

A Comparative Evaluation of Induction Characteristics of Propofol with Fentanyl and Ketamine as Total Intravenous Anaesthesia

Roseline Zohra Ali¹, Sanjeev Kumar Agrawal², Priyadershini Rangari³

¹MD(Anaesthesiology), Associate Professor, Department of Anaesthesiology, Sri Shankaracharya Medical College, Bhilai, Durg, Chhattisgarh, ²MD(Anaesthesiology), Assistant Professor, Department of Anaesthesiology, Sri Shankaracharya Medical College, Bhilai, Durg, Chhattisgarh, ³ Assistant Professor, Department of Dentistry, Sri Shankaracharya Medical College, Bhilai, Durg, Chhattisgarh.

Abstract

Background: Total intravenous anaesthesia has gained popularity, partly in order to reduce pollution by volatile agents. Propofol has proven to be suitable as a hypnotic for TIVA. The drug has fast onset of action and rapid metabolism without accumulation. **Objectives:** To compare propofol in combination with ketamine and fentanyl in TIVA technique in a population of Chhattisgarh region. **Subjects and Methods:** Patients of group-I were induced with ketamine and propofol. Patients of group-II were induced with fentanyl and propofol. Parameters like Induction time, induction dose and total dose of propofol, top up doses of ketamine and fentanyl were observed and recorded. Continuous monitoring of pulse rate, arterial blood pressure, respiratory rate and arterial oxygen saturation was done throughout peri-operative period and readings were recorded at different time interval. **Results:** Propofol and ketamine combination took less time. The induction dose and total dose of propofol was less in propofol ketamine as compared to in propofol fentanyl group. Number of top-ups of ketamine were less than the number of top ups of fentanyl. Stability of pulse and blood pressure with propofol ketamine combination were comparable and better. In propofol ketamine group respiratory rate was well maintained within normal range. Maintenance of arterial oxygen saturation was good with both the groups. Propofol ketamine combination took longer time for recovery from anaesthesia in comparison with propofol fentanyl combination. **Conclusion:** So to conclude, combination of propofol and ketamine gives better haemodynamic stability during induction and maintenance of total intravenous anaesthesia. Sub anesthetic doses of ketamine may be an alternative, cheaper analgesic to supplement propofol anaesthesia, instead of short acting potent expensive opioids like fentanyl.

Keywords: Anesthesia, Fentanyl, Ketamine, Propofol, Total Intravenous Anaesthesia (TIVA).

Corresponding Author: Dr. Sanjeev Kumar Agrawal, MD (Anaesthesiology), Assistant Professor, Department of Anaesthesiology, Sri Shankaracharya Medical College, Bhilai, Durg, Chhattisgarh.

Received: December 2019

Accepted: December 2019

Introduction

The world is changing at an ever increasing speed. Before the advent of anaesthesia till 1846, surgery was done only as an emergency and was a dreadful experience for the patient during surgery, sometimes attenuation of surgical pain was accomplished with alcohol, hashish, opium derivatives or with physical methods like packing limb in ice, making limb ischemic with tourniquet, making patient unconscious by blow to the head and by strangulation.^[1]

After successful demonstration of ether anaesthesia in 1846 by W.T.G. Morton, inhalation anaesthesia becomes popular. But due to delayed onset and recovery, nausea, vomiting, sensation of smothering and drowning due to face mask and inability to put mask in patients with facial injury or deformity, there was need for alternative technique to induce anaesthesia.^[2]

History of intravenous anaesthesia begins in 15th and 16th century, when anatomist Leonardo & coworkers speculated on the functional significance of the heart and blood vessels.^[3]

The concept of intravenous anaesthesia is attractive both for the patient as well as for the anesthetist. For patient, it had the advantage of producing rapid loss of consciousness without excitement, distress or sensation of smothering after produced by tightly pressed facemask. The use of intravenous agents for total Intravenous anaesthesia (TIVA) began with introduction of rapidly acting barbiturates in 1934.^[4] One of the more important studies in the development of TIVA was that reported by Savage and colleagues in 1975 using the steroid althesin and pethidine to supplement oxygen enriched air in the spontaneously breathing patient. Subsequent developments included the uses of the carboxylated imidazoline and etomidate, Diazepam, Midazolam, fentanyl and infusion of ketamine. Disadvantages of cumulative effects of these intravenous agents resulting in long recovery times, more chances of post operative nausea and vomiting and post operative sedation hampered their use in TIVA. Now presently propofol the most recent non barbiturate intravenous anaesthetic is introduced in clinical practice by Kay and Rolly in 1977.^[5] TIVA is a natural extension of balanced anaesthesia. TIVA is

