CLINICAL INVESTIGATION

Oxymetazoline Metered Dose Spray: Factors Affecting Delivery Volume

Mumin Hakim, MBBS,¹ Hina Walia, MBBS,¹ Mahmood Rafiq, MD,¹ Timothy Grannell, CRNA,¹ Richard S. Cartabuke, MD,^{1,2} and Joseph D. Tobias, MD^{1,2}

¹Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio; ²Department of Anesthesiology & Pain Medicine, The Ohio State University, Columbus, Ohio

OBJECTIVES: The current study compared the amount of oxymetazoline delivered by various anesthesia providers when holding the bottle in the upright and inverted position. Additionally, the amount delivered from a full bottle and a half-full bottle was also investigated.

METHODS: Using an analytical balance that was calibrated to zero, we evaluated the impact the position of the bottle and the volume of oxymetazoline in the bottle had on the amount being delivered by both anesthesia staff and trainees.

RESULTS: When using both filled and half-filled bottles, the amount delivered increased significantly when comparing the upright versus inverted position. With a full bottle, the amount delivered when the bottle was inverted increased almost 10-fold from 62 ± 80 to 606 ± 366 μ L ($p < 0.0001$). Similarly, even with a half-filled bottle, the amount delivered increased in the inverted positions from 41 ± 48 to 645 ± 393 μ L. Regardless of the scenario, we also noted significant variation from provider to provider.

CONCLUSIONS: Our results demonstrate that several factors may affect the amount of oxymetazoline delivered for metered dose bottles. Given the potential for severe end-organ effects with excessive dosage, alternative means of delivery are needed for its perioperative use.

INDEX TERMS: α_2 -adrenergic agonist, hypertension, oxymetazoline

J Pediatr Pharmacol Ther 2016;21(3):247–251

INTRODUCTION

Oxymetazoline is a topical sympathomimetic agent that is the active ingredient in over-the-counter nasal decongestant sprays such as Afrin (Merck Schering-Plough Pharmaceuticals, North Wales, PA).¹ It is an imidazoline derivative that causes vasoconstriction of blood vessels through its direct effect on α -adrenergic receptors. In addition to its utility as a nasal spray for allergic and viral rhinitis, it is also administered in the operating room during otorhinolaryngological procedures to improve visualization of the airway, minimize perioperative bleeding, and decrease the risk of epistaxis during nasotracheal intubation due to its topical vasoconstrictive effect on blood vessels.^{2,3} When administered in excessive doses, systemic absorption and high plasma concentrations of oxymetazoline may lead to serious complications and even fatal consequences.^{4,5}

When used in clinical practice, oxymetazoline is most commonly administered via a meter dosed plastic bottle. The bottle is meant to be held in the upright position and squeezed to deliver a fine mist containing the medication. However, alterations of the position of the bottle, such as holding it in the inverted position, may significantly affect the amount that is delivered.⁶ Latham and Jardine⁶ demonstrated as much as a 75-fold increase in the volume delivered when the bottle was held inverted during administration. Squeezing the bottle in the upright position delivered 28.9 ± 6.8 μ L of fluid, while 1037 ± 527 μ L (range: 473–2196 μ L) was delivered when the bottle was squeezed in the inverted position. Given the supine position of patients on the operating room table, it is common practice to squeeze the bottle while it is inverted.

We hypothesized that effort or the total amount of solution within the bottle might also affect the

Table 1. Volume of Oxymetazoline Delivered

Position and Bottle Volume*	Amount Delivered (μ L) Mean $\pm$ SD (Range)
Filled and upright	62 $\pm$ 80 (10-490)
Filled and inverted	606 $\pm$ 366 [†] (60-1830)
Half-filled and upright	41 $\pm$ 48 [‡] (10-320)
Half-filled and inverted	645 $\pm$ 393 [†] (70-1610)

* For each position and volume, n = 87.

[†] p < 0.0001 versus filled and upright as well as half-filled and upright.

[‡] p = 0.0372 versus filled and upright.

amount of delivered volume. The current study compared the volume delivered by various anesthesia providers when holding the bottle in the upright and inverted position. Additionally, the volume delivered from a full bottle and a half-full bottle was also investigated.

