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# Anesthetic management for medialization laryngoplasty using concurrent infusions of dexmedetomidine, remifentanil, and propofol *versus* controls☆

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A B S T R A C T

*Purpose:* Medialization laryngoplasty (ML) ± arytenoid adduction (AA) surgery poses a unique anesthetic challenge that requires periods of deep sedation and patient cooperation with phonation to assess voice function. The purpose of this study was to assess if the protocolized administration of dexmedetomidine, remifentanil, and propofol (DRP) is associated with reduced procedural duration and administration of other sedating medications.

*Materials and methods:* This was a retrospective 2:1 case matched study design; matched on age, sex, body mass index, AA, and surgical revision status. Data was obtained from the electronic medical record of a tertiary referral center. Cases underwent ML ± AA using DRP. Control subjects underwent surgery ML ± AA without DRP.

*Results:* 58 DRP cases (43.1% AA) were matched with 116 control patients (44.8% AA). DRP was associated with decreases in fentanyl dose (50 [25, 100] *vs.* 100 [50, 150] mcg; $p < 0.01$), incidence and dose of midazolam (4 [6.9%] *vs.* 70 [60.3%]; $p < 0.01$; 1 [1, 1] *vs.* 2 [2, 2]; $p < 0.02$), operative duration (131 ± 33 *vs.* 160 ± 50 min; $p < 0.01$), and anesthetic duration (182 ± 35 *vs.* 219 ± 60.3 min; $p < 0.01$). When adjusted for timeline, it was observed that case duration was declining prior to DRP introduction; this trend persisted after DRP introduction. Hypopnea was more common with DRP (14 [24.1%] *vs.* 7 [6.0%]; $p < 0.01$).

*Conclusions:* DRP was associated with a substantial decrease in opioid and benzodiazepine administration. A reduction in procedural duration over time was also observed.

## 1. Introduction

Medialization laryngoplasty (ML) is an operation for voice reconstruction performed for correction of unilateral vocal cord paralysis. The operative goal of ML is to move the edge of the paralyzed vocal fold closer to midline, which allows closure of the glottis during phonation. In some cases, a larger posterior glottal gap is present that requires arytenoid adduction (AA). ML is unique in that it requires intraoperative voice monitoring where the patient needs to phonate during the procedure [1]. Historically, ML was performed under local anesthesia, which was sometimes uncomfortable for the patient and technically difficult for the otolaryngologist due to coughing and laryngeal movement [2]. Sedation using a variety of monitored anesthetic care techniques can improve patient tolerance during ML [1–5], but a successful procedure requires the patient to maintain spontaneous breathing despite periods of deep sedation followed by periods of rapid emergence in order to phonate.

An anesthetic technique which uses a combination of dexmedetomidine, remifentanil, and propofol (DRP) for sedation has recently been described in a case series for ML [6]. This novel anesthetic combination offers several theoretical advantages owing to the pharmacology and clinical effects of these agents. Dexmedetomidine is a central alpha-2 agonist with anxiolytic, analgesic, and sedative effects which mimic normal sleep cycles. Importantly, dexmedetomidine is not known to induce respiratory depression [7,8]. Remifentanil is a potent ultra-short acting synthetic opioid with a blood brain equilibrium half-life of 12 min and a context-sensitive halftime of 3 to 8 min, thus is easily titratable. It is eliminated rapidly by nonspecific esterases; therefore, there is no accumulation in the setting of renal or hepatic dysfunction. Propofol is a gamma-aminobutyric acid agonist and is one of the most widely used anesthetic agents for sedation and general anesthesia and is generally well tolerated at low doses [9]. It does not have analgesic properties. Propofol is rapidly metabolized to inactive metabolites and can be used without extensive dosing changes in patients with hepatic and renal failure, unlike many other sedation agents [9,10]. Using DRP together has potential advantages, including

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antiemetic effects, short acting titratable analgesia, improved pharyngeal muscle relaxation, and the ability to deeply sedate the patient while allowing for rapid titration to an awake state for phonation owing to the drugs' short half-lives.

