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BORIC ACID AURAL APPLICATION VERSUS ANTIBIOTIC-STEROID OTIC DROP IN THE MEDICAL MANAGEMENT OF DIFFUSE OTITIS EXTERNA*

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ABSTRACT

OBJECTIVE: This study aims to compare the effectiveness of boric acid powder versus an antibiotic steroid otic drop in the treatment of acute diffuse otitis externa, with regard to the mean time-to-end of otalgia and the 3-day cure rate based on otalgia and canal edema.
DESIGN: Randomized single blind controlled trial
SETTING: Outpatient clinic of an otolaryngologic department in a tertiary hospital
SUBJECTS: All patients aged 18 and above diagnosed clinically to have diffuse otitis externa, characterized by the presence of otalgia, canal edema, redness/erythema and discomfort on moving the ear. Exceptions include patients with circumscribed otitis externa and patients with frank/gross otomycosis.
RESULTS: Forty-three of the 47 patients who were initially included in the study qualified to finish it. Group A (antibiotic-steroid arm) had 19 patients, while group B (the boric acid arm) had 23 patients. The mean time-to-end from the start of therapy was 2.42 $\pm$ 1.35 for group A and 1.58 $\pm$ 1.25 in group B. Group B had a significantly shorter mean time-to-end from intiation of therapy as compared to group A, $(t_{0.05} < 2.11)$. The mean time-to-end of otalgia from the onset of symptom in group A was 6.47 $\pm$ 1.93. In group B, it was 5.13 $\pm$ 2.27, which proved to be significantly shorter, $(t_{0.05} < 2.07)$. There was no statistically significant difference on the 3-day cure rate between groups A and B $(z_{0.05} = 0.9)$. The 6-day cure rate for both treatment arms likewise did not show any statistical difference $(z_{0.05} = 0.54)$. Mild stinging was the only adverse effect noted by 1 patient for each treatment arm, but the intensity was not strong enough to cause discontinuation of the treatment.
CONCLUSION The effectiveness of boric acid powder, in terms of 3- and 6-day cure rates is comparable to the standard therapy for acute otitis externa, which is an antibiotic-steroid otic solution. However, a shorter treatment duration was attained with the boric acid powder which could alter the current trend in the management of otitis externa in terms of patient convenience and compliance as well as cost-effectiveness.

INTRODUCTION

A. Review of literature and significance of the study

Otitis externa encompasses all infectious and inflammatory disorders involving the skin of the external ear. It is one of the most common condition seen in an otolaryngologic practice affecting 3-10% of the patient population[1],

Acute diffuse otitis externa, often referred to as swimmer's ear, is the most frequently encountered disease process.[2] It is characterized by otalgia, edema, erythema and discomfort in moving the ear. Otalgia is cited by a majority of the adult and pediatric population as the primary reason for consultation.[3]

The usual treatment consists of debridement of the external auditory canal and administration of topical medications. A recent review article on the treatment patterns for otitis exerna in the United States revealed that the antibiotic-steroid combination is the most popular treatment medication prescribed, followed by an acetic acid solution and ophthalmic prednisolone.[3] The risk of ototoxicity, sensitization and development of resistance have become

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controversial issues related with the use of these topical antibiotics. Furthermore, compliance with the otic drops becomes less with increased number of required daily administration.[3,4] Thus, the need to search for an alternative drug which requires less patient participation and carries less risks yet is as effective as the currently available topical antibiotics surfaced.

Boric acid has been used as an adjunct to the treatment of otitis externa in the past. Slack (1987) compared this acidifying agent to the traditional antibiotic-steroid drops and an antifungal-antibiotic-steroid combination. His study showed that the antibiotic-based drops had no real advantage over boric acid in spirit, based on the bacteriologic cultures done. No inferences were made as to the length of time it took for the different otic preparations to produce cure.[5]

This study is designed to compare the effectiveness of a one time application of boric acid powder versus a thrice daily antibiotic-steroid otic drop regimen in the treatment of otitis externa with regard to 3-day cure rates and mean time to symptom resolution, among others.

The combination of polymyxin-neomycin-fluocinolone (Aplosyn™, Pharex) is chosen as the drug for comparison due to the following reasons:

1. it covers a broad range of gram-positive and gram-negative organism
2. it is locally available and relatively low priced .

OBJECTIVES

1. General

• To compare the effectiveness of boric acid powder versus an antibiotic steroid drop in the treatment of acute diffuse otitis externa.

2. Specific Primary effectiveness variable

• To compare the mean time-to-end of otalgia for each treatment arm from the time of initiation of therapy

Secondary effectiveness variables

• To determine the 3-day cure rate for each treatment arm with regard to the resolution of otalgia and canal edema

• To compare the mean time-to-end of otalgia for each treatment arm from the time of onset of symptom

• To determine the 6-day cure rate for both treatment arm with regards to otalgia

• To determine the mean number of patients who developed adverse reaction to the test drug on both groups

METHODS

A. Design: Randomized, single-blind, controlled trial

B. Setting: out-patient clinic of an otorhinolaryngologic department in a tertiary hospital

C. Subjects: All patients aged 18 and above diagnosed clinically to have diffuse otitis externa, characterized by the presence of otalgia, canal edema, redness/erythema and discomfort on moving the ear.

Exclusion criteria.

1. patients who had previous systemic/topical antibiotic treatment
2. patients with circumscribed otitis externa
3. patients with malignant otitis externa
4. patients with frank/gross otomycosis
5. patients with laceration/abrasion/avulsion on the skin of the external auditory canal
6. patients with history of chronic suppurative otitis media or ear perfoartion
7. history of hypersensitivity to any of the trial drug
8. pregnant or lactating patients.

D. Sample size

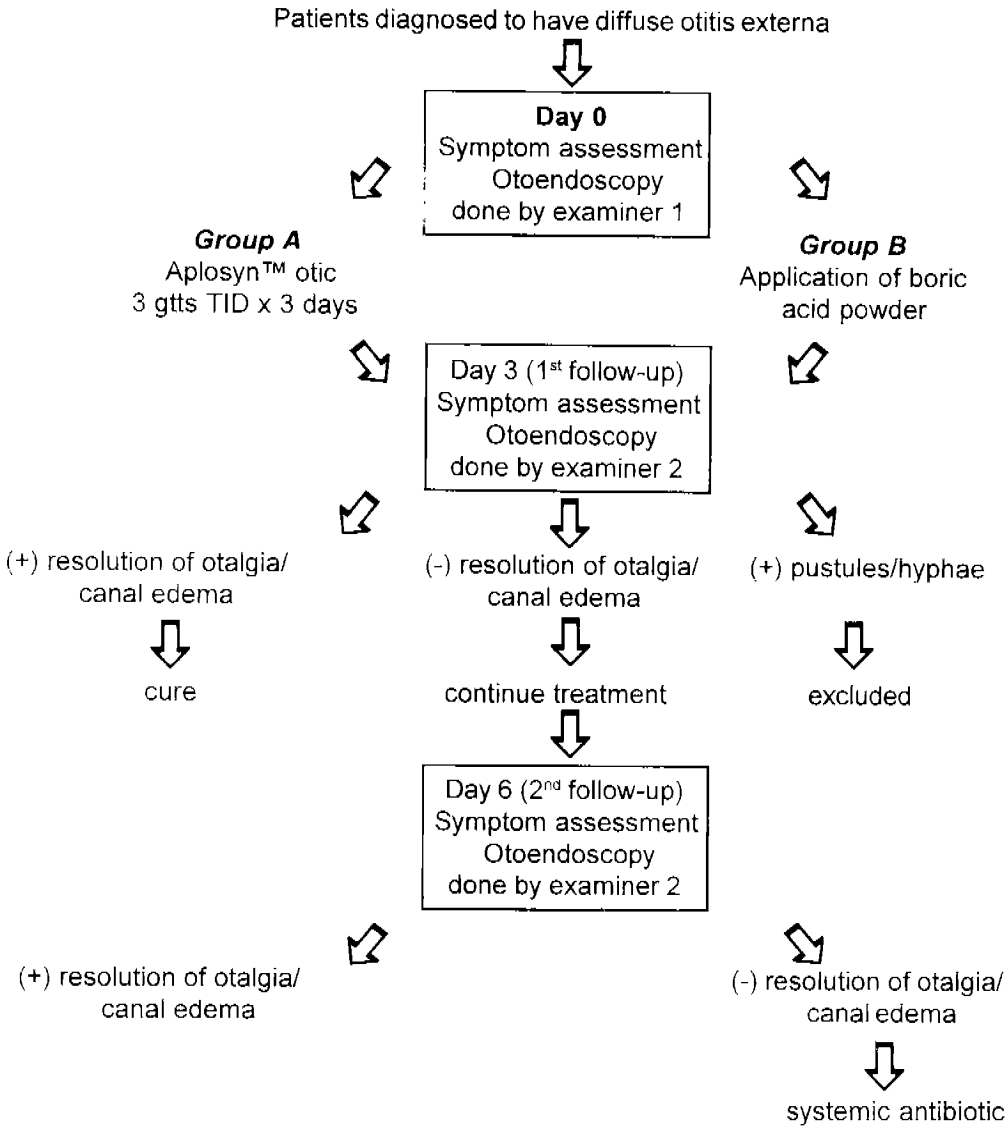
Using an á= .05 and â= .80 and ã= .80 two-tailed, the sample size estimate to detect a difference between two means can be computed using the following equation:

$$N = 2 \times (ä/ ã)^2$$

$$N = 2 (2.8 / 0.8)^2$$

N = 25 subjects per group

E. Experimental maneuver



All eligible patients signed a consent (Appendix A) to participate after explanation of the objectives and methods of the study. The first examiner interviewed the patients and filled up a questionnaire (Appendix B). The presence or absence of symptoms (otalgia, pruritus, discharge, hearing loss) were noted by the examiner. Pain was graded by both the patient and examiner to serve as a gauge for improvement or cure. Grading was based on the following guidelines:

Pain / otalgia as perceived by the patient was classified as

- *mild* minimal discomfort to the patient, does not affect activities of daily living;
- *moderate* discomfort that causes temporary interruption of activities of daily living
- *severe* discomfort that disrupts activities of daily living, such as chewing, prompts urgent consult.

Pain / tragal tenderness as assessed by the examiner was classified as

- *mild* patient verbalizes pain with deep pressure;
- *moderate* patient verbalizes pain/ grimaces, but does not withdraw, with slight pressure;
- *severe* patient withdraws to slight pressure on the tragus.

Otoendoscopy of the affected ear was done using a 2.7 mm 0° endoscope to note for the presence of canal edema, canal erythema, and discharge. Assessment of the external auditory canal was based on the description of Senturia.[6] (Figure 1,2)

- *mild* evidenced by edematous and erythematous canal skin, odorless secretions with or without desquamated debris in the lumen;

- *moderate* lumen diameter decreases and becomes partially occluded with seropurulent material;

- *severe* lumen completely obstructed, drains grey-green secretion with desquamated debris, sagging of the superior canal.

Patients were randomly assigned to one of the two treatment. (Figure 3) Suctioning of the ear discharge, if present, was done prior to application of the assigned treatment. Those who were classified under treatment A (Aplosyn™ otic), were instructed to instill 3 drops into the affected ear 3 times a day for the next 3 days. Using a cerumen spoon, boric acid powder was placed in the affected ear of the patients who were classified under treatment B. An ear speculum was used as a guide to ensure adequate and equal distribution of the powder within the external ear.(Figure 4,5) Both groups were instructed to come back after 3 days.

On follow-up (day 3), a different examiner did the assessment using the same questionnaire and the otoendoscopy. Those who had resolution of otalgia and canal edema were considered cured of the disease. Those who were noted to have pustules or hyphal elements with the decrease in canal edema were given the appropriate systemic or topical medication and were excluded from the study. The patients who still manifested the same signs/symptoms were given the same medication corresponding to their grouping. These patients were advised to come back after another three days (day 6) for re-assessment by the same examiner.

Persistence of the disease beyond 6 days *(failure)* was managed with systemic antibiotics. Factors that could contribute to the worsening of the disease were determined.

Those who were eventually discovered to have pustules or hyphal elements on follow-up were given the appropriate systemic or topical medication and were excluded from the study.

All patients were followed up until the day of improvement. The failure was included in the computation for mean time-to-end of otalgia for the corresponding group.

The patients were asked for the development of any adverse effects such as stinging, itchiness and increase in erythema/edema.

F. Data treatment and analysis

Primary outcome measure - Otalgia, being the most common complaint of patients with otitis externa and is meaningful to both physician and patient, was used to assess clinical success. The number of days it took for the otalgia to resolve from the time of initiation of therapy was determined and tabulated for each treatment arm. The mean time-to-end of otalgia was calculated and compared.

Secondary outcome measures

1. In addition to otalgia, disappearance of canal edema was used to denote cure. The mean number of patients who were cured on the first follow-up (day 3) was determined for each treatment arm.

2. The mean time-to-end of otalgia from the time of onset of symptom for each treatment arm was also determined and compared using the same statistical test.

3. The mean number of patients who achieved cure on day 6 was also ascertained and compared.

4. Development of adverse drug reaction such as stinging, itchiness or progression of the condition was noted for both groups and the mean number of patients who manifested such was compared.

All results were compared using the *student's t-distribution test.*

RESULTS

Patient characteristics. A total of 47 patients were qualified for the study. Twenty patients were enrolled in group A (Aplosyn™ otic), with a male to female ration of 1:1. Group B (Boric acid powder) had 27 patients with a 1:1.7 male to female ratio. The mean age of the patients in group A was 31.7 ($\pm$ 13.0), while those in group B had a mean age of 33.4 ($\pm$ 13.1). The duration of illness for both groups was 1-7 days, with a mean of 3.6 ($\pm$ 1.8) for group A and 3.37 ($\pm$ 1.8) for group B. The primary reason for consult among the two groups is otalgia (n=40, 85%), followed by pruritus (n=6, 13%) and hearing loss. On physical examination, all patients had tragal tenderness and canal edema. Sixty-four percent had discharge and 34% had swelling of the pinna. *(Table 1)*

Time-to-end. The mean time-to-end from the start of therapy was 2.42 $\pm$ 1.35 for group A and 1.58 $\pm$ 1.25 in group B. Group B had a significantly shorter mean time-to-end from intiation of therapy as compared to group A, ($t_{0.05}$) < 2.11. The mean time-to-end of otalgia from the onset of symptom in group A was 6.47 $\pm$ 1.93. In group B, it was 5.13 $\pm$ 2.27, which proved to be significantly shorter with ($t_{0.05}$) < 2.07. *(Table 2)*

Mean cure rate. Out of the 20 patients enrolled for treatment in group A, only 19 were qualified to continue the study. Seventeen of the 19 (89%) patients manifested resolution of the otalgia and canal edema by day 3. One patient was excluded from the study due to the presence of pustules which became apparent after the canal edema subsided. In group B, a total of 24 patients finished the study. Two were excluded due to the presence of pustules, while another was excluded due to the presence of hyphal elements in the ear canal. Resolution of otalgia and canal edema was evident in 23 (96%) of the 24 patients by day 3. There was no statistically significant difference on the 3-day cure rate between groups A and B *($z_{0.05} = 0.9$)*

By day 6, the clinical success rate of group A approached 100%, with the 2 patients who still had evidence of disease at day 3 and were given extended therapy finally achieving cure (19/19). That of group B remained at 96% (23/24), The patient who required additional treatment still had evidence of the disease *(failure)*. Cure was achieved at day 12 after he was shifted to systemic antibiotics, thus, he was not included in the computation for the 6-day cure rate. The 6-day cure rate for both treatment arms likewise did not show any statistical difference *($z_{0.05} = 0.54$, p-value = 0.34). (Table 3)*

Adverse reactions. Mild stinging was the only adverse effect noted by one patient in each treatment arm (Group A = 5%, Group B = 4%), but the intensity was not strong enough to cause discontinuation of the treatment.

