Short Communication

Karoline Kolås Andersen* and Gunnvald Kvarstein

Postoperative opioids and risk of respiratory depression – A cross-sectional evaluation of routines for administration and monitoring in a tertiary hospital

Abstract

Objectives: Opioids are the most potent analgesics in the treatment of postoperative pain. Respiratory depression is, however, a serious side effect. The aims of this study were to evaluate current practice and routines for post-operative administration of opioids in a Norwegian university hospital and to evaluate whether the clinical safeguards adequately protected patients' safety regarding risk of respiratory depression.

Methods: The study had a retrospective cross-sectional design and included 200 patients, treated with opioids postoperatively. The patients were treated in a post-anesthesia care unit (PACU) before transferal to a surgical ward. Relevant data such as opioid dosages, routes of administration, sedation and respiratory function, routines for patient monitoring, and numbers of patients with opioid induced respiratory depression was collected.

Results: Two patients (1%) developed respiratory depression that needed naloxone to reverse the effect, and 32 patients (16%) had a respiratory rate (RR) <10/min, which may have been caused by opioids. In the PACU, the patient's RR was evaluated on a routine base, but after transferal to a surgical ward RR documented in only 7% of the patients.

Conclusions: The lack of routines for patient monitoring, especially RR, represented a risk of not detecting opioid induced respiratory depression.

Keywords: clinical monitoring; opioids; pain treatment; post-operative; respiratory depression; tertiary hospital setting.

Introduction

Opioids are the most potent analgesics in the treatment of postoperative pain. Respiratory depression is, however, a serious side effect. Since 2001, at least nine patients have died due to opioid overdose administered by health care providers in Norway, and in three cases, this happened post-operatively[1]. In a large systematic review of 165 articles, addressing effects of opioids in a postoperative setting [1], the authors calculated an incidence of 0.3% for opioid induced and naloxone requiring respiratory depression. Respiratory rates (RR) below 10/min were observed in 1.1% of the cases. Another study found the risk of respiratory depression postoperatively to be highest during the first 24 h, including 77% of the incidents [2]. Others have claimed that respiratory depression can be avoided by individualized pain treatment and systematic monitoring focusing on sedation and respiratory depression [3].

The aims of our study were to evaluate current practice and routines for post-operative administration of opioids in a Norwegian university hospital and evaluate whether the clinical safeguards adequately protected patients' safety regarding risk of respiratory depression. An overriding routine or guideline for pain intensity scoring and monitoring of patients who received opioids postoperatively in

*Corresponding author: Karoline Kolås Andersen, Department of Anesthesiology, Haraldsplass Deaconess Hospital, Bergen, Norway, E-mail: karoline.kolas@gmail.com
Gunnvald Kvarstein, Department of Clinical Medicine, UIT, The Arctic University of Norway, Tromsø, Norway; and Department of Anesthesiology, University Hospital of North Norway (UNN), Tromsø, Norway, E-mail: gunnvald.kvarstein@uit.no

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1 Fatalities reported by the media.

the University Hospital of North Norway (UNN) in Tromsø had not been implemented. Therefore, we hypothesized that patients were not sufficiently monitored to discover respiratory depression. The original study was presented in a master thesis in 2017 and is published in a full version in Norwegian and accessible online [4].

Methods

The study had a retrospective cross-sectional design including 200 patients, treated with opioids postoperatively in 2015 at UNN Tromsø. The patients were taken care of in a post-anesthesia care unit (PACU) and then transferred to one of three surgical wards. All surgical patients (orthopedic, abdominal, endocrine or urology), were ≥18 years old and had received at least one dose of a potent opioid postoperatively.

All data was collected from the electronic patient journal from arrival to the PACU until 22 pm the following post-operative day. Data describes opioid dosages, routes of administration, sedation, respiratory function, RR and routines for patient monitoring. Opioid dosages were converted to Morphine Milligram Equivalents (MME, i.e., mgs morphine given orally). Epidural dosages could not be converted and were calculated and presented separately (see Table 1). We counted the numbers of patients with naloxone requiring respiratory depression, patients with a RR<10/min, and how many of these who had a RR<8/min, patients with oxygen saturation (SpO$_2$)<90%, and patients with arterial hypoxemia and hypercapnia by cut off values of PaO$_2$<8 kPa and PaCO$_2$>6 kPa or end tidal CO$_2$>6 kPa, respectively. Descriptive statistics were used.

