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Analgesic Efficacy of Dexmedetomidine Versus Fentanyl as an Adjunct to Thoracic Epidural in Patients Undergoing upper Abdominal Surgery: A Prospective Randomized Controlled Trial

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Abstract: ***Background: This prospective, randomised, double-blind study was designed to assess the analgesic efficacy of dexmedetomidine as compared with fentanyl as an adjunct to local anaesthetic in thoracic epidural for upper abdominal surgeries. Methods: 40 adult patients of American Society of Anaesthesiologists grade I–II undergoing upper abdominal surgery were randomly allocated into two groups to receive 50 µg fentanyl or 50 µg dexmedetomidine as an adjunct to 10 ml 0.125% bupivacaine via thoracic epidural. Anaesthesia was induced with morphine, propofol and vecuronium and maintained by isoflurane with 60% nitrous oxide in oxygen. In the postoperative period patient-controlled analgesic pumps were used to deliver similar types of mixtures via the epidural catheter. Patients were evaluated for rescue analgesic requirements, haemodynamic stability, postoperative pain, sedation and any adverse events. Results: The groups were comparable regarding intraoperative analgesic requirements, recovery times and postoperative pain scores. The total consumption of rescue analgesia was significantly less in the dexmedetomidine group as compared with the fentanyl group (p = 0.046). Two patients in the fentanyl group had vomiting and one had pruritus. None of the patients had bradycardia, hypotension, excessive sedation or respiratory depression. Patients receiving epidural dexmedetomidine were more satisfied with the technique than those receiving fentanyl (p < 0.001). Conclusion: It was concluded that the addition of dexmedetomidine with 0.125% bupivacaine in thoracic epidural provides effective perioperative analgesia with greater patient satisfaction compared with fentanyl.***

Keywords: adjuvants, dexmedetomidine, fentanyl, postoperative pain, thoracic epidural

1. Introduction

Upper abdominal surgeries are usually associated with large surgical incisions and extensive gut handling and manipulation, which increasesthe need for intraoperative and postoperative analgesia.

Uncontrolled postoperative pain and pathophysiological response to surgery make these patients prone to high stress, sympathetic activation and slow convalescence, and may cause significant complications of many organ systems.[1]

Thoracic epidural analgesia (TEA) provides good postoperative pain relief and facilitates deep-breathing exercises and early ambulation. TEA also decreases the sympathetic outflow, preventing ileus and the incidence of postoperative myocardial infarction by providing favourable redistribution of coronary blood flow, attenuating the stress response and hypercoagulability.[2,3] Although adjuvants like fentanyl have a dose-sparing effect and provide superior analgesia after major upper abdominal surgeries,[4] there is always the possibility of an increased incidence of pruritus, urinary retention, postoperative nausea and vomiting and respiratory depression with the use of opioids.[5,6]

Recently α2-agonists have shown promise as an adjuvant to local anaesthetics in epidural anaesthesia.[7–10] Dexmedetomidine, a highly selective α2-adrenoreceptor agonist, has effective analgesic and sedative properties[11,12] and lacks opioid-related side effects.[13,14] The effects of a dexmedetomidine–bupivacaine mixture in thoracic epidural are mainly studied in patients undergoing thoracic surgery with one-lung ventilation in respect of the intraoperative awareness and analgesic benefits.[15] A study comparing the analgesic efficacy of dexmedetomidine with fentanyl as an adjunct to ropivacaine in lumbar epidural in patients undergoing lower limb orthopaedic procedures under regional anaesthesia demonstrated that dexmedetomidine may be a better alternative to fentanyl as it provided early onset of sensory anaesthesia and prolonged postoperative analgesia.[16] In this study we compared the postoperative analgesic efficacy of bupivacaine with dexmedetomidine against bupivacaine with fentanyl administered using patient-controlled epidural anaesthesia (PCEA) in patients undergoing upper abdominal surgery. The primary outcome of this study was postoperative analgesic requirements and pain scores while the secondary outcomes were intraoperative analgesic consumption, haemodynamic stability and adverse effects.

2. Methods

After receiving approval from our institutional ethics committee and obtaining written informed consent from the patients, this prospective, randomized, double-blind controlled trial was conducted in 40 adults ASA grade I–II, undergoing elective upper abdominal surgery (hepaticojejunostomy/hemicolectomy). This study was undertaken in General Surgery department from April 2019 to September 2019 at Government General Hospital, Kakinada, Andhra Pradesh.