DISCUSSION

Acute otitis externa is a common infection of the outer ear canal. The most common clinical manifestation is pain or earache, followed by erythema, edema, itching, discharge, and hearing loss. Earache was cited as the most frequent reason for consult among the adult and pediatric population.[3] Our findings correlate well with this study, with otalgia (85%) as the primary complaint, followed by pruritus (13%), discharge (1%) and hearing loss (1%), for both treatment groups.

There are several factors mentioned by Senturia as the possible causative factors in the pathogenesis of acute otitis externa. The most frequently mentioned are high humidity and temperature levels, tissue maceration from exposure to moisture or water while swimming, contamination or trauma from scratching or careless otologic instrumentation, and allergy to chemicals such as hair dyes.[5] In our study, majority (53%) of the patients acquired the disease after ear manipulation secondary to pruritus. Others had the disease after meticulous cleaning of the ear canal (28%), while a minority was secondary to manipulation after bathing/swimming (19%). Contact with water is recognized almost universally as a major pathogenic component.[7]

Treatment of acute otitis externa involves a strategy intended to resolve the infection while promoting the restoration of the external auditory canal to its original state.

The most common therapy for otitis externa is a topical agent containing antibiotics (an aminoglycoside and polymyxin B) and a corticosteroid. These medications are thought to reduce the inflammation and treat the underlying pathogen. This medication, however, require three administrations per day, and as with other forms of medications, compliance becomes a problem. Furthermore, otic aminoglycoside therapy can lead to ototoxicity or cutaneous sensitization. With prolonged use, it can lead to resistance and, eventually, fungal overgrowth. Steroids, on the other hand, can allow overgrowth of bacteria.

Acidity seems to be the primary protective mechanism that the ear canal has against otitis externa. An important dictum in the treatment of the disease is the restoration of the normal acidic (pH 6.5-6.8) environment of the external auditory canal. Thus, acidifying agents such as acetic and boric acid, have been used as an adjunct in the treatment of otitis externa. Clayton et. al. (1990) indicated that there was no difference between the use of a topical antiseptic and a topical antibiotic in the initial treatment of otorrhea, whether it is caused by otitis externa, acute otitis media or chronic otitis media. These authors favored the use of topical antiseptics rather than antibiotics on the grounds of cost, avoidance of resistance and toxicity.[8]

In the study done by Slack (1987) wherein the bacteriologic efficacy of three topical preparations (namely, boric acid in spirit, polymyxin-neomycin-hydrocortisone solution and polymyxin-fluocinolone-econazole solution) were compared, three patients responded well to a treatment with no specific agent against the growth. It was then concluded that the nature of the topical agent is probably unimportant.[5] In this study, clinical success of both therapeutic agents (boric acid and Aplosyn™otic) was statistically equivalent based on the 3- and 6-day cure rates ($z_{0.05} = 0.81$, *p-value* = 0.58 and $z_{0.05} = 0.54$, *p-value* = 0.34, respectively). The

patient who had failure of treatment in group B may be attributed to the severity of his condition on initial consult which was aggravated by continuous trauma (scratching).

Symptoms of otitis externa usually show a dramatic improvement within 3 days after the ear canal is cleansed and the antibiotic therapy is initiated with complete resolution in 7-10 days.[9] This duration of treatment is not an established fact according to the literature reviewed, and it is a derivative of the duration of treatment for strep throat which carries the same infectious organism.

In terms of mean time-to-end of otalgia from the onset of therapy and of symptoms, group B showed significantly shorter durations than group A ($t_{0.05} < 2.11$ and $t_{0.05} < 2.07$, respectively).

Antibiotic steroid drops use parabens as its vehicle which usually causes a stinging sensation that is tolerated by most patients.[10] Boric acid, on the other hand, produces skin irritation particularly on broken skin.[11] Mild stinging was manifested by one patient from each treatment arm.

CONCLUSION

By conducting a study involving 19 patients treated with an antibiotic-steroid otic drop and 24 patients treated with boric acid powder, we were able to conclude that the effectiveness of boric acid powder, in terms of 3- and 6-day cure rates, is comparable to the standard therapy for acute diffuse otitis externa, which is an antibiotic-steroid otic solution. However, a shorter treatment duration was attained with boric acid powder as evidenced by the mean time-to-end of otalgia. This finding could alter the current trend in the management of otitis externa in terms of patient convenience and compliance as well as cost-effectiveness.

RECOMMENDATION

We recommend that the study be performed on a larger population size. Also, culture of the ear swab may be done to support the eradication of pathogenic bacteria by the boric acid powder.

BIBLIOGRAPHY

1. Bojrab DI, Bruderly T, Abdulrazzak Y. Otitis Externa. *Otolaryngologic Clinics of North America.* 1996; 26: 761-782.
2. Cantor RM. Oitis externa: not always simple. *Emergency Medicine.* 1999; 31: 40-54.
3. Halpern MT, Palmer CS, Seidlin M Treatment Patterns of Otitis Externa. *Journal of the American Board of Family Practice.* 1999; 12: 1-7.
4. Guthrie RM, Bailey BJ, Baroody FM, et.al. Diagnosis and Treatment of Acute Otitis Externa. *Roundtable Discussion.* 1998: 1-23.
5. Slack RW. A study of there preparations in the treatment of otitis externa. *The Journal of Laryngology and Otology.* 1987; 101: 533-535.
6. Senturia BH. *Disease of the External Ear: an otologic-dermatologic manual,* New York, 1980, Grune & Stratton.
7. Cassisi N, Davidson T, Cohn A, Witten B. Diffuse Otitis externa: Clinical and Microbiologic Findings in the Course of a Multicenter Study on a New Otic Solution. *Annals of Otology, Rhinology and Laryngology.* 1986; 39 (supplement): 1-16.
8. Clayton MI, Osborne JE, etal. A double-blind, randomized, prospective trial of a topical antiseptic versus a topical antibiotic in the treatment of otorrhea. *Clinical Otolaryngology.* 1990: 15: 7-10.
9. Otitis externa. Electronic literature review: *Physician assistant.* June 2000.
10. Rohn GN, Meyerhoff WL, etal. Ototoxicity of Topical Agents. Otolaryngologic Clinics of North America. October 1993: 26(5): 747-758.
11. Toxicity of Boric acid. Electronic literature review: *Doctor's Guide.* May 1990.
12. Pistorius B, Westberry K, etal Prospective, randomized, comparative trial of ciprofloxacin otic drops, with or without hydrocortisone vs Polymyxin B-Neomycin-Hydrocortisone otic suspension in the treatment of Acute diffuse otitis externa. Infectious Disease in Clinical Practice. 1999: 8: 387-395.
13. Balkany TJ, Ress BD. Infections of the External Ear in Cummings CW. Otolaryngology-Head and Neck Surgery 3rd ed. Vol. 4; Mosby-Yearbook, Inc., Missouri; 1998.
14. Welkowitz,J, et.al. Introductory Statistics for the Behavioral Sciences, 3rd ed. Academic Press, Inc. New York 1982.

APPENDIX A

INFORMED CONSENT

I, _____, ___ y/o, residing at _____,

Hereby consent to participate in the study: "*BORIC ACID AURAL APPLICATION VERSUS ANTIBIOTIC-STEROID OTIC DROP IN THE MEDICAL MANAGEMENT OF DIFFUSE OTITIS EXTERNA*".

I have been made to fully understand the following:

1. That the main objective of the study, as has been explained to me, is to determine if treatment of otitis externa with Boric acid powder will reduce symptoms faster and more effectively than Aplosyn otic drops.

2. That the test drugs being used are not by themselves experimental/untested in nature.
   That their safety spectrum and acceptability has been established previously and it is only the comparison being made that is experimental.

3. That I agree to undergo physical examination (otoscopy/videoendoscopy) and which are considered necessary for diagnosis and evaluation. I understand that the above procedures will be free of charge.

4. That I have been given the opportunity to ask questions regarding the study and that the doctors are willing to answer these queries to my satisfaction.

5. That I can, at any time of my choosing, for any reason I may have, without prejudice to my person, withdraw from the study.

6. That if any adverse effects develop which is attributable to the drug/s being used in the study, the responsible entities will provide the appropriate medical care directed towards the management of such adverse events.

7. Be it known that this consent was freely and voluntarily given without influence, force, or intimidation from any person after I have fully understood the procedure of the treatment I will receive.

_____	_____
Signature	Witness
_____	_____
Signature	Witness

APPENDIX B

DATE _____ GROUP _____
NAME _____ AGE _____ SEX _____

HISTORY (indicate chief complaint (CC) and duration)

L R duration

_____ _____ _____ PRURITUS
_____ _____ _____ MANIPULATION
_____ COTTON BUDS _____ FINGER _____ OTHERS
_____ _____ _____ OTALGIA
_____ _____ _____ DISCHARGE
_____ CLEAR _____ WHITE _____ YELLOW

_____ _____ _____ HEARING LOSS

PE (otoendoscopy)

	DAY 0			DAY 3			DAY 6		
	MILD	MOD	SEV	MILD	MOD	SEV	MILD	MOD	SEV
SWELLING, PINNA SWELLING/ERYTHEMA, EAC									
TRAGAL TENDERNESS									
DISCHARGE									

Adverse reaction

____Stinging
____Itchiness
____Increased swelling/erythema

APPENDIX C

Table 1. Demographics and Baseline Medical Characteristics of Efficacy-Valid Population

	GROUP A n = 20	GROUP B n = 27
AGE, years		
Mean ± SD	31.7 ± 13.0	33.4 ± 13.1
range	18-65	18-65
SEX (M:F)	10:10	10:17
DURATION, days		
Mean ± SD	3.65 ± 1.8	3.37 ± 1.8
range	1-7	1-7
PRIMARY COMPLAINT		
Otalgia	16 (80%)	24 (89%)
Pruritus	4 (20%)	2 (7%)
Hearing loss	0	1 (4%)
PE FINDING		
Tragal tenderness	20 (100%)	27 (100%)
Canal edema/erythema	20 (100%)	27 (100%)
Discharge	11 (55%)	19 (70%)
Swelling, Pinna	5 (25%)	11 (41%)

Table 2. Time-to-end of Otalgia between the two treatment arms from onset of symptom and from initiation of therapy

	GROUP A n = 19	GROUP B n = 24
Time-to-end of otalgia, from onset	8.7 ± 2.0	5.5 ± 1.8
Time-to-end of otalgia, from initiation of treatment	1.8 ± 1.2	1.1 ± 0.8

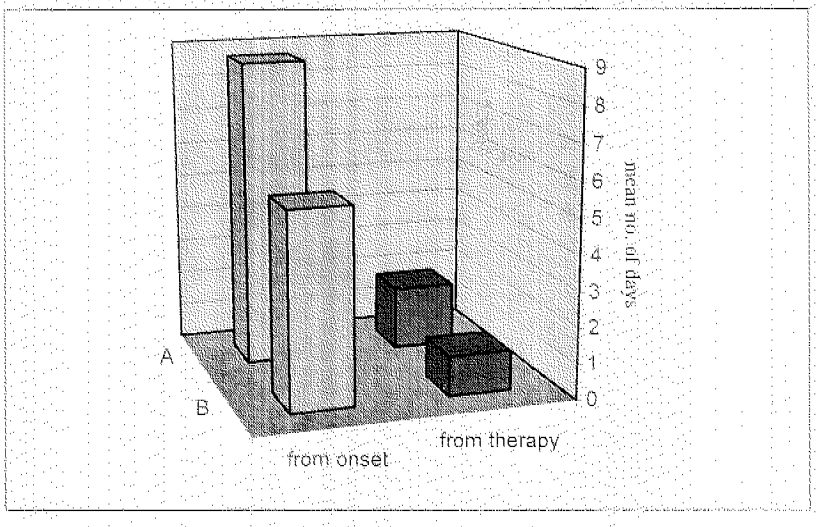
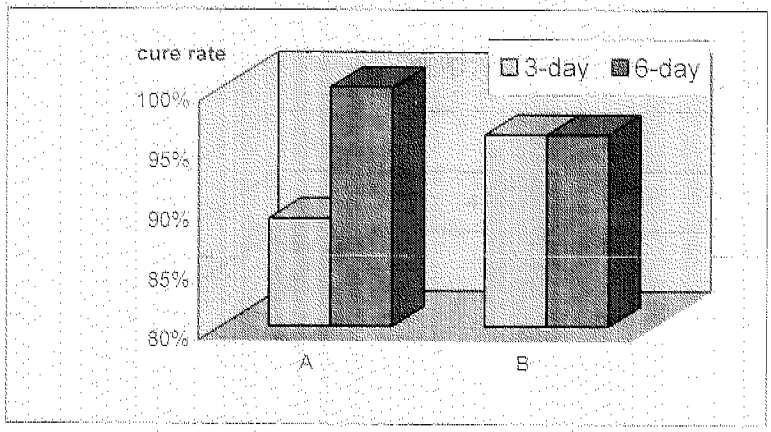


Table 3. Three-day and Six-day cure rate between the two treatment arms based on otalgia and canal edema

	GROUP A n = 19	GROUP B n = 24
3 - day	17 (89%)	23 (96%)
6- day	19 (100%)	23 (96%)



APPENDIX E

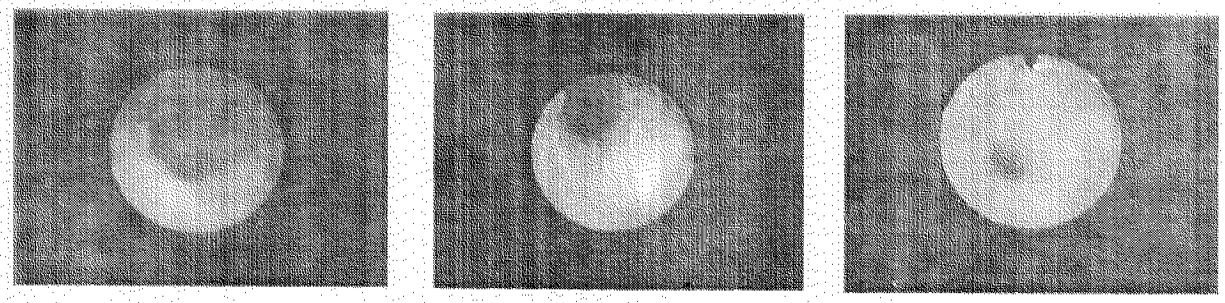


Figure 1. Classification of canal edema as to (a)mild, (b) moderate, (c)severe, based on Senturia's description.

