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

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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

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Conflict of interest

None.

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.

Keywords

Intranasal dexmedetomidine; Intranasal fentanyl; Myringotomy; Post-operative analgesia; Recovery

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 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 α_2 -adrenergic agonists. Compared to clonidine, dexmedetomidine exhibits a higher ratio of specificity for the α_2 versus the α_1 receptor (1600:1 versus 200:1), thereby making it a complete agonist at the α_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 (Wolfe 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 (SpO₂). 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 3 min after anesthetic induction in all patients per the study protocol. The average procedure length assessed as the time between the completion of anesthetic induction and arrival in the PACU unit was 12 min. There was no difference in the timing of the study drug administration or procedure length between the 4 groups.

There were no clinically significant differences in the baseline HR and mean arterial pressure (MAP) between the groups (Tables 2 and 3). Although there were no clinically significant differences in HR or BP during the study period among the four groups, there were some statistical significance in the HR and MAP between the groups. The HR was lower in group 3 when compared to the other groups at several different times after arrival to the PACU (lower than group 1 at 0, 5, 15 and 30 min; lower than group 2 at 15 and 60 min, and lower than group 4 at 15 min) (Table 2). Group 2 had a higher MAP at 60 min post PACU arrival when compared to groups 1 and 3 (Table 3). There were no adverse hemodynamic effects such as bradycardia or hypotension noted in any study patient. Similarly, no respiratory depression or desaturation events were observed.

There were no differences in total time in the PACU or time from arrival in the PACU until hospital discharge between the 4 groups (Table 4). There were no consistent differences in recovery scores between groups across all time intervals, although at various time intervals

some differences were noted. Using the Steward scale, group 1 had a significantly lower score than both groups 2 and 4 at two of the 5 observed time intervals. Group 3 had a lower score than group 4 at 15 min (Table 5). Looking at Aldrete scores, group 2 had lower scores than both groups 1 and 4 at 5 min. At 30 min, Aldrete scores were significantly lower in group 1 than group 4 (Table 6).

FLACC pain scores were higher in group 1 than groups 3 and 4 at 30 min after PACU arrival and when all time interval scores were averaged and compared (Table 7). This difference between groups 1 and 3 was mirrored by the Hannallah scores (Table 8). Additionally, Hannallah scores were higher for group 2 than group 3 at 30 min. Overall, there were more time points with patients manifesting severe pain (greater than 6) in group 1 than the other groups. However, supplemental analgesia was not provided to any patient in the recovery unit or prior to hospital discharge.

4. Discussion

Children undergoing BMT can experience pain; however, due to the routine lack of intravenous access and limited data demonstrating an effective non-intravenous regimen, the provision of analgesia may be problematic. One commonly used option, the administration of rectal acetaminophen, has been shown to provide insufficient analgesia when used alone [1–3]. In many centers, IN fentanyl remains a commonly used analgesic although there are questions regarding its efficacy and investigations continue in the hopes of finding a better alternative. Regardless of the agent used, one potential drawback of the IN administration of medications especially to patients requiring BMT is that ongoing respiratory issues including chronic rhinitis may interfere with absorption and could theoretically alter efficacy. The current study compared the efficacy of IN dexmedetomidine and IN fentanyl with and without the use of oral midazolam premedication as a means of providing postoperative analgesia and optimizing recovery in children undergoing BMT. Given the common practice in our operating room, the administration of rectal acetaminophen was provided to all patients.

In the current study, we noted that IN dexmedetomidine did not provide superior analgesia or improve the recovery of patients following BMT when compared with IN fentanyl. Overall, there were no clinically significant differences between the pain and recovery scores of patients receiving IN dexmedetomidine 1 µg/kg (group 3) and IN fentanyl 2 µg/kg (group 4) alone. In fact, when combined with oral midazolam, IN dexmedetomidine provided a less favorable analgesic and recovery profile compared to patients not receiving midazolam. Additionally, the results suggested that patients who were premedicated with oral midazolam and received IN fentanyl did not do as well as patients who received only IN fentanyl, with higher pain scores at isolated time intervals. However, this pattern was less pronounced than for patients receiving IN dexmedetomidine.

Paradoxical reactions to midazolam including restlessness, agitation and inconsolable crying have been reported in children [23,24]. This may explain poorer outcome measures in group 1 and to a lesser extent group 2, when compared to both groups 3 and 4. This is especially

likely during brief procedures such as BMT as the mean OR time in the current study was only 12 min.

