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Case Report

Respiratory Depression Following Spinal Fentanyl Anaesthesia for Total Knee Replacement: A Rare Case Report

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Abstract:

Case summary

This case described profound respiratory depression in a-67-year-old woman 12 hour after spinal fentanyl 25 µg for total knee replacement on 13.09.2022. She had intravenous morphine 2.5 mg as post operative analgesia at 20:00 hour. Twelve hours after spinal fentanyl (22:00 hour), she got respiratory depression, type 2 respiratory failure reversed with naloxone. The effect lasted only 30 minutes; second dose of naloxone made no difference. Therefore, ventilatory support was initiated. At 20:00 hour 14.09.2022 (30 hours after initiation of spinal fentanyl 25 µg), both force of chest wall movement and respiratory rate were back to normal; she was completely normal at 44 hours after spinal fentanyl.

Keywords: spinal anaesthesia, fentanyl, respiratory depression, ventilatory support

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Introduction

Intrathecal opioids have been used widely in obstetric surgery (LSCS, lower segment cesarian section), orthopedic surgery (hip and knee replacement), major abdominal and thoracic surgery as it gives effective analgesia for long-duration. Moreover, there are several advantages: they provide more continuous and less labor-intensive analgesia once the initial dose is given; the dose of intrathecal narcotics required to produce analgesia is much lower than the intravenous dose; and, the potential for postoperative respiratory depression is less likely.

Lipophilic opioids diffuse rapidly into both neuronal tissues and non-neuronal tissues producing rapid onset of action and shortening duration of action and limiting spread to patient's head. Lipophilic opioids such as fentanyl have rapid onset of action (10-20 minutes) but short duration of action (4-6 hours); the duration of respiratory depression is 0-1 hour. On the other hand, hydrophilic opioids such as morphine have slow onset of action (60 minutes) but longer duration of action (18-24 hours); the duration of respiratory depression is up to 24 hours.

Regarding the various dosage of fentanyl, one study reported that fentanyl 12.5 μg added to low-dose bupivacaine (5 mg) intrathecally provides better surgical anaesthesia and increased reliability of block than intrathecal fentanyl 7.5 or 10 μg. Haemodynamic stability was the same for all dosage combinations and all were safe (Goel et al., 2003).

The most dangerous complication of intrathecal opioids is respiratory depression. The prevalence of respiratory depression did not change significantly with the addition of spinal fentanyl; it was reported as 0.7% when spinal fentanyl was added and 0.8% when it was not added. Furthermore, the episodes of respiratory depression were very rare and uneventful. Because it occurred intraoperatively it was recognized timely; therefore it was easily manageable (Fonseca et al., 2021) (Etches et al., 1989). Intrathecal opioids were effective and safe both to mother and baby in LSCS (Rahimzadeh et al., 2018) (Aslan & Moraloğlu, 2020) (González Cárdenas, 2012); neonatal respiratory depression was rarely reported (Liu et al., 1997). Spinal administration of fentanyl was safe even in the elderly; intrathecal fentanyl produced no significant reduction of cortical activity or clinical sedation in elderly patients during spinal anaesthesia (Syed Othman et al., 2016) (Shah & Bhat, 2017).

Case presentation

A-67-year-old woman underwent total knee replacement (right) on 13.09.2022 under spinal anaesthesia. Spinal anaesthesia was given with bupivacaine 12.5mg and fentanyl 25 μg at 10:00 hour. Operation time was 2 hours; it was uneventful. Blood pressure 120/70 mmHg, pulse rate 75/minutes, respiratory rate 18/ minutes, SaO2 99% through-out surgery.

Regarding past history, she was neither hypertensive nor diabetics; she had cerebrovascular accident (cerebral infarct) 10 years ago with resultant left hemiparesis, left facial palsy (upper motor neuron type) and dysarthria. She was ambulating well without aids; however, motor power was less than 5/5 MRC score on left side. Her body weight was 115 lb.

Immediate post-operative period was well; she was on oxygen therapy 2L/minute. All vital signs were stable till 22:00 hour. She had intravenous morphine 2.5 mg at 20:00 hour. Her attendant noticed that she became restless at 22:00 hour; she felt sudden onset of dyspnoea though on oxygen and SaO_2 was 90%. Her respiratory rate dropped to 12/minutes. She had to sit up as lying flat position made her worse. Her chest wall expansion was very limited. The attendant had to remind her to breathe. SaO_2 decreased to 80%; then it dropped to 68% when she did not breathe.

