 DOI: 10.18231/2394-4994.2017.0053

A study on the feasibility of using ENTONOX as an analgesic in the casualty for pain relief vs fentanyl

R. Brindha[1,*], B. Arun Kumar[2], M. Aathura Das[3], M. Senthil[4], R. Shankar[5]

[1,5]Associate Professor, [2,3]Assistant Professor, Dept. of Anaesthesia, [4]Assistant Professor, Dept. of Emergency Medicine, Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Salem, Tamil Nadu

***Corresponding Author:**
Email: shnkr_radhakrishnan@yahoo.com

Abstract

Background: Nitrous oxide (N2O) is a gas, which provides good analgesia without many side effects for short procedures outside the operating room.It is combined with 50% oxygen and is available in premixed cylinders as Entonox . In our quest to find a safer alternative we decided to compare fentanyl with Entonox for acute pain and for small painful procedures in the casualty.

Aim: To assess the effectiveness, feasibility and acceptance of Entonox in providing pain relief for patients who present with acute pain and for providing pain relief in short procedures in the casuality in comparison with fentanyl.

Materials and Methods: A prospective single blinded randomized comparative study was conducted in Vinayaka Missions superspeciality hospital a unit of VinayakaMissions KirupanandaVariyar Medical College, Salem during the period between March 2014 and Feb 2015. The patients with pre- treatment score more than six (Pre VAS > 6) or planned for painful procedures were taken up for the study. . Group A was considered as the control group where all the patients received injection Fentanyl 2 micrograms per kg and group B was considered as the study group where all the patients received entonox.Fifty patients were done under each group.

Results: The pain score of the patients were measured after giving the drugs at the interval of 10mins, 20mins and 30mins. The mean score of the patients in the entonox group at the end of 10mins was 3.16 and in fentanyl group it was 3.91 and similarly at the end of 20mins it was 2.98 in the entonox group and 3.42 in fentanyl group and there was a statistically significant difference between the two groups. The mean pain score at the end of 30mins was 1.48 and 1.78 in entonox and fentanyl group respectively and there was no statistical significant difference between the two groups. The adverse events like drowsiness and hypotension was more common in fentanyl group than that of entonox group and the difference was statistically significant ($p<.05$). In fentanyl group four patients developed respiratory failure and required assisted ventilation for 30mins,whereas no such incident had occurred in entonox group.

Conclusion: Entonox is a safe and effective analgesic for minor procedures and in alleviating acute pain. It is cost effective and poses no significant risk to the patients in the form of hemodynamic changes or respiratory depression.

Keywords: Fentanyl, Entonox, Acute pain management.

Date of Acceptance: 23th January, 2017 **Date of Manuscript Receive:** 24th September, 2016

Introduction

Pain is an agonising symptom mentally and physically that any person could suffer and treatment of pain is the most important, yet difficult and challenging task for any physician.The treatment of pain has now come under the purview of both anaesthesiologist and physician. The sensation of pain can range from a vague nagging pain to the utmost intolerable pain. In addition to pain, patient needs to get relief from anxiety associated with trauma, and disease. Many modalities of treatment are being tried to curtail the sensation of pain and associated discomfort including anxiety.(1)

Emergency physicians and anaesthesiologists are called initially to stabilise any trauma patient especially to provide pain relief as analgesia breaks the vicious cycle of haemodynamic instability and anxiety associated with trauma. Moreover, sedation and analgesia lead to improved patient care and satisfaction, which, ultimately, facilitates diagnostic and therapeutic procedures.(2) There are many medications used for sedation and analgesia that have the potential to suppress respiratory, cardiovascular, and central nervous systems.(3)

Nitrous oxide (N2O) is a gas, which when combined with oxygen in 50:50 proportion (Entonox), creates an excellent analgesia and sedation required in a number of medical procedures. This mixture spreads rapidly in the alveoli and it has a rapid and predictable onset time of about 1 to 2 minutes, with a rapid clearance time of about 3 to 5 minutes. This gas is administered through a mask or a unilateral oral piece held by the patient.(4) The amount of gas which inhaled can be controlled by the patient. Thus, inhalation stops when the gas takes effect, and it creates sedation at the minimum required dose. The patient drops the mask when he becomes drowsy and soon regains consciousness. Entonox has many advantages like it is tasteless, odourless, colourless, easy for self-administration, and with rapid onset and offset. Its filtration is totally by lungs, and so it can be safely used in patients with liver or renal diseases.(6) Also it is very cost effective and non-invasive with very minimal side

effects like drowsiness and vomiting which would disappear in few minutes after discontinuation of gas.