IN dexmedetomidine has been used in various clinical scenarios in the pediatric population including its non-intravenous administration as a premedication for the operating room [25,26]. In a similar study to ours, Pestieau and colleagues examined the efficacy of IN dexmedetomidine in 101 children undergoing BMT, comparing IN dexmedetomidine at 1 µg/kg or 2 µg/kg with IN fentanyl 2 µg/kg and a control group [27]. Although the administration of either IN fentanyl or dexmedetomidine decreased the need for rescue analgesia, there was a significant prolongation of the PACU stay with the administration of 2 µg/kg of dexmedetomidine (median of 70 min versus 40–42 min), leading to early termination of the study after an interim analysis. As in our study, they found no advantage with the use of IN dexmedetomidine when compared with IN fentanyl. Our study differed from the aforementioned, as we did not have a 2 µg/kg dexmedetomidine group or a control group not receiving any preemptive analgesia. We also administered rectal acetaminophen to all patients, rather than reserving this for rescue analgesia. Finally, premedication was not used in the study by Pestieau.

One plausible explanation for both of these studies demonstrating a lack of advantage of dexmedetomidine following BMT is a prolonged time to peak plasma concentration following IN administration. When using IN dexmedetomidine (1–1.5 µg/kg) as a premedicant for the OR, Yuen et al. noted an onset time of 45 min with a peak effect of 90–150 min when using hemodynamic parameters, sedation scoring systems, and the bispectral index [17]. Following IN administration in adults, peak plasma dexmedetomidine concentrations are achieved in 15–60 min with a bioavailability of 65% (range: 35–93%) further demonstrating variability with the IN route [28]. Studies with fentanyl have demonstrated a more rapid achievement of peak plasma concentrations perhaps explaining its superiority over dexmedetomidine when administered via this route [6]. Based on this information, a possible recommendation would be to administer the intranasal dexmedetomidine in the preoperative area, allowing peak concentration to be achieved in the immediate postoperative period. However, this would also add the potential discomfort of the administration of an intranasal medication to toddlers and small children.

In summary, our study demonstrates that for children undergoing BMT, when no premedication is administered, there was no clinical advantage in regards to analgesia and recovery characteristics when comparing IN dexmedetomidine (1 µg/kg) to IN fentanyl (2 µg/kg). The addition of oral midazolam as a premedication worsens the outcome measures particularly for children receiving IN dexmedetomidine. Given that a previous study has demonstrated prolonged recovery times with the use of a higher dose of IN dexmedetomidine (2 µg/kg) as well as the higher acquisition prices for dexmedetomidine, we would suggest that the optimal regimen continues to be rectal acetaminophen and IN fentanyl.

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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.

Table 2

Heart rate in the post-anesthesia care unit.

	Preoperative	Arrival	5 min	15 min	30 min	60 min
Group 1: midazolam premedication + IN dexmedetomidine	113 ± 20	126 ± 19	132 ± 26	133 ± 31	129 ± 30	114 ± 16
Group 2: midazolam premedication + IN fentanyl	112 ± 20	118 ± 21	124 ± 23	132 ± 31	126 ± 21	118 ± 21
Group 3: IN dexmedetomidine only	111 ± 22	108 ± 23 [†]	110 ± 33 [†]	104 ± 29 ^{†,*,#}	108 ± 23 [†]	102 ± 20 [*]
Group 4: IN fentanyl only	117 ± 20	115 ± 16	121 ± 24	135 ± 22	121 ± 21	114 ± 20

All 4 groups also received acetaminophen (40 mg/kg) per rectum. The values are provided in beats per minute as the mean ± standard deviation. IN = intranasal.

* $p < 0.05$ when compared to group 2.

$p < 0.05$ when compared to group 4.

[†] $p < 0.05$ when compared to group 1.

Table 3

Mean arterial pressure in the post-anesthesia care unit.

	Preoperative	Arrival	5 min	15 min	30 min	60 min
Group 1: midazolam premedication + IN dexmedetomidine	74 ± 10	69 ± 11	71 ± 13	75 ± 14	76 ± 17	71 ± 17
Group 2: midazolam premedication + IN fentanyl	78 ± 11	67 ± 12	70 ± 15	80 ± 15	89 ± 15	82 ± 13*
Group 3: IN dexmedetomidine only	78 ± 9	68 ± 10	73 ± 16	79 ± 15	79 ± 14	69 ± 11
Group 4: IN fentanyl only	80 ± 12	65 ± 11	76 ± 14	80 ± 10	80 ± 14	78 ± 12

All 4 groups also received acetaminophen (40 mg/kg) per rectum. The values are provided in mmHg as the mean ± standard deviation. IN = intranasal.

* $p < 0.05$ when compared to groups 1 and 3.

Table 4

Post-anesthesia care unit and hospital discharge times.

	Group 1	Group 2	Group 3	Group 4
Length of PACU stay (min)	21.3 ± 12.1	18.1 ± 8.7	22 ± 8.0	18.8 ± 9.1
Discharge time (min)	74.6 ± 15.9	68.7 ± 7.1	74 ± 16.3	70.2 ± 5.3

All 4 groups also received acetaminophen (40 mg/kg) per rectum. The values are presented in minutes as the mean ± SD. There was no statistically significant difference among the 4 groups.

