Entonox Efficacy for Procedural-Sedation and Analgesia in Pediatrics Undergoing Bone Marrow Aspiration: A Randomized Clinical Trial

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Abstract

**Background:** The current study aimed at investigating the effect of using entonox gas during sedation and analgesia induction in pediatric candidates of bone marrow aspiration.

**Methods:** It was a single-blind, randomized clinical trial. All pediatric candidates of first-time bone marrow aspiration were included and allocated to either group 1 or 2, using a random number table. In group 1, a combination of midazolam, fentanyl, ketamine, and propofol was injected intravenously. In group 2, the mentioned combination was injected intravenously and entonox gas was used for patients’ ventilation. The goal was to reach level 4 sedation based on the Ramsay sedation scale. If needed, extra propofol was injected intravenously every minute. Physician and the helping nurse satisfaction of the procedure were evaluated. Duration of the procedure, the administered dosage for each patient, occurrence of any complications, and the recovery time were recorded.

**Results:** A total of 88 cases with the mean age of 6.8 ± 3.6 years, and mean weight of 25.4 ± 12.5 kg were included in the study (50% female). Baseline and demographic data of the groups showed no significant difference. Propofol consumption was significantly lower in group 2, for whom entonox gas was prescribed, compared with group 1 (P value < 0.001). Decrease of recovery time in group 2 compared with group 1 was evident (P value < 0.001). Physician and nurse’s satisfaction was higher in group 2 compared to group 1, and the difference was statistically significant.

**Conclusions:** It is likely that entonox prescription during bone marrow aspiration in pediatric leads to decrease in consumption of propofol to provide proper sedation, shorter recovery time of the patients, and increased satisfaction in both the physician and nurse in charge of performing the procedure.

**Keywords:** Nitrous Oxide, Pain Management, Pediatrics, Bone Marrow Aspiration, Conscious Sedation, Analgesia

1. Background

Performing aspiration and biopsy of bone marrow is a common procedure to diagnose and treat pediatric with malignancies. These procedures are very painful and need to be implemented under procedural sedation and analgesia (PSA) (1, 2). If sufficient and proper sedation is provided, the procedure is done more easily and rapidly, the child is more cooperative during treatment, there is less pain and discomfort for the child, and it leads to decrease in morbidity and mortality (3-7). One of the new and effective methods frequently used to relieve pain in painful outpatient procedures is using nitrous oxide gas along with O₂, known as entonox, and it seems to be effective in reducing the dose of intravenous sedative drugs (8-10). This gas probably induces its analgesic effects by stimulating supraspinal centers and activating endorphin releasing neurons in the spinal cord, and consequently inhibiting transmission of pain signals to upper centers. Nitrous oxide leads to changes in stimulation threshold of sense, heat, light, and sound, and causes deficiencies in short-term memory and dissociation. The effect of this gas initiates after 30 seconds and reaches its peak in 2 minutes (11-13). A significant number of clinical trials, using entonox, was performed on adult patients and especially in pregnant females to reduce labor pain (14, 15). Current resources assessing entonox efficacy in pediatric are limited and equivocal, which indicate the need for more research in this area (8, 9). The current study aimed at evaluating the effect of using entonox gas during sedation and analgesia induction in pediatric candidates of bone marrow aspiration.

2. Methods

2.1. Study Design

The current single-blind, randomized clinical trial was conducted from April 2015 to March 2016 in Imam Hossein hospital, Tehran, Iran. It is an educational medical center, including totally 614 active beds for 25 specialties and subspecialties. It is a state referral hospital affiliated to Shahid Beheshti University of Medical Sciences.
2.2. Study Population

All pediatric candidates of 1st time bone marrow aspiration were eligible and included in the study if the parents signed the written consent forms. The exclusion criteria were: having common cold, history of asthma, non-fasting, and known history of allergic reaction to any of the drugs used for sedation.

