Original Article

Indian Journal of Anaesthesia and Analgesia
Volume 4 Number 2, April - June 2017 (Part–2)
DOI: http: / / dx.doi.org / 10.21088 / ijaa.2349.8471.4217.26

A Clinical Comparative Study of Pre-Emptive Analgesia by Intranasally Instilled Ketamine Vs Fentanyl in Endoscopic Nasal Surgery

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Abstract

Background: This study was undertaken for the study of pre-emptive analgesic effects of intranasal ketamine and intranasal fentanyl in patients undergoing endoscopic nasal surgery. *Material and Method:* Patients were allocated in one of the following three groups. Group C for Intranasal Normal saline (3ml) as control group, Group F for Intranasal Fentanyl (2mcg / kg) and Group K for Intranasal Ketamine (1.5mg / kg). All patients observe for intraoperative hemodynamic monitoring and in postoperative visual analoge pain score, rescue analgesia requirements and possible side effects. *Results:* In our study, we found results in the following order for the three groups:- VAS scoring : Group C > Group K > Group F; Sedation scoring : Group K > Group C > Group F; Total rescue analgesic requirements : Group C > Group K > Group F; Time to first analgesic requirement : Group K > Group F > Group C; Total side effects : Group K > Group F > Group C. *Conclusion:* Postoperative analgesia was best in intranasal fentanyl group, sedation was maximum in intranasal ketamine group, adverse effects although minimal, were mostly observed in intranasal ketamine group. Intranasal fentanyl group showed good cardiovascular stability during perioperative period as compared to the other two groups. Fentanyl and ketamine both produced significant post-operative analgesia in good number of patients without any significant adverse effects. Hence, they are recommended for use in post-operative analgesia by intranasal instillation in nasal endoscopic surgeries.

Keywords: Fentanyl; Ketamine; Intranasal Instilled; Pre-Emptive Analgesia.

Introduction

Pre-emptive analgesia initiated before the surgical procedure to prevent pain in the postoperative period has the potential to be more effective than a similar analgesic treatment initiated after completion of surgery, since treatment is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period. As a consequence, pre-emptive analgesia can reduce immediate postoperative pain and also prevent the development of chronic pain by decreasing the altered central sensory processing.

The nasal cavity is easily accessible, rich vascular plexus permits topically administered drugs to rapidly achieve effective blood levels while avoiding intravenous catheters. Because of this easily accessed vascular bed, nasal administration of medications is emerging as a promising method of delivering medications directly to the blood stream.

Nasal therapy also called 'Nasya karma' has been recognized form of treatment in the Ayurveda system of Indian medicine's [1]. Introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. Due to its non-invasive mode of administration intranasal application of drugs may be a valuable alternative to invasive pain management [3]. Nasal administration with trans-mucosal absorption may offer advantages such as ease of administration, rapid onset, and patient control. It bypasses gastrointestinal and hepatic

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Received on 20.03.2017
Accepted on 07.04.2017

presystemic elimination, and is applicable in patients with nausea and vomiting [4]. The enormous surface area (150-180 cm^2) and the rich blood supply of the mucosa allows small molecules to be rapidly transported into bloodstream. It is generally accepted that drugs applied to the nasal cavity can directly access the brain and the CNS, which could provide therapeutic advantages such as rapid onset and lower systemic exposure. The olfactory region of the nasal cavity has been implicated in facilitating this direct nose-to-CNS transfer.

It was reported that lipophilic drugs like Fentanyl are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100% on the other hand absorption of hydrophilic drugs can be increased by means of absorption enhancers. Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity [5].

On the basis of above information, the study was undertaken to evaluate the efficacy of absorption of analgesic drugs - fentanyl & ketamine through nasal mucosa, in certain operative procedures of nose with the aim to provide pre-emptive analgesia.

Materials and Methods

The proposed study was carried out over a period of one year (2015-2016) in S.R.N Hospital associated with M.L.N Medical College, Allahabad. After approval from ethical committee and obtaining written and informed consent from the patient,sixty adult male and female patients belonging to ASA physical status I – II, age group 18-60 yrs posted for Elective Endoscopic Nasal Surgeries were allocated in one of the following groups.

