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A COMPARISION OF MORPHINE AND FENTANYL ANALGESIA IN PATIENTS UNDERGOING CARDIAC SURGERY ON CARDIOPULMONARY BYPASS.

Anesthesiology

Dr. Sushma Nandipati Assistant Professor of Anaesthesiology, Sree Balaji Medical College and Hospital, Chennai, Tamilnadu.

Dr. S. Balachander* Department of cardio thoracic surgery, Sree Balaji Medical College and Hospital, Chennai, Tamilnadu. *Corresponding Author

ABSTRACT

AIM: To compare Morphine and Fentanyl analgesia used intraoperatively in terms of haemodynamic changes and postoperative recovery , in patients undergoing cardiac surgery on cardiopulmonary bypass.

METHOD: Thirty patients undergoing cardiac surgery with cardiopulmonary bypass were randomized to receive either morphine or fentanyl as part of a standardized opioid - isoflurane anaesthesia.

Group M - 15 patients received morphine intravenously.

Group F - 15 patients received fentanyl intravenously.

Haemodynamic variations were recorded in both groups and compared. Immediate postoperative recovery of the patients was also observed –in terms of haemodynamic changes, patient cooperation, time of extubation and length of ICU stay.

RESULTS: Morphine group has statistically significant haemodynamic variations intraoperatively and initial postoperative period as compared with fentanyl group with stable haemodynamics. The analgesic effect and postoperative patient recovery are significantly better with morphine than with fentanyl.

CONCLUSION: Analgesia with Morphine provided better pain relief and equally stable haemodynamics with comparable side effects as with Fentanyl analgesia, with early extubation and comfortable postoperative period in patients undergoing cardiac surgery on cardiopulmonary bypass.

KEYWORDS

Cardiopulmonary bypass; Morphine; Fentanyl; Haemodynamic changes; postoprecovery; extubation.

INTRODUCTION:

First Cardiac surgery was done in 1895, since then cardiac surgery has undergone various modifications and reached the current stage. Two major advances in medicine made heart surgery possible:

- Cardiopulmonary bypass or the heart-lung machine, which takes over the work of the heart.
- Body cooling techniques, which allow more time for surgery without causing brain damage[1].

Cardiopulmonary bypass (CPB) is a form of extracorporeal circulation whose function is circulatory and respiratory support along with temperature management to facilitate surgery on the heart and great vessels. The first successful human cardiac surgery using CPB was performed by John Gibbon in 1952[2] for repair of the atrial septal defect. Inspite of a number of technical and surgical developments in the field of cariothoracic surgery and associated complication with CPB, CPB still stands out to be the standard procedure for cardiac surgery [3].

Sources of pain during cardiac surgery include- median sternotomy or thoracotomy incisions, rib retraction, harvesting of vessels from the forearm or legs for grafting, dissection of internal mammary arteries, and the presence of (and removal of) chest drains. Other potential causes include incomplete revascularization of the myocardium, the presence of sternal wires or epicardial pacing leads, and sternocostal and costovertebral pain from excessive retraction. Pain should be an important anesthetic consideration and should be addressed promptly both intraoperatively and post operatively. Several techniques are in use for pain alleviation during cardiac surgery like – intravenous opioids, intrathecal and epidural injections; local infiltration, intravenous paracetamol and nerve blocks after the procedure. Of all these techniques intravenous opioids have been proven as an effective method given either as patient controlled analgesia or bolus doses.

In this study we desire to compare the differences between two opioids- morphine and fentanyl in terms of analgesia produced and postoperative recovery while maintaining haemodynamic stability.

AIM OF THE STUDY:

To compare Morphine and Fentanyl analgesia used intraoperatively in terms of haemodynamic changes and postoperative recovery , in patients undergoing cardiac surgery on cardiopulmonary bypass.

MATERIALS AND METHODS:

This is a comparative randomised prospective double blind controlled study involving 30 patients coming for cardiac surgery on CPB. The study was approved by the institutional review board of our hospital. Written informed consent was obtained from all patients in the study.

INCLUSION CRITERIA

1. ASA physical status II and III.
2. Patients undergoing cariac surgey using cardiopulmonary bypass .

EXCLUSION CRITERIA

1. ASA physical status > IV and emergency cases.
2. Hypertensive patients on antihypertensives.
3. Patients allergic to opioids
4. Patients with difficult intubation.

