A randomised controlled trial to compare TIVA infusion of mixture of ketamine-propofol (ketofol) and fentanyl-propofol (fentofol) in short orthopaedic surgeries

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Abstract

Background: Propofol does not possesses the analgesic properties but is a safe anaesthetic agent for day care surgeries while ketamine is an excellent analgesic but has concerns regarding recovery. Fentanyl is a short acting potent opioid with pharmacokinetics suitable for day care anaesthesia. There are many short procedures in which you need procedural sedation with good analgesia and calm patient without need of intubation and relaxation. This study was conducted to compare and find suitable sedoanalgesia regime of TIVA using Propofol- Ketamine (Ketofol) or Propofol -Fentanyl (Fentofol) mixture infusion to facilitate comfortable and stable sedation experience with rapid recovery in short orthopaedic surgeries.

Settings and Design: Randomized, Double blind.

Patients and Methods: This prospective, randomized, double-blind study was conducted on 100 adult patients of age 20–55 years of either sex having ASA physical status I-II, posted for short orthopaedic procedures. Patients were assigned to receive slow bolus of fresh premixed injection of either ketofol or fentofol followed by TIVA infusion to a predetermined sedation level using Ramsay sedation scale. Haemodynamics, vital signs, side effects and recovery profiles were recorded.

Results: There was significant decrease ($P<0.001$) in the pulse rate, systolic and diastolic blood pressure in intraoperative and postoperative period in group II (FP, fentanyl group) whereas there was significant rise in pulse rate and systolic and diastolic blood pressure in group I (KP, ketamine group). Respiratory depression was more pronounced in fentofol group. Total dose of propofol consumed was less in ketofol group with less involuntary movements. Mean total sedation time as well as recovery time was significantly prolonged in fentofol group compared to ketofol group. No major adverse effects were observed with ketofol group.

Conclusion: As compared to fentofol, continuous TIVA infusion with ketofol (1:1) provided better sedoanalgesia, stable haemodynamics with favourable recovery profile.

Keywords: Propofol, Fentanyl, Ketamine, Ketofol, mixture infusion, Procedural sedation, PSA, TIVA

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Introduction

Propofol is a non-barbiturate sedative hypnotic. Its lipid solubility confers it a favorable pharmacokinetic profile of quick onset and rapid recovery. Although it has antiemetic, amnestic, anticonvulsant, antipruritic properties and is highly potent and effective anaesthetic, it lacks analgesic properties and its use is limited by high incidence of dose dependent hypotension and respiratory depression.[1]

Ketamine, a phencyclidine derivative, a N-methyl-D-aspartate (NMDA) receptor antagonist and a neuroleptic anaesthetic agent, provides excellent analgesia and amnesia simultaneously preserving muscle tone, airway reflexes and spontaneous respiration. It has some peculiar disadvantages of causing emergent reactions, exessive salivation, emesis and increased sympathomimetic effects.[1] Ketamine in sub-anaesthetic doses (0.3-0.5 mg/kg) has recently gained more attention as an analgesic in day care anesthesia. For induction of general anesthesia: 0.5 to 2 mg /kg body weight i.v. For maintenance of good analgesia: 0.5 to 1 µg/kg iv. For sedoanalgesia: 0.2-0.8 mg/kg i.v.[2]

Fentanyl, a synthetic opioid related to the phenylpiperidine, a potent narcotic analgesic with a rapid onset and short duration of action, is an important constituant of day care anaesthesia. Generally given iv and the dose being 2-4 µg/kg. Supplemental doses are needed every 30 min.[3]

At present no sole anaesthetic agent is having all requisite properties to fulfill an ideal agent for procedural sedation in ambulatory set up. Using propofol with ketamine or fentanyl, in combination, allows sedation to be achieved with lower doses of each drug thereby decreasing adverse effects of individual drugs while improving overall recovery profiles.

Short orthopaedic procedures under TIVA infusion without intubation, using anaesthetic agents having rapid onset and quick recovery characteristics, offers many advantages such as quick completion of long OT list and shortened hospital stay required for ambulatory

day care anaesthesia as there is huge saving of time by avoidance of intubation-extubation sequence and/or performance of blocks and time needed for block to come into effect. The present study was planned to comparatively evaluate the two TIVA infusion regimens ketamine-propofol (ketofol) and fentanyl-propofol (fentofol) for haemodynamic parameters, duration of sedation, recovery characteristics and complications in patients undergoing adults short orthopaedic surgeries.

