

## Safety and Analgesic Efficacy of Pre-Emptive Intranasal Ketamine versus Intranasal Fentanyl in Patients Undergoing Endoscopic Nasal Surgery

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**Abstract: Objectives:** No clinical studies investigated nasal mucosal coverage and nasal integrity as local causative factors for inter-individual variation in clinical effects commonly reported with intranasal opioid administration. Moreover, most of published clinical trails investigated the use of intranasal analgesic medications in extranasal painful settings. The purpose of this study was to demonstrate safety and analgesic efficacy of pre-emptive intranasal ketamine (non-opioid) vs. intranasal fentanyl (opioid) in patients undergoing endoscopic nasal surgery. **Methods:** 60 adult normotensive patients were randomly assigned to receive intranasal administration of either 1.5mg/kg ketamine 50mg/ml (INK group, n=20) or 1.5µg/kg fentanyl 50µg/ml (INF group, n=20), or saline (placebo group, n=20) 30 min. before induction of general anesthesia. Assessment parameters included; hemodynamics, postoperative pain, sedation and adverse effects. **Results:** Intranasal fentanyl significantly attenuated hemodynamic changes in SBP, DBP and HR at 1, 3, 5 and 7min. after intubation. INK and INF significantly prolonged time to first analgesic request (253.74±25.01min.  $P<0.000$  vs. 233.80±24.57min,  $P<0.000$ ), compared with placebo (120.71±24.64min.). Diclofenac consumption was significantly reduced in INK (85.32±10.31mg) and INF (81.42±8.48mg) compared with placebo (150.00±0.00mg). VAS scores were significantly lower with INK and INF in first 4h postoperative ( $P<0.000$ ) with a trend towards lower values at all recorded time points. Incidence of adverse effects was higher in INK, While the surgeon ( $P<0.000$ ) and patient ( $P<0.000$ ) satisfaction indices were higher with INF. **Conclusion:** Intranasal ketamine or intranasal fentanyl enhanced postoperative analgesia after endoscopic nasal surgery. Psychomimetic side effects of ketamine still occur with intranasal administration and the clinical goal of ketamine must be defined [Hala S. Abdel-Ghaffar and Mohamed A M. Salem. **Safety and Analgesic Efficacy of Pre-Emptive Intranasal Ketamine versus Intranasal Fentanyl in Patients Undergoing Endoscopic Nasal Surgery.** Journal of American Science 2012; 8(3):430-436]. (ISSN: 1545-1003). <http://www.americanscience.org>. 57

**Key words:** Anesthesia, endoscopic, nasal, analgesia, ketamine, fentanyl.

### 1. Introduction

Due to its non-invasive mode of administration, intranasal (IN) application of drugs may be a valuable alternative to invasive pain management(1). Nasal administration with transmucosal absorption may offer advantages; such as ease of administration, rapid onset and patient control. It bypasses gastrointestinal and hepatic presystemic elimination, and is applicable in nauseated and vomiting patients(2). The enormous surface area (150-180 cm<sup>2</sup>) and the rich blood supply of the mucosa allows small molecules to be rapidly transported into the blood stream(3). For example, dipping a cotton swab tip into sufentanil and applying it to the nasal mucosa of the ferret produces an effect within seconds(3).

Studies investigating the treatment of pain via opiate delivery across the nasal mucosa note an equivalent or superior pain control to IV, IM and subcutaneous delivery methods(4-7). In the postoperative setting, patient controlled intranasal analgesia (PCINA) systems used to deliver intranasal fentanyl or sufentanil result in equivalent pain control as IV PCA devices, and superior pain control to customary ward-delivered pain medication(8-12). Being a NMDA (N-methyl-D-aspartate) - receptor antagonist, an analgesic sub-anesthetic low dose of

intranasal ketamine as a non-opioid medication was successfully used for postoperative acute pain(13), neuropathic pain(14), and also in burn dressing changes(15).

