Original Article

Efficacy and safety of a generic remifentanil formulation versus fentanyl and Ultiva during general anaesthesia: A phase III, prospective, multi-centric, observer-blind, randomised controlled trial

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ABSTRACT

Background and Aims: Remifentanil and fentanyl are potent opioid analgesics commonly used during surgery due to their distinct pharmacological profiles. This study aimed to compare the efficacy and safety of a generic remifentanil (test drug) with fentanyl and Ultiva (innovator formulation) during general anaesthesia in the Indian population. **Methods:** This phase III, multi-centre (n = 13), randomised, three-arm, comparative study was conducted from 24 November 2021 to 31 March 2022. Eligible subjects scheduled for elective therapeutic and diagnostic surgical procedures (n = 314) were randomised into generic remifentanil, Ultiva, and fentanyl groups. An independent anaesthetist blinded to treatment allocation assessed efficacy and safety parameters. The primary efficacy endpoint was haemodynamic response during specific activities (endotracheal intubation, skin incision, skin closure, and extubation). **Results:** The study groups exhibited no significant differences in demographic and baseline characteristics. Heart rate was similar between the remifentanil and Ultiva groups measured during laryngeal intubation, skin incision, skin closure, and extubation ($P > 0.05$ in all four procedures). Heart rate was significantly higher in the fentanyl group in comparison to the remifentanil group during laryngeal intubation ($P = 0.035$), skin incision ($P = 0.017$), skin closure ($P = 0.001$), and extubation ($P = 0.026$). The need for vasopressor and anti-cholinergic drugs was similar between groups, and no subject required naloxone administration. **Conclusion:** Our study's findings demonstrated that generic remifentanil is non-inferior to fentanyl and equivalent to Ultiva for general anaesthesia in Indian patients undergoing various surgical and diagnostic procedures. Remifentanil offers advantages in terms of optimum haemodynamic stability, fast equilibrating analgesia, and rapid emergence from sedation, making it a suitable alternative to fentanyl.

Keywords: Analgesia, conscious sedation, fentanyl, haemodynamics, remifentanil

INTRODUCTION

Advancements in anaesthesiology are continually pursued to achieve optimal analgesic strategies to reduce surgical stress response during general anaesthesia induction and maintenance.[1] The foremost objective is to attain unwavering haemodynamic stability by effectively suppressing sympathetic

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stimulation caused by pain while simultaneously mitigating adverse effects, thus optimising patient outcomes.[2] The combination of an opioid analgesic agent with intravenous and inhalation anaesthetic agents presents a promising approach to achieving balanced analgesia during the induction and maintenance phases of general anaesthesia.[3]

Remifentanil and fentanyl, two synthetic selective μ-opioid receptor agonists, have emerged as the primary analgesic choices during anaesthesia across a spectrum of surgical procedures.[4] Remifentanil is twice as potent as fentanyl. It is more lipophilic, has a more rapid distribution and metabolism, a shorter elimination half-life, and a more rapid onset with a shorter duration of analgesic effect than fentanyl.[5,6]

Remifentanil (Ultiva) was first approved by the United States Food and Drug Administration in 1996. However, neither the innovator's product nor any generic formulation of this drug was registered or available in India when this study proposal was initiated in 2017.

The primary objective of this study was to evaluate the equivalence between generic remifentanil and Ultiva and the non-inferiority between generic remifentanil and fentanyl for general anaesthesia in Indian patients undergoing various surgical and diagnostic procedures over 24 hours. The study aimed to assess the safety of generic remifentanil, Ultiva, and fentanyl.

METHODS

This phase III, multi-centre (n = 13), observer-blind, randomised, three-arm, parallel-group, comparative study evaluated the safety and efficacy of two formulations of remifentanil (generic and the innovator's), and fentanyl was assessed for analgesia during the induction and maintenance of general anaesthesia from 3rd December 2021 to 31st March 2022. This study was conducted at multiple centres in India, including Hyderabad, Pune, Mysore, Patna, Varanasi, Bangalore, Mumbai, Aurangabad, Chennai, and New Delhi. Details of ethical clearance from all the sites are provided in Annexure 1. The respective institutional ethics committees or review boards approved the study protocol. The study was conducted in accordance with ethical principles consistent with the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all patients to participate in the study and use their data for research and educational purposes. This clinical trial was registered with the Clinical Trials Registry-India (CTRI/2021/01/030800, https://www.ctri.nic.in/).