There are several potential advantages of Entonox over Fentanyl mentioned in the literature like rapid onset and offset of analgesic effects, self-administration on demand and minimal cardiovascular depression. The greatest advantage is airway patency. This makes it an excellent choice of analgesia in short procedures.[7]

The predictability, safety, simplicity makes it a useful drug which can be given in repeated doses with no fear of any significant side effects. Although the newer approaches have threatened the widespread use of nitrous oxide, this simple gas still has much to offer in the field of emergency medicine.[8]

We see many patients in our casualty soon after trauma and our options were to give intravenous or intramuscular analgesics which were invariably respiratory depressants compromising the airway and cardiovascular depressants or nerve blocks needing technical expertise. In order to overcome these barriers we decided to undertake this study by using Entonox inhalation for pain relief and comparing its efficacy with fentanyl.

Aim

To assess the effectiveness, feasibility and acceptance of Entonox in providing pain relief for patients who present with acute pain to the emergency department and for short painful procedures in comparison with fentanyl.

Materials and Methods

A prospective single blinded randomized comparative study was conducted in Vinayaka Missions super speciality hospital a unit of Vinayaka Missions KirupanandaVariyar Medical College Hospital, Salem during the period between March 2014 and Feb 2015. The study was conducted after getting the clearance from the institutional ethical committee.

Inclusion criteria: Any person above 15 years who presents with acute pain was subjected to visual analogue scale pain assessment score. The patients with pre- treatment score more than six (Pre VAS > 6) or planned for painful procedure was included in the study. Patients with musculoskeletal injuries, reduction of joint dislocations, as adjunct to lignocaine in laceration repair, changing of dressings removal of packs drains, soon after trauma were taken up for the study.

Exclusion criteria: Patients who presents to ER with chest injuries, pneumothorax, decompression sickness, chronic lung diseases, gross abdominal distension, head Injuries, maxillofacial injuries, unconscious patients, ntoxicated and psychiatric patients were excluded from the study.

The patients on arrival to the casualty were initially stabilised before administering the drug.Informed consent was obtained from all patients.

The included patients was randomly allocated to two groups, namely group A and group B by picking up tokens labelled A or B by a blinded treating emergency physician in emergency room. Group A was considered as the control group where all the patients received injection Fentanyl 2 micrograms per kg and group B was considered as the study group where all the patients received entonox. The patients on arrival to emergency room were initially stabilized before administering the drug. Informed consent was taken from the patients after explaining the effects of Entonox.

Entonox was administered by the following equipment

1. **Entonox Cylinder** available in blue with white segments on the neck which contained a pre mixture of Oxygen 50.0% +/- 2.0% and Nitrous oxide 50.0% +/- 2.0% was used
2. **Pin Index Cylinder Valve** is fitted to cylinder which is designed to be used with a pressure regulator. It is made from high tensile brass with a steel spindle fitted with a Nylon 6.6 insert
3. **Demand Valve** allows the Entonox to be self-regulated by the patient. The demand valve is opened by the act of inhalation of the patient and closes down on exhalation
4. **Facemask or Mouthpiece**is connected to an Entonox supply through a demand valve system.

The cylinder is turned on with the key and pointer on the pressure gauge is observed to ensure there is sufficient gas in the cylinder for the procedure.An airtight seal must be maintained when using a mouthpiece or facemask to ensure the patientsrespiratory effort istransmitted to the demand valve, a special precaution is takento keep away sources of ignition as Entonox strongly supports combustion. For a cylinder of entonox filled to 2000psi the new critical temperature of nitrous oxide known as pseudocritical temperature that is the temperature at which condensation into gas will occur decreases from 36.4^0C to -6^0C. Hence when temperature reduced to such low levels phase separation can occur. But any liquid nitrous oxide formed as a result of colling the cylinder to not lower than -40^0C could be revaporised into gaseous state by storing the cylinder horizontally for 24 hours at a temperature of atleast 5^0C. The horizontal orientation increases the area of contact between liquid and gaseous phases and decreases the distance between liquid surface and cylinder wall.

The treating doctors and the paramedical staff were given proper training in using the entonox mixture for acute pain management.

The change in sensorium, blood pressure, heart rate, respiratory rate, saturation and severity of pain before and after treatment with the drug was measured with visual analogue score. The patients were asked about comfort level and pain reduction while using entonox.

The data were entered and analysed by using SPSS version 18, mean and standard deviation was calculated

for all the parametric variables and student t test was applied to compare the pain score between the two groups and chi-square test was used to derive the statistical significance between the adverse events occurred between the two groups.

