CLINICAL STUDY

Instant Pain Reduction
in
Adults and Children

Urology - Cystoscopy, Vasectomy, Prostate Biopsy
Plastic Surgery - Botox Injections, Other
Dentistry - Dental Carries

Hand Held Nitrous®
Nitrous Oxide Inhaler

Property
of
Strata Medical Innovations

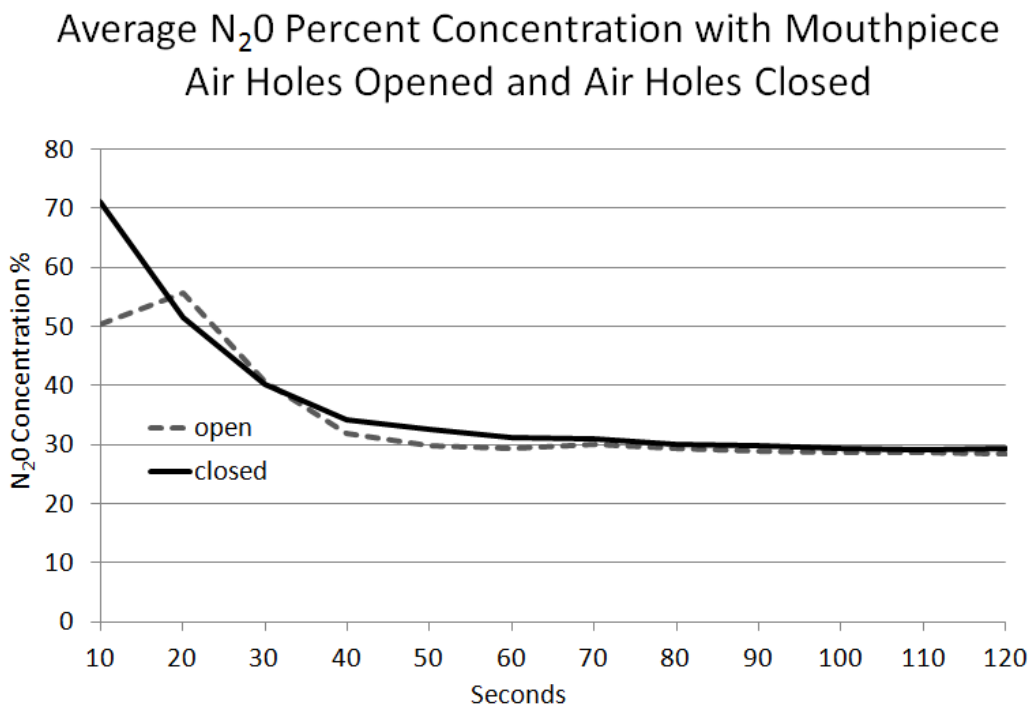
Table of Contents

PURPOSE:

The purpose of this study is to evaluate the safety and effectiveness of the Hand Held Nitrous®.

Hand Held Nitrous® is a nitrous oxide inhaler designed to create instant pain and anxiety reduction in patients undergoing painful or uncomfortable medical office procedures in adults and children. The inhaler delivers a limited 120 seconds of gas.

The graph below shows the percent nitrous oxide delivered to patients using the two dosing configurations: adults (closed) and children (open).



INTENDED USE:

Hand Held Nitrous® is intended to create short term analgesia and anxiety reduction by delivering a limited 16 grams of nitrous oxide (N_20) over a total of 120 seconds of inhalation time. The effects last approximately five (5) minutes. Not for use for patients under three years of age or if you are pregnant.

METHODS

Device

This study used the Hand Held Nitrous® device. The inhaler is reusable, the gas cylinder and mouth piece are disposable. As of the date of this submission, a total of 4 inhalers where used and 86 gas cylinders and mouth pieces were used. The inhaler was removed from the box and the Instructions for Use where readily available and read. The gas cylinder and mouth pieces were removed from their boxes. The mouth piece was placed onto the nozzle outlet and the gas cylinder was placed inside the inhaler cup and twisted onto the inhaler head section as instructed in the Instructions for Use.

Physician Recruitment

Patients who regularly performed short, painful procedures or injections were recruited. For this study 2 urologists, 1 plastic surgeon, and 2 pediatric dentists were recruited to assist in patient recruitment. These physicians' offices were located in Lubbock Texas, Payson, Utah, and Springville, Utah. In order for a physician to be eligible to assist with the study they needed to comply with Texas or Utah state requirements for handling and dispensing nitrous oxide. For the State of Texas (see Texas Medical Board Rules 192.2) these included requirements for meeting level 1 services: at least two personnel must be present, including the physician who must be currently certified at least in AHA-approved Basic Life Support Course; the presence of a bag mask and oxygen. (http://www.tmb.state.tx.us/page/renewal-office-based-anesthesia) In the State of Utah, nitrous oxide is not a controlled substance. No permit or special license is required. Health care professionals are expected to follow their own internal office policies for applying minimal sedation with nitrous oxide.

Hand Held Nitrous® is optional for the patient and should only be used if the patient desires it (see Instructions for Use)

Patient Selection

To test the safety and efficacy of the Hand Held Nitrous® device adult and pediatric patients who were receiving a variety of procedures were recruited. All patients receiving N2O sedation underwent a pre-sedation assessment to identify subjects who met the study inclusion and exclusion criteria. In order to participate in this study, patients had to meet the following criteria:

- must be over 3 years of age
- not currently be under sedation
- must sign consent form (children sign assent form as well)
- be willing to stop nitrous oxide use immediately if they feel any nausea or discomfort.
- not be pregnant or nursing
- be willing and able to follow the study directions and procedures
- tell the study staff about any side effects or problems
- ask questions as needed

- tell the investigator or health care staff if they wish to stop participating in the study

Observations of subjects prior to sedation was used to exclude any patient that appeared to be previously sedated.