The physician on call found that she was drowsy; both pupils were small and pinpoint. Crackles were audible in both lungs. Blood pressure and pulse rate were 105/70 mmHg and 88/minutes. Chest wall movement was restricted and respiratory rate was 8/minute. As the features were compatible with narcotics overdose, intravenous naloxone 0.2 mg was given. She made dramatic response: alertness, respiratory rate 16/minute, increased chest expansion, SaO_2 94 % and pulse rate 78/minute.

However, the response lasted only 45 minutes; her force and rate of respiration diminished again. Subsequently, SaO_2 fell and drowsiness recurred. Unlike first dose, repeating the second dose of naloxone did not reverse the respiration. Therefore, ventilatory support was initiated.

ECG (Figure 2) was normal: CXR too. Figure (3) shows CXR before surgery; figure (4) reveals CXR at the time of low SaO2. Blood tests: total WBC was $19.3X10^9$

/L with neutrophil 84%; hemoglobin 9.8 gm%; and, platelets 195 x 10^9 /L. Troponin I was 5 times normal. CKMB was normal. D dimers was 3 times normal. Renal function tests were marginally raised; urea 80 mg% and creatinine 1.3 mg%. Electrolytes were normal; sodium 146.4 mmol/L, potassium 3.88 mmol/L, Chloride 107.1 mmol/L and HCO3 25.7 mmol/L. Serum calcium was normal 9 mg%. ABG done on 5L of oxygen with nasal canula showed respiratory acidosis with hypoxia and hypercapnia: pH 7.342; PCO2 48.5 mmHg; PO2 85.5mmHg; BE -0.3 mmol/L; Anion gap was 17.4 mmol/L.

Even with ventilatory support, the respiratory rate was 8/minute and she was having Cheyne-Stoke respiration for 3 hours. One hour later, she became alert but respiratory rate was 10-12/minutes. Eight hours later, her respiratory rate became 18/minutes and chest wall expansion improved too.

At 20:00 hour 14.09.2022 (30 hours after initiation of spinal fentanyl 25 µg), both force of chest wall movement and respiratory rate were back to normal (respiratory rate 16/minute). She could breathe well with nasal oxygenation 2L/minute with propped up position for another 12 hours.

At 08:00 hour 15.09.2022 (44 hours after initiation of spinal fentanyl 25 µg), she was completely normal. She could breathe well without oxygen; she could sleep in flat position.