a technique in which induction and maintenance of anaesthetic state is achieved with intravenous drugs alone, avoiding both volatile agents and nitrous oxide. In this process the patient either breaths spontaneously or is artificially ventilated with an air/ oxygen mixture.^[6] Newer intravenous drugs now allow reliable anaesthesia to be produced entirely with intravenous anaesthesia and rapid recovery to occur even after long infusion. TIVA has developed into an acceptable and satisfactory technique which offers many advantages like, high concentrations of oxygen can be administered, usefulness in difficult situations, provides speedy and complete recovery, there is avoidance of deleterious effects of volatile anaesthetics, minimal cardiovascular depression, a lesser neuro-humeral response to surgery, decreased incidence of post-operative nausea & vomiting, no increase in oxygen consumption, no adverse effects on hypoxic pulmonary vasoconstriction reflex the lack of trigger effects for Malignant Hypothermia, reduction in theater pollution and no adverse effects on anaesthetist.^[7,8]

There are also some difficulties and limitations of TIVA, because of the disadvantages felt with the conventionally suggested methods of administrations of the drugs used for TIV A, have been suggested to attain drug concentration in the blood quickly at the site of action in the CNS and maintain the desired effect site concentration. However, these methods need appropriate and sophisticated infusion pumps. There is unpredictable dose response relationship due to varied patients' response, use of premedication and bolus dosing. There is unpredictable recovery from anaesthesia and post anaesthetic side effects due to varied distribution and elimination kinetics of the drugs and because of gender and other non physiological factors. Other disadvantages are cumulative properties of TIVA drugs that prolong the recovery time, drug interactions, possibility of awareness and ability to control depth of anaesthesia, requirement of a separate and dedicated i/v line. Propofol is the hypnotic most suitable for intravenous infusion in TIVA, because it has a short elimination half life and high clearance.^[9] Propofol rapid onset of effect and recovery time compares favorably with those of the barbiturates and Etomidate, the elimination rate of Propofol is slightly smaller than those of thiopental and Etomidate and thus the onset of effect is slower. The metabolic clearance rate for propofol exceeds hepatic blood flow, a most important difference from thiopental. In contrast to barbiturates, propofol causes less residual post operative sedation and psychomotor impairment. The incidence of post operative side effects i.e. nausea and vomiting are low. Opioid analgesics are essential for the suppression of reflex responses to noxious anaesthetic and surgical stimuli during TIV A. Fentanyl is synthetic opioid, its analgesic potency is 100 times greater than that of morphine but duration of action is short.^[8-10] In clinical doses it has little effect on cardiovascular system. There is often respiratory depression and it is often dose related. In procedures in which marked stimulation is produced, the inclusion of Fentanyl as a component of TIV A not only provides analgesia but also permits reductions in the required doses of other agents and contributes significantly to hemodynamic stability. As propofol has very little nociceptive effect, it is generally combined with an analgesic, the popular combination being

either propofol with fentanyl or propofol with fentanyl. Ketamine in subanaesthetic doses with propofol have gained attention in TIVA technique because of its powerful analgesic action in a small dose without causing myocardial and respiratory depression. Ketamine also causes some degree of sympathetic stimulation, which tends to counterbalance, the cardiovascular effects of propofol. One of the main drawbacks with ketamine anaesthesia has been emergence delirium, which propofol seems to be effective in eliminating.^[1,11] Fentanyl non availability, it is less economic and its congener's muscular rigidity encouraged ketamine to replace fentanyl as an analgesic for TIV A. So it was thought, worthwhile to compare propofol in combination with ketamine and fentanyl in TIV A technique in a population of Chhattisgarh region.

Subjects and Methods

This study was carried out in the various surgical wards of Sri Shankaracharya Medical College and hospital, Bilai, Durg, Chhattisgarh, over 60 young adult patients of either sex in the period of six months march 2019 to September 2019.

Selection of cases: The patients selected for study were those kept for surgery by various surgical departments like general surgery, gynecology and orthopaedics. These patients belonged to ASA grade I and II, of either sex, between the age groups of 20-60 years.

