Comparison of Effects of Intrathecal Fentanyl versus Dexmedetomidine in Patients undergoing Transurethral Resection of Prostate

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Abstract

Objectives: Comparison of block characteristics and postoperative analgesic efficacy of Fentanyl and Dexmedetomidine, as a adjuvant to intrathecal hyperbaric 0.5% Bupivacaine for patients undergoing Transurethral resection of Prostate(TURP). *Methods:* 100 patients belonging to ASA physical status I & II were divided into two groups of 50 each. Group F (Fentanyl group) received 2ml Inj. Bupivacaine heavy with 25µg of Fentanyl. Group D (Dexmedetomidine group) received 2ml Inj. Bupivacaine heavy with 5µg of Dexmedetomidine. The time of onset of sensory and motor block, haemodynamic status, duration of motor blockade and postoperative analgesia and adverse effects, if any were compared in both the groups. *Results:* Time from injection to highest sensory level and Onset of Bromage 3 was similar in both groups. The time taken to reach the level of T10 after injection was significantly less and the time taken to regression to Bromage 0 was significantly more in group D compared to group F (p<0.001). Intraoperatively both groups remained haemodynamically stable. Incidence of bradycardia was more in Group D and incidence of pruritus was more in Group F, though it was not statistically significant (p=0.402). Intraoperative sedation was higher in Group D (p<0.001) and postoperatively Visual analogue scores were significantly lower with group D (p<0.001). *Conclusion:* Dexmedetomidine appears to be an attractive adjuvant to intrathecal Bupivacaine than Fentanyl as there is significantly longer duration of motor block. It provides good quality of intraoperative analgesia, haemodynamically stable conditions, minimal side effects, and excellent quality of postoperative analgesia.

Keywords: Intrathecal; Bupivacaine; Fentanyl; Dexmedetomidine; Bromage; Postoperative Analgesia; Transurethral Resection of Prostate.

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Introduction

The patients undergoing Transurethral resection of prostate (TURP) are elderly, with co-existing cardiac and pulmonary diseases with compromised reserves. Spinal anesthesia is the anesthetic technique of choice for this procedure, as these elderly patients tolerate regional anesthesia better and the signs and symptoms associated with TURP like water intoxication, fluid over load, bladder perforation can be detected at the earliest [1,2]. Moreover these patients often suffer from severe postoperative pain due to the usage of transurethral balloon to prevent bleeding from the prostatic bed or capsule [3]. Adequate postoperative pain control is essential to prevent adverse consequences of surgical insult.

The concept of adding adjuvants to spinal anesthesia has come forward by administering opioids like morphine, fentanyl and α_2 agonists like

clonidine, dexmedetomidine. Thereby reducing the dose requirement of bupivacaine and its adverse effects and also enhancing postoperative analgesia [2,4]. Intrathecal morphine was more frequently used for excellent and long lasting postoperative analgesia. But because of its hydrophilic properties, it caused delayed respiratory depression. Whereas for lipophilic opioids like fentanyl and sufentanil, the risk of respiratory depression is predominantly limited to the initial 2 hours after intrathecal injection. Dexmedetomidine, a selective α_2 receptor agonist is the d- enantiomer of medetomidine, a substance that provides sedation, anxiolysis, hypnosis, analgesia and sympatholysis. Intrathecal α_2 receptor agonists have been found to have antinociceptive action for both somatic and visceral pain [5].

The present study is aimed at evaluating the efficacy of intrathecal Fentanyl and dexmedetomidine as an adjuvant to intrathecal Bupivacaine (Hyperbaric) in patients undergoing TURP.

Materials and Methods

Source of Data

This Prospective, Randomized, controlled study was conducted on hundred consecutive patients undergoing TURP between June 2014 to December 2015 in our hospital. They were randomly assigned in to 2 groups, group F (*Fentanyl,* n=50) and group D (*Dexmeditomidine*, n=50). Randomization was done using sealed envelope technique. The study was approved by the institutional ethics committee. Written informed consent was obtained from all the patients enrolled in the study.

Inclusion Criteria

- ASA physical status class I and II
- Age between 60–80 years.