Material and Methods

This prospective, randomized, double-blind, trial was conducted after getting the approval from the institutional Ethics and scientific Committee of Geetanjali University, Udaipur. 100 Adults patients, aged 20-55 years, of American Society of Anesthesiologist (ASA) physical status I-II, scheduled for short orthopaedic procedures of less than 30 minutes like reduction of fracture dislocation, closed k-wire fixation, tension bend wiring, external fixator application and debridement of wounds were included in this study. Written informed consent was obtained from all the patients before being included in the study.

Exclusion criteria: Known allergy or contraindication to either study drug, allergy to egg, head injury, seizure disorder, psychiatric disorders, hepatic, pulmonary or congenital heart disease, coronary artery disease, severe obesity (body mass index >35 kg/m2), duration of surgery more than 30 minutes, acid reflux and full stomach patients.

Randomization and Blinding: Patients were randomly allocated by a computer-generated random number table. The random numbers were written in the chits and one of the anesthesiologist who was blinded to the groups picked up the chit (chit-in-box technique). Patients were divided in two groups of 50 patients each according to drug combination they received:

1. KP Group – Ketamine group, n=50
2. FP Group – Fentanyl group, n=50

The study was double-blinded with three different anesthesiologists involved. The drugs were prepared by an anaesthesia resident not involved in the study and was blinded to the study groups. The anesthesiologist who pretreated the patients was blinded to each patient's allocation. The study drug solutions were identical in appearance.

In a single 20-mL syringe, a mixture of propofol-ketamine or propofol-fentanyl was prepared using an aseptic technique for delivery via an infusion pump. In case of group I (KP), a ketamine–propofol (Ketofol) solution (1:1) was prepared by mixing 4 mL ketamine (50 mg/ mL) with 20 mL propofol 1% (10 mg/mL). Total 24 ml.

In group II (FP), a fentanyl-propofol (fentofol) solution (1:1), was prepared by mixing 4 ml (50 mcg/ml) of fentanyl mixed with 20 ml 1% propofol (10 mg/ml) mixed in a single syringe. Total 24 ml.

Patients were assigned to receive premixed injection of either ketamine 1.0 mg/kg + propofol 1 mg/kg (Group KP, *n*=50) or fentanyl 1.5 µg/kg + propofol 1.5 mg/kg (Group FP, *n*=50).

Anaesthetic Technique: Standard anaesthetic technique was used in all patients. In the operation theatre, monitors were attached and pulse, NIBP, ECG and SpO2 readings were continuously recorded along with baseline readings recorded. All patients in both groups were premedicated with injections glycopyrrolate 0.2 mg, midazolam 0.03 mg/kg and ondansetron 4mg IV 2 minutes before induction. All patients received IV diclofenac 1.5 mg/kg preoperatively. Supplemental oxygen flow was started to all patients @ 4 L/min, administered by ventimask.

Induction of anaesthesia: Induction of anaesthesia in patients of group I (KP) was given with premixed iv infusion bolus of ketofol (1:1), 1mg/kg body wt. or more until a Ramsay sedation scale (RSS) of 6 was achieved. In patients of group II (FP), induction was done with fentofol, 1.5 µg/kg body wt. or more until a RSS of 6 was achieved. Haemodynamic and other vital parameters were observed continuously and recorded at interval of 1 minute for first 5 minutes. (Ramsay sedation score, 1 = anxiety and completely awake, 2 = completely awake, 3 = awake but drowsy, 4 = asleep but responsive to verbal commands, 5 = asleep but responsive to tactile stimulus, and 6 = asleep and not responsive to any stimulus).