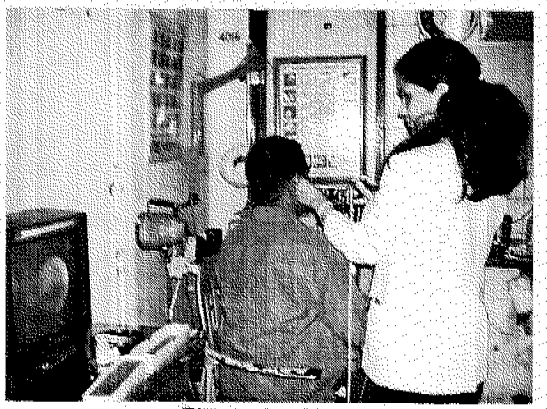


Figure 2. Otoendoscopy

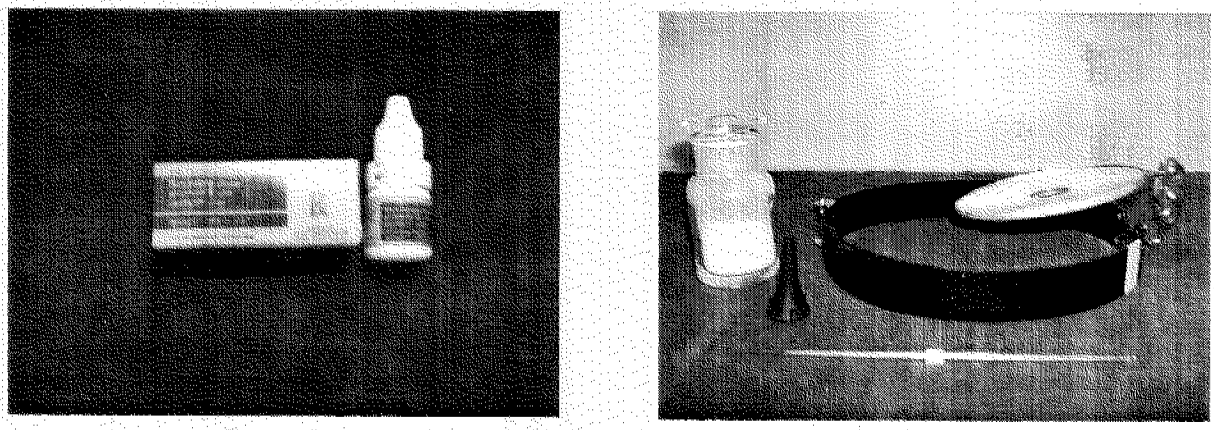


Figure 3. The test drugs (a)Aplosyn ™ otic , (b)Boric acid powder.

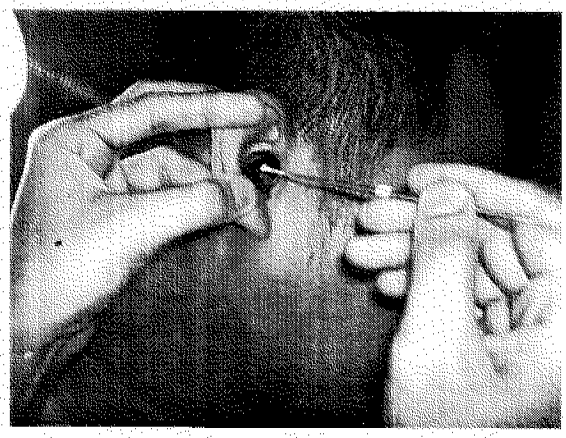


Figure 4. Application of boric acid powder within the ear canal.

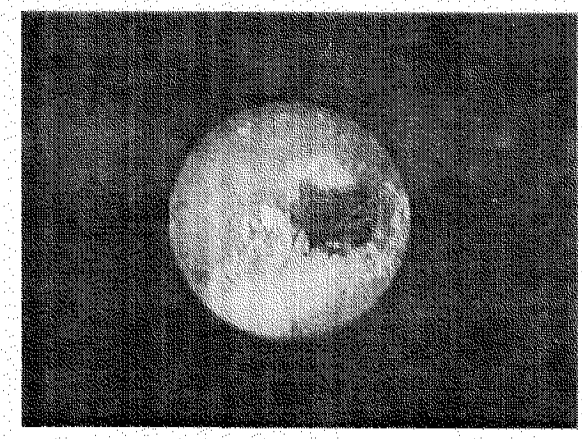


Figure 5. Boric acid powder within the ear canal.

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SCHOOL PERFORMANCE OF OTITIS-PRONE VERSUS OTITIS-FREE GRADE ONE PUPILS OF BAGONG ILOG ELEMENTARY SCHOOL*

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ABSTRACT

OBJECTIVE: To investigate if a difference in school performance exists between Otiitis-prone and Otitis-Free Grade 1 pupils in a school setting.
STUDY DESIGN: Cross-sectional Study.
SETTING: Bagong Ilog Elementary School, Bagong Ilog, Pasig City.
SUBJECTS/METHOD: 163 (67.63%) out of 241 Grade 1 pupils were included in the study. Twenty-two were excluded due to presence of impacted cerumen by otoscopy. A total of 141 pupils were included. Those whose parents/caretakers were interviewed regarding the child's history of otitis since birth to present and who were examined otoscopically and whose grades for the 1st Grading Period were gathered. Of the 141 pupils, 59 (41.84%) were positive for otitis media by history and otoscopy. They were grouped as Otitis-Prone. Eight-two (58.15%) were negative and were grouped as Otitis-Free.
OUTCOME MEASURES: Grades of 141 pupils for the 1st Grading Period were gathered from their teachers which included ratings for all subjects, general weighted average, class participation, sociability and attendance.
DATA ANALYSIS: 1) Association of Otitis Media with Class Participation was computed using chi-square with chi square value of 16.35 and p value= 0.0000527. 2) Otitis Media with Sociability using chi-square with chi-square value= 21.6, p value= 0.0000034. 3) Otitis Media with general weighted average using t-test, t-test value=4.446, p value= <0.001 and using chi-square (pass/fail), chi-square vale= 20.930, p value=<0.001. D) Otitis Media with Attendance using t-test, t-test value= -4.926, p value=<0.001.
RESULTS: Association between Otitis Media and A) Class Participation, B) Sociability, C) General Weighted Average, and D) Attendance were all statistically significant.
CONCLUSION: Otitis-Prone Grade 1 pupils have poorer school performance (lower general weighted average, lower ratings for class participation and sociability and poorer attendance) compared to their Otitis-Free counterpart.

INTRODUCTION

Otitis media is the most prevalent disease in children next to respiratory tract infections. Infants and young children are at highest risk for otitis media. Incidence rates are 15-20% with peaks occurring from 6-36 months and 4-6 years of age. About 85% of children will have at least one episode of acute otitis media by 3 yrs of age and 50% of children will have 2 or more episodes. [1] Growing evidence supports the hypothesis that hearing loss that accompanies otitis media may be associated with speech and language delay in children especially if it coincides with a period of rapid language acquisition.[1,2,3,4,5] Otitis media brings about fluctuating hearing loss ranging from mild to moderate and in some cases, severe. In children, however mild the degree of hearing loss, the impact is greater compared to an adult with the same degree of hearing loss. Without appropriate intervention, even mild hearing loss in early childhood may have long-term consequences in terms of social, emotional and academic performance.[1,6] This study hopes to investigate the association of otitis media with school performance.

Hearing loss during the first five years of life can affect the development of speech and language, social and emotional development, behavior, attention and academic achievement. A child with an undiagnosed hearing impairment who goes to school with unfavorable classroom conditions (background noise, poor acoustics), would probably have below-par performance.[1]

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Various literature regarding the risks and lasting effects of otitis media in the child's performance have been published.[7] A prospective study by Gravel et al included only 14 children (7 otits-prone and 7 otitis-free) whose academic performance were evaluated[8]. Standardized tests were implemented to assess the impact of otitis media on speech and language development such as Reynell Developmental Language Scales and Illinois Test of Psycholinguistic Abilities.[10,11,12,13] This study hopes to investigate performance using 4 parameters: General Weighted Average, Class Participation, Sociability and Attendance, all of which are actual measures of school performance.

Research Question:

Is there a difference between the school performance of Otitis-Prone versus Otitis-Free Grade 1 pupils of Bagong Ilog Elementary School?

OBJECTIVES

General Objectives:

To know if there is an association between school performance and Otitis Media among Grade 1 pupils of Bagong Ilog Elementary School.

Specific Objectives:

To determine the relationship between Otitis Media and the different parameters of school performance among Grade 1 pupils of Bagong Ilog Elementary School namely:

a) general weighted average
b) class participation
c) sociability
d) attendance

METHODOLOGY

Research Design

Cross-sectional Study

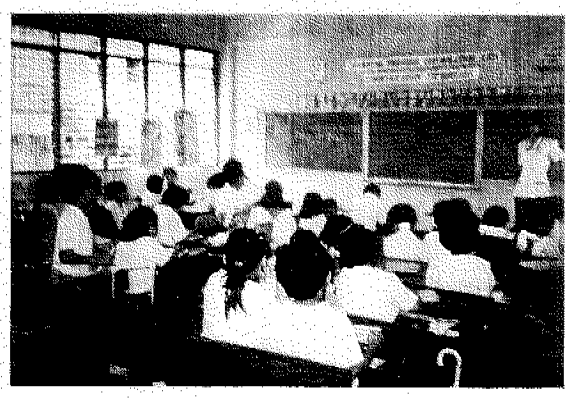
This design measures cause and outcome at the same time. Cause is history of otitis media and outcome is school performance.

Setting:

Bagong Ilog Elementary School, Bagong Ilog, Pasig City

Subjects:

The study was conducted in Bagong Ilog Elementary School where there is a total of 241 pupils. Only 163 Grade 1 pupils were present during the study. The parents/caretakers of the participants were given a questionnaire to fill up. The questionnaire inquires on presence of signs and symptoms observed by the parent/caretaker (otorrhea, otalgia, ear swelling, foul-smelling ear, hearing loss) from birth until present. Likewise, history of consultation, previous diagnosis, treatment and date of last episode of otitis media were noted. Answers were also confirmed by asking the pupil. The pupils were then examined by otoscopy for presence of tympanic membrane perforation, discharge, fluid, tympanosclerosis, healed perforation, bulging, retracted, hyperemic tympanic membrane and other findings suggestive of remote, recent or active otitis media. Pneumatic otoscopy was also employed to check compliance of tympanic membrane and to distinguish perforated versus healed tympanic membrane perforation.



Inclusion Criteria:

All Grade 1 pupils attending regular classes with no known history of learning disability, physical handicaps (deaf, mute, blind), CNS disturbances.

Exclusion Criteria:

Total Grade 1 pupils is 241. Seventy-eight pupils were not present during the study, 12 of the 78 were dropped from the roll at the end of the 1st Grading Period. Only a total of 163 pupils were present during the study. Of the 163, twenty-two (13.496%) pupils were excluded due to presence of impacted cerumen which may also cause hearing loss. Therefore, only a total of 141 pupils were included in the study.

METHOD

The parents/caretakers of the pupils were given a questionnaire to fill up. The questionnaire inquired about:

1) history (from birth to present) of otitis media by presence of symptoms (otorrhea, otalgia, ear swelling, otorrhea, foul-smelling ear),
2) diagnosis
3) treatment and
4) date of last episode.

(see appendix A)

The pupils were then examined via otoscopy to check for presence of findings suggestive of remote, recent or active Otitis Media

such as frank otorrhea, tympanic membrane changes: hyperemic, bulging, retracted, sclerotic, perforated tympanic membrane, effusion, healed perforation or poor mobility .*(see appendix B)*

The pupils were then labelled as **Otitis-Prone** when they meet any ONE of the following criteria:

1) presence of any one of the symptoms (otorrhea, foul-smelling ear, otalgia, ear swelling, hearing loss) and otoscopic findings (discharge, tympanic membrane changes: perforation, healed perforation, tympanoclerosis, effusion, retraction, hyperemia, bulging tympanic mebrane, poor mobility) suggestive of remote, recent or present Otitis Media
2) no history of symptoms but positive for otoscopic findings previously mentioned in criteria # 1
3) with previous diagnosis of Otitis Media by history

The pupils were then labelled as **Otitis-Free** when they meet ALL of the following criteria:

1) no history of symptoms and with normal otoscopic findings
2) no previous diagnosis of Otitis Media

Outcome Measurement:

Report cards of pupils were then reviewed and 1st Grading Period ratings for the following were noted:

a) General Weighted Average (average of 7 subjects, expressed in percentage)
b)Class Participation (in letter grades:A,B,C,D,F)
c) Sociability (in letter grades:A,B,C,D,F)
d)Attendance (number of days absent)

(see appendix C)

Analysis:

Chi-Square was used as a test of significance of the association between Otitis Media and Class Participation also between Otitis Media and Sociability. Letter grades were used as ratings for these parameters. However, the expected cell in order to be valid has to be less than 5, therefore letter grades C and D were grouped together.

T-test, on the other hand, was used to test the significance of the association between Otitis Media and General Weighted Average also between Otitis Media and Number of Days Absent. Likewise, Chi-square was used to test significance of association between Otitis Media and Pass/Fail ratings for General Weighted Average.

RESULTS

A total of 141 pupils were included in the study. Ninety-six (58.9%) were positive for history of Otitis Media and 67(41.1%) denies history of Otitis Media.

History of OTITIS MEDIA

	Frequency	Percent	Valid Percent
Valid (-)	96	58.9	58.9
(+)	67	41.1	41.1
Total	163	100.0	100.0

Otoscopic examination revealed normal findings in 84 (51.5%) of the 163 pupils examined while 57 (35%) were positive for otitis media and 22 (13.5%) had impacted cerumen. Thirteen from the Otitis-Free group and 9 from the Otitis-Prone group and were excluded from the study. Of the 58 pupils with a positive history of Otitis Media, fifty-six (97.6%) had a positive otoscopic finding while only one of the 83 pupils with no history of Otitis media had a positive otoscopic finding.

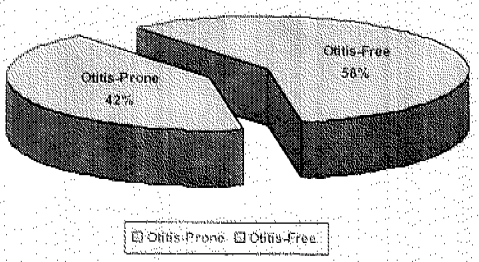
OTOSCOPIC FINDINGS

	Frequency	Percent	Valid Percent
Valid	(-)	84	51.5
	(+)	57	35.0
	IC	22	13.5
Total	163	100.0	100.0

HISTORY of OTITIS MEDIA and OTOSCOPIC FINDINGS (Impacted Cerumen excluded)

History of Otitis Media	No. of Pupils	(+) PE findings	(-) PE findings
(-)	83	1	82
(+)	58	56	2
Total	141	57	84

Fifty-nine (41.8%) met the criteria for Otitis-prone and 82 (58.2%) were grouped as Otitis-Free.



Otitis-Prone (58.2%) versus Otitis-Free (47.5%)

Sixty-seven (47.5%) had a grade of B for Class Participation, 68 (48.2%) with a grade of C and 6 (4.3%) with a grade of D. Sociability ratings revealed 60 (42.6%) had a grade of B, 77 (54.6%) with a grade of C and 4 (2.8%) with a grade of D. Mean number of days absent was 2.6959, median of 2.0, standard deviation was 2.9202, minimum days absent is 0 and maximum of 19,. General weighted average had a mean of 77.8764, a median of 78.0, standard deviation of 4.0631, minimum GWA of 67.86 and maximum of 85.0.