Researcher Training

Prior to initiating the study, all researchers involved in the study were certified as having successfully completed the NIH Web-based training course “Protecting Human Research Participants. Proficiency in using the device and handling nitrous oxide followed a training curriculum previously described. (Zier, 2007; Farrell, 2008) Researchers also demonstrated proficiency in teaching other health care providers how to use the device correctly.

IRB Approval

IRB approval was obtained on April 30, 2013 from IRB Solutions, Austin, TX. Before each procedure patient demographics, blood pressure, heart rate and O2 saturation level were recorded.

GCP Statement

Strata Medical Innovations has made every effort to conduct this clinical trial to adherence to Good Clinical Practice (GCP) requirements in regards 21 CFR 50 - Protection of Human Subjects, 21 CFR 56 - Institutional Review Boards, 21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies and all other required regulations.

Calibration of Equipment Used

To determine the dose of nitrous oxide used, the device was weighed before and after each procedure using American Weigh Scales AMW-SC-501 Digital Scale. The scale is recalibrated digitally each time the scale is powered on. Oxygen saturation was determined using Choicemmed Oxywatch fingertip pulse oximeter with continuous monitoring. Calibration was completed during fabrication.

Who Administrated the Gas

In all cases, the health care professional or researcher administered the gas.

Analgesia/Sedation Depth

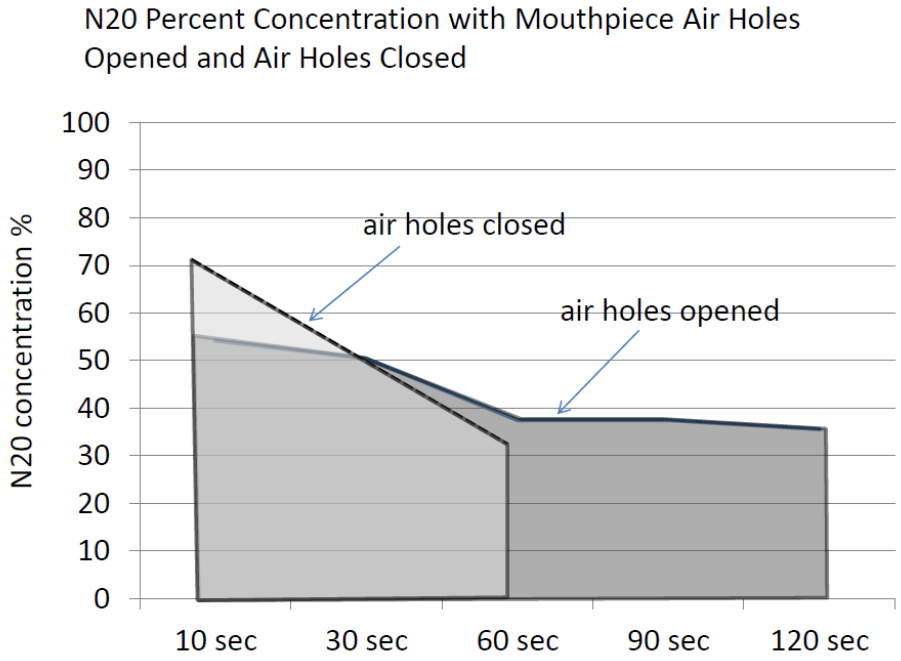
Sedation depth was determined by using the Modified Observer’s Assessment of Alertness/Sedation Scale (MOAA/S).(Kowalski, 2007). Additional Definitions were taken from the *Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists (Anesthesiolgy 2002; 96; 1004-17).*

Table 1. Level of Sedation

Level	Descriptors
6. Inadequate	anxious, agitated, or in pain
5. Minimal	spontaneous awake without stimulus
4. Drowsy	eyes open or closed, but easily arouses to consciousness with verbal stimulus
3. Moderate deep	arouses to consciousness with moderate tactile or loud verbal stimulus
2. Deep	arouses slowly to consciousness with sustained painful stimulus
1. Anesthesia	unresponsive to painful stimulus

Gas Concentration

The mouth piece is designed with two ambient air holes placed laterally. The holes allow ambient air to mix with the nitrous oxide gas as the patient inhales. Nitrous oxide concentrations in the maximum ranges from 54.2 % to 37.5 % at 60 seconds with two "open" air holes to 72.0 % to 33% in 60 seconds with two "closed" air holes (see graph below). Open or closed ambient air holes control the gas concentration (See Performance Test: Percent N20 Deliver to Patient Using Different Nozzle, Nozzle Cap and Mouth Piece Designs and see Performance Test: Analysis of N20, Ambient Air O2 Levels and O2 Saturation in Humans)



The health care administrator can stop or modify administering the gas at any time should any problems express themselves by pressing the compression switch intermittingly, letting up on the compression switch or by covering one or two of the air holes with the index finger/s (see Instructions for Use) The patient can stop inhalation at any time by simply stop inhaling or gently pushing the device away (see Instructions for Use). The gas is delivered over a maximum 120 seconds of inhalation time.

The multiple variables mentioned above made it difficult to track the specific concentration of gas during the study (for example, in the 120 seconds of inhalation time, did the doctor or nurse ever cover a hole on the mouth piece, stop pressing or let up on the compression switch, etc. As a result, we report herein the maximum possible concentrations of gas that could be delivered for any given patient. As the chart above shows, the maximum concentration the device can deliver in the first few seconds of use is 72%. The study measures how much gas was release by the cylinder as seen by the weight, before and after the procedure.