Careful clinical history and physical examination was done to exclude any cardiovascular and respiratory disease and their age, sex, weight, baseline haemodynamic and respiratory variables were recorded. The patients suffering from any psychiatric illness and hypertension were excluded from the study. These patients were subjected to various routine investigations for that age group viz haemogram, blood sugar, blood urea, serum creatinine, one for routine and microscopic examination, ECG and chest X-ray. The procedure and possible risks were explained to the patients as a part of an informed written consent for anaesthesia and surgery. Patients were kept fasting 8 hours prior to surgery. These patients were allocated randomly into two groups as follows:

- **Group-I:** Patients were induced with propofol and ketamine.
 - **Group-II:** Patients were induced with propofol and fentanyl.
- Trade name of drugs used:
- Propofol 1% (Claris Lifesciences limited)
 - Trofentanyl (Troikaa Parenterals Pvt. Limited)
 - Ketamine (Neon Laboratories Limited)

Premedication: All patients were premedicated with:

- Injection glycopyrolate slow intravenous in the dose of 0.2mg, 5 minutes prior to surgery.
- Injection medazolam slow intravenous in the dose of 2.0mg, followed by injection glycopyrolate.

Each patient was reviewed thoroughly before conduct of anaesthesia. Patients were placed in supine position and an intravenous line was established with 18 gauge i.v. canula 5 % dextrose. Necessary monitoring gazettes were connected to the patients, via pulse oximeter (ohmada) and non invasive blood pressure instrument pulse rate, arterial blood pressure,

respiratory rate and arterial oxygen saturation were recorded. Now patients of both groups were premedicated as mentioned earlier.

Group-I

Patients of group-I were induced with ketamine 0.5mg/Kg body weight over a period of 15 seconds followed by propofol 3mg/Kg body weight bolus till the end point of induction was reached (i.e. loss of consciousness and loss of eyelash reflex). Infusion of propofol at a rate of 3mg/minute was started immediately with infusion pump. When patient responds to pain, sweating, lacrimation, limb movements, a bolus of one fifth the original dose of ketamine was given. Airway maintained with head and neck positioning and spontaneous breathing was maintained with air. If oxygen saturation fell below 97% then 100% oxygen was given by mask, while patient breathing spontaneously.

Group-II

Patients of group-II were induced with fentanyl 1 µg/Kg body weight over a period of 15 seconds followed by propofol 3mg/Kg body weight bolus till the end point of induction was reached (i.e. loss of consciousness and loss of eyelash reflex). Infusion of propofol at a rate of 3mg/minute was started immediately with infusion pump. When patients responds to pain, viz increased heart rate, increased respiratory rate, sweating, lacrimation, limb movements a bolus of one fifth of original dose of fentanyl was given. Airway maintained with head and neck positioning and spontaneous breathing was maintained with air. If oxygen saturation fell below 97% then 100% oxygen was given by mask while patient breathing spontaneously.

The following parameters were observed and recorded.

- Induction time.
- Induction dose and total dose of propofol.
- Top up doses of ketamine and fentanyl.

Continuous monitoring of pulse rate, arterial blood pressure, respiratory rate and arterial oxygen saturation was done throughout peri-operative period and readings were recorded at following time interval.

- Before induction
- One minute after induction
- Five minutes after induction
- Ten minutes after induction
- Twenty minutes after induction
- Immediate post-operative period.

Recovery time: The time at which each patient was able to open the eyes, responds to verbal commands and able to tell his or her name after the withdrawal of propofol infusion.

Post operatively patients were enquired about acceptance. Patients were asked if they had slept well and asked about their experience pleasant or unpleasant during the recovery period. Post operative pain relief in immediate post-operative period judged by requirement of analgesic in immediate post operative period. Side effects or complications.

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation (student's 't'

test), and chi-square test by SPSS Version 21.

Results

[Table-1] shows that minimum number of patients 33 (55%) belong to 20-29 years of age group. Out of 60 patients 37 (67.67%) were male and 23 (38.33%) were female.

Table 1: Distribution of patients according to Age and Sex

Age in Years	No. of patients							
	Group-I			Group-II				
	Male	Female	Total	Male	Female	Total		
20-29	18	6	24	3	6	9	33	55
30-39	2	1	3	10	8	18	21	35
40-49	-	-	-	2	1	3	3	5
50-59	2	1	3	-	-	-	3	5
Total	22	8	30	15	15	30	60	100

[Table-2] shows that maximum number of patients 29(48.33%) were weighing between 51-60Kg in both the groups.

