Original Article

Comparison between Effects of Fentanyl and Fenofol as Sedative in Elective Caesarean Section under Subarachnoid Anaesthesia

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Abstract

Background: *Regional anaesthesia has become an important anaesthetic technique now a days. Pharmacologically induced tranquility improves acceptance of regional technique.*

Objective: *To compare Fentanyl and Fenofol (Fentanyl+Propofol) in terms of onset and recovery of sedation, haemodynamic effects, respiratory effects and adverse effects of both the drugs during elective Caesarian section under spinal(subarachnoid) anaesthesia.*

Materials and Methods: *This randomized clinical trial included 60 ASA (American Society of Anaesthesiologists) grade I or II patients between age 20-40 years undergoing elective Caesarean sections under Subarachnoid anaesthesia during the period January 2022 to June 2022. Patients were randomly allocated to one of two groups: Fentanyl group (Group F, n=30), who received Fentanyl in a single dose of 0.5mcg/kg and Fenofol group (Group FP, n=30), who received Fenofol in a single dose of Fentanyl-0.5mcg/kg+Propofol-0.5mg/kg. Spinal anaesthesia was conducted by injecting a hyperbaric solution of 0.5% bupivacaine 3ml through a 25G spinal needle at L3-4 level. All parameters were documented at 5 min intervals until arousal of the patient. The onset of sedation i.e. time from iv (intravenous) injection of Fentanyl or Fenofol to closure of eye lids (OAA/S score of 3) and the arousal time from sedation i.e. time from closing of the eye lids to OAA/S score of 5 (patient is awake clinically) were noted. Any complication during operation was documented. The patient's satisfaction with the sedation was assessed by the 5 point 'Likert verbal rating scale.'*

Results: *There was no significant difference of mean blood pressure and mean heart rate between the two groups in different time intervals (P>0.05). Time of onset of sedation and the arousal time i.e. duration of sedation was comparable between the two groups (P>0.05). Significant percentage of patients required O2 supplementation in Fenofol group due to hypoventilation (66.66% vs 10%, P<0.001). Pain in arm during drug administration was significantly more with Fenofol (46.66% vs 6.66%, P<0.001).*

Conclusion: *As significantly higher percentage of patients required O2 supplementation during sedation with Fenofol and pain in arm during drug administration was significantly more in Fenofol group, it is recommended that Fentanyl is a better choice than Fenofol for sedation in single dose technique during subarachnoid block for Caesarean section.*

Key words: *Fentanyl, Fenofol, Sedation, Subarachnoid Anaesthesia.*

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Introduction

Spinal (Subarachnoid) anaesthesia is the method of choice for elective Caesarean section. It allows mother to be involved in the child's delivery but also exposes them to awareness related stress during the procedure. The stress intensity is higher in women undergoing a Caesarean section compared with women delivering spontaneously.[1] The use of pharmacological sedation after extraction of the foetus by Caesarean section under Subarachnoid anaesthesia is useful in some patients e.g. those presenting with high stress. Enhanced stress can result from poor foetal health after delivery, discomfort associated with immobilization on the operating table, chills that accompany anatethesia, nausea, vomiting and environment of operating room.[2]

Sedation is a valuable tool to provide general comfort for the patient. Oversedation may jeopardize the safety of the patient. While levels of sedation progress in a dose response continuum, it is not always possible to predict precisely how an individual patient will respond to a particular dose.[3] Oversedation may be associated with untoward effect of respiratory and cardiovascular depression resulting in higher chances of airway instrumen

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tation and hypotension leading to a prolonged stay in the post anaesthetic care unit, entailing increased burden on staff, bed availability and associated costs.[4,5] Thus judicious use of sedation can make surgeries under spinal anaesthesia more comfortable for the patient, the surgeon and the anaesthesiologist. As a result, it can increase the patient's acceptance of regional anaesthetic technique.[6]