2.3. Sampling, Randomization, and Blinding

Based on $\alpha = 5\%$, $1-\beta = 90\%$, $S_1 = 14$, $S_2 = 14$, and $\varepsilon = 0.2$, and using the following formula, minimum required sample size for each group was calculated 44 cases.

$$n = \frac{(Z_{1-\frac{\alpha}{2}})^2 \times (S_1^2 + S_2^2)}{(d - \varepsilon)^2}$$

(1)

Based on the above mentioned inclusion and exclusion criteria, sampling was performed by the available sampling method in consecutive manner to achieve the calculated sample size. Then, patients were allocated to either group 1 or 2 using the table of random numbers. Due to the method of entonox administration, the physician who performed the procedures and the patients were aware, but the main investigator who interviewed the physician and nurse and also did the follow-up for possible side effects was blind to the intervention and control groups.

2.4. Intervention

Initially, all the demographic characteristics of patients including age, gender, and weight were recorded in a pre-designed checklist.

In group 1, a combination of 0.03 mg/kg midazolam, 1 µg/kg fentanyl, 1 mg/kg ketamine, and 1 mg/kg propofol was injected intravenously. The goal was to reach level 4 sedation based on the Ramsay sedation scale. Also, 1 mg/kg/minute propofol was injected intravenously, where necessary.

In group 2, a combination of 0.03 mg/kg midazolam, 1 µg/kg fentanyl, 1 mg/kg ketamine, and 1 mg/kg propofol was injected intravenously and from 2 minutes before the initiation of the procedure until its end, and entonox gas (combination of $O_2$ and nitrous oxide gases with 50% ratio) was used for the patients’ ventilation. To reach sedation level 4, based on the Ramsay sedation scale, 1 mg/kg/minute propofol was injected intravenously, where necessary.

It should be noted that the same physician and nurse conducted the bone marrow aspiration process on all patients. In group 1, during the procedure and recovery, and in group 2 after procedure and recovery, 100% $O_2$ was used for ventilation of the patients using a pediatric $T$ piece. In case of any complications during the procedure such as respiratory apnea, $O_2$ saturation dropping to less than 90%, and more than 30% decrease in heart rate compared to the baseline before drug injection, the procedure was aborted.

$O_2$ saturation percentage and heart rate of the children were controlled and recorded before drug administration, immediately before, at the initiation, and by the end of the procedure. Satisfaction of the physician performing the procedure and the helping nurse was evaluated and recorded based on the visual analog scale (VAS). Based on this scale, 0 shows the highest satisfaction rate and 10 shows the lowest satisfaction rate. Duration of the procedure, amount of drug administered to each patient, occurrence of any complications, and recovery time were recorded. Recovery time is the interval between the end of procedure and the time that the patients easily wake up when hear their names, and can talk and sit without help from others, which was defined considering the age of the child and their status before carrying out the procedure and sedation.

2.5. Statistical Analysis

Comparison of the groups was performed for all patients as originally allocated after randomization; therefore, intention-to-treat analysis was performed in the current study. All the collected data were analyzed by SPSS version 21. To express data, frequency, mean, and standard deviation (SD) were used. To express the accuracy of estimations, 95% confidence interval (CI) was considered. To compare the groups based on the type of variable and obtained result, $t$ and Mann-Whitney tests were used for continuous variables; in nominal variables Chi-square or the Fisher exact test were used according to the situation. Finally, to eliminate the effect of confounding factors, analysis of covariance was applied.

2.6. Ethical Consideration

The current study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (No. IR.SBMU.MSP.REC.1393.363). The protocol of the study was registered in the Iranian registry of clinical trials (www.IRCT.ir) (Reg. code: RCT2015090513364N2). All the children enrolled in the study after signing the written consent by their parents. All the experiments and procedures adhered to the principles introduced in the declaration of Helsinki.

3. Results

3.1. Descriptive FINDINGS

A total of 91 subjects were eligible. The consort diagram of patients flow is shown in Figure 1. Finally 88 cases with
the mean age of 6.8 ± 3.6 years and mean weight of 25.4 ± 12.5 kg were included in the study; 50% of which were female. Mean duration of procedure and recovery time in all the patients were 3.9 ± 1.4 and 11.3 ± 6.3 minutes, respectively. There was no significant difference between the groups regarding the baseline and demographic data (Table 1).