Group C : Patients who received Intranasal Normal saline (3ml) as control group

Group F: Patients who received Intranasal Fentanyl (2mcg/kg) to make volume (3ml) with normal saline

Group K: Patients who received Intranasal Ketamine (1.5mg/kg) to make volume (3ml) with normal saline

Preoperatively patients were explained about visual analogue pain scales (VAS); 0-10 with 10= the worst pain imaginable and 0=no pain. Thirty minutes before induction of anaesthesia, the fasted unpremedicated patients were placed in supine position. The study drug was instilled drop by drop slowly over 10 minutes via an insulin syringe half volume inside each nostril in 0.5 ml increments with the head turned towards the opposite side so that the study drug solution stayed in contact with the lateral surface of the nasal cavity and did not drip or run off into the nasopharynx. We maximally administered 3ml volume, 1.5ml inside each nostril, After intravenous access had been established.

General Anaesthesia Protocols were Followed

1. *Premedication:* By giving Inj Glycopyrrolate (0.2mg) i.v with Inj Midazolam 30mcg/kg intravenous 15 mins before induction
2. *Preoxygenation:* For 3 minutes with 100% oxygen
3. *Induction:* Intravenous route by Inj Propofol (2-2.5mg/kg) till loss of verbal commands + Inj Succinylcholine (1.5-2mg/kg) i.v. Intubation by oral route was done with cuffed PVC endotracheal tube.
4. *Maintenance of Anaesthesia with:* 50:50 N2O + O2 +Isoflurane (0.5-1.0%) + Vecuronium(0.02-0.04mg/kg).
5. *Reversal:* Non depolarising muscle blockade was reversed with Inj Neostigmine (0.05mg/kg)+ Glycopyrrolate (0.01mg/kg).

Postoperatively, Visual Analog Scale (VAS) assessments and Ramsay Sedation score were observed and recorded. Assessments were performed at rest in the following time points: at 0,15minutes and every 30 minutes thereafter till analgesic effect weared off. Maximum sedation score was noted.Diclofenac sodium 75 mg i.m was given as rescue analgesic if post-operative VAS≥3 or requested by the patient . Time duration (post-operatively) after which rescue analgesic was required was noted. Any adverse effects in the first 24hrs postoperative was recorded and treated. Statistical data- For statistical analysis, SPSS version 12.0 was used. Data were presented as mean±SD or proportion (%). Statistical analysis was performed with an ANOVA test and a $P<0.05$ was considered significant.

Observations and Results

A total of sixty patients participate in this study, and they were subsequently consented, and enrolled (n = 20 per group), with no patient dropouts The groups were similar with respect to age, weight and

height as well as found no significance difference with one way ANOVA test ($p > 0.05$) (Table 1). By including only ASA–I and ASA–II patients, we tried to eliminate any systemic problems confounding our results. Intra and inter-group comparisons for the mean arterial blood pressure (Graph 1) and heart rate (Graph 2) demonstrated that patients in the Group F significantly exhibited the least hemodynamic changes among all three groups in intraoperative as well as in postoperative period . The mean time to first analgesic request (Graph 3) significantly prolonged in the Group F (246.8 ± 23.78 min) and group K (250.27±23.71 min) than group C (130.56±26.44 min) which was statistically significant ($p<0.05$). First analgesic requirement between Group F and Group K found to be insignificant ($p>0.05$).

