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The Use of Inhalational Nitrous Oxide (Entonox) As The Sole Analgesic Agent During Colonoscopy is Feasible and Efficacious in a Substantial Proportion of Patients: A Review of a Surgeon's Experience

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1. Abstract

1.1. Objective: Colonoscopy is associated with significant discomfort requiring administration of intravenous (IV) sedation and analgesia. Nitrous Oxide (Entonox) has been shown as an alternative analgesic modality but is less frequently used in practice. This study examined the efficacy and applicability of Entonox as sole analgesic agent during colonoscopy.

1.2. Methods: A prospectively-held database of colonoscopies between May 2011-August 2019 was reviewed. Standard colonoscopy practice involved offering Entonox as the sole analgesic method; with provision of intravenous sedation/analgesia if requested or required.

1.3. Results: A total of 1664 colonoscopies were performed: 855 males (51.4%) and 809 females (48.6%). Median age was 64(17-94) years. Indications included Diagnostic (1349;81%), Surveillance (241;14.5%), Therapeutic (68;4%) and Screening (4;0.25%). 737 patients attempted Entonox (44.2%): 678 (92%) completed the procedure, however, 59 (8%) required additional IV sedation. 813 patients requested IV sedation (48.9%) and 114 patients opted for no sedation or Entonox (6.9%). There were more males in the Entonox group (59.7% vs 41.1%; *P*:0.003). Average Comfort Score was similar in the successful Entonox and the Sedation groups (2±1); but was higher in the Entonox Failure group (3.1 ± 1.1; *P*:<0.0001). Caecal intubation rate, proportion of polyp diagnosis and polypectomy rate were similar in all three main groups (*P*:0.02, *P*:0.932 and *P*:0.612).

1.4. Conclusions: Entonox provides effective analgesia during colonoscopy in a significant proportion of patients. The study reflects the totality of practice in a District General Hospital, highlighting that potential cost-effectiveness and risk reduction are potentially achievable by adopting Entonox.

2. Introduction

Colonoscopy is an integral part of any modern-day healthcare system. It is a commonly indicated procedure and is conducted to achieve definitive diagnosis or therapy in patients with a wide range of bowel symptomatology and pathology [1, 2]. Colonoscopy is a safe and effective procedure with a low complication profile [3]. However, it is often associated with anxiety and discomfort, and the use of intravenous (IV) sedation during the procedure is common practice [4]. However, IV sedation and the use of narcotics for pain control during colonoscopy come with potential adverse effects, some of which include significant respiratory or cardiovascular complications which can in turn lead to mortality [5], [6]. Moreover, IV sedation increases the disruption to patients' daily activities that can ensue as a result of the procedure due to hangover effect from sedation [4], [7] and the need for an escort after the procedure [8]. Additionally, administering IV sedation carries service delivery and cost implications as it involves establishing a safe venous access and provision for post-procedure recovery with subsequent prolongation of the process.

A number of non-sedative analgesic alternatives have been trialled for use in colonoscopy, with Nitrous Oxide gas being the most widely considered non-sedative and non-narcotic option [4]. Nitrous Oxide (N_2O) is an inert gas of low solubility which is rapidly absorbed and eliminated via the lungs and is available in a 50:50 combinations with Oxygen (commonly known as Entonox). It has been successfully used for analgesia in obstetrics [9], minor orthopaedic procedures [10], paediatric dental practice [11] and dermatology procedures [12]. Entonox has an analgesic effect through inhibitory action on N-methyl D-aspartate receptors and an anxiolytic effect through stimulatory mechanism on gamma-aminobutyric acid receptors, and both these effects are achieved without loss of consciousness [13].