This study included eligible subjects scheduled for elective therapeutic and diagnostic surgical procedures, aged 18–65 years, with a surgery duration of 30–120 minutes. Subjects needed an American Society of Anesthesiologists (ASA) physical status I/II and a minimum hospital stay of 24 hours. Subjects with known or suspected allergies to anaesthesia medications; body mass index (BMI) >35 kg/m^2; regular benzodiazepine use; neurological or psychiatric disorders; severe cardiac, hepatic, gastrointestinal, renal, pulmonary, or skin diseases; recent use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, gabapentin, or pregabalin; hypersensitivity to test ingredients; abnormal screening lab values; positive serology tests to rule out human immunodeficiency virus (HIV); hepatitis B and C during eligibility check; pregnancy or lactation; and participation in another clinical study were excluded. Subjects meeting the predefined eligibility criteria were randomised using Interactive Web Response Systems (IWRS) to receive either of the three interventions: Group I (generic remifentanil—test product), Group II (innovator product Ultiva), and Group III (reference product fentanyl) in a ratio of 1:1:1, in blocks of three. The study was observer-blinded. The assessment of efficacy and safety parameters was done by an independent anaesthetist who was unaware of the opioid given to the patient. The study drugs were administered by another anaesthetist who did not inform the independent evaluator anaesthetist.

The study had a screening period, baseline/randomisation followed by drug administration on day 1, and an observation period for 24 hours post surgery outlined as follows:

Screening period (day 0): Patient eligibility was confirmed through a standard medical, medication, and surgical history with a review of the inclusion and exclusion criteria; a complete physical/general and systemic examination; height, body weight, and calculation of BMI; vital signs (resting and supine blood pressure, temperature, and pulse and respiratory rate); laboratory investigations (urine pregnancy test, urine analysis, complete blood count, erythrocyte sedimentation rate, serum glutamic-oxaloacetic

transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, serum proteins, albumin/globulin ratio, serum bilirubin, random blood glucose, blood urea nitrogen, serum electrolytes, and serum creatinine); radiography and electrocardiogram (ECG); coronavirus diseases 2019 (COVID-19) test result evaluation; adverse event (AE)/serious adverse event (SAE); and concomitant medications questioning.

Treatment period (day 1, baseline visit): Patients were examined for vital signs, followed by physical/general and systemic examination; prior and concomitant medication history; laboratory investigation result assessment including pregnancy test for female subjects; radiography (if applicable); and ECG report evaluation. Patients were randomised to receive either of the three interventions as mentioned earlier.

The saturation of peripheral oxygen (SpO_2), end-tidal carbon dioxide ($ETCO_2$), respiratory rate, mean arterial pressure (MAP), and heart rate were recorded at 5-minute intervals prior to anaesthesia, at induction, and during surgery until the end of the surgery. High-quality anaesthetic monitors, such as the Datex-Ohmeda S/5 TM, monitored ECG, MAP, oxygen, carbon dioxide (CO_2) inspiratory and expiratory concentrations, and neuromuscular transmission (NMT).

Each remifentanil formulation was intravenously administered with an initial dose of 0.5 μg/kg/min over 1 minute, followed by a maintenance dose of 0.15 μg/kg/min. Intravenous fentanyl was administered with an initial dose of 2 μg/kg over 1 minute, followed by a maintenance dose of 0.75 μg/kg/h. The test drug was remifentanil 100 μg/mL, manufactured by Yichang Humanwell Pharmaceutical Co., Ltd, China. It was not marketed in India during the study period.

Reference drug 1: Fentanyl 100 μg/2 mL manufactured by Themis Medicare Limited, Mumbai. Marketed in India as Themifent.

Reference drug 2: Ultiva 100 μg/mL manufactured by GlaxoSmithKline US. Not marketed in India during the study period.

Propofol and sevoflurane were used as anaesthetic agents for induction and maintenance. For intraoperative rescue analgesia, 1 mL of the study drug of the respective group was repeated as necessary after 5 minutes. Intravenous fentanyl was used for postoperative rescue analgesia as and when required. For transitional analgesia, intravenous paracetamol 1 g, 30 minutes before completion of the surgery and intravenous ketorolac 30 mg at wakeup were administered. Intravenous atracurium 1 mg/kg bolus was used for neuromuscular blockade during tracheal intubation, followed by 0.2 mg/kg as and when required.

Heart rate, blood pressure, and temperature were recorded every 15 minutes post surgery for the first hour. Respiratory rate, heart rate, blood pressure, and temperature were recorded at 2-, 4-, and 6-hour intervals during the postoperative period. Patients were subjected to an evaluation of intraoperative analgesia, muscle rigidity, propofol requirements, vasopressor drugs (e.g. mephenteramine), anti-cholinergic drugs (e.g. atropine and glycopyrrolate), and the use of naloxone (yes/no). Haemodynamic responses were evaluated during laryngeal intubation, skin incision, skin closure, and extubation. Adverse events were recorded and assessed, including bradycardia, tachycardia, hypertension, hypotension, respiratory depression, and agitation.