Table 1. Baseline and Demographic Data of the study Subjects in the Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Control)</th>
<th>Group 2 (Entonox)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.38 ± 1.59</td>
<td>7.22 ± 1.64</td>
<td>0.305</td>
</tr>
<tr>
<td>Gender, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (50.0)</td>
<td>22 (50.0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Female</td>
<td>22 (50.0)</td>
<td>22 (50.0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>23.6 ± 10.9</td>
<td>27.1 ± 13.8</td>
<td>0.367</td>
</tr>
<tr>
<td>Height, cm</td>
<td>113.6 ± 12.4</td>
<td>115.3 ± 11.7</td>
<td>0.578</td>
</tr>
</tbody>
</table>

3.2. Analytical Findings

Comparison of propofol consumption, side effects, recovery time, and physician and nurse's satisfaction between the groups is summarized in Table 2.

Table 2. Final Outcomes of the Study Subjects in the Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol consumption, mg</td>
<td>1.14 ± 0.55</td>
<td>0.07 ± 0.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Complication</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Recovery time, min</td>
<td>16.73 ± 3.63</td>
<td>5.77 ± 2.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Physician satisfaction</td>
<td>0.91 ± 0.13</td>
<td>0.16 ± 0.45</td>
<td>0.001</td>
</tr>
<tr>
<td>Nurse satisfaction</td>
<td>1.05 ± 1.29</td>
<td>0.25 ± 0.58</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Dose of propofol: Based on the results obtained from the study, propofol consumption was significantly lower in group 2, for whom entonox gas was prescribed, compared to group 1.
- Side effects: No side effect was observed in either of the groups.
- Recovery time: Based on the obtained results, there was evident decrease of recovery time in group 2, compared to group 1 (Figure 2).
- Physician and nurse's satisfaction: Mean satisfaction rate of the physician was 0.91 for group 1 and 0.16 for group 2. The smaller the number, the higher the satisfaction. In the statistical analysis of physician's satisfaction, the results showed a significant difference regarding physician's satisfaction between the groups, which was higher in group 2, compared with group 1. In line with physician's satisfaction, nurse's satisfaction was also higher in the group 2, compared with group 1 and the difference was statistically significant.

3.3. The Effect of Baseline Variables on Recovery Period

In the current study, the effect of gender, age, and weight on recovery time was also evaluated. The results of fitted regression showed that none of the 3 qualitative variables mentioned the affected recovery time with 95% CI. The formula for fitted regression was recovery duration = 13.56 - 0.868sex + 0.267age + 0.146weight, the coefficients of this regression were not approved statistically.

3.4. Relationship Between Procedure Duration and Recovery Time

The effect of procedure duration on recovery time was assessed statistically. Fitted regression formula was recovery duration = 2.6 + 2.2procedure. Independent variable coefficient of the study (2.2) was approved statistically in 95% CI level. In other words, as the procedure duration increased, the recovery time increased with a 2.2 coefficient; a coefficient in this regression was not approved.

4. Discussion

Based on the findings of the current study, entonox administration during bone marrow aspiration in pediatric led to decrease in the required dose of propofol for the induction of proper sedation, shorter recovery time of the patients and increased satisfaction of the physician and nurse in terms of performing the procedure.

Sedation induction to facilitate the procedure on pediatric is increasingly considered and numerous studies are conducted aiming to evaluate the safety and efficacy of various methods and drugs.

Hartling et al., performed a review on the systematic reviews carried out in this field and in total deemed the use of ketamine, propofol, and entonox superior to other agents, but affirmed that standardized outcome sets and reporting should be encouraged to facilitate evidence-based recommendations for care (16).