Entonox usage is generally safe and is not associated with significant complications, however, it has been reported to cause nausea and vomiting in some studies [14], [15]. Another toxicity associated with Entonox is that of interaction with vitamin B12 metabolism [16] which can potentially lead to haematological complications such as megaloblastic anaemia in cases of extremely prolonged exposure [17]. However, Entonox has become an acceptable alternative to IV sedation in colonoscopy practice and has been shown to be safe in a number of studies [2], [18]. Entonox carries the properties of rapid onset and offset of action, the ease of titration to desired level, the combination of both analgesic and anxiolytic effects and it has an excellent safety profile; thus, making it an ideal agent for use in patients undergoing colonoscopy. A recent Cochrane review concluded that Entonox is as efficient as other analgesic methods; however further studies were recommended [19].

There are few contraindications to the use of inhalational Nitrous Oxide. The high inspired concentrations of the gas can lead to tension pneumothorax in vulnerable patients and therefore is contraindicated in those with history of spontaneous pneumothorax or bullous emphysema. It is also contraindicated in patients with recent craniotomy as it can lead to intracranial hypertension [20]. Other contraindications include recent eye surgery and middle ear procedures, head and maxilla-fascial trauma, suspected bowel obstruction, recent scuba diving [21].

Despite promising results, the use of Entonox as the sole analgesic agent during colonoscopy is still not widely practised. A national survey of English screening colonoscopists reported very selective use of Nitrous Oxide in 2014 [22]. Similarly, a national audit had also reported the use of Entonox in only 8.4% of the colonoscopies in the United Kingdom [23]. The aim of this study was to further examine the applicability and effectiveness of Nitrous Oxide as applied to the totality of practice in a busy endoscopy unit in a District General Hospital, studying its analgesic efficacy as well as the other technical procedural aspects of colonoscopy which can be impacted by sub-optimal patient experience.

For the purpose of this study, results were compared in terms of patients' comfort score, caecal intubation rate (CIR), polyp detection rate (PDR) and polypectomy rate (PR) in patients receiving IV sedation, Entonox, a combination of both or no analgesia/ sedation for the colonoscopy procedure.

3. Materials and Methods

Data was prospectively collected for patients undergoing colonoscopy under the care of a single surgeon endoscopist (the senior author MK) using Unisoft, a dedicated electronic endoscopy reporting system (Unisoft Medical Systems, United Kingdom) from May 2011 to August 2019. The database parameters included the variables set by the Joint Advisory Group on Gastro-Intestinal Endoscopy (JAG), a United Kingdom (UK) based advisory body which runs the accreditation scheme for endoscopy services across the UK and is affiliated with the Royal College of Physicians, UK. The parameters included patient demographics, details of analgesia and sedation techniques, caecal intubation rate, polyp detection rate and polypectomy details. The study included all 16 years old and above patients undergoing colonoscopy. Patients were excluded from the study if Nitrous Oxide was contraindicated due to any condition outlined in the BOC Healthcare's essential guide document.

The database was examined with the aim to assess the efficiency of Entonox as a sole alternative analgesic during colonoscopy, and the proportion of its uptake by patients. Patients' demographics, indications of procedures and modes of analgesic methods used were identified. The primary outcome of the study was determined as the patients' Comfort Score. The Comfort Score is a surrogate marker for the adequacy of the analgesic method administered to the patient during the procedure and is recorded independently by the nurse attending to the patient during the procedure. The Comfort Score represented a scale from 1 to 5 as follows: 1 = comfortable, 2 = minimal discomfort, 3 = mild discomfort, 4 = moderate discomfort and 5 = severe discomfort. Secondary outcomes included proportion of patients with successful caecal intubation, proportion of patients diagnosed with polyps and the proportion of patients who were able to have a completed polypectomy during the procedure in various study groups.

The approach to analgesia during colonoscopy adopted by the endoscopy unit at which the senior author practiced involved giving the patients (unless Entonox was contraindicated) the choice between attempting the procedure under Entonox alone or under intravenous (IV) sedation, with the understanding that IV sedation will be available if the examination was poorly tolerated under Entonox alone. Patients who underwent the procedure under IV sedation were freely offered adjunct Entonox usage as required.