Results

Thirty-two (16%) patients had a RR<10/min, and among these 12 (6%) had a RR<8/min, while 24 (12%) had SpO$_2$<90% and 10 (5%) had hypoxia and/or hypercapnia on arterial blood gas test (ABG). Two patients (1%), one in the PACU and another after arrival in the surgical ward, developed respiratory depression and needed naloxone to reverse the effect (see Table 2).

Average MME during the first 24 h was 55.5 mg and more than 10% of the patients received more than 100 mg. Among patients who received fentanyl epidurally, the average daily dose was 332 µg (see Table 3).

In the PACU opioids were mostly given intravenously (85%) and/or epidurally (26%). Relatively few patients (7%) received opioids orally. Transdermal and intramuscular administration was infrequent (3% and 0.5%, respectively), and none were given opioids subcutaneously or rectally. In the surgical wards, the proportion who received opioids intravenously (37%), equaled the number

Table 1: Conversion factors to orally administered morphine milligram equivalents (MME) for the different opioids and routes of administration.

Drug	Route of administration	Ratio
Morphine	Oral	1
	IV/SC/IM	3
Oxycodone	Oral	1.65
	IV/SC/IM	6
Buprenorphine	Dermal	100
	Sublingual	46.5
Fentanyl	Dermal	109
	Epidural	N.A.
	IV/SC/IM	5000
	Sublingual/nasal	50
Hydromorphone	Oral	5.8
Ketobemidone	Oral	1
	IV/SC/IM	3
Pethidine	Rectal	0.08
	IV/SC/IM	0.3
Codeine	Oral	0.1
Tramadol	Oral	0.15
Tapentadol	Oral	0.25

Conversion factors are provided by the Norwegian handbook for medical drugs "Norsk legemiddelhåndbok", Chapter L20.2 and by "Guideline for opioid conversion" from the University Hospital of North Norway and "Opioid Dose Equivalence" from Faculty of Pain Medicine ANZCA. NA, not applicable. We could not find a valid conversion factor from epidural to oral fentanyl administration.

Table 2: Number of patients with respiratory depression or impaired respiratory function postoperatively (N: 200).

Impaired respiratory function	PACU n, %	Surgical ward n, %	Total N, %
Respiratory depression with naloxone requirement	1 (0.5)	1 (0.5)	2 (1)
RR<10/min	31 (15.5)	2 (1)	32 (16)
RR<8/min	12 (6)	1 (0.5)	12 (6)
SpO$_2$ <90%	6 (3)	18 (9)	24 (12)
Hypoxia or hypercapnia (ABG)	10 (5)	0 (0)	10 (5)

PACU, post-anesthesia recovery unit; RR, respiratory rate; SpO$_2$, oxygen saturation measured by pulse-oximetry; ABG, arterial blood gas test.

treated by oral administration (36.5%). In cases where epidural or transdermal administration was established, the treatment was continued in the ward. Only one patient was given opioids intramuscularly or rectally, and none subcutaneously. Both in the PACU and in the surgical wards most patients received opioids by one single route, and only a few patients through three or four routes. We noted that the physicians' discretion rarely defined maximal dose of supplemental opioids.

Table 3: Total opioid dosages and routes of administration (N: 200).

Total opioid dosages	n, %	
Numbers and percentages of patients given >100 MME* within 24 h	21 (10.5)	
Average MME given within 24 h (min-max)	55.5 (0**–308.6)	
Average dose epidural fentanyl within 24 h among 51 patients µg (min-max)	332 µg (96–576)	

Routes of administration	PACU n, %	Surgical ward n, %
IV	169 (84.5)	74 (37.0)
Oral	13 (6.5)	73 (36.5)
Epidural	51 (25.5)	51 (25.5)
Dermal	6 (3.0)	6 (3.0)
IM	1 (0.5)	1 (0.5)
Rectal	0 (0.0)	1 (0.5)
SC	0 (0.0)	0 (0.0)