End of the study (day 2): Laboratory assessments, vitals, and physical examinations were repeated. All safety and efficacy parameters were monitored, along with drug administration compliance, followed by close-out documentation and discharge of the subject. The primary efficacy endpoint was to evaluate the adequacy of intraoperative analgesia, as measured by the hemodynamic response to noxious stimuli during specific activities, including tracheal intubation, skin incision, skin closure, and extubation. Haemodynamic parameters were measured at several critical time points: before anaesthesia, at induction, and at 5-minute intervals from 5 to 120 minutes. This methodology was applied consistently across all activities. Secondary endpoints were the incidence of muscle rigidity, the number of additional doses of propofol or any study drugs required during the surgical procedure, the requirement of vasopressor drugs (e.g. mephenteramine), the need for anti-cholinergic medications (e.g. atropine and glycopyrrolate), and the incidence of naloxone administration. Safety assessments included the evaluation of bradycardia, tachycardia, hypertension, hypotension, respiratory depression, and agitation.

A total of 321 subjects (107/group) were planned to be enroled to achieve 85% power at a 5% level of

significance, assuming a 20% dropout rate, to detect a 10% non-inferiority margin with an expected difference of 0.09 between the treatment arms. The 10% non-inferiority margin was estimated based on the criterion that the test product must be effective (i.e. non-inferior to an active control) and that the difference between the test product and active control should not exceed 10%.

Data were analysed using Statistical Analysis System (SAS), version 9.4 (SAS Institute, Cary, NC). Demographic and baseline characteristics were summarised using standard descriptive statistics. All continuous variables (age, height, weight, BMI, and body surface area [BSA]) were presented with a number (n) of non-missing observations, mean, standard deviation, median, minimum and maximum (range), and 95% confidence interval (CI). For categorical data (gender and ethnicity), the descriptive statistics were presented with the number of subjects and number (n) with the percentage of observations in various categories of the variable, where the percentage was based on the subjects. Individual data listings were also provided by the treatment group and subjects. All comparisons were made using the Chi-square/Fisher's exact test for categorical variables (subjects experiencing muscle rigidity, additional doses of any study drugs required, need for vasopressor drugs, need for anti-cholinergic drugs, and need to administer naloxone). The paired *t*-test was used to compare within the treatment group for continuous variables (haemodynamic responses). ANOVA was used to compare parameters between groups for laryngeal intubation, skin incision, skin closure, and extubation. P value < 0.05 was considered to be statistically significant.

RESULTS

Among the subjects scheduled for elective therapeutic and diagnostic surgical procedures, 314 received at least one dose of the investigational product and were included in the study for analysis [Figure 1]. Three subjects with major deviations in the fentanyl group and one subject discontinued due to SAE in the remifentanil group were not included in the per-protocol population.

The mean age of the participants was approximately 38.6 years [standard deviation (SD: 12.4)]. There were 146 (46.5%) male and 168 (53.5%) female subjects [Table 1].

