

# Comparison of recovery characteristics with two different washout techniques of desflurane anaesthesia: A randomised controlled trial

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## ABSTRACT

**Background:** Rapid emergence with low soluble inhalational agents (IA) is offset by a significant association with emergence agitation (EA). Research on the influence of elimination methods of IA on recovery characteristics is very few. We conducted this study to compare the recovery characteristics of slow elimination (SE) of desflurane with purging technique. **Methodology:** Forty-five participants, 18–60 years, undergoing elective laparoscopic surgeries were randomised either into Group-P ( $n = 23$ ) or Group-SE ( $n = 22$ ). A standardised induction-maintenance protocol including desflurane and fresh gas flow (FGF) of 0.8 l/min was followed. During recovery, the FGF was increased in Group-P to 10 L/min and in Group-SE it was continued at 0.8 L/min. The decrement in end-tidal concentration of desflurane, time for emergence and extubation, EA and time for psychomotor recovery were noted. **Results:** Time for emergence (Group-SE:  $22.8 \pm 9$  vs. Group-P:  $5.6 \pm 1.5$  min;  $P = 0.000$ ) and emergence to extubation duration (Group-SE:  $128 \pm 36$  s vs. Group-P:  $11.5 \pm 1.7$  s;  $P = 0.000$ ) were longer in the Group-SE than in Group-P. EA occurred in 22.7% patients in Group-SE and in 4.3% patients in Group-P ( $P = 0.07$ ). Psychomotor recovery to baseline values was seen in more number of patients in Group-SE than Group-P at 30 min. There was no difference between the groups at 60 min post-extubation. **Conclusions:** Slow elimination using FGF of 0.8 L/min significantly prolongs emergence even with low soluble agent like desflurane. SE is not beneficial in decreasing the incidence of EA or hastening psychomotor recovery. Purging technique is, therefore, a better-suited technique with fewer complications for eliminating desflurane.

**Key words:** Anaesthetics, cognition, desflurane, inhalational anaesthesia, recovery period

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## INTRODUCTION

Inhalational agents (IA) with low solubility are preferred due to their shorter recovery time and earlier readiness for home discharge.<sup>[1]</sup> Desflurane due to its low blood-gas partition coefficient causes rapid emergence.<sup>[2,3]</sup> This advantage is offset by a significant association of low soluble IA with emergence agitation (EA), an acute change in cognition and fluctuating consciousness during recovery.<sup>[4,5]</sup> Recovery of subcortical structures (locus coeruleus and amygdala) prior to cerebral cortex during rapid emergence has been postulated as a causative factor for EA. Pharmacological methods (opioids, benzodiazepines and alpha-2 agonists) and elimination

methods of IA have been proposed to curtail EA without affecting awakening and extubation time.<sup>[6,7]</sup> Elimination methods for curtailing EA aim at slowing the elimination of IA, thereby decreasing the gap in concentration between cortical and subcortical centres.

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Few studies have tested the elimination method. Slow elimination (SE) of sevoflurane has been shown to be favourable for curtailing EA in paediatric patients without prolonging time for emergence.<sup>[8]</sup> In this study, we hypothesised that SE of desflurane will not delay the time for emergence and at the same time will have better recovery characteristics in adult patients receiving general anaesthesia.

## METHODOLOGY

This prospective, randomised study was approved by the institutional human ethics committee and registered at the Clinical Trial Registry of India (CTRI/2018/02/011924). The study was done from March-2018 to June-2019. Fifty patients from the study population were selected by computer-generated random numbers.

Of the 50 patients screened for recruitment, 48 American Society of Anesthesiologists (ASA) physical status 1 or 2 patients, 18–60 years, who gave written informed consent and scheduled for elective laparoscopic surgeries were included [Figure 1]. Patients with obesity, psychiatric illness, psychomotor dysfunction, unable to perform psychomotor testing or developing surgical complications were excluded. During pre-anaesthetic evaluation, patients were explained about the digit symbol substitution test (DSST) and trail making tests (TMT)-part A and baseline record was taken after adequate trial.<sup>[9]</sup> They were explained that the same tests would be repeated post-operatively. Pre-operative nil-per-oral orders and anti-aspiration prophylaxis was as per hospital protocol.