METHOD

30 patients scheduled for elective cardiac surgery under general anesthesia were included in the study. All patients were visited and evaluated by anaesthesiologist on the previous day of surgery. The anaesthetic procedure was explained to all the patients and informed consent was obtained. They were randomly allocated by picking of lots into one of the two groups equally with 15 patients in each group.

Group M : Morphine (0.1mcg/kg)
Group F : Fentanyl (5mcg/kg)

After shifting patients into operation theatre and placing electrocardiographic leads and pulse-oximeter, a peripheral IV using 16G venflon and arterial access with 20G jelco on radial artery were attained under local anesthesia. Central venous catheter also inserted in the right internal jugular vein under local anaesthesia. Premedicated with IV midazolam (0.05 mg/ kg) and anaesthesia was induced with Etomidate (0.03mg/kg) and vecuronium (0.1 mg/kg) intravenously, then either (0.1 mg/kg) of morphine or (5 µg/kg) of fentanyl was administered as bolus dose. Syringes were labelled and covered to blind the anaesthesiologist and the infusion pump was then programmed to deliver either morphine at a rate of (1-2 mg/h) or fentanyl at a rate of (1 µg/kg/h), (Dosing of fentanyl reflected the lower range of equipotence of fentanyl to morphine (40-50:1)[4] and the infusion was continued until the end of surgery and the arrival to the ICU. Anaesthesia was maintained pre- and post-CPB using isoflurane and vecuronium (0.1 mg/kg) and patients were ventilated with a mixture of oxygen and nitrousoxide [50:50].

Median sternotomy was done in all patients. An initial dose of 4mg/ kg of heparin was used to obtain an activated clotting time (ACT) >400sec before going on CPB. CPB was instituted with a non-pulsatile

heartlung machine. Mean blood pressures of 50-70 mm Hg and blood flows of 2-2.4 L min^{-1} m^{-2} was maintained during CPB. The priming volume contains, non-glucose containing crystalloids and heparin. Moderate hypothermic CPB (28-30°C) was used in all patients. Cardiac arrest was achieved and maintained using cold cardioplegic solution at 4°C. Patient characteristics such as age, weight, height, sex were recorded. Surgical details including the operation type, bypass time, cross clamping time, duration of surgery, were all recorded. Haemodynamic data included heart rate, mean arterial blood pressure, and central venous pressure are collected at several times in the perioperative period: immediately preinduction (Tbaseline); 30 min postinduction (T_1), 30 min post-bypass (T_2), 1hr post-bypass (T_3), 2hrs post-bypass (T_4), upon ICU admission (T_5), 3hrs (T_6) and 6hrs (T_7) after ICU admission. The pain was assessed using the VAS; however, for statistical comparison the pain control was divided into good pain management (VAS <4) and suboptimal (VAS from 5 to 10). Pain was measured at 2hrs, 4hrs, 8hrs, 12hrs, 24hrs period. Opioid infusion was stopped after 8hrs after surgery. Rescue analgesic used was Inj.Paracetamol 1g intravenously if the VAS score is more than 8. Also, the presence of side effects from the opioids was evaluated (hypotension, bradycardia, respiratory depression, excessive sedation, nausea, vomiting, pruritus).

Primary outcome

- Pain scores ranged from mild (VAS <4) to suboptimal (VAS from) from 5 to 10)
- Haemodynamic variations.

Secondary outcome

- Sedations using University of Michigan sedation scale

0 = Awake/Alert
1 = Minimally sedated
2 = Moderately sedated
3 = Deeply sedated
4 = Unarousable.

- Side effects included respiratory depression and bladder function.
- The incidence of intraoperative arrhythmias was also recorded.
- Time taken for extubation and the length of ICU stay postoperativly were also recorded.

Statistical analysis

The data were presented as number and percentage and continuous data as mean and standard deviation. Analysis of continuous variables was done using One way ANNOVA test categorical variables were analysed with chi-square test. A probability (p) value of less than 0.05 was taken as significant. The difference in the average pain score between the two groups for was compared using nonparametric Wilcoxon's ranked sum test.

RESULTS

Demographic features:

There were no significant demographic differences among the 2 groups with respect to age, weight, sex as shown in Table 1. Data presented as median (interquartile range). p value by ANNOVA test is (p<0.5).

