SCIENTIFIC ARTICLES

COMPARATIVE HEMODYNAMIC ADVANTAGES OF SUBARACHNOID ADMINISTRATION OF ATYPICAL AND NON-ATYPICAL OPIOIDS

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Abstract

Backgound: Subarachnoid administration of opioids such as pethidine and fentanyl had been proven safe but that of tramadol has been controversial. Tramadol is cheap and readily available, hence the need to further evaluate its intrathecal safety.

Purpose: The study aimed at determining the hemodynamic and side effect profile of intrathecal tramadol.

Methods: One hundred and eighty six (186) ASA I or II patients scheduled for emergency open appendicectomy under spinal anesthesia were included in the study. Group BF (n=62) received intrathecal fentanyl 25µg plus 3ml of 0.5% hyperbaric bupivacaine, Group BS (n=62) received 0.5ml normal saline plus 3ml of 0.5% hyperbaric bupivacaine and Group BT (n=62) received intrathecal tramadol 25mg plus 3ml of 0.5% hyperbaric bupivacaine. Hemodynamic profile and side effects were monitored intraoperatively and 12 hours postoperatively.

Results: Fifteen (24.2%), 13 (20.9%) and 15 (24.5%) patients respectively in Groups BF, BS and BT had hypotension (P = 0.886). The incidence of postoperative vomiting occurred in 2 patients (3.2%) in Group BF as compared to 3 patients (4.8%) in Group BS and 10 patients (16.1%) in Group BT (P=0.016).

No surgeon in Group BF reported dissatisfaction but 18 patients (29%) in Group BS and 1 patient (1.6%) in Group BT had their surgeons reporting dissatisfaction (P = 0.0001)

Conclusion: This study shows that intrathecal tramadol 25mg has higher incidence of post operative nausea and vomitting than 25µg of intrathecal fentanyl but both drugs were safe.

Conflict of interest: None.

Keywords: Subarachnoid block, appendicectomy, fentanyl, hemodynamics

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Introduction

The early experience with addition of large doses of opioids to local anesthetic agents for subarachnoid block produced not only prolonged duration of analgesia and anesthesia, but also side effects such as delayed emergence, respiratory depression, nausea and pruritus, which dampened the early enthusiasm of using spinal opioids[1,2]. Sudarshan et al demonstrated that intrathecal fentanyl with 0.5% heavy bupivacaine provided excellent surgical anesthesia with few side effects[3]. Lack of side effects is related to the dose of fentanyl used. Gielen et al also reported that intrathecal fentanyl is one of the safest opioids that were not associated with any troublesome side effect[4]. In developing countries like Nigeria, opioids like fentanyl, morphine and pethidine are not only scarce but controlled and expensive. Moreover, the problem of getting fentanyl or pethidine by most hospitals in Nigeria contributes to its under-utilization. Recently, the search for less expensive, readily available but safe subarachnoid opioids drew attention to intrathecal tramadol. Researchers have demonstrated administration of preservative-free tramadol in both appendicectomies, obstetric and major gynecological surgeries[5,6,7] with resultant difference in side effect profile.

The aim of the current study is to compare the hemodynmic profile and side effects of subarachnoid tramadol compared to subarachnoid fentanyl in patients undergoing emergency open appendectomy under spinal anesthesia.

Methods

Ethical clearance and approval were obtained from the University of Benin Teaching Hospital Ethical Committee (Institution Approved Protocol Number: ADM/E.22 A/VOL. VII/416). Informed consent of every participating patient was obtained before the study was commenced.This was a prospective, randomized, placebo-controlled clinical study, comparing safety of subarachnoid tramadol with subarachnoid fentanyl and a normal saline placebo-controlled bupivacaine subarachnoid block.

One hundred and ninety five ASA I or II patients

scheduled for emergency appendicectomy, aged between 18 and 60 years were included in the study.

Exclusion criteria included patients who had appendicular mass, rupture appendix or any co-existing surgical procedure. Patients for elective appendicectomy were not included because their overnight fast might affect incidence of nausea and vomiting. Patients with history of hypersensitivity to local anesthetic agent and opioids were also excluded. Patients with peripheral neuropathy or having contraindications to regional anesthesia or patients who could not attain a minimum height block of T_6 at 4th minute following injection of spinal solution were also excluded.