In the operating theatre, monitoring (GE Aisys Carestation™, GE Healthcare, US) included electrocardiography, pulse oximetry, non-invasive blood pressure, minimum alveolar concentration (MAC) of anaesthetic agent [Identification threshold-0.15% and accuracy  $\pm$  (0.15 vol% + 5% of reading)], end-tidal carbon dioxide (EtCO<sub>2</sub>) and train-of-four (TOF) monitor (Organon Ltd. Ireland). Group allocation was done just before induction, using sealed envelope technique into Group-P (purging) and Group-SE (slow-elimination). Patients were blinded to the allocated group. Limb-O circuit, a single tube anaesthesia breathing circuit with a flexible septum dividing the inspiratory and expiratory channels, was used for all patients. Following pre-oxygenation, anaesthesia was induced with inj. fentanyl 2 µg/

kg and propofol 2 mg/kg. Effective bag and mask ventilation was tested and inj. vecuronium 0.1 mg/kg was given. Patients were ventilated with 2 l: 4 l-oxygen: nitrous-oxide (N<sub>2</sub>O) mixture and desflurane 6% for 3 min before intubation. After intubation, mechanical ventilation was initiated and end-tidal control mode of GE Aisys Carestation™ (GE Healthcare, United States) was activated with a fresh gas flow (FGF) of 800 mL/min. End-tidal oxygen (EtO<sub>2</sub>) was set at 35% and end-tidal anaesthetic agent (EtAA) concentration was adjusted to rapidly achieve a minimum alveolar concentration (MAC)<sub>age</sub> of 1. No further alteration was made in the concentration of desflurane. Inj. fentanyl 0.5 µg/kg was repeated hourly and inj. vecuronium repeated to maintain a TOF count  $\leq$  1. At the end of surgery, port sites were infiltrated with a total of 10 ml 0.5% bupivacaine hydrochloride and inj. paracetamol 1 g was administered intravenously (i.v.). Ventilator mode was then changed from volume control to synchronised intermittent mandatory mode with pressure support ventilation. An oro-pharyngeal airway was inserted to prevent biting of tracheal tube during emergence.

Reversal of neuromuscular blockade with standard doses of neostigmine and glycopyrrolate was given when the fourth twitch on TOF was present and 30 min had elapsed after the last dose of opioid. When the TOF ratio was  $\geq$  0.7, desflurane and N<sub>2</sub>O were discontinued and the time of discontinuation was taken as time-zero. In Group-P, O<sub>2</sub> was increased to 10 L/min to purge desflurane. In Group-SE, O<sub>2</sub> was continued at 800 mL/min. The fraction of inspired anaesthetic agent (FiAA) and EtAA, end-tidal nitrous oxide (EtN<sub>2</sub>O) concentrations and MAC values during the emergence phase were collected at 1-min intervals. Response to oral commands was checked every minute after time-zero, by asking the patient to open eyes to verbal commands. Opening of eyes to verbal commands or spontaneously or return of reflexes like coughing was taken as emergence. The duration from time-zero to emergence was taken as time for emergence.