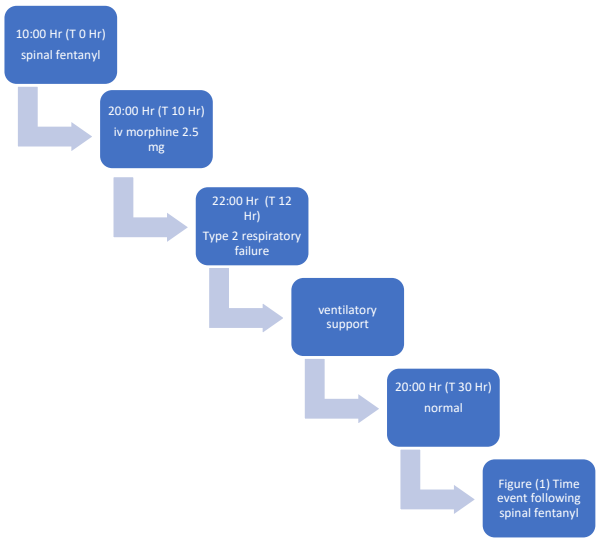

Figure (1) Time event following spinal fentanyl

Table (1) Serial laboratory parameters

Parameter	Before surgery	24 hours after surgery (at the time of event)	48 hours after surgery	72 hours after surgery
Hemoglobin (gm%)	11.5	10.2	9.8	10.2
Total WBC (x10^9/L)	8.2	11.6	12.8	11.68
Neutrophil (%)	71	84.6	82	
Platelets (x10^9/L)	248	207	195	187
Blood urea (mg/dl)	30	70.4	59.1	
Serum creatinine (mg/dl)	1.0	1.45	1.15	
Serum sodium (mmol/l)	142	144		143
Serum potassium (mmol/l)	4.2	3.8		4.6
Serum chloride (mmol/l)	83	107		105
Serum HCO3 (mmol/l)		25.7		
Troponin T (pg/ml)		22.73		21.22
D dimer (mg/L)	0.48	6.12		1.08
CK MB (U/L)		19.3	19.3	28.7
Arterial PaO2 (mmHg) (70-700)		85.5		
Arterial PaCO2 (mmHg) (30-50)		48.5		
pH (7.2-7.6)		7.34		
Anion gap (mmol/l)		17.4		
BE (mmol/l)		-0.3		
Serum calcium (mg/dl)		9.75	9.4	
LDH (U/L)			272	
Total protein (g/l)	62.2			57.2
Albumin (g/l)	43.3			34.8
Globulin (g/l)	19			22
Phosphate (mmol/l)				0.53

