International Journal of Pediatric Otorhinolaryngology 78 (2014) 1090–1094

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

# Pain management following myringotomy and tube placement: Intranasal dexmedetomidine versus intranasal fentanyl

Elisabeth Dewhirst [a,1,*], Gina Fedel [b], Vidya Raman [b], Julie Rice [b], N'Diris Barry [b], Kris R. Jatana [c], Charles Elmaraghy [c], Meredith Merz [c], Joseph D. Tobias [b,d]

[a] Department of Anesthesiology & Pain Medicine, Wexner Medical Center at Ohio State University, OH, United States
[b] Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, OH, United States
[c] Department of Otolaryngology-Head and Neck Surgery, Nationwide Children's Hospital and the Wexner Medical Center at Ohio State University, Columbus, OH, United States
[d] Department of Pediatrics, Nationwide Children's Hospital and the Wexner Medical Center at Ohio State University, Columbus, OH, United States

ARTICLE INFO

*Article history:*
Received 22 November 2013
Received in revised form 7 April 2014
Accepted 8 April 2014
Available online 16 April 2014

*Keywords:*
Intranasal dexmedetomidine
Intranasal fentanyl
Myringotomy
Post-operative analgesia
Recovery

ABSTRACT

*Purpose:* Despite the brevity of the procedure, bilateral myringotomy and tympanostomy tube placement (BMT) can result in significant postoperative pain and discomfort. As the procedure is frequently performed without intravenous access, non-parenteral routes of administration are frequently used for analgesia. The current study prospectively compares the efficacy of intranasal (IN) dexmedetomidine with IN fentanyl for children undergoing BMT.

*Methods:* This prospective, double-blinded, randomized clinical trial included pediatric patients undergoing BMT. The patients were randomized to receive either IN dexmedetomidine (1 μg/kg) or fentanyl (2 μg/kg) after the induction of general anesthesia with sevoflurane. All patients received rectal acetaminophen (40 mg/kg) and the first 50 patients also received premedication with oral midazolam. Postoperative pain and recovery were assessed using pediatric pain and recovery scales, and any adverse effects were monitored for.

*Results:* The study cohort included 100 patients who ranged in age from 1 to 7.7 years and in weight from 8.6 to 37.4 kg. They were divided into 4 groups with 25 patients in each group: (1) midazolam premedication + IN dexmedetomidine; (2) midazolam premedication + IN fentanyl; (3) no premedication + IN dexmedetomidine; and (4) no premedication + IN fentanyl. Pain scores were comparable when comparing groups 2, 3 and 4, but were higher in group 1 (midazolam premedication with IN dexmedetomidine). There was no difference in total time in the post-anesthesia care unit (PACU) or time from arrival in the PACU until hospital discharge between the 4 groups. The heart rate (HR) was significantly lower in group 3 when compared to the other groups at several different times after arrival to the PACU. No clinically significant difference was noted in blood pressure.

*Conclusion:* Following BMT, when no premedication is administered, there was no clinical advantage when comparing IN dexmedetomidine (1 μg/kg) to IN fentanyl (2 μg/kg). The addition of oral midazolam as a premedication worsened the outcome measures particularly for children receiving IN dexmedetomidine.



## 1. Introduction

Bilateral myringotomy and tympanostomy tube placement (BMT) is commonly performed in infants and children for recurrent acute otitis media or chronic serous otitis media with effusion. Due to the brief and relatively simple nature of this surgery, as well as the otherwise healthy profile of most patients, anesthetic management frequently consists of general anesthesia without placement of an airway device or intravenous cannula (IV). However, the tympanic membrane is quite sensitive and given that

* Corresponding author at: Department of Anesthesiology & Pain Medicine, Wexner Medical Center at Ohio State University, 410 W 10th Ave, Columbus, OH 43210, United States. Tel.: +1 614 293 8487; fax: +1 614 293 8153.
*E-mail addresses:* elisabeth.dewhirst@osumc.edu (E. Dewhirst), joseph.tobias@nationwidechildrens.org (J.D. Tobias).
[1] Previously, at the time of study: Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, OH, United States.

http://dx.doi.org/10.1016/j.ijporl.2014.04.014
0165-5876/

intravenous access is not available, an alternative route of drug delivery for postoperative analgesia is needed. In many cases, acetaminophen is administered per rectum; however, this alone is generally not sufficient to provide effective analgesia [1–3]. Other suggested regimens for the provision of postoperative analgesia have included oral acetaminophen–codeine, intramuscular (IM) ketorolac and intranasal (IN) butorphanol; although perhaps the most commonly employed analgesic method is IN fentanyl [4–7]. Despite this practice, there are limited studies comparing intranasal fentanyl with other techniques.

Along with clonidine, dexmedetomidine (Precedex®, Hospira Worldwide Inc, Lake Forest, IL) is a member of the imidazoline subclass of $\alpha_2$-adrenergic agonists. Compared to clonidine, dexmedetomidine exhibits a higher ratio of specificity for the $\alpha_2$ versus the $\alpha_1$ receptor (1600:1 versus 200:1), thereby making it a complete agonist at the $\alpha_2$-adrenergic receptor [8]. Central activation of this negative feedback receptor leads to the clinical effects of sedation, anxiolysis, analgesia and sympatholysis [9–11]. Although not currently FDA approved for use in children, dexmedetomidine has been shown to be efficacious and safe in several different pediatric clinical scenarios [12]. There is also increasing information regarding its potential use by the IN route [13–17].