Agitation during emergence was assessed on Aono's four-point agitation scale (1-calm, 2-not calm but could be easily calmed, 3-not easily calmed, moderately agitated or restless, 4-combative, excited or disoriented), by an independent anaesthesiologist not included in the study.<sup>[10]</sup> Scores 1 and 2 were considered as smooth emergence and 3 and 4 as EA. Combative patients were treated with intravenous bolus of 25 µg fentanyl. Any jaw-clenching, shivering and vomiting during this

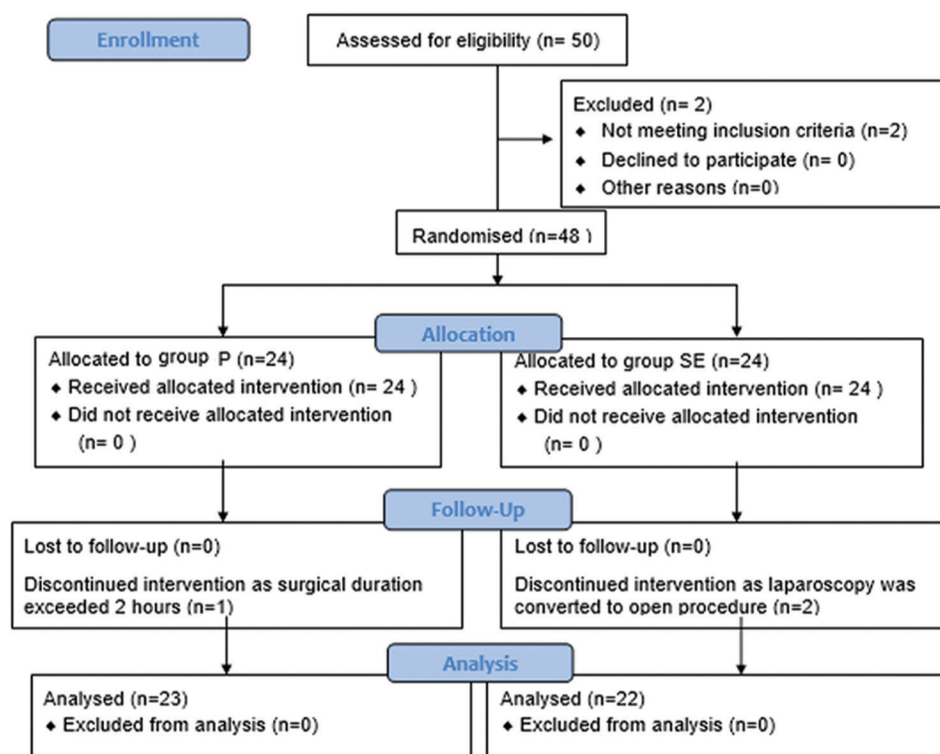


Figure 1: Consort diagram

period was noted. Patients were extubated only when minute ventilation was adequate, the airway reflexes had returned and agitation had settled. Emergence to extubation time was also noted.

Post-extubation, pain scores were noted on a numeric rating scale (NRS). DSST and TMT were performed at 15, 30, 45, 60 min and 24 h after extubation and these values were compared with the pre-operative values to determine the time to return of psychomotor functions to baseline values.

Sample size was calculated based on the time for emergence using “Statistics and Sample Size” App (version 5.0 developed by Thai Thanh Truc). The mean time for emergence from desflurane-N<sub>2</sub>O anaesthesia has been reported to be  $5.1 \pm 2.4$  min with purging technique.<sup>[14]</sup> Assuming that SE will not delay the time for emergence beyond 50% (7.5 min) of purging technique, the minimum number of patients to be recruited for the study with an alpha value of 5% and power of 80% was calculated as 16 patients per group. To account for dropouts, 50 patients were recruited.

Statistical analysis was carried out using International Business Machine Statistical Package for Social Sciences version 16.0 (IBM SPSS, US) software.

Unpaired Student’s t test was used for parametric data and Chi-square test for non-parametric data.

## RESULTS

Forty-five patients completed the study [Figure 1]. The two study groups were comparable with respect to age, weight, sex, ASA physical status and type of surgeries [Table 1].