Results

The age and sex wise distribution of the study population among the two groups was shown in Table 1. It is seen from thetable that in both the groups' males were majority than the females and they were almost in equal numbers among the entonox and fentanyl group. In both the groups the minimum age was 15 and the maximum age was 78 and the mean age among both the groups ranged between 35–38 years. The study population were almost matched without any statistically significant difference between the two groups with respect to age and gender.

Table 1: Age and sex wise distribution of the study population

Age group	Entonox group		Fentanyl group	
	Male	Female	Male	Female
15 – 25	6	3	8	4
26 – 35	8	3	10	6
36 – 45	9	5	7	4
46 – 55	4	3	3	1
56 – 65	2	2	4	1
66 – 75	1	1	1	0
>75	2	1	1	0
Total	32	18	34	16
Mean ± SD	35.4 ± 6.24	38.2 ± 5.82	34.28 ± 4.6	34.9 ±5.24

The study subjects who were included in our study with acute pain were all due to trauma in both the groups. The pain score at the time of admission was measured by using the visual analogue scale and it was seen that the mean score for the patients in the entonox group was 7.35 and in fentanyl group it was 7.13 and there was no statistical significant difference in the pain score at the time of admission (p=0.879) (Table 2). After making the patient stable with appropriate first aid measures the patients were given either fentanyl or entonox in fixed doses. The pain score of the patients were measured after giving the drugs at the interval of 10mins, 20mins and 30mins. The mean score of the patients in the entonox group at the end of 10mins was 3.16 and in fentanyl group it was 3.91 and similarly at the end of 20mins it was 2.98 in the entonox group and 3.42 in fentanyl group and there was a statistically significant difference between the two groups. It was proven that entonox has a more rapid pain relief action than fentanyl. The mean pain score at the end of 30mins was 1.48 and 1.78 in entonox and fentanyl group respectively and there was no statistical significant difference between the two groups (Table 3).

Table 2: Distribution of the study population based on the visual analogue score before the start of treatment

Visual analogue score (Pain score)	Entonox group		Fentanyl group		P value
	Frequency	%	Frequency	%	
6	5	10	3	6	0.8791
7	35	70	37	74	
8	8	16	7	14	
9	2	4	3	6	
Mean score	7.356		7.138		
Total	50	100	50	100	

P value derived by applying student unpaired T test

Table 3: Distribution of the study population based on the visual analogue score after the start of treatment

Time interval of pain assessment after initiating the treatment	Visual analogue score (Pain score)	Entonox group		Fentanyl group		P value
		Frequency	%	Frequency	%	
After 10 mins	4	6	12	15	30	<.0001
	3	23	46	30	60	
	2	21	42	5	10	
	1	0	0	0	0	

Mean score	3.164			3.918		
After 20 mins	3	37	74	44	88	0.0283
	2	10	20	6	12	
	1	3	6	0	0	
Mean score	2.987			3.421		
After 30 mins	2	39	78	41	82	0.652
	1	11	22	9	18	
Mean score	1.487			1.797		

P value derived by student unpaired T test.

The time required for initiation of treatment was much less in entonox group when compared to fentanyl group and the difference was found to be statistically significant, as the mode of delivering entonox was easier than fentanyl. The adverse events like drowsiness vomiting bradycardia hypotension and vomiting were more common in fentanyl group than that of entonox group and the difference was statistically significant ($p<.05$). In fentanyl group four patients developed respiratory failure and required assisted ventilation for 30mins,whereas no such incident had occurred in entonox group (Table 4).

Table 4: Time for initiation of treatment and the various adverse events occurred among the two study groups

Parameters studied		Entonox group	Fentanyl group	P value
Mean time required for initiation of treatment (in secs)		39.64	429.12	<.0001*
Adverse events	Drowsiness	6 (12%)	29 (58%)	<.0001**
	Hypotension	0	6(12%)	<.0001**
	Bradycardia	0	1 (2%)	0.472**
	Respiratory failure	0	4 (8%)	0.0291**
	Vomiting	2 (4%)	2 (4%)	1.000**

*- p value derived by using unpaired student T test
**- p value derived by applying chi-square test.

Discussions

Entonox is cheap, easily available, safe, fast acting and rapidly reversible with minor and transient side effects. It is convenient to use and provides patients with an active role in their own pain management. The transient nature of the effects of Entonox may have a positive impact on financial and workforce resources.[9]

Over the years, IV fentanyl has been demonstrated safe and effective for a breadth of conditions in acute pain management.[10,11] Data support that the analgesic effect was almost in par with morphine as well as the time of onset.[12] The newer advances in the usage of fentanyl is that it can be used in the form of intranasal route and the efficacy was almost similar to that of the intravenous route.[13] In our study we used the intravenous route with a fixed dose of 2microgram/kg.