Maintenance of anaesthesia: In both groups, maintenance of anaesthesia was achieved with continuous infusion of ketofol or fentofol at a rate to maintain RSS of 6. In both groups, this was achieved by infusion rate of around 20 ml/hr (3.33mg/kg/hr) or more. Total dose of propofol consumed was also noted. A score of 6 on the RSS was required to begin the procedure and was maintained throughout the procedure. Haemodynamic and other vital parameters and RSS were observed continuously and recorded at interval of every 5 minutes during operation. Muscle relaxant was not used and patients were not intubated. After or just before completion of the surgery, infusion was stopped and patients were transferred to the recovery room and then to the postoperative orthopaedic ward. The incidence of adverse effects like apnea, hypotension, bradycardia, hypoxia, seizures, allergic reaction, vomitings and airway intervention during the procedure and vomitings, emergence phenomena such as agitation and hallucination after the procedure were recorded. Saturation < 90% was considered desaturation. Duration of surgery, awakening time, and recovery time were also recorded. Total sedation time (Awakening time) was defined as the time from the first administration of the drug to the

opening of eyes to verbal commands after surgery. Recovery time was defined as the time taken from stopping the infusion of the study drug to the point when the patient achieved a Modified Aldrete Score of ≥ 8. Time taken to achieve this score was recorded.

Data were analysed using Chi-square test for categorical data. Student's *t*-test for quantitative variables for comparison between the two groups. For intra group comparison, paired *t*-test was used. Results were expressed as mean±SD. Probability value less than 0.05 was considered significant.

Results

Hundred patients were enrolled for the study. Demographic characteristics such as age, sex, weight, and duration of surgery among all the patients were comparable [Table 1].

Mean preoperative pulse rate were comparable in both the groups, group KP 77.11±8.23 and group FP 75.62±6.73. There was increase in pulse rate in KP group from 77.11±8.23 to 84.38±7.96, while there was decrease in FP group from 75.62±6.73 to 66.27±7.21 intragroup from preoperatively to intraoperatively, the difference found highly significant. Mean postoperative pulse rate in KP group was 82.86±8.01 compared to 67.45±7.14 in FP group, the difference found highly significant.

Preoperative systolic blood pressure (SBP) were comparable in both group, KP 131.56±8.37 and group FP 130.66±8.12 (p = 0.58). Intraoperatively, SBP is increased in group KP to 139.10 ±7.98 while it is decreased in group FP to 118.57±7.97, which was found highly significant (p<0.001). SBP in group KP was 136.37±7.44 compared to 121.60±7.58 in group FP postoperatively, the difference found to be highly significant (p<0.001).

Preoperative diastolic blood pressure (DBP) were comparable in both the groups, KP 86.63±6.32 and FP 87.91±4.66 (p = 0.25). DBP was increased to 89.74±6.56 in group KP while it was decreased in group FP to 76.85±5.16 intraoperatively, the difference found to be highly significant (p<0.001). Postoperatively, DBP in group KP was 88.53±6.23 and 78.21±5.22 in group FP, the difference found to be highly significant (p<0.001).

Preoperative respiratory rate (RR) were comparable in both groups, KP 16.67±1.17 and FP 16.84±1.00 (p = 0.43). Intraoperatively, RR is decreased in both the groups, though the decrease is more pronounced in FP group, 16.12±1.02 versus 12.21±1.32, the difference found to be highly significant (p<0.001). Postoperatively, RR in KP group was 16.53±1.19 and 13.54±0.96 in group FP, the difference being highly significant (p<0.001).

SpO2 readings were comparable in both groups preoperatively, 98.95±0.81 in group KP and 98.36±0.91 in group FP. Readings decreased in both groups intraoperatively, to 97.79±1.15 in group KP and 94.65±1.33 in group FP , the difference found to be highly significant (p<0.001). Postoperatively, SpO2 was 98.30±0.84 in KP group while 96.04±0.79 in FP group, the difference found to be highly significant (p<0.001) [Table 2].

Mean total sedation time was significantly prolonged in patients in group FP 30.40±2.55 minutes as compared to groups KP 28.60±2.35 minutes (p<0.001)[Table 3].

There was statistically significant difference between patients in the two groups with respect to recovery time. Mean recovery time was 5.64±1.25 minutes in group KP while in group FP it was 6.38±1.02 minutes. (p< 0.002) [Table 3].