We hypothesized that IN dexmedetomidine would provide effective analgesia and smooth the emergence from general anesthesia in infants and children following BMT placement. The current study prospectively compares the efficacy of IN dexmedetomidine with IN fentanyl in this clinical scenario. The primary measure was to evaluate the recovery characteristics and pain scores following general anesthesia for BMT. As oral midazolam is frequently used in this population as premedication for the operating room; as a secondary measure, we also sought to evaluate its impact on the effects of IN fentanyl and dexmedetomidine.

## 2. Methods

Institutional Review Board approval was obtained for this prospective, double-blinded, randomized clinical trial. The study was registered at www.clinicaltrials.gov as study NCT01188551. An Investigational New Drug approval was received from the Food and Drug Administration for the off-label use of dexmedetomidine (IND # 110589). Written informed consent was obtained from a parent or guardian. Per our IRB policy, assent was obtained for patients who were ≥9 years of age. One hundred patients with American Society of Anesthesiologists (ASA) classification 1 or 2, ranging in age from 1 to 8 years of age and undergoing BMT for recurrent acute otitis media or chronic serous otitis media with effusion were included in the study. Patients with a history of allergy to dexmedetomidine or fentanyl or patients with concomitant use of medications which may exaggerate the heart rate response of dexmedetomidine including digoxin or β-adrenergic antagonists were excluded.

Premedication for the first 50 subjects consisted of oral midazolam (0.5 mg/kg). To evaluate the impact of premedication on the effects of IN fentanyl and dexmedetomidine, the subsequent 50 study subjects received no premedication. Randomization to IN dexmedetomidine or fentanyl was performed by the pharmacy using a computer generated randomization list. The pharmacist drew up the study drug (either fentanyl or dexmedetomidine) into a tuberculin syringe that was labeled study drug. To ensure blinding, the volume of the study medication was standardized at 0.04 mL/kg. In this way, the four study groups were: (1) midazolam premedication + IN dexmedetomidine ($n = 24$); (2) midazolam premedication + IN fentanyl ($n = 25$); (3) no premedication + IN dexmedetomidine ($n = 25$); and (4) no premedication + IN fentanyl ($n = 25$). Patients entered the operating room without parental accompaniment, which is the majority practice at our institution. After placement of standard ASA monitors, anesthesia was induced with sevoflurane in nitrous oxide (70%) and oxygen. Maintenance anesthesia consisted of sevoflurane in air and oxygen with an inspired oxygen concentration of 40–45%. Following anesthetic induction and prior to the start of the surgical procedure, an acetaminophen suppository (40 mg/kg) was placed and the study drug was administered by the attending anesthesiologist using the MADgic® MAD700, mucosal atomization device (Wolfectory Medical, Inc, Salt Lake City, UT).

The procedure was performed by an attending surgeon involved in the study or a resident/fellow under their direction supervision. After completion of the surgical procedure, the patient was transported to the post-anesthesia care unit (PACU) where recovery and pain variables were measured. Supplemental analgesia was available as needed at the discretion of the nursing staff in the PACU with single dose oral ibuprofen (10 mg/kg). The anesthesiologist administering the study drug and the study staff evaluating the patients in the PACU were blinded to the drug administered. Pain scores using the FLACC and Hannallah scoring systems and Aldrete and Steward recovery scores were recorded in recovery [18–22]. Two scoring systems for pain and recovery were used to ensure capture of any existing trend. Other PACU data collected included need for supplemental analgesia, heart rate (HR), blood pressure (BP) and oxygen saturation ($SpO_2$). These data were collected on arrival to the PACU and at 5, 15, 30 and 60 min intervals. At our institution, there is no minimum time that patients must remain in the PACU. They are moved to phase 2 recovery once PACU discharge criteria have been met. These include hemodynamic stability, adequate respiratory function, a normal mental status, as well as control of pain and agitation. In this secondary area, parents are able to see their children and patient observation including vitals and pain assessment continue while discharge preparations are coordinated. Length of time in PACU and total time to hospital discharge were also recorded for this study.

Statistical analysis consisted of non-parametric analysis for pain scores and recovery scores. Power analysis, performed using software PASS 2008 (NCSS LLC, Kaysville, Utah, www.ncss.com), indicated a sample size of 50 for the two groups (IN fentanyl versus dexmedetomidine) would detect a difference of 2 in pain scores with a significance level of 0.05. Chi-square analysis with a contingency table was used for gender between the groups. Non-paired *t*-test evaluated parametric data including HR, BP, oxygen saturation, age, weight and PACU discharge times.

## 3. Results

The study cohort included 100 patients. One patient was withdrawn from the study as an earlier than scheduled surgical start time necessitated unblinded drug administration. The remaining 99 patients ranged in age from 1 to 7.7 years and in weight from 8.6 to 37.4 kg. There were 62 male and 37 female patients. There were no differences in the demographics of the 4 groups (Table 1). The study drug was administered approximately

**Table 1**
Patient demographics.

| | Number | Age (years) | Weight (kg) | Gender (M/F) | ASA (1/2) |
|---|---|---|---|---|---|
| All patients | 99 | 2.6 ± 1.6 | 14 ± 4.7 | 62/37 | 52/47 |
| Group 1 | 24 | 2.1 ± 1.0 | 13.1 ± 2.6 | 15/9 | 13/11 |
| Group 2 | 25 | 2.9 ± 2.1 | 14.9 ± 6.1 | 11/14 | 16/9 |
| Group 3 | 25 | 2.9 ± 1.8 | 15.3 ± 4.5 | 16/9 | 13/12 |
| Group 4 | 25 | 2.1 ± 1.2 | 13.1 ± 3.0 | 20/5 | 10/15 |

The values are expressed as the mean ± standard deviation, absolute values or ratios. There were no statistically significant differences between the 4 groups.