Results of Class Participation and Sociability

	Class Participation	Sociability
B	67 (47.5%)	60 (42.6%)
C	68 (48.2%)	77 (54.6%)
D	6 (4.3%)	4 (2.8%)

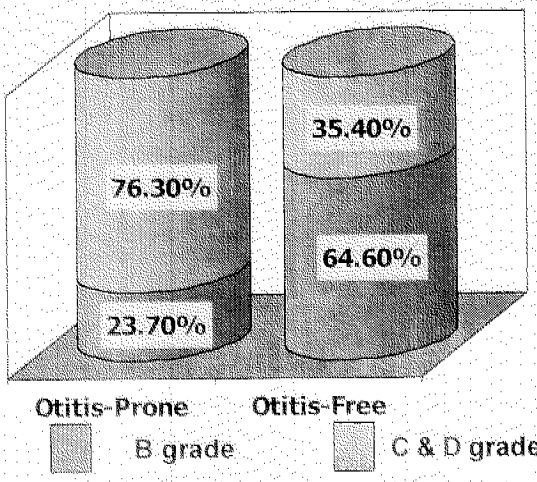
Results of Attendance and General Weighted Average

	Attendance (number of Days)	General Weighted Average (%)
Mean	2.6959	77.8764
Median	2.0	78.0
Standard Deviation	2.9202	4.0631
Minimum	0	67.86
Maximum	19	85.0

ASSOCIATION OF OTITIS MEDIA with PARAMETERS of SCHOOL PERFORMANCE

A) Otitis Media versus Class Participation

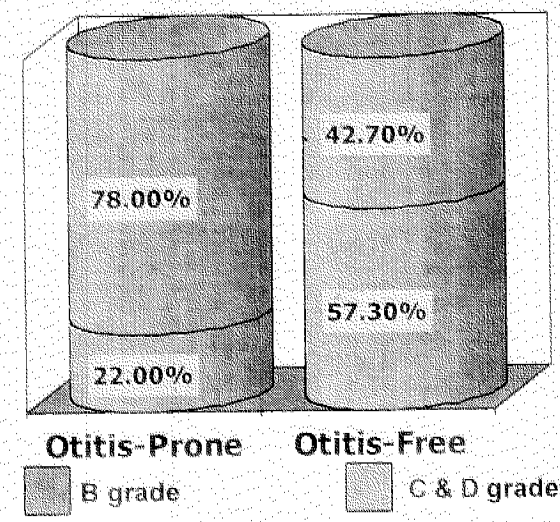
Using chi-square, value obtained was 16.35 with a p value of 0.0000527. Otitis Media has a statistically significant association with Class Participation. 76.3% of the Otitis-Prone group have C and D grades compared to 35.4% C and D grades of the Otitis-Free group. (see appendix D)



Class Participation of Otitis-Prone and Otitis-Free Groups

B) Otitis Media versus Sociability

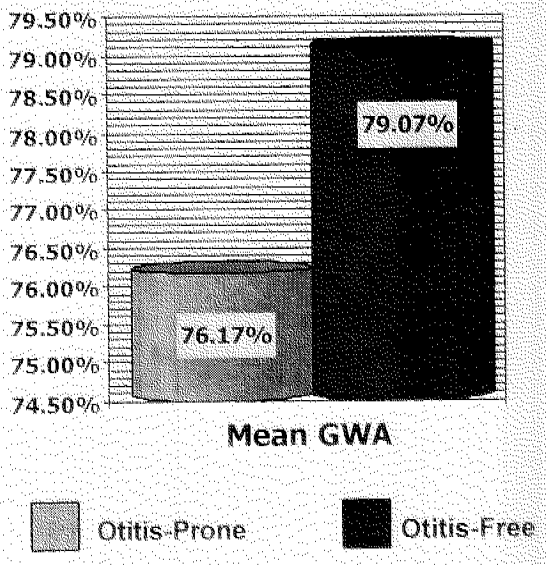
Using Chi-square, value obtained was 21.6, p value of 0.0000034. Otitis Media has a statistically significant association with sociability. 78.0% of the Otitis-Prone pupils have C and D grades compared to 42.7% with C and D grades of the Otitis-Free group. *(see appendix D)*



Sociability of Otitis-Prone and Otitis Free Groups

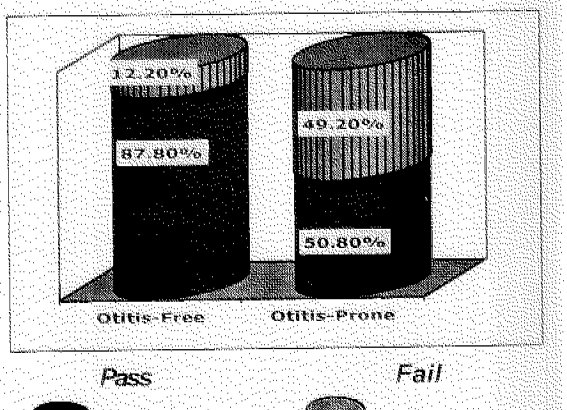
C) Otitis Media versus General Weighted Average

Using t-test, value obtained was 4.446, p value of <0.001, the difference in mean General Weighted Average between Otitis-Prone and Otitis-Free group is statistically significant.



General Weighted Average of Otitis-Prone and Otitis-Free Groups

Using chi-square, value obtained was 20.930, p value of 0.001, there is statistically significant association between General Weighted Average and Otitis Media. 87.8% of the Otitis-Free students passed compared to only 50.8 % of the Otitis-Prone group. *(see appendix D)*

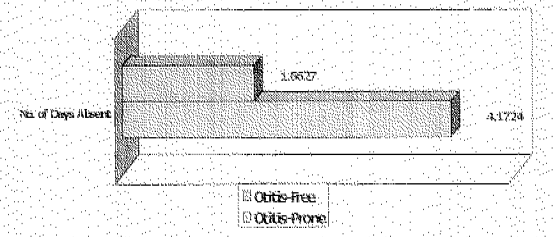


Pass and Fail Grades of Otitis-Prone and Otitis-Free groups

D) Otitis Media versus Number of Days Absent

Using t-test, value obtained is –4.926, p value <0.001, the difference in mean Number of days absent between Otitis-Prone and Otitis-Free pupils is statistically significant.

(see appendix D



Number of Days Absent of Otitis-Prone and Otitis-Free Groups

DISCUSSION

A child's entry into school is always met with a lot of anticipation and anxiety. Is the child mentally, physically and emotionally prepared to hurdle the obstacles of school life? Will the child be able to listen to lessons and instructions of his/her teacher? Will the child be able to communicate his/her needs to his/her teachers and classmates? These are a few of the questions that confront a parent of a child who will enter school for the first time. This study hopes to produce awareness among parents and teachers alike, as well as otolaryngologists, regarding a possible yet important condition that may affect school performance of children.

Otitis Media is the most common diagnosis for children in the United States where there is an estimated 25 million yearly visits to pediatricians related to this condition[1]. According to Gates, it is also the most common bacterial infection in children and is the leading cause of hearing loss in the pediatric age group[13].

Otitis media is diagnosed clinically in the pediatric age group by presence of otalgia, ear tugging or irritability, otorrhea, less commonly postauricular swelling, facial paralysis, vertigo and tinnitus. However, even with the presence of these signs and symptoms, only a small percentage of these children belonging to the lower socio-economic status will be brought to pediatricians or otolaryngolgists. Only a few will be diagnosed and most of these will suffer the complications of an undiagnosed and recurrent otitis-media.

More so, it is important to note that otitis media also plays an important role in a child's attendance in school. A child who has otitis media will complain of otalgia, otorrhea and fever which prevents him from attending classes, thus poor Attendance. Likewise, unsightly and foul-smelling otorrhea that accompanies otitis media is a source of embarrassment to a child who may find himself rejected by his classmates thus contributing to poor grades for Sociability.

In children with otitis media with effusion, air conduction thresholds average 20-27dB, and the bone conduction threshold is not affected. In a study by Newton[23]. Thirteen (65%) of 20 objectively confirmed hearing loss in pediatric subjects was secondary to otitis media. A retrospective study of MacAndie[22] proved that there is a statistically significant association between history of chronic otitis media with sensorineural hearing loss from 5.24 to 9.02 dB across the frequency range. Studies have shown that associated persistent or episodic conductive hearing loss in children may affect their cognitive, language and emotional development[1].

Teele et al emphasized that otitis media which most commonly occurs between the ages 1 and 4 years coincides with a period of rapid language development[14]. This is important because episodes of otitis media during this period will produce mild hearing loss which prevents assimilation of important auditory input to a child who is just beginning to learn from his environment. Gravel confirms this by stating that performance in higher-order auditory processing appears to be associated with the mild hearing loss experienced during an important period of early development[15].

Sininger et al elaborates that infants spend the first year of life learning about their environment through experience. He therefore describes hearing loss as an interruption of sensory input to the auditory nervous system during this crucial stage in development which corresponds to peak of incidence of otitis media with hearing loss[16].

A retrospective study of 19 children with earlier history of otitis media with effusion was compared with age-matched control group of 19 children with no history of otitis media or hearing impairment showed that the OME group were found to have significant lower scores in the articulation test and small, but significant, lower scores in the test regarding sound discrimination.[24] While a prospective study by Friel-Patti[25] proved that better language is associated with better average hearing levels. These findings suggest that the relationship between OME and language is mediated by hearing. This study has proven that a significant association between otitis media and four parameters of school performance exists.

Otitis media is a major cause of auditory dysfunction in pre-school and grade school aged

children.[19] The intellectual and linguistic sequelae of middle ear diseases has been thoroughly documented. Otitis in the first 3 years of life in 207 children results in significantly lower scores in mathematics, reading and articulation skills.[20] Even unilateral effusion for as short as 3 months will produce delays or regression in speech development in toddlers.[21]

Hearing loss associated with otitis media during the crucial years of language and speech development may bring about a child who will hear less, talk less and know less. A child who has difficulty hearing his teacher's lessons, instructions and questions will participate less in class recitation or discussion and will have less academic input therefore lower over all grades. This study shows us that Otitis-Prone group had significantly lower grades for class participation and mean general weighted average and less passing grades compared to the Otitis-Free group.

On the contrary, Schilder et al who studied long-term effects of otitis media with effusion on language, reading and spelling concluded that the association between early otitis media and language development found at pre-school age was no longer present at school age[10]. The reason for which is still unknown.

There is no debate that there are other causes of language delay and Brookhouser et al proved that lower socio-economic status predisposes to language delay[17]. Otitis media with effusion may affect performance and has an additive effect with both intrinsic factors, such as central processing, and extrinsic factors, such as socioeconomic status[18]. However, this study has chosen a public school setting to eliminate the factor of socio-economic status.

Overall, an interplay of factors may have caused poor school performance among the Otitis-Prone group such as hearing loss, presence of otalgia and otorrhea associated with history of otitis media. A statistically significant association between Otitis Media and different parameters (General Weighted Average, Class Participation, Sociability and Attendance) was established by this study.

CONCLUSION

A child's poor school performance is indeed a source of anxiety to parents most especially if the root of the cause is not recognized early. We were made to think that some children were born with above-average intelligence while the rest were not as fortunate. Some children are inherently smarter while the rest were labeled by society as "dumb". The sad truth is that parents and teachers have simply accepted this statement and have failed to investigate the cause of a child's poor school performance.

The authors hope that by proving that a strong association exists between school performance and otitis media, it is imperative that children with poor school performance be investigated on for an underlying ear condition such as otitis media. The authors hope to create awareness among educators and school administrators regarding the importance of screening for otologic conditions such as otitis media as a possible cause of poor school performance. Nevertheless, the authors cannot discount the fact considerable attention should be given first and foremost to the early recognition of otitis media in children in order to prevent future complications and consequences to the child's development.

This study was designed to determine the association between otitis media and different parameters of school performance. Review of literature proved that otitis media during the early years of development have consequences in children's social, emotional and academic performance[6]. Thus, this study has fulfilled its goal of determining the association that exists between otitis media and Class Participation, Sociability, General Weighted Average and Attendance. Otitis-Free children are more likely to perform better in school compared to their Otitis-Prone counterpart.

RECOMMENDATIONS

The authors hope to make the following recommendations:

a) That all grade school entrants be screened for Otitis Media and Hearing Loss and that baseline Audiometry be determined
b) That pupils with relatively below average School Performance (low General weighted Average, poor Sociability, Class Participation and Attendance) be investigated on for an underlying cause such as otitis media
c) A prospective 5-year study be done on the effects of otitis media on school performance in a similar setting eliminating other confounding factors such as parental attitude and value

placed on education, classroom setting etc.

BIBLIOGRAPHY

1 Arnold, James E.: The Ear. Nelson's Textbook of Pediatrics, 15th ed. Philadelphia, USA, W.B. Saunders, 1996 pp.1804-1826

2 Wallace IF, Gravel JS, Mc Carton CM, Stapells DR, Bernstein RS, Ruben RJ. Otitis Media, auditory sensitivity and language outcomes at one year. Laryngoscope 1988; 98:64-70

3 Wright PF, Sel SH, Mc Connell KB, et al. Impact of recurrent otitis media on middle ear function, hearing and language. J Pediatr 1988; 113:581-87

4 Klein JO: Otitis media and the development of speech and language.Pediatr Infect Dis 3(4):389-91: 1984 Jul-Aug

5 Roberts JE, Sanyal MA, Burchinal MR,Collier AM, Ramey CT, Henderson FW.Otitis Media in early childhood and its relationship to later verbal and academic performance. Pediatrics 1986; 78:423-30

6 Stelmachowicz PG, Gorga MP.: Audiology: Early Identification and Management of Hearing Loss. In: Cummings CW, Richardson MA, (eds): Otolaryngology-Head & Neck Surgery, Pediatric vol 5, 3rd ed. St Louis, Mosby 1998, pp 401-417

7 Klausen O, Moller P, Holmefjord A, Reisaeter S, Asbjornsen A. Lasting effects of otitis media with effusion on language skills and listening performance. Acta Otolaryngol Suppl 543:73-6; 2000

8 Gravel JS, Wallace IF, Ruben RJ. Early otitis media and later educational risk. Acta Otolaryngol 115(2): 279-81; 1995 Mar

9 Maw R, Wilks J, Harvey I, Peters T, Golding J. Early surgery compared with watchful waiting for glue ear and effect on language development in preschool children: a randomized trial. The Lancet 353(9157)960-3; 1999 Mar

10 Schilder AG, Van Manen JG, Zielhuis GA, Grievink EH, Peters SA, Van Den Broek P. Long-term effects of otitis media with effusion on language, reading and spelling. Clin Otolaryngol 18(3):234-41; 1993 Jun

11 Rach GH, Zielhuis GA, van den Broek P.The influence of chronic persistent of otitis media with effusion on language development of 2 to 4 y/o. Int J Pediatr Otorhinolaryngol 15(3):253-61; 1998 Sep

12 Vermeulen A, Hoekstra C, Brokx J, van den Broek P. Oral language acquisition uin children assessed with the Reynell Developmental Scales. Int J Pediatr Otorhinolaryngol 47(2):153-5; 1999 Feb

13 Gates GA.: Acute Otitis Media and Otitis Media with Effusion. In: Cummings CW, Richardson MA, (eds): Otolaryngology-Head & Neck Surgery, Pediatric vol 5, 3rd ed. St Louis, Mosby 1998, pp 461-477

