However, the use of opioids often leads to adverse effects such as nausea, vomiting, sedation and respiratory depression. Patients' comorbidities such as advanced age, respiratory disease and obstructive sleep apnoea can affect a patient's response and may significantly increase the risk of respiratory depression with repeated dosing of opioids [5]. There are also interindividual variations in the response to opioids. Hence, even with the correctly programmed PCA pump, therapeutic doses of opioids can be associated with somnolence, decreased respiration, which may be associated with an increase length of stay and overall costs [6-7]. Failure to detect patient's deteriorating oxygenation or respiratory status can lead to significant complications requiring critical healthcare resources. To prevent the aforementioned difficulties, it is necessary for the patients' vital signs such as oxygen saturation, heart rate, blood pressure and respiratory rate to be regularly monitored. However, such measures are not only highly labor intensive, but are also incapable of reliably recognizing opioid-induced respiratory depression in the postoperative period [8].

It is therefore imperative to improve the safety of PCA opioids to enhance the quality of postoperative care while reducing unnecessary costs. Currently, there is no existing opioid delivery pump with a decision-support based on continuous monitoring system of patients' vital signs. Therefore, our overall aim is to develop a Vital-signs-integrated Patient-assisted Intravenous opioid Analgesia (VPIA)

analgesic infusion pump: a closed-loop vital signs monitoring and drug delivery system which embodies a novel algorithm that accounts for patients' vital signs (oxygen saturation, heart rate). In this preliminary study, our primary aim is to investigate the incidence of oxygen desaturation (defined as having oxygen saturation of <95% in a patient for more than 60 seconds) in patients using our VPIA analgesic infusion pump. We investigated the side effects of opioid administration (nausea and vomiting, sedation), patients' satisfaction and vital signs monitoring.

Methods

This study was approved by the SingHealth Centralized Institutional Review Board, Singapore (SingHealth CIRB Ref: 2015/3062), and registered on Clinicaltrials.gov (NCT02804022). Written informed consent was obtained from every patient before any study procedure. The study period was between January 2017 and June 2017.

We recruited female patients aged 21 to 70 years old with American Society of Anesthesiologists (ASA) status I or II, undergoing elective surgery with the intent of using postoperative PCA with morphine for postoperative analgesia. The exclusion criteria were patients with allergies to morphine, history of significant respiratory disease or obstructive sleep apnea, unwilling to wear oxygen saturation monitoring devices throughout the study duration, and unable to comprehend the use of PCA. Obstetric patients were also excluded from the study. Recruitment was performed either in the pre-operative assessment clinic or on the same day of surgery if they had not attended pre-operative assessment clinic. An information brochure describing the use of VPIA analgesic infusion pump for post-operative analgesia, including potential side effects and complications was provided to patients. Study personnel then took written informed consent from the patients.

Setting up of Infusion Pump

The algorithm and the VPIA analgesic infusion pump ("Intellifuse pump"; Model: Opiva) was designed

by Innovfusion Pte Ltd, Singapore. Intravenous morphine used in the VPIA analgesic infusion pump was administered according to institutional guidelines: morphine diluted in normal saline to a concentration of 1 mg/ml, with bolus doses of 1 mg morphine delivered as per patient demand. In the VPIA analgesic infusion pump, vital signs monitoring (oxygen saturation, pulse rate) is programmed into the VPIA variable lockout algorithm allowing a temporary pause to the pump when vital signs safety threshold is breached and subsequent increase the lockout interval upon re-starting, thereby improving the safety of this device. When the vital signs are within normal range, the system is able to increase or decrease the lockout interval according to the analgesic needs of the patient. This lockout interval is a safety mechanism that limits the frequency of demands made by patients. By allowing an adequately long interval between each dose, patients are given sufficient time to achieve the opioid's effects before the next dose. However, if interval were prolonged, the effectiveness of patient controlled analgesia would be reduced. This bolus lockout interval starts at 7 minutes, and is adjusted automatically for enhanced treatment efficacy and patient safety. Conversely, for every breach in patients' vital signs, the pump reacts in the interest of patient safety and pauses itself. Lastly, the VPIA variable lockout algorithm reassesses for the recovery of patients' vital signs at the end of the safety lockout period. If patients' vital signs have not recovered to safe levels, the pump automatically raises the on-board alarm. Conversely, if patients' vital signs have recovered beyond the threshold limits by the end of the safety lockout period, the lockout interval is prolonged to increase safety. If at any time, there is severe deterioration of vital signs or critically abnormal vital sign parameters, the system will trigger the "Emergency Safety Stop" function to cease all bolus doses. The system would then have to be manually restarted by the anesthetist after reviewing the patient. The detailed VPIA variable lockout algorithm is illustrated in Figure 1.