Table 1: Demographic data in the two groups (mean ± SD) ,NS= Non-Significant.

	Morphine(n=15)	Fentanyl(n=15)	p
Age(years)	30.4 ± 11.2	30.47 ± 10.8	< 0.5 (NS)
Weight (kg)	60.27 ± 9.88	57.07 ± 11.8	
Height (cm)	164.1 ± 8.5	160.4 ± 6.13	
Sex (male/female)	10/5	10/5	

Surgery details:

There were insignificant statistical differences between the two studied groups as regarding type of the operation, bypass time (min), cross-clamping time (min), duration of surgery (min), as shown in Table 2. Data presented as median (interquartile range), frequency (%). p value by ANNOVA test found to be non-significant.

Table 2: Operative data in the two study groups,) NS=Non-Significant.

		Morphine	Fentanyl	p
Type of the operation	CABG	11 (73%)	13 (87%)	>0.05 (NS)
	Valve Replacement	4 (27%)	2 (13%)	
Bypass time (min)		151 ± 38	148 ± 32	
Cross -Clamping time (min)		120.6 ± 38.2	123.8 ± 30.5	
Surgery duration(min)		396 ± 63.79	354.33 ± 52.3	

Haemodynamic data

Haemodynamic data like heart rate, mean arterial blood pressure and central venous pressure were collected at several times in the perioperative period: immediately pre-induction (Tbaseline); 30 min postinduction (T_1); 30 min post-bypass (T_2); 1hrs post-bypass (T_3); 2hrs post-bypass (T_4); upon ICU admission (T_5); and 3hrs (T_6), 6hrs (T_7) after ICU admission.

Heart rate (HR):

In morphine group, there was significant decrease in HR from baseline reading only at 30 min post-bypass (p<0.01) while there were insignificant differences at the other times of the study (Table 3 and Figure 1). Data presented as median (interquartile range). p value analysed by ANNOVA test. Intergroup differences (p<0.05) by Tukey's test after log transformation: NS=Non-Significant, **p<0.01 compared to $T_{baseline}$. ***p<0.001 compared to $T_{baseline}$.

Table 3: Heart rate changes (beats/min) in the two studied groups.

	Morphine	Fentanyl	p
Pre-induction (Tbaseline)	89.93 ± 18.49	94.93 ± 11.34	NS
30 min post-induction (T_1)	83 ± 17.33	83 ± 17.33 **	NS
30 min post-bypass (T_2)	78.73 ± 8.92 **	83.73 ± 4.27 **	NS
1 hour post-bypass (T_3)	98.27 ± 3.63	113.4 ± 15.34 ***	p<0.05
2 hours post-bypass (T_4)	87.53 ± 9.57	93.73 ± 6.75	p<0.05
On ICU admission (T_5)	81.47 ± 7.35	87.4 ± 3.44	p<0.05
3 hours after ICU admission (T6)	82.07 ± 15.25	89.87 ± 11.81	p<0.05
6 hours after ICU admission (T7)	83.07 ± 12.85	85.33 ± 6.63 **	NS

In fentanyl group, compared with baseline reading there was significant decrease in HR at 30 min post-induction (p<0.003), 30min post-bypass (p<0.005) and 6hrs after ICU admission (p<0.01). A significant increase in HR from baseline reading at one hour postbypass was reported (p<0.001). However, there were insignificant differences at 2hrs post-bypass, on ICU admission and 3hrs after ICU admission (Table 4 and Figure 1).

Comparing the groups the heart rate values did not change much from the baseline. The postoperative readings are much lower in morphine group suggesting good pain relief unlike in fentanyl group.

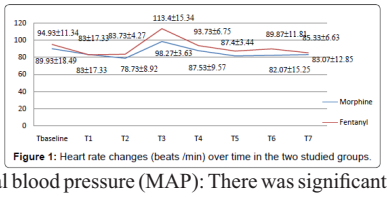


Figure 1: Heart rate changes (beats /min) over time in the two studied groups.

Mean arterial blood pressure (MAP): There was significant decrease in MAP value in morphine group. p value <0.001 as shown in Table 4 and Figure 2. Data presented as median (interquartile range). p value by ANNOVA test. Intergroup differences (p<0.05) by Tukey's test after log transformation: NS=Non-Significant. **p<0.01 compared to $T_{baseline}$ *p<0.05 compared to $T_{baseline}$ ***p<0.001 compared to $T_{baseline}$.