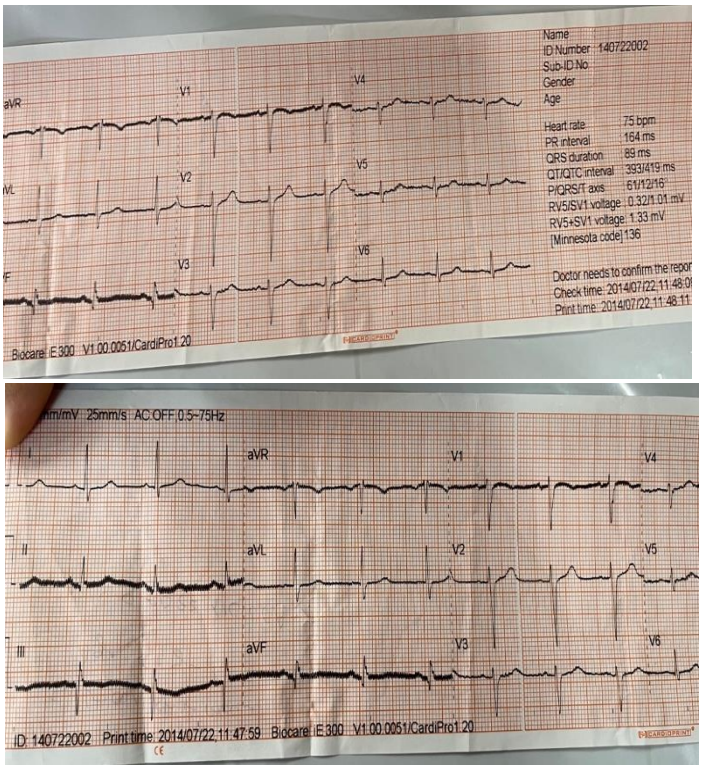

Figure (2) ECG

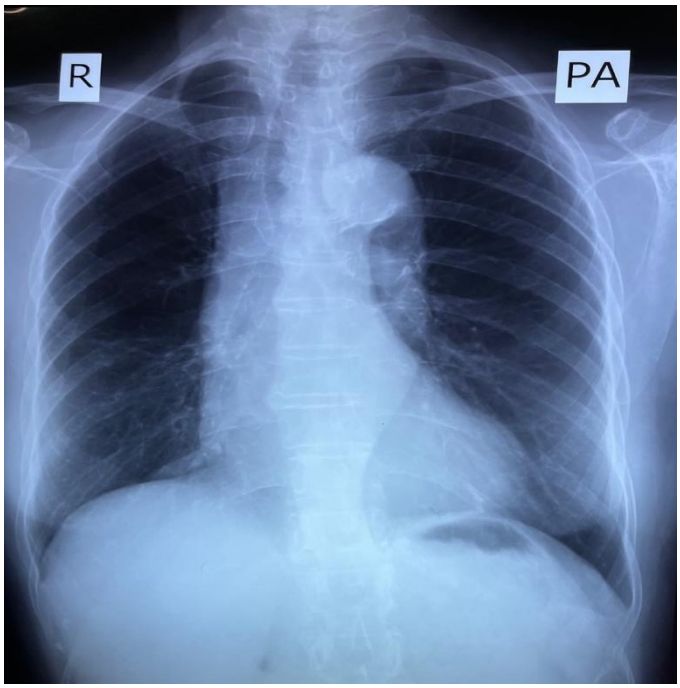

Figure (3) shows CXR before surgery

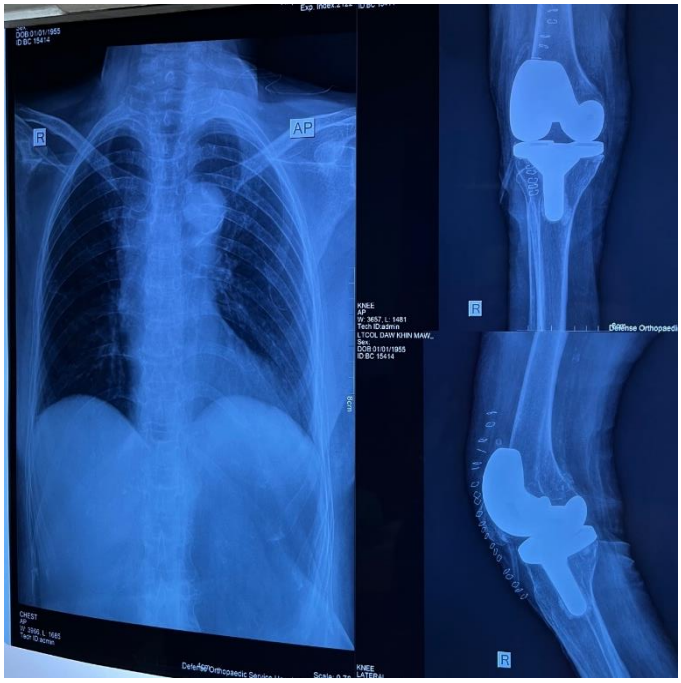

Figure (4) CXR at the time of low SaO2.

Discussion

The initial differential diagnoses in acute dyspnoea in post operative period in a-67-year-old woman with the background history of cerebrovascular accident were: (1) acute pulmonary oedema either due to acute myocardial infarction or fluid overload; (2) pulmonary embolism; (3) severe COVID-19 pneumonia; and (4) opioids induced respiratory depression. Acute myocardial infarction was less likely as ECG did not show ST changes though Troponin T was high (3 times normal). Fluid overload was impossible because of underlying normal renal function and normal fluid balance in reviewing fluid intake-output chart. Immediate chest radiograph did not have evidence of pulmonary venous congestion. Pulmonary embolism was unusual with relatively short bed-bound hours- 12 hours; the patient was on prophylactic dose of low-molecular weight heparin though D dimer was mildly increased (3 times normal). Severe COVID-19 pneumonia was ruled out because her nasopharyngeal swab prior to surgery negative and clear lung fields in chest radiograph.

Therefore, opioids induced respiratory depression was the most likely diagnosis; the favoring was force of chest wall expansion and respiratory rate. Having increasing weakness of chest wall movement together with falling respiratory rate were indicators of central respiratory failure- type 2 respiratory failure. It was supported by pinpoint pupil, drowsiness, crackles in both lungs and arterial blood gas analysis (hypoxia, hypercapnia and respiratory acidosis, normal bicarbonate level). In addition, respiratory depression reversed with intravenous naloxone. In this patient, the onset/timing of respiratory depression was 12 hours after intrathecal administration fentanyl.

The causative factor for opioids induced respiratory depression in this patient was not likely to be due to intravenous morphine: the dose of morphine was 2.5 mg; and, there was a time gap of 120 minutes between injection morphine and the onset of respiratory depression. Hence, opioids induced respiratory depression was most likely due to intrathecal fentanyl administration. Nonetheless, intrathecal fentanyl administration causing respiratory depression was extremely rare unlike intrathecal morphine. It can be explained with pharmacokinetics of intrathecal opioids. When administered intrathecally, opioids can travel cephalad within the CSF, spread inward to the spinal cord and spread outward into the epidural space. The degree to which each of these effects occurs differs for lipophilic opioids (e.g., fentanyl) and hydrophilic opioids (e.g., morphine). Lipophilic opioids deliver fast-onset but short-duration analgesia with little cephalad spread, producing a band of spinal level near level of injection. Hydrophilic opioids will remain largely confined to the CSF and bind to opioid receptors in the spinal cord, resulting in a slow onset and wide band of affected spinal levels for a long period of time. For long-acting agents, spinal fluid circulation may eventually carry the drug all the way to the brain stem. For this reason, respiratory depression is uncommon with intrathecal fentanyl

(primarily redistributed to the epidural space) or sufentanil (primarily redistributed to plasma), but a significant risk with intrathecal morphine. This patient had respiratory depression 12 hours after intrathecal administration fentanyl. The prevalence of respiratory depression following intrathecal fentanyl was 0.7%: main reason for reporting.