Time for emergence (Group-SE:  $22.8 \pm 9$  min vs. Group-P:  $5.6 \pm 1.5$  min;  $P = 0.000$ ) and emergence to extubation duration (Group-SE:  $128 \pm 36$  s vs. Group-P:  $11.5 \pm 1.7$  s;  $P = 0.0001$ ) were longer in the SE group than the purging group [Figure 2]. The end-tidal desflurane concentration at emergence (Group-SE:  $1.13 \pm 0.28$  min vs. Group-P:  $0.52 \pm 0.18$  min;  $P = 0.000$ ) and MAC value at emergence (Group-SE:  $0.35 \pm 0.07$  min vs. Group-P:  $0.15 \pm 0.5$  min;  $P = 0.19$ ) were also higher in the SE group. EA occurred in 22.7% patients in Group-SE and in 4.3% patients in Group-P ( $P = 0.07$ ) [Table 2]. One patient in Group-SE manifested EA score 4 and was administered a bolus dose of 25 µg fentanyl. Other emergence reactions such as jaw-clenching, shivering and vomiting were not significantly different [Table 2]. None of the patients reported a NRS pain score >3 in the

**Table 1: Demographic data of patients in the two groups**

|                           | GROUP-P<br>(n=23) | GROUP-SE<br>(n=22) | P     |
|---------------------------|-------------------|--------------------|-------|
| Sex (M:F)                 | 13:10             | 15:7               | 0.42  |
| ASA (1: 2)                | 20:3              | 21:1               | 0.317 |
| Age (mean±SD) (Years)     | 35±14             | 31±10              | 0.28  |
| Weight (mean±SD) (kg)     | 64±8              | 61±12              | 0.39  |
| Duration of surgery (min) | 115±18            | 107±20             | 0.17  |
| Surgeries                 |                   |                    |       |
| Lap Appendectomy          | 10                | 15                 | 0.248 |
| Lap Cholecystectomy       | 9                 | 5                  |       |
| Lap Meshplasty            | 4                 | 2                  |       |

SD=Standard deviation, ASA =American Society of Anesthesiologists

**Table 2: Emergence parameters in the two study groups**

| Parameter                  | GROUP-P<br>(n=23) | GROUP-SE<br>(n=22) | P      |
|----------------------------|-------------------|--------------------|--------|
| Time for emergence in min* | 5.57±1.5          | 22.77±9            | 0.000  |
| E-E duration in s*         | 11.5±1.7          | 128±36             | 0.0001 |
| MAC at emergence*          | 0.15±0.5          | 0.35±0.07          | 0.190  |
| Et Des at emergence*       | 0.52±0.18         | 1.13±0.28          | 0.000  |
| Emergence reactions        |                   |                    |        |
| Agitation                  | 1 (4.3%)          | 5 (22.7%)          | 0.07   |
| Jaw clenching              | 6 (26%)           | 11 (50%)           | 0.098  |
| Shivering                  | 6 (26%)           | 11 (50%)           | 0.098  |
| Vomiting                   | 2 (8.7%)          | 3 (13.6%)          | 0.589  |