Patients on beta-blockers or antipsychotic drugs, with cardiac conduction defects, renal or hepatic dysfunction, morbid obesity, high risk for postoperative nausea and vomiting (history of smoking, motion sickness or excessive postoperative vomiting) or any contraindication to epidural catheter insertion (local infection, spine deformities etc.) were excluded.

Patients were randomly allocated into two groups by computergenerated random numbers. Group D patients received 50 µg dexmedetomidine with 10 ml of 0.125% bupivacaine via thoracic epidural catheter after induction of anaesthesia. Postoperatively, the patients used PCEA, each 1 ml containing 1 µg of dexmedetomidine in 0.125% bupivacaine. Group F patients received 50 µg fentanyl in addition to 10 ml 0.125% bupivacaine via thoracic epidural catheter during the intraoperative period, and the PCEA with each 1 ml containing 1 µg of fentanyl in 0.125% bupivacaine, postoperatively. The patients as well as the anaesthesiologist involved in the perioperative management and data collection were blinded to the group assignment.

The patients underwent preoperative anaesthesia assessment on the previous evening and were premedicated with alprazolam 0.5 mg and ranitidine 150 mg orally the evening before and at 6:00 am on the morning of surgery. Inside the operating theatre routine monitors were attached and baseline readings of heart rate, non-invasive blood pressure (NIBP) and oxygen saturation (SpO2) were taken. A thoracic epidural catheter was inserted at the T8–T9 or T9–T10 intervertebral space, with the patient in the sitting position with standard aseptic precautions using an 18-G Tuohy needle via a midline approach with a loss of resistance method. A test dose of 3 ml of 2% lignocaine with 1:200 000 adrenaline was given.

Anaesthesia was induced with morphine 0.1 mg/kg followed by propofol 2–3 mg/kg until loss of verbal response. Muscle relaxation was achieved with vecuronium bromide 0.1 mg/kg and the patient's trachea was intubated when train of four (TOF) count reached 0. Anaesthesia was maintained by isoflurane with 60% nitrous oxide in oxygen titrated to maintain a Bispectral index (BIS) value of 40–60. Muscle relaxation was maintained with top-ups of vecuronium bromide guided by neuromuscular monitoring. The lungs were ventilated with positive pressure ventilation to maintain end-tidal carbon dioxide (EtCO2) between 32 and 36 mmHg. The epidural drug was administered according to the group allocation immediately after intubation over a period of 10 minutes. Patients' heart rate, electrocardiography (ECG), SpO2, BIS, nasopharyngeal temperature and EtCO2 were monitored continuously and blood pressure was taken at five-minute intervals. The data were recorded every 5 minutes for the first 30 minutes and then every 15 minutes till completion of surgery.

All patients received a continuous infusion of normal saline at the rate of 5–8 ml/kg/hour during the intraoperative period. If the BIS value was within the targeted range and mean arterial pressure (MAP) exceeded baseline by more than 20% for two consecutive readings, a 0.5 µg/kg bolus of intravenous fentanyl was given. Hypotension (MAP 20% below baseline) was treated with normal saline, and if required I.V. ephedrine 5 mg boluses. For bradycardia (heart rate of < 40 bpm) atropine 0.5 mg was administered intravenously. Antiemetic prophylaxis was given with ondansetron 0.15 mg/kg at the time of closure of the surgical wound. At the end of surgery residual neuromuscular blockade was reversed with neostigmine sulphate 50 µg/kg and glycopyrrolate 10 µg/kg and the endotracheal tube was removed when the TOF ratio was > 90% and BIS > 80, with the patient breathing adequately.