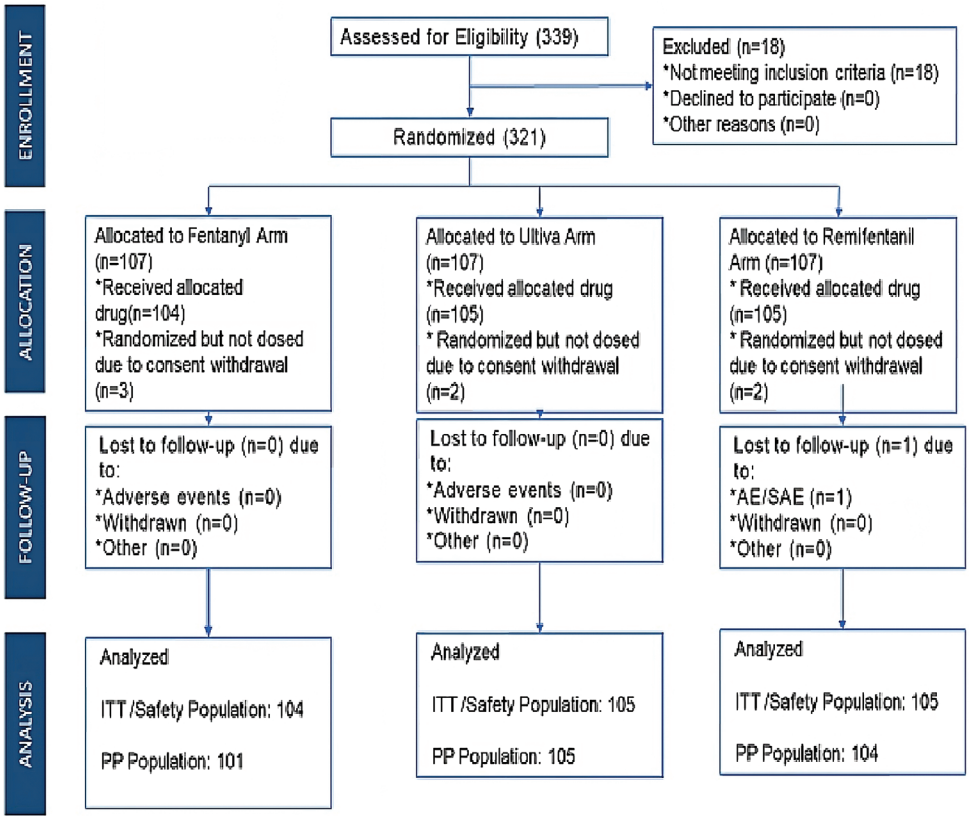

Figure 1: Consolidated Standards of Reporting Trials flow diagram

Table 1: Patient demographics

Parameter	Fentanyl (*n*=104)	Ultiva (*n*=105)	Remifentanil (*n*=105)
Age (years), mean (SD)	38.6 (12.1)	38.7 (11.9)	38.4 (13.3)
Gender: Male/Female, *n* (%)	35 (33.7)/69 (66.3)	45 (42.9)/60 (57.1)	66 (62.9)/39 (37.1)
Height (cm), mean (SD)	158.8 (7.8)	161.3 (8.3)	163.9 (8.0)
Weight (kg), mean (SD)	60.7 (11.6)	62.5 (11.6)	63.0 (11.3)
BMI (kg/m^2), mean (SD)	24.0 (4.2)	24.1 (4.6)	23.4 (3.7)
BSA (m^2)	1.6 (0.2)	1.6 (0.2)	1.7 (0.2)
Ethnicity: Asian, *n* (%)	104 (100.0)	105 (100.0)	105 (100.0)

Data expressed as mean (SD) or *n* (%). BMI=body mass index, BSA=body surface area, SD=standard deviation, *n*=number of patients

A comparison of haemodynamic responses between the three groups is summarised in Table 2. During endotracheal intubation, no significant difference in heart rate was observed between the remifentanil and Ultiva groups ($P = 0.655$). During skin incision, the fentanyl group had a significantly higher heart rate than the remifentanil and Ultiva groups ($P = 0.002$). For skin closure, the fentanyl group exhibited significantly higher heart rate 79.02 (SD: 11.60) (95% CI: 76.76, 81.28) compared to remifentanil 72.98 (SD: 11.77) (95% CI: 70.70, 75.26) and Ultiva 74.51 (SD: 11.25) (95% CI: 72.34, 76.79) groups ($P < 0.001$ and $P = 0.005$, respectively). In addition, there was no significant difference in heart rate between the remifentanil and Ultiva groups.

During endotracheal intubation, skin incision, skin closure, and extubation, the fentanyl group showed higher systolic blood pressure, but the difference was not statistically significant compared to the remifentanil and Ultiva groups. There were no significant differences in systolic blood pressure between the remifentanil and Ultiva groups.

There were no significant differences in diastolic blood pressure between the study groups during endotracheal intubation, skin incision, skin closure, and extubation.

A total of 167 patients had at least one adverse event (fentanyl: n = 48 [46.2%]; Ultiva: n = 53 [50.5%]; and remifentanil: n = 66 [62.9%]). Hypotension (n = 123 [39.2%]) was the most commonly observed event, followed by bradycardia (n = 61 [19.4%]), hypertension (n = 41 [13.1%]), and tachycardia (n = 19 [6.1%]). One serious adverse event observed was causally unrelated to the study drug.

During tracheal intubation, skin incision, skin closure, and extubation, no statistically significant differences were observed in mean arterial pressure between the fentanyl and remifentanil groups or between the remifentanil and Ultiva groups. The mean SpO_2 levels in the fentanyl, Ultiva, and remifentanil groups were more than 99% during tracheal intubation, skin incision, skin closure, and extubation. There were no significant differences in SpO_2 levels between the remifentanil and fentanyl groups during any of the anaesthesia stages.

The majority of the subjects did not experience muscle rigidity during the procedures.

The additional doses of propofol required were nearly the same in all three treatment groups in the ITT population. The majority of the subjects did not require vasopressor drugs during the procedure. Anti-cholinergic requirements were insignificant, and none of the subjects required naloxone during the study [Table 3].

DISCUSSION

Our study showed that heart rate during laryngeal intubation, skin incision, skin closure, and extubation was significantly higher in the fentanyl group than in the remifentanil and Ultiva groups, indicating better haemodynamic control with remifentanil.