All study subjects had mandatory intravenous access established before surgery. The patients were instructed on the use of the VPIA analgesic infusion pump prior to the study and educated to press the demand button whenever they needed pain relief. While in the recovery room after surgery, the VPIA analgesic infusion pump secured with a 50ml syringe of 1mg/ml morphine was connected to the

patient's intravenous line for analgesia. An integrated pulse oximeter for continuous monitoring of oxygen saturation, and heart rate was also connected to the patient. A repeat demonstration of the system was subsequently performed to ensure patient's understanding of the VPIA analgesic infusion pump. Intravenous morphine was administered via the intravenous line with an anti-reflux and anti-siphon valve.

Data Collection

We collected and analyzed three sets of data: (1) patient demographic, medical and nursing parameters, hospital medical records; (2) VPIA analgesic infusion pump data including opioid consumption, patient demands, successful demands, pattern of demands, oxygen saturation and heart rate; and (3) VPIA analgesic infusion pump user feedback survey that was conducted at the end of the study. Following the initiation of VPIA analgesic infusion pump, attending nurses who were educated on the usage and side effects of morphine therapy would monitor the patient at regular intervals and document pain scores (0-10 numeric rating scale), blood pressure, heart rate, oxygen saturation and sedation score (0 for "awake, alert", 1 for "occasionally drowsy, easy to rouse, responds to calling", 2 for "occasionally drowsy, difficult to rouse, responds to shaking only"; 3 for "unresponsive and unarousable; defined as no response to voice or physical stimulation"; D for "distressed; defined as awake and in great pain"). Side effects such as nausea and vomiting were also recorded. An independent observer (acute pain service) would visit the patient on the following day to assess the patient's overall satisfaction (numerical score between 0-100%) with the postoperative analgesia provided.

The acute pain service would assess the patient based on the number of days she was placed on the VPIA analgesic infusion pump, during which the feedback on pain relief effectiveness and any side effect from the therapy was gathered. Once the indications for PCA opioid for pain management were deemed unnecessary by the patient's primary care team, the VPIA analgesic infusion pump was

disconnected.

Sample size calculation and statistical analysis

The primary outcome measure of the study is the incidence of oxygen desaturation (defined as having oxygen saturation of < 95% in a patient for more than 60 seconds) in patients using the VPIA analgesic infusion pump, while the secondary outcome measures are bradycardia, sedation, nausea/vomiting, pain scores, total consumption of morphine, patient's satisfaction score. Patient's oxygen saturation and heart rate were measured every minute for 24 hours. Assuming that patients have < 3% oxygen desaturation, 0.005 width of interval and 95% confidence interval, we would require 18,000 oxygen saturation readings. Each patient would provide at least 1200 readings. Therefore, the study is adequately powered for 18 patients with 1200 readings (= 18 X 1200 ~ 21,600) for both the primary and secondary aims.

Patient demographics, surgical and anesthetic characteristics were summarized as frequency with corresponding proportion for categorical data and as mean \pm standard deviation (SD) or median [interquartile range IQR], whichever applicable. The incidence rate, and 95% confidence intervals (CI), of binary outcomes (such as desaturation, bradycardia) were estimated based on the exact method by Wilson [9], which have demonstrated to have good statistical properties even for small number of subjects and/or extreme probabilities [10-11]. Significance level was set at 0.05 and all tests were two-tailed. SAS version 9.3 software (SAS Institute; Cary, North Carolina, USA) was used for the analysis.