Number of routes applied simultaneously	n, %	n, %
0***	9 (4.5)	64 (32)
1	145 (72.5)	77 (38.5)
2	43 (21.5)	51 (25.5)
3	3 (1.5)	7 (3.5)
4	0 (0.0)	1 (0.5)

*MME, morphine milligram equivalents (1 MME equals 1 mg morphine by oral administration); **Three patients received only epidural analgesia. Since there is no valid conversion factor from epidural to oral fentanyl administration, the epidural dose of fentanyl was not included in MME and presented separately. Epidural dose of fentanyl were imputed as zero mgs in the MME calculation; ***Patients who received opioids either only in the PACU or after arrival to the surgical ward; IV, intravenous. IM, intramuscular, SC, subcutaneous. PACU, Post-anesthesia care unit.

When monitoring the patient, sedation level was usually documented as a qualitative description rather than a quantitative score. Around 10% of the journals provided no sedation level. After a supplementary opioid dose, sedation level was documented in 9% of all dosages given in the PACU and only 3% in the surgical wards (see Table 4).

In the PACU, RR and SpO$_2$ were documented at least once and respiratory function was assessed by either a qualitative description, capnography and/or blood gas levels in 1/3 of the patients. RR was documented after 77% of the supplementary opioid doses. During the stay in the surgical ward, however, RR was rarely documented (7%) and other tools than oxygen saturation was seldom used to assess respiratory function.

Table 4: Methods and frequency for patient monitoring (N: 200).

Vital sign assessment	PACU n, %	Surgical ward n, %
Sedation assessment		
Qualitative description	182 (91)	177 (88.5)
Qualitative description + GCS	2 (1)	0 (0)
None	18 (9)	23 (11.5)
Average number of documented sedation level per hour (min-max)	0.3 (0.0–1.5)	0.1 (0.2–3.7)
Ratio number documented sedation level and supplemental opioid dosages	45/531 (8.5)	7/272 (2.6)
Respiratory assessment		
RR	200 (100)	14 (7)
Pulse oximetry	200 (100)	124 (62)
Capnography	1 (0.5)	0 (0)
Arterial blood gas test	47 (23.5)	1 (0.5)
Qualitative description	24 (12)	36 (18)
Average number of documented RR per hour (min – max)	1.0 (0.0–0.5)	0.0 (0.0–0.4)
Ratio number documented RR and supplemental opioid dosages	410/531 (77.2)	7/272 (2.6)

GCS, Glasgow Coma scale; RR, respiratory rate; PACU, Post-anesthesia care unit.

Discussion

In this study 1% of the 200 patients developed respiratory depression requiring naloxone, and 16% a documented RR<10/min, which may indicate that ventilation was affected by opioids. This represents a substantially higher rate compared to the incidence of naloxone requirement at 0.3% and RR<10/min or 8/min at 1.1% presented in a large systematic review by Cashman et al. (1) including pooled data from 165 studies and nearly 20 000 patients. The higher incidences in our study may reflect a small sample size, and probably methodical differences in the ways of data collection. Due to the lack of documented RR in the surgical wards, however, we cannot rule out other cases with respiratory depression or serious respiratory impairment, which went undiscovered. Unfortunately, the present study design cannot derive causal relationships between opioid consumption and respiratory depression or impaired respiratory function, which could have been affected by for example sleep apnea, chronic obstructive pulmonary disease, residual muscular relaxation, type of surgery et cetera. However, the two cases of naloxone administration was thoroughly documented and left no uncertainty regarding opioid overdose as the cause of respiratory depression.

The large variation in opioid consumption in our sample does not surprise considering the variation in surgical procedures and an inter-individual variation in pain intensity which has been shown even after similar surgical procedures [5, 6]. In our material, average opioid consumption after 24 h equaled 55.5 mg morphine and more than 10% of the patients received more than 100 mg during a time period of 24 h. For one patient the total opioid dose equaled 309 mg morphine. A dose of 40–60 mg morphine can be toxic in an opioid naive patient [7, 8], and still, the physicians did not routinely set a maximal dose of supplemental opioid. Although the dosages were spread over several hours, we question whether this practice was adequate regarding the risk of opioid overdose. With a preset maximum opioid dose the physician on duty would have been contacted whenever the patient demanded higher opioid dosages, and been able to exclude possible postoperative complications, evaluate the opioid regime and discuss other treatment measures.