Table 4: Mean arterial blood pressure changes (mm Hg) in the two studied groups.

	Morphine	Fentanyl	p
Pre-induction (Tbaseline)	88.27 ± 13.78	83.67 ± 6.6	NS
30 min post-induction (T1)	71.87 ± 9.2 ***	77.1 ± 14.67 *	NS
30 min post-bypass (T2)	69.8 ± 8.9 ***	69.13 ± 9.49 ***	NS
1 hour post-bypass (T3)	67 ± 10.64 ***	71 ± 8.4 ***	NS
2 hours post-bypass (T4)	68.73 ± 8.2 ***	74.87 ± 7.51 **	NS
On ICU admission (T5)	70.13 ± 6.1 ***	78.87 ± 6.1	p<0.001
3 hours after ICU admission (T6)	72.47 ± 5.05 ***	79.9 ± 6	p<0.01
6 hours after ICU admission (T7)	76.4 ± 6 ***	80.33 ± 5.3	NS

In fentanyl group, there was significantly decrease in MAP value from baseline reading at 30min post-induction (p<0.05), 30min postbypass (P<0.001), 1hour post-bypass (p<0.001) and 2hrs post-bypass (p<0.005). On ICU admission; 3 and 6hrs after ICU admission MAP increased gradually but still insignificantly decreased from baseline (Table 4 and Figure 2).

There was significant decrease in MAP values in morphine group from fentanyl group on ICU admission and 3hrs after ICU (p<0.001, p<0.01 respectively) as shown in Table 4 and Figure 2.

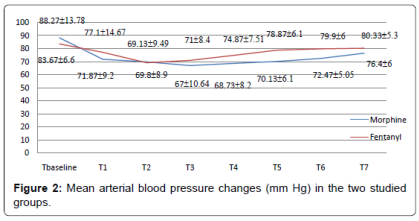


Figure 2: Mean arterial blood pressure changes (mm Hg) in the two studied groups.

Central venous pressure (CVP): In morphine group, there was significant decrease in CVP value measured in cm H2O from its baseline reading at 1hr and 2hrs post-bypass (p<0.001and p<0.05 respectively) while there were insignificant differences at the other study times (Table 5 and Figure 3). Data presented as median (interquartile range). P value by Kruskall-Wallis. Intergroup differences (p<0.05) by Tukey's test after log transformation: N.S=Non Significant **p<0.01 compared to $T_{baseline}$ *p<0.05 compared to $T_{baseline}$ ***p<0.001 compared to $T_{baseline}$

Table 5: Central venous pressure changes (cm H2O) in the two studied groups.

	Morphine	Fentanyl	p
Pre-induction ($T_{baseline}$)	9.6 ± 2.5	9.1 ± 2.7	NS
30 min post-induction (T_1)	8.9 ± 1.5	8.8 ± 2.1	
30 min post-bypass (T_2)	9.9 ± 1.9	8.8 ± 2.1	
1 hour post-bypass (T_3)	7.3 ± 2.7 ***	6.5 ± 1.4 ***	
2 hours post-bypass (T_4)	8.1 ± 1.9 *	7.7 ± 1.1 **	
On ICU admission (T_5)	8.6 ± 1.9	8.3 ± 1.2	
3 hours after ICU admission (T_6)	8.8 ± 2.8	7.9 ± 2.2 *	
6 hours after ICU admission (T_7)	8.3 ± 0.7	8.4 ± 0.9	

In fentanyl group, there was significant decrease from baseline reading at 1hr, 2hrs post-bypass and 3hrs after ICU admission (P<0.001, P<0.01 and P<0.04 respectively), while there were insignificant differences at the other times of the study (Table 5 and Figure 3).

CVP values in both the groups are almost similar at all the study times as shown in Table 5 and Figure 3.

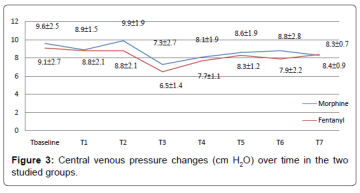


Figure 3: Central venous pressure changes (cm H_2O) over time in the two studied groups.

Pain score:

Table 6: showing VAS scores as mean±standard deviation.

