Comparison Between Effects of Ketofol 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. The use of spinal (subarachnoid) anaesthesia is often limited by the unwillingness of patients to remain awake during surgery. Pharmacologically induced tranquility improves acceptance of regional technique.

Objective:
This study compares Ketofol (Ketamine+Propofol) 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 anaesthesia.

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 of January 2022 to June 2022. Patients were randomly allocated to one of two groups: Ketofol group (Group KP, n=30), who received Ketofol in a single dose of 0.5mg/kg (Ketamine- 0.5mg/kg+Propofol-0.5mg/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 Ketofol or Fenofol to closure of eye lids 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. 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 (P>0.05). Time of onset of sedation was comparable between the two groups (P>0.05). Duration of sedation was significantly less in Fenofol group (p value=<0.001). Significant percentage of patients required oxygen supplementation after sedation with Fenofol due to hypoventilation (66.66% vs 10%, p value <0.001). Incidence of nausea and vomiting was significantly more with Fenofol (46.66% vs 10%, p value >0.001).

Conclusion:
The study showed that the arousal time i.e. duration of sedation was significantly more with Ketofol than Fenofol which is beneficial for the patient in single dose technique for sedation. Fenofol was associated with significantly high incidence of nausea, vomiting. Moreover, significantly higher percentage of patients required O_2 supplementation due to hypoventilation during sedation with Fenofol. Thus it is recommended that Ketofol is a better choice than Fenofol for sedation in single dose technique during subarachnoid block for Caesarean section.

Keywords: Ketofol, Fenofol, Sedation, Subarachnoid anaesthesia.

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 instrumentation 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]

Ketofol, a combination of the drugs ketamine and propofol has good analgesic and sedative properties in addition to fast onset of action. Sedation with Ketofol decreases the side effects of both ketamine and propofol as they potentiate each other and thus smaller doses are used.[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 find out the time of onset and recovery from sedation with Ketofol 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.

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 anaesthesia during the period of 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: Ketofol group (Group KP, n=30), who received Ketofol in a single dose of 0.5mg/kg (propofol 0.5mg/kg and ketamine 0.5mg/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. Ketofol was prepared with Ketamine: Propofol mixture in 1:1 ratio in a 10 ml syringe which contained Ketamine 5mg/ml and Propofol 5mg/ml. Fenofol solution was prepared in 10ml syringe containing Fentanyl 5mcg/ml and Propofol 5mg/ml. A written informed consent was taken from all patients. 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 Ketofol and Fenofol was administered after extraction of the foetus . O_2 inhalation by ventimask was given when SpO_2 (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), SpO_2 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 Ketofol 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 SpO_2 at various time intervals. Chi square test was applied for adverse effects and oxygen supplementation. Paired 't' test was applied for intra-group variation in heart rate and mean arterial pressure. Data were expressed in mean, SD and percentage and p-value <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 KP (Ketofol 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 KP (n=30)	Group FP (n=30)	p-value
Age (years)	30.23±5.3	30.10±5.4	0.925
Weight (kg)	66.51±9.8	67.53±8.8	0.673
Duration of surgery (min)	51.66±4.5	50.16±3.4	0.150

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 (Table-II).

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

Time Interval	Group KP (n=30)	Group FP (n=30)	p-value
Before Anaesthesia (baseline)	79.1±7.54	80.1±6.78	0.591
After Spinal block	76.3±5.59	75.4±5.41	0.528
Before drug administration	73.7±7.41	74.3±6.41	0.738
After drug administration	72.1±8.41	70.7±8.39	0.521

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 KP (n=30)	Group FP (n=30)	p-value
Before Anaesthesia (baseline)	79.3±9.69	79.4±11.39	0.970
After Spinal block	86.3±11.17	88.3±10.57	0.479
Before drug administration	81.6±11.71	80.6±9.71	0.720
After drug administration	86.5±10.07	84.5±11.18	0.469

Values are expressed in mean±SD
SD- Standard deviation

Although onset of sedation was comparable between the two groups (p-value=0.327), duration of sedation was significantly less in Fenofol group (p-value=<0.001). Percentage of patients satisfied with sedation was significantly more in Ketofol group (p-value=0.002) (Table-IV).

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

Variable	Group KP (n=30)	Group FP (n=30)	p-value
Time required for onset of sedation (eye closure) (min)	1.67±0.51	1.54±0.51	0.327
Arousal time from sedation in min (OAA/S score of 5)	25.3±6.37	10.3±2.37	<0.001
Satisfaction with sedation (good)	20(66.66%)	08(26.66%)	0.002

Values are expressed in mean±SD
SD- Standard deviation

Incidence of nausea and vomiting was significantly more in Fenofol group (p-value=<0.001). In Fenofol group, significant percentage of patients required oxygen supplementation after sedation due to hypoventilation (p-value=<0.001). Other complications were comparable between the two groups (Table-V).

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

Variable	Group KP (n=30)	Group FP (n=30)	p-value
Nausea and Vomiting	3(10%)	14(46.66%)	<0.001
Chills	3(10%)	4(13.33%)	0.690
Restlessness	6(20%)	7(23.33%)	0.756
Pain in arm	10(33.33%)	14(46.66%)	0.296
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 hypnotics 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 equipment 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 sedatives in the technique of regional anesthesia, the anesthesiologist attempts to titrate the drug in a way that optimizes patient comfort while keeping cardiorespiratory stability and defensive reflexes intact. Traditionally, depth of sedation was assessed by observing clinical parameters such as appearance, response to voice, and pain on surgical stimulation. These parameters are qualitative in nature and assessment of voice response requires stimulation of the patient, which in turn can alter the 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]

In theory, the combination of ketamine and propofol (ketofol) should have the benefits of both drugs and complement each other. The hemodynamic disturbances caused by propofol can be compensated by the sympathomimetic effect of ketamine. It is known that concomitant use of propofol reduces the effect of psychomimetic side effects. Indeed the combination has been shown to be useful in many clinical situations, with better profiles in haemodynamic stability, respiratory depression, analgesia, and recovery than each agent alone.[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]

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 Ketofol 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 100 mg 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.14 In our study, duration of sedation was significantly less in Fenofol group compared to Ketofol group. 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 (1 mg/kg) and Ketamine (0.5 mg/kg), Fenofol group with Propofol (1 mg/kg) and Fentanyl (1.5mcg/kg). Sedation, analgesia and hemodynamic changes were reported better in Ketofol group.15 In our study, dose of Fentanyl and Propofol in drug combination were different from the above study but we also found less sedative effect with Fenofol. Haemodynamic effects were comparable between Ketofol and Fenofol.

Conclusion:

The study showed that the arousal time i.e. duration of sedation was significantly longer with Ketofol than Fenofol which is beneficial for the patient in single dose technique for sedation. Fenofol was associated with significantly high incidence of nausea, vomiting. Moreover, significantly higher percentage of patients required O2 supplementation due to hypoventilation during sedation with Fenofol. Thus it is recommended that Ketofol is a better choice than Fenofol for sedation in single dose technique during subarachnoid block for Caesarean section.

Study limitations:

The intervention was not placebo-controlled and was not blinded to physicians or patients. In addition, the group sizes were small and it was a single-centre study. Therefore, the clinical relevance remains undetermined and more research is needed to confirm the potential benefits between these two sedatives.

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Conflict of Interest:

There is no conflict of interest.

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