A total of 51 patients received fentanyl epidurally additional to other opioids or as the only route. Unfortunately, we could not find a valid conversion factor from epidural to oral opioids, and therefore the fentanyl dosages were not included in the number of MME. Considering the high number of patients receiving epidural analgesia, the total opioid dose in our material, presented as MME, is systematically underestimated. Some of the patients received different opioids by three or four different routes. Different routes of administration increase risk of respiratory depression [9]. In such cases, the time point of maximal blood concentration and effect is hard to foresee and may from a pharmacodynamic and pharmacokinetic perspective expose the patient to an unnecessary high risk of undetected overdose if the patient is not sufficiently monitored.

Sedation usually occurs at lower opioid dosages and is a sensitive indicator for a forthcoming respiratory depression [10]. Some authors recommend an evaluation of sedation and RR every hour during the first 24 h postoperatively [10], and more often in cases with a high risk of side effects [11]. Among patients who receive small dosages, such a frequent surveillance may seem exaggerated. We found no systematic documentation on sedation level in the records in this study. This indicates that sedation was not systematically assessed after supplemental opioid doses, which is essential to detect an overdose. In the PACU, the routine for evaluating RR was sufficient in relation to international standard. In the surgical wards however, RR was documented in only 7% of the patients. The risk of overseeing serious respiratory depression was therefore present.

At the time of data collection, there was no overriding, institutional guideline for clinical monitoring after postoperative opioid administration implemented. The clinical monitoring should include a systematic evaluation of pain intensity, as well as sedation and respiratory rate to reduce the risk of overdose and respiratory depression. Our findings indicate a strong need for such routines. Though limited by a small sample size, our findings may be generalized to other hospitals without such guidelines.

Conclusion

The monitoring of patients receiving opioids in the surgical wards seemed not sufficient with a risk of not detecting opioid induced respiratory depression. There were no overriding routine or guidelines available for pain intensity scoring and monitoring of patients who receive opioids postoperatively. Implementation of such guidelines would improve the postoperative pain treatment and increase patient safety.

References

1. Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. Br J Anaesth 2004;93:212–23.
2. Taylor SJ, Kirton OC, Staff II, Kozol RA. Postoperative day one: a high risk period for respiratory events. Am J Surg 2005;190: 752–6.
3. Smith LH. Opioid safety: is your patient at risk for respiratory depression? Clin J Oncol Nurs 2007;11:293.
4. Andersen KK, Johansen A, Kvarstein G. En kartlegging av rutiner og praksis for postoperativ administrasjon av opioider ved et norsk universitetssykehus – med fokus på pasientsikkerhet: UiT. Norway: The Arctic University of Norway; 2017.

5. Palada V, Kaunisto M, Kalso E. Genetics and genomics in postoperative pain and analgesia. Curr Opin Anaesthesiol 2018; 31:1.

6. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after LC. Pain 2001;90:261–9.

7. Norwegian Poison Information Center, Norwegian Institute of Public Health. Treatment after morphine overdose. Helsebiblioteket. Available from: http://www.helsebiblioteket. no/224305.cms [Accessed 2 Feb 2017].

8. Norwegian handbook for medical drugs. G12.5.13M Drug Overdose And Treatment. Available from: https://www. legemiddelhandboka.no/G12.5.13/Forgiftninger [Accessed 4 Jul 2020].

9. Gupta KPA, Nagappa M, Wong J, Abrahamyan L, Chung F. Risk factors for opioid-induced respiratory depression and failure to rescue: a review. Curr Opin Anaesthesiol 2018;31:110–9.

10. Pasero CC. Assessment of sedation during opioid administration for pain management. J PeriAnesthesia Nurs 2009;24:186–90.

11. Pasero CC. Opioid-induced sedation and respiratory depression: evidence-based monitoring guidelines. J PeriAnesthesia Nurs 2012;27:208–11.