METHODS

The study was conducted in the Department of Anesthesiology and Pain Medicine at Nationwide Children's Hospital, Columbus, Ohio. As it did not involve patient care, no institutional review board approval was required. There were 87 study participants including faculty, fellows, residents, certified registered nurse anesthetists (CRNAs), and student registered nurse anesthetists (SRNAs) who have active clinical roles in the department.

The study consisted of 2 phases. During phase 1, the participants were given a new 15-mL bottle of the nasal decongestant spray (Oxymetazoline hydrochloride 0.05%, 12-hour nasal decongestant spray, Major Pharmaceuticals, Livonia, MI). The baseline weight of the bottle was measured using an analytical balance that had been calibrated and zeroed prior to use. The participants were asked to deliver the clinically recommended dose of 2 sprays from the bottle in the upright position. The bottle was then weighed again to determine the amount delivered, using the conversion: 10 mL = 10 mg (This was determined by weighing 10 mL of the medication solution that had been withdrawn from a bottle). Two sprays were delivered in the inverted position and the bottle weighed again to determine the amount delivered. In phase 2 of the study, the same sequence of events was followed, but 50% of the initial volume in the bottle was utilized (half-filled bottle).

Statistical analysis included a paired t-test to compare the amount delivered in the upright

and inverted position, as well as comparing the amounts delivered from full and half-filled bottles. An analysis of variance was used to compare the amount delivered based on level of training, which was separated into staff (anesthesiology faculty and CRNAs) and trainees (fellows, residents, and SRNAs). The data are presented as the mean $\pm$ SD with p < 0.05 considered significant.

RESULTS

There were 87 participants in the study including 31 anesthesiology faculty, 31 CRNAs, and 25 trainees (residents, fellows, and SRNAs). The amount delivered from the full and half-filled bottles in the upright and inverted positions is listed in Table 1. When using both filled and half-filled bottles, the amount delivered increased significantly when comparing the upright versus inverted position. With a full bottle, the amount delivered when the bottle was inverted increased almost 10-fold from 62 $\pm$ 80 to 606 $\pm$ 366 μ L (p < 0.0001). Similarly, even with a half-filled bottle, the amount delivered increased in the inverted positions from 41 $\pm$ 48 to 645 $\pm$ 393 μ L (p < 0.0001). Additionally, in the upright position, there was a greater volume delivered with a full bottle when compared to a half-filled bottle (62 $\pm$ 80 versus 41 $\pm$ 48 μ L, p = 0.037). No difference was noted in the inverted position between a full and half-filled bottle. The amount delivered from the full and half-filled bottles in the upright and inverted positions separated by type of provider (staff versus trainee) is listed in Table 2. No difference in the amount delivered was noted in the upright position based on provider (staff versus trainee) when using a filled (56 $\pm$ 66 versus 78 $\pm$ 108 μ L, p = 0.2497) or half-filled bottle (45 $\pm$ 55 versus 30 $\pm$ 17 μ L, p = 0.1858) in the upright position. In the inverted position, the amount delivered by trainees was greater with a full bottle (750 $\pm$ 366

Table 2. Volume of Oxymetazoline (μL) Delivered Based on Provider

Position and Bottle Volume	Amount Delivered (μL) (mean $\pm$ SD)		p value*
	By Faculty (n = 62)	By Trainees (n = 25)	
Filled and upright	56 $\pm$ 66	78 $\pm$ 108	0.2497
Filled and inverted	549 $\pm$ 352	750 $\pm$ 366	0.0194
Half-filled and upright	45 $\pm$ 55	30 $\pm$ 17	0.1858
Half-filled and inverted	553 $\pm$ 334	872 $\pm$ 434	0.0004

*Versus corresponding faculty group.

versus 549 $\pm$ 352 μL , $p = 0.0194$) or a half-filled bottle (872 $\pm$ 434 versus 553 $\pm$ 334 μL , $p = 0.0004$) than the amount delivered by staff.