Successful anesthetic management using combinations of these medications have been described for other procedures. For cystoscopy, co-administration of dexmedetomidine and remifentanil has been reported to result in optimization of analgesia, onset of appropriate level of sedation, speed of emergence and surgeon satisfaction [8]. Arpaci et al. compared the co-administration of dexmedetomidine/remifentanil to midazolam/remifentanil and found that the dexmedetomidine/remifentanil combination produced faster onset of targeted level of sedation, faster recovery times, and less postoperative cognitive dysfunction [7]. Kim et al. assessed the efficacy of dexmedetomidine/remifentanil compared to propofol/remifentanil in patients undergoing endoscopic submucosal dissection and found that propofol produced a more profound decrease in pharyngeal muscle tone and pharyngeal reflex compared to dexmedetomidine [10].

Our practice has developed a protocol using DRP sedation which has been accepted for publication as a case series of 75 patients [6]. To support this practice change, we performed a retrospective case controlled study to assess if DRP is associated with improvements in procedural time or reduction in the use of other sedating medications. Our hypothesis is that this technique is superior for ML ± AA compared to our traditional anesthetic management.

## 2. Methods

This study was approved by the Mayo Clinic, Rochester MN, Institutional Review Board (protocol number 16-002294, approved on 4/18/2016, handled by Ellen Olson). Consistent with Minnesota Statute 144.295, all patients in this study provided prior authorization for research use of their medical records.

### 2.1. Study design

This study used a retrospective case matched study design that compared the study group (ML patients anesthetized with DRP) with a control group who did not receive this combination of anesthetics. Study subjects were identified through electronic queries for patients undergoing ML procedures with DRP from the Mayo Clinic electronic medical record (EMR) from June 1st, 2015 through June 30, 2017. Eligibility included patients ≥ 18 years of age who underwent ML ± AA with DRP after the protocol's initiation in June 2015. Exclusion criteria included patients whose medical records did not include research authorization or patients < 18 years of age at the time of surgery. Control subjects who underwent ML surgery prior to these dates (from August 1, 2008 through May 31, 2015) were also identified using the EMR. For each patient who received DRP, two control patients were randomly selected from the pool of all potential control patients who underwent the same surgery and were the same age ( ± 12 years), sex, BMI ( ± 6 $kg/m^2$), and surgical revision status as the DRP case.

### 2.2. Data collection

Demographic, procedural, pharmacologic, and outcome data were extracted from the EMR. Demographic and procedural information was obtained using database queries of the EMR. Manual chart review for comorbidities, vital signs, perioperative medications, bolus medication administration events, and adverse perioperative events was done by authors KSH and MCH. Specifically, comorbidity variables included the presence or absence of diabetes, hypothyroidism, obesity, obstructive sleep apnea (OSA), coronary artery disease (CAD), hypertension, congestive heart failure (CHF), dysrhythmias, peripheral vascular disease, central nervous system disease, renal disease, psychiatric disease, chronic obstructive pulmonary disease (COPD), and asthma. Data including history of tobacco exposure, otolaryngological disease, oncologic history, and use of outpatient benzodiazepines, narcotics, and antipsychotics were also obtained *via* manual chart review. Manually collected pharmacologic variables included presence or absence of propofol, dexmedetomidine, and remifentanil infusions and their mean and total doses. Use of phenylephrine infusion, phenylephrine bolus, midazolam or fentanyl boluses, post-operative nausea and vomiting prophylaxis (PONV), and paralytic medication was documented. Manually collected outcome data included adverse respiratory events (need for placement of an advanced airway, laryngospasm, bronchospasm, hypopnea, or intraoperative aspiration), adverse cardiovascular events (chest pain, electrocardiogram changes, infarction, ischemia, or bradycardia), disposition, discharge status, and other adverse events. For this study, hypopnea was defined as a decrease in respiratory rate which was temporally associated with SpO2 < 90%, and bradycardia was defined as a heart rate < 50 requiring pharmacologic intervention. Intraoperative vital signs (maximum and minimum heart rate, blood pressure, SpO2, and respiratory rate) were manually collected. Discrete perioperative variables such as surgical time, anesthetic time, and post-anesthesia care unit (PACU) time were obtained from EMR queries.