After surgery the patients were transferred to the Post Anaesthesia Care Unit (PACU) and were monitored for 24 hours by an anaesthesia a resident blinded to the patients' group allocation. Postoperative analgesia was managed with intramuscular diclofenac 75 mg eight-hourly. For rescue analgesia, a PCEA pump containing the drug as per the allotted group was connected to the patients' epidural catheter and set to deliver a bolus of 3 ml with a lock-out interval of 10 minutes. Patients' heart rate, blood pressure, oxygen saturation and respiratory rate were recorded at regular intervals and the pain score and sedation level were assessed at 30-minute interval for the first 3 hours and then at 4, 6, 8, 12 and 24 hours. The assessment of pain was done using modified visual analogue scale (VAS, 0–10, wherein 0 stands for 'no pain' and 10 stands for 'worst imaginable pain'). Level of sedation was assessed using a modified observer's assessment of alertness/sedation (OAA/S) scale with a score of 1 = asleep/unrousable to 6 = awake/alert.[17] The time 0 started at the point when the patient's epidural catheter was connected to the PCEA pump. The total amount of rescue drug required during 24 hours was noted.

All complications such as bradycardia, hypotension, hypoxia (SpO2<92) and respiratory depression (respiratory rate < 8) were noted and promptly corrected. Other postoperative adverse events like nausea, vomiting, pruritus and urinary retention were also recorded and treated accordingly. Postoperative nausea and vomiting (PONV) was rated on a three-point scale (0 = no PONV, 1 = mild nausea, 2 = severe nausea or vomiting ≤ 2 occasions, 3 = vomiting on 3 or more occasions) and treated by injecting with ondansetron 0.15 mg/kg if the scale was ≥ 2. Pruritus was treated with iv diphenhydramine 0.2 mg/kg. Patients' satisfaction with the technique was assessed at 24 hours postoperatively on a 0–10 point scale (0 = unsatisfied, 10 = fully satisfied).

3. Statistical Analysis

Statistical analysis was performed using SPSS® software (version 22.0, SPSS Inc, Chicago, IL, USA). Normally distributed variables were presented as mean and standard deviation (SD) and compared using independent Student's t-test. Fisher's exact test or chi-square test was used for comparisons of categorical variables. Non-parametric data were expressed as median and interquartile range and compared by chi-square test or Mann– Whitney U test. The VAS scores and the haemodynamic changes were analysed by repeated measures of analysis of variance with subsequent comparisons made using Student's t-test with Bonferroni's post hoc test. A p-value less than 0.05 was considered as significant.

Sample size was calculated to detect a 30% reduction in total PCEA consumption in the dexmedetomidine group. On the basis of previous study, by taking a mean of 15 ml PCEA consumption with standard deviation (SD) of 6 ml we required a minimum of 18 patients in each group to have 80% power with α-value of 0.05.Hence we have included 20 patients in each group.

4. Results

The groups were comparable in respect of demographic data and ASA physical status (Table 1). There was no statistically significant difference among groups with regard to the duration of surgery, intraoperative fentanyl requirement, total intravenous fluid administration, blood loss and recovery times (Table 2). The total consumption of rescue analgesia via PCEA pump was significantly less in the dexmedetomidine group as compared with the fentanyl group ($p = 0.046$) (Figure 1). The postoperative pain scores were comparable among groups throughout the postoperative period (Figure 2).

The heart rate was statistically lower in the dexmedetomidine group as compared with the fentanyl group at any point in time (Figure 3). The mean arterial pressures were comparable among groups during the intraoperative and the postoperative period (Figure 4). None of the patients had bradycardia and only one patient in each group had hypotension. Sedation scores were comparable in both groups in the postoperative period except at 30 minutes postoperatively where the sedation scores were lower in the dexmedetomidine group as compared with the fentanyl group ($p < 0.001$) (Figure 5). The patients were easily rousable and none of them had respiratory depression or hypoxia.

One patient in the fentanyl group had pruritus and two patients had postoperative vomiting (grade 2) whereas two patients in the dexmedetomidine group had mild nausea. No other adverse effects were reported in either of the two groups. Patients receiving dexmedetomidine were more satisfied with their postoperative pain management as compared with the patients having epidural fentanyl ($p < 0.001$).

Table 1: Demographic data

Variables	Group F (n=20)	Group D (n=20)	P value
Age (years)	39.23 ± 14.46	38.57 ± 12.16	0.8767
Weight (kgs)	54.56 ± 7.65	55.30 ± 8.06	0.7675
Height (cms)	157.57 ± 7.31	156.20 ± 5.72	0.5132
Gender (M/F) *	9/11	7/13	0.5157
ASA status (I/II) *	15/5	14/6	0.7263

Notes: Values are expressed as mean ± SD; *presented as number of patients.