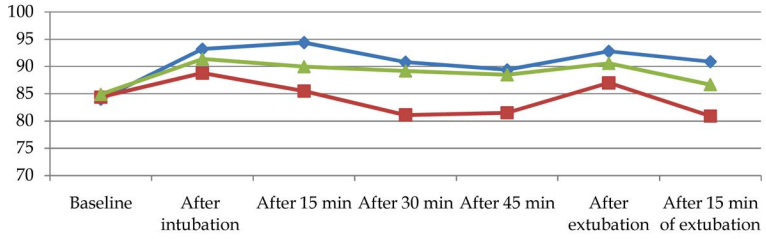
Total number of rescue analgesics in 24 hours (Graph 4) given as intravenous diclofenac in Group F (86.25±27.48 mg) and in Group K (93.75±33.31 mg) was statistically significant ($p <0.05$) than Group C (153.75±16.77 mg), whereas this was found insignificant between Group K and Group F ($p>0.05$). Compared Group C patients with Group K and Group F (Graph 5) exhibited significantly lower mean VAS scores in group K and Group F in the postoperative period ($p <0.05$) with a trend towards lower values at all recorded time points. There were also significant ($p<0.05$) difference in Group F and K for VAS score. Nausea and vomiting were noted in all three groups, two patients in Group K, five patients in Group F, one patient in Group C and these Patients were treated successfully with inj.ondansetron 4 mg intravenous. Hallucination was noted in three and Nystagmus in one patient in group K. In comparison to Group C and Group F, Ramsay Sedation Score was significantly higher in Group K ($p<0.05$).

In our study we found results in the following order amongst the three groups:-

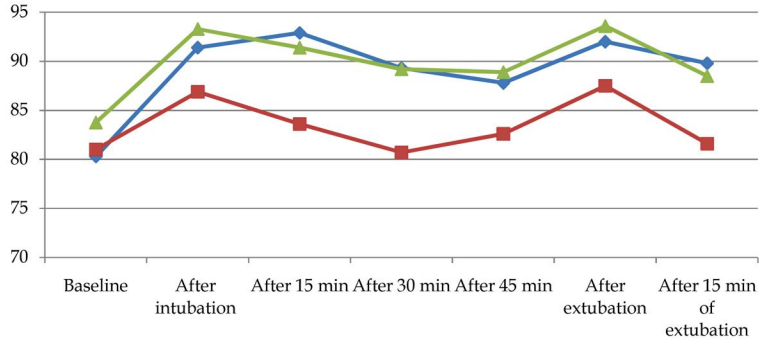
I. VAS scoring : Group C > Group K > Group F
II. Sedation scoring : Group K > Group C > Group F
III. Total rescue analgesic requirements : Group C > Group K > Group F
IV. Time to first analgesic requirement : Group K > Group F > Group C
V. Total side effects : Group K > Group F > Group C

Table 1: Comparison of age, weight and height in the three groups

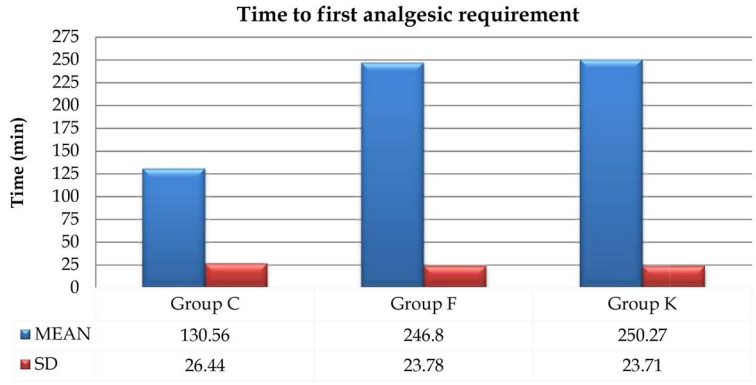
Demographic Profile	Group C	Group F	Group K	p value (ANOVA)
Age(yrs) (Mean ± SD)	26.3 ± 2.92	24.6 ± 3.32	25.1 ± 2.94	0.20
Range (yrs)	20-30	20-32	20-30	
Wt.(kg) (Mean ± SD)	56.65 ± 4.03	55.5 ± 3.74	55.75 ± 4.40	0.645
Range (kg)	50-62	50-62	50-62	
Ht.(cm) (Mean ± SD)	157.5 ± 3.39	158.75 ± 3.55	156 ± 3.73	
Range (cm)	150-162	150-164	150-162	0.058