DISCUSSION

The current study confirms and expands previous data showing significant variability in the amount of oxymetazoline that is administered from metered dose bottles. We noted that with the bottle inverted, there was a significant increase (10-fold) in the volume delivered when using either a full or half-filled bottle compared to the upright position. When comparing a filled to a half-filled bottle, we also noted variations in the amount delivered based on the volume of liquid in the bottle. Also of note was the significant user-dependent variation in the amount delivered with a range of 10 to 490 μL with a filled bottle in the upright position and 60 to 1830 μL with a filled bottle in the inverted position. User variation was also noted based on the experience of the anesthesia provider (i.e., staff versus trainees). We would postulate that this variation results from the fact that the amount delivered is effort-dependent and affected by the speed and force used to squeeze the bottle. These may be other factors leading to alterations in dosage.

Similar results were demonstrated by Latham and Jardine⁶ in another *in vitro* study that examined the impact of bottle position (both upright and inverted) when dispensing 5 sprays of oxymetazoline.⁶ Squeezing the bottle in the upright position resulted in a fine spray of fluid that delivered 28.9 $\pm$ 6.8 μL . The authors noted that the amount delivered was largely independent of effort and similar to the volume of oxymetazoline measured in a drop (30 μL). Squeezing the bottle in the inverted position delivered a volume of 1037 $\pm$ 527 μL (range: 473-2196 μL) with a steady stream of fluid, which was completely effort

dependent. Overall, the study demonstrated up to a 75-fold increase in volume of oxymetazoline when expelled from the bottle in the inverted compared with the upright position.

The significant variation in delivery is of significant concern given the potential for adverse systemic effects with excessive doses. Although, imidazoline derivatives have been used for many years as over-the-counter medications, there are numerous anecdotal case reports describing significant adverse systemic effects involving the central nervous, cardiovascular, and respiratory systems.^{4,7-14} When considering all of these case reports, the etiologic event may have been an idiosyncratic reaction, interaction with other medications, inadvertent overdose due to delivery technique, accidental ingestion, or excessive dose due to small patient size. Case reports from the perioperative setting are likely related to alterations in dosage related to the position of the bottle. The risk of inadvertent overdosage is increased by the fact that the patient is lying supine on the operating room table and hence the bottle is held in the inverted position for delivery into the naris. As noted in our current study and the recent publication by Latham Jardine,⁶ bottle position significantly affects the amount delivered. Another source that can increase the administration of oxymetazoline is the use of pledgets. As demonstrated by Latham Jardine,⁶ medication-soaked pledgets placed in the naris held a significant volume of oxymetazoline, with 1 pledget holding a volume (1500 $\pm$ 184 μL) similar to a spray in the inverted position in their study.⁶

In summary, our study demonstrated up to a 10-fold increase in the volume of oxymetazoline dispensed in the inverted position. This predisposes the delivery of a much higher dose than required for clinical effect, which can lead to toxicity. This suggests caution when using the

spray bottle in the inverted position. In order to improve patient safety, it is important to develop a set of guidelines when administering oxymetazoline especially in the pediatric population. Since there are no pharmacokinetic studies to quantify the absorption characteristics of oxymetazoline, it is a common practice to use 2 to 3 sprays per nostril, the dose listed by the package insert for patients over 6 years of age.

When used in the pediatric population, we would not recommend the use of the over-the-counter bottles. The amount to be administered should be measured, especially if pledgets are used. This would allow more accurate dosage given the various factors, which have been outlined above, that can affect the dosage. To limit excessive dosage for nasal administration, after the medication is drawn up in a tuberculin syringe, it can be administered using an atomizer device that is not position dependent (MAD Nasal or MADgic, Teleflex, San Diego, CA) for the administration of medications. Even with such care, there are still no pharmacokinetic data on which to base recommendations for oxymetazoline dosage. Although delivered to the nasal mucosa, there is systemic absorption with the potential for systemic effects. The current recommendations from the package insert is to use 2 to 3 sprays in each nostril; not more often than every 10 to 12 hours with the caveat not to exceed 2 doses in any 24-hour period. Although the insert provides instructions to spray, squeeze bottle quickly and firmly, there is no information regarding the amount (volume) delivered with each spray. One is also instructed to not tilt the head backward while spraying.