Statistical analysis was conducted using StatsDirect® software package (StatsDirect Ltd, Birkenhead, Merseyside, UK). Categorical variables were analysed using chi-square and Fisher's exact tests while continuous variables were analysed using unpaired t-test, one-way ANOVA or Kruskall-Wallis tests based on the normality of the data. *P*-values less than 0.05 were considered statistically significant.

4. Results

4.1. Demographics and Indications

A total of 1664 colonoscopies were performed and prospectively recorded during the study period. Median age of the patients was 63 years, with an age range of 17-94 years. The number of male patients was 855 (51.4%) and 809 patients were female (48.6%). Patients in the study cohort fell into three main groups: Group A: Sedation group (with or without Entonox), Group B: Entonox group, and Group C: No sedation or analgesia group. Group B was further divided into sub-group B1 (successful Entonox group) and sub-group B2 (failed Entonox group where patients needed additional IV sedation to continue the procedure). The main indication for colonoscopy in the majority of cases (81.1%) was diagnostic. Indications in the remainder of cases were for surveillance (14.5%), therapeutic (4.1%) and screening purposes (0.2%). No data was recorded for an indication in 2 patients (0.1%) See (Table 1 and Figure 1).

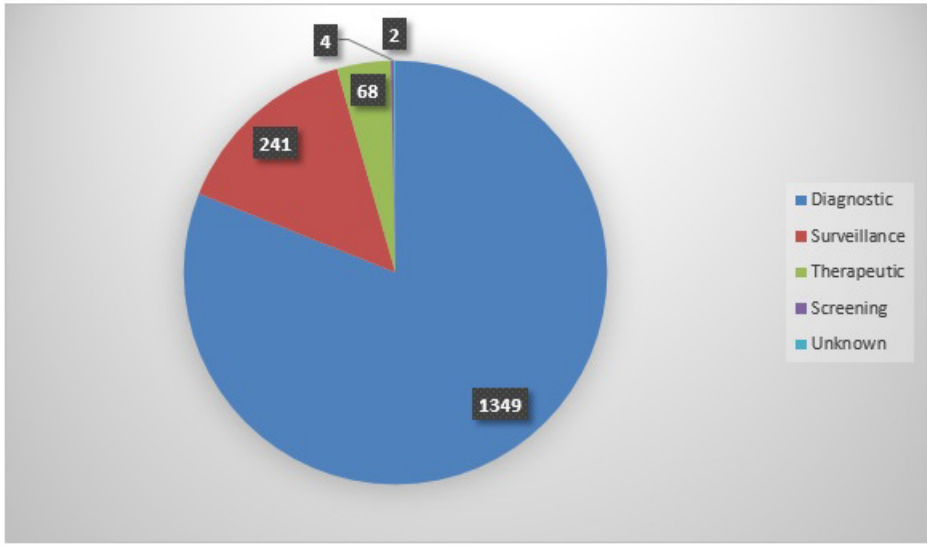

Figure 1: Indications for colonoscopy (number of cases)

Table 1: Patient demographics/ Indications

	Group A (Sedation +/- Entonox)	**Group B** (Entonox)			**Group C** (No analgesia or sedation)
		All patients in group B (Attempted Entonox)	Sub-group B1 (Successful Entonox)	Sub-group B2 (Failed Entonox)	
Number of patients:	813	737	678	59	114
Proportion:	48.90%	44.20%	40.70%	3.50%	6.90%
Median age:	64(17-94)	66(21-91)	66(21-91)	64.5(21-87)	68(26-92)
Sex distribution:					
F:	479(58.9%)	297(40.3%)	264(38.9%)	33(55.9%)	33(28.9%)
M:	334(41.1%)	440(59.7%)	414(61.1%)	26(44.1%)	81(71.1%)
Indications:					
Diagnostic:	669	585	540	45	95
Surveillance:	97	128	116	12	16
Therapeutic:	44	21	19	2	3
Screening:	3	1	1	0	0
Unknown:	0	2	1	0	0