The effective management of surgical stress response is paramount to ensure successful surgical outcomes and patient safety. Amongst the potent analgesics used for this purpose as a component of general anaesthesia, opioids such as remifentanil and fentanyl have long been recognised.[1,7] Our findings are consistent even in the Indian population with earlier research suggesting that remifentanil effectively attenuates the sympathetic response during intubation, rendering it a favourable choice in managing airway manipulation-induced haemodynamic changes; moreover, during skin incision, skin closure, and extubation, remifentanil helps in maintaining stable haemodynamics during surgical stress.[8-13] No significant difference in heart rate was observed between the remifentanil and Ultiva groups.

Table 2: Summary of haemodynamic response - ITT Population* (*n*=314)							
Parameter	**Group Name**	**Group Name**	**Group Name**	***P***	**Ultiva vs Fentanyl**	**Remifentanil vs Fentanyl**	**Remifentanil vs Ultiva,**
	Mean (SD) (95% CI)	**Mean (SD) (95% CI)**	**Mean (SD) (95% CI)**		**Mean difference between groups, 95% CI; *P***	**Mean difference between groups, 95% CI; *P***	**Mean difference between groups, 95% CI; *P***
	Fentanyl (*n*=104)	**Ultiva (*n*=105)**	**Remifentanil (*n*=105)**	**Mean difference between groups, 95% CI; *P***			
				Ultiva vs Fentanyl	**Remifentanil vs Fentanyl**	**Remifentanil vs Ultiva**	***P* (ANOVA)**
Heart rate (bpm)							
Endotracheal intubation							
Mean (SD) (95% CI)	87.49 (16.81) (84.22, 90.76)	81.49 (14.91) (78.60, 84.37)	82.49 (17.36) (79.13, 85.85)	-6.00, -10.97, -1.04; *P*=0.0069	-5.00, -10.34, 0.33; *P*=0.0354	1.00, -3.40, 5.40; *P*=0.6548	0.0189
Skin incision							
Mean (SD) (95% CI)	79.73 (12.80) (77.24, 82.22)	73.79 (15.08) (70.87, 76.71)	75.28 (13.91) (50.00, 116.00)	-5.94, -10.31, -1.57; *P*=0.0024	-4.45, -8.63, -0.28; *P*=0.0169	1.49, -2.46, 5.43; *P*=0.4588	0.0065
Skin closure							
Mean (SD) (95% CI)	79.02 (11.60) (76.76, 81.28)	74.51 (11.25) (72.34, 76.69)	72.98 (11.77) (70.70, 75.26)	-4.50, -8.07, -0.94; *P*=0.0048	-6.04, -9.69, -2.39; *P*=0.0002	-1.53, -4.67, 1.60; *P*=0.3357	0.0005
Extubation							
Mean (SD) (95% CI)	88.45 (16.30) (85.28, 91.62)	83.30 (15.32) (80.33, 86.26)	83.21 (17.54) (79.82, 86.60)	-5.16, -10.10, -0.22; *P*=0.0194	-5.24, -10.53, 0.05; *P*=0.0262	-0.09, -4.57, 4.39; *P*=0.9699	0.0316
Systolic blood pressure (mmHg)							
Laryngeal Intubation							
Mean (SD) (95% CI)	119.68 (17.19) (116.34, 123.02)	114.96 (17.89) (111.50, 118.42)	116.68 (17.69) (113.25, 120.10)	-4.72, -10.20, 0.76; *P*=0.0531	-3.01, -8.45, 2.44; *P*=0.2141	1.71, -3.13, 6.56; *P*=0.4859	0.1474
Skin incision							
Mean (SD) (95% CI)	109.46 (14.95) (106.55, 112.37)	107.25 (16.34) (104.09, 110.41)	105.96 (14.69) (103.12, 108.80)	-2.21, -7.11, 2.68; *P*=0.3078	-3.50, -8.13, 1.13; *P*=0.0893	-1.29, -5.51, 2.94; *P*=0.5494	0.2506
Skin closure							
Mean (SD) (95% CI)	116.45 (14.81) (113.57, 119.33)	111.50 (14.41) (108.72, 114.29)	109.14 (15.02) (106.24, 112.05)	-4.95, -9.51, -0.38; *P*=0.0152	-7.31, -11.97, -2.65; *P*=0.0005	-2.36, -6.37, 1.64; *P*=0.2463	0.0014
Extubation							
Mean (SD) (95% CI)	127.39 (16.94) (124.10, 130.69)	125.06 (18.18) (121.54, 128.58)	123.84 (19.07) (120.15, 127.53)	-2.34, -7.83, 3.15; *P*=0.3374	-3.56, -9.19, 2.08; *P*=0.1555	-1.22, -6.29, 3.85; *P*=0.6359	0.3539
Diastolic blood pressure (mmHg)							
Laryngeal Intubation							
Mean (SD) (95% CI)	74.79 (11.35) (72.58, 76.99)	71.13 (12.63) (68.69, 73.58)	73.55 (12.99) (71.04, 76.07)	-3.66, -7.41, 0.10; *P*=0.0288	-1.24, -5.05, 2.57; *P*=0.4644	2.42-1.07, 5.90; *P*=0.1727	0.0949
Skin incision							
Mean (SD) (95% CI)	69.39 (11.48) (67.16, 71.63)	67.84 (12.38) (65.44, 70.23)	66.26 (11.59) (64.01, 68.50)	-1.56, -5.29, 2.17; *P*=0.3472	-3.14, -6.74, 0.47; *P*=0.0507	-1.58, -4.84, 1.68; *P*=0.3406	0.1608
Skin closure							
Mean (SD) (95% CI)	72.11 (10.23) (70.12, 74.09)	68.38 (10.98) (66.26, 70.51)	66.48 (10.60) (64.43, 68.53)	-3.72, -7.04, -0.41; *P*=0.0119	-5.63, -8.88, -2.38; *P*=0.0001	-1.90, -4.84, 1.03; *P*=0.2023	0.0006
Extubation							