Total dosage of the propofol consumed was more in fentofol (164 mg) group as compared to ketofol group (148 mg). Minor adverse effects were in the form of airway mal-alignments which required simple maneuvering like head extension, jaw thrust and chin lift in both groups, difference being insignificant. None developed laryngospasm or apnea requiring bag-mask ventilation or intubation. One patient in fentofol group had nausea-vomiting. None of the Patient in ketofol group developed emergence reaction or psychomimetic effects. No patient in the two study groups complained of postoperative pain.

Table 1: Demographic Parameters

Parameter	Group I (KP) n=50	Group II (FP) n=50	Statistical Test	*P* value
Age	43.87±14.80	47.25±15.32	1.12	0.26 (NS)
Sex (M:F) ratio	26:24(54%)	28:22(62%)	0.161 (chi)	0.68 (NS)
Weight	52.43±5.32	54.32±5.94	1.68	0.09 (NS)
Duration of surgery	25.68±4.26	27.11±3.92	1.74	0.08 (NS)

Data are expressed as mean ± SD

Table 2: Perioperative hemodynamics and vital parameters in both the groups

Parameter	KP		FP			
Pulse	**Mean**	**SD**	**Mean**	**SD**	**T value**	**P value**
Pre-operative	77.11	8.23	75.62	6.73	0.99	0.324
Intra-operative	84.38	7.96**	66.27	7.21**	11.92	0.000
Post-operative	82.86	8.01**	67.45	7.14**	10.15	0.000
SBP						
Pre-operative	131.56	8.37	130.66	8.12	0.55	0.586
Intra-operative	139.10	7.98**	118.57	7.97**	12.87	0.000
Post-operative	136.37	7.44**	121.60	7.58**	9.83	0.000
DBP						
Pre-operative	86.63	6.32	87.91	4.66	1.15	0.252
Intra-operative	89.74	6.56*	76.85	5.16**	10.92	0.000
Post-operative	88.53	6.23	78.21	5.22**	8.98	0.000
Respiratory rate						
Pre-operative	16.67	1.17	16.84	1.00	0.78	0.437
Intra-operative	16.12	1.02*	12.21	1.32**	16.57	0.000
Post-operative	16.53	1.19	13.54	0.96**	13.83	0.000
SpO2						
Pre-operative	98.95	0.81	98.36	0.91	3.42	0.001
Intra-operative	97.79	1.15**	94.65	1.33**	12.63	0.000
Post-operative	98.30	0.84**	96.04	0.79**	13.86	0.000

Table 3: Propofol consumption and recovery profile

Analysis	Group I (KP)(n=50)	Group II (FP) (n=50)	T value	P value
Recovery time (min.)	5.64±1.25	6.38±1.02	3.24	0.002 (S)
Total sedation time (min.)	28.60±2.35	30.40±2.55	3.67	<0.001 (HS)
Mean propofol doses (mg)	148	164	-	-

Data expressed as mean±SD.

Discussion

The ability to rapidly titrate intense but short periods of sedoanalgesia is a key. TIVA in short orthopaedic surgeries has many advantages. Many orthopaedic cases can be comfortably managed with TIVA using propofol based infusion protocols without need for intubation anaesthesia. Infusion based TIVA protocols gives the ability to rapidly change and maintain smooth and uniform depth of anesthesia according to the level of surgical stimulation throughout the procedure.

Propofol lack analgesic properties and if used alone for anaesthesia, the dose required will be large enough to cause cardiorespiratory compromise, this necessitates concurrent administration of intravenous opioids and paracetamol/NSAIDS as apart of multimodal balanced analgesia. Fentanyl is a commonly used opioid that provide rapid onset, short duration potent analgesia, useful during anesthetic induction. Using ketamine and propofol in combination allows sedation to be achieved at lower total doses of each drug.[3]

To our knowledge, fentofol with the ketofol, in the

same syringe has never been compared directly for non-intubation TIVA infusion in short orthopaedic surgeries in adults. Administering ketamine and propofol mixed in the same syringe (ketofol) has been shown to be efficacious in the operating room & in ambulatory settings. Ketamine and propofol have been shown to be pharmaceutically compatible when mixed together in the same syringe.[4] Several authors have used ketamine–propofol combinations in various ratios (2:1,1:1 to 1:5).[3,4,5,6,7] The combination of fentanyl and propofol has been efficiently used in separate syringes,[5,8,9] as well as mixed in the same syringe,[4,10] in a variety of settings.