4.2. Mode of Analgesia Used and Comfort Scores

The uptake between IV sedation and Entonox amongst patients was almost equally distributed, with 813 patients (48.9%) opting for IV sedation (group A) and 737 patients (44.2%) selecting Entonox (group B). A smaller proportion of patients (114; 6.9%) decided to undergo the procedure without sedation or Entonox (group C). The majority of patients opting for Entonox alone (678; 92%) managed to complete the procedure without any additional analgesia or sedation (sub-group B1). However, a total of 59 patients out of the 737 in the Entonox group (8%) required additional IV sedation in order to complete the procedure (sub-group B2). Average amount of Midazolam required was 1.3 (± 0.6) milligrams in group A and 1.2 (± 0.5) milligrams in sub-group B2 (P= 0.1993; unpaired t test). Similarly, there was no difference when these two groups were compared for the amount of Pethidine used [Group A: 41(±12.4) micrograms; sub-group B2: 38.6(±15) micrograms; P= 0.0489; unpaired t-test]. See (Table 2).

Table 2: Analgesia and comfort score data

	Group A (Sedation +/- Entonox)	Group B Attempted Entonox		Group C (No sedation/ Analgesia)	*P*- value
		Sub-group B1 (Successful Entonox)	Sub-group B2 (Failed Entonox)		
No.of patients	813	678	59	114	
Proportion of cases:	48.90%	40.70%	3.50%	6.90%	
Amount of Midazolam:	1.3mg(±0.6)	Nil	1.2mg(±0.5)	Nil	*P:* 0.1993 (Comparison between group A and subgroup B2; Un-paired t-test)
Amount of Pethidine:	41mcg (±12.4)	Nil	38.6mcg (±15)	Nil	*P:* 0.0489 (Comparison between group A and subgroup B2; Unpaired t-test),
Average comfort score:	2.2 (±0.9)	2.1 (±0.8)	3.1 (±1.1)	1.5 (±0.8)	*P:*< 0.0001 (Comparison between all four groups; one way ANOVA); and *p:* 0.0535 (Between group A and subgroup B1; Un-paired t-test

The number of female patients in the IV Sedation group was significantly higher when compared to the Entonox group ($P < 0.0001$; Fisher Exact test). Also, the number of female patients was significantly higher in the failed Entonox group compared with those who had successful Entonox ($P= 0.0126$; Fisher Exact test). There were more male patients in group C where the procedure was performed without Entonox or IV sedation/ analgesia ($P < 0.0001$; Fisher Exact test).

There was a statistically significant difference between comfort scores for the different groups of patients (one-way ANOVA; $P= <$ 0.0001). Patients who suffered the highest average levels of discomfort were those who failed Entonox with subsequent need for IV sedation (sub-group B2). However, there was no statistically significant difference between the IV sedation (group A) and the successful Entonox group (sub-group B1) when average comfort scores were compared ($P= 0.116$, Mann Whitney test) See (Table 2).

4.3. Caecal Intubation Rate (CIR)

There was no significant difference in the CIR among the different groups of patients, with pain being the main reason for failure of caecal intubation in all groups See (Table 3).

Table 3: Data on Caecal intubation rate

	Group A	Group B		Group C	*P*-value
		Sub-group B1 (Sucessful Entonox)	Sub-group B2 (failed Entonox)		
No. of patients:	813	678	59	114	
Proportion of cases:	48.90%	40.70%	3.50%	6.90%	
Successful caecal inubation:	759/813 (93.4%)	644/678 (95%)	52/59 (88.1%)	101/114 (88.6%)	*p*: 0.02 (Chi-square test)
Failed caecal intubation due to pain:	33/54(61%)	18/34 (53%)	6/7 (85.7%)	8/13 (61.5%)	*p*: 0.444 (Chi-square test)

4.4. Polyp Detection and Polypectomy Rates

Polyp detection rate (PDR) was 30% in group A, 30.8% in sub-group B1, 28.8% in sub-group B2 and 28.1 % in group C ($P = 0.932$; chi-square test). The average number of polyps detected per patient in each group was also similar between the groups. Polypectomy was successfully performed in a similar proportion of patients in each group (80.3% patients in group A, 83.7% in sub-group B1, 82.4% in sub-group B2 and 75% in group C; $P= 0.612$, chi-square test). Moreover, there was no statistically significant difference in the average number of polyps removed per patient in each group See (Table 4).