In the present study the rapid onset of analgesic effect was seen with entonox when compared to fentanyl as within 10mins of administration of entonox mixture the patient's pain score had started to decrease but the analgesic effect for fentanyl and entonox at the end of 30mins was almost similar. The rapid onset of action for entonox was also proven in studies done by Kamis Mouzambi et al[14] where he compared the entonoxmisture with midazolam among the patients undergoing cardioversion and another study done by A. Young et al[15] is assessing the effectiveness of entonox in urological procedures. Maslekar*etal*[16] found that in patients undergoing colonoscopy, those receiving Entonox had a shorter time to discharge and reported significantly less pain and higher patient satisfaction than those who received intravenous sedation.There were also reports quoting that entonox being used in the management of refractory pain in the terminally ill patients.[17]

The blood/gas partition coefficient of nitrous oxide is 34 times greater than that of nitrogen. This differential solubility means that nitrous oxide can leave the bloodstream and enter air-filled cavities 34 times faster than nitrogen. As a result, nitrous oxide is contraindicated in patients in whom expansion of these air-filled cavities could compromise patient safety. This includes patients with pneumothorax, pulmonary blebs, air embolism, bowel obstruction, and those undergoing surgery of the middle ear.[18] So in our study we excluded all patients with the history of COPD.

Entonox is usually self-administered and so the time required for initiating the drug is very minimal when compared to any other drug as shown in the present study and a similar study done by Onody et al[19] and another study by Mazdak et al[20] had also proven the same.

The common adverse effects of most of the sedatives and analgesics is drowsiness, which in our study it was found to be more common in the patients who had used fentanyl and none of the patient in the entonox group experienced drowsiness at the end of one hour. So entonox has the property of rapid and fast action with a short duration when compared to fentanyl, which is an important quality of a sedative or analgesic. Entonox has no effect on the hemodynamic system as none of the patients in this group had developed hypotension or bradycardia and studies done by Calleary JG et al[21] and McIntyre IG et al[22] had also quoted the same.

Another most important quality of a sedative or analgesic is that it should not have any effect over the respiratory system leading on to the warrant the use of ventilator support, in the present study four patients in the fentanyl group developed respiratory depression for whom ventilation support with a ambu bag and oxygen was given for 30mins and later they were weaned from it but among the entonox group none of the patient had developed respiratory depression which proves that entonox can be used safely without the fear of respiratory depression and the studies done by Trojan et al[23] and Martin JP et al[24] had also proven the same.

Most of the previous studies which were mentioned were all done comparing the entonox with morphine or midazolam as no studies were conducted by comparing entonox with fentanyl our study is first of its kind. The only major limitation of the present study was the sample size as only 50 patients were taken in each group.

Conclusions

Despite significant evidence in the literature supporting the effectiveness of Entonox as an analgesic for acute pain management, to confirm its superiority over fentanyl still more research and multi-centric RCT's has to be conducted to infer that entonox is more effective than fentanyl in acute pain management. We believe that Entonox would significantly enhance patients experience as it is cost effective and poses no significant risk to the patients in the form of hemodynamic changes or respiratory failure. We would encourage the wider use of Entonox as an analgesic in patients with acute pain.