14 Teele DW, Klein JO, Rosner BA. Otitis media with effusion durinfg the first three years of life and development of speech and language. Pediatrics 1984; 74:282-87. [Medline link]

15 Gravel JS, Wallace IF, Ruben RJ. Auditory consequences of early mild hearing loss associated with otitis media. Acta Otolaryngol 116(2):219-21; 1996 Mar

16 Sininger YS, Doyle KJ, Moore JK: The case for early identification of hearing loss in children. Auditory system development, experimental auditory deprivation, and development of speech perception and hearing. Pediatr Clin North Am 46(1): 1-14; 1999 Feb

17 Brookhouser PE, Goldgar DE. Medical Profile of the language-delayed child: otitis-prone versus otitis-free. In J Pediatr Otorhinolaryngol 12(3):237-71; 1987 Feb

18 Friel-Patti S, Finitzo T. language learning in a prospective study of Otitis Media with effusion in the first two years of life. J Speech Hear Res; 33:188-94; 1990

19 Tharpe AM, Bess FM. Identification and management of children with minimal hearing loss. Int J Ped Otorhinolaryngol. 1;21:41-50; 1999

20 Teele DW, Klein JO, Chase C; et al. Otitis media in infancy and intellectual ability, school achievement, speech and language at age 7 years. J Inf Dis.; 162:685-94; 1990

21 Wallace, Gravel J, McCarton C.Otitis media and language development at 1 year of age. J Speech Hear Disord.; 53:245-51; 1988

22 MacAndie C, O' Reilly BF. Sensorineural hearing loss in chronic otitis media. Clin Otolaryngol ;24(3):220-2;1999
23 Kramer AH, McCullough DW. The prevalence of otitis media with effusion among Inuit children. Int J Circumpolar Health 1998; 57 Suppl 1:265-7
24 Klausen o, Moller P, et al. Lasting effects of otitis media with effusion on language skills and listening performane. Acta Otolaryngol Suppl 2000; 543:73-6

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ANATOMIC MEASUREMENTS OF THE LARYNGEAL FRAMEWORK IN FILIPINO ADULT CADAVERS*

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ABSTRACT

OBJECTIVE: To determine the size and proportion of the laryngeal cartilage framework in adult Filipino cadavers and its possible clinical and surgical implications.
DESIGN: Descriptive study
SETTING: Tertiary hospital
PATIENTS: Twenty human larynges (15 males and 5 females) were harvested from cadavers. The age range of the male subjects was 36 to 65 years and for the female subjects was at 37 to 56 years.
RESULTS: Most of the laryngeal framework measurements (except the angulation of the thyroid ala and cricoid cartilage) were larger in males compared to females. The location of the anterior commissure (B) in relation to the midpoint of the midline length of the distance from the superior thyroid notch to the lower edge of the thyroid ala on the thyroid cartilage was approximately 1.00 mm slightly above or below midpoint in females and approximately 1.00 mm above to 2.0 mm below midpoint in males. The angle made between the lines of the upper and lower edge of cricoid cartilage (FF) was approximately 35° in males and 45° in females. The internal antero-posterior (WX) and lateral distances (YZ) of the cricoid cartilage in males ranged from 16.0 to 19.60 mm and 14.00 to 32.50 respectively, while in females, it measured from only 7.70 mm to 13.20 mm and 8.00 to 12.50 mm. The mean distance between the tip of the vocal cord process and muscular process of the arytenoid cartilage in males is approximately 11.44 mm whereas that of the female arytenoids cartilage is measured at 10.26 mm on the average.
CONCLUSION: Considerable gender and race related differences in many of the geometric measurements of the laryngeal framework were observed in the study. These morphological differences have important clinical and surgical implications. They are critical to the accurate placement of needles and probes in laryngeal electromyography and vocal cord injection, medialization procedures, in performing supraglottic laryngectomy, as well as the precise planning of laryngeal framework surgery.

INTRODUCTION

Knowledge of the size and proportions of the human larynx and its cartilaginous components is essential in the increasing application of sophisticated electrophysiological, radiological, and surgical methods to the diagnosis and treatment of laryngeal disorders [1,2]. In addition to its value in the biomechanical modeling of the larynx (e.g. finite-element models), knowledge of these data may contribute to the planning of laryngeal framework surgery to the study of voice production, and to the analysis of CT- and MRI-scans of the larynx [3,4,5].

In 1971, Maue and Dickson investigated the range of normal distribution in the shape, size, and configuration of the human laryngeal cartilage and in the size, symmetry, and placement of the articulations and ligaments of these cartilages [6].

In 1992, Meiteles and colleagues made measurements of the external laryngeal framework in North American cadavers in order to identify landmarks that will aid the surgeon in supraglottic laryngectomy and thyroplasty type I [3]. Geometric characterization of the human laryngeal framework, including its cartilaginous components were done by Eckel et al. and Sprinzl et al. in 1994 and 1999, respectively [1,2]. Hirano et al. in 1999, did a morphologic study of cadaver larynges to investigate the asymmetry of the laryngeal framework [7]. In 2001, Tayama and associates made linear and angular geometric measurements on the thyroid, cricoid, and arytenoid cartilages using both human and canine larynges for biomechanical modeling [4]

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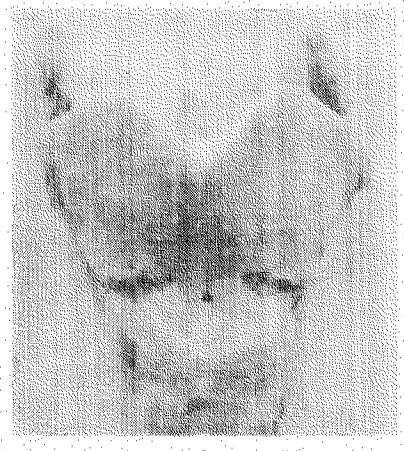
The aim of the study is to determine the size and proportions of the laryngeal cartilage framework in adult Filipino cadavers and its possible clinical and surgical implications.



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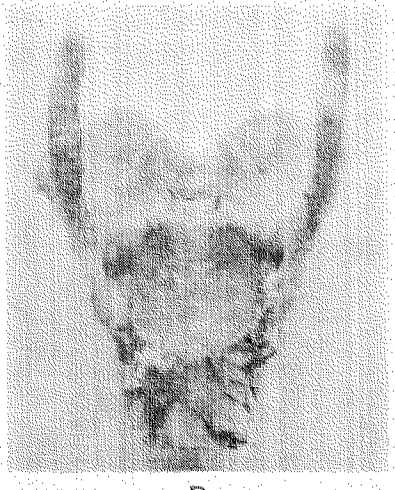

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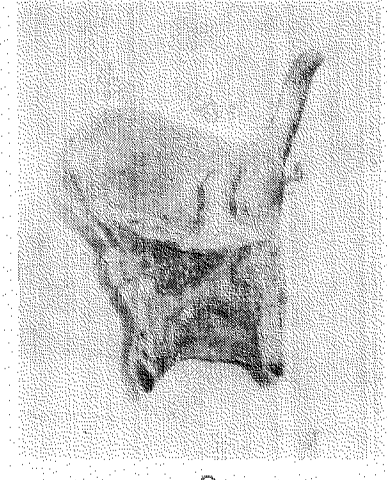


C

Figure 1: External laryngeal cartilaginous framework (A= anterior view; B= posterior view; C= sagital view)

METHODS

Tissue Specimens

Twenty human larynges (15 males and 5 females, See Table 1) were harvested from cadavers, preserved in 10% formaldehyde solution. The ages of the male subjects ranged from 36 to 65 years (mean, 49.8 yrs), and the ages of the female subjects ranged from 37 to 56 years (mean, 46.8 yrs). A midline incision was made on the anterior region of the neck and dissection done to expose the strap muscles. External musculature was sharply removed to expose the laryngeal cartilaginous framework (Figure 1). Specimens were placed in 10% formaldehyde solution. All larynges obtained from the cadavers had no signs of trauma or diseases of the larynx.

Measurements

A total of 31 parameters (12 in thyroid cartilage, 9 in cricoid cartilage, 8 in the arytenoid, 2 in the epiglottis) per laryngeal specimen were obtained using a single protractor and a Vernier caliper corrected to the nearest 0.05mm. A needle was passed from the endolarynx externally through the thyroid cartilage and perpendicular to the thyroid cartilage at the level of the anterior commissure. External laryngeal measurements were then made (Figures 2,3,4) and are listed in below.

Thyroid Cartilage (Refer to figure 2)

AB = from the upper edge (anterior notch) at the anterior midline up to the level of the anterior commissure

AC = from the upper edge (anterior notch) at the anterior midline up to the lower edge of the thyroid ala

CD = from the lower edge of the thyroid ala at the anterior midline to upper edge at the anterior midline of cricoid cartilage (cricothyroid membrane)

E'F' = height of the left thyroid ala

E"F"= height of the right thyroid ala

G'H' = height of thyroid ala at the inferior tuberculum, left

G"H" = height of thyroid ala at the inferior tuberculum, right

IB = width of thyroid lamina at the level of the anterior commissure viewed laterally

K'K" = width of the thyroid lamina at the level of the anterior commissure viewed posteriorly

GG = angle of the thyroid lamina

HH'H' = oblique line of the thyroid lamina, left

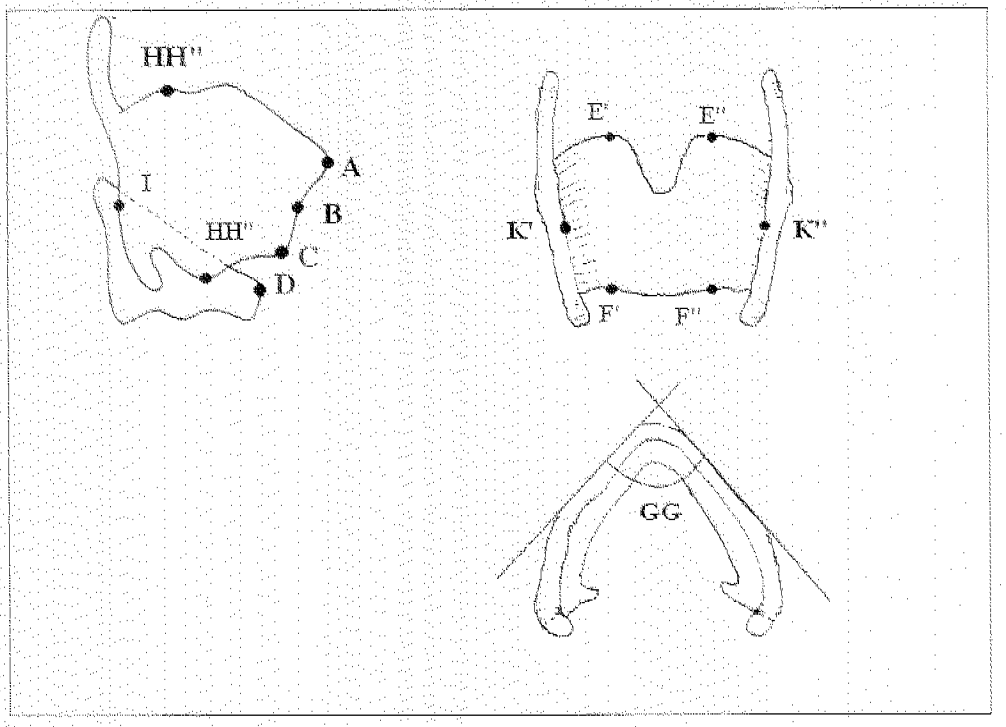


Figure 2: Schematic diagram of thyroid cartilage measurements

HH"H" = oblique line of the thyroid lamina, right

Cricoid Cartilage (Refer to figure 3)

DL = upper edge of cricoid cartilage to lower edge of cricoid cartilage at anterior midline

LO = anteroposterior width of cricoid cartilage at lower edge

DN = distance between the anterior upper edge to the posterior upper edge of the cricoid cartilage

FF = angle made between the lines of the upper and lower edge of cricoid cartilage

NO = height of cricoid cartilage at posterior midline

P'Q' = height of the cricoid cartilage at the highest location posteriorly, left

P"Q" = height of the cricoid cartilage at the highest location posteriorly, right

WX = internal anteroposterior distance of the cricoid cartilage

YZ = internal lateral distance of the cricoid cartilage

Arytenoid Cartilage (Refer to figure 4)

AA'T' = distance between the tip of the vocal cord process of the arytenoid and the midpoint between the apex and the muscular process, left

AA"T" = distance between the tip of the vocal cord process of the arytenoids and the midpoint between the apex and the muscular process , left

U'S' = height of the arytenoid cartilage from the apex to the cricoarytenoid facet, left (without the cuneiform)

U"S" = height of the arytenoid cartilage from the apex to the cricoarytenoid facet, right (without the cuneiform)

R'T' = distance between the tip of the vocal cord process and the muscular process of the arytenoid cartilage, left

R"T"= distance between the tip of the vocal cord process and the muscular process of the arytenoid cartilage, right

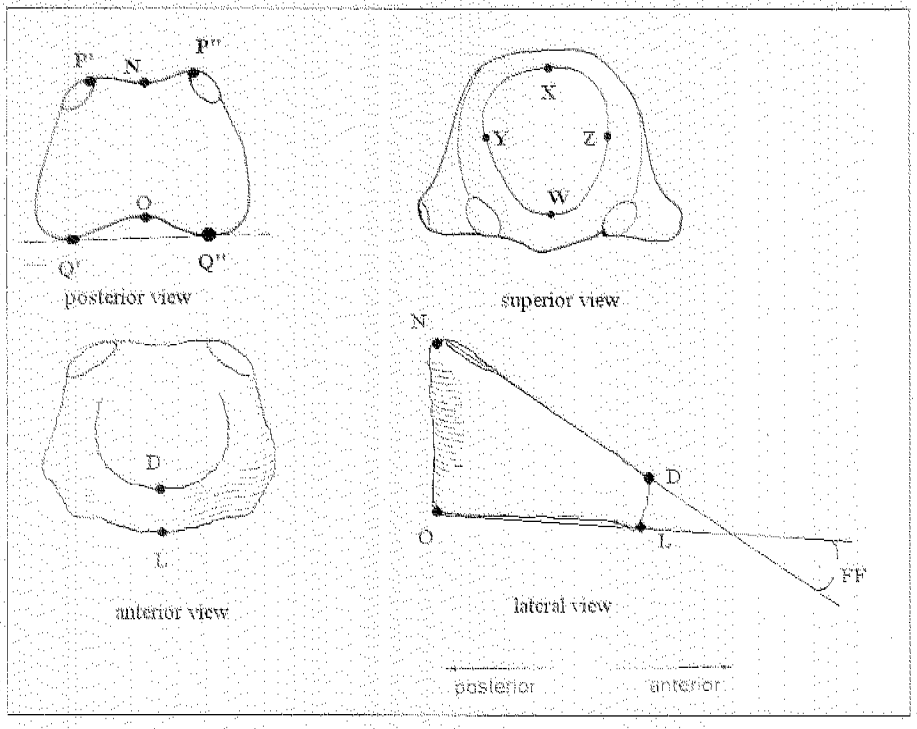


Figure 3: Schematic diagram of the cricoid cartilage measurements

T'B = length of the true vocal cord from the anterior commissure to the tip of the vocal cord process of the arytenoids cartilage, left

T'B = length of the true vocal cord from the anterior commissure to the tip of the vocal cord process of the arytenoids cartilage, right

Epiglottic Cartilage (Refer to figure 4)

BBCC = height of the epiglottic cartilage
DDEE = width of the epiglottic cartilage

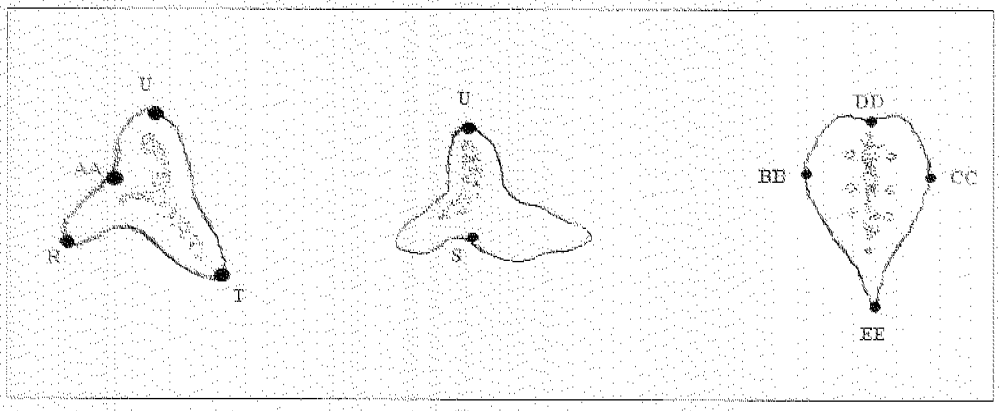


Figure 4: Schematic diagram of the arytenoid and epiglottic cartilage measurements

RESULTS

Table 1 shows the age and sex distribution of the specimens. Table 2 shows the results of the geometric measurements done on the thyroid, cricoid, arytenoid, and epiglottic cartilages respectively. Data are shown as ranges, averages (mean) and standard deviations.