Pre and Post Procedure Pain

Pre and post procedure pain was assessed using the Simple Descriptive Pain Distress Scale (Acute, 1992). Urology patients only.

Recovery from Analgesia

Clinical recovery from sedation was determined using baseline observations; patient was no longer dizzy and return to pre-dosing levels of blood pressure, heart rate,O2 saturation level, able to ambulate, minimal nausea, absence of reparatory distress, alert and oriented as appropriate for age. This determination was used to measure the total time from beginning of inhalation of the gas to full patient recovery.

Complications

To accurately identify any complications, a list of previously reported complications associated with nitrous oxide use was compiled.(Babl, 2008; Zier, 2010) This list included, vomiting, nausea, inadequate sedation, agitation/delirium, apnea >15 seconds, hypoxemia, stridor, seizure, diaphoresis, burpy/hiccup, gaggy, and expectoration of a large amount of clear phlegm. The attending health care practitioners and the researcher were also on alert for any other complications not on this list.

Pre Procedure Interview

Baseline data was taken in regards to age, approximate weight, sex, blood pressure, heart rate, and O2 saturation level, how long ago did the patient eat, and type of procedure being performed. The inhaler and gas were weighed (to compare with after the procedure to determine how much gas was released). Informed Consent form and if applicable Child Assent forms where signed.

Only the researcher and health care providers were permitted to administer the device.

When confirmation that the patient wanted nitrous oxide was obtained, and the patient and doctor were ready, each patient was read or told similar words to that found in the Instructions for Use.

The mouth piece section of the device was placed in the mouth of the patient and gas was administered by pressing the compression switch.

Once minimal sedation was achieved the procedure or exam began, which usually occurred after the 4th to 5th inhalation.

Recovery from sedation was determined using the clinical recovery score described by Quinn, 1993. Once full recovery was established, the time was noted and the total time from first use of the device till full recovery time was recorded.

Depending on the length of the procedure, time was recorded from the moment gas was delivered to the time the patient returned to baseline status.

Post Procedure Interview

As in the pre procedure interview, after the procedure or exam the researcher measured blood pressure, heart rate, and O2 saturation level and compared them to the patient pre assessment measurements. Ability to communicate, level of alertness, absence of respiratory distress, absence of nausea, dizziness and ability to stand were also observed.

Post procedure patient and physician interviews were also used to assess satisfaction and any adverse events or complications associated with the device. Post procedure documentation also included description of the completeness of the procedure with limited options:

completed, patient calm and still during procedure
completed, patient unable to stay still or calm
not completed, complications with sedation
not completed, problems not related to sedation
Comments:

This descriptive set corresponds to standardized study data collected by the Sedation Research Consortium (SRC) for analysis of multi-institutional sedation practices.

The patient and health care provider were also asked other questions:

Patient:
Have you had this procedure before?
If Yes, would you use nitrous oxide again?
If No, would you want to have nitrous oxide again for this procedure?

Person administrating the gas:
Was the device easy to use?
Was oxygen used for this patient?
Did the device function as expected?
Was there a definitive benefit from the use of N2O for the patient?
Explain any problems resulting from the use of the device.

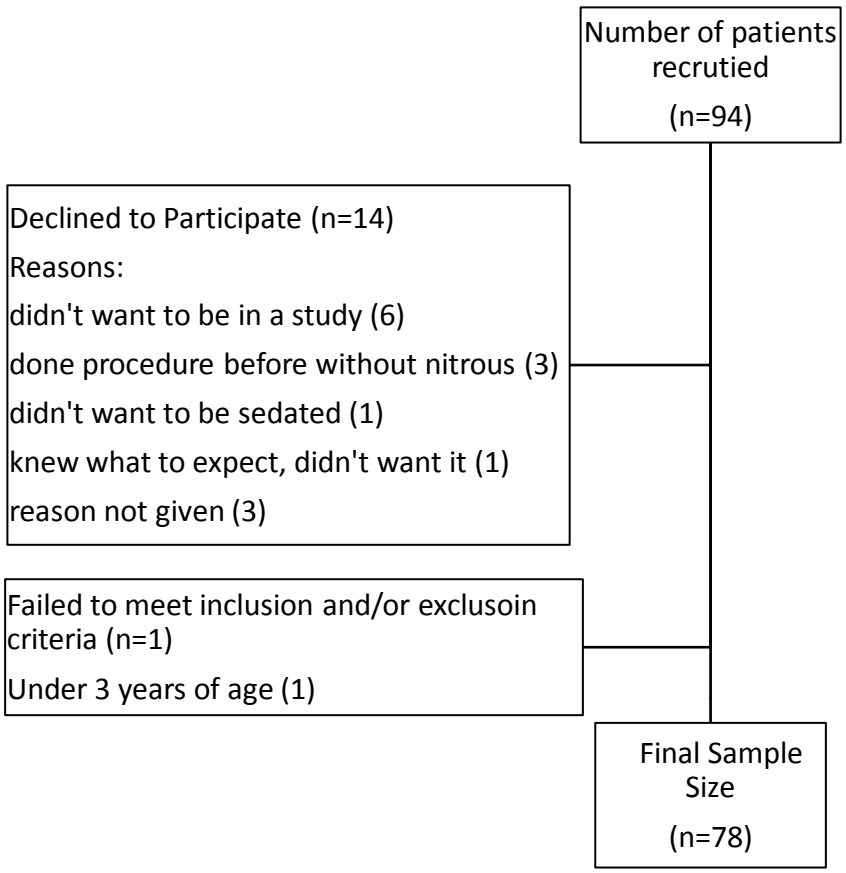
STATISTICAL ANALYSIS

Descriptive and univariate statistics including mean and variance were used to describe the continuous variables such as age and sedation level. Pre and post measures of blood pressure, heart rate, O2 saturation, and perceived pain were analyzed using paired t-tests. To control for the familywise error rate, the Bonferroni correction was applied to the a priori alpha. Five pre/post comparisons were made across the total patient dataset. Between group comparisons were conducted using ANOVA with reported F and p values. The coding, merging, and statistical analysis of these data were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA, 2011).