Fentanyl is a potent narcotic analgesic with rapid onset and short duration of effect following a single intravenous dose. It provides analgesia with sedation but it has the propensity of respiratory depression when used in higher doses.[7] Fenofol is a combination of drugs Fentanyl and Propofol. Propofol is a short acting, sedative, intravenous anaesthetic drug which causes fall in blood pressure in some patients. Fentanyl is an opioid analgesic with longer duration of action which also has sedative properties and cardiovascular stability. Using Fentanyl with Propofol reduces dose amount of both the drugs and potentiates the effect of each other.[8]

There are a good number of studies regarding the use of sedative agents during regional anaesthesia but it is scarce in case of Caesarian section where a pregnant woman has anatomical and physiological changes from a non-pregnant woman. The aim of this study was to compare the time of onset and recovery from sedation with Fentanyl and Fenofol, to evaluate and compare the properties of both drugs in terms of haemodynamic effects, respiratory effects and adverse effects, as adjuncts to spinal anaesthesia.

Materials and Methods

This randomized clinical trial included 60 ASA (American Society of Anesthesiologists) grade I or II patients between age 20-40 years undergoing elective Caesarean sections under Subarachnoid (Spinal) anaesthesia during the period January 2022 to June 2022 in Combined Military Hospital, Chattogram. The exclusion criteria were positive history of drug allergies, patients suffering from heart disease, hypertension, diabetes, spinal deformity, neurological disorder, any bleeding disorder and unwilling to accept sedation during spinal anaesthesia. Patients were randomly allocated to one of two groups: Fentanyl group (Group F, n=30), who received Fentanyl in a single dose of 0.5mcg/kg and Fenofol group (Group FP, n=30), who received Fenofol in a single dose of Fentanyl 0.5mcg/kg and Propofol 0.5mg/kg. Fenofol solution was prepared in 10ml syringe containing Fentanyl 5mcg/ml and Propofol 5mg/ml. Written informed consent were taken from all participants. Ethical approval was obtained from proper authority. They were fasted for a minimum of 6 hours before surgery. No preoperative opioid or prophylactic antiemetic were given. No other preoperative medication was allowed. All patients were monitored with electrocardiograph, non-invasive blood pressure and pulse oximeter monitor. Baseline vital parameters were recorded. Preloading was done with 300ml Ringer lactate within 5-10 minutes prior to block. Spinal anaesthesia was conducted by injecting a hyperbaric solution of 0.5% bupivacaine 3ml through a 25G spinal needle at L3-4 level. After spinal block, patients were placed on the operating table in horizontal position. Sedation with Fentanyl and Fenofol was administered after extraction of the foetus . O2 inhalation by ventimask was given when SpO2 (saturation percentage of arterial oxygen) came down below 90% and vasopressor was given if MAP (mean arterial pressure) decreased beyond 20% of baseline. MAP was measured continually at 5 min interval and heart rate (HR), SpO2 were monitored throughout the surgery. All parameters were documented at 5 min intervals until arousal of the patient. The onset of sedation i.e. time from iv injection of Fentanyl or Fenofol to closure of eye lids (OAA/S score of 3) and the arousal time from sedation i.e. time from closing of the eye lids to OAA/S (Observer's Assessment of Alertness/ Sedation) score of 5 (patient is awake clinically) were noted. Any complication during operation was documented. The patient's satisfaction with the sedation was assessed by the 5 point 'Likert verbal rating scale' with some questions like 'where will you put your experience with this sedation on the scale?' in a language which the patient understands, at a point of time when the patient had a mental state suitable for communication.

Observer's Assessment of Alertness/ Sedation (OAA/S) Scale:

Category	Observation	Score Level
Responsiveness	Responds readily to name spoken in normal tone	5
	Lethargic response to name spoken in normal tone	4
	Responds only after name is called loudly and/or repeatedly	3
	Responds only after mild prodding or shaking	2
	Does not respond to mild prodding or shaking	1
Speech	Normal	5
	Mild slowing or thickening	4
	Slurring or prominent slowing	3
	Few recognizable words	2
Facial expression	Normal	5
	Mild relaxation	4
	Marked relaxation (slack jaw)	3
Eyes	Clear, no ptosis	5
	Glazed, or mild ptosis (less than half the eye)	4
	Glazed and marked ptosis (half of the eye or more)	3

Figure 1: Likert Scale for satisfaction

Data were analysed using Statistical Package for the Social Science (SPSS) for Windows (version 12.0,SPSS Inc,. Chicago, IL, USA). Independent 't' test was used for age, weight, duration of surgery, time for recovery, heart rate, mean arterial pressure and SpO2 at various time intervals. Chi square test was applied for adverse effects. Paired 't' test was applied for intra-group variation in heart rate and mean arterial pressure. Data were expressed in mean, SD and percentage. P<0.05 was taken to be of statistically significant.