Contd...

Table 2: Contd...

Parameter	Group Name	Group Name	Group Name	*P*	Ultiva vs Fentanyl	Remifentanil vs Fentanyl	Remifentanil vs Ultiva,
	Mean (SD) (95% CI)	Mean (SD) (95% CI)	Mean (SD) (95% CI)		Mean difference between groups, 95% CI; *P*	Mean difference between groups, 95% CI; *P*	Mean difference between groups, 95% CI; *P*
	Fentanyl (*n*=104)	Ultiva (*n*=105)	Remifentanil (*n*=105)	Mean difference between groups, 95% CI; *P*			
				Ultiva vs Fentanyl	Remifentanil vs Fentanyl	Remifentanil vs Ultiva,	*P* (ANOVA)
Mean (SD)	79.63 (14.78)	77.00 (12.80)	77.31 (12.76)	-2.63, -6.95, 1.68;	-2.32, -6.63, 1.99;	0.31, -3.16, 3.79,	0.3057
(95% CI)	(76.76, 82.51)	(74.52, 79.48)	(74.84, 79.78)	*P*=0.1701	*P*=0.2262	*P*=0.8587	
Mean arterial pressure (mmHg)							
Laryngeal intubation							
Mean (SD)	88.6 (13.64)	84.2 (14.28)	87.7 (15.25)	4.36, -0.00, 8.72;	0.89, -3.63, 5.41;	3.47, -0.55, 7.49;	0.0706
(95% CI)	(85.9, 91.2)	(81.4, 87.0)	(84.7, 90.6)	*P*=0.0251	*P*=0.6565	*P*=0.0906	
Skin incision							
Mean (SD)	81.4 (11.94)	79.9 (12.72)	78.6 (11.71)	1.48, -2.37, 5.33;	2.77, -0.93, 6.46;	-1.29, -4.61, 2.04;	0.2583
(95% CI)	(79.1, 83.7)	(77.5, 82.4)	(76.4, 80.9)	*P*=0.3867	*P*=0.0924	*P*=0.4470	
Skin closure							
Mean (SD)	86.1 (11.13)	82.6 (11.41)	80.0 (11.71)	3.51, -0.02, 7.03;	6.05, 2.48, 9.62;	-2.54, -5.69, 0.60;	0.0007
(95% CI)	(83.9, 88.2)	(80.3, 84.8)	(77.7, 82.3)	*P*=0.0256	*P*=0.0002	*P*=0.1126	
Extubation							
Mean (SD)	95.4 (14.55)	92.0 (14.35)	92.0 (14.54)	3.35, -1.17, 7.86;	3.32, -1.23, 7.86;	0.03, -3.90, 3.96;	0.1603
(95% CI)	(92.5, 98.2)	(89.2, 94.8)	(89.2, 94.9)	*P*=0.0957	*P*=0.1007	*P*=0.9886	
SpO_2 (%)							
Laryngeal intubation							
Mean (SD)	99.88 (0.46)	99.85 (0.48)	99.84 (0.54)	-0.03, -0.17, 0.12;	-0.04, -0.19, 0.12;	-0.01, -0.15, 0.13;	0.8535
(95% CI)	(99.79, 99.96)	(99.76, 99.94)	(99.73, 99.94)	*P*=0.6714	*P*=0.5935	*P*=0.8922	
Skin incision							
Mean (SD)	99.90 (0.43)	99.80 (0.66)	99.86 (0.43)	-0.10, -0.28, 0.07;	-0.05, -0.18, 0.09;	0.06, -0.09, 0.21;	0.3465
(95% CI)	(99.82, 99.99)	(99.67, 99.93)	(99.77, 99.94)	*P*=0.1774	*P*=0.4310	*P*=0.4559	
Skin closure							
Mean (SD)	99.90 (0.45)	99.81 (0.56)	99.90 (0.34)	-0.09, -0.25, 0.06;	-0.01, -0.13, 0.12;	0.09, -0.04, 0.21;	0.2577
(95% CI)	(99.82, 99.99)	(99.70, 99.92)	(99.83, 99.96)	*P*=0.1799	*P*=0.8763	*P*=0.1789	
Extubation							
Mean (SD)	99.88 (0.48)	99.77 (0.59)	99.90 (0.36)	-0.10, -0.27, 0.06;	0.02, -0.11, 0.15;	0.12; -0.01, 0.26;	0.1438
(95% CI)	(99.78, 99.97)	(99.66, 99.89)	(99.82, 99.97)	*P*=0.1651	*P*=0.7308	*P*=0.0700	