Post extubation VAS score	Morphine	Fentanyl	p >0.05
Immediate	3.3±2.6	3.7 ± 2.7	
2hrs	2.8±1.4	3.2±2.4	
4hrs	2.6±1.5	3.2±1.9	
8hrs	3.5±1.9	4±2.1	
12hrs	4.2±2.6	5±3.1	
24hrs	6±2.8	7.8 ± 1.1	

The mean (95% CI) value for initial pain after extubation on the VAS was 3.3 ± 2.6 for the morphine group and 3.7 ± 2.7 in the fentanyl group was obtained (p > 0.05). The values of VAS after extubation measured at 2hrs and 4hrs are low in both the groups compared to immediate values after extubation, which can be accounted because of suctioning and coughing during extubation causing mild raise in pain. The infusions were continued till 8hrs post operatively and stopped. Over pain score is low for morphine group as compared to fentanyl group and is statistically significant.

Duration of {HYPERLINK "https://www.omicsonline. org/anesthesia- clinical-research.php" }**mechanical ventilation and sedation:** The time taken to extubate the patients in morphine group is around 2hr to 2hr30min whereas patients on fentanyl infusion were extubated within 1-2hrs. Sedation after stopping the infusions at 8hrs post operatively lasted for more than 5hrs in morphine group but only for 2hrs in fentanyl group.

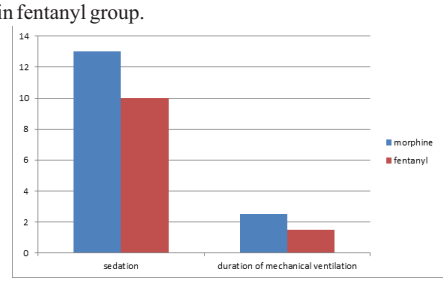


Fig 4: comparing the duration of sedation and mechanical ventilation between two groups

Length of ICU stay : no much difference is observed in the duration of ICU stay in two groups. Morhine group were discharged from ICU after2 days on an average but patients in fentanyl group had relatively longer stay for about 4dys.

Side effects:

The incidence of itching, nausea, and vomiting was low in the two groups; however, drawing statistical conclusions from these data were not possible because of the rarity of the occurrence. There was one case of respiratory depression in the morphine group. The respiratory rate dropped to 6 breaths/min, and it was treated with naloxone and discontinuation of the PCA. Meanwhile, two patients in the fentanyl group dropped their respiratory rate to between 8 and 9/min and were treated with naloxone and the reduction of PCA fentanyl boluses.

Intraoperative Arrhythmias: As regarding the incidence of intraoperative arrhythmias there were insignificant statistical differences when comparing between both groups. Three patients (20%) in morphine group and four patients (33%) in fentanyl group developed { HYPERLINK "https://www.omicsonline.org/hong-kong/arrythmia-peer-reviewed-pdf-ppt-articles/" } ventricular arrhythmias. Electrical defibrillation was used to control the arrhythmias. The number of defibrillations ranged from (1-2) per patient of (20-30) joules.

DISCUSSION:

Cardiac surgery can be associated with a significant amount of postoperative pain and its management should be an anesthetic consideration for all patients. The surgical approach has an obvious impact on the severity of postoperative pain. For example, minimally invasive cardiac procedures such as port access coronary artery bypass (PACAB) and minimally invasive coronary artery bypass (MIDCAB) carry less overall tissue injury and result in less postoperative pain. Postoperative pain for midline sternotomy has often been described to be moderate by patients than the anticipated pain. On the other hand, thoracotomy has been associated with a greater degree of both pain and functional limitation, due to the pain associated with breathing and coughing. Endoscopic vein graft harvesting has decreased the severity of postoperative leg pain, as well as the infection and wound dehiscence rate. Addressing the pain not only result in patients comfort but it also relieves the stimulation of cascade of neurohormonal system causing stress response.