Table 2: Distribution of patients according to Age and Sex

Weight (kg)	No. of patients			
	Group-I	Group-II	Total	%
41-50	10	12	22	36.66
51-60	15	14	29	48.33
61-70	5	4	9	15.00
70<	-	-	-	-
Total	30	30	60	100

[Table-3] shows that maximum number of cases had undergone for orthopaedic surgery i.e. group-I 18 (60%) and group-II 14 (46.6%). All the surgical procedures were of about same duration.

Table 3: Distribution of patients according to nature of surgery

Nature of Surgery	No. of patients	
	Group-I	Group-II
Orthopedic surgery		
Open reduction and internal fixation	6	4
Amputation	2	2
Sequestrectomy	4	3
Curettage	4	3
k- nail removal	2	2
General surgery	-	-
Skin grafting	5	5
Gynaecological surgery	-	-
MTP and ligation	7	11
Total	30	30

[Table-4] shows that time for onset of induction in group-I (propofol-ketamine) 43.8±5.90 as compared to in group- II (propofol-fentanyl), 0.5±6.76. Difference between group-I and group-II was statistically highly significant (p<0.001). Induction dose of propofol in group-I was 142.0±12.70 and group-II was 155.0±18.89. Total dose of propofol in group-I was 223± 1 0.20 and group II was 236.0±12.22. And number of top up doses of ketamine in group-I was 2.20±1.4 and fentanyl in group II was 3.50±1.8. The mean induction dose of propofol and total dose of propofol were less in group 1 as compared to group - II. The difference between both the group was statistically significant (p<0.05).

Table 4: time for onset of induction, Total and induction dose of propofol and number of top up doses of ketamine and fentanyl

(mean \pm SD)	Group-I	Group-II
Time (seconds)	43.8 \pm 5.90	50.5 \pm 6.76
Induction dose of propofol (mg)	142.0 \pm 12.70	155.0 \pm 18.89
Total dose of propofol (mg)	223.0 \pm 10.20	236.0 \pm 12.22
Number of top ups of ketamine and fentanyl	2.20 \pm 1.4	3.50 \pm 1.8

Table 5: changes in mean pulse rate (mean \pm SD)

Time interval	Group-I	Group-II
Pre induction	92.20 \pm 9.85	92.00 \pm 8.33
1 min after induction	90.20 \pm 8.05	79.4 \pm 7.50
5 min after induction	88.0 \pm 8.38	87.4 \pm 7.50
10 min after induction	87.2 \pm 8.29	86.8 \pm 7.51
20 min after induction	87.8 \pm 7.41	89.00 \pm 7.46
Post operative	87.6 \pm 7.54	88.80 \pm 8.87

Table 6: Recovery time and pain relief (n%)

	Group-I	Group-II
Time (min) (mean \pm SD)	5.0 \pm 1.57	3.6 \pm 1.99
Analgesic requirement	1(1.66)	4(6.66)

Table 7: Complications

Complications	Group-I		Group-II	
	N	%	N	%
Pain on injection	-	-	9	15
Laryngospasm	-	-	-	-
Episodes of desaturation	-	-	1	1.66
Apnea	-	-	1	1.66
Nausea and vomiting	-	-	4	6.66
Abnormal limb movement	1	1.66	-	-
Dreams	1	1.66	-	-

Discussion

The concept of intravenous anaesthesia is attractive both for the patient as well as for the anesthetist. For patient it had the advantage of producing loss of consciousness without excitement, distress or sensation of smothering after produced by tightly pressed face mask. For the anesthetist there is advantage of predictable anaesthesia which is rapid in onset without coughing or movement. Also, the incidence of postoperative side effects i.e. nausea and vomiting are low. Propofol has no analgesic effect and is administered therefore in combination with a potent analgesic.

Ketamine in substance esthetic doses with propofol has gained attention in TIV A technique because of its powerful analgesic action in small doses without causing myocardial and respiratory depression. So it was though worthwhile to compare propofol in combination with ketamine from the popular combination i.e. propofol with fentanyl.