Many clinical trials have reported a significant inter-individual variation in pharmacokinetics and clinical effects of a standard dose of intranasal opioid medication. This variation has been attributed to three factors; improper drug volumes and concentrations, inadequate mucosal coverage, and the well known inter-individual responses to all opiates regardless of the method of administration (2,16). Much of the published data tend to report the use of low doses of inadequately concentrated formulations with large volumes of medication delivered in various fashions (drops, sprays, atomization, and nebulization), as a confounding factor. To our knowledge no clinical studies investigated the nasal mucosal coverage as a local causative factor for such inter-individual variation in clinical effects. Moreover, most of published clinical trials investigated the use of intranasal analgesic medications in extranasal painful settings.

Several endoscopic ear-nose and throat (ENT) procedures such as functional endoscopic sinus surgery (FESS) and endoscopic turbinectomy, have been recently developed, with the aim of minimizing

surgical invasiveness(17). They are associated with mild to moderate postoperative pain related to both the surgical trauma and nasal packing(19).

We designed this prospective double-blind placebo-controlled study to investigate the safety and analgesic efficacy of pre-emptive intranasal Ketamine (1.5mg/kg, 50mg/ml) (as a non opioid) versus generic fentanyl (1.5µg/kg, 50µg/ml) (as an opioid) in patients undergoing endoscopic nasal surgery. As drugs studied were administered pre-emptively, their possible effects on hemodynamic response to laryngoscopy and intubation were also investigated.

## 2. Patients and methods:

With local institutional research committee approval (in the faculty of medicine, Assiut University, Egypt) and patient's written consent, 60 ASA I/II adult normotensive patients aged 18-65 years who were scheduled to do elective endoscopic nasal surgery, were prospectively enrolled in the study. The indications for nasal surgery were recurrent or chronic sinusitis refractory to medical treatment, and nasal polyposis. Excluded from the study patients with: hepatic, renal, respiratory, neurologic, or psychiatric disease, BMI>25kg/m<sup>2</sup>, history of drug allergy or drug abuse, use of analgesics or central nervous system depressants over the previous 24 hours, patients showed difficulty in understanding and interpreting the pain assessments and patients showed difficulties in laryngoscopy and intubation.

Patients were randomly allocated before surgery according to a computer-generated randomization list to three groups of 20 patients each. In the INK group, patients received intranasal ketamine 1.5mg/kg (50mg/ml), In the INF group, patients received intranasal generic fentanyl 1.5µg/kg (50µg/ml), and the placebo controls whose received intranasal saline 0.9%. Preoperatively, patients were instructed in how to evaluate their own pain using the Visual Analogue Pain Scale (VAS) score ranging from 0 to 10 (with Zero =no pain and 10= the worst pain imaginable).

The attending anesthesiologist, surgeon and data collection personnel were blinded to patient group assignment and to the nature of the study medication.

Thirty minutes before induction of anesthesia, the fasted unpremedicated patients were placed in the supine position. The undiluted study drug was dripped slowly via an insulin syringe half inside each nostril in 0.3ml increments, with the head turned towards the administration side so that the study drug solution stays in contact with the lateral surface of the nasal cavity and does not drip into the nasopharynx. Patients were asked to report about any pharyngeal drug entrance. We maximally administered 2ml volume, 1ml inside each nostril. If the calculated dose exceeded 2ml volume, the remaining dose was given 10 min. later. Patients were strictly observed in well equipped setting, and monitoring included: heart rate, respiratory

rate, noninvasive arterial blood pressure, oxygen saturation, and the Modified Observer's Assessment of Alertness/Sedation scale (OAA/SS). No local anesthesia was used.