RESULTS

A total of 94 patients were invited to participate in the study. Patient flow is shown the patient flow chart below:

Figure 1. Patient Recruitment Flow Chart



Adults were primarily recruited from a urology practice and a plastic surgery practice. Pediatric data was gathered from plastic surgery and two pediatric dentists. Data analysis was conducted on all patients combined and with patients categorized into one of three cohorts, urology patients, plastic surgery patients, and pediatrics. Table 2 shows the demographics of the total patient population.

Table 2. Subject Demographics & Procedures

Variable	N (percentage)
Total subjects	78
Male	35 (45%)
Female	43 (55%)
Age	
4-18	9 (11%)
18-30	7 (9%)
30-50	13 (16%)
>50	50 (64%)
Urology patients	52 (67%)
Average age	62 years
Average weight	184 lbs
Procedures received	Cystoscopy (41)
	Cystoscopy – stent removal (8)
	Cystoscopy rigid scope (1)
	Vasectomy (1)
	Prostate Biopsy (1)
Plastic surgery patients	17 (22%)
Average age	46 years
Average weight	146 lbs
Procedures received	Breast Lift (Bilateral)
	Botox and Belly button revision
	Lip Incision (2)
	Lip Filler (5)
	Nasal Alar Excision
	Botox (2)
	Filler- Injectables (2)
	Tatoo Removal
	Colposcopy
	Nexplanon
Pediatric patients	9 (11%)
Average age	8 years
Average weight	58 lbs
Procedures received	Cavity- Filling
	Mole Removal

Table 3. Clinical Results

All Subjects Combined	Mean	SD
Time to recover (sec)	296	111
Hours since last eaten	6.65	3.0

	Pre		Post			
	Mean	SD	Mean	SD	Diff	p value**
Device weight (g)	118.52	4.22	106.08	2.77	-12.43	.0000
Systolic BP (mmHg)	124.62	18.32	130.53	24.66	5.91	.0159
Diastolic (mmHg)	75.11	9.48	80.15	10.85	5.04	.0032
Heart rate (beats/min)	74.96	13.26	74.99	12.36	0.03	.9816
O2 saturation (%)	96.34	2.31	96.89	2.42	0.54	.0317

	Yes	No
Received benefit from use	92%	8%
Would use device again	91%	9%
Adverse events	0%	100%
Complications (see Table 4)	2.6%	97.4%

Level of Sedation Reached	
6. Inadequate	1 (1%)
5. Minimal	77 (99%)
4. Drowsy	0 (0%)
3. Moderate deep	0 (0%)
2. Deep	0 (0%)
1. Anesthesia	0 (0%)

Urology Patients Only	Mean	SD
Time to recover (sec)	301	46.3
Hours since last eaten	4.7	2.74

	Pre		Post			
	Mean	SD	Mean	SD	Diff	p value**
Device weight (g)	119.76	3.10	106.41	3.61	-13.30	.0000
Systolic BP (mmHg)	129.43	12.81	136.34	22.40	6.91	.0146
Diastolic (mmHg)	75.18	10.95	78.51	12.09	3.33	.0069
Heart rate (beats/min)	73.09	12.53	72.49	11.21	-.60	.6197
O2 saturation (%)	96.25	2.14	96.70	2.56	0.45	.1709
Pain Scale (1-10)*	4.10	2.70	0.90	1.64	3.27	.0000

Plastic Surgery Patients Only	Mean	SD
Time to recover (sec)	377.82	88.23
Hours since last eaten	4.0	3.83

	Pre Mean	SD	Post Mean	SD	Diff	p value**
Device weight (g)	119.17	1.89	107.35	1.84	-11.91	.0000
Systolic BP (mmHg)	123.88	21.29	128.53	24.88	4.65	.4918
Diastolic (mmHg)	80.88	11.39	82.80	10.84	1.92	.2392
Heart rate (beats/min)	75.35	14.38	74.47	12.36	-0.88	.7474
O2 saturation (%)	95.59	2.87	96.65	2.32	1.06	.0669

Pediatric Patients Only	Mean	SD
Time to recover (sec)	379.7	80.7
Hours since last eaten	4.5	4.38

	Pre Mean	SD	Post Mean	SD	Diff	p value**
Device weight (g)	110.11	3.18	102.00	4.03	-8.11	.0000
Systolic BP (mmHg)	97.67	18.11	99.67	11.38	2.00	.7980
Diastolic (mmHg)	64.78	11.57	61.67	11.09	-3.11	.4377
Heart rate (beats/min)	85.22	12.04	90.67	11.09	5.44	.1963
O2 saturation (%)	98.33	0.50	98.44	0.73	.11	.0317

*Pre post pain measures were only taken on urology patients
**p values are statistical significant if they are less than.003 (Bonferroni adjustment)

Systolic and diastolic blood pressures increased 5.9 mmHg ($p<.0159$) and 3.3 mmHg ($p<.0069$) respectively during the course of the procedure. There was also a significant decrease in self-reported pain ($p<.0000$) among urology patients. Oxygen saturation and heart rate remained relatively unchanged during the use of the device. All notable events are highlighted in Table 6.

In no cases were more than two gas cylinders (doses) used.