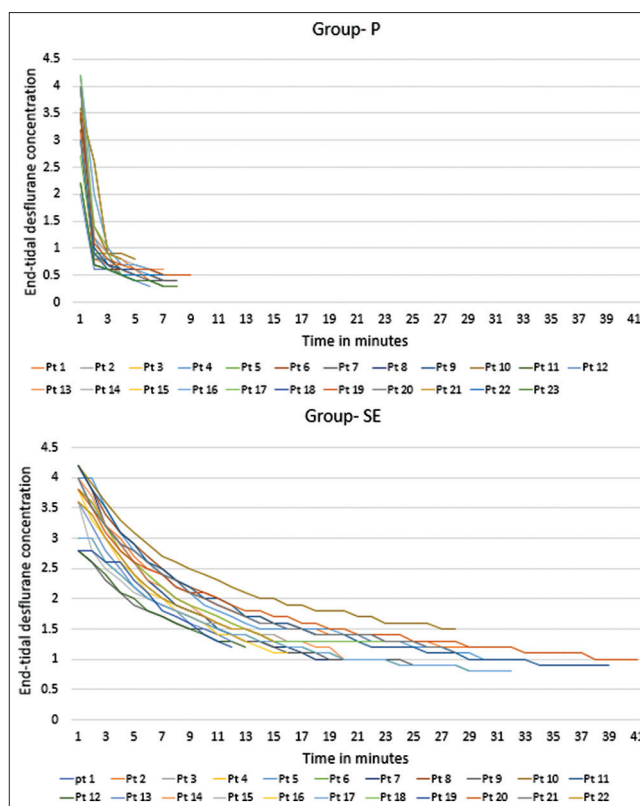
\*Mean±SD

immediate recovery period. Relatively, more number of patients were unable to do the psychomotor tests in Group-P compared to Group-SE at 15 min (17 vs. 10) and at 30 min (10 vs. 7) [( $P = 0.07$ )]. There was no statistical difference between the two groups with regard to return of DSST scores ( $P = 0.4$ ) and TMT scores ( $P = 0.4$ ) to baseline values [Table 3].

## DISCUSSION

Our study showed that it takes 22.8 min to eliminate even a low soluble agent like desflurane if FGF of 0.8 L/min is used. The time taken for emergence using 0.8 L/min FGF was four times longer than with FGF of 10 L/min and the incidence of EA was also five times higher in this group. This contradicts Yang *et al.*'s observations in paediatric patients.<sup>[8]</sup> This is probably due to differences in pharmacokinetic-pharmacodynamic properties of IA in adults and children.

In our study, factors which delay emergence or factors associated with EA such as benzodiazepine premedication, breast and open abdominal surgeries and pre-existing psychiatric illnesses were excluded. MAC<sub>age</sub> of 1 was maintained in all patients for a uniform depth. It was ensured that fentanyl was given at least 30 min prior and TOF  $\geq 0.7$  before



**Figure 2:** Graph showing the decrement in end-tidal desflurane concentrations over time after time-zero in the two groups. Each line represents the decrement in an individual patient. The end-tidal desflurane concentration at 0 min was the desflurane concentration that was needed to maintain MAC<sub>age</sub> of 1 in that particular patient. The lines showing the decrement in desflurane concentrations are more or less parallel indicating that a fixed fraction of desflurane was eliminated from the system with the set fresh gas flow rate. The time at which the lines end indicates the time to emergence in the particular patient

discontinuing desflurane. Time taken for emergence was, therefore, attributed to the elimination method employed. Only patients undergoing laparoscopic surgeries were included so that the intensity of pain in either group is similar at emergence and any EA could be attributed to the IA used.

In Group-P, emergence was predictable (SD = 1.5 min). Predictable recovery from desflurane has been reported earlier too.<sup>[12,13]</sup> Similar predictability was not observed with SE (SD = 9 min). Time for emergence of 5.6 min in Group-P is consistent with the time for emergence reported in various other studies where FGF  $\geq 4$  L/min was used for washout. Jeong *et al.* have reported the mean times to eye opening with 2, 4 and 6 L/min FGF following desflurane anaesthesia as  $16.4 \pm 5.4$ ,  $9.1 \pm 2.7$  and  $8.0 \pm 3.1$  min, respectively. Their time for emergence is higher probably because N<sub>2</sub>O was not used and desflurane was titrated to maintain an end-tidal concentration of 5%–6%.<sup>[14]</sup>

**Table 3: Return of psychomotor function to baseline in the two groups**

| Psychomotor test  | Time   | Number of patients showing return to baseline values |                 | P   |
|-------------------|--------|--|-----------------|-----|
|                   |        | Group-P (n=23)                                       | Group-SE (n=22) |     |
| DSST              | 15 min | 0  | 0               | 0.4 |
|                   | 30 min | 2  | 4               |     |
|                   | 45 min | 2  | 3               |     |
|                   | 60 min | 6  | 8               |     |
|                   | 24 h   | 13   | 7               |     |
| Trail making test | 15 min | 0  | 1               | 0.3 |
|                   | 30 min | 2  | 6               |     |
|                   | 45 min | 9  | 4               |     |
|                   | 60 min | 8  | 8               |     |
|                   | 24 h   | 4  | 3               |     |

