INTRODUCTION

Unilateral vocal fold paralysis (UVFP) is traditionally managed with observation or delayed intervention. Roughly 50% of iatrogenic (most common) or idiopathic UVFP will recover enough vocal function to preclude further treatment, but the other half will have absent function or suboptimal laryngeal function due to either incomplete recovery or synkinesis that necessitates further intervention. 1

Use of a neurotoxic agent (vincristine or paclitaxel) has been shown to inhibit neural regeneration in a rat post-traumatic nerve injury model.2,3,4 A single vincristine injection to the posterior cricoarytenoid (PCA) muscle has been shown in a canine laryngeal model to improve the strength of laryngeal adduction via blockade of aberrant recurrent laryngeal nerve (RLN) fiber growth into the PCA. 5 This subsequently prevented any antagonism of the properly reinnervated adductor muscles, which would otherwise have resulted in synkinesis. Both vincristine and paclitaxel are well-established chemotherapeutic agents known to be potent microtubule inhibitors that interfere with cellular division which leads to mitotic arrest in metaphase. The effect of paclitaxel has yet to be studied in a laryngeal model.

This study investigates the neural regeneration inhibitory effects of paclitaxel in a canine post-traumatic RLN injury model. We hypothesized that paclitaxel would result in improved strength of laryngeal adduction and that it would be non-inferior to the effect observed with vincristine.

MATERIALS & METHODS

Forty-nine hemilaryngeal preparations were divided into 5 experimental groups (Table 1).

Protocol was approved by the Washington University School of Medicine’s Institutional Animal Care and Use Committee (IACUC).

PROCEDURE

1. General Anesthesia was induced and the neck was prepped with betadine solution.
2. Tracheostomy was performed & RLN identified. 6
3. The strength of adduction was measured via laryngeal adductory pressures (LAP) 7
4. RLN was transected ~4cm inferior to the cricothyroid joint. End-to-end reanastomosis was performed using 9-0 nylon sutures & microscope.
5. The stoma was matured and the neck wound closed with 3-0 prolene sutures.
6. Intramuscular (IM) injection of saline or neurotoxic agent into PCA via transoral approach or under direct visualization at 0 or 3 months.

At 6 months (terminal), under general anesthesia the RLN was identified, LAPS measured, and the larynges were harvested for further analysis.

DATA ANALYSIS

LAPs at the 4 adductor plateau values (70, 80, 90, and 100 Hz) were averaged for each animal. 

Final mean LAP value is expressed as a fraction of the pre-injury value.

Two-tailed student t test was used to make comparisons between the experimental groups.

EXPERIMENTAL GROUPS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>DETAILS</th>
<th>NUMBER</th>
<th>RLN INJURY</th>
<th>NT AGENT</th>
<th>TIME OF INJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Saline (Control)</td>
<td>16</td>
<td>+</td>
<td>None</td>
<td>0 months</td>
</tr>
<tr>
<td>B</td>
<td>Immediate Vincristine</td>
<td>12</td>
<td>+</td>
<td>0.4mg Vincristine</td>
<td>0 months</td>
</tr>
<tr>
<td>C</td>
<td>Paclitaxel</td>
<td>8</td>
<td>+</td>
<td>3 mg Paclitaxel</td>
<td>0 months</td>
</tr>
<tr>
<td>D</td>
<td>Delayed Vincristine</td>
<td>5</td>
<td>+</td>
<td>0.4mg Vincristine</td>
<td>3 months</td>
</tr>
<tr>
<td>E</td>
<td>Paclitaxel</td>
<td>8</td>
<td>+</td>
<td>Vincristine</td>
<td>3 months</td>
</tr>
</tbody>
</table>

RESULTS

IMMEDIATE INJECTION OF NT AGENTS

IMMEDIATE VS. DELAYED NT INJECTION

TIME OF INJECTION (MONTHS)

FIGURE 1. Mean 6 month LAP After NT Injection at Time 0. Paclitaxel and vincristine (Groups B & C) demonstrated significantly increased recovery in mean LAPs compared with saline (Group A), p<0.003. There was no difference in effect between paclitaxel and vincristine. (SD: saline, paclitaxel and vincristine were 0.125, 0.199 and 0.103, respectively.)

FIGURE 2. Effect of NT Injection at 0 vs. 3 months. There was no significant difference in effect between paclitaxel or vincristine when either agent was given immediately after neural injury and repair vs. after a 3-month delay. One animal received a transoral injection of paclitaxel without any adverse effects/mortality and no difference in efficacy. (SD for paclitaxel and vincristine at 3 months were 0.139 and 0.191, respectively.)

DISCUSSION

This study confirmed our hypothesis that a single IM injection of paclitaxel into the PCA at the time of RLN injury, or up to 3 months after, effectively inhibited neural regeneration and resulted in increased adductor strength. Our data shows that paclitaxel is just as effective as vincristine in inhibiting PCA neural reinnervation in a post-traumatic nerve injury canine laryngeal model. Delayed injections >3 months were not attempted as prior studies showed diminished efficacy after 3 months.5 Since these neurotoxins target cellular division, they have no effect on a completely regenerated nerve. Thus, there is a 3-month “window-of-opportunity” within which this targeted intervention must be given.

Vincristine is oft ill-famed for its low therapeutic index and several clinical case reports note toxicity within its narrow therapeutic range. Paclitaxel has a known relatively higher therapeutic index and is a viable alternative agent to vincristine. Dose limiting toxic side effects with paclitaxel, such as neuropathy and neutropenia, are typically observed at a level 50 fold higher than the dose used in this study.

This increase in mean LAP is attributed to the neurotoxin’s ability to block aberrant nerve reinnervation of the PCA, thereby preventing the antagonism of adduction as is seen with synkinesis. Further human testing with paclitaxel and vincristine is needed to determine the degree of clinical utility and benefit.

CONCLUSIONS

1. A single paclitaxel injection into the PCA muscle just after RLN transection and reanastomosis yielded improved adductor strength at 6 months post-injury in a canine laryngeal model.
2. The degree of improved adductor strength was similar between the paclitaxel and vincristine groups after a single injection at 0 or 3 months.
3. There was no significant difference in adductor strength recovery when either neurotoxin was injected into the PCA muscle immediately post-injury (0 months) or later on at 3 months.
4. No adverse drug reactions or mortalities were observed with the use of a single, localized, intramuscular injection of paclitaxel.
5. Paclitaxel is a viable alternative to vincristine.
6. 52% of the injected paclitaxel entered the systemic circulation and was cleared within 48 hours.

REFERENCES