### 2.3. DRP protocol for case anesthetics

Based on a previously described protocol [6], cases were provided with dexmedetomidine at a loading dose of 1 μg/kg administered over 10–15 min followed by an infusion titrated from 0.4 to 1.5 μg/kg/h (typically 0.8 μg/kg/h). Remifentanil was initiated concurrently and infused at rates of 0.05–0.15 μg/kg/min. Dexmedetomidine or remifentanil boluses were not provided. A propofol infusion was initiated at rates of 25 μg/kg/min, and up to three 10–20 mg bolus doses were permitted prior to local anesthetic infiltration by the surgical team. After the dexmedetomidine load was completed, sedation and anxiety level were assessed and propofol was allowed to be titrated down as tolerated. Titrations of infusions were permitted within the ranges described at the discretion of the anesthesia provider.

### 2.4. Traditional management for control anesthetics

The control anesthetics were administered at the anesthesia provider's discretion without the use of a protocol, standardized approach, or guidance on dosing or titration schedule. Most pre-protocol patients received dexmedetomidine with a lesser subset concurrently receiving propofol; however the simultaneous addition of remifentanil was not applied to this group. Midazolam and fentanyl were provided at the discretion of the provider for the purposes of anxiolysis and analgesia. Most patients in the control group also received antiemetic prophylaxis, but this was not by protocol.

### 2.5. Statistical analysis

The sample-size for the present study was determined based on the number of patients who underwent ML surgery with DRP at our institution between 6/1/2015 through 6/30/2017. No formal statistical power analysis was performed.

Continuous variables are expressed as mean ± standard deviation or median [25th, 75th] and compared between groups using the two sample *t*-test or rank sum test as appropriate. Categorical variables are summarized as frequency and percentage and compared between groups using the chi-square test or Fisher's exact test.

Since DRP use represented a practice change at our institution, the comparison between DRP and control groups is confounded by other changes that may have occurred over calendar time. For the primary outcomes, additional analyses were performed using linear regression to assess patterns of temporal changes. Statistical analysis was performed utilizing JMP software (JMP®, Version 13.2, SAS Institute Inc.,

**Table 1**
Demographics for patients managed with the DRP protocol with matched controls.[a]

| Variable | Cases (N = 58) | Controls (N = 116) | p |
|---|---|---|---|
| Age, years | 61.1 ± 14 | 61.3 ± 12.4 | [a] |
| Male | 21 (36.2) | 42 (36.2) | [a] |
| BMI | 28.1 ± 6.7 | 27.3 ± 5.6 | [a] |
| Comorbidities | | | |
| HTN | 25 (43.1) | 63 (54.3) | 0.16 |
| CAD | 6 (10.3) | 13 (11.2) | 0.86 |
| DM | 8 (13.8) | 11 (9.5) | 0.39 |
| CNS Disease | 13 (22.4) | 19 (16.4) | 0.33 |
| Psychiatric Disease | 19 (32.8) | 35 (30.2) | 0.73 |
| Outpatient Opioid | 6 (10.3) | 15 (12.9) | 0.62 |
| Outpatient Benzodiazepine | 7 (12.1) | 12 (10.3) | 0.73 |
| OSA[b] | 9 (15.5) | 21 (18.1) | 0.67 |
| COPD | 5 (8.6) | 15 (12.9) | 0.40 |
| Asthma | 3 (5.1) | 11 (9.5) | 0.32 |
| CKD | 7 (12.1) | 3 (2.6) | 0.01 |
| AA with laryngoplasty | 25 (43.1) | 52 (44.8) | 0.83 |
| Revision laryngoplasty | 1 (1.7) | 3 (2.6) | 0.72 |

Abbreviations: DRP, dexmedetomidine-remifentanil-propofol, BMI, body mass index calculated as weight in kilograms divided by height in meters squared; HTN, hypertension; CAD, coronary artery disease; DM, diabetes mellitus; CNS disease, central nervous system disease; OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; AA, arytenoid adduction.