References

1. B. Krauss and M. S. Green, "Systematic analgesia and sedation for procedures," in Roberts and Hedges' Clinical Procedures in Emergency Medicine, J. R. Roberts, J. R. Hedges, C. B. Custalow, and T. W. Thomsen, Eds., 2014, pp. 586–610, Elsevier Saunders, Philadelphia, Pa, USA, 6th edition.
2. D. B. Burbulys, "Procedural sedation and analgesia," in Rosen's Emergency Medicine Concepts and Clinical Practice, J. A. Marx, R. S. Hockberger, and R. M. Walls,2014, Eds., vol. 1, pp. 50–60, Elsevier Saunders, Philadelphia, Pa, USA, 8th edition.
3. M. G. Roback, J. E. Wathen, L. Bajaj, and J. P. Bothner, "Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs," Academic Emergency Medicine,2005, vol. 12, no. 6, pp. 508–513.
4. F. G. Cunningham, J. K. Leveno, L. S. Bloom, C. J. Hauth, J. D. Rouse, andY. C. Spong, Williams Obstetrics,2010, McGraw-Hill,New York, NY, USA, 23th edition.
5. M. R. Collins, S. A. Starr, J. T. Bishop, and C. L. Baysinger, "Nitrous oxide for labor analgesia: expanding analgesic options for women in the United States," Reviews in Obstetrics &Gynecology, 2012,vol. 5, no. 3-4, pp. e126–e131.
6. C. A.Wong, "Advance in labor analgesic," International Journal ofWomen's Health,2010, vol. 1, pp. 139–154.
7. T. L. King and C. A. Wong, "Nitrous oxide for labor pain: is it a laughing matter?" Anesthesia and Analgesia, 2014,vol. 118, no. 1, pp. 12–14.
8. S. Maslekar, A. Gardiner, M. Hughes, B. Culbert, and G. S. Duthie, "Randomized clinical trial of Entonox versus midazolam-fentanyl sedation for colonoscopy," British Journal of Surgery,2009, vol. 96, no. 4, pp. 361–368.
9. Triner WR, Bartfield JM, Birdwell M, Raccio-Robak N. Nitrous oxide for the treatment of acute migraine headache. Am J Emerg Med .1999,17:252-254.
10. P. DeVellis, S. H. Thomas, and S. K. Wedel, "Prehospital and emergency department analgesia for air-transported patients with fractures," Prehospital Emergency Care,1998, vol. 2, no. 4, pp. 293–296.
11. S. H. Thomas, "Fentanyl in the prehospital setting," American Journal of EmergencyMedicine,2007,vol. 25, no. 7, pp. 842–843.
12. B. R. Wenderoth, E. T. Kaneda, A. Amini, R. Amini, and A. E. Patanwala, "Morphine versus fentanyl for pain due to traumatic injury in the emergency department," Journal of Trauma Nursing,2013, vol. 20, pp. 10–15.
13. S. Grassin-Delyle, A. Buenestado, E. Naline et al., "Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids," Pharmacology andTherapeutics,2012, vol. 134, pp. 366–379.
14. Kambiz Masoumi,1Arash Forouzan,1 Sina Saghari,2 Maryam Feli,1 Ali Reza Sattari,1 and Ali Asgari Darian. Sedative and Analgesic Effects of Entonox Gas Compared with Midazolam and Fentanyl in Synchronized Cardioversion. Critical Care Research and Practice.2015, Volume 2015, Article ID 798478, 6 pages http://dx.doi.org/10.1155/2015/798478.
15. A. Young, M. Ismail, A. G. Papatsoris, J. M. Barua, J. G. Calleary, and J. Masood, "Entonox inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence," Annals of the Royal College of Surgeons of England, 2012,vol. 94, no. 1, pp. 8–11.
16. S. Maslekar, A. Gardiner, M. Hughes, B. Culbert, and G. S. Duthie, "Randomized clinical trial of Entonox versus midazolam-fentanyl sedation for colonoscopy," British Journal of Surgery, 2009,vol. 96, no. 4, pp. 361–368.
17. Fosburg MT, Crone RK. Nitrous oxide analgesia for refractory pain in the terminally ill. JAMA. 1983;250:511–513.
18. Masood J, Shah N, Lane T. Nitrous oxide (Entonox) inhalation and tolerance of transrectal ultrasound guided prostate biopsy: a double-blind randomized controlled study. J Urol. 2002;168:116–120.
19. P. Onody, P. Gil, and M. Hennequin, "Safety of inhalation of a 50% nitrous oxide/oxygen premix. A

prospective survey of 35 828 administrations," Drug Safety, 2006,vol. 29, no. 7, pp. 633–640.
20. H. Mazdak, P. Abazri, F. Ghassemi. "The analagesic effect of inalationalentonox for ESWL," Urological Research,2007, vol. 35, no. 6, pp. 331–334.
21. Calleary JG, Masood J, Van-Mallaets R, Barua JM. Nitrous oxide inhalation to improve patient acceptance and reduce procedure related pain of flexible cystoscopy for men younger than 55 years. J Urol. 2007;178:184–188.
22. McIntyre IG, Dixon A, Pantelides ML. Entonox analgesia for prostatic biopsy. Prostate Cancer Prostatic Dis. 2003;6:235–238.
23. Trojan J, Saunders BP, Woloshynowych M, et al. Immediate recovery of psychomotor function after patient-administered nitrous oxide/oxygen inhalation for colonoscopy. Endoscopy. 1997;29:17–22.
24. Martin JP, Sexton BF, Saunders BP, Atkin WS. Inhaled patient-administered nitrous oxide/oxygen mixture does not impair driving ability when used as analgesia during screening flexible sigmoidoscopy. GastrointestEndosc. 2000;51:701–703.