Results

60 respondents (30 in each group) were included in this randomized clinical trial. The Group F (Fentanyl group) and Group FP (Fenofol group) were found to be comparable in respect of age, weight, duration of surgery (time from surgical incision to surgical closure) (Table I).

Table I: Demographic data of the patients under study (N=60)

Variable	Group F (n=30)	Group FP (n=30)	P value
Age (years)	30.46±4.5	30.10±5.4	0.780
Weight (kg)	66.53±9.8	67.53±8.8	0.679
Duration of surgery (min)	48.66±3.6	50.16±3.4	0.102

Values are expressed in mean±SD
SD- Standard deviation

There was no significant difference in mean arterial pressure between the two groups before Spinal anaesthesia (baseline), after spinal block, before sedative drug administration. Greater fall in MAP was observed in Fenofol group, but that was not statistically significant (P value 0.238) (Table II).

Table II: Comparison of MAP (mmHg) in study groups at various time intervals (N=60)

Time Interval	Group F (n=30)	Group FP (n=30)	P value
Before Anesthesia (baseline)	83.1±6.53	80.1±6.78	0.086
After Spinal block	77.5±5.69	75.4±5.41	0.148
Before drug administration	73.6±6.57	74.3±6.41	0.677
After drug administration	72.1±7.28	69.7±8.2 9	0.238

Values are expressed in mean±SD
SD- Standard deviation

There was no significant difference in mean heart rate between the two groups before Spinal anaesthesia (baseline), after spinal block, before sedative drug administration and after drug administration (Table III).

Table III: Comparison of mean heart rate (bpm) in study groups at various time intervals (N=60)

Time Interval	Group F (n=30)	Group FP (n=30)	P value
Before Anesthesia (baseline)	79.6±11.69	79.4±11.39	0.946
After Spinal block	86.5±11.97	88.3±10.57	0.539
Before drug administration	82.6±12.31	79.6±9.71	0.299
After drug administration	86.5±8.08	84.5±11.18	0.430

Values are expressed in mean±SD
SD- Standard deviation

Time of onset of sedation and duration of sedation i.e time for arousal from sedation were comparable between the two groups (P>0.05)(Table IV).

Table IV: Comparison of Sedation characteristics in study groups (N=60)

Variable	Group F (n=30)	Group FP (n=30)	P value
Time required for onset of sedation (eye closure) (min)	1.7±0.25	1.54±0.51	0.128
Arousal time from sedation in min (OAA/S score of 5)	10.3±2.37	11.1±2.37	0.196
Satisfaction with sedation (good)	20 (66.66%)	14 (46.66%)	0.121

Values are expressed in mean±SD
SD- Standard deviation

Incidence of pain in arm was significantly more in Fenofol group (P<0.001). In Group FP, significant percentage of patients required oxygen supplementation after sedation due to hypoventilation (P<0.001). Other complications were comparable between the two groups (Table V).