Table 4. Complications Observed in Total Population

Side Effects Reported in the Literature	Number of Effects Identified in This Study
Vomiting	0
Nausea	0
Inadequate sedation	0
Agitation/delirium	0
Apnea > 15 Seconds	0
Hypoxemia (89% O_2 Sat)	2
Stridor	0
Seizer	0
Diaphorisis	0
Burppy/hiccups	0
Gaggy	0
Expectorated large amount of clear phlegm	0
Oxygen required	0
Other side effects	0

No adverse events reported

No complications regarding the functionality of the device or gas administration were reported. Previously published studies of the effects of nitrous oxide show that complications are shown to occur in less than three percent (3%) of the population. With an n = 78, this study, using the same known side effects, shows complications to occur in less than .03%

Table 5. Between Group Comparisons

Variable	Urology	Plastic Surgery	Pediatric	F	p value
Age (years)	62.0	45.8	8	42.4	.0000
Weight (lbs)	183.2	145.7	58.4	33.2	.0000
Hour since last eaten	4.7	4.0	4.5	.16	.8444
Baseline heart rate (beats/min)	73.0	75.3	85.2	3.35	.0400
Device weight (g) difference (dose)	-13.30	-11.91	-8.11	23.63	.0000
Systolic BP (mmHg) difference	6.91	4.65	2.00	2.45	.0928
Diastolic (mmHg) difference	3.33	1.92	-3.11	2.07	.1334
Heart rate (beats/min) difference	-.60	-0.88	5.44	1.68	.1921
O2 saturation (%) difference	0.45	1.06	.11	0.64	.5298
Time to recovery	301.36	377.82	379.7	11.6	.0000

There is a statistically significant difference between the dose of nitrous oxide taken between the groups and the time it took them to recover.
The pediatric population took a significantly smaller dose.
Patients in the Urology group recovered quicker than the other two groups.

Table 6. Notable Events or Comments in Total Population

ID	Procedure	Age	Sex	Effects on Patient	Minimal Sedation Achieved Y/N	Definite Benefit From Use Y/N	Proced. Complete Y/N	Use Again Y/N	Researcher Observation or Patient Comments	Comments
7/24/1927/EDWA	Cysto-scopy	86	f	Not relaxed	yes	yes	yes	no	Pt. was not very relaxed. She was not sure that she got any benefit from the gas, and would not matter to her if she had it again.	86 year old patient required cystoscopy. The patient took 14.5 grams of gas. Coordinator stated on form minimal sedation achieved, there was a benefit from use and the procedure was completed. The patient stated they would not used the device again. No complications reported. No problems associated with the device reported
1/20/1958/RODR	Prostate Ultra-sound Biopsy	55	m	Not Relaxed	yes	no	yes	no	Pt. has had biopsy before, says that the gas did not make a difference; he would not use it again.	55 year old male had a prostate biopsy. Coordinator reported minimal sedation achieved and procedure was completed but that the patient reported no benefit and that they would not use the device again. Patient took 14.3 grams. No complications reported. No problems associated with the device reported

01/06/ 1933/ CANT	Cysto-scopy	80	f	Pt. uncoope r-ative	no	no	no	no	Nitrous dose was not completed. Nitrous oxide dose was inadequate and did not result in mild sedation. Elderly patient was uncooperative.	80 year old female presented for cystoscopy. Patient would not allow the cystoscpy to be performed and stopped dose. 10 grams were taken. Procedure was not completed. Minimal sedation not achieved. The device was easy to use and functioned as expected. No complication reported other than the procedure was aborted. No problems associated with the device reported
07/04/ 1946/ POFF	Cysto-scopy/ Stent Pull	67	m	Not Relaxed	yes	no	yes	no	Pt. felt discomfort, not sure if he got any gas, minimal light head. Does not think nitrous helped, unsure if he got any gas.	67 year old male required stent pull. Coordinator reported minimal sedation achieved and procedure was completed but that the patient reported no benefit and that they would not use the device again. Patient received 15.6 grams. In some cases like this one the attending physician perceived a patient benefit but the patient did not. In this case the patient may have also felt a need for bravery, in that his wife was with him during the procedure. No complications reported.

										No problems associated with the device reported
2/12/1946/GOME	Cysto-scopy	66	m	Tense	yes	no	yes	no	Pt. said it did not help at all and the next time he would tough it out and not use the gas	66 years old male required stent pull. 15.9 grams were used. Coordinator reported minimal sedation achieved and procedure was completed but that the patient reported no benefit and that they would not use the device again. No complications reported No problems associated with the device reported
02/03/1970/FLEM	Cysto-scopy	43	f	Tense, very nervous	yes	no	yes	no	After two inhalations, pt. asked to stop gas. Made her feel funny, pt. very nervous, not sure if it helped.	43 year old female required cystoscopy. Only 5.3 grams were used. Coordinator reported minimal sedation achieved and procedure was completed but that the patient reported no benefit and that they would not use the device again. After two inhalation, patient asked to stop gas. No complications reported No problems associated with the device reported
9/18/2008/GUZM	Cavity-Filling	5	m		yes	yes	yes	yes	Oxygen saturation dropped to 89%,	Oxygen saturation dropped below 90.

									returned to 95% in 5-15 seconds	No problems associated with the device reported Label change on Instructions for Use under children. See instruction for use under dosage.
8/24/2007/HAMB	Cavity-Filling	6	m		yes	yes	yes	yes	Oxygen saturation dropped to 89%, returned to 95% in 5-15 seconds	Oxygen saturation dropped below 90. No problems associated with the device reported Label change on Instructions for Use under children. See instruction for use under dosage.
01/10/1950/MORT	Cysto-scopy	47	F	Somewhat Relaxed	Yes	Yes	Yes	no	Patient did not think the gas really helped.	47 year old female required a cystoscopy. The patient took 14.5 grams of gas. Coordinator stated on form minimal sedation achieved, there was a benefit from use and the procedure was completed. The patient stated they would not use the device again. No complications reported No problems associated with the device reported.