Table 2: Intraoperative data

Variables	Group F (n=20)	Group D (n=20)	P value
Duration of surgery (min)	179.52 ± 9.26	177.86 ± 8.32	0.5545
Total IV fluids (ml)	2940 ± 529.72	3105 ± 421.87	0.2827
Blood loss (ml)	349.57 ± 72.82	319.7 ± 65.36	0.1802
Recovery time (min)	18.60 ± 4.1	19.70 ± 5.82	0.4938
Fentanyl top-up required *	2	1	0.3271

Notes: Values are expressed as mean ± SD, *presented as number of patients.

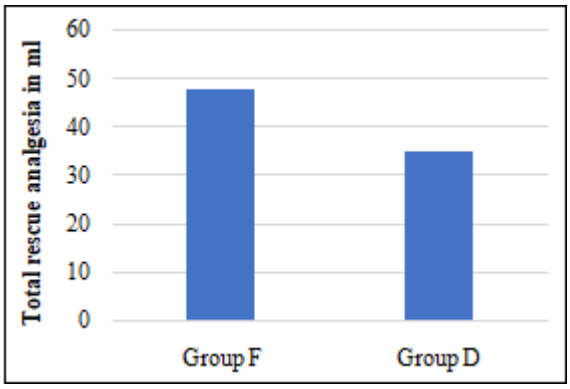

Figure 1: Total rescue analgesia requirement in 24 hours via PCEA pumps

There is a significant difference between the two groups (p=0.046)

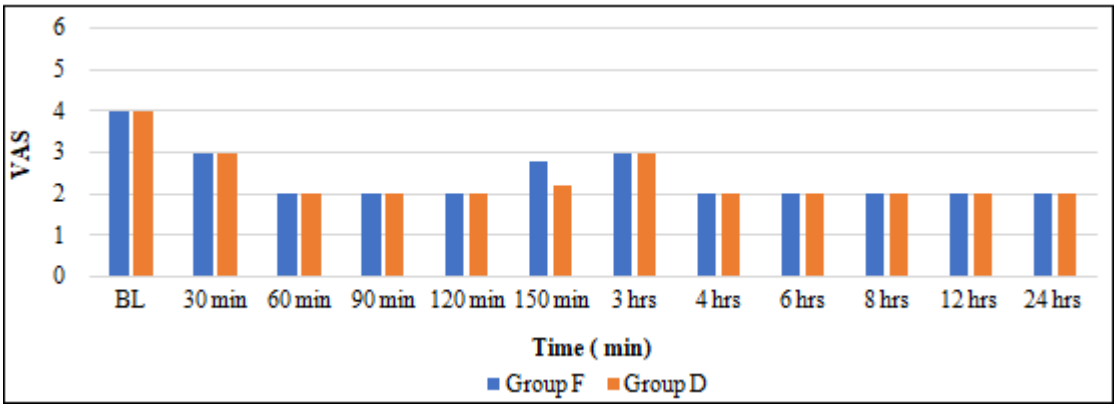

Figure 2: Postoperative pain scores (modified VAS) at various time intervals.