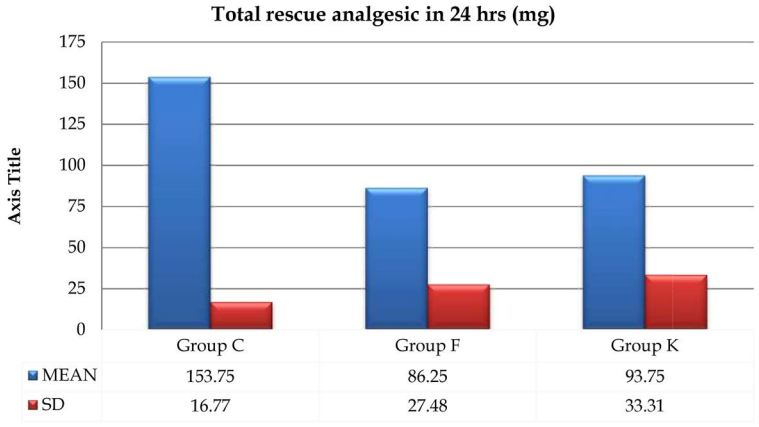
Graph 1: Overall comparison of Mean arterial pressure (MAP)



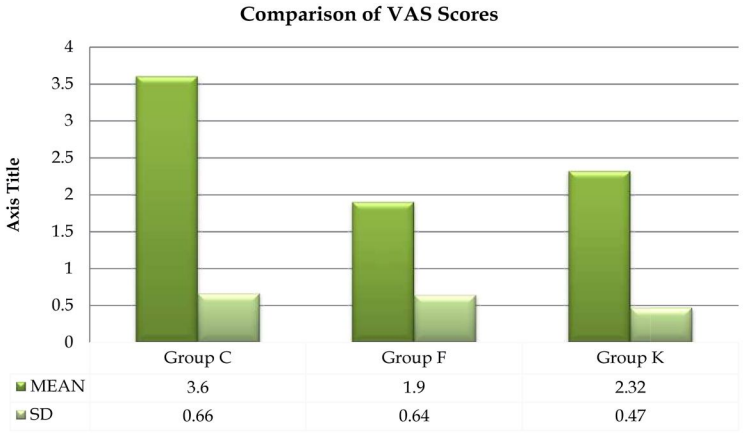
Graph 2: Overall comparison of Heart rate (HR)



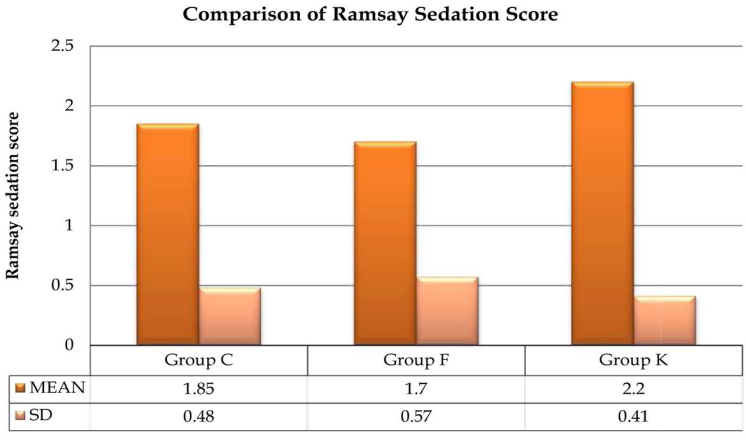
Graph 3: Time to first analgesic requirement



Graph 4: Total rescue analgesic in 24 hrs (in mg)



Graph 5: Comparison of VAS Scores



Graph 6: Comparison of Ramsay Sedation Score

Discussion

Prevention of injury-induced functional alterations in the CNS by pre-emptive analgesia is a fascinating working hypothesis based on substantial scientific evidence. Studies investigating the treatment of pain via drug delivery across the nasal mucosa show an equivalent or superior pain control to intravenous, intramuscular or subcutaneous delivery methods. Several endoscopic ENT procedures have been recently developed with the aim of minimizing surgical invasiveness; they are associated with mild to moderate post-operative