In our study, continuous infusion was used to maintain a steady state level of sedation. The sedative infusion rate was varied to maintain a deep level of sedation (RSS score 6). This simple and easy to use scoring is used due to nonavailability of sophisticated monitors like bispectral index and electroencephalography. Premedication with antisialogogue glycopyrrolate, antianxiety midazolam and antiemetic ondansetron were used as we want to compare the test solutions in practical settings in which these drugs are used in day to day practice to bring out merits and demerits.

In our study, ketamine and propofol in a ratio of 1:1 provided haemodynamic stability and is supported by the studies of Feky and koptan and Tosun et al. who compared the addition of propofol and ketamine with propofol and fentanyl in pediatric patients who underwent upper gastrointestinal endoscopy, they concluded that the PK combination resulted in stable hemodynamics.[11,12] Goyal et al also concluded that ketamine as premedicant was better than fentanyl with respect to hemodynamic stability and caused less adverse effects intra and postoperatively.[13] Nalini et al reported that none of the patients in PK group recorded any significant change in BP or heart rate.[9]

There was pronounced bradycardia and hypotension in fentanyl-propofol group. Our observations are supported by Khutia et al, who compared the infusion of both propofol-ketamine with propofol-fentanyl in pediatric patients undergoing emergency short surgical procedures and found that HR and MAP were significantly decreased in the fentanyl group.[6] Mayer et al also found that propofol-fentanyl group showed extreme bradycardia to 40 bpm and hypotension. Propofol produces a reduction in both cardiac index (CI) and mean arterial pressure (MAP). Fentanyl intensified the fall in MAP after propofol.[14] Nalini et al in their trial on patients undergoing puerperal sterilization also reported that patients receiving propofol-fentanyl recorded fall in heart rate and blood pressure during anaesthesia.[9] Bajwa et al observed significantly greater fall in pulse rate and in both systolic and diastolic blood pressures in fentanyl-propofol group while ketamine-propofol group produced stable haemodynamics.[8]

There was higher incidences of respiratory depression in fentanyl group as compared to ketamine group. There were no cases of oxygen desaturation in the present study. Our findings were supported by Goyal & singh study where incidence of apnoea was significantly high in patients who received fentanyl as premedicant.[13] Bajwa et al found slight respiratory depression in patients who received propofol-fentanyl as compared to those who received propofol-ketamine.[8] This was due to central depressant effect of fentanyl. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics may last longer than the analgesic effect. The respiratory depressant properties of fentanyl appear to be due to a central effect by decreasing the sensitivity of the respiratory centre to carbon dioxide. As the dose of the narcotic is increased, the decrease in pulmonary exchange becomes greater. Larger doses may produce apnoea. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection. Fentanyl frequently slows the respiratory rate, but this effect is seldom noted for longer than 30 minutes regardless of the dose administered.[15]

Respiratory depression was not found in patients of ketofol group in our study. Our observations are supported by study of Nalini et al who reported that none of the patients who received ketamine-propofol had any episodes of oxygen desaturation, airway obstruction or apnoea, in contrast to patients who received fentayl-propofol, significant number had oxygen desaturation caused by airway obstruction.[9] Bajwa et al reported better ventilation scores in patients who received ketamine -propofol during recovery postoperatively as compared to fentanyl-propofol group.[8] The addition of low dose ketamine to propofol improves ventilation and reduces the risk of respiratory depression. This may be due to effect of ketamine-induced sympathoadrenal activation.[6]

Kurdi and deva compared ketofol in two doses with fentofol and concluded that ketofol provides better sedation level compared to the propofol-fentanyl. Ketofol (1:1) had better postoperative analgesia than the ketofol (1:2) and fentofol groups. Both ketofol ratios (1:1 and 1:2) were similar in terms of providing hemodynamic and respiratory stability and producing adverse effects.[5]