Preoperative assessment of the patients was carried out. Routine investigations such as hemoglobin concentration, urinalysis, serum electrolytes and urea were done for every patient. Visual Analogue Scale [VAS] score for pain assessment, consisting of 100mm line with 0=no pain and 100 = worst pain ever, was adequately explained to every patient during the preoperative visit.

In the operating room, baseline pulse rate, non-invasive blood pressure, oxygen saturation and respiratory rate were obtained and recorded before administration of spinal anesthesia and subsequently during the procedure. A venous access was secured using 16 or 18 gauge cannula and the patient was preloaded with normal saline (15ml/kg) before the injection of spinal anesthesia. In ensuring correct blinding, one anaesthetist was responsible for patients' randomization while a second anaesthetist was responsible for peri-operative data collections. Neither the patient nor the second anaesthetist was aware of group allocation. Aseptically, induction of spinal anesthesia was carried out in a sitting position, using 25G Quincke spinal needle at L_{3-4} or L_{2-3} interspace. Having observed a free flow of cerebrospinal fluid, patients in Group BF (n=65), Group BS (n=65) or Group BT (n=65) received the following spinal solution combinations. Group BF received 0.5ml (25μg) fentanyl plus 3ml (15mg) of 0.5% heavy bupivacaine. Group BS received 0.5ml of normal saline plus 3ml (15mg) of 0.5% heavy bupivacaine. Group BT received 0.5ml (25mg) tramadol plus 3ml (15mg) of 0.5% heavy bupivacaine.

Maximum sensory block height was assessed at one minute, two minutes, 3 minutes and 4 minutes following injection of spinal solution, using loss of sensation to cold and gentle pin prick test. A minimum sensory block height of T6 at 4th minute was the minimum desired level for commencement of surgery. Any patient who did not meet this minimum sensory block height was excluded from the study. The level of sensory analgesia defined as loss of sensation to pin prick test was recorded. Pulse rate, blood pressure, respiratory rate and oxygen saturation were also recorded every 3 minutes for the first eighteen minutes and then at interval of 5 minutes until the end of surgery. Time of skin incision was noted. Following skin incision, VAS scores were recorded every 3 minutes for the first eighteen minutes and then at interval of 5 minutes until the end of surgery. Intraoperative complications such as hypotension (reduction in systolic blood pressure greater than 30% of the baseline), bradycardia (reduction in pulse rate greater than 30%), itching, paraesthesia, vomiting and shivering were identified and treated accordingly. Pain and discomfort such as dragging sensation, chest tightness, nausea, vomiting and retching were documented and treated appropriately. The time surgery ended was noted and duration of surgery in minutes was calculated and recorded.

Postoperative complications were assessed and recorded within 12 hours following surgery. The effectiveness of analgesia produced by either intrathecal fentanyl, tramadol or normal saline placebo intraoperatively was judged by presence or absence of pain.

Degree of both patient's and doctor's satisfaction with the subarachnoid block for the procedure was sought and each of them responded to the different grades of satisfaction: Not satisfied, satisfied, very satisfied or excellent.

A minimum of 65 patients were adequate for the study based on effect size of 0.2 reduction in side effects at a power of 0.8 and alpha of 0.05. The data obtained were analysed using statistical programme for social sciences (SPSS) 16.0 software (Chicago Illinois, USA). All parametric data were analyzed using one way ANOVA. Non-parametric data were analyzed using chi square, Fisher's exact or Mann-Whitney test where applicable. Probability values <0.05 were considered statistically significant.

Result

Sixty two patients were analyzed in each of the groups having excluded nine patients for protocol violations.There was no statistically significant difference amongst the three groups with regard to age, height and weight (Table 1).

Fifty patients (80.3%) in group BS as compared with 11 patients (17.7%) in Group BF and 19 patients (30.6%) in Group BT attained T6 dermatomal level at the 4th minute. The difference was statistically significant (P-value = 0.0001).