Results

Twenty patients were recruited for this study over a 6-month period (December 2016 to May 2017), however one was withdrawn as there was an exclusion criteria of ASA III. The baseline and demographic characteristics are shown in Table 1. The mean age of patients was 51.5 ± 8.8 years (ranged 36-66 years), with an average body mass index (BMI) of 24.7 ± 4.42 mean (SD) kg/m^2 . Out of

these nineteen patients, thirteen (68.4%) were Chinese. All patients recruited went through scheduled open surgery, with the majority (n=15) under Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy (TAHBSO). The rest were open myomectomy (n=2) and salpingo-oophorectomy (n=2). During the surgery, intraoperative morphine and/or fentanyl was administered to the patients with a median [IQR] dosage of 8.0 [2.0] mg and 100 [0.0] mcg respectively according to the attending anesthetist routine practice.

The patients were offered pain relief via VPIA analgesic infusion pump once they were transferred to the Post-Anesthesia Care Unit (PACU; Table 2). The median [IQR] dosage of morphine consumption during the stay was 4.0 [5.0] mg, whereas the last pain score before sending to ward was 3.0 [2.0]. Minimal to moderate sedation was observed in 15 patients, whereas 4 other patients exhibited no sedation, having an overall median sedation scoring (n=19) of 1.0 [0.0]. Only one patient showed nausea/ vomiting during this period. The first 12 hours post-operative in 19 patients showed pain score at rest and movement of 2.0 [5.0] and 5.0 [3.0] respectively (Table 2). At 24 hours, patients had pain scores of 0.0 [2.0] and 3.0 [2.0] at rest and movement respectively. The average \pm SD morphine consumption in the first 24 hours was 12.5 ± 7.1 mg. Patients during the hospitalization had minimal nausea/vomiting and sedation.

The primary outcome measure of incidence of oxygen desaturation (Figure 2) showed that all patients had at least one episode of oxygen saturation (SpO_2) decreasing below 95% transiently during the study period. Only 13 (68.4%, 95%CI 46.0% - 84.6%) patients had oxygen desaturations that persisted for more than 60 seconds. However, only 8 (42.1%, 95%CI 23.1% - 63.7%) and 6 (31.6%, 95%CI 15.4% - 54.0%) patients had persisted oxygen desaturation for both 3 and 5 minutes respectively. The average time and percentage of time that SpO_2 fell below 95% was 10.1 ± 14.9 minutes and 4.6% respectively. All patients had at least one episode of heart rate (HR) <60 /min with 3 (15.8%, 95%CI 5.5% - 37.6%) patients experiencing a HR of <60 /min for longer than 60 seconds

duration (Figure 3). The average time and percentage of time on treatment that HR fell below 60/min was 43.9 (143.1) minutes and 8.8% respectively. Only 1 (5.3%, 95%CI 1.0% - 24.6%) patient had HR <60 for both 3 and 5 minutes. There was no clinically significant respiratory event of note.

Fourteen out of 19 (73.7%) patients encountered safety pause, whereas ten (52.6%) patients had experienced emergency safety stop during the study period. Median (range) number of safety pause was 5 (1 - 21). Reasons for safety pause either occurrence of oxygen desaturation or heart rate < 60. Eleven (57.9%) patients had safety pause due to SpO₂ < 95% but all had HR > 60 during the episode. Six (31.6%) patients had HR < 60 but all had SpO₂ > 95% during the episode. There were 2 (10.6%) patients experiencing oxygen desaturation <90% for more than one minute. A total of seven patients reported post-operative side effects including nausea / vomiting (6/19) and pruritus (1/19).

The median [IQR] number of demands of bolus was 21 [19] per patient. The patients' mean \pm SD pain scores at rest and at movement after 24 hours surgery were 3.2 ± 3.3 and 6.11 ± 2.7 respectively. Feedback received on VPIA analgesic infusion pump showed that patients agreed that the pump was safe and effective to use, although they remained neutral on the mobility of the pole when the pump was mounted onto it (Table 3).

Discussion

We presented a case series on a novel drug delivery system that was designed with a novel reactive clinical algorithm and integrated with continuous physiological monitoring, thus providing appropriate response to any breach of safety. VPIA analgesic infusion pump comprises in-built vital signs monitors and an adaptive algorithm that takes advantage of the vital signs integration and patient initiation to modulate the consumption of analgesia by varying the lockout time of patient bolus (and therefore the dose). The results of the present study suggest that the use of VPIA analgesic infusion pump, when integrated with a VPIA variable lockout algorithm, is able to provide pain relief with good patient satisfaction in post-operative acute pain management. No significant adverse event was observed in this study.