The anesthetic technique was standardized. Induction started with iv propofol 2-3mg/kg, fentanyl 1µg/kg, and cisatracurium 0.15mg/kg to facilitate endotracheal intubation. Propofol was administered in 20mg increments assessed by verbal contact. Anesthesia was maintained with isoflurane (1MAC) in oxygen/air mixture and propofol infusion (4-6mg/kg/hr). The propofol infusion rate was adjusted aiming to maintain a mean arterial blood pressure around 65 mmHg. Patients were mechanically ventilated in ventilation parameters that maintain an endtidal CO<sub>2</sub>~32-35mmHg. Monitoring included; electrocardiography (ECG), non-invasive blood pressure, peripheral arterial oxygen saturation (SaO<sub>2</sub>%) and end-tidal carbon dioxide (EtCO<sub>2</sub>). Intraoperative data recorded included; heart rate, systolic and diastolic pressure continuously monitored and recorded before and after induction of anesthesia, and at 1, 3, 5, 7, 10, and 15min. after intubation, in addition to propofol's induction and maintenance doses. At the end of surgery, the surgeon graded his satisfaction with the technique (very satisfied, mildly satisfied, or not satisfied) based on surgical conditions and bleeding during surgery, and bilateral nasal packing was performed. Anesthesia was discontinued and neuromuscular relaxation was reversed using neostigmine 40 µg/kg and atropine 20 µg/kg slowly intravenous, and patients were turned aside in the recovery position. Extubation performed awake after return of protective airway reflexes, and the extubation time (the time in minutes from discontinuation of anesthesia till extubation) was recorded. Patients were transported to PACU, where postoperative recovery was assessed according to the modified Aldrete& Kroulik Score(19). They were discharged to the surgical ward if had got a score>9, and the recovery time was recorded (the time in minutes from discontinuation of anesthesia till attaining an Aldrete score>9). Postoperatively, the Visual analogue scale (VAS) assessments were performed at rest in the following time points; at 30min., and 1, 2, 4, 6, 12, and 24 hrs postoperative. Diclofenac sodium 75mg im. was given if requested or if VAS scores were ≥3, and the total consumption of rescue analgesics in the first 24 hrs postoperatively was calculated.

Any adverse effects in the 1st 24 hrs postoperative were treated and recorded including; nausea and vomiting, respiratory depression, sedation, hallucinations, delirium, disorientation, agitation, restlessness, nightmares, nystagmus, photophobia, hyperalgesia, salivation, skin rash, and Others. The patients graded their satisfaction regarding analgesia

(very satisfied, mildly satisfied, or not satisfied) at the end of the 24-hrs study period.

### Statistical analysis:

Analysis was performed using SPSS version 17(Chicago-USA). Data were presented as mean±SD, numbers, frequencies, and percentages. ANOVA followed by post-hoc test were used for comparison of parametric data. Kruskal Wallis test was used to compare non-parametric data while Mann-Whitney used to compare between two groups. Chi-square test was used for comparison between percentages and frequencies.  $P < 0.05$  was considered significant.

### 3. Results:

Seventy two patients were screened for eligibility to participate in this study, and 60 patients were subsequently consented and enrolled (n = 20 per group), with no patient drop outs. There were no differences between groups in demographic characteristics as regards to age, weight, sex, ASA class, operative procedure and also in operation time and anesthesia time (Table.1). There were no significant differences between groups in recovery characteristics including extubation time and recovery time (Table.1). The mean induction and maintenance doses of iv. propofol were significantly lower in the INF group ( $P < 0.03$  and  $P < 0.000$ ) compared with INK and placebo groups (Table.1).

Since the administration of study drugs till the induction of general anesthesia, there were no significant intra- or inter-group differences in the mean arterial blood pressures, heart rate, respiratory rate, or

peripheral arterial oxygen saturation (data not shown). Sedation scores for 60 patients are shown in Table 2.

Intra and inter-group comparisons for the mean systolic (Fig.1), diastolic blood pressure (Fig. 2) and heart rate (Fig. 3) demonstrated that patients in the INF group significantly exhibited the least hemodynamic changes to laryngoscopy and intubation; at 1, 3, 5, and 7min. after intubation. With non-significant differences between groups at 10 and 15min. after intubation.

The mean time to first analgesic request (Table 3) was significantly prolonged in the INK and INF groups ( $253.74 \pm 25.01$ min,  $P < 0.000$  vs.  $233.80 \pm 24.57$ min,  $P < 0.000$ ), compared with placebo ( $120.71 \pm 24.64$ min.). The mean diclofenac consumption dose was significantly reduced in INK ( $85.32 \pm 10.31$ mg,  $P < 0.000$ ) and INF ( $81.42 \pm 8.48$ mg,  $P < 0.000$ ) groups compared with placebo ( $150.00 \pm 0.00$ mg). With a non significant difference between INK and INF groups. Compared with placebo controls, patients in INK and INF groups (Fig.4) exhibited significantly lower mean VAS scores in the first 4h postoperative ( $P < 0.000$ ) with a trend towards lower values at all recorded time points. With no significant difference between the two treatment groups.