Table V: Incidence of complications in study groups (N=60)

Variable	Group F (n=30)	Group FP (n=30)	P value
Nausea and Vomiting	10(33.33%)	8 (26.66%)	0.576
Chills	3 (10%)	4 (13.33%)	0.690
Restlessness	6 (20%)	7 (23.33%)	0.756
Pain in arm	2 (6.66%)	14 (46.66%)	<0.001
Hypoventilation (↓SpO_2)	3 (10%)	20 (66.66%)	<0.001

Discussion

Pregnant women undergoing elective Caesarean sections under Subarachnoid anaesthesia are often anxious about the unpleasant experience associated with awareness during surgery. After being informed about the possible use of sedative after baby extraction, the patients usually more eagerly accept this suggested method of anaesthesia.[2]

The most widely used technique for administering sedation in regional anaesthesia is the intermittent bolus dose technique. This technique has been shown to be associated with peaks and troughs in plasma concentration producing significant side effects and delayed recovery.[9] Continuous infusions have been proved to produce, lesser side effects, faster recovery, easy controllability over the desired depth of sedation but requires some especial equipments e.g. syringe pump, BIS monitor etc, which is expensive and not available everywhere. Moreover, it needs more expertise like interpretation of EEG.[10]

When using sedative medication during regional anaesthesia technique, the anaesthesiologist attempts to titrate the drug to optimize patient comfort while maintaning cardiorespiratory stability and intact protective reflexes. The assessment of depth of sedation has been traditionally performed by observing clinical parameters such as appearance, response to voice, and pain on surgical stimulation. These parameters are qualitative and assessment of response to voice requires patient stimulation, which may itself alter depth of sedation.[11]

We chose the OAA/S scale for assessment of sedation over other scales as it was easier to use, comprehensive and inclusive of parameters such as facial expression and eyelid ptosis in addition to speech and responsiveness, which are not there in other sedation scales.[12] Similarly the OAA/S scale has been shown to have an inter-rater agreement that varies between 85% and 96% depending on the level of sedation, which is higher than most of the other scales used for the same purpose, making it the most suitable choice if precise assessment of sedation is required.[10]

Opioids bind to specific receptors located throughout the central nervous system and other tissues. Four major types of receptors have been identified. Fentanyl bind mostly to mu (μ) receptor. Opioid receptor activation inhibits the presynaptic release and post synaptic response to excitatory neurotransmitters (e.g. acetylcholine, substance P) from nociceptive neurons. The cellular mechanism for this neuromodulation may involve alteration in potassium and calcium ion conductance.[13] The combination of Fentanyl and Propofol (Fenofol) is theoretically expected to have the advantages of reducing the dose of both the drugs. Haemodynamic compromise induced by Propofol may be compensated by the cardiovascular stability by Fentanyl. Moreover, addition of Fentanyl may add analgesic effect to the drug combination and prolong the sedative effect of Propofol. But there is possibility of respiratory depression which needs close monitoring.[8]

Minami et al. conducted a prospective clinical trial on safety and discomfort during bronchoscopy performed under sedation with Fentanyl and Midazolam. Fentanyl 20 mcg was administered to the patients just before bronchoscopy, and Fentanyl (10 mcg) and Midazolam (1mg) were added as needed during the procedure. A questionnaire was completed 2 hours after the examination. 70.2% patients agreed to undergo a second bronchoscopic examination and only 37.8% of the patients remembered the bronchoscopic examination. No severe complication was reported.[14] In our study, we compared the sedative effect between Fentanyl and Fenofol during Caesarean section which showed more favorable sedative effect with Fentanyl. Fentanyl was associated with less adverse effects like pain in arm and hypoventilation than Fenofol.

Frolich et al. conducted a double blinded, randomized, placebo controlled trial, where 60 healthy pregnant women received either a combination of Fentanyl (1mcg/kg) and Midazolam (0.02mg/kg) intravenously or an equal volume of iv saline at the time of their skin preparation for a bupivacaine spinal anaesthetic. Foetal outcome measures included Apgar Score, continuous pulse oximetry, and neurobehavioral Scores. Maternal outcomes included catecholamine levels, recall of anaesthesia and delivery. There were no between-group differences of neonatal outcome variables. Mothers in both groups showed no difference in their ability to recall the birth of the babies. So, they concluded that maternal analgesia and sedation with Fentanyl and Midazolam immediately prior to spinal anaesthesia is not associated with adverse neonatal effects.[15] In our study, we compared the sedative effect between Fentanyl and Fenofol after delivery of the baby which showed more favorable sedative effect with Fentanyl. Foetal outcome was not included in our study. Maternal satisfaction was comparable between the two groups.