Chou et al. found that 80 patients that underwent total abdominal hysterectomy and later given acute postoperative morphine analgesia (1-mg bolus of morphine solution with lockout time of 5 min and a maximum dosage of 15 mg within a 4-hour period in the absence of background infusion) had an average pain score (visual analogue scale VAS; at rest) of 3.75 and 2.8 at 6 hour and 24 hour post-operatively, scorings of 0.9 and 0.5 in nausea and sedation respectively, and a further 15% (12/80) in vomiting [12]. The same study also found an average morphine consumption of 40mg in 48 hours, which is higher than our present data. Another study on patients after total knee arthroplasty showed an approximate VAS pain score of 2 and 1.5 at 12 and 24 hours respectively as well as an average morphine consumption of 27mg in 48 hours, indicating the different opioid consumption and pain scores across various surgical procedures [13].

Respiratory depression is reported in up to 5% with the use of PCA opioid and this can potentially cause brain damage or death [14-15]. A retrospective study on Chinese patients receiving PCA intravenous morphine showed that the incidence of respiratory depression (as defined by oxygen desaturation <90% for longer than one minute) is 1.62% (20/1233), however our results showed a higher incidence, indicating that there could be significant under-diagnosis of oxygen desaturation during conventional routine monitoring, which might raise concerns over patient safety [16].

In this case series, we proposed a closed-loop system that could temporarily lock out any demands from the patient, if at any point of time, the patient breaches any vital signs safety threshold. These vital signs safety thresholds can be adjusted by the healthcare provider, especially for patients deemed to be of higher risk, such as the elderly, patients with respiratory disease or morbidly obese. While optimizing the size of bolus dose appears to provide good pain relief with minimal side effects, there are limited data available concerning the effects of various dose sizes. Owen et al. examined the effects of morphine dose by prescribed patients with 0.5 mg, 1 mg or 2 mg demand bolus dose of morphine. The results revealed that most of those who were prescribed 0.5 mg demand dose were

unable to achieve adequate analgesia, whereas a high incidence of ventilatory depression was reported in those who received 2 mg, and hence concluded that the optimal PCA bolus dose for morphine was 1 mg [17]. We therefore chose to vary the duration of the lockout interval as a safety mechanism that limited the frequency of demands made by the patient. This safety of margin was done by allowing the interval to be long enough for patient to receive the drug effect from the bolus dose before the next bolus was delivered. Currently there is no optimal lockout interval and previous studies have not shown superiority of any particular interval to be optimal [18].

Safety features based on abnormal patient safety parameters were also incorporated in this algorithm and were proven to be useful as judged from >50% patients experiencing safety pause and/or emergency safety stop during the study period. This is important to the current clinical practices whereby postoperative patients on PCA opioids are still intermittently monitored for vital signs via manual or electronic measurements, which is highly labor intensive. There is a strong likelihood that these early signs of deteriorating vital signs may go undetected and cause serious complications, further demonstrating the importance of continuous and sensitive monitoring during PCA opioids usage that could provide early response to improve patient safety.

To determine whether the novel computer-integrated drug delivery system was user friendly, we also gathered feedback from patients on various aspects on the device setup (patient handset, pole stand) and overall treatment experiences (interference with treatment, safety and effectiveness). The overall feedback positively agreed that the pump was safe and effective in PCA opioid administration to treat post-operative pain, but the mobility of the pump remained an issue due to the size of the pump. Future plans will include a more portable PCA administration by reducing the pump form factor to allow more flexibility in mobilizing the PCA resources within the healthcare premises.