Exclusion Criteria

- Deformities of the spine
- Hypersensitivity to any of the drugs in the study
- Contraindications to spinal anaesthesia – patient refusal, bleeding diathesis Infection at the site of injection, Severe hypovolemia, Increased intracranial tension
- Heart block or dysrhythmia
- Patient on calcium channel blockers, adrenergic antagonist or ACE inhibitor

- Severe stenotic valvular heart disease.

Sample Size Calculation:

Based on the following formula,

$$n = \frac{2\,(Z_\alpha + Z_\beta)^2\ \sigma^2}{\Delta^2}$$

Where,

Z_α is the standard normal value (95% confidence interval) = 1.96

Z_β is the power of the test (80%) = 0.84

To detect the mean difference of 82.7 minutes (time to rescue analgesia) and the pooled standard deviation of 24.4 we need a sample size of 50 in each group.

Methodology

Preanesthetic evaluation was done one day prior to the surgery. Patients were evaluated for any systemic diseases and laboratory investigations recorded. The procedure of spinal anaesthesia was explained to the patients and written consent was obtained. The patients were educated about the use of visual analogue scale. After preparation of operating room, the patients are shifted, intravenous access was secured with 18G cannula. Baseline vitals were recorded. Under strict asepsis, using 25 G Quincke spinal needle, lumbar puncture was performed at $L_3 – L_4$ space in left lateral position, midline approach. Group F received 2ml of 0.5 % hyperbaric bupivacaine + 25µg Fentanyl (vol 0.5ml) and Group D received 2ml of 0.5 % hyperbaric bupivacaine + 5µg Dexmedetomidine (vol 0.5 ml). The following parameters were studied.

- Intraoperatively pulse rate, Non-invasive blood pressure (systolic, diastolic and mean), electrocardiogram, SpO_2 were recorded every 2 minutes for the first 10 minutes, every 10 minutes for the next 50 minutes and every 15 minutes till the end of surgery.
- Time of onset of T_{10} sensory block and peak sensory block was noted using pin prick method, time of onset of Bromage 3 motor block was noted.
- Motor block was assessed with *Modified Bromage scale* [6]: *Bromage 0-* the patient is able to move the hip, knee and ankle, *Bromage 1-* the patient is unable to move the hip but is able to move the knee and ankle, *Bromage 2-* the patient is unable to move the hip and knee but able to move the ankle, *Bromage 3 -* the patient is unable to move the hip, knee and ankle.

- *Modified Ramsay sedation scale [7]* was used for assessing intraoperative sedation 1 = agitated, restless, 2 = cooperative, tranquil, 3 = responds to verbal commands while sleeping, 4 = brisk response to glabellar tap or loud noise while sleeping, 5 = sluggish response to glabellar tap or loud noise while sleeping, 6 = no response to glabellar tap or loud noise while sleeping.

- Hypotension (> 20% fall of baseline blood pressure) was treated with bolus dose of 6 mg ephedrine intravenously. Bradycardia (pulse rate < 50 bpm), was treated with 0.6 mg atropine intravenously. Incidence of respiratory depression defined as respiratory rate < 9 breaths / min and SpO_2 < 90% on room air, was noted. Side effects if any were noted.

- Postoperatively regression of the motor blockade to reach modified Bromage 0 was noted.

- *Visual analogue scale* was used to assess postoperative pain. Supplemental analgesia was given for visual analogue score ≥ 6. Time of supplemental analgesia was noted.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 16. Patient demographic characteristics, continuous variables, time to T10, time to peak sensory block level, time to two segment regression, time of first analgesic requirement were analysed using students 't' test. American Society of Anaesthesiologist (ASA) physical status, Peak sensory block level, maximum motor blockade and other categorical data (side effects) were analysed using chi square. p value < 0.05 was considered as statistically significant.

Results

The mean age of group F is 67.2 years and group D is 68.0 years and the difference is not statistically significant. Similarly, the mean height (cm) and weight (kg) in both the groups are comparable statistically. The distribution of ASA grade is also similar between both the groups (Table 1).