The analysis of data obtained from observation made on 60 patients of ASA grade I and II undergoing surgery under general anaesthesia, induced with either propofol and ketamine (group-I) or propofol and fentanyl (group-II) depicted that maximum number of patients (55%) belong to age group of 20-29 years and maximum number of patients (48.33%) were weighing between 51-60Kg. Out of 60 patients 37(61.67%) were male and 23(38.33%) were female though age and sex has no correlation with the selection of inducing agents.

In the present study, it was observed that induction of anaesthesia was faster with propofol and ketamine than the propofol and fentanyl. Mean induction time was 43.8 \pm 5. 90

seconds in group-I while it was 50.5 \pm 6.76 in group II, this could have been because when propofol and ketamine were used in combination, are additive as hypnotic and anaesthetic end points and also because of onset of action is faster with ketamine than the fentanyl.

Propofol exert its action through GABA receptors. The doses used for induction was fixed accordingly to body weight to reach the induction criteria i.e. loss of consciousness and loss of eyelid reflex; propofol in the dose of 3 mg/Kg body weight ketamine in the dose of 0.5mg/Kg body weight and fentanyl in the dose of 1.0 μ g/Kg body weight. The infusion rate of propofol for the maintenance of anaesthesia was 3mg/minute. The induction dose of propofol was less in group-I, 142.0 \pm 12.70 as compared to group-II, 155.0 \pm 18.89. Total dose of propofol was also less in group-I, 223.0 \pm 10.20 as compared to group-II, 236.0 \pm 12.22. Number of top ups of ketamine in group-I was less than the number of top-ups of fentanyl in group-II. This could have been because when propofol and ketamine were used in combination, additive at hypnotic and anaesthetic end points.

The doses were almost similar and findings are in agreement with the work of Guit JBM et al (1990),^[2] Robert k Stirling (1999)^[7], Sicignano A et al (1990)^[10], HamdanGA et al (1999)^[3] used ketamine in a dose of 0.3mg/Kg and was thought to be inadequate to provide sufficient analgesia for the surgical stimulus. They used propofol in dose of 2mg/Kg body weight and fentanyl 1.0 μ g/Kg body weight. SahaK. et al (2001)^[8] use ketamine in the dose of 0.5mg/Kg body weight and fentanyl in the dose of 1. 5 μ g/Kg body weight and found that dose of propofol for induction of an aesthesia with ketamine was less as compared with fentanyl.

Following administration of propofol and fentanyl i.e. group-II there was highly significant fall (p<0.001) in mean pulse rate at 1 minute, 5 minutes and 10 minutes after induction from pre-induction value as compared to in group-I where there is no significant fall in mean pulse rate after induction. This may be because ketamine causes some degree of sympathetic stimulation, which tends to counter balance the cardiovascular effects of propofol.

The findings are in agreement with the studies of Schuttler J et al (1991),^[9] Mayer M et al (1990)^[6] and Hernandez C et al (1999)^[4], Saha et al^[8], found reduction in pulse rate after 5 and 10 minutes after induction with propofol and fentanyl.

Fall in systolic blood pressure was highly significant in group-II at 1,5 and 10 minutes after induction from premedication value as compared to in group-I where there was no significant change after induction.

In group-I there was no significant change in diastolic blood pressure as compared to in group-II as there was highly significant fall (p<0.001) at 1 and 5 minutes and fall was significant (p<0.05) at 10 minutes after induction from pre-induction value.

In group-I there was no significant change in mean arterial pressure after induction as compared to in group-II where there was highly significant fall (p<0.001) at 1 and 5 minutes and fall was significant (p<0.05) at 10 minutes after induction from pre-induction value. These findings are consistent with the work of Schuttler J et al (1991),^[9] Mayer M et al (1990)^[6] and Hernandez C et al (1999).^[4]

The intra-operative haemodynamic variables were found to be reasonably stable in group-I, this may be because of the

counter balancing the cardiovascular effects of propofol by ketamine, which causes some degree of sympathetic stimulation. Patients in group-II showed a significant fall in haemodynamic variable which could be because of the additive cardio depressant effects of propofol and fentanyl.

In group-I there was no significant change in respiratory rate after induction while in group-II there was significant fall in respiratory rate at 1 minute after induction from pre-induction value. This fall may be because of respiratory depression produced by fentanyl. The findings are in agreement with Mayer Me et al (1990)^[6] and Hernandez C et al (1999)^[4] and Sternlo JB et al (1998)^[11] found respiratory depression after total intravenous anaesthesia with propofol and alfentanil.