Previous studies used fentanyl by aerosol for postoperative analgesia and They concluded that inhaled fentanyl is an effective, safe and convenient method of analgesia which merits further investigation into such areas as mode of action and method of administration [6]. Similarly, we also found a good analgesic effect of fentanyl by instillation via the intranasal route in doses of 2mcg / kg without any significant adverse effect. J M Malinovsky et al (1996) [7] did a study in which during halothane anaesthesia, 32 children, aged 2-9 year, weight 10-30 kg were allocated randomly to receive ketamine 3 mg kg-1 nasally (group IN3) or ketamine 9 mg kg-1 nasally (group IN9); ketamine 9 mg kg-1 rectally (group IR9); or ketamine 3 mg kg-1 i.v (group IV3). They concluded that nasal administration of low doses of ketamine produced plasma concentrations associated with analgesia but using high doses via the nasal route produced high plasma concentrations of ketamine similar to those that induce anaesthesia. Although we did not assay the blood level of intranasally instilled ketamine in our study, but our observation of adequate postoperative analgesia in a good number of patients shows sufficient absorption of the drug when instilled intranasal.

Patient-controlled intranasal or intravenous analgesia with fentanyl in 48 patients (ASA I-III) on the day of surgery (orthopedic, abdominal or thyroid). They concluded that intranasal PCA with fentanyl is an effective alternative to i.v. PCA in postoperative patients [8] nasal administration of opioids (fentanyl, alfentanil, sufentanil, butorphanol) may be an alternative route to intravenous, subcutaneous, oral, transmucosal or rectal administration in some patients. They concluded that nasal administration of opioids has promising analgesic features [9,10]. Similarly we also showed by our study that intranasal fentanyl had analgesic features.

Now a days ketamine gaining importent role in postoperative pain management by various routes. huge V et al [11] randomized sixteen patients with neuropathic pain of various origins into two treatment groups: (S)-ketamine 0.2mg / kg (group 1); (S)-ketamine 0.4mg / kg (group 2). They concluded that Intranasal administration of low dose (S)-ketamine rapidly induces adequate plasma concentrations of (S)-ketamine and subsequently of its metabolite (S)-norketamine. The time course of analgesia correlated with plasma concentrations. In our study with intranasal ketamine (1.5mg / kg) we observed (mean±S.D) VAS score (2.32±0.47) in the postoperative period, which was inferior to fentanyl group but definitely better when compared to control group.

Hala S. Abdel Ghaffar and Mohamed A M Salem [12] demonstrated safety and analgesic efficacy of pre-emptive intranasal ketamine (non-opioid) vs. intranasal fentanyl (opioid) in patients undergoing endoscopic nasal surgery. They concluded that intranasal ketamine or intranasal fentanyl enhanced postoperative analgesia after endoscopic nasal surgery. Similarly we also demonstrated analgesic efficacy of intranasal fentanyl & ketamine. Time to first analgesic request is almost similar to our findings. effectiveness of sub-dissociative Intranasal ketamine as a primary analgesic agent for adult patients in which Intranasal ketamine, at a dose of about 1 mg / kg, was an effective analgesic agent in 56% of study patients [15]. The place of intranasal ketamine in analgesic guidelines for adults requires further investigation.

Bettina N. Nielsen et al [14] investigated a pediatric formulation of intranasal sufentanil 0.5 $mcg.kg^{-1}$ and ketamine 0.5 $mg.kg^{-1}$ for procedural pain and to characterize the pharmacokinetic (PK) profile. They concluded that sufentanil / ketamine nasal spray provided rapid onset of analgesia for a variety of painful procedures with few adverse effects and has promising features for use in pediatric procedural pain management.

Postoperative analgesic and behavioral effects of 3 frequently used intraoperative techniques for postoperative pain control for patients undergoing BMT under general anaesthesia. There were no difference in the efficacy of intranasal fentanyl, intravenous or intramuscular in controlling postoperative pain and emergence delirium. intranasal route fentanyl has potency for analgesia [13]. The intranasal dose of fentanyl used in this study 2 μg / kg also produced good post-operative analgesia in our observations also.

Conclusion

We concluded that postoperative analgesia was best in intranasal fentanyl group, sedation was maximum in intranasal ketamine group and adverse effects, although minimal, were mostly observed in intranasal ketamine group. Intranasal fentanyl group showed good cardiovascular stability during perioperative period as compared to the other two groups.

Fentanyl and ketamine both produced significant post-operative analgesia in a good number of patients without any significant adverse effects. Hence, they are recommended for use in post-operative analgesia by intranasal instillation in nasal endoscopic surgeries.

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