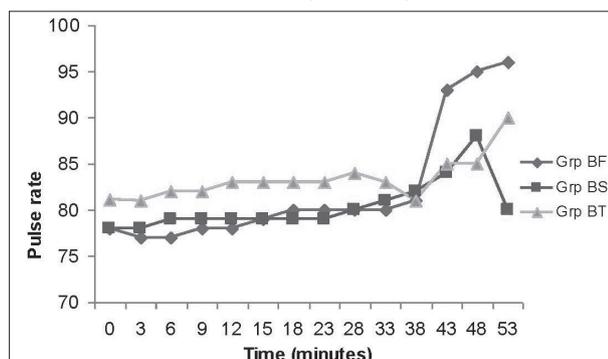*Table 1*
Patient's demographic and surgical data

Parameter	Group BF (n = 62)	Group BS (n = 62)	Group BT (n = 62)	P. value
Age (years)	28.58 ± 1.37	28.79 ± 1.34	28.55 ± 1.23	0.54
BMI (Kg/m²)	25.34±1.01	25.03±1.01	25.28±1.01	0.17
Gender [n(%)]				
Male	23 (37.1%)	25 (40.3%)	22 (35.5%)	
Female	39 (62.9%)	37 (59.7%)	40 (64.5%)	0.85
Onset Time: At 4th Min				
T2	15 (24.2%)	0 (0.0%)	8 (12.9%)	0.0001
T4	36 (58.1%)	12 (19.7%)	35 (56.5%)	0.0001
T6	11 (17.7%)	50 (80.3%)	19 (30.6%)	0.0001

Figure 1 shows the trend in pulse rate over time. The differences in mean pulse rates at 3min, 6min, 9min, 12min and 15min did not achieve any statistical significance at each of these time interval (P-values = 0.71, 0.65, 0.32, 0.15 and 0.97 respectively). However the difference in the mean pulse rate among the three groups at 43min, 48min, and 53min was statistically significantt (P-values = 0.01, 0.02 and 0.012 respectively).

The trend in systolic blood pressure over time is shown in Figure 2. Intra-operative trend in systolic blood pressure showed a non-statistically significant fall in systolic blood pressure at 3min, 6min, 9min, 12min and 15min. Similarly, the mean value of systolic blood pressure at 18min, 23min, 28min and 33min did not achieve any statistical significant difference. However, the difference in the mean systolic blood pressure at 38min, 43min, 48min and 53min was statistically significant. Trends in diastolic blood pressure and mean arterial blood pressure over time are illustrated in Figures 3 and 4 and they were similar to the trend observed with systolic blood pressure.
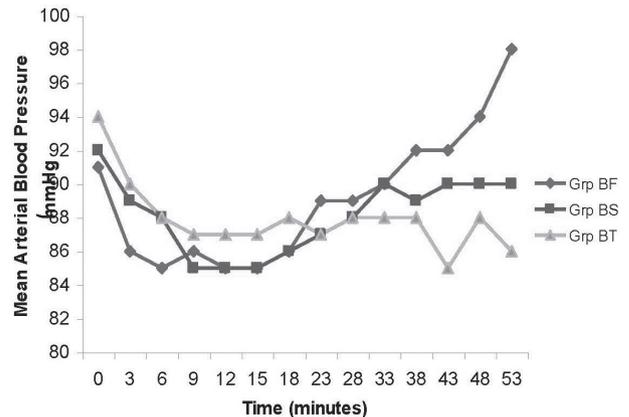
Table 2 shows the incidence of perioperative complications. None of the patients in Group BF and BT had any complaint of pain, chest tightness, vomiting, retching or nausea. Five patients (8.1%), 7 patients (11.1%), and 3 patients (4.8%) in Group BS reported pain, chest tightness and vomiting respectively. The difference in the incidence of pain or chest tightness was statistically significant (P-value=0.011 and 0.001 respectively). Three patients (4.8%) had episodes of nausea and another three (4.8%) had retching in Group