Arterial oxygen saturation readings in both the groups had not shown any significant changes after induction from pre induction values.

In present study, the recovery time i.e. patients fully conscious and oriented to time, place and person in group I (5.0±1.57) was longer than in group-II (3.6±1.99) and the difference was statistically significant. The prolonged recovery time in group-I could be because of longer elimination half life of ketamine as compared to fentanyl Janstrup M et al (1990),^[5] Hamdan GA et al (1999),³ Sahai K et al (2001)⁸ have the same opinion about the recovery time i.e. prolonged with propofol and ketamine combination than the propofol and fentanyl combination.

Post-operatively, analgesic for post-operative pain relief was required by 1 patient (1.66%) in group-I and by 4 patients (6.66%) in group-II. This may be because in fentanyl group analgesia was still inadequate as compared to ketamine group. The findings are in consistent with the work of Mayer Met al (1990).^[6]

In present study pain on injection was experienced by 9 patients (15%) in group-II during propofol injection as compared to none in group-I. In group-II pain on propofol injection may be due to alkaline nature of solution and more frequent when small veins are used for induction. In group-I no pain on propofol injection may be due to the local anaesthetic action of ketamine when administered intravenously as well as the central analgesic effect. This was in agreement with the findings of Tan CH et al (1998).^[12]

In present study episodes of desaturation occur in 1 patient (1.66%) in group-II as compared to none in group I. Fentanyl causes alteration in arterial oxygen saturation as observed by Tan CH et al (1998).^[12]

Apnoea had occurred in 1 patient (1.66%) in group-I as compared to none in group-II. This may be due to respiratory depressant action of fentanyl, this findings is consistent with the Adams AP, Pious DA (1978)^[1]. Nausea and vomiting was found in 4 patients (6.66%) in group-I and none in group-II. As propofol possesses significant antiemetic activity the presence of nausea and vomiting in group-II may be due to fentanyl at analgesic doses by stimulating chemoreceptor trigger zone. This is also comparable with the vomiting observed with the work of Tan CH et al (1998).^[12]

Dreams and emergence delirium was found in 1 patient (1.66%) in group-I as compared to none in group II. Therefore in the present study propofol also seems to be effective in eliminating the adverse emergency reaction of ketamine in sub anaesthetic doses. This finding is consistent with the work of Guit JBM et al (1990)^[2] that propofol has proved to

eliminate this adverse emergency reaction associated with ketamine.

Acceptance of induction phase was good in 15 patient (28.33%), satisfactory in 12 patients (20%) and 1 patient (1.66%) complained about bad experience and 2 patient (3.33%) could not say in group-II. This comparison of acceptance is entirely subjective.

In group-I acceptance of anaesthesia was good in 17 patient (28.33%) satisfactory in 10 patient (16.66%) and bad in 1 patient (1.66%) and 2 patient (3.33%) could not tell. Compared to patients of group I, patients of group-II remains sedated for prolonged period after surgery although they are arousable.

Thus it appears that combination of propofol and ketamine in total intravenous anaesthesia gives better haemodynamic stability during induction and maintenance of general anaesthesia, when compared with the use of propofol and fentanyl in combination, superior analgesia with less respiratory depression. However one of the main drawbacks with ketamine anaesthetic has been the emergence reaction, in the present study propofol also seems to be effective in eliminating the adverse emergence reaction of ketamine in sub anaesthetic doses.

Conclusion

So to conclude, combination of propofol and ketamine gives better haemodynamic stability during induction and maintenance of total intravenous anaesthesia. Sub anaesthetic doses of ketamine may be an alternative, cheaper analgesic to supplement propofol anaesthesia, instead of short acting potent expensive opioids like fentanyl.

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How to cite this article: Ali RZ, Agrawal SK, Rangari P. A Comparative Evaluation of Induction Characteristics of Propofol with Fentanyl and Ketamine as Total Intravenous Anaesthesia. *Acad. Anesthesiol. Int.* 2019;4(2):323-28.

DOI: [dx.doi.org/10.21276/aan.2019.4.2.73](https://doi.org/10.21276/aan.2019.4.2.73)

Source of Support: Nil, **Conflict of Interest:** None declared.