As stated before, efficiency of entonox in PSA was challenged in many studies and yielded various results (16). Michaud et al., evaluated the efficacy of entonox for the induction of analgesia during endoscopy in pediatric and reported that prescription of entonox led to better cooperation in patients and its short duration of action decreased the recovery time in the patients, and had little side effects (17). In addition, Cleary et al., also revealed similar
Assessed for eligibility (n = 91)

Excluded (n = 0)
Refused to participate (n = 3)

Randomized (n = 88)

Allocated to patient controlled analgesia (n = 44)
Received allocated intervention (n = 44)
Did not receive allocated intervention (n = 0)

Allocated to pudendal nerve block (n = 44)
Received allocated intervention (n = 44)
Did not receive allocated intervention (n = 0)

Lost to follow up (n = 0)
Discontinued the intervention (n = 0)

Analyzed (n = 44)
Excluded from analysis (n = 0)

Figure 1. The Consort Diagram of Patients Flow

Figure 2. Comparison of the Recovery Duration Between the Entonox and Control Groups with Interquartile Range

results regarding the use of inhaled entonox during intra-articular injections in children with juvenile idiopathic arthritis (18). Based on the results of the present study and other similar studies, it seems that short duration of action of entonox has a significant effect on recovery time after painful procedures.

In another study by Hee et al., efficacy of entonox in venous cannulation was compared with that of Emla cream and it was concluded that both methods had similar efficacy and their combination led to more proper analgesia and higher satisfaction. The notable finding in the mentioned study was that in older children, avoidance behaviors improved by entonox (19). The effect of the underlying variable of age on entonox efficiency during PSA is an important finding that unfortunately was not assessed in the present study.

In contrast with the present study, despite acknowledging the high rate of satisfaction among the children's families, Babl et al., deemed the efficacy of this gas unsuitable for solo use during the highly painful procedures such as orthopedic procedures (20). However, it should be noted that Babl et al., only used entonox for PSA, while in the present study it was used as an adjuvant.

To evaluate the side effects of nitrous oxide, Tsze et al., studied 1634 cases of prescribing this gas and recorded side effects in about 6.5% of the subjects, the most common of which was vomiting and serious side effects were observed.
in only 0.2% of the subjects (21). In line with this finding, no cases with side effects were detected in the present study that entonox was used as an adjuvant.

Nitrous oxide, which may be safely used by the children themselves, has considerably rapid onset and shorter duration of action compared with other modalities; therefore, it is quickly reversible (22-26). Minor painful procedures and cooperative children were predictive factors of nitrous oxide efficacy during PSA, but it was suggested that another method should be prepared in case of failure (22-24, 27). Nausea, vomiting, voice change, dysphoria, and dizziness were considered as minor side-effects that were rarely reported, and it was emphasized that major adverse events such as hypotension or oxygen desaturation could not be attributed to nitrous oxide inhalation (22, 23, 27). Age under 1 year and simultaneous use of other sedatives were the mentioned risk factors for the occurrence of serious adverse effects (27).

It seems that entonox efficacy is valuable in performing bone marrow aspiration and such painful procedures and could be considered as a proper option for pain control in pediatrics. Findings of the present study could encourage physicians to use this agent.

4.1. Limitation

Although the study population in the current study was unique compared with other clinical trials using entonox, still further well-designed studies are needed before generalizing the results. Conducting double-blind studies and calculating the patient pain score during the procedure with proper quantitative or qualitative scales are more valuable. Definitely such measurements in children are not devoid of problems. Considering baseline and demographic characteristics such as age and gender via multivariate analysis is accompanied with useful findings. The current study focused on the propofol consumption dose and recovery time as quantitative variables and physician and nurse’s satisfaction as qualitative variables. But unfortunately, vital signs and other clinical findings were not recorded to be statistically analyzed.

4.2. Conclusion

It is likely that entonox prescription during bone marrow aspiration in pediatric leads to decrease of propofol consumption to provide proper sedation, shorter recovery time, and increased satisfaction of both the physician and nurse in charge of performing the procedure.

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Footnotes

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