The time taken to reach the level of T10 after injection was significantly less and the time taken to regression to Bromage 0 was significantly more in group D compared to group F (Table 2). Though there is fall in heart rate, systolic, diastolic and mean blood pressure in both the groups, the degree of fall is similar (Table 4,5 and Graph 1). No significant difference in respiratory rate and oxygen saturation between both

Table 1: Demographic data

Variables	Group F	Group D
Age (years)	67.2±4.73	68.0±5.39
Height (cm)	155.66±5.16	156.10±5.83
Weight (kg)	58.12±12.35	56.90±10.18
ASA 1/2	26/24	31/19

Values are mean ± Standard Deviation, number (frequency).
ASA: American Society of Anesthesiologist physical status.

Table 2: Comparison of Block characteristics

Variables	Group F	Group D	P value
Time from injection to T10 (minutes)	3.38±0.83	2.62±0.56	<0.001
Time from injection to highest sensory level (minutes)	11.47±1.23	11.72±1.23	0.314
Onset of Bromage 3(minutes)	10.38±1.08	10.59±1.00	0.317
Regression to bromage 0 (minutes)	152.90±8.31	419.70±16.85	<0.001

Table 3: Highest sensory level of patients studied

Highest sensory level	Group F		Group D	
	No.	Percentage	No.	Percentage
T8	0	-	2	4
T9	11	22	12	24
T10	39	78	36	72
Total	50	100	50	100

the groups (Table 6). Few side effects were noted (Table 7) but was not statistically significant.

Group D patients had more sedation when compared to group F patients particularly at 60 and 90 minutes after the injection (Table 8, Graph 2). Finally group D patients had lower Visual Analog score than group F for 24 hours postoperatively (Table 9, Graph 3) and was statistically significant.

Table 4: Comparison of Mean Arterial Pressure (mmHg)

MAP (mmHg)	Group F	Group D	P value
Pre op	97.02±9.99	94.98±7.02	0.238
2 minutes	93.29±10.02	89.25±8.97	0.036
4 minutes	88.00±8.86	85.65±9.27	0.198
6 minutes	84.44±8.48	83.88±9.50	0.757
8 minutes	81.31±7.67	82.13±10.08	0.648
10 minutes	78.27±8.37	81.28±9.98	0.105
20 minutes	77.10±8.63	79.87±9.84	0.138
30 minutes	76.79±7.38	79.31±9.50	0.142
40 minutes	76.14±8.15	79.06±9.35	0.099+
50 minutes	76.46±8.49	78.88±8.95	0.169
60 minutes	78.31±8.62	79.38±8.41	0.533
75 minutes	80.91±7.65	79.94±7.98	0.541
90 minutes	84.19±7.14	81.64±8.02	0.096+

Table 5: Comparison of Heart Rate (beats per minute)

HR (BPM)	Group F	Group D	P value
Pre op	82.68±12.42	84.36±13.71	0.522
2 minutes	82.04±12.16	83.36±13.94	0.615
4 minutes	81.02±11.16	83.82±14.32	0.278
6 minutes	79.78±10.72	83.02±14.03	0.198
8 minutes	78.58±9.67	80.34±12.51	0.433
10 minutes	77.60±8.79	77.75±10.80	0.938
20 minutes	76.42± 8.14	76.26±11.38	0.936
30 minutes	75.46±7.70	75.48±11.20	0.992
40 minutes	74.68±7.67	74.92±10.87	0.899
50 minutes	74.48±7.70	74.92±9.70	0.802
60 minutes	74.18±7.57	74.98±8.64	0.624
75 minutes	73.40±7.57	74.90±8.54	0.355
90 minutes	72.78±7.11	73.84±8.22	0.492

Table 6: Comparison of RR and SpO_2 of two groups

Variables	Group F	Group D	P value
Respiratory rate(RR)	16.10±1.61	16.10±1.61	1.000
SPO2	97.92±0.75	97.92±0.75	1.000

Table 7: Side effects noted

Side effects	Group F		Group D	
	No.	Percentage	No.	Percentage
Nausea	3	6	0	0
Vomiting	1	2	0	0
Pruritus	3	6	0	0
Hypotension	6	12	8	16
Bradycardia	0	0	7	14
Urinary retention	0	0	0	0
Respiratory depression	0	0	0	0