Shin et al. assessed the effect of adding Fentanyl to Midazolam on sedation level and intraoperative nausea and vomiting (IONV) during Caesarean section under spinal anaesthesia. Following foetal delivery, patients were administered 0.05mg/kg of Midazolam plus 0.03ml/kg of normal saline (M group) or 0.05mg/kg of Midazolam plus 1.5mcg/kg of Fentanyl (MF group). The primary outcome was the incidence of IONV. The secondary outcomes were incidence of post operative nausea and vomiting (PONV), intraoperative sedation level and 5 point patient satisfaction score (PSS). The IONV incidence was significantly lower in the MF group compared with the M group (5% vs 25%). The PONV incidence did not differ significantly between the groups. The intra operative sedation level tended to be deeper in the MF group. The 5-point PSS was significantly higher in the MF group. There was a strong correlation between the sedation level and IONV incidence. They concluded that adding Fentanyl to Midazolam is effective for sedation and to prevent IONV in women who underwent Caesarean section under spinal anaesthesia.[16] In our study, we compared the adverse effects between Fentanyl and Fenofol while used as sedative during Caesarean section. Incidence of intra operative nausea and vomiting (IONV) was comparable between the two groups. Our study did not include incidence of PONV. Patient satisfaction was comparable between Fentanyl and Fenofol.

Nazemroaya et al. conducted a randomized, double-blind clinical trial on 64 patients to compare Propofol and Ketamin

combination (Ketofol) vs Propofol and Fentanyl combination (Fenofol) on quality of sedation and analgesia during lumpectomy. The patients were divided into two groups. The mean arterial blood pressure, systolic blood pressure, and heart rate did not show any significant difference between the two groups, but the Fenofol group had a significantly lower oxygen saturation than the Ketofol group. The sedation level was significantly lower in the Fenofol group than the Ketofol group. The mean pain intensity was significantly lower in the Fenofol group than the Ketofol group. They concluded that Ketofol may be a superior alternative to Fenofol combination in terms of respiratory depression.[8] In our study, we compared the effects between Fentanyl and Fenofol in which significant percentage of patients required oxygen supplementation due to low SpO2 after sedation with Fenofol. Sedation level was comparable between the two groups. Haemodynamic effects were also comparable. Pain intensity measurement was not included in our study.

Kurdi et al. conducted a prospective randomized double-blind study on 60 adult female scheduled for elective tubal sterilization. Patients were divided into 3 groups: Group A (Kermine: Propofol-1:1), Group B (Ketamine : Propofol- 1:2) and Group C (Fentanyl:Propofol- 100mcg of Fentanyl mixed with 100mg Propofol). Group A and Group B were comparable in respect of onset of sedation, intraoperative sedation scores, recovery time, haemodynamic and respiratory profile. Group C (Fentanyl-Propofol) patients were less sedated and had poor analgesia compared to Group A and B.[17] In our study, duration of sedation was comparable between Fentanyl and Fenofol groups. Analgesic effect was not included in our study. Shetabi et al. conducted a randomized clinical trial on 68 adult patients who were candidates for placement and removal of port catheter for chemotherapy. Anesthetic induction was done in Ketofol group with Propofol (1mg/kg) and Ketamine (0.5mg/kg), Fenofol group with Propofol (1mg/kg) and Fentanyl (1.5mcg/kg). Sedation, analgesia and hemodynamic changes were reported better in Ketofol group.[18] In our study, dose of Fentanyl and Propofol in drug combination were different from the above study. Haemodynamic effects were comparable between Fentanyl and Fenofol. Analgesic effect was not included in our study.

The intervention was not placebo controlled and blinded to neither clinicians nor patients. Additionally, group sizes were small and it was a single centre study. Consequently the clinical relevance remains undetermined and further studies are necessary to confirm potential benefits between the two drugs.

Conclusion

The study showed that Significantly higher percentage of patients required O_2 supplementation during sedation with Fenofol due to hypoventilation. Thus it is recommended that Fentanyl is a better choice than Fenofol for sedation in single dose technique during subarachnoid block for Caesarean section.

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