The clinical significance of the VPIA analgesic infusion pump is mainly threefold. Firstly, the system allows better and responsive titration of personalized pain relief to optimize pain relief. This improves

patient satisfaction and promotes pain relief. Secondly, clinical management is improved for patients with high risk of opioid respiratory depression on opioid therapy with earlier detection based on trends of opioid use and vital signs monitoring trends. Thirdly, with the VPIA analgesic infusion pump being an automated system that incorporates both vital sign monitoring and drug delivery. Hence, potentially this could address the limitation of healthcare manpower resource and lower cost required to monitor patients. According to Anesthesia Patient Safety Foundation, it is observed that patients having vital signs charted every 4 hours are usually left unmonitored >90% of the time, and since these patients are commonly administered with supplemental oxygen, this may eventually complicate the monitoring by masking hypoventilation, causing the signs of respiratory depression to be recognized only in its later stage provided pulse oximetry monitoring is used [19]. This is further worsened by the fact that more than 75% of patients with moderate to severe sleep apnea are undiagnosed with a 7-22% prevalence, and the conventional risk stratification for heightened post-op monitoring could potentially miss a large population of patients that is in fact at increased risk for post-op drug-induced respiratory depression [20]. Subsequently this could result in increased length of stay, risk of hospital-acquired infections and increased costs [21].

The limitations of the study would be the small sample size by which this case series was conducted only 19 females with specific gynecological procedures. Patients with different gender and surgical procedures would need to be investigated in future larger trials that may require different predefined critical values. Majority of the study population are Asian Chinese females (70%) and therefore no conclusions could be drawn from other surgical populations. In this study, we intended to incorporate the information obtained from both the pattern of analgesic use as well as continuous pulse oximetry, heart rate and respiratory rate values into the VPIA analgesic infusion pump. Despite having successful readings on oxygen saturation and heart rate to achieve safety pause, the use of respiratory rate for decision-making was limited due to missing data during the volunteer testing. Hence, the study proceeded without decision making from respiratory rate monitoring. Future study plans will include refining new vital signs sensors and better integration with the delivery system to

ensure better data capture.

Conclusions

In conclusion, closed-loop opioid delivery systems like the VPIA analgesic infusion pump help to improve patient safety and are able to respond rapidly to patients' changing hemodynamic conditions. Our preliminary results showed that the system is able to automatically respond appropriately by improving monitoring in opioid delivery and could prevent further oxygen desaturation and bradycardia. The VPIA analgesic infusion pump has good patient satisfaction and user feedback. Therefore, the VPIA analgesic infusion pump could serve to be pivotal in providing a holistic care to postoperative patients in a safe and regulated environment for opioid pain management.

Abbreviations

ASA: American Society of Anesthesiologists; BMI: Body mass index; CI: Confidence intervals; IQR: Interquartile range; PACU: Post-Anesthesia Care Unit; PCA: Patient controlled analgesia; SD: Standard deviation; SpO₂: Oxygen saturation; TAHBSO: Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy; VAS: Visual analogue scale; VPIA: Vital-signs-integrated Patient-assisted Intravenous opioid Analgesia.

Declarations

Ethical approval and consent to participate

This study was approved by the SingHealth Centralized Institutional Review Board, Singapore (SingHealth CIRB Ref: 2015/3062), and registered on Clinicaltrials.gov (NCT02804022). The authors declare that all the recruited patients provided informed consent, and that this work was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed in this work are available for anyone who wishes to access the data by contacting the corresponding author.

Competing interests

Ban Leong Sng is an associate editor of BMC Anesthesiology. Ban Leong Sng and Alex Sia Tiong Heng have filed a patent related to this work (SG 10201801161P, filed 12 Feb 2018, Singapore). Alex Sia Tiong Heng has intellectual property ownership and is the founding scientific director of Innovfusion Pte Ltd. All other authors reports no conflicts of interest in this work.

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Authors' contributions

All authors contributed to the study design, data analysis and discussion, drafting and/or revising the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of this work.

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Tables

Table 1 Baseline and demographic characteristics of recruited subjects

Parameters	No. of patients	Mean (SD)/ Median [IQR] /Percentage
Age; years	19	51.5 (8.8)
Race	19	
Chinese	13	68.4%
Indian	3	15.8%
Malay	2	10.5%
Others	1	5.3%
Weight; kg	19	62.0 (9.85)
BMI; kg/m ²	19	24.7 (4.42)
ASA Status	19	
I	5	26.3%
II	14	73.7%
Intraoperative morphine (mg)	19	8.0 [2.0]
Intraoperative fentanyl (mcg)	19	100 [0.0]

SD: Standard deviation. IQR: Interquartile range.