Table 1: Age and sex distribution of specimens

SPECIMEN #	AGE	SEX
1	46	M
2	36	M
3	45	M
4	54	F
5	54	M
6	56	M
7	65	M
8	56	F
9	40	M
10	40	F
11	37	F
12	40	M
13	55	M
14	45	M
15	53	M
16	54	M
17	60	M
18	48	M
19	50	M
20	47	F

Thyroid Cartilage (Figure 2)

The midline length, from the superior thyroid notch to the lower edge of the thyroid ala (AC) ranged from 11.50 to 20.50 mm (mean of 18.05 mm) in the male larynges. In the female larynges, it ranged from 12.00 to 14.30 mm with a mean of 13.10 mm.

There was approximately a 24° gender related difference in the average angle between the thyroid ala (GG) (Table 2), with the larynges of men showing a more acute (smaller) angle (73.73°) than those of women (98.40°).

The anterior commissure (B) was noted to lie above the midpoint of the midline length of the thyroid cartilage in 7 out of 15 male larynges (47%) with a range of 0.25 to1.15 mm. In 8 out of 15 male larynges (53%), the anterior commissure was noted to lie below the midpoint of the midline length of the thyroid cartilage with a range of 0.15

Table 2: Laryngeal framework measurements in present study (range, mean, and standard deviation)

	MALE			FEMALE		
	RANGE (mm)	MEAN (mm)	STD DEV (+ / -) (mm)	RANGE (mm)	MEAN (mm)	STD DEV (+ /-) (mm)
AB	7.80 - 12.40	9.58	1.33	6.00 - 6.70	6.32	0.31
AC	11.50 - 20.50	18.05	1.54	12.00 - 14.30	13.10	0.83
CD	7.30 - 11.80	9.80	1.67	7.00 - 9.00	8.00	0.71
T'B	7.80 - 20.00	13.80	3.89	4.50 - 9.00	7.00	2.52
T"B	7.50 - 18.00	13.47	3.97	4.00 - 9.30	6.70	2.32
E'F'	17.60 - 30.00	25.09	3.26	17.00 - 20.30	18.90	1.36
E"F"	17.20 - 29.50	24.75	3.08	16.00 - 19.50	18.24	1.47
G'H'	19.50 - 29.50	26.00	2.96	16.00 - 22.10	19.22	2.62
G"H"	22.00 - 30.00	25.98	2.41	16.00 - 23.40	19.68	3.16
IJ	23.60 - 33.30	30.06	2.70	19.00 - 27.70	24.22	3.94
DL	5.40 - 8.50	6.66	0.96	4.80 - 7.60	5.80	1.14
LO	18.00 - 26.00	23.05	2.29	13.50 - 23.50	17.36	3.93
DN	28.00 - 32.65	29.95	1.62	20.00 - 24.50	22.92	1.91
FF *	31° - 40°	34.40°	3.89°	35° - 55°	43.60°	9.29°
NO	18.50 - 28.00	21.55	2.19	17.00 - 20.50	18.90	1.43
P'Q'	19.50 - 26.50	22.79	2.12	18.00 - 22.10	20.48	1.88
P"Q"	19.00 - 25.90	22.59	1.80	17.70 - 20.90	19.36	1.50
K'K"	25.00 - 37.20	29.46	3.17	20.00 - 25.75	23.01	2.21
GG *	52° - 95°	73.73°	11.57°	90° -104°	98.40°	5.32°
WX	16.00 - 19.60	17.80	1.28	7.70 - 13.20	10.84	2.51
YZ	14.00 - 32.50	17.45	4.37	8.00 - 12.50	9.78	2.26
AA'T'	6.00 - 10.00	8.10	1.26	6.30 - 7.00	6.70	0.29
AA"T"	6.00 - 11.00	8.49	1.36	6.00 - 9.00	7.50	1.41
U'S'	10.30 - 18.00	13.92	2.45	7.00 - 11.30	9.30	2.12
U"S"	10.00 - 16.50	13.37	2.12	6.60 - 11.20	9.20	2.34
R'T'	8.00 - 15.00	11.22	1.90	10.00 - 11.00	10.54	0.39
R"T"	9.00 - 14.00	11.64	1.73	9.00 - 10.80	9.98	0.73
HH'H'	21.00 - 28.30	24.69	3.31	14.00 - 16.40	15.24	0.96
HH"H"	19.40 - 28.50	23.98	2.71	15.00 - 16.00	15.58	0.44
BBCC	31.00 - 41.00	36.65	2.77	30.00 - 32.00	30.70	0.84
DDEE	16.00 - 26.50	22.02	2.43	19.00 - 20.00	19.38	0.41

* unit is in degrees ; ' = left; " = right

to 3.90 mm. In the female larynges, the anterior commissure was noted to lie above the midpoint of the midline length in 2 out of 5 larynges (40%). The anterior commissure was noted to lie below the midpoint of the midline length in only 1 female larynx (20%) and in the remaining 2 female larynges (40%), the anterior commissure was noted to lie at the midpoint of the midline length (Table 3).

Cricoid Cartilage (Figure 3)

The distance from the upper edge to the lower edge of the cricoid cartilage at the anterior midline (DL) ranged from 5.40 to 8.50 mm (mean 6.66 mm) in the male larynges and 4.80 to 7.60 mm (mean 5.80 mm) for the female larynges. The height of the cricoid cartilage at the posterior midline (NO) ranged from 18.50 to 28.00 mm (mean = 21.55 mm) for the male larynges and for the females, it ranged from 17.00 to 20.50 mm (mean 18.90 mm). The internal anteroposterior (WX) and lateral (YZ) distance ranged from 16.00 to19.60 mm (mean = 17.80 mm) and 16.90 to 32.50 mm (mean = 17.45 mm) respectively in the male larynges. On the other hand, the anteroposterior (WX) and lateral (YZ) distances in the female larynges were noted to be smaller with a range of 7.70 to 13.20 mm (mean = 10.84 mm) and 8.00 to 12.50 mm (mean = 9.78 mm) respectively. The mean angle of the line between the upper and lower edge of cricoid cartilage (FF) is 34.40 degrees (°) in male and 43.60° in females. Examination of the height of the cricoid cartilage at the highest location posteriorly (PQ) revealed higher cricoid lamina on the left (11 out of 20, 55%) compared to the right (6 out of 20, 30%) producing asymmetry of the cartilage.

Arytenoid Cartilage (Figure 4)

The distance between the tip of the vocal cord process and muscular process of the arytenoid cartilage (RT) in males ranged from 8.00 to 15.00 mm (mean = 11.44 mm) whereas that of the arytenoid cartilage in females ranged from 9.00 to 11.00 mm (mean = 10.26 mm). An extraordinary degree of left-right symmetry was also observed in all dimensions of the arytenoid cartilages in both male and female larynges.

Epiglottic Cartilage (Figure 4)

Examination of the epiglottic cartilage was done. The height of the epiglottis in males (BBCC) ranged from 31.00 to 41.00 mm with a mean of 36.65 mm whereas that of the females ranged from 30.00 to 32.00 mm (mean = 30.70 mm). The width of the epiglottic cartilage (DDEE) ranged from 16.00 to 26.50 mm (mean = 22.02 mm) and 19.00 to 20.00 mm (mean = 19.38 mm) for the males and females respectively.

DISCUSSION

It is evident in this study that sexual dimorphism exists in the human larynx. The height, width, and angulation of the thyroid cartilage are larger in males compared to females. The male thyroid cartilage (mean=18.50 mm; range=11.50 to 20.50 mm) is longer than the female (mean=13.10; range=12.00 to 14.30 mm) by approximately 5.00 mm. These findings do not differ from the findings of Isshiki [5] wherein the midline height of the thyroid notch to the lower edge of the thyroid ala was a mean of 18.13 mm in males and mean of 13.25 mm in females. Moreover, the angulation of the thyroid ala in males were more acute than in females by 25 ° (mean: males= 73.73 °; females=98.40 °). The difference in thyroid ala angulation was higher in our study than those reported previously among Caucasians (mean= 10 to 20°) as observed by Sprinzl et al [2]. This would explain the voice pitch and quality difference between the two sexes and possibly among the different racial groups. The dimensions and proportions of the cricoid, arytenoid and epiglottic cartilages also differ between genders (Table 2).

Racial differences also exist with regard to morphometric characteristics of the larynx as have been noted above. Although there is yet no comparative study on morphometric measurements among racial groups, the dimensions of the external laryngeal framework measured in the literature among Caucasians[1,2,6,9] were larger compared with that reported in Asians[4,5,7,8,12]. This was also confirmed in this study (Tables 4,5,6). While differences of the laryngeal apparatus among the age groups were also studied,[10,11] it is not within the realm of this study.

The projection of the anterior commissure is a very important landmark in laryngeal framework surgery. As such, a study by Isshiki[12] offered to map this vital point using selected variable landmarks in the external laryngeal framework. In our study, we have marked this point at midpoint along the anterior midline of the thyroid cartilage or approximately 1.00 mm slightly above or below midpoint in females. In males, the anterior commissure is located approximately 1.00 mm above to 2.00 mm below midpoint in most of the cases. Isshiki [13], on the other hand, stated that the projection of the anterior commissure on the thyroid cartilage is most frequently found slightly 1.00 mm higher

than the midpoint between the thyroid notch and the lower margin of the thyroid cartilage, though the individual variation is great: +/- 2.50 mm in men and +/- 1.50 mm in women. In our study, the individual variation was +/- 1.00 to 2.00 mm in men and +/- 1.00 mm in women which would still fall under Isshiki's reported variation. The determination of the precise location of the anterior commissure is very important in supraglottic laryngectomy and medialization thyroplasty. If a different laryngeal region is inadvertently entered during supraglottic laryngectomy as a result of inadequate identification, the voice of the patient can be placed at great risk post-operatively. Moreover, if this landmark is not identified properly during procedures to medialize the true vocal cords (either through a lateral thyroplasty window or lateral transcutaneous injection of biomaterials) the desired results of the surgery will ultimately not be optimal. With this local study on determining the location of the anterior commissure and the true vocal cords using morphometric analysis, we suggest that external laryngeal framework incision be placed during supraglottic laryngectomy at the junction between the superior one-third and inferior two-thirds of the anterior midline of the thyroid cartilage to avoid true vocal cord iatrogenic trauma (Figure 5). This study also confirms the guidelines for supraglottic laryngectomy proposed by Ogura [14] in which he stated that "the thyroid cartilage is transectioned at a level one third of the distance between the thyroid notch and the inferior border to maintain a level above the true vocal cords. Conversely, the thyroplasty window should be made at an area approximately 1.00 mm above to 2.00 mm below the midpoint along the thyroid cartilage anterior midline (Figure 6). Formation of the cartilage / thyroplasty window according to this guideline will ensure its placement lateral to the vocalis muscle.

Figure 5: Line A' to A (solid line) indicates recommended area of thyrotomy (junction of the superior third and inferior two third of the whole anterior midline thyroid cartilage length) on the thyroid cartilage in supraglottic laryngectomy. Point B is the midpoint where the anterior commissure is usually located.

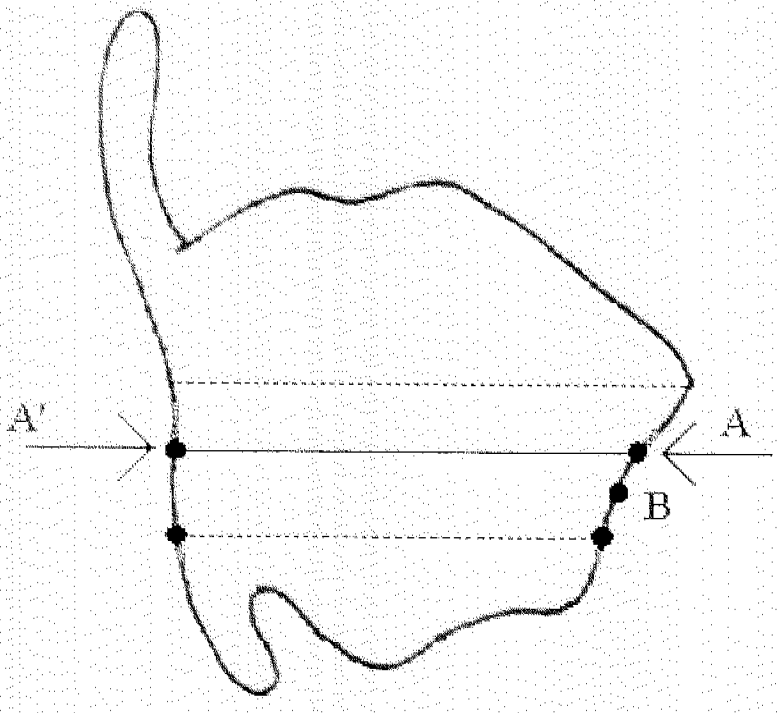
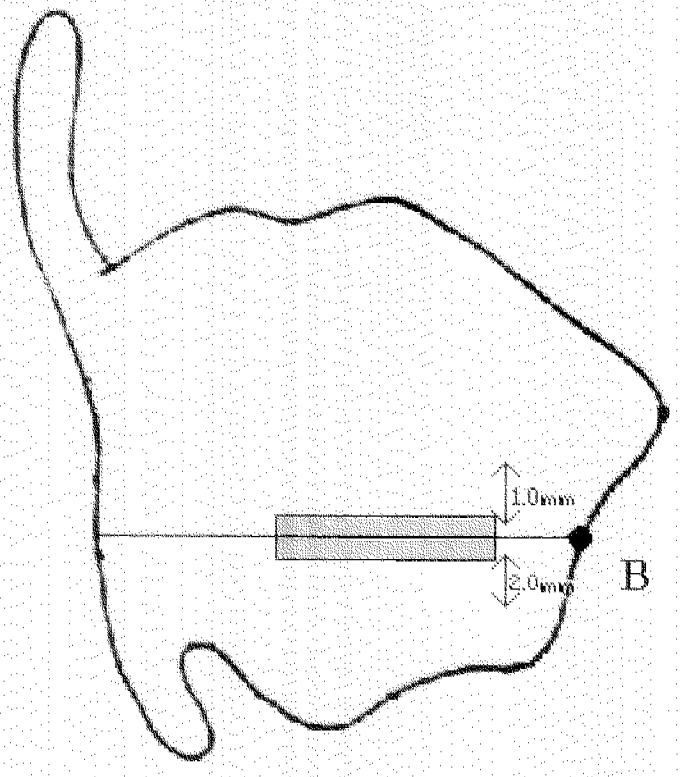


Figure 6. Shaded area indicates recommended location of the thyroplasty window where the lateral projection of the true vocal cord on the thyroid cartilage is usually located. (B= midpoint).