Table 7. Two Doses Given

12/02/1980/JIME	Breast Lift (Bilateral) Office	32	f	Relaxed - one dose per breast	yes	yes	yes	yes	**Two doses taken.** This was a prolonged bilateral breast lift performed in the office Patient was very appreciative for the gas.	Two doses taken, one for each breast. This was an interoffice breast reduction performed under local anesthesia. The gas was administrated primarily for the local injections she received, which were numerous. No complications reported. No problems associated with the device reported
8/03/1958/SCHR	Botox and Belly button revision	55	f	Relaxed - two doses used	yes	yes	yes	yes	**Two doses** administered during procedures - glad to have the gas	Two doses taken one for each procedure. The gas was primarily for the local injections she received. No complications reported. No problems associated with the device reported
02/26/1979/FRIE	Vasectomy	34	m	Relaxed, mild discomfort	yes	yes	yes	yes	Pt. felt very relaxed, took the edge off of the procedure. Used **two doses**	Two doses where administered, one for each testicle during the most uncomfortable part of the procedure. No complications reported. No problems associated with the device reported
07/16/1992/	Colposcopy	21	f		yes	yes	yes	yes	**Two doses** on this pt..	Two doses were given to this patient primarily due to a

CHAI										miscommunication from the nurse. The first was given a little early in her procedure, another was giving during the more sensitive part of the procedure. No complications reported. No problems associated with the device reported

RESULTS CONTINUED

Adverse Events
Zero (0) adverse events recorded

Minimal Sedation Achieved
99% of patients experienced minimal sedation.

Received Benefit from Device
92% stated they received a benefit from the device

Use the Device Again
91% of patients stated they would use the device again

Procedures Completed
100% of the procedures that were started were successfully completed.

Device Easy to Use
When the health care professionals and researches that were using the device were asked if Hand Held Nitrous® was easy to use, 100% answered in the affirmative.

No problems associated with any part of the device including the inhaler, gas or mouth piece where observed. There were no incidents of ice burn, the gas not leaving the device properly, placing the mouth piece inside the mouth of the patient or the patient covering any of the ambient air holes with their mouth. The lot number on the inhaler and gas cylinders were clearly visible. The safety lock mechanism was never used during the study.

Pediatric Observations
Among the pediatric patients, young age and small body sized accounted for considerably higher heart rates and blood pressures when compared to adult patients.

Compared with adults pediatric patients also used considerable less nitrous oxide. The average dose for adults was approximately 12 grams of nitrous oxide while the dose of nitrous oxide used by children averaged 8 grams ($p<.0001$). Children expressed reaching a minimal level of sedation while using one-third less gas.

Researcher and Patient Comments
Researcher notes of patients that underwent urology procedures used the following descriptors and number of occurrences to describe patient reactions to the nitrous oxide gas: not relaxed (3), little dizzy/lightheaded (6), laughed (2), relaxed (32), not relaxed (2), tense/nervous (2), very relaxed (7). Researcher comments for this group of patients include the follow:

- Did very well
- Felt very relaxed, took the edge off of the procedure. Used two devices
- Laughed during the procedure and after the procedure was over
- Was a little dizzy after, said he would not want this procedure without the gas

- Said he felt more effect from the gas after the procedure was done
- Said he felt out there.
- Said she felt happy, smiled through procedure
- Said he felt like he could take a nap
- Felt a little fuzzy
- Did really well
- Felt like he could go to sleep, slurred speech
- Said it did not help at all and the next time he would tough it out and not use the gas
- Showed signs of not being relaxed during the procedure, tensed up.
- Was not comfortable, states that the procedure was through before he realized it had started
- No discomfort as she expected there would be for this procedure
- Never had this before, felt some pressure no pain, stated procedure did not take as long as expected
- Stated the procedure was easier this time.
- No discomfort she felt very relaxed, laughing after the procedure
- Very relaxed, a little fuzzy
- Stated anyone having this procedure needs gas, said she was less tense after getting gas
- Stated that she was relaxed and felt good.
- After two inhalations, asked to stop gas. Made her feel funny, very nervous, not sure if it helped.
- Stated she had an out there feeling, like she was floating, would want the gas again
- Stated he felt at ease, it took the edge off of the discomfort he thought he would have with the vasectomy.
- Was very tense before the procedure, this eased off the tension, helped take mind off of procedure
- Stated that the gas was some good stuff, very relaxed, ended the procedure smiling
- Felt somewhat dizzy during and before the procedure, felt relaxed and did not have any discomfort
- Felt discomfort, not sure if he got any gas, minimal light head. Does not think nitrous helped.

DISCUSSION

Under Section 576 of the Food and Drug Administration Safety and Innovation Act, Nitrous Oxide is a designated medical gas certified (deemed to have in effect an approved application) for analgesia (See Guidance for Industry, Certification Process for Designated Medical Gases, Section 5 of this PMA).

Nitrous oxide should conform to the requirements and standards set forth in the USP monograph entitled "Nitrous Oxide" and all applicable requirements and standards contained in the USP General Notices.

"Analgesia and Sedation" comprise a continuum of stages ranging from minimal sedation through general anesthesia. Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. For example moderate sedation/analgesia is defined as "purposefully" to verbal commands and cardiovascular function is "usually" maintained. In response to verbal commands, minimal sedation is "normally" and "unaffected". This clinical study used "minimal sedation" as an endpoint. Minimal sedation is a drug induced state during which patients respond normally to verbal commands, although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

EFFICACY

Using minimal sedation as the outcome measure, this clinical study has demonstrated that the Hand Held Nitrous® device delivers a mixture of nitrous oxide gas and ambient air that produces analgesia in the level of minimal sedation. In all subjects, the lowest level of analgesia reached was minimal sedation. One patient (01/06/1933/CANT) was uncooperative and failed to complete the dose. This patient did not reach minimal sedation.