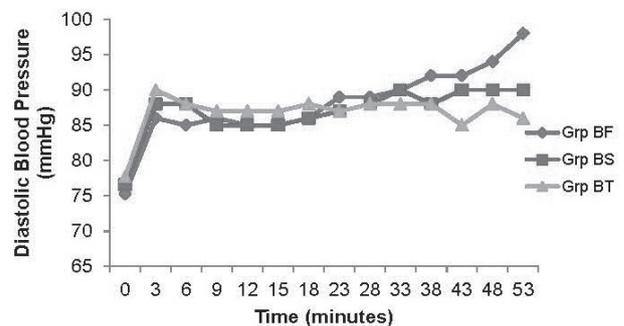*Fig. 2*
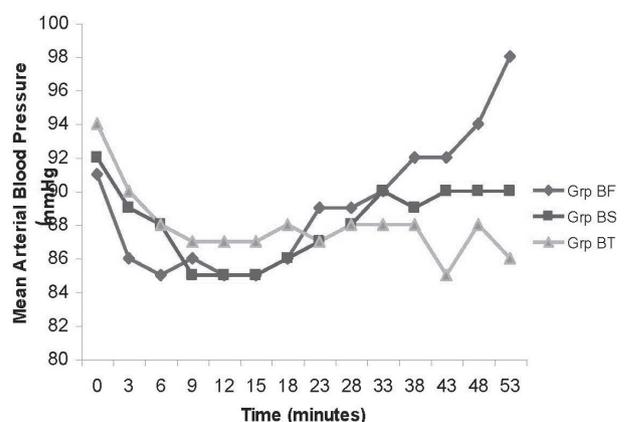*Trend in Systolic Blood Pressure (mmHg) over Time*

0 = Baseline

Fig. 3
Trend in Diastolic Blood Pressure (mmHg) over Time

0 = Baseline

Fig. 4
Trend in Mean Arterial Blood Pressure over Time

0 = Baseline

Fig. 1
Trend in Pulse Rate (beats/min) over Time

0 = Baseline

Table 2
Peri-operative complications n (%)

Complication	Group BF (n = 62)	Group BS (n = 62)	Group BT (n = 62)	P. value
Pain	0(0.0)	5(8.1)	0(0.0)	0.011
Chest tightness	0 (0.0)	7 (11.3)	0 (0.0)	0.001
Vomiting	0 (0.0)	3 (4.8)	0 (0.0)	0.108
Retching	0 (0.0)	3 (4.8)	0 (0.0)	0.108
Nausea	0 (0.0)	3 (4.8)	0 (0.0)	0.108
Bradycardia	0 (0.0)	1 (1.6)	0 (0.0)	1.000
Hypotension	15 (24.2)	13 (20.9)	15 (24.2)	0.886
Shivering	0 (0.0)	3 (4.8)	0 (0.0)	0.108
Itching	4 (6.5)	0 (0.0)	0(0.0)	0.035
Paraesthesia	1 (1.6)	0 (0.0)	0 (0.0)	1.000
PDPH	1 (1.6)	0 (0.0)	0 (0.0)	1.000
PONV	2(3.2)	3 (4.8)	16 (16.1)	0.016

BS. The difference in the incidence of vomiting, nausea or retching among the three groups was not statistically significant. No patients in Group BF and Group BT had bradycardia whereas one patient (1.6%) in Group BS had bradycardia. Fifteen (24.2%), 13 (20.9%) and 15 (24.5%) patients respectively in Groups BF, BS and BT had hypotension with no statistical significance. Apart from headache and vomiting, there were no other complications within 12 hours postoperatively among the study population. Vomiting was observed in 2 patients (3.2%) in Group BF as compared to 3 patients (4.8%) in Group BS and 10 patients (16.1%) in Group BT. The incidence of post-operative vomiting was statistically significant.

Table 3 shows the degree of patient's satisfaction for each group. Every patient was satisfied in Group BF and BT while 17 patients (27.4%) in Group BS were not satisfied with the quality of analgesia produced. This difference was statistically significant. Forty six patients (73.8%) and 45 (72.1%) in Groups BF and BT respectively were excellently satisfied with the analgesia as compared to 21 (33.9%) in Group BS.The difference was statistically significant.

Table 4 shows degree of surgeon's satisfaction for each group. No surgeon in Group BF reported dissatisfaction while 18 patients (29%) in Group BS and 1 patient (1.6%) in Group BT had their surgeons reporting dissatisfaction. The difference was statistically significant.