The cricoid cartilage is the only complete cartilaginous ring making up the laryngeal apparatus and the laryngotracheobronchial tree making it prone to iatrogenic injury during intubation. The internal antero-posterior (WX) and lateral distances (YZ) of the cricoid cartilage in males ranged from 16.00 to 19.60 mm and 14.00 to 32.50 respectively. In females, it measured from only 7.70 mm to 13.20 mm and 8.00 to 12.50 mm. This does not include the mucosal lining and does not correct for shrinkage brought about by the preservation process. It has been a general guideline according to Morgan et al[15] that a size 7.00 to7.50 mm (internal diameter) endotracheal tube be used in the female and a size 7.00 to 9.00 mm tube be placed in males. The recommended size in the male may be adequate, but for a small percentage of females, this can be hazardous to the cricoid endolaryngeal mucosa. This may be the cause for cicatrisation or granuloma formation. We therefore recommend that in all patients particularly among females, endotracheal and tracheostomy tubes be carefully selected and airway dimensions adequately assessed prior to tube insertion. Moreover, the angle of line between the upper and lower edge of the cricoid cartilage (FF) is an important landmark in performing laryngeal electromyography. The needle is inserted along this angulation to hit the vocalis muscle attached to the vocal process of the arytenoids. The mean angulation was measured in the cadaver specimens at a range of 31° to 55°. With this in mind, we recommend that an angulation of approximately 30 to 40° be performed when inserting the needle probe in the cricothyroid membrane perpendicular to the line drawn between the anterior and posterior upper edge of the cricoid cartilage (DN) to hit the vocalis muscle.

The mean distance between the tip of the vocal cord process and muscular process of the arytenoid cartilage in males is approximately 11.44 mm whereas that of the female arytenoid cartilage is measured at 10.26 mm on the average. Knowing the distance between the vocal cord process and muscular process of the arytenoids has surgical significance, especially in the adequacy and safety in performing Woodman's operation (arytenoidectomy) [16], arytenoid lateralization, or arytenoidopexy [14]. We recommend that dissection of the arytenoids from the muscular process to the vocal process should not extend more than 15.00 mm as the airway can be entered unjudiciously.

CONCLUSION

Anatomic study of the human larynx was performed and the external laryngeal landmarks were identified to aid the surgeon intraoperatively. Considerable gender and race related differences in many of the geometric measurements of the laryngeal framework were observed in the study. These morphological differences have important clinical and surgical implications. They are critical to the accurate placement of needles and probes in laryngeal electromyography and vocal cord injection medialization procedures, in supraglottic laryngectomy, as well as the precise planning of laryngeal framework surgery. However, owing to the presence of a fair amount of intersubject variability in the data and the small amount of subjects, these data should be interpreted cautiously, and they may not be universally applicable to individual patients in clinical situations.

RECOMMENDATION

Based on the study the authors recommend a larger sample size to be able to establish significant differences when compared to previously done studies. The organ preservation procedure should also be assessed as it may cause significant shrinkage of tissue particularly the soft tissue components and may affect measurements in vivo. Further studies on the laryngeal framework on Filipinos is recommended.

BIBLIOGRAPHY

1. Eckel HE, Sittel S, Zorokowa P, and Jerke A: Dimensions of the laryngeal framework in adults. Surgical Radiology Anst 1994; 16(1): 31-36
2. Sprinzl GM, Eckel HE, Sittel C, Potoschnig C, and Koebke J: Morphometric measurements of the cartilaginous larynx: an anatomic correlate of laryngeal surgery. Head and Neck 1999;21(8): 743-750
3. Meiteles LZ, Lin PT, and Wenk EJ: An anatomic study of the external laryngeal framework with surgical implications. Otolaryngology Head and Neck Surgery 1992; 106(3): 235-240Bailey BJ, Biller HF. Surgery of the Larynx, WB Saunders Company; Philadelphia, 1985, pp 15-18
4. Tayama N, Chan RW, Kaga K, and Titze IR: Geometric characterization of the laryngeal cartilage framework for the purpose of biomechanical modeling. Annals of Otology, Rhinology and Laryngology 2001; 110(12): 1154-1161
5. Tayama N, Chan RW, Kaga K, Titze IR: Functional definitions of the vocal fold geometry for laryngeal biomechanical modeling. Annals of Otology, Rhinology and Laryngology 2002 January:111(1):83-92
6. Maue WM, Dickson DR: Cartilages and ligaments of the adult human larynx. Archives of Otolaryngology 1971; 94 : 432-9
7. Hirano M, Yukizane K, Kurita S, and Hibi S: Assymetry of the laryngeal framework: a morphologic study of cadaver larynges. Annals of Otology, Rhinology, and Laryngology 1989; 98(2): 135-140
8. Isshiki N. Phonatory surgery: external laryngeal surgery not requiring entry into the vocal tract. In: Gould WJ, Lawrence VL, eds. Surgical care of voice disorders. New York: Springer-Verlag, 1984:59-109.
9. Bailey BJ, Biller HF. Surgery of the larynx, WB Saunders Company; Philadelphia 1985;15-18
10. Eckel HE, Sprinzl GM, Sittel C, Koebke J, Damn M, Stennert E: Anatomy of the glottis and subglottis in the pediatric larynx. HNO 2000 July;48(7):501-7
11. Eckel HE, Koebke J, Sittel C, Sprinzl GM, Pototsching C, Stennert E: Morphology of the human larynx during the first five years of life studied on whole organ serial sections. Annals of Otology, Rhinology and Laryngology 1999 March;108(3):232-8

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NON-INVASIVE MUCORMYCOSIS: A CASE SERIES *

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ABSTRACT

OBJECTIVES: To document four cases of histologically proven *Mucor* colonization of the paranasal sinus without mucosal invasion and to report our treatment of this condition.
DESIGN: Case series
SETTING: Tertiary hospitals
PATIENTS: Four patients
RESULTS: We report four patients, one diabetic and three non- immunocompromised, with chronic rhinosinusitis in whom *Mucor* organisms were histologically identified within the sinus but not in the mucosa. This represents a colonization of the sinus; and in the classification of fungal sinusitis, it falls under the classification of fungus ball or mycetoma, which is a non-invasive type. All patients were successfully treated with endoscopic sinus surgery (ESS) with wide middle meatal antrostomy. No antifungal agent was administered. After a year of regular follow-up, examination revealed no recurrence.

Conclusion: Four cases of non-invasive Mucormycosis were identified and successfully treated with endoscopic sinus surgery with wide middle meatal antrostomy. We conclude that ESS is a treatment option for this condition.

INTRODUCTION

Mucormycosis of the paranasal sinuses and nasal cavity, as we know it, is a rare, invasive mycotic infection with a rapidly progressive clinical course and a fatal outcome[1]. The infection often begins in the nasal mucosa and extends to the adjacent paranasal sinuses. It is caused by saprophytic fungi of the class Zygomycetes and the order Mucorales. Patients who harbor this disease are usually immunocompromised or debilitated as a consequence of systemic disease such as diabetis mellitus, leukemia, lymphoma, cancer, or burns[1-4, 6, 7]. The classical finding on physical examination is the black necrosis of the septum or turbinates on intranasal examination. Accepted treatment is immediate surgical debridement of all involved tissue plus Amphotericin B, a systemic antifungal agent[1,2,3,4].

We are presenting four cases of chronic sinusitis in whom Mucor organisms were histologically identified in the paranasal sinuses *without mucosal invasion.* These four uncommon and unusual cases defy the definition of mucormycosis. Hence, there is no accepted treatment protocol for such an entity.

CASE REPORTS

Case 1. A 65-year-old woman presented with a chronic cough and post- nasal drip. She gave a history of diabetes that was controlled with oral hypoglycemic agents. There was no fever and change in sensorium, no periorbital swelling, nor proptosis and ophthalmoplegia. Endoscopic examination revealed mucopurulent discharge along the nasopharynx with polypoid masses on the right middle meatus (Fig. 1). No necrotic tissue nor black eschar found within the nasal cavity. She was diagnosed with chronic rhinosinusitis and given antibiotics for 1 month. Computerized tomography (CT) done showed right unilateral complete maxillary sinus opacification with microcalcification (Fig.2). Functional endoscopic sinus surgery was done with wide middle meatal antrostomy. Intraoperative findings revealed yellowish-tinged, black, cheesy material occupying the right maxillary (Fig.3). Endoscopic removal of the fungus ball was done.. Histopathology revealed a broad nonseptate hyphae with 90 degree angled branching (Fig.4B) with no evidence of mucosal invasion and angioinvasion. This was signed out

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as " Mucormycosis." Post-operatively, the patient was given intravenous amphotericin B for a total of 2.5 grams. However, she developed acute renal failure. Regular follow-up for 2 years failed to demonstrate a recurrence.

Case 2. A 72-year-old non-diabetic male was seen due to chronic cough and postnasal drip. Nasal endoscopy showed mucopurulent secretions (Fig.5) originating from the right nasal cavity and is seen up to the nasopharynx. CT showed right, unilateral, complete maxillary sinus opacification (Fig.6). Endoscopic sinus surgery with wide middle meatal antrostomy was done. Noted intraoperatively was soft, black cheesy material in the maxillary antrum (Fig.7). The sinus was eventually cleaned out. Histopathology revealed broad non-septate hyphae with 90 degree branching. No mucosal invasion noted. Final reading was "Mucormycosis." Post-operatively, patient was managed further with endoscopic inspection and saline irrigation. No antifungal agent was given. No recurrence noted after a year of regular follow-up examination.

Case 3. A 68-year-old, non-diabetic, male referred for postnasal drip, chronic cough and nasal congestion with CT findings of left unilateral, homogenous, maxillary sinus opacity. He was diagnosed with chronic rhinosinusitis and had an inferior meatal antrostomy on the left by another ENT doctor a year ago. Endoscopic sinus surgery done showed black, soft, friable, clay-like material (Fig.8). Broad, non-septated hyphae were seen on microscopy with no note of mucosal or soft tissue invasion. Final histopathology reading was "Mucormycosis." No antifungal agent given and only saline irrigation was done on follow-up. No recurrence noted after 1 year.

Case 4. A 70-year-old non-diabetic male presented with post nasal drip, chronic cough and nasal discharge and diagnosed with chronic rhinosinusitis. CT showed right, unilateral, complete maxillary sinus opacification (Fig.9). ESS with wide meatal antrostomy was done. Black, cheesy materials noted intraoperatively (Fig.10). Histopathology result was Mucormycosis. No antifungal agent was given.

DISCUSSION

Mucormycosis of the nasal cavity and paranasal sinuses is an invasive fungal infection of the class Zygomycetes (also called Phycomycetes) and the order Mucorales. The family Mucoraceae includes the most commonly found genera in mucormycosis, including the most common, Mucor, Rhizopus, and Absidia[5].

The Mucorales are ubiquitous, and commonly found in high-organic matter and soil. They invade the sinuses, orbital tissue, central nervous system, lungs, gastrointestinal tract, cutaneous and subcutaneous tissues. Rhinocerebral (cephalic) mucormycosis begins in the nasal passages or paranasal sinuses and may extend into the intracranial cavity. It is the most common type and usually develops in immunocompromised patients[5]. Clinical findings of facial cellulitis, acute sinusitis, bloody or purulent nasal discharge, and black necrotic lesions of the nasal mucosa, turbinates, and palate are usually rapid in onset and progression. Spread to the orbit is heralded by mild proptosis, periorbital edema, lacrimation, blurred vision and ophthalmoplegia, and paresis of cranial nerves III, IV, and VI. With involvement of the orbital vessels, a fixed and dilated pupil with blindness may occur. An altered sensorium and other cranial nerve involvement signal intracranial extension.

The pathophysiology of the disease is brought about by the invasion of blood vessel walls and the plugging of small vessels by fungal mycelia, which lead to extensive endothelial damage and vascular thrombosis followed by tissue necrosis and suppuration. This invasive character is enhanced by ketoacidosis in diabetics. Ketoacidosis is known to impair immunity by causing abnormal polymorphonuclear (PMN) chemotaxis and decreased PMN phagocytic activity. Furthermore, the hyperglycemia and acidosis provide an excellent media for the fungus to grow.

Biopsy of involved areas provides the best diagnostic yield. Direct microscopic examination with potassium hydroxide or after staining with Hematoxylin and eosin or Gomori's methenamine silver nitrate typically reveals broad non-septate irregularly and widely branching hyphae. Culture on Sabouraud-dextrose agar yields a rapidly growing fungus with grayish white mycelia.

Aggressive surgical debridement and administration of Amphotericin B have been the classic treatment of rhinocerebral mucormycosis[2,3,4,6]. Control of underlying systemic disease is an important adjunctive treatment. Surgery is usually extensive, requiring debridement of all infarcted, necrotic tissues. All nonviable tissues are excised because lack of blood supply to these tissues has eliminated the ability of antifungal chemotherapy to reach the disease process. Traditionally, various external and transantral procedures such as external ethmoidectomy and Caldwell-Luc's procedure have been used to effect debridement, depending on the extent of invasion.

All four cases reported vary from the usual invasive cephalic mucormycosis. Our cases have no evidence of mucosal and bony invasion but represents simple mucor colonization. Moreover, three patients have no underlying systemic disease. Literature review dealing with this type of entity is scanty. To our knowledge, there has been only one report of a mucor colonization case series[7]. In the classification of fungal sinusitis, our cases belong to fungus ball or mycetoma, which is under the non-invasive type. The diagnostic criteria set for the diagnosis of sinus mycetoma as proposed by deShazo[8] include, 1) radiologic evidence of sinus opacification with or without flocculent calcifications, 2) mucopurulent cheesy or clay-like materials within a sinus, 3) a matted, dense conglomeration of hyphae separate from but adjacent to sinus respiratory mucosa 4) a chronic inflammatory response of variable intensity in mucosa adjacent to fungal elements (allergic mucin is absent) 5) no histologic evidence of fungal invasion of mucosa, associated blood vessels or underlying bone visualized microscopically on Gomori methenamine silver or other special stains for fungus. Our 4 cases fulfilled the above criteria for fungus ball.