We recorded MAC at emergence of  $0.35 \pm 0.07$  and a mean end-tidal desflurane in Group-SE of  $1.13 \pm 0.28\%$ . The balance to MAC was contributed by end-tidal  $N_2O$  ( $18.4 \pm 4.9$ ). Eger has described MAC-awake for desflurane as 0.3 MAC.<sup>[15]</sup> MAC at emergence in Group-P was  $0.15 \pm 0.5$ . Eger and Gaumann *et al.* have also observed higher MAC awake values with slow washout compared to fast washout.<sup>[15,16]</sup> They reasoned that equilibrium between the alveolar and brain concentrations of agent occurred during slow washout resulting in higher MAC-awake values, whereas during fast washout there was a failure of equilibration.

Rapid emergence has been proposed as a cause of EA with low soluble agents. The changes in neurological circuits and neurotransmitters during emergence have not been fully understood. It is considered that anaesthetics disrupt thalamo-cortical connectivity and awakening from anaesthesia is not always associated with return of cortical function.<sup>[8]</sup> Return of consciousness is linked with phylogenetically older brain structures (locus coeruleus, amygdala) and not the neocortex. The locus coeruleus and the amygdala are also linked with fear conditioning and hence activation of these centres prior to recovery of the cortex has been postulated to result in sympathetic response and EA. Our observations of higher EA in Group-SE question the current concept of the gap in the desflurane concentrations between the cortical and subcortical centres to be the cause for EA. If gap was the cause, the gap was well mitigated during SE.

Shivering and jaw-clenching were noted to occur in the same patients. They can, therefore, be considered as different manifestations of the same emergence phenomenon. Emergence reactions when they

occurred lasted for <15 s in Group-P, compared to 2–3 min in Group-SE. One patient in Group-SE had agitation score 4, which settled in about 3 min.

Although time for emergence and emergence to extubation time were prolonged in Group-SE, recovery of DSST occurred earlier in more number of patients in Group-SE. We postulated that a higher IA concentration in the brain at emergence was the cause for a higher incidence of EA in Group-SE. At the same time, redistribution from the muscle group could have delayed recovery of psychomotor functions in Group-P. Unlike induction which can be accelerated by several factors like increasing the agent concentration or FGF, there is nothing much that can be done to accelerate recovery beyond maintaining an adequate alveolar ventilation for elimination. Washout from tissue groups basically depends on circulation and has to occur over a period of time. In Group-SE, 23 min had already elapsed before emergence, while only 5 min had elapsed in Group-P.

This is the first study to compare two different elimination methods on recovery characteristics from desflurane. The observer could not be totally blinded to the FGF during recovery. DSST and TMT could have been continued at hourly intervals to find out when baseline values were reached to determine the time to home readiness.

Although a variety of drugs have been suggested to decrease EA, it is our opinion that if patients can be kept just adequately sedated, with the same opioid used intra-operatively till the washout of desflurane ( $5.57 \pm 1.5$  min), a smooth emergence can be achieved without polypharmacy. With proper planning, agent consumption can be decreased during SE by stopping desflurane at-least 15 min prior to the timing of reversal and extubation.

## CONCLUSIONS

Slow elimination using 0.8 L/min FGF significantly prolongs emergence from anaesthesia even with low soluble agent like desflurane. However, slow elimination is not beneficial in decreasing EA or hastening psychomotor recovery. Therefore, purging technique is a better-suited technique with fewer complications for eliminating desflurane.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the

patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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