*The ITT population comprised all subjects who were randomised into the study, received at least one dose of the study drug (test or reference), and had at least one post-baseline assessment. Data expressed as mean (SD) (95% CI). ANOVA used to compare parameters between groups. ANOVA=analysis of variance, CI=confidence interval, ITT=intent-to-treat, SD=standard deviation, n=number of patients

The observed blood pressure responses reflected similar trends consistent with the heart rate observations. Both systolic and diastolic blood pressure were significantly higher in the fentanyl group during skin closure. Such haemodynamic variability during surgical manipulation has been associated with potential adverse outcomes, underscoring the significance of using opioids with stable haemodynamic profiles.[11,12] Regarding MAP, no significant differences were observed in any group during laryngeal intubation, skin incision, and extubation. However, MAP was significantly higher in the fentanyl group during skin closure. This finding aligns with previous research emphasising remifentanil's superior haemodynamic stability during surgery.[8,11-13]

The findings of our study demonstrated the non-inferiority of the generic remifentanil compared to fentanyl and equivalence to Ultiva, thus indicating that the generic remifentanil is a suitable alternative analgesic option during induction and maintenance of general anaesthesia in the Indian population. The results observed in the Indian patients in this mandated trial align with the results previously evidenced and chronicled in the literature.[7,8,14,15]

The literature is replete with studies comparing the efficacy and safety of remifentanil and fentanyl during general anaesthesia. A review by Scott *et al*.[7] found that remifentanil, when used in

Table 3: Secondary endpoints - ITT Population (*n*=314)

Parameter	Fentanyl (*n*=104)	Ultiva (*n*=105)	Remifentanil (*n*=105)	*P*
Subjects experiencing muscle rigidity				
No, *n* (%)	101 (97.1)	99 (94.3)	102 (97.1)	0.913[a], 0.654[b], 0.915[c]
Yes, *n* (%)	3 (2.9)	6 (5.7)	3 (2.9)	
Additional doses of propofol or any study drugs required during the entire surgical procedure period				
Mean (SD) (95% CI)	1.7 (0.49) (1.7, 1.8)	1.8 (0.48) (1.7, 1.9)	1.8 (0.52) (1.7, 1.9)	0.880[a], 0.229[b], 0.276[c]
Need for vasopressor drugs				
No, *n* (%)	85 (81.7)	87 (82.9)	78 (74.3)	-
Yes, *n* (%)	19 (18.3)	18 (17.1)	27 (25.7)	
Mephentermine, *n* (%)	15 (14.4)	12 (11.4)	15 (14.3)	
Ephedrine, *n* (%)	4 (3.9)	5 (4.8)	12 (11.4)	
Need for anti-cholinergic drugs				
No, *n* (%)	98 (94.2)	82 (78.1)	81 (77.1)	-
Yes, *n* (%)	6 (5.8)	23 (21.9)	24 (22.9)	
Atropine, *n* (%)	5 (4.8)	18 (17.1)	20 (19.1)	
Need for administration of Naloxone				
No	104 (100.0)	105 (100.0)	105 (100.0)	-

Data expressed as mean (SD) or *n* (%). [a]Fentanyl vs Ultiva; [b]Fentanyl vs Remifentanil; [c]Ultiva vs Remifentanil. CI=confidence interval, SD=standard deviation, *n*=number of patients

combination with intravenous or volatile hypnotic agents, demonstrated efficacy comparable to fentanyl- or alfentanil-containing regimens. These remifentanil-based regimens effectively attenuated haemodynamic, autonomic, and somatic intraoperative responses while promoting postoperative recovery. Similarly, a randomised, double-blind study by Möllhoff *et al*.[13] compared the efficacy and safety of high-dose remifentanil administered by continuous infusion with fentanyl in 'fast track' coronary artery bypass graft surgery. The study found that remifentanil is significantly more effective than low/medium-dose fentanyl and provides superior control of some of the major stress events. Moreover, a systematic review by Zhang *et al*.[16] reported that a relatively high dose of intraoperative remifentanil attenuated postoperative pain by reducing postoperative visual analogue scale (VAS) scores and morphine consumption.