Andolfatto et al suggest that ketamine may provide patients with an increased sedation consistency or sedation depth; without ketamine providers will probably have to rely solely on intermittent doses of propofol in response to patient agitation.[16] Overall quality of sedation was found to be better with ketofol. Kurdi et al also reported that patients in both ketofol groups (1:1 & 1:2) maintained a higher RSS compared to fentanyl-propofol group intra-operatively.[5] Similar results have been reported by Nejati et al. and Tosun et al. who showed that the propofol-ketamine combination

was superior to the propofol-fentanyl combination in view of more restlessness in patients given propofol-fentanyl.[12,17]

In the present study, the mean total sedation time was significantly prolonged in the fentofol group. Similar results were found by kurdi et al in their study. Nalini et al in their study on females undergoing puerperal sterilization found that patients of propofol-fentanyl group were more sedated at 2nd and 4th hours postoperatively as compared to propofol-ketamine and suggested that sedative effects of propofol may be partially antagonized by the arousal effects of ketamine.[9] In fact, ketamine in sedative doses, is associated with EEG activation and it increases arousal.[7]

The psychotomimetic responses (emergence delirium, unpleasant dreams, and hallucinations) to ketamine, often referred to as "emergence reactions," are well known sequelae of ketamine anesthesia. The incidence ranges from 5% to 30% which is mostly dose related.[18] Larger dosages of ketamine, $24 \pm 8\ \mu g \cdot kg^{-1} \cdot min^{-1}$, were associated with a clinically significant increase in postoperative nausea and vomiting (PONV) and psychotomimetic side effects.[19] Hence, there is an ever-increasing quest to overcome these adverse effects with appropriate medication.[18] To prevent ketamine-induced emergence reactions, pretreatment with benzodiazepines is commonly used. Likewise, the incidence of psychotomimetic responses was small when ketamine was combined with propofol for general anesthesia or sedation.[19] Emergence reaction or psychomimetic effects and vomitings, the two significant adverse effects in previous studies done with either higher ketamine ratio solutions[10,19] or non-usage of premedications in their studies[20] , was not seen in our study as we used ketamine with propofol with midazolam premedication. Increased oral secretions was main side effect of Bajwa et al.[8] There was no complication like emergence reaction, agitation, increased oral secretions in our study and only one patient in fentanyl group had nausea-vomiting. It seems use of routine premedication in our study helped us in prevention of these adverse effects. We used individual agents to address all parameters of balanced anaesthesia technique and drugs to counter possible adverse effects of constituents of sedation solutions. Midazolam premedication to took care of anxiety, agitation and emergence reaction. Glycopyrrolate controlled excessive bradycardia and salivation preventing laryngospasm and apnea while ondansetron premedication mitigated incidence of nausea and vomiting in our study. All patients were satisfied with their anaesthesia experience. Orthopaedicians found their experience and working conditions convenient and excellent and they even demanded it for other short procedures that we usually used to do under regional anaesthesia.

General anaesthesia remains the most popular technique for many day care procedures and TIVA using balanced anaesthesia using agents having rapid induction and rapid recovery finds important place in short day care procedures. We found early recovery in both TIVA combinations practically. Infusion rate was more important criteria to keep balance between smooth conduction of anaesthesia with least patient movements intraoperatively and quick recovery postoperatively. Tapering of infusion rate towards the end of procedure and stopping the infusion once skin suturing started helped us to achieve quick recovery.

None of our patient complained of any pain postoperatively, this might be because we have included intravenous diclofenac in premedication as pre-emptive analgesic.

Conclusion

Continuous TIVA infusions of fentofol and ketofol provided remarkably comparable deep sedoanalgesia for short orthopaedic surgeries in adults. Respiratory depression, hypotension and bradycardia were the major side effects while marginal but significantly prolonged emergence and delayed recovery was associated with Fentofol group. Fentofol group had mean decrease in repiratory rate of 4.63 breaths per minute (27.49%) with mean 3.77% drop in SpO2 levels despite supplemental oxygenation intraoperatively. Ketofol produced a statistically and clinically significant increase in mean heart rate of approximately 7 beats per minute. Ketofol has advantage of stable hemodynamics, smooth pain free intraoperative as well as postoperative period with no appreciable side effects and favourable recovery profile. Recovery profile of both group is comparable with marginal better scores with ketofol group. So it may be recommended that though both ketofol and fentofol with routine premedication can be used as combination in TIVA infusion for elective day care adult orthopaedic surgeries, ketofol is safer and more efficacious.

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