Table 3
Degree of patient's satisfaction for each group n(%)

Satisfaction	Group BF (n = 62)	Group BS (n = 62)	Group BT (n = 62)	P. value
Not satisfied	0 (0.0)	17 (27.4)	0 (0.0)	0.0001
Satisfied	5 (8.2)	8 (12.9)	7 (11.5)	0.676
Very satisfied	11 (18.0)	16 (25.8)	10 (16.4)	0.351
Excellent	46 (73.8)	21 (33.9)	45(72.1)	0.0001

Satisfaction	Group BF (n = 62)	Group BS (n = 62)	Group BT (n = 62)	P. value
Not satisfied	0 (0.0)	18 (29.0)	1 (1.6)	0.0001
Satisfied	4 (6.6)	11 (17.7)	5 (8.2)	0.090
Very satisfied	12 (19.7)	13 (21.0)	11 (17.7)	0.902
Excellent	46 (73.8)	20 (32.3)	45 (72.6)	0.0001

Discussion

Experimental studies have shown that addition of opioids to local anesthetic agent intrathecally was able to relieve pain and discomfort[8,9]. Subarachnoid tramadol had been studied by few researchers such as Parthasarathy et al[5], Susmita et al[7], Alhashemi et al[10] and Frikha et al[6], however its subarachnoid safety profile is still controversial. Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a dual mechanism of action[11]. It stimulates the μ- receptor and to a lesser extent δ- and κ- opioid receptors. Like tricyclic antidepressants, it also activates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin. This produces a non-opioid basis of analgesia[11,12]. A report suggesting that tramadol may have a direct serotonin- releasing action has been documented[13]. Analgesic doses of tramadol may produce less respiratory depression in part because of its non-opioid receptor mediated actions[12,14].

The dose regime used in this study was based on the study carried out by Belzarena[15] which demonstrated that intrathecal fentanyl 0.5-0.75 μg/kg provided excellent surgical anesthesia. Mean intrathecal fentanyl doses used by Techanivate et al[16] were 0.18 and 0.33 μg/Kg. In the present study, a fixed dose (25μg) of fentanyl was used. Based on the average weight of patients in the fentanyl Group, the average intrathecal dose of fentanyl used in this study was 0.36μg/Kg. This dose was more than the dose used by Techanivate et al[16] but less than the dose used by Belzarena[15]. Twenty five milligram of intrathecal tramadol was considered adequate for the study based on the work carried out by Alhashemi[10] where 25mg of intrathecal tramadol was proven to be safe during

spinal anesthesia. Although Frickha et al[6] used 50mg tramadol, Parthasarathy[5] used 10mg and Susmita[7] used 20mg of tramadol in their studies but 25μg of fentanyl is equipotent with 25mg of tramadol according to report by Duthie[17]. He also reported that tramadol has the same analgesic potency as pethidine, one fifth (1/5) that of nalbuphine, one-tenth (1/10) that of morphine and one-thousandth (1/1000) that of fentanyl.

Side-effects are mediated by opioid receptors[18,19]. Segmental analgesia after intrathecal opioids administration should confer a lower side-effect profile compared with systemic opioids administration[20,21,22]. A recent prospective survey of 6000 patients reported a low incidence of side effects and good patients' satisfaction after single adminstration of low dose intrathecal opioids[23]. The side effects of intrathecal opioids are sedation, sweating, delayed gastric emptying, urinary retention, pruritus, nausea and vomiting and respiratory depression[24,25], however previous studies have suggested that side-effects are dose-related[15]. High dose intrathecal opioids administered in error may result in an acute apneic episode requiring naloxone and supportive ventilation[26].

This study also compares the trends of hemodynamic changes following induction of spinal anesthesia using bupivacaine with or without opioids. The current findings support the previous findings that showed no significant difference in the episode of hypotension between fentanyl group and control group[1,16,27]. Alhashemi et al[10] and Frikha et al[6] found that intrathecal tramadol did not affect blood pressure which was in agreement with the findings of Parthasarathy et al[5] and this present study. This indicates that intrathecal

opioid did not result in significant hypotension and the episodes of hypotension in these different studies could be probably due to the effect of different doses of bupivacaine.

In this current study, no patient in fentanyl and tramadol groups had bradycardia. One patient (1.6%) in placebo group had bradycardia. One patient in group 20 had bradycardia, no one had bradycardia in groups 10 and 0 in Techanivate et al[16] study. There was no significant difference in the incidence of bradycardia amongst the study population of John et al[27]. Bogra et al[28] reported that bradycardia resulted from the blockade of sympathetic cardio-accelerator fibres and decreased venous return to the heart. In their study, bradycardia occurrence was overall 7%, with no significant intergroup variation. This is in keeping with the findings of Parthasarathy[5], Alhashemi[10] and Susmita[7].

