Original Article

Comparison between Effects of Fentanyl and Ketofol 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 Fentanyl and Ketofol (Ketamine+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.* ***Materials and method:*** *This randomized clinical trial included 60 ASA (American Society of Anaesthesiologists) grade I 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 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). 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 Ketofol 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 was significantly less with Ketofol than Fentanyl ($p<0.05$). The arousal time i.e. duration of sedation was significantly longer with Ketofol than Fentanyl ($p<0.05$). Fentanyl was associated with high incidence of some adverse effects like nausea, vomiting than Ketofol (46.66% vs 16.70%, $p<0.05$). Pain in arm during drug administration was significantly more with Ketofol (33.33% vs 6.66%, $p<0.05$). Significant percentage of patients was satisfied with Ketofol than Fentanyl (66.66% vs 20%, $p<0.001$).* ***Conclusion:*** *The study showed that the time to reach effective sedation was less with Ketofol than Fentanyl and the*

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arousal time i.e. duration of sedation was significantly longer with Ketofol which is beneficial for the patient in single dose technique for sedation. Although incidence of pain in arm was more with Ketofol, Fentanyl was associated with high incidence of some adverse effects like nausea and vomiting. Thus it is recommended that Ketofol is a better choice than Fentanyl for sedation in single dose technique during subarachnoid block for Caesarean section.

Keywords: *Fentanyl; Ketofol; Sedation; Subarachnoid anaesthesia.*

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Introduction

Spinal 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 anaesthesia, nausea, vomiting and environment of operating room.[2]

Sedation is a valuable tool to provide general comfort for the patient. But 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]

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] 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.[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 Ketofol, 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 method

This randomized clinical trial included 60 ASA (American Society of Anesthesiologists) grade I patients between age 20-40 years undergoing elective Caesarean sections under subarachnoid anaesthesia during the period January 2022 to June 2022. 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 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). 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. Written informed consent was 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 and 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 either Fentanyl or Ketofol 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 mean arterial pressure (MAP) decreased beyond 20% of baseline. Mean arterial pressure (MAP) was measured continually at 5 min interval and heart rate (HR) and 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 Fentanyl or Ketofol to closure of eye lids OAA/S (Observer's Assessment of Alertness/ Sedation) 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' 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[9]

Category	Observation	Score Level
Responsoveness	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

Fig. 1: Likert Scale for satisfaction[10]

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. 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 KP (Ketofol group) were found to be comparable in respect of age, weight, duration of surgery (time from surgical incision to surgical closure) (Table I). There was no significant difference in Mean arterial pressure between the two groups before Spinal anaesthesia (baseline), after spinal block, before sedative drug administration and after drug administration (Table II). 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). Mean values of SpO_2 remained stable throughout the surgical procedure in both the groups, with no statistically significant aberrations ($p>0.5$).

Time of onset of sedation was significantly less in Ketofol group ($p<0.05$). Duration of sedation i.e time for arousal from sedation was significantly more in Ketofol group ($p<0.05$). Significant percentage of patient was satisfied with Ketofol than Fentanyl (66.66% vs 20%, $p<0.001$) (Table IV).

Incidence of nausea and vomiting was significantly more in Fentanyl group ($p<0.05$). Incidence of pain in arm was significantly more in Ketofol group ($p<0.05$). Other complications were comparable between the two groups (Table V).

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

Variable	Group F (n=30)	Group KP (n=30)	p value
Age (years)	30.46±4.5	30.23±5.3	0.785
Weight (kg)	66.53±9.8	66.51±8.8	0.753
Duration of surgery (min)	48.66±3.6	51.66±4.5	0.683

Values are expressed in mean±SD
SD- Standard deviation

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

Time Interval	Group F (n=30)	Group KP (n=30)	p value
Before Anaesthesia (baseline)	83.1±6.53	79.1±7.54	0.674
After Spinal block	77.5±5.69	76.3±5.47	0.641
Before drug administration	73.6±6.57	73.7±7.41	0.757
After drug administration	72.1±7.28	72.1±8.41	0.779

Values are expressed in mean±SD
SD- Standard deviation

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

Time Interval	Group F (n=30)	Group KP (n=30)	p value
Before Anaesthesia (baseline)	79.6±11.69	79.3±9.69	0.837
After Spinal block	86.5±11.97	86.3±11.17	0.851
Before drug administration	82.6±12.31	81.6±11.71	0.759
After drug administration	86.5±8.08	86.5±10.07	0.581

Values are expressed in mean±SD
SD- Standard deviation

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

Variable	Group F (n=30)	Group KP (n=30)	p value
Time required for onset ofsedation (eye closure) (min)	4.3±0.25	1.49±0.51	<0.05
Arousal time from sedation in min (OAA/S score of 5)	9.3±2.37	25.3±6.37	<0.05
Satisfaction with sedation (good)	6 (20%)	20 (66.66%)	<0.001