[a] Continuous data are presented as mean ± standard deviation; categorical data as number of patients (percentage of sample).

[b] Diagnosis from a documented history or a positive screen for OSA.

Cary, NC, 1989–2017).

## 3. Results

During the study time frame, 58 cases of patients who underwent ML ± AA utilizing DRP were identified. These patients were matched with 116 control patients who underwent ML with traditional anesthetic management. Patient characteristics are presented in Table 1. Table 2 compares the administration of different anesthetic agents between cases and controls. There was a reduction in the use of other sedating medications with DRP.

**Table 2**
Protocol medications administered.[a]

| Characteristic | Cases (N = 58) | Controls (N = 116) | p value |
|---|---|---|---|
| Preoperative medication | | | |
| Acetaminophen | 18 (31) | 3 (2.9) | < 0.01 |
| Intraoperative infusions | | | |
| Dexmedetomidine | | | |
| Administered | 58 (100) | 113 (97.4) | – |
| Mean dose (mcg/kg/h) | 0.46 (0.19) | 0.45 (0.22) | 0.7 |
| Total dose mcg | 109.3 (59.3) | 129.8 (79.4) | 0.08 |
| Propofol[b] | | | |
| Administered | 57 (98.3) | 85 (73.3) | – |
| Mean dose (mcg/kg/min) | 13.9 (9.5) | 23.1 (17.8) | < 0.01 |
| Total dose mg | 183.7 (119) | 430 (424) | < 0.01 |
| Remifentanil | | | |
| Administered | 58 (100) | 11 (9.5) | – |
| Mean dose (mcg/kg/min) | 0.047 ± 0.02 | 0.031 ± 0.03 | 0.02 |
| Total dose mcg | 668.6 ± 373 | 396.2 ± 333.4 | 0.03 |
| Antiemetic prophylaxis | | | |
| Dexamethasone | 57 (98.3) | 104 (89.7) | 0.06 |
| SHT3 antagonist[c] | 55 (94.8) | 86 (74.1) | < 0.01 |
| Droperidol | 16 (27.6) | 18 (15.5) | 0.07 |

[a] Continuous data are presented as mean ± standard deviation; categorical data as number of patients (percentage of sample).

[b] All patients in the protocol group and zero patients in the control group received concurrent infusions of dexmedetomidine, propofol, and remifentanil.

[c] All patients in the protocol group and 65 patients in the control group received ondansetron 4 mg while 21 patients in the control group received granisetron 0.1 mg (total n = 86).

**Table 3**
Intraoperative and postoperative outcomes among patients managed with DRP protocol and matched controls.[a]

| Outcome | Cases (N = 58) | Controls (N = 116) | p value |
|---|---|---|---|
| Anesthesia duration (min) | 182 (35) | 219 (50) | < 0.01 |
| Surgical duration (min) | 131 (33) | 160 (50) | < 0.01 |
| Hypopnea events[b] | 14 (24.1) | 7 (6) | < 0.01 |
| Bradycardia requiring treatment[c] | 0 | 4 (3.5) | 0.3 |
| Fentanyl | 38 (65.6) | 87 (75) | 0.21 |
| Dose (mcg) | 50 [25, 100] | 100 [50, 150] | < 0.01 |
| Midazolam | 4 (6.9) | 70 (60.3) | < 0.01 |
| Dose (mg) | 1 [1, 1] | 2 [2, 2] | < 0.02 |
| Post procedure | | | |
| Bypass PACU phase 1 recovery | 19 (32.8) | 28 (24.1) | 0.28 |
| PACU duration (min) | 75 ± 26.7 | 78 ± 27.3 | 0.49 |
| Hospital admission | 1 (1.7) | 4 (3.5) | 0.66 |

Abbreviations: DRP; dexmedetomidine-remifentanil-propofol, PACU; post-anesthesia care unit.