Shivering occurrence did not achieve any significant difference when comparing patients in tramadol group with fentanyl and control groups. No patient in fentanyl group and tramadol group had shivering but three (4.8%) patients in control had shivering in the current study. This was not in accordance with Techanivate et al[16] who observed shivering in fourteen patients (70%) in placebo group and nine (45%) and eight (40%) in the groups with 10µg fentanyl and 20µg of fentanyl respectively. This might be due to the sympatholytic effect of high dose of intrathecal bupivacaine used in their study (4ml) of 0.5% as compared to 3ml of 0.5% used in the current study. Biswas et al[1] and Bogra et al[28] found no significant difference in the episodes of shivering. However, Wheelahan[29] reported that adding epidural fentanyl to epidural lidocaine decreases the shivering threshold compared with epidural lidocaine alone. Petel et al[30] demonstrated that intrathecal fentanyl was significantly better than placebo in the prevention of intra-operative shivering.

In this study, itching occurrence was 6.5% in the fentanyl group with significant intergroup variation. In a similar study conducted by John et al[27] nine patients (33.3%) out of 27 with intrathecal fentanyl had itching intra-operatively and finding from these studies also corroborated finding of Hunt et al[31]. Techanivate et al[16] did not record any itching episode amongst their

study population. Unlike John et al[27], Techanivate[16] and the current study recorded lower incidence of itching probably because higher doses of hyperbaric bupivacaine were administered when compared with the dose administered by John et al[27]. It has been documented that local anesthetic agent and dextrose independently decrease the incidence of pruritus when added to intrathecal fentanyl solution[32,33]. This might be attributed to low dose of intrathecal fentanyl used (10µg and 20µg) in the two groups treated with fentanyl. Biswas[1], Bogra et al[28] and Dahlgren et al[34] reported no significant difference in the incidence of pruritus among their study population. Parthasarathy[5] and Susmita et al[7] recorded no itching in the group treated with tramadol in their studies which was in agreement with the current study. Frickha et al[6] finding was not in support of Parthasarathy[5], Susmita[7] and this present study as they reported more episodes of itching in the tramadol group. The high incidence of itching reported by Frickha[6] might be associated with high dose of opioids (50mg of tramadol plus 10µg of fentanyl) administered to each of the patients in one of the groups in the obstetric population studied.

Reuben et al[35] reported that patients who received intrathecal fentanyl up to 50µg did not experience respiratory depression, even in elderly patients who had cardiac and pulmonary diseases. Also in the study carried out by Techanivate[16], none of the patients experienced respiratory rate < 12 cycles per minute and S_pO_2 < 92% during the operation. This was in accordance with the current study where no patient had respiratory depression and S_pO_2 never dropped below 95%.

There was a low incidence of post-dural puncture headache among patients in this current study. One patient in the fentanyl group had post-dural puncture headache. This was similar to the works of Techanivate et al and Parthasarathy et al where low incidence of post-dural puncture headache was observed. The low incidence of post-dural puncture headache in these study groups may be due to the use of smaller spinal needles (25-27) by these authors. Akpa and colleagues, in a series of spinal anethetics using 16 guage spinal needles, demonstrated a high incidence of post-dural puncture headache[21]. It has been documented that the larger the bore of the spinal needles, the bigger the

opening left in the meninges, the greater the amount of cerebrospinal fluid that is drained and the higher the incidence of post-dural puncture headache[36,37,38].

In the current study, post operative vomiting was highest in the tramadol group. This was significantly high compared with the work of Parthasarathy[5], where only (4%) of the patients vomited post-operatively. Since incidence of vomiting is dose dependent, the difference between Parthasarathy's study and this study in terms of post-operative vomiting might be due to low dose (10mg) of intrathecal tramadol used by Parthasarathy and colleagues[5]. Frikha et al[25] reported higher frequency in vomiting when a high dose (50mg) of intrathecal tramadol was injected into subarachnoid space in pregnant women undergoing Caesarean section.

Conclusion

Intrathecal tramadol 25mg has higher incidence of post operative nausea and vomitting than 25μg of intrathecal fentanyl. Both intrathecal opioids produced comparable adequate analgesia and low side effects and hemodynamic changes.

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