Each canister of nitrous oxide holds approximately 16 grams of liquid nitrous oxide. Based on pre and post device weight, patients received between 8 and 13 grams of nitrous oxide gas. The effects of the gas lasted for an average time of about 6 minutes.

Among urology patients pre (4.1 SD 2.70) to post (0.90 SD 1.64) pain measures showed a significant reduction (-3.27, $p \leq .0000$) across time. Reduced pain sensation is a well-known effect of nitrous oxide.(Zier, 2007) Besides the obvious clinical outcomes, another method to quantify the beneficial effect of the device is to ask patients if they received any benefit from using the device and if they would use the device again. Of the 78 patients, 72 stated that they did receive benefit from using the device and 71 stated that if given the option they would use it again. Though these subjective questions and responses are not the main outcome of the study, they do encapsulate significant information on device efficacy. Feelings of euphoria, light headedness, and pain reduction were substantial enough for patients to state that would use it again if they had to repeat the medical procedure.

This study has shown that like previous studies of analgesia (Becker, 2008), sedation with nitrous oxide gas using the ® device appears to deliver an effective dose of nitrous oxide that produces short-term analgesia or minimal sedation.

SAFETY

Previously published studies of the effects of nitrous oxide show that complications are shown to occur in less than three percent (3%) of the population. With an n = 78, this study, using the same known side effects, shows complications to occur in less than .03% (2/78). Known side effects reported in the literature and the incidence of occurrence identified in this study is shown in the Table 4.

The complications identified in this study are two cases of oxygen saturation dropping below 90% for a few seconds. These two cases and all other notable events are documented previously in the comments sections of Tables 6 and 7. These same tables also include specific comments regarding patient safety for each patient case. In this study no adverse events were observed.

Both systolic and diastolic blood pressure increased slightly in patients receiving the gas. There are several possible explanations for the small increases in blood pressure shown. It is possible that the increases could be due to the effects of the nitrous gas, however, there is no published evidence that lists elevated blood pressure as an effect of nitrous oxide inhalation. A more plausible explanation is that the increased pressure is due to the activation of the sympathetic nervous system which is a normal response to a painful medical procedure.

Monitoring of oxygen saturation during each procedure revealed that with the exception of two pediatric patients, hypoxemia does not appear to be a safety issue. Two pediatric patients presented oxygen saturate levels of 89 percent for a few seconds. These cases are discussed in Table 6. The Instructions for Use were modified to reflect that when administering to pediatric patients the both air holes in the mouth piece should be open.

Earlier discussions with FDA reviewers revealed several patient safety concerns. These include the possibility of the device delivering a lethal dose of nitrous oxide and the possibility of patients entering hypoxia because the device mixes nitrous oxide gas with ambient air rather than pure oxygen. These two concerns are addressed more fully in performance tests already supplied to FDA. Based on the pulse oximetry data collected in this study, and in performance tests there is little evidence to suggest that when used correctly the device produces a hypoxic environment in adults or in the pediatric populations (see Clinical Study Results and Data Analysis herein, See Performance Test: Percent N_20 Deliver to Patient Using Different Nozzle, Nozzle Cap and Mouth Piece Designs, See also Performance Test: Analysis of N_20, Ambient Air O_2 Levels and O_2 Saturation in Humans).

Reviewers also expressed concern that the cylinders do not use any propriety or standardized DISS/PISS connectors. This concern of the safety of the device is addressed. (see Clinical Study Results and Data Analysis herein, See Performance Test: Percent N_20 Deliver to Patient Using Different Nozzle, Nozzle Cap and Mouth Piece Designs, See Performance Test: Analysis of N_20, Ambient Air O_2 Levels and O_2 Saturation in Humans, See Design History File).

Other discussions with FDA reviewers expressed concerns that because the device delivered nitrous oxide gas in an "uncontrolled environment" that the device could potentially deliver a lethal dose of nitrous oxide and/or create hypoxemia. No problems associated with this issue were observed.

Several important facts enhance the safety of Hand Held Nitrous®.

First, this device is optional for the patient in that the patient should be asked if they would like nitrous oxide before their procedure, as directed by the health care professional. Under no circumstances is this device designed to create or replace local anesthesia or general anesthesia and nothing should change in the way the procedure is normally performed (See Instructions for Use)

Second, the health care administrator can stop or modify administering the gas at any time should any problems express themselves by releasing the compression switch or, letting up on the compression switch (see Instructions for Use).

Third, the patient can stop inhalation at any time by simply stop inhaling or gently pushing the device away (see Instructions for Use).

Fourth, the gas is delivered over a maximum 120 seconds of inhalation time and is limited to 16 grams.

RISK-BENEFIT ANAYLSIS

A variety of factors should be considered when making assessments of the risk-benefit of the device. Nitrous oxide was first used in the dental practice in 1844.(Sneader, 2005) In the past 170 years nitrous oxide has become one of the most commonly used and evaluated analgesics used today. Advances in the way the gas is delivered to the patient have occurred regularly over the past century. However despite its evidence for effectiveness and safety, nitrous oxide is almost exclusively used by the dental industry. Lack of convenience, equipment requirements, and required changes to office design and planning have made it unattractive to physicians. In short, before the invention of the Hand Held Nitrous® device, other than dentists, licensed health care professionals have not had the ability to offer patients analgesia (minimal sedation) with nitrous oxide.