The incidence of postoperative adverse effects was higher in the INK group patients compared with patients in the INF and placebo groups (Table 4). Finally, significantly higher surgeon ( $P < 0.000$ ) and patient ( $P < 0.000$ ) satisfaction indices were recorded in INF group compared with INK and Placebo groups (Table 5).

**Table (1): Demographic and recovery characteristics.**

	Placebo group	INK group	INF group	p1	P 2	P3
Age(yr)	31.40±12.35	30±12.76	33.80±12.64	NS	NS	NS
Weight(kg)	69.60±13.67	70.20±15.83	70.60±11.76	NS	NS	NS
Sex(M/F)	15/5	14/6	12/8	NS	NS	NS
ASA I/II	20/0	20/0	19/1	NS	NS	NS
Anesthesia time(min.)	76.31±30.25	74.45±31.03	71.40±31.09	NS	NS	NS
Operation time(min.)	69.30±28.76	66.80±30.87	63.40±30.61	NS	NS	NS
Extubation time (min.)	9.54±3.63	10.10±3.53	10.15±3.26	NS	NS	NS
Recovery time (min.)	31.54±10.65	34.45±10.57	33.28±10.89	NS	NS	NS
Propofol induction dose (mg).	146.21±30.54	140.00±30.86	121.00±16.49	NS	0.03	NS
Propofol maintenance dose (mg).	443.60±97.43	413.50±90.33	292.70±60.26	NS	0.000	0.000

Data are expressed as mean±SD and number (n).

P1: Significance between the INK and placebo groups. P2: Significance between the INF and placebo groups.

P3: Significance between the INK and INF groups

**Table (2): Modified Observer's Assessment of Alertness/Sedation Scale.**

Responsiveness	Score	Placebo group	INK group	INF group
Agitated.	6	0	0	0
Responds readily to name spoken in normal tone (alert).	5	20	12	19
Lethargic response to name spoken in normal tone.	4	0	4	1
Responds only after name is called loudly and/or repeatedly.	3	0	4	0
Responds only after mild prodding or shaking.	2	0	0	0
Does not respond to mild prodding or shaking.	1	0	0	0
Does not respond to deep stimulus.	0	0	0	0
<b>P value</b>		0.03		

Values indicate the number of patients demonstrating each degree

**Table (3): Time to first analgesic request and Diclofenac consumption in 1st 24h postoperative.**

	Placebo group	INK group	INF group	P1	P2	P3
Time to first analgesic request(min.)	120.71±24.64	253.74±25.01	233.80±24.57	0.000	0.000	0.000
Diclofenac consumption in 1 <sup>st</sup> 24h postoperative (mg).	150.00±0.00	85.32±10.31	81.42±8.48	0.000	0.000	NS

Data are expressed as mean±SD.

P1: Significance between the INK and placebo groups. P2: Significance between the INF and placebo groups.

P3: Significance between the INK and INF groups.

**Table (4): Perioperative side effects.**

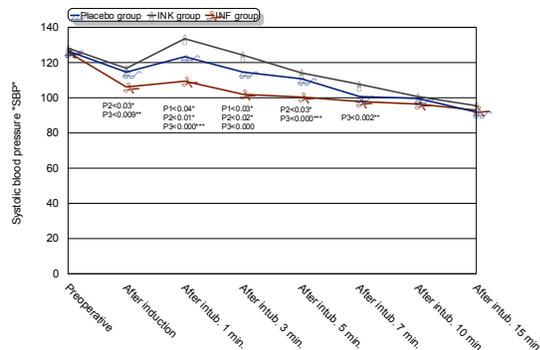
	Placebo group	INK group	INF group	P value
<b>Postoperative:</b>				
Vomiting	5(25%)	3(15%)	4(20%)	NS
Photophobia	None	3(15%)	None	NS
Nystagmus	None	1(5%)	None	NS
Hallucination	None	3(15%)	None	NS
Headache	None	1(5%)	None	NS

Data are expressed as number and percentages.