Table 4: Polyp detection and polypectomy data

	Group A (Sedation +/- Entonox)	Group B Attempted Entonox		Group C (No analgesia or sedation)	*p*-value
		Sub-group B1 (Sucessful Entonox)	Sub-group B2 (failed Entonox)		
No. of patients:	813	678	59	114	
Proportion of cases:	0.489	0.407	0.035	0.069	
Proportion of patients diagnosed with polyps:	244/813 (30%)	209/678 (30.8%)	17/59 (28.8%)	32/114 (28.1%)	*p*: 0.932 (Chi-square test)
Average number of polyps diagnosed per patient:	1(1-15)	1 (1-14)	2(1-5)	2 (1-9)	*p*: 0.761 (Kruskall-Wallis)
Proportion of patients who underwent polypectomy:	196/244 (80.3%)	175/209 (83.7%)	14/17(82.4%)	24/32 (75%)	*p*: 0.612 (Chi-square)
Average number of polyps removed per patient:	1 (1-13)	1 (1-6)	1 (1-3)	2 (1-8)	*p*: 0.585 (Kruskall-Wallis)

5. Discussion

This study was conducted in order to assess the efficacy of Entonox as the sole analgesic agent during colonoscopy in the totality of practice in a busy general hospital, with consideration and assessment of all relevant quality indicators for the procedure. Approximately half of the patients in our study selected Entonox as their analgesic method for the procedure when given the choice between it and Sedation; and the majority of them were able to complete the procedure without any additional IV sedation or analgesia. We have also demonstrated no significant difference in the Comfort Scores between the patients who successfully completed the procedure under Entonox alone and those who took IV sedation. Moreover, there were no significant differences in caecal intubation rate, polyp detection rate and polypectomy rates between those two groups of patients.

This pattern of Entonox uptake amongst our cohort of patients which represented the generality of practice in a district general hospital is probably reflective of patients' perception about the procedure and their varied level of anxiety and apprehension regarding its invasiveness. Moreover, the study has shown variation in the uptake of Entonox based on gender, with female patients significantly less likely to choose to undergo the procedure under Entonox.

The efficacy of Entonox in our cohort measured by the ability of patients to complete the examination without additional analgesia or sedation reached around 91%, with all the quality indicators for colonoscopy being comparable to those for patients who received sedation. These results concur with the findings of other reports in the literature. Notini-Gudmarsson et al demonstrated that the analgesic effect of Entonox is comparable to Pethidine with the advantages of less induced-nausea and subsequent reduced hospital stay [18]. Moreover, a randomised clinical trial found that the use of Nitrous Oxide during colonoscopy provides better pain relief and earlier recovery of psychomotor function when compared to IV Midazolam and Fentanyl [2]. In agreement with Saunders et al [24], Comfort scores in our cohort of patients were similar amongst those who successfully used Entonox and those who took IV sedation.

This comparable efficacy of Entonox was not uniformly experienced by all patients in our study. A small proportion of those who have chosen Entonox failed to complete the procedure without additional IV sedation and analgesia and have seemingly experienced increased levels of pain which was reflected in higher Comfort Scores. The selective uptake of Entonox amongst our cohort and its failure in a subset of patients suggest there are wider factors influencing its outcomes. There is little doubt that colonoscopy as an invasive procedure can be associated with significant levels of anxiety, and analgesic methods without sedation are not going to suit all individuals. It is worth noting here that some studies have reported that patients were less tolerant and in more discomfort during colonoscopy under Entonox when compared to the use of IV sedation [25]. Anxiety and other patient related factors are likely to be implicated here, but moreover, a technically-challenging colonoscopy procedure could lead to sedation and additional analgesia being required alongside Entonox.