Considering these findings, our study supports remifentanil as a suitable alternative analgesic for the induction and maintenance of general anaesthesia in Indian patients. Adverse events were most commonly hypotension, with a higher incidence in the remifentanil group. No serious adverse events were associated with the study drugs.

The strengths of this study include its robust, randomised, observer-blind, multi-centre design, which minimises bias and enhances generalisability. Rigorous monitoring of hemodynamic parameters and thorough safety assessments, combined with clearly defined primary and secondary endpoints, ensure reliable and actionable results. There are certain limitations to the current study. As the assessment parameters were objective, it is unlikely to impact the study results significantly. In the current study, Indian subjects of only 18–65 years have been included; pregnant and lactating women, obese and patients with severe cardiac, hepatic, gastrointestinal, renal, pulmonary, and skin disease have not been included, which limits generalisability. The study's single geographic focus on India may limit external validity. The dependence on objective hemodynamic measures without incorporating subjective pain assessments may overlook important patient-reported outcomes. Another limitation was the measurements and comparison of end-tidal sevoflurane concentration (ET); measuring it was not in the scope of the study protocol. Future research should include a broader range of patient populations, such as the elderly, paediatric, and high-risk groups, to enhance the generalisability of findings. Extended follow-up periods are necessary to capture long-term outcomes, including chronic pain and recovery quality. Incorporating patient-reported outcomes alongside objective measures could provide a more comprehensive assessment of analgesic efficacy. Integrating advanced monitoring tools, such as continuous end-tidal sevoflurane concentration measurements, could refine the understanding of drug interactions and optimise anaesthesia management.

CONCLUSION

This phase III trial conducted within the Indian population supports the non-inferiority of the generic remifentanil to fentanyl and its equivalence with Ultiva, thus establishing it as an alternative analgesic component of general anaesthesia for various surgical procedures.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

All the authors, except for Dr. Ashok Kumar Swain, acted as principal investigators in the clinical trial at the respective study sites and have received their investigator's fees for this study. Dr. Ashok Swain is an Ex-employee of Themis Medicare Limited, Mumbai, India, the study's sponsor. Dr. Indrani Hemantkumar has received honoraria from Themis Medicare Limited, Mumbai, India, as a Speaker and is associated with Themis as a therapeutic area advisor in the field. All other authors have no other conflict of interest to declare.

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Annexure 1: Details of ethical clearance		
IRB name/Ethical Committee name	**Approval number**	**Approval date**
Institutional Ethics Committee (IEC)-I Seth GS Medical College and KEM Hospital, Mumbai	IEC (I)/OUT/579/2021	07.06.2021
Institutional Ethics Committee Institute of Medical Sciences Banaras Hindu University, Varanasi	NA	22.06.2021
Institutional Ethics Committee Indira Gandhi Institute of Medical Sciences, Patna	01/IEC/IGIMS/2021	23/03/2021
Institutional Ethics Committee JSS Medical College, Mysore	NA	25.02.2021
Panimalar Medical College Hospital & Research Institute - Institutional Human Ethics Committee (PMCHRI-IHEC)	NA	29.01.2021
NIMS Institutional Ethics Committee	EC/NIMS/2684/2021	04.03.2021
Institutional Ethics Committee Basavatarakam Indo-American Cancer Hospital & Research Institute	139	28.12.2020
Sapthagiri Institute of Medical Sciences & Research Centre Institutional Ethics Committee	SIMS&RC/IEC/AP-009/2020-21	01.03.2021
Noble Hospital Institutional Ethics Committee	NHIEC/FEB/2021/235	24.02.2021
Institutional Ethics Committee Kempegowda Institute of Medical Sciences, Bangalore	KIMS IEC/S05/2021	19.03.2021
Ethics Committee Sri Ganga Ram Hospital	EC/02/21/1839	24.03.2021
Ethics Committee Inamdar Multi-specialty Hospital	NA	21.01.2021
Institutional Ethics Committee Columbia Asia Hospital Mysore	NA	01.02.2021