From our study, we noted an average volume delivered with 2 sprays from a full bottle of 62 μ L (0.062 mL). However, there was significant variation in deliver with the multiple providers ranging from 10 to 490 μ L. Assuming a volume of 62 μ L and a concentration of 0.05%, two sprays would deliver 0.031 mg of oxymetazoline. As up to 3 sprays can be delivered into each nare (total of 6 sprays), the amount delivered would be 0.093 mg (93 mcg). Although we can arrive at this information, there is nothing available regarding the pharmacokinetics of intranasal oxymetazoline in adults or children on which to determine the safety of this regimen. Furthermore, given the weight variation from a 6-year-old to an adult, further issues arise with dosage, as well

as interpatient variability to the systemic effects of oxymetazoline based on associated comorbid conditions.

The key to the management of oxymetazoline-related adverse effects must start with prevention. However, when perioperative problems arise including hypertension, pulmonary edema, or cardiac arrest, oxymetazoline should be considered in the differential diagnosis for the etiology. Treatment should be directed at reducing the α -adrenergic receptor-induced vasoconstriction. As such, direct and rapid acting vasodilators (sodium nitroprusside) should be considered the drugs of choice.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations CRNA, certified registered nurse anesthetist; SRNA, student registered nurse anesthetist

Correspondence Mumin Hakim, MBBS, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, email: mumin.hakim@nationwidechildrens.org

REFERENCES

1. Haenisch B, Walstab J, Herberhold S, et al. Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline. *Fund Clin Pharmacol*. 2009;24(8):729-739.
2. Katz RI, Hovagim AR, Finkelstein HS, et al. A comparison of cocaine, lidocaine with epinephrine, and oxymetazoline for prevention of epistaxis on nasotracheal intubation. *J Clin Anesth*. 1990;2(1):16-20.
3. Riegle EVE, Gunter JBJ, Lusk RPR, et al. Comparison of vasoconstrictors for functional endoscopic sinus surgery in children. *Laryngoscope*. 1992;102(7):820-823.
4. Ramesh AS, Cartabuke R, Essig C, et al. Oxymetazoline-induced postoperative hypertension. *Pediatr Anesth Crit Care J*. 2013;1(2):72-77.
5. Tobias JD, Cartabuke R, Taghon T. Oxymetazoline (Afrin®): maybe there is more that we need to know. *Pediatr Anesth*. 2014;24(8):795-798.

6. Latham GJ, Jardine DS. Oxymetazoline and hypertensive crisis in a child: can we prevent it? *Pediatr Anesth*. 2013;23(10):952-956.
7. Tobias JD. Central nervous system depression following accidental ingestion of Visine eye drops. *Clin Pediatr (Phila)*. 1996;35(10):539-540.
8. Fabi M, Formigari R, Picchio FM. Are nasal decongestants safer than rhinitis? A case of oxymetazoline-induced syncope. *Card Young*. 2009;19(6):633-634.
9. Thrush DN. Cardiac arrest after oxymetazoline nasal spray. *J Clin Anesth*. 1995;7(6):512-514.
10. Mahieu LM, Rooman RP, Goossens E. Imidazoline intoxication in children. *Eur J Pediatr*. 1993;152(11):944-946.
11. Buysschaert I, Van Dorpe J, Dujardin K. Hypertensive crisis and end-organ damage induced by over-the-counter nasal decongestant abuse. *Eur Heart J*. 2011;32(24):3114.
12. Leupold DD, Wartenberg KEK. Xylometazoline abuse induced ischemic stroke in a young adult. *Neurologist*. 2011;17(1):41-43.
13. Klein KU, Wisser G, Engelhard K, et al. Pulmonary edema and prolonged awakening after nasal naphazoline application in a transsphenoidal hypophysectomy patient. *J Neurosurg Anesthesiol*. 2010;22(3):269.
14. Fukushima H, Norimoto K, Seki T, et al. Acute pulmonary edema associated with naphazoline ingestion. *Clin Toxicol*. 2008;46(3):254-256.