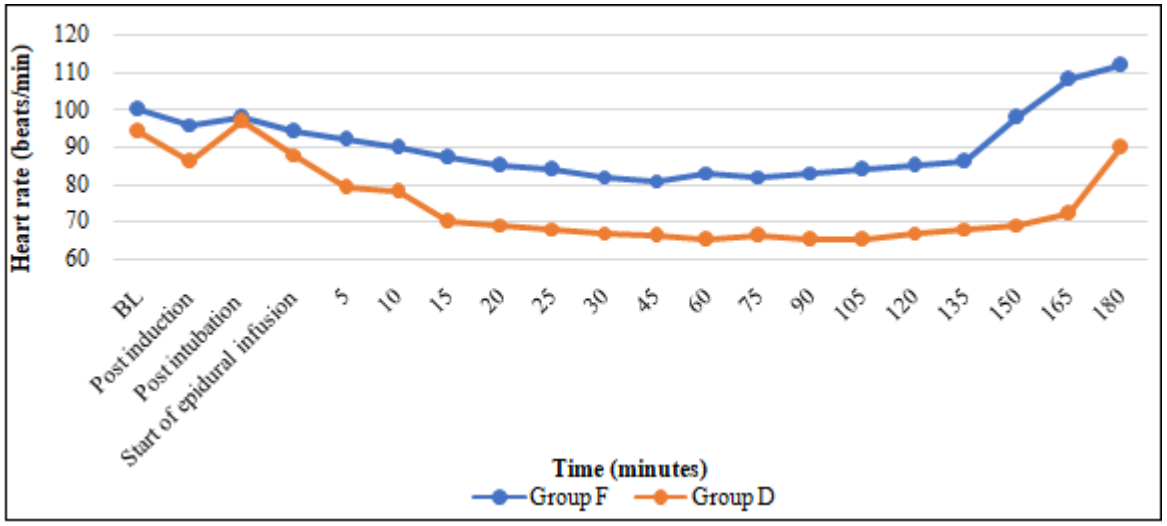

Figure 3: Intraoperative heart rate at various time intervals

There is significant difference between the two groups ($p < 0.05$)