**Table 8:** Comparison of Modified Ramsay Sedation Score(MRSS) of two groups

MRSS	Group F	Group D	P value
30 mins	2.00±0.00	2.00±0.00	1.000
60 mins	2.00±0.00	3.00±0.00	<0.001
90 mins	2.16±0.37	3.40±0.49	<0.001
120 mins	2.14±0.35	2.00±0.00	0.006
150 mins	2.00±0.00	2.00±0.00	1.000
180 mins	2.00±0.00	2.00±0.00	1.000

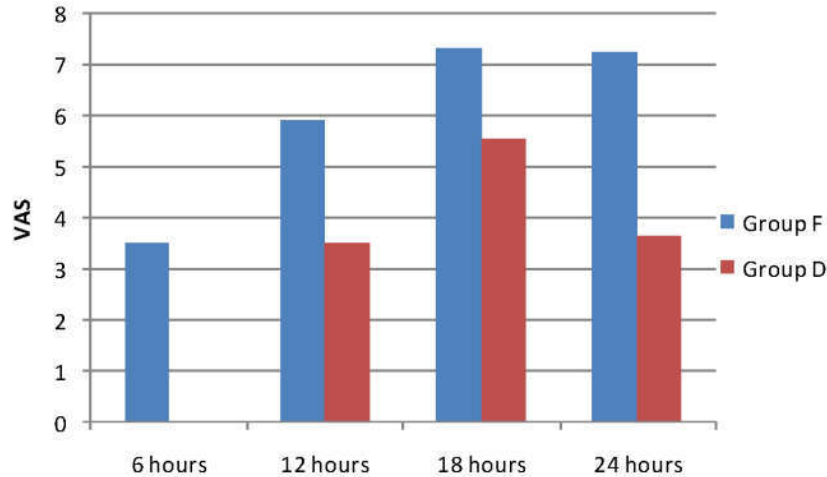**Table 9:** Comparison of Visual Analogue Scale (VAS) of two groups

VAS	Group F	Group D	P value
6 hours	3.50±0.51	0.00±0.00	<0.001
12 hours	5.90±0.97	3.50±0.51	<0.001
18 hours	7.28±0.95	5.52±0.51	<0.001
24 hours	7.24±0.96	3.62±0.69	<0.001
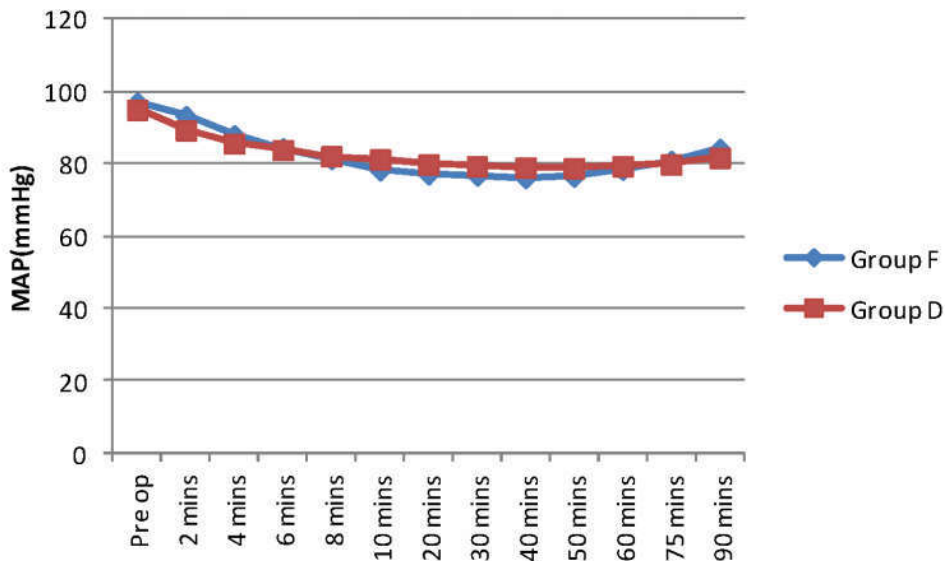
Graph 1: Comparison of Mean arterial pressure (MAP) changes in both groups
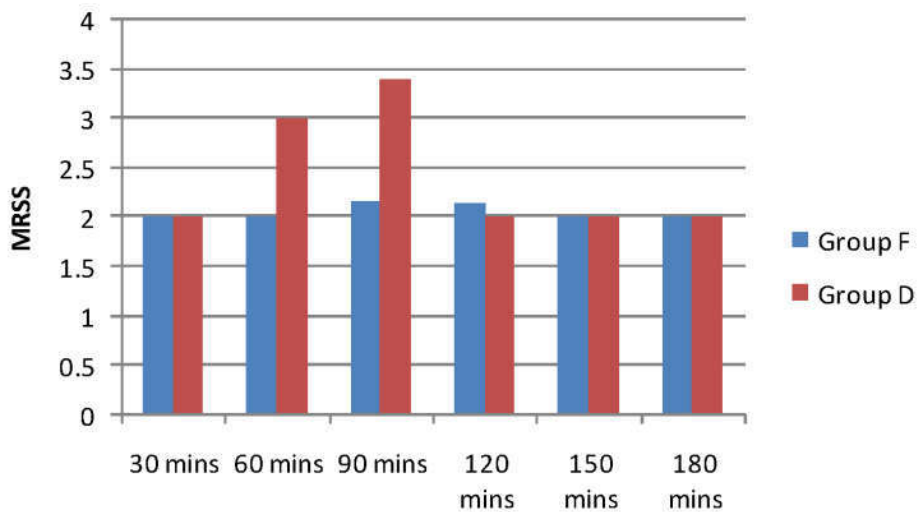
Graph 2: Modified Ramsay Sedation Score (MRSS) in both groups