[a] Categorical data are summarized as number of patients (percentage of sample) and compared with the Fisher exact test; continuous data are summarized as mean ± standard deviation or median [25th, 75th] and compared with the rank sum test.

[b] Decrease in respiratory rate associated with pulse oximeter reading < 90%.

[c] Heart rate < 50 requiring pharmacologic intervention. 4 patients in the control group experienced bradycardia requiring treatment with glycopyrrolate. 18 patients (11 in protocol group) had a transient documented heart rate < 50 not requiring pharmacologic intervention.

DRP was associated with a decrease in anesthetic and surgical time compared to traditional techniques (Table 3). However, when adjusted for time, it was observed that case duration was declining prior to DRP introduction. Nevertheless, this pattern of reduced anesthesia and surgical durations continued after DRP introduction (Fig. 1a and b).

DRP was associated with increased hypopnea events during procedures; however these events did not require any specific intervention other than supportive care. There were no other adverse events with DRP technique (Table 3). In each group, one patient required subsequent surgery for post-surgical bleeding after hospital discharge.

## 4. Discussion

The main finding in this study is that a novel DRP anesthetic for sedation with ML procedures was associated with a meaningful reduction in anesthetic and surgical durations. In addition, the DRP anesthetic allowed less additional sedating medications (fentanyl and midazolam) to be administered in the perioperative period. Subjectively, it was the perception of the surgical team that DRP sedation provided superior titratability and assessment of phonation with improved surgeon and patient satisfaction. However, these observations must be tempered by the fact that the surgical team was not blinded to the anesthetic technique.

ML ± AA is a procedure with unique anesthetic requirements requiring patients to phonate during the procedure. Multiple anesthetic techniques to achieve this goal have been described: 1) GA, 2) sequential anesthetic with GA followed by sedation, or 3) monitored anesthesia care (MAC) [1,3–5]. Previous studies have shown overall similar results for operative times between GA and sedation care [4]. Liu et al. demonstrated faster emergence times and lower chances of prolonged emergence with total intravenous anesthesia (TIVA) technique using propofol compared to inhalational GA with desflurane [11]. However, the factors playing into overall operating room efficiency are much more complex; the choice of anesthetic technique is