Table 2 Pain characteristics during Post Anesthesia Care Unit (PACU) and ward stay

Parameters	No. of patients	Mean (SD)/ Median [IQR] /Percentage
During PACU stay	19	
Morphine (mg)	19	4.0 [5.0]
Last pain score before discharge (0-10)	19	3.0 [2.0]
Last sedation score before discharge (0-3)	19	1.0 [0.0]
Nausea/vomiting before discharge (0-3)	19	0.0 [0.0]
During Ward stay		
12 hours Post-op	19	
Pain score (at rest) (0-10)	19	2.0 [5.0]
Pain score (movement) (0-10)	19	5.0 [3.0]
Sedation score (0-3)	19	0.0 [0.5]
Nausea/vomiting	18	0.0 [1.0]
24 hours Post-op	19	
Pain score (at rest) (0-10)	19	0.0 [2.0]
Pain score (movement) (0-10)	19	3.0 [2.0]
Sedation score (0-3)	19	0.0 [0.0]
Nausea/vomiting	19	0.0 [0.0]
Morphine consumption (24 hours; mg)	19	12.5±7.1
Side effect		
Nausea / vomiting	6	31.6%
Pruritus	1	5.3%

Table 3 Post-operative feedback (n=19) on the VPIA analgesic infusion pump

Parameters	Values
Feedback (1-5; 1: Strongly disagree; 5: strongly agree)	
Patient handset button	4.0 (1.0)
Mobility of pole with mounted pump	3.0 (0.0)
No interference of vital signs monitoring with treatment	4.0 (2.0)
Pump safety	4.0 (1.0)
Pump effectiveness	4.0 (1.0)

Figures

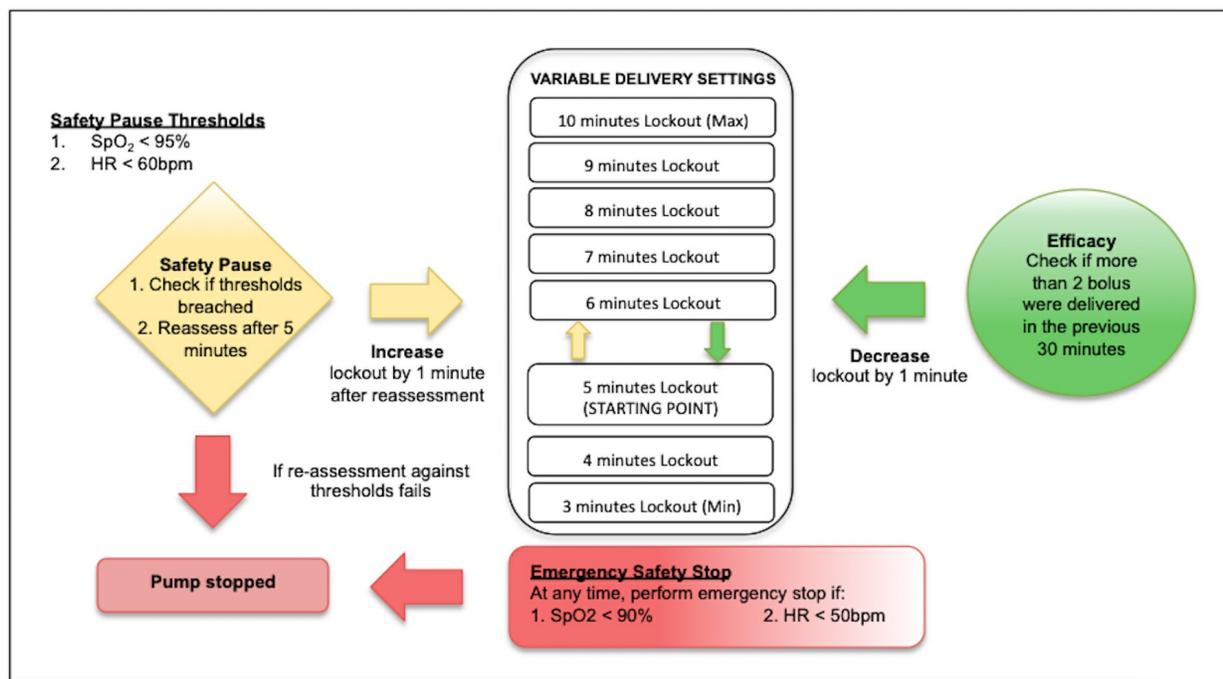


Figure 1

The proposed Vital-signs-integrated Patient-assisted Intravenous opioid Analgesia (VPIA) analgesic infusion pump and the variable lockout algorithm.