There is no other alternative to Hand Held Nitrous® other than the status quo: "I've been performing cystoscopies for 20 years, why change now?" Numbing gels, local anesthetic, IV medicines (which by itself is painful to perform) compete indirectly. With this device, other health care providers other than dentists (trained in nitrous oxide administration), can provide their patients with a little nitrous oxide for their office procedures and exams.

This clinical study has shown that analgesia (minimal sedation) is reached by 99% of patients who use the device. Its sedative effect is sufficient to provide substantial benefits to patients. Over 92 percent of patients who used the device, even for simple procedures such as cystoscopy, stated that they received a benefit from the device. For some patients pain was significantly reduced while the side effects of the device are rare. Its effects were consistent across genders, age groups and procedures received. Attending health care providers made comments such as:

"I've done this procedure before on that patient. He tolerated it much better with nitrous oxide." and "Usually patients cry with I inject Botox into the lips. There is no crying or crying is greatly reduced when we start the procedure off with a dose of nitrous oxide."

These observations suggest that the device not only has value for patients, but that health care providers recognize the effect of the device as a way to improve the patient/ doctor relationship and improve patient satisfaction. The device has value for both patients and health care providers.

On the risk side of this analysis, the device and the use of the nitrous oxide gas have produced no adverse events and few side effects. This clinical study does not prove that side effects are not possible, but it does suggest that side effects are exceptionally rare. The results of this clinical study agree with other published studies of the use of nitrous oxide that show that when used to produce minimal sedation, nitrous oxide is one of safest analgesics available and that adverse events and complications are rare.

LIMITATIONS

This clinical study has several limitations. The subject size is limited to 78 patients. The device was used across a variety of procedures but could be used for many other procedures not completed as part of this study. Different researchers were used to collect study data at the different research locations. Inter researcher variability could explain some of the variability on recorded data. The study itself was not a randomized, controlled trial. There was no comparison group. In actual use, the device and gas will be administered only by health care professionals without the help of a researcher. This study is the first of its kind to evaluate the Hand Held Nitrous® device, but it is not the first to study both the efficacy and safely if nitrous oxide. This device has the privilege of relying on the efficacy and safety findings of nitrous oxide that have been documented in over 140 randomized clinical trials that have been previously published.(Collado, 2007; Onody, 2006; Gall, 2001)

CONCLUSIONS

Indications For Use

Hand Held Nitrous® is intended to create short term analgesia (minimal sedation) by delivering a limited 16 grams of nitrous oxide over a total of 120 seconds of inhalation time. The effects last approximately five (5) minutes. Not for use for patients under three years of age or if you are pregnant.

Dosage:
Adults: Limit to two doses - pending on level of patient discomfort, plug holes with finger on mouth piece to increase dosage.
Children: Limit to one dose - leave holes open on mouth piece.

Based on the information provided with this clinical study we conclude that Hand Held Nitrous® is safe and effective for its intended use and should be down classed to Class II status.

The clinical results presented herein with the additional bench test data, already sent to the FDA CDRH shows that Hand Held Nitrous® is safe and effective for its intended use.

The complications observed in this clinical trial are much less than complications observed in the deliverance of procedural nitrous oxide using nitrous oxide / oxygen delivery devices.

Furthermore we conclude that that the risk associated with Hand Held Nitrous® is less than the risk associated with other nitrous oxide delivery devices already sold under Class II premarket notification requirement.

REFERENCES

Zier JL, Drake GJ, McCormick PC, Clinch KM, Cornfield DN. Case-series of nurse-administered nitrous oxide for urinary catheterization in children. Anesth Analg 2007;104:876-9

Farrell MK, Drake GJ, Racker D, Finkelstein M, Zier JL. Creation of a nurse-administered nitrous oxide sedation program for radiology and beyond. Pediatr Nurs 2008;34:29-35

Kowalski R, P. Mahon, G. Boylan, B. McNamara, G. Shorten, Validity of the modified observer's assessment of alertness/sedation scale (MOAA/S) during low dose propofol sedation: 3AP6-3 European Journal of Anaesthesiology 01/2007; 24:26-27.

Acute Pain Management Guideline Panel. 1992. Acute pain management: Operative or medical procedures and trauma. Clinical practice guideline. (Agency for Health Care Policy and Research Publication No. 92–0032). Rockville, MD: Agency for Health Care Policy and Research, United States Department of Health and Human Services, Public Health Service.

Babl FE, Oakley E, Seaman C, Barnett P, Sharwood LN. High-concentration nitrous oxide for procedural sedation in children: adverse events and depth of sedation. Pediatrics. 2008 Mar;121(3):e528-32.

Quinn C. L., Weaver J. M., Beck M. Evaluation of a clinical recovery score after general anesthesia. Anesth Prog. 1993; 40(3): 67–71.

Becker D, Rosenberg M, Nitrous Oxide and the Inhalation Anesthetics. Anesth Prog. 2008 Winter; 55(4): 124–131

Sneader W (2005). "Drug Discovery –A History". (Part 1: Legacy of the past, chapter 8: systematic medicine, pp. 74–87) John Wiley and Sons. ISBN 978-0-471-89980-8.

Collado V, Nicolas E, Faulks D, Hennequin M. A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. Expert Opin Drug Saf. 2007 Sep;6(5):559-71.

Onody P, Gil P, Hennequin M. Safety of inhalation of a 50% nitrous oxide/oxygen premix: a prospective survey of 35,828 administrations. Drug Saf 2006;29:633-40.

Gall O, Annequin D, Benoit G, Glabeke E, Vrancea F, Murat I. Adverse events of remixed nitrous oxide and oxygen for procedural sedation in children. Lancet 2001;358:1514-5.