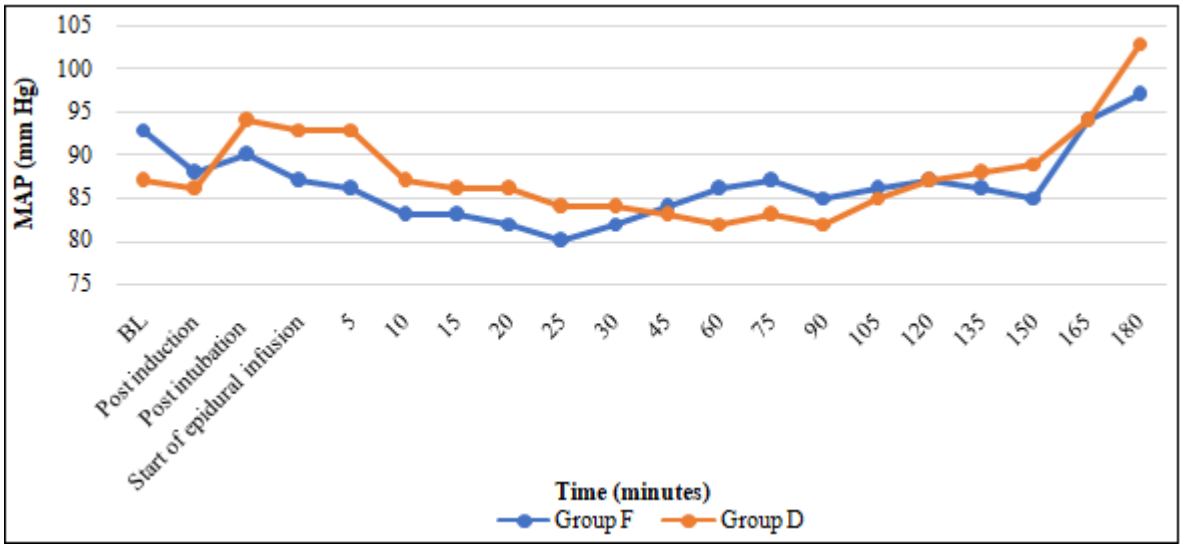

Figure 4: Intraoperative mean arterial pressure (MAP) at various time intervals

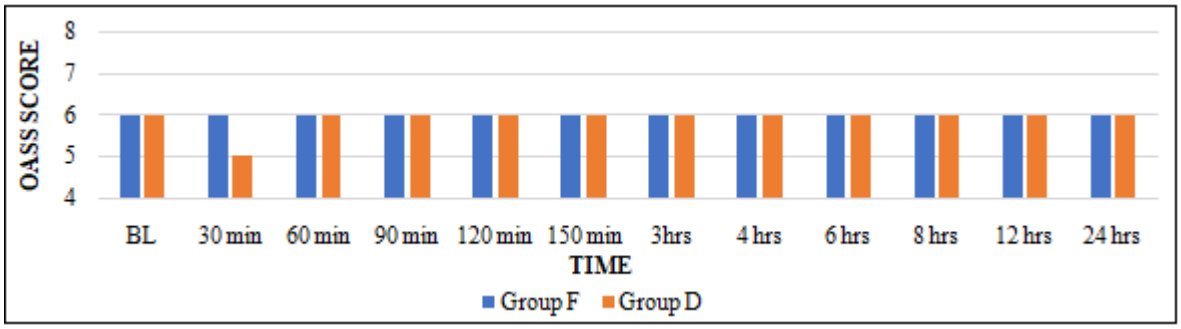

Figure 5: Sedation scores at various time intervals

5. Discussion

In the present study, we found that addition of dexmedetomidine to epidural bupivacaine provided effective intraoperative as well as postoperative analgesia comparable to fentanyl with greater patient satisfaction. There was no significant difference in intraoperative fentanyl requirement between the groups. The postoperative pain scores were comparable among groups at all time intervals during the 24-hour postoperative period with lesser requirement for rescue analgesia in the dexmedetomidine group. Our results are similar to the previous study by Selim et al.,[18] which also reported comparable VAS scores in patients receiving dexmedetomidine and fentanyl (1 µg/kg each) for labour analgesia with greater patient satisfaction in the dexmedetomidine group.[18]Previous studies have shown that intraoperative dexmedetomidine promotes postoperative analgesia and reduces the requirement for rescue analgesia. Elhakim et al.[15] evaluated the effects of dexmedetomidine administration in thoracic epidural in patients undergoing

thoracic surgery and reported significantly decreased consumption of intraoperative fentanyl and improved postoperative analgesia in patients receiving dexmedetomidine as compared with bupivacaine only. Bajwa et al.[16] have also shown that dexmedetomidine provided superior postoperative analgesia compared with fentanyl in patients undergoing orthopaedic procedures under regional anaesthesia. The study found less postoperative ropivacaine consumption over 24 hours in the dexmedetomidine group with comparable VAS scores. However, none of the studies have used PCEA dexmedetomidine as rescue analgesia.

The analgesic effect of dexmedetomidine is mediated by its action at the brain, brainstem, spinal cord and peripheral tissues.[19]Dexmedetomidine causes hyperpolarisation of nerve tissues by altering transmembrane action potential and ion conductance at the brainstem locus ceruleus. In the spinal cord, the analgesic effect is related to the activation of the descending medullospinal noradrenergic pathway or to the reduction of spinal sympathetic outflow at presynaptic ganglionic sites. Epidural opioids have their major site of action on pre- and postsynaptic receptors in the substantia gelatinosa of the dorsal horn, producing selective block of nociceptive pathways.

In the present study we noticed a significant decrease in the heart rate in both groups as compared with their baseline value, whereas heart rate in the dexmedetomidine group was significantly lower than the fentanyl group during the intraoperative as well as in the postoperative period. However, there was no significant fall in blood pressure in either group. Bajwa et al.[16] also observed a more prominent reduction in heart rate in patients receiving epidural dexmedetomidine as compared with fentanyl. They also reported significant decreases in MAP compared with baseline in both groups of patients that may have been caused by their use of 0.75% ropivacaine. Dexmedetomidine leads to reductions in heart rate by increasing vagal tone and reducing sympathetic drive. Opioids like fentanyl maintain cardiovascular homeostasis mainly via action on the nucleus solitarius, dorsal nucleus of the vagus, nucleus ambiguus and parabrachial nucleus. However, the predominant effect of opioids on the heart rate is to produce bradycardia via central vagal nucleus stimulation.

We could not find a statistically significant difference in sedation scores between the groups except at 30 minutes post-surgery. Administration of dexmedetomidine causes the absence of inhibitory control over the ventrolateral preoptic nucleus, resulting in a state of 'rousable sedation'. Fentanyl, being an opioid, is also expected to have sedative effects. Intraoperative use of opioids is a well-known risk factor for postoperative nausea and vomiting. In our study only two patients in the fentanyl group had vomiting that can be attributed to the use of a prophylactic antiemetic and exclusion of high-risk patients for PONV.

The limitation of the present study is that we assessed the analgesic requirements for the first 24 hours after surgery. Also we did not assess the late postoperative complications, length of hospital stay and mortality. Further large multicentre studies are required to assess the long-term efficacy and safety of dexmedetomidine in different patient populations.

We conclude that the addition of dexmedetomidine to bupivacaine in thoracic epidural provided effective perioperative analgesia comparable to fentanyl without any significant adverse effect in patients undergoing upper abdominal surgery. Dexmedetomidine significantly reduces the requirement for rescue analgesia during the postoperative period and leads to more patient satisfaction than fentanyl.

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