Transient Otoacoustic Emissions in Children with Retinoblastoma Submitted to Chemotherapy with Carboplatin

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SUMMARY

Objective: To verify the occurrence of transient otoacoustic emissions in carrying patients of retinoblastoma, submitted the chemotherapy treatment with carboplatin.

Method: From 18 evaluated subjects with ages between nine months and nine years, being 10 of feminine sex and 8 of the masculine sex. The evaluation by means of the transient otoacoustic emissions was initiated the chemotherapy treatment after.

Results: Verified 100% of the occurrence of the transient otoacoustic emissions and significant statistical difference (p=0.001) for the average levels of reply it enters the bands of frequencies. With regard to changeable side of the ear and sex significant statistical difference was not verified.

Conclusion: The occurrence of 100% of the transient otoacoustic emissions showed that the carboplatin did not caused alterations of the hair cells of the cochlea and that them could be carried through in 100% of the studied population, showing to be a fast, objective and easy instrument of being tested in this type of population.

Key words: hearing loss, carboplatin, retinoblastoma.
INTRODUCTION

Retinoblastoma (RB) is an intraocular tumor affecting especially children (15,000 in 20,000 when born alive) in their first years of life in general. It is of genetic origin affecting the chromosome 13, more specifically the locus 13q14 when in deletion or mutation processes (1).

The effectiveness of chemotherapy for intraocular tumors has always been questionable due to the difficulty for the drugs to pass through ocular limits. Lately, new chemotherapy substances have been tested in order to evaluate their effectiveness on such tumors and the carboplatin has been effectively presenting on the control of the tumor growth (2). Some side effects such as: nephrotoxicity, diarrhea, nausea, vomiting, loss of the hair and ototoxicity (1, 2) can be noticed during or after chemotherapy substance administration.

Ototoxic drug usage results in hearing loss, rising toxic reactions of the inner ear by affecting hearing and/or vestibular systems. Aminoglycosides, antineoplastic and loop diuretic agents and others are drugs considered ototoxic type (3, 4). Managing drug determines its ototoxic effect, as the use of high quantity only once can damage hearing ability more than if taken in several doses. Besides, hearing ability may vary from patient to patient (5, 6)

Spoken language acquisition and development processes are the most important aspects on children’s progress, thus it is through language everyone is able to express their feelings, needs and wishes. The hearing sensorial system is directly connected to language development, so the use of diagnostic resources, which brings information on the hearing status of children with RB submitted to chemotherapy the early as possible, has been a routine search by the researchers and professionals, in order to reduce the psychosocial impacts of hearing loss.

The literature has been highlighting two procedures, which has been used in order to early diagnose hearing loss process by ototoxic drugs. They are: audiometry in high frequencies and evoked otoacoustic emissions (EOAEs) (7). Therefore it is important to point that the audiological evaluation in children should follow proper procedures according to age.

It is believed that patients who make use of cisplatin and carboplatin substances undergo lesions in the cochlea, initially on the base in frequencies between 6000 and 8000 Hz (8, 9). The impact of hearing loss depends on its degree as well as affected frequencies. Hearing reduction in 6000 and 8000 Hz has low impact on hearing process. Therefore, if such reduction is affected by frequencies above 3000 Hz, there is a higher possibility of damaged speech understanding. If it is lower than 3000 Hz, then, speech understanding is certainly damaged, for being an important area on understanding process (10).

Before all this, the current study aims to verify occurrences of transient evoked otoacoustic emissions (TEOAEs) in patients with RB submitted to chemotherapy with carboplatin substance.

METHOD

This study was previously approved by the Research Ethics Committee of the INIFESP-EPM, # 0524/04.

Subjects were sent to IOP – GRAAC of UNIFESP-EPM in the audiological clinic department of hearing disorders. The following criteria should be strictly followed by patients for the sample composition:

- Subjects assisted with RB assisted at IOP.
- Subjects with bilateral typanometric curve type A.
- Subjects with no family history of hearing loss.
- Subjects submitted to carboplatin-use chemotherapy.

10 female and 8 male patients aging between nine months and nine years were evaluated after chemotherapy process. The procedure for those patients was from four to six cycles of carboplatin substance (560mg/ m²/ cycle) with breaks of 21 days.

First proposal suggested by professionals was an audiological evaluation consisted of audiometry and OAE records. Therefore, applying all procedures was not to be meant viable, due to the fact that patients used to come for therapy after the fundoscopic examination, which is performed under sedative use. So, it was performed an exam that did not depend on subject’s response and was done in shorter term.

TEOAEs Records

TOAEs records were performed in acoustically designed booth by using ILO 92 – Otodynamics, which was connected to an ACER MATE 486 computer. Patients were laid on parent’s lap and then had a probe introduced in their external acoustic canal of each ear. It was presented a nonlinear stimulus click with a range of analysis of 12ms, by using “QuickScreen” program in order to record TOAEs. A load of 260 stimuli was presented in each test, and responses were analyzed in frequencies of 1000, 1500, 2000, 3000 and 4000 Hz.

The exam result considered suitable was: intensity
of stimulus ranged between 75 and 80 pe NPS; stimulus stability $\geq 70\%$; presence of response when general reproducibility and frequency was $\geq 50\%$ and when sign/noise relation in frequency was $e \geq 5$ dB NPS on frequencies of 2000, 3000 and 4000 at least.