**Table (5): Surgeon and patient satisfaction.**

	Very satisfied	Mildly satisfied	Not satisfied
<b>Surgeon satisfaction index:</b>			
Placebo group	5(5%)	14(14%)	1
INK group	3 (15%)	13 (65%)	4(20%)
INF group	12 (60%)	8 (40%)	-----
<b>P value</b>	0.000		
<b>Patient satisfaction index:</b>			
Placebo group	-----	16(80%)	4(20%)
INK group	-----	13(65%)	7(35%)
INF group	14(70%)	6(30%)	-----
<b>P value</b>	0.000		

Data are expressed as number and percentages.

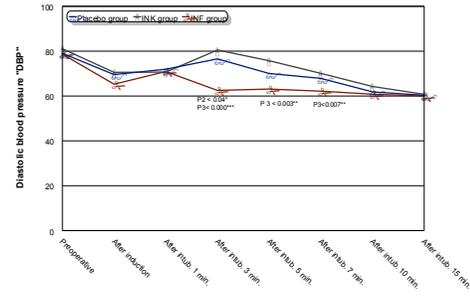


**Figure (1): Changes in the mean systolic blood pressure (SBP) with time**

P1: Significance between the INK and placebo groups.

P2: Significance between the INF and placebo groups.

P3: Significance between the INK and INF groups.

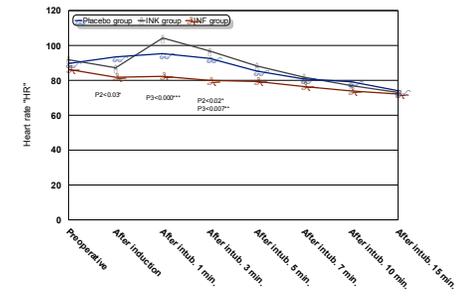


**Figure (2): Changes in the mean diastolic blood pressure (DBP) with time.**

P1: Significance between the INK and placebo groups.

P2: Significance between the INF and placebo groups.

P3: Significance between the INK and INF groups.

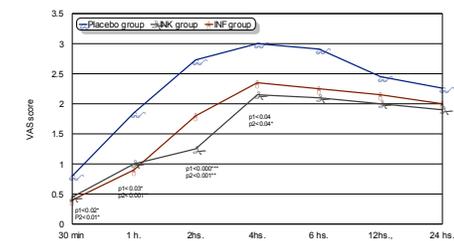


**Figure (3): Changes in the mean heart rate(HR) with time.**

P1: Significance between the INK and placebo groups.

P2: Significance between the INF and placebo groups

P3: Significance between the INK and INF groups.



**Figure (4): The Visual Analogue pain Scale in the three studied groups.**

P1: Significance between the INK and placebo groups.

P2: Significance between the INF and placebo groups.

P3: Significance between the INK and INF groups.

#### 4. Discussion:

In this study we found that both pre-emptive intranasal ketamine or fentanyl enhanced postoperative analgesia after endoscopic nasal surgery. Compared with placebo group, the Incidence of adverse effects was higher with INK, While the surgeon and patient satisfaction indices were higher with INF.

Current evidence suggests that INF is an effective safe and well tolerated method of analgesia in pediatric preoperative and postoperative pain control(20), and adult acute pain in emergency department, prehospital and hospital settings(21,22). It also proved effectiveness in managing breakthrough pain in cancer patients(23). In accordance with these studies, INF was an effective method for pain relief even in patients undergoing nasal surgery. The weak point in this study, is that we didn't measure serum levels for the studied drugs. Further studies are needed to stress on pharmacokinetics and pharmacodynamics of nasally administered drugs in patients with nasal pathology. Local factors that can affect nasal drug absorption include; membrane permeability, environmental PH, mucociliary clearance, cold and rhinitis. Atrophic rhinitis is the nasal pathology that is associated with well documented impaired absorptive capacity of the nasal mucosal coverage. The nasal pathology encountered in this study included chronic sinusitis, nasal polyposis, hypertrophied turbinates with or without deviated septum. The morphological derangements in nasal passages and the presence of infection altering the PH can hinder absorption of nasally administered drugs to some extent. However, the large surface area and high absorptive capacity of nasal mucosa can circumvent these changes.