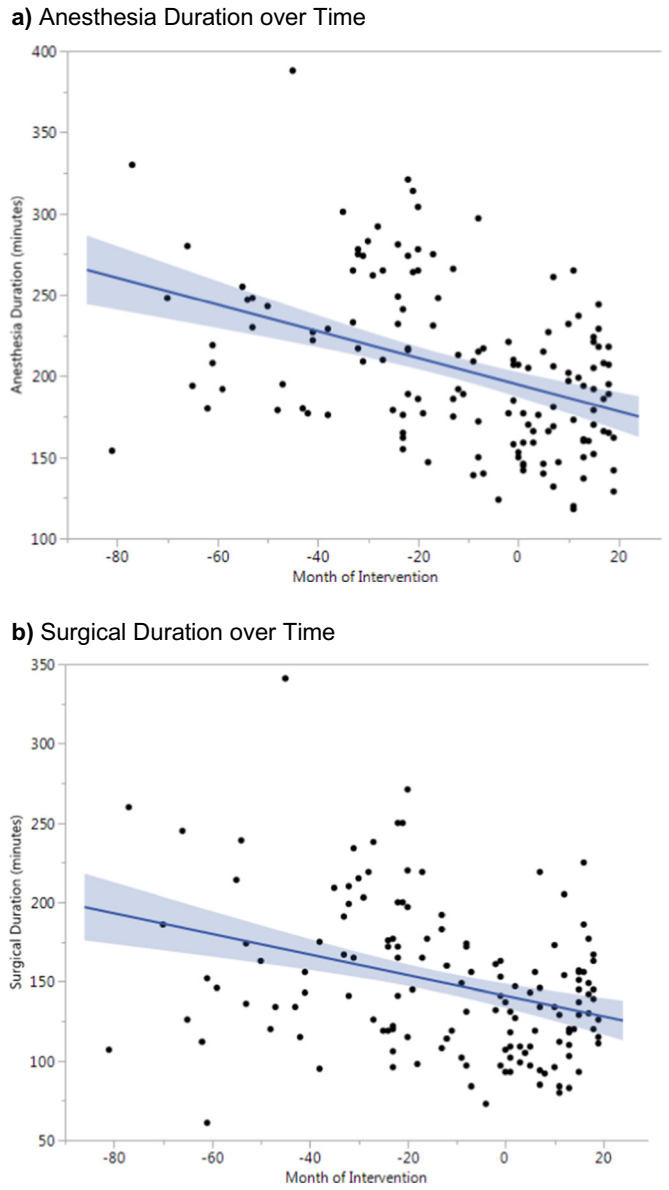


**Fig. 1.** a: Anesthesia duration over time.
b: Surgical duration over time.
Panels a and b: Time 0 indicates the month the DRP protocol was introduced. Line of fit shows linear regression with confidence intervals represented in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

one component of a large variety of factors that contribute to overall operative efficiency [12–14].

The DRP combination used in this study has not been previously described in a case controlled fashion. Although surgical and anesthetic times were reduced in the DRP group, these were found to be continuing a trend of decreasing times prior to the introduction of the protocol. It is possible the DRP protocol directly facilitated ongoing reduction in surgical and anesthetic duration. Alternatively, as a single surgeon was involved in this study, this finding may indicate that the efficiency of surgical technique was being improved before the protocol was introduced with ongoing continued improvement post implementation.

Per the DRP protocol instructions, midazolam and fentanyl were not prohibited, but were generally not needed. Thus, their use was substantially reduced with DRP. There are several theoretical reasons why DRP can reduce the need for these drugs. There are intermittent periods during ML that are transiently extremely stimulating. During these periods, the ultra-fast metabolized remifentanil can provide analgesia, whereas the use of fentanyl would extend the opioid effect unnecessarily into non-painful portions of the procedure. DRP also offers rapidly titratable analgesic and anxiolytic effects, supplanting the need for midazolam and allowing patients to participate in phonation. A reduction of midazolam and fentanyl may offer other benefits as both these medications have been found to increase anesthesia recovery duration and postoperative complication rate [15–17]. Further, anesthetic approaches that minimize exposure to benzodiazepines along with antiemetic therapy administered by protocol have been demonstrated to reduce episodes of respiratory depression and overall recovery time [18].

Another important finding from this study is that there was an increase in the number of hypopnea episodes during surgery using the DRP technique. We speculate the addition of remifentanil infusion contributed to this observation, as this medication is known to have a greater respiratory depressive effect than dexmedetomidine [19,20]. Generally, the doses of dexmedetomidine and propofol were greater in control patients than the DRP group, further implicating remifentanil. However, all observed episodes of hypopnea were self-limited and of unclear clinical significance. However, anesthesia and surgical personnel should be prepared to manage hypopnea or apnea if remifentanil is introduced to their practice. The postoperative course between patients in both groups was similar.

This report has all the inherent limitations of a retrospective study design. The timeframe of this study spans nine years (August 2008–June 2017), and the DRP technique was introduced in June 2015. Thus, the observed reduction in anesthetic and surgical time may reflect unaccounted improvements in surgical technique during this time frame. A potential source of bias is that the surgical team was not blinded to the anesthetic technique. Further, this population represents a practice that is highly specialized with ML procedures which could limit generalizability. A future area of study could include comparison of anesthetic techniques between ML with AA and standard ML procedures. While the size of this cohort is sufficient to identify an association between the DRP technique and reduced anesthetic and surgical time as well as use of supplemental sedation agents, it is insufficient to establish safety.

## 5. Conclusions

The novel monitored anesthetic care technique using a combination of dexmedetomidine, remifentanil, and propofol for outpatient ML ± AA was associated with decreased surgical and anesthetic durations and a statistically significant reduction of supplemental midazolam and fentanyl use. However, increased rates of hypopnea associated with DRP need to be recognized and the perioperative team must be prepared to manage this complication if using this technique.

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