Graph 3: Visual analogue scale scores in both groups

Discussion

One of the age related conditions in males is benign hyperplasia of the prostate; as such the patients undergoing TURP are elderly, with co-existing cardiac, pulmonary and metabolic disorders and compromised reserves. Spinal anaesthesia is the most widely used technique for the procedure, as the elderly tolerate regional anaesthesia better. With spinal anaesthesia physiological disturbances are minimal and adequate muscle relaxation is provided which allows relaxation of the pelvic floor, perineal and thigh muscles for improved surgical access and also early recognition of fluid overload, bladder perforation [1,2]. Due to the age related changes in spinal anatomy, nerve physiology and cardiovascular reflexes in elderly, it is important to limit the distribution of spinal block to reduce the adverse haemodynamic and pulmonary effects. Low-dose bupivacaine causes minimum haemodynamic alterations, but may provide insufficient surgical anaesthesia and postoperative analgesia [8]. Various adjuvants such as opioids and α_2 agonists have been added to bupivacaine to shorten the onset of block, increase block quality and prolong the duration of block and postoperative analgesia, without compromising patient safety [2,4].

Fentanyl, a lipophilic opioid agonist, is used as an adjuvant, which prolongs the duration of spinal anaesthesia. Intrathecally, Fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and also have a supraspinal spread and action [9]. *Dexmedetomidine*, an α_2 agonist drug, when given intrathecally, significantly prolongs the duration of spinal anaesthesia. Stimulation of the α_2

adrenoceptors in the substantia gelatinosa of the dorsal horn of the spinal cord, inhibits the firing of nociceptive neurons stimulated by peripheral Aγ and C fibres. It also inhibits the release of substance P by primary afferents of the dorsal horn, and suppresses the activity of wide dynamic range neurons evoked by noxious stimuli. Recent evidence suggests that the antinociception produced by alpha-2 agonists may be due in part to acetylcholine release in the spinal cord. As it has been suggested that the spinal cord is the major site of analgesic action for alpha-2 agonists, the epidural and intrathecal routes have been considered preferable to the intravenous route [10,11].

In our study design, Group F received 0.5% hyperbaric Bupivacaine 2ml with Fentanyl 25µg and Group D received 0.5% hyperbaric Bupivacaine 2ml with Dexmedetomidine 5µg intrathecally to the patients undergoing TURP. Fentanyl in the dose of 25µg had been successfully used as an adjuvant intrathecally for various lower abdominal surgeries [12,13]. Similarly, Dexmedetomidine in the dose of 5µg was found to provide good, prolonged analgesia for various urological procedures [12,14,15]. And hence we have decided the doses accordingly.