Due to its high potency and lipophilicity, intranasal fentanyl has a bioavailability of 89% with a short onset of action (approximately 7min.) and duration times (approximately 1h)(24). As our study drugs were given pre-emptively, we couldn't report the onset of analgesic effect for INF neither INK. In this study, the mean request times in INF group exceeded the expected duration of a single dose. Three factors might be responsible for such enhancement; First, the pre-emptive administration of INF before surgical stimulation and its possible role in blocking or reducing the hypersensitivity and hyperalgesia thus decrease postsurgical pain (25). Such reduction in hypersensitivity and hyperalgesia might be in part responsible for the trend towards lower VAS scores in whole 24hrs postoperative that shown in this study with both INK and INF. Second, the additive effect of iv. fentanyl used during induction of general anesthesia. Third, the minimally invasive nature of endoscopic nasal surgery which is associated with pain of mild to moderate intensity that easily controlled.

We administered fentanyl and ketamine pre-emptively, because the presence of nasal packs hinders their administration postoperatively. However, most patients complain from moderate to severe pain during pack removal in the 2<sup>nd</sup> day postoperative. Further studies are needed to investigate the role of INF in controlling such pain and for further comparisons between nasal and extranasal painful settings.

Nasal drugs must be administered in concentrated small volumes with out irritation of nasal mucosal membranes. The maximum volume to avoid run off into the pharynx by a single administration in one nostril in man is 150mcg/ml. Thus, the therapeutic dose should ideally be contained in 150mcg/ml or 2 x 150mcg/ml formulation if both nostrils are used in a single session(2). Due to its low cost and availability, we used the standard generic fentanyl(50mcg/ml). In 2011, Dr. Borland and colleagues published a randomized controlled trial comparing generic fentanyl to the more expensive custom concentrated fentanyl (300mcg/ml) in children (3-15yr) with painful extremity fracture. They found that the two concentrations of INF were equivalent in reducing pain with a trend to increased oral additional agents in the more dilute solution. They and also Crelin *et al.*, concluded that the wide spread use of this readily available analgesic in the standard concentration can be supported, particularly in patients <50 kg (26,27).

The dose of INF selected in this study was in accordance with previous studies that used a mean dose of 1.4mcg/kg in adult trauma patients and proved analgesic effectiveness(28). Higher doses would increase the volume delivered with possible pharyngeal runoff. Sufentanil 0.5-0.7mcg/kg(50mcg/ml) provides an effective alternative to INF in patients>50kg(29).

Being a competitive NMDA-receptor antagonist, a subanesthetic dose of ketamine is hypothesized to prevent or reverse (already established) central sensitization and thus to reduce postoperative pain. Results of studies evaluating efficacy of preemptive ketamine are promising and consistent with the pharmacology and physiological importance of NMDA-receptors in nociceptive pain pathogenesis(25,30). In this study, pre-emptive intranasal ketamine 1.5mg/kg alone successfully reduced postoperative pain after endoscopic nasal surgery.

However, in this study two major drawbacks were observed with INK; First, the cardiovascular stimulating properties of ketamine that yielded undesirable hemodynamic response to intubation and hindered intraoperative elective hypotension, especially in the 1<sup>st</sup> 15 min. intraoperative with frequent surgeon complains. Second, the postoperative psychic side effects; as 3 patients(15%) from a total of 20 patients were hallucinating. In two studies by the same research group, a total of 5(5%) of 85 patients

received ketamine had severe enough psychomimetic effects to require benzodiazepines or to be withdrawn from the study(31,32). The incidence of psychomimetic side effects varies from 5% to greater than 30% after high dose of ketamine anesthesia(33). Several factors associated with psychomimetic effects include age, sex, subjects who normally dream or have a history of psychopathology, high doses of ketamine(>2mg/kg, iv) with high serum levels (200ng/ml), and rapid intravenous administration (>40mg/min.)(30,33).

In conclusion, Intranasal ketamine or intranasal fentanyl enhanced postoperative analgesia after endoscopic nasal surgery. Within limits and under appropriate monitoring, low dose ketamine can be used safely either alone or as an adjunct to other analgesic therapies in the management of postoperative pain. Further dose finding studies for intranasal ketamine alone or as an adjunct to other analgesics in terms of analgesic efficacy versus psychomimetic adverse effects, are needed.

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