Intrathecal opioids have better analgesic efficacy with fewer systemic complication compared to systemic administration. Hence, they become more popular. The common causes of postoperative respiratory depression are excessive opioid administration, inadequate recovery from neuromuscular blockade, laryngospasm, and prolonged sedative effects of methadone (which can outlast the analgesic effects). The route, frequency and quantity of opiates administered in the perioperative period all influence the risk of postoperative respiratory depression. Postoperative respiratory depression is especially problematic in patients administered opioids by both the systemic and neuraxial route, and in those with increased sensitivity to opioids, such as patients with obstructive sleep apnea and intermittent hypoxemia.This patient got both systemic and intrathecal opioids so that she developed postoperative respiratory depression.

Regarding the timing of onset of respiratory depression, the patient developed respiratory depression at 12 hours after intrathecal administration of fentanyl. Lipophilic opioids diffuse rapidly into both neuronal tissues and non-neuronal tissues producing rapid onset of action and shortening duration of action: limiting spread to patient's head. Lipophilic opioids (e.g., fentanyl) deliver fast-onset (10-20 minutes) but short-duration analgesia (4-6 hours) with little cephalad spread. In this patient, having the onset of respiratory depression 12 hours after spinal injection was unusual. This demonstrated the unpredictable nature of respiratory depression, the potentially serious complication. This is another reason for sharing experience; close care on respiration particularly in first 24 hour after intrathecal opioids.

The duration of respiratory depression with lipophilic opioids is usually 0-1 hour. In this patient, total duration of respiratory depression was 30 hours with ventilatory support and another 14 hours with nasal oxygen supplementation (total 44 hours including ventilatory support). Even with hydrophilic opioids (e.g., morphine.), the maximum duration of respiratory depression is 24 hours. Therefore, unusually long duration of respiratory depression, 44 hours, in this patient can be explained by unpredictable nature of respiratory depression by intrathecal opioids; not to overlook unusual fatal sequelae.

In this case, the effect of first dose of naloxone (0.2 mg) lasted only 45 minutes. And repeating the second dose did not make any improvement. Therefore, we were reluctant to give infusion. Although naloxone infusion is recommended for respiratory depression due to intrathecal morphine (Iwata et al., 2016), naloxone over dose may also result in similar effect. In fact, total duration of respiratory support (ventilator and oxygen) required in this patient was 44 hours i.e., till the effect of tissue fixed opioids disappeared. This is another learning point from this patient.

The risk factors for development of 'respiratory depression' include increasing age, the concomitant use of long-acting sedatives, positive pressure ventilation, and co-existing respiratory disease. Co-administration of opioid analgesics during the first 12–24 h after intrathecal administration has long been a concern regarding the development of early and late onset respiratory depression. In this patient, giving intravenous morphine 2.5 mg as post-operative analgesia might precipitate respiratory depression though it happened 2 hours after intravenous administration.

Conclusion

Respiratory depression (type 2 respiratory failure) is one of important differential diagnoses of acute dyspnoea in 24-hour post-operative period. Falling SaO_2 is one feature of hypoxia requiring urgent attention. Reduction in chest wall expansion as well as rate of respiration is the clue to respiratory failure possibly central cause like opioids overdose. Awareness of respiratory depression following intrathecal opioids is important particularly in elderly, neurological disorder like stroke and parkinsonism, concomitant use of sedatives or other opioids.

Recommendations

It is important to anticipate respiratory depression in patients after intrathecal opioid. Patients receiving intrathecal opioids should receive only small amounts of short-acting intravenous narcotic. Extreme caution is necessary in giving intravenous narcotics in controlling post-operative pain to those receiving intrathecal opioids; only small amounts of short-acting form should be used.

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Declaration of conflict of interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting cases.

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Informed consent

The informed consent for publication in this article was obtained from patient.

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