In our study there was no significant difference between the studied groups as regard patient characteristics and operative data. Furthermore, we found a statistical significant decrease in HR and MAP in morphine group compared to fentanyl group. However, there were no statistical significant differences between both groups in CVP and the incidence of intra operative arrhythmias. Stoelting and Gibbsb [5], studied the effect of morphine in patients who either had aortic valve or coronary vein graft operations. They agree with our result which found that a dose of 1mg/kg of morphine used alone or with nitrous oxide significantly lowered the arterial pressure. However Camu et al.[6] found that morphine caused a significant reduction in MAP in patients after major vascular surgery. Alavi et al.[7] compared IV sufentanil and morphine for post-cardiac surgery pain relief using patient-controlled analgesia (PCA) device. They found that, systolic blood pressure was reduced more in morphine group than sufentanil group. Noorizan Abd Aziz et al., found that, both groups showed a transient increase in

MAP[8] during the first hour postoperatively, especially in the dexmedetomidine group, followed by decrease in MAP 8. Frank et al., also suggested that the use of morphine intra-operatively may reduce the incidence of postoperative fever by attenuating the inflammatory response to surgery and CPB [9].

In our study there were no significant differences between the two groups regarding the duration of tracheal intubation, length of ICU stay and length of postoperative ward stay. In addition Murphy et al., studied 90 patients were randomized to receive either morphine (40 mg) or fentanyl (600 mcg) as part of a standardized opioid-isoflurane anaesthetic technique underwent cardiac surgery with CPB. They established that the use of morphine provided early recovery and reduced the postoperative febrile reactions compared with fentanyl in elective cardiac surgery patients, which was comparable to our results [10].

In a study done by **Sherif Sayed** {HYPERLINK "file:///C:\\Users\\New\\Desktop\\ sushma\\Effect%20of %20 Morphine%20 and %20 Fentany l%20on% 20Inflammatory%20 Biomarkers% 20in%20 Rheumatic %20Heart%20 Patients%20Undergoing% 20 Valve%20 Replacement%20 Surgery% 20%20%20OMICS%20International.html" \l "a1" }showed that the use of morphine when compared to fentanyl as a part of a balanced anesthetic technique in valve replacement surgery after CPB, attenuates the release of inflammatory mediators and produce a greater reduction in adhesion molecule expression.[11], and reduce the incidence of postoperative hyperthermia without affecting the duration of tracheal intubation, the length of ICU stay and the length of postoperative ward stay. According to McCarthy D et al , who studied pain scores and investigate analgesic administration in postoperative cardiac surgery patients in the coronary intensive care unit (CICU) found that most commonly recorded pain score was 1in patients receiving an average of 1.75mg/hr of morphine infusion in the first 24 hours after admission to the ICU.

Our study results were comparable to those of Howell *et al.*[12] {HYPERLINK "http://www.saudija.org/article.asp?issn=1658 354X;year=2018;volume=12;issue=2;spage=250;epage=255;aulast= Nada" \l "ref15" }who compared PCA morphine to fentanyl in postoperative pain control of cesarean section with doses comparable to those used in this study and found no differences in the quality of analgesia produced or in the incidence or severity of major side effects. Similarly, to maintain adequate analgesia with PCA fentanyl, more than 70% of patients required several readjustments to the PCA settings or supplemental boluses. PCA morphine provided more reliable analgesia and required little alteration or attention once established. Howell *et al*. {HYPERLINK "http://www.saudija.org /article.asp? issn=1658-354X; year=2018; volume=12; issue=2; spage=250; epage=255; aulast=Nada" \l "ref15"}concluded that frequent readjustments can increase the incidence of the human error and can lead to inappropriate doses.

Our study shows that the analgesia with morphine is better than with fentanyl in terms of VAS and patient comfort with no much difference in side effects. Morphine even improved the patient outcome in terms of early extubation and decrease length of ICU stay. Though the sedation effect of morphine is prolonged than fentanyl there were no difference in side effects between the two drugs. Morphine even increased the pain free period for the patients and the patients had a smooth extubation and comfortable post extuabation period unlike fentanyl. Rescue analgesia was not used during the opioid infusion period in either of the groups. Patients receiving fentanyl required inj.paracetamol only after 12hrs but none in morphine group. The incidence of itching, nausea, and vomiting was low in the two groups; however, drawing statistical conclusions from these data were not possible because of the rarity of the occurrence.

CONCLUSION:

We conclude that there were a small number of significant differences between morphine and fentanyl statistically with respect to hemodynamic parameters. But the analgesia with Morphine provided better pain relief with comparable side effects as with Fentanyl analgesia with early extubation and shortened ICU stay in patients undergoing cardiac surgery on cardiopulmonary bypass.

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