Demographic characteristics were comparable in both the groups (Table 1). The distribution of ASA grade was also similar between both the groups. The difference was not statistically significant. Our study has shown that the addition of either 5µg Dexmedetomidine or 25µg Fentanyl with hyperbaric bupivacaine significantly prolongs both sensory and motor block. But the time taken to reach the level of T10 after injection was significantly less in Dexmedetomidine group. The duration of motor blockade i.e) the time to regression was significantly

prolonged to 419.70±16.85 minutes in the Dexmedetomidine group while it was 152.90±8.31 minutes in the Fentanyl group. But the highest sensory level attained, the time taken to reach that level and the onset of Bromage 3 was comparable in both the groups. Thus Dexmedetomidine group of patients had early onset and more prolonged duration of blockade when compared to Fentanyl group.

Al-Ghanem et al. [12] had studied the effect of addition of 5μg Dexmedetomidine or 25μg Fentanyl intrathecally to 10mg isobaric bupivacaine in patients undergoing vaginal hysterectomy and concluded that Dexmedetomidine produces more prolonged motor and sensory block than Fentanyl. Similarly, Esmaoglu A et al. [16] had studied the effects of Dexmedetomidine added to Spinal Levobupivacaine for Transurethral Endoscopic Surgery and concluded that addition of intrathecal dexmedetomidine for spinal anaesthesia shortens sensory and motor block onset time and prolongs block duration without any significant adverse effects. Many other studies also support this finding [13,17,18].

Though there is fall in heart rate, systolic, diastolic and mean blood pressure in both the groups, the degree of fall is similar. No significant difference in respiratory rate and oxygen saturation were found between both the groups. Incidence of nausea (6%), vomiting (2%) and pruritus (6%) was noted only in fentanyl group (Table 7). The incidence of hypotension (12% vs 16%) was similar in both the groups. But there was significant incidence of bradycardia (0% vs 14%) in Dexmedetomidine group. Nausea, vomiting and pruritus after intrathecal Fentanyl is known but it was not significant in the present study. Biswas et al in their study had observed pruritus in 15% of patients who received intrathecal fentanyl [19]. Gupta R et al. had observed that intraoperative hypotension and ephedrine requirement was more in the Dexmedetomidine group [18]. Halder et al. had noticed statistically significant occurrence of bradycardia in dexmedetomidine groups in a randomized trial performed on eighty patients scheduled for elective lower limb surgeries [20].

Group D patients had more sedation when compared to group F patients particularly at 60 and 90 minutes after the injection. Finally group D patients had lower Visual Analog score than group F for 24 hours postoperatively and was statistically significant. So there was no requirement for rescue analgesia in Dexmeditomidine group for 24 hours postoperatively. Whereas fentanyl group of patients required supplementary analgesia from 12th hour onwards. Gupta R et al. [13] in their comparative study of intrathecal Dexmedetomidine 5μg and Fentanyl 25μg as adjuvants to bupivacaine, found that intrathecal Dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics in 24 hours as compared to Fentanyl. They also found that the sedation score was more in group D patients. Their mean sedation score was 3.8±0.5 in group D as compared to 2.2±0.53 in group F, which was statistically significant (p<0.05). In our study, the mean sedation score for group F was 2.16±0.37 and group D was 3.40±0.49 , which was statistically significant (p <0.001). Similarly, Eid HEA et al had observed that intrathecal dexmedetomidine group of patients had higher sedation score, lower post-operative analgesic requirement and hemodynamic stability [21]. Similar observation had been made in many other studies [18,22,23].

As the study involved 100 patients undergoing TURP, it was also easier to study the incidence of TURP Syndrome. Not even a single case of TURP syndrome was noted. The incidence was 0% and none of our patients required blood transfusion intra-operatively.

Conclusion

Addition of 5μg Dexmedetomidine with hyperbaric bupivacaine significantly prolongs both sensory and motor block. The post operative 24 hours analgesic requirement was also significantly less in the Dexmedetomidine group than Fentanyl group. To conclude, 5μg Dexmedetomidine seems to be an attractive alternative to 25μg Fentanyl as an adjuvant to spinal bupivacaine in surgical procedures. It provides good quality of intraoperative analgesia, haemodynamically stable conditions, minimal side effects, and excellent quality of postoperative analgesia.

Hence, Dexmedetomidine seems to be a better choice as intrathecal adjuvant with Bupivacaine when compared with Fentanyl.

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