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

Variable	Group F (n=30)	Group KP (n=30)	p value
Nausea and Vomiting	14 (46.66%)	5 (16.7%)	<0.05
Chills	3 (10%)	4 (13.33%)	0.858
Restlessness	6 (20%)	4 (13.33%)	0.756
Pain in arm	2 (6.66%)	10 (33.33%)	<0.05

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.[11] 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.[12]

When using sedative medication during regional anaesthesia technique, the anaesthesiologist attempts to titrate the drug to optimize patient comfort while maintaining 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.[13]

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.[14] 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.[12]

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.[15] The combination of Ketamine and Propofol (Ketofol) is theoretically expected to have the advantages of both drugs and to complement each other's disadvantages. Haemodynamic compromise induced by Propofol may be compensated by the sympathomimetic effect of Ketamine. Psychomimetic adverse effects are known to be reduced by concomitant use of Propofol. 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.[16]

Minami et al.[17] 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 (10mcg) and Midazolam (1mg) were added as needed during the procedure. A questionnaire was completed 2 hours after the examination. About 70% patients agreed to undergo a second bronchoscopic examination and only 37.8% of the patients remembered the bronchoscopic examination. No severe complication was reported.[17] In our study, we compared the sedative effect between Fentanyl and Ketofol during Caesarean section which showed more favorable sedative effect with Ketofol. Fentanyl was associated with more adverse effects like nausea and vomiting than Ketofol.

Frolich et al.[18] 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. Neonatal 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.[18] In our study, we compared the sedative effect between Fentanyl and Ketofol after delivery of the baby which showed more favorable sedative effect with Ketofol than Fentanyl. Maternal satisfaction was significantly more with Ketofol. Foetal outcome was not included in our study.

Shin et al.[19] 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.[19] In our study, we compared the adverse effects between Fentanyl and Ketofol while used as sedative during Caesarean section. Incidence of intra operative nausea and vomiting (IONV) was significantly more in Fentanyl group. Patient satisfaction was significantly more with Ketofol. Our study did not include incidence of PONV.

Akcaalan et al.[20] carried out prospectively a double blind randomized study to compare Propofol and Ketofol for sedation in patients who underwent shoulder arthroscopy under anaesthesia with interscalene and suprascapular block. In group 1, Propofol 1mg/kg iv, and in group 2, Ketofol 1mg/kg iv was administered. More patients required esmolol in the Ketofol group compared to Propofol group; 71.4% vs 33%, $p<0.05$. In the absence of esmolol, pulse measurements were statistically significantly higher in the Ketofol group than the Propofol group ($p<0.05$). The mean values of the SpO_2 measurements were significantly lower in the Ketofol group ($p<0.05$). No statistically significant difference was determined in respect of the postoperative modified Aldrete Scores (MAS). They concluded that both agents have different superior properties and can be used for sedation.[20] In our study, haemodynamic parameters and SpO_2 were stable with Ketofol. Postoperative recovery scoring was not included in our study.

Gamal et al.[8] conducted a prospective study on evaluation of Ketofol for deep sedation and analgesia in minor painful operations in 90 ASA class I & II patients with age ranging from 1 month up to 75yrs. They received Ketofol in a dose ranging from 0.5mg to 0.8mg/kg per dose given iv. Incremental doses were given according to the duration of operation, using Ramsay Scale of Sedation (RSS). They concluded that Ketofol was very effective as a sole agent for painful procedure with a low incidence of side effects as emergence phenomena, hypoxia and transient apnoea. Haemodynamic stability was reported. No nausea or vomiting was reported. Supplemental analgesia for increased pain was not required.[8] In our study, paediatric patients were not included. Haemodynamic stability was also reported with Ketofol in our study. Ketofol also had low incidence of side effects.

Ayman et al.[21] conducted a randomized trial to evaluate the use of Ketofol "Ketamine:Propofol mixtures" in two different ratios (1:1 and 1:2) for sedation and analgesia for outpatient transrectal

ultrasound prostate biopsy. No reported cases of hypotension or bradycardia were detected in Ketofol groups, while hypotension occurred in 48.6% and bradycardia occurred in 11.4% in Propofol group. The incidence of hypoxaemia and the need to perform airway support maneuvers were higher in Propofol group. Patients' satisfaction was not different among the groups. No difference was found as regard to postoperative adverse effects or pain on injection to Propofol.[21] In our study, Ketofol contained Ketamine-Propofol in 1:1 ration only. Haemodynamic stability and patient's satisfaction were also good with Ketofol in our study. Incidence of peroperative complications was also less.

Conclusion

The study showed that the time to reach effective sedation was less with Ketofol than Fentanyl and the arousal time i.e. duration of sedation was significantly longer with Ketofol which is beneficial for the patient in single dose technique for sedation. Although incidence of pain in arm was more with Ketofol, Fentanyl was associated with high incidence of some adverse effects like nausea and vomiting. Thus it is recommended that Ketofol is a better choice than Fentanyl for sedation in single dose technique during subarachnoid block for Caesarean section.

Study limitations

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

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Conflict of Interest

There is no conflict of interest.

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