**Statistical Analysis**

In the current study, the analysis of variance (ANOVA) was considered the most suitable test according to the variables of this study. The level of significance was 0.05 (5%).

**RESULTS**

Charts and tables from measurements and ANOVA will be presented next.

**DISCUSSION**

Data analysis showed 100% of TOAE occurrences on boys and girls. Researches on carboplatin substance did not show expressive hearing loss after its use (11, 12, 13, 14, 15). These findings agree with the ones from the current study as all subjects presented with TOAE under the evaluated frequencies. Hearing loss was not expected to occur on current patients because they did not make use of cisplatin substance.

Several researches on ototoxicity of chemotherapeutic substances were performed with cisplatin, though carboplatin was introduced on those researches in the 80s. They observed more use of cisplatin substance due to its toxicity (16, 17, 18, 19, 20, 21, 22, 23, 24).

Hearing loss on frequencies of 4000, 6000 and 8000 Hz was present on patients who made use of carboplatin (25, 26). Therefore, involvement of the external ciliated cells with TOAE, which helped the response record up to the frequency of 4000 Hz, was not observed. This finding is related to the procedure used in this study, which is limited, as frequencies of 6000 and 8000 HZ could not be

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**Table 1. Measures – summary and results of inferential analysis of the response levels for bands of frequencies. kHz**

<table>
<thead>
<tr>
<th>Bands of Frequency</th>
<th>1 kHz</th>
<th>1.5 kHz</th>
<th>2 kHz</th>
<th>3 kHz</th>
<th>4 kHz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium</strong></td>
<td>5.92</td>
<td>9.00</td>
<td>14.00</td>
<td>15.94</td>
<td>14.06</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>4</td>
<td>9</td>
<td>15</td>
<td>17.5</td>
<td>13.5</td>
</tr>
<tr>
<td><strong>Standard Deviation</strong></td>
<td>6.32</td>
<td>7.55</td>
<td>6.32</td>
<td>5.76</td>
<td>7.23</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>-2</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Maximum</strong></td>
<td>26</td>
<td>28</td>
<td>31</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>25</td>
<td>33</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td><strong>Inferior Limit</strong></td>
<td>3.44</td>
<td>6.42</td>
<td>11.94</td>
<td>14.06</td>
<td>11.69</td>
</tr>
<tr>
<td><strong>Superior Limit</strong></td>
<td>8.40</td>
<td>11.58</td>
<td>16.06</td>
<td>17.83</td>
<td>16.42</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>$&lt;0.001^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Measures – summary and results of inferential analysis of the response levels for bands of frequencies according to the side of ear. kHz**

<table>
<thead>
<tr>
<th>Bands of Frequency</th>
<th>OD Medium</th>
<th>OD Median</th>
<th>OD Standard Deviation</th>
<th>OD Minimum</th>
<th>OD Maximum</th>
<th>OD Inferior Limit</th>
<th>OD Superior Limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kHz</td>
<td>6.75</td>
<td>4</td>
<td>7.14</td>
<td>0</td>
<td>26</td>
<td>2.71</td>
<td>10.79</td>
<td>0.540</td>
</tr>
<tr>
<td>1.5 kHz</td>
<td>5.15</td>
<td>3</td>
<td>5.65</td>
<td>-2</td>
<td>16</td>
<td>2.08</td>
<td>8.23</td>
<td>0.498</td>
</tr>
<tr>
<td>2 kHz</td>
<td>9.88</td>
<td>9</td>
<td>7.95</td>
<td>0</td>
<td>28</td>
<td>6.10</td>
<td>13.66</td>
<td>1.000</td>
</tr>
<tr>
<td>3 kHz</td>
<td>8.06</td>
<td>9</td>
<td>7.23</td>
<td>0</td>
<td>23</td>
<td>4.52</td>
<td>11.61</td>
<td>0.821</td>
</tr>
<tr>
<td>4 kHz</td>
<td>14.00</td>
<td>14.5</td>
<td>6.36</td>
<td>3</td>
<td>26</td>
<td>11.01</td>
<td>16.94</td>
<td>0.752</td>
</tr>
</tbody>
</table>

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**Graphics 1.** Distribution of level averages of TOAE Responses for band of frequencies. TEOAE - Transient Evoked Otoacoustic Emissions
evaluated. Distortion product otoacoustic emissions and audiometry in high frequencies could identify alteration in higher frequencies.

Comparative studies between cisplatin and caboplatin ototoxicity showed hearing loss on frequencies of 4000, 6000 and 8000 Hz in patients who used cisplatin substance as an antineoplastic agent (27, 28).

The literature points that cisplatin has greater ototoxic effect than carboplatin. So, the latter do not seem to affect cochlea structures, being considered a less toxic neoplasic agent.

The current study could show that frequencies between 1000 and 4000 Hz were not affected with the use of carboplatin. Longitudinal studies show that individuals presenting hearing loss with frequencies below 3000 Hz are expressively harmed regarding conversations. Children treated with RB by having six cycles of carboplatin (doses of 560mg/m2) with breaks of 21 days, did not have their social hearing affected (21).

**Conclusion**

TOAE occurring in 100% of the cases showed that carboplatin did not cause alteration on external ciliated cells of the cochlea, in the studied frequencies and also TOAE can be used as a tool of evaluation on this population as it is a quick, objective and easy-to-be-tested procedure.

**References**


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