The demonstration of Mucor in the sinuses does not necessitate aggressive surgical resection in the absence of deep tissue invasion. Henderson reported 4 patients successfully treated with local debridement and drainage procedure[7]. For colonization by Mucor confined to the sinus cavity and not accompanied by mucosal invasion, symptoms of systemic toxicity, or cranial nerve or intracranial abnormalities, endoscopic sinus surgery with wide meatal antrostomy is recommended. Antifungal agent is not necessary. The patient is advised to have regular follow-up examinations.

CONCLUSION

We identified four cases of non-invasive Mucormycosis in the paranasal Sinuses, one with controlled diabetis mellitus and three immunocompetent.

Endoscopic sinus surgery (ESS) without systemic antifungal agent were used to treat all the 4 patients. All were alive and free of the disease after a year of regular follow-up examinations. Based on this experience, we conclude that ESS with middle meatal antrostomy is an effective alternative treatment of Mucor colonization of the sinuses in the absence of tissue invasion.

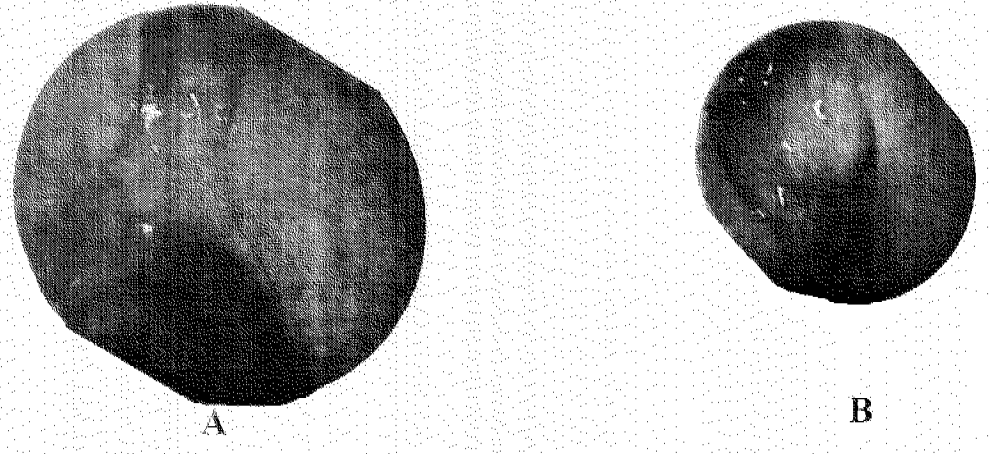


FIGURE 1
(Case 1) Endoscopic examination showing mucopurulent discharge (A) and polypoid mass (B)

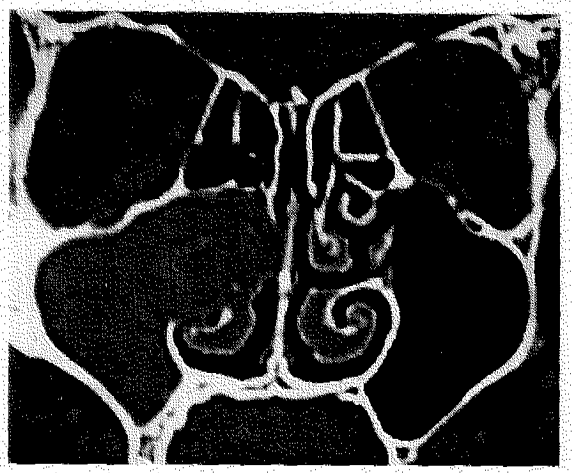
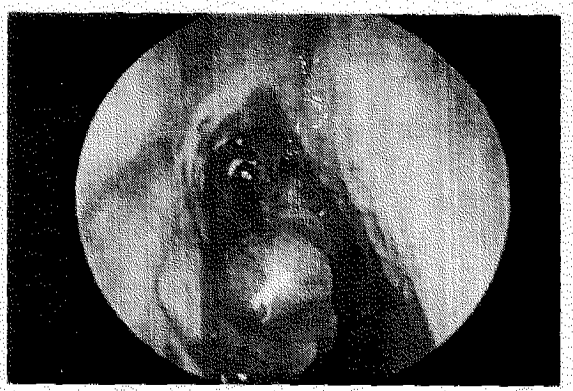


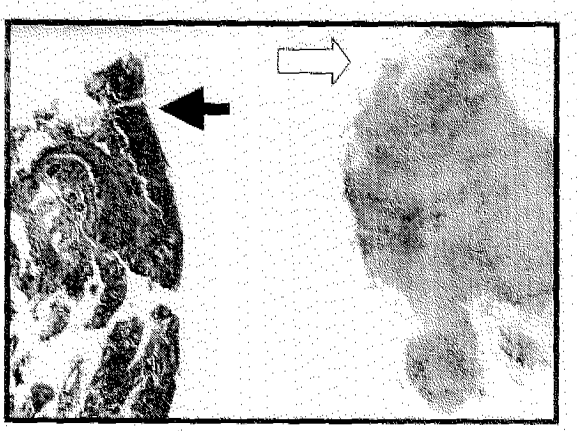
Fig. 2. CT scan of the PNS, coronal view, shows maxillary sinus opacification with microcalcification, right.



A

B

Fig. 3. Intra-operative findings of yellow to black, cheesy material occupying the right maxillary sinus. (A & B).



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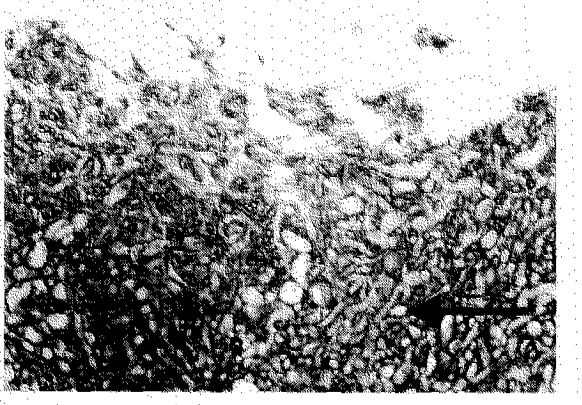

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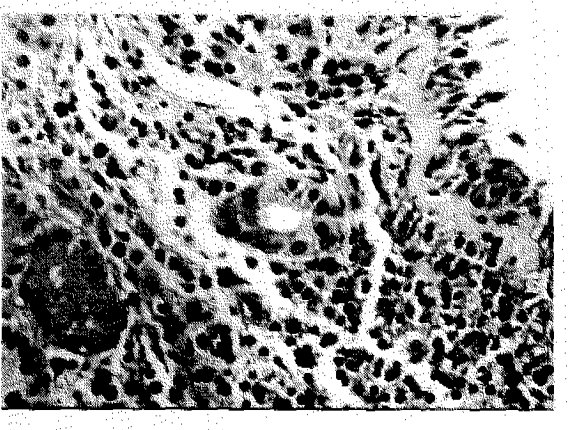


C

Fig. 4. Histologic section of the specimen (Case 1) showing the hyphal colony (white arrow) and adjacent respiratory epithelium (black arrow) (A). Higher magnification of the hyphal colony shows non-septated, branching hyphae (B). Inflammatory infiltrates in the mucosa with no fungal invasion (C).

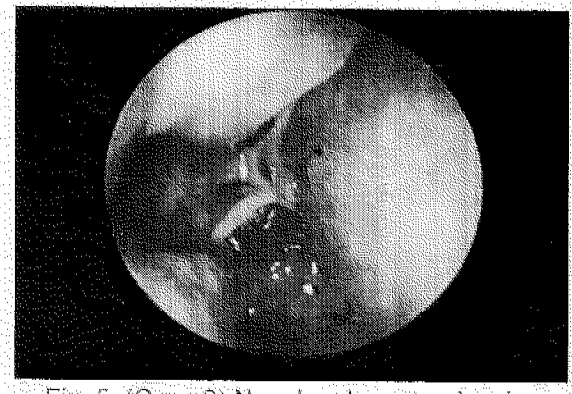


Fig. 5. (Case 2) Nasal endoscopy showing mucopurulent discharge.

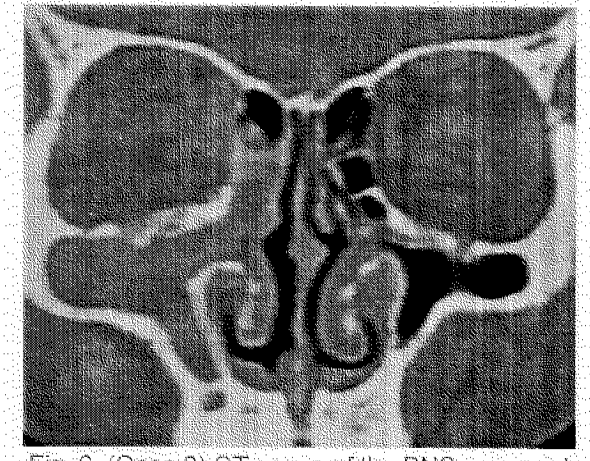
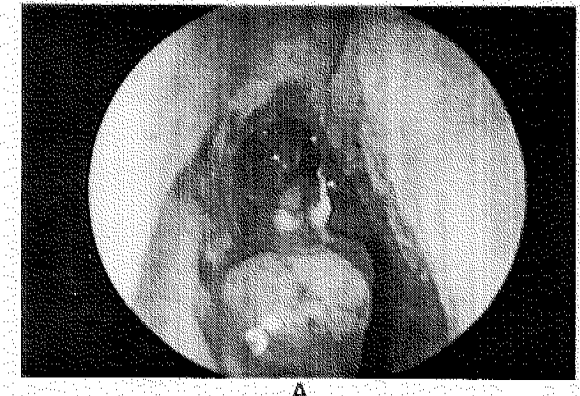
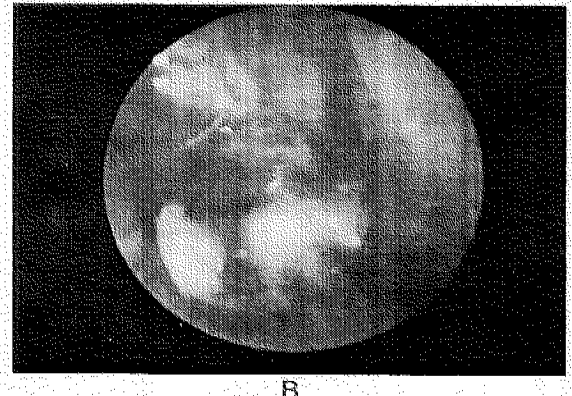


Fig. 6. (Case 2) CT scans of the PNS – coronal view – shows right maxillary sinus opacification.



A



B

Fig.7 Endoscopic sinus surgery shows soft, black, cheesy materials (A & B)

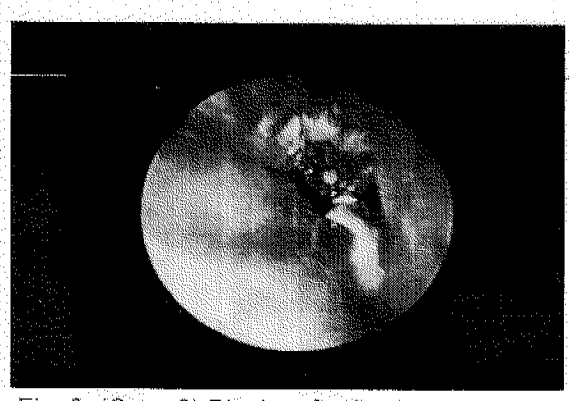


Fig. 8. (Case 3) Black,soft, clay-like materials noted on ESS

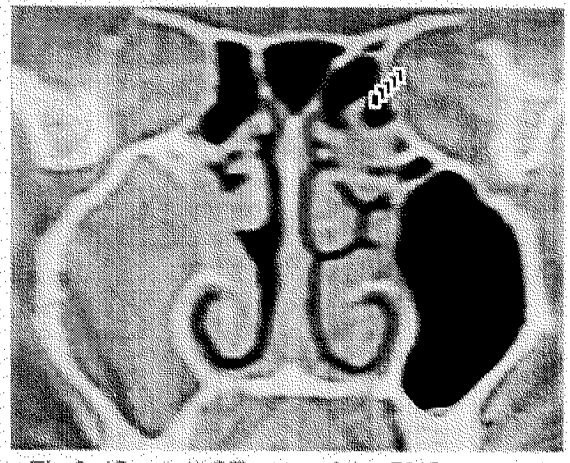
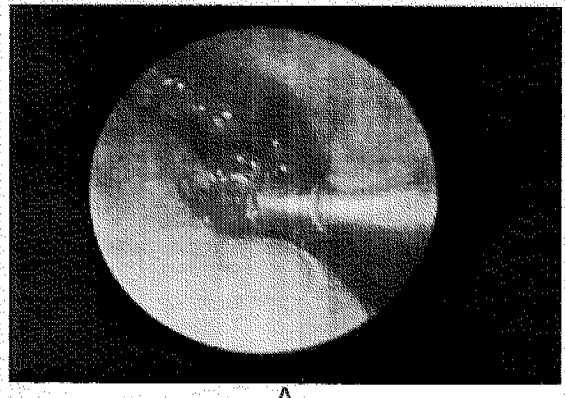
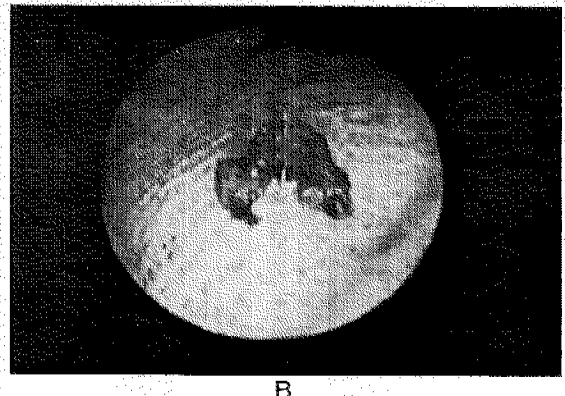


Fig.9. (Case 4) CT scan of the PNS, coronal view, shows right maxillary sinus opacification



A



B

Fig. 10. (Case 4) Black, cheesy materials noted intra-operatively (A), on closer view (B).

BIBLIOGRAPHY

1 Blitzer A, Lawson W. Patient survival factors in Paranasal Sinuses Mucormycosis.Laryngoscope 90:635-648. 1980

2 Ochi J, Harris J, Feldman. Rhinocerebral Mucormycosis: Result of Aggressive Surgical Debridement and Amphotericin B. Laryngoscope 98:1339-1342. 1988

3 Anand V, Alemar G. Intracranial Complications of Mucormycosis: An Experimental Model and Clinical Review. Laryngoscope 102:656-662. 1992

4 Donald Paul. Fungal infection of Sinuses. 271-285

5 Ciesla M, Kammeyer P, et al. Identification of the Asexual State of Rhizopus species on Histologic Tissue Sections in a Patient with Rhinocerebral Mucormycosis. Arch Pathol Lab Med. 125:883-887. 2000

6 Rong-San J, Chen-Yi H. Endoscopic Sinus Surgery for Rhinocerebral Mucormycosis; Am J Rhinology; Vol 13; 105-109; 1999.

7 Henderson L, Robbins T, Weitzner S. Benign Mucor Colonization (Fungus Ball) Associated with Chronic Sinusitis. Southern Medical Journal. 81:846-850. 1988

8 DeShazo R, O'Brien M, et al. Criteria for the Diagnosis of Sinus Mycetoma. J Allergy Clin Immun 