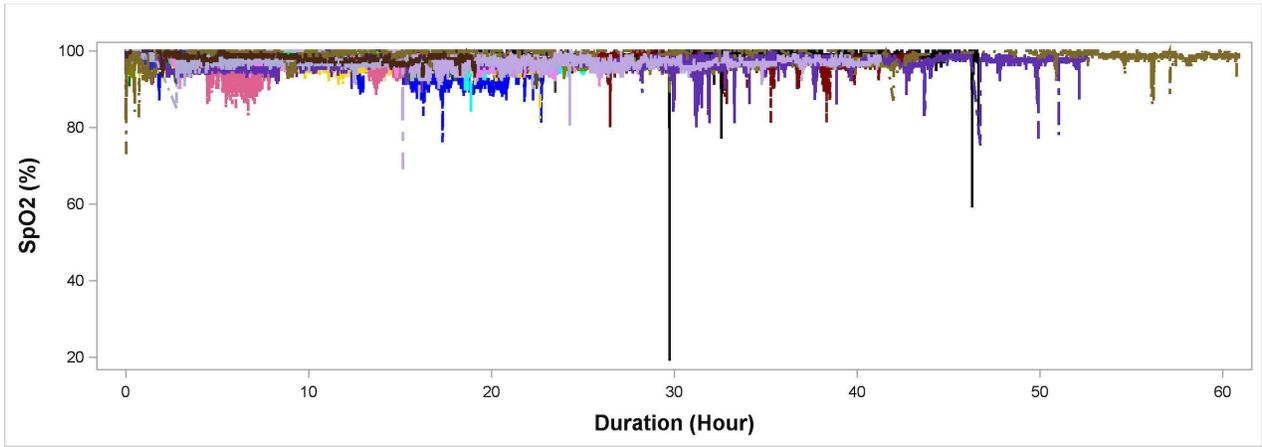


Figure 2

Level of oxygen saturation (SpO2) versus time (hour) in all 19 patients expressed in different colors.

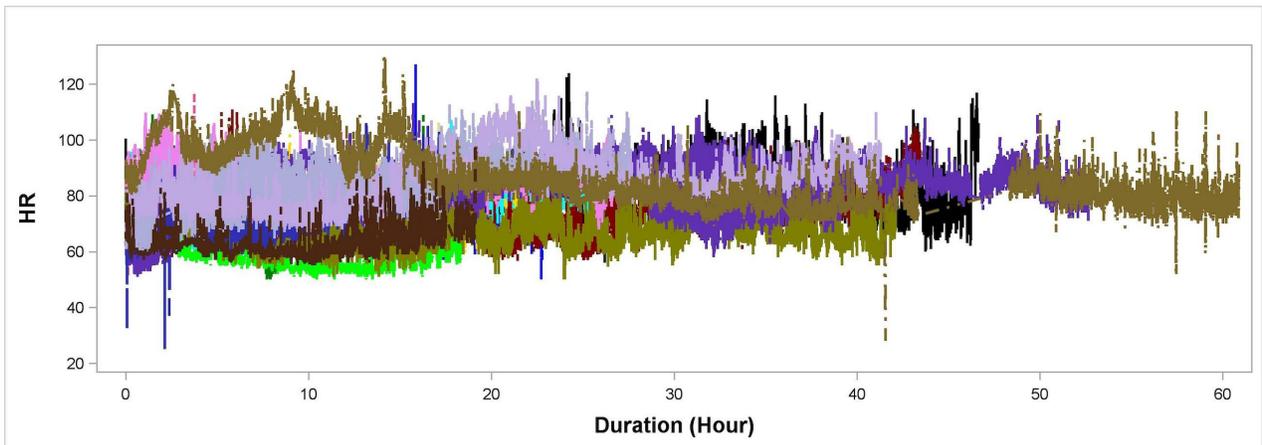


Figure 3

Heart rate (HR) versus time (hour) in all 19 patients expressed in different colors.