An interesting finding in this study which supports the relevance of patient-related factors in determining the successful method of analgesia for colonoscopy, is the demonstration that a significant proportion of patients completed the procedure without the need for any analgesia or sedation whilst reporting comparable comfort scores to those who did receive Entonox or sedation.

Although analysis of comfort scores in the various patient groups based on gender was not conducted, the study did show that female patients were more likely to choose and receive IV sedation compared to male patients. Also, there were significantly more men than

women who successfully underwent the procedure under Entonox only or without any sedation or analgesia in our cohort. This conforms with similar findings in other studies [26], [27], and could be related to the fact that performing a colonoscopy in female patients is demonstrably technically more challenging. It has been shown that females have an inherently longer colon [28], [29] and it has been suggested that it is therefore more likely to be acutly angulated and tortuous [30]. Moreover, the colonoscope's tendency to loop in the sigmoid colon was found to occur more readily in women than in men [29].

Our study is based on prospectively gathered and maintained data which reflects the practice of a single experienced operator therefore eliminating any operator bias and variability. Moreover, the data represents the generality of practice within a busy general hospital. The practice within the unit involved the routine discussion of both analgesic options with patients at the point of their admission for the procedure by an experienced nurse which eliminates selection bias. We, however, recognise that the study has its own weaknesses as a single-centre study with no participant's randomisation. Moreover, the data did not include information on the duration of the patient's colonoscopy, which would have been a useful comparative variable that represents a surrogate marker of the complexity and technical difficulty of the procedure.

Although the summative Caecal Intubation Rate (CIR) for the whole cohort of patients in the study met the guidelines' recommendations by the Joint Advisory Group on GI Endoscopy (JAG) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI), there were variations between the various groups of patients in the study. Pain was the main reason for failed caecal intubation in all groups, highlighting the importance of successful analgesia for the completion of this procedure in the majority of patients.

The important index Adenoma Detection Rate (ADR) depends on Polyp Detection Rate (PDR) and Polypectomy Rate (PR), with an expected proportional relationship between PR and ADR [31]. The UK guidelines have set a standard acceptable ADR of 15% for the general population, with an inspirational target of 20% [32]. In our cohort, PDR and PR were very significant suggestive of a satisfactory ADR in our cohort. Moreover, there was no significant difference in PDR or PR between the various groups of patients based on the analgesic method followed, further demonstrating that Entonox usage was not associated with any compromise to the quality indicators of the colonoscopy procedure. This was in concordance with the findings of Robertson et al in their recently published large retrospective series of cases, demonstrating that Entonox usage was not associated with lower colonoscopy quality when compared to intravenous sedation with Midazolam [26].

Our study demonstrated that Entonox is feasible, effective and safe as the sole analgesic method for colonoscopy in a significant proportion of patients. Its usage is not associated with any decline in the quality indicators of this important diagnostic and therapeutic procedure. This has significant clinical and practical implication as with appropriate teaching and counselling of patients, the likelihood is the uptake of Entonox in the day-to-day practice will be further established. Although not assessed in this study, but we believe that the wider uptake of Entonox can lead to clinical and logistical gains namely with regards to enhancement of patients' recovery times after colonoscopy.

6. Conclusion

The results from our study confirm that Entonox is an effective and feasible sole analgesic agent in a significant proportion of patients undergoing colonoscopy. We believe that along with the progress in colonoscopy techniques including the use of the technological aids such as magnetic imaging, appropriate patient counselling and education is likely to be associated with increased patient uptake of this analgesic modality leading to potential clinical and logistical gains. Randomised studies will further establish the evidence in this area, and ongoing research around patient factors which can lead to failure of analgesia during colonoscopy will also be required to develop our understanding of this complex phenomenon.

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