Table 5

Recovery assessed using the Steward score.

	Arrival	5 min	15 min	30 min	60 min
Group 1: midazolam premedication + IN dexmedetomidine	1.0 ± 1.1	2.8 ± 2.3	4.2 ± 2.4	4.5 ± 2.0*	4.4 ± 1.9*
Group 2: midazolam premedication + IN fentanyl	0.8 ± 0.5	1.7 ± 1.7	4.5 ± 2.0	5.7 ± 0.9	5.8 ± 0.7
Group 3: IN dexmedetomidine only	1.1 ± 1.1	2.0 ± 2.1	3.8 ± 2.3**	5.0 ± 1.4	4.8 ± 1.5
Group 4: IN fentanyl only	0.9 ± 0.8	2.7 ± 2.2	5.4 ± 1.2	5.7 ± 0.6	5.5 ± 1.1

All 4 groups also received acetaminophen (40 mg/kg) per rectum.

* $p < 0.05$ when compared to groups 2 and 4.** $p < 0.05$ when compared to group 4.

Table 6

Recovery assessed using the Aldrete score.

	Arrival	5 min	15 min	30 min	60 min
Group 1: midazolam premedication + IN dexmedetomidine	6.4 ± 1.7	7.5 ± 2.1	8.0 ± 2.1	8.7 ± 1.3**	9.0 ± 1.4
Group 2: midazolam premedication + IN fentanyl	5.3 ± 1.1	6.0 ± 1.5*	8.4 ± 1.4	9.4 ± 1.0	9.5 ± 0.8
Group 3: IN dexmedetomidine only	5.5 ± 0.8	6.2 ± 1.5	8.1 ± 1.7	9.3 ± 0.9	9.2 ± 0.8
Group 4: IN fentanyl only	5.5 ± 1.0	7.4 ± 1.8	9.3 ± 1.0	9.5 ± 0.7	9.5 ± 0.8

All 4 groups also received acetaminophen (40 mg/kg) per rectum.

* $p < 0.05$ when compared to groups 1 and 4.

** $p < 0.05$ when compared to group 4. Group 1 was significantly lower than group 4 at 30 min.

Table 7

Pain assessed using the FLACC score.

	Arrival	5 min	15 min	30 min	60 min	Average of all time intervals (% of scores >6)
Group 1: midazolam premedication + IN dexmedetomidine	0.2 ± 1.0	2.9 ± 4.3	4.8 ± 4.5	4.7 ± 4.2*	1.4 ± 3.0	2.8 ± 4.0* (21.7)
Group 2: midazolam premedication + IN fentanyl	0.0 ± 0.0	0.9 ± 2.4	3.6 ± 4.4	2.9 ± 3.6	1.1 ± 2.2	1.7 ± 3.2 (10.4)
Group 3: IN dexmedetomidine only	0.4 ± 2.0	1.8 ± 3.8	2.4 ± 3.6	0.6 ± 2.2	0.9 ± 2.6	1.2 ± 3.0 (9.6)
Group 4: IN fentanyl only	0.2 ± 1.0	2.2 ± 3.5	2.8 ± 3.7	1.1 ± 2.5	0.8 ± 1.8	1.4 ± 2.8 (7.2)

All 4 groups also received acetaminophen (40 mg/kg) per rectum.

* $p < 0.05$ when compared to groups 3 and 4.

Table 8

Pain assessed using the Hannallah score.

	Arrival	5 min	15 min	30 min	60 min	Average of all time intervals (% of scores >6)
Group 1: midazolam premedication + IN dexmedetomidine	0.4 ± 1.1	2.4 ± 3.1	3.3 ± 3.1	2.9 ± 3.1 [†]	1.0 ± 2.3	2.2 ± 3.0* (17.8)
Group 2: midazolam premedication + IN fentanyl	0.2 ± 0.6	0.8 ± 2.0	2.5 ± 2.9	2.3 ± 2.4 [†]	1.4 ± 1.7	1.6 ± 2.4 (8.0)
Group 3: IN dexmedetomidine only	0.1 ± 0.4	1.0 ± 2.4	2.2 ± 2.8	0.6 ± 1.3	0.5 ± 1.1	1.1 ± 2.2 (8.8)
Group 4: IN fentanyl only	0.3 ± 1.1	1.7 ± 2.4	2.0 ± 2.7	1.1 ± 1.7	1.0 ± 1.6	1.4 ± 2.2 (5.6)

All 4 groups also received acetaminophen (40 mg/kg) per rectum.

* $p < 0.05$ when compared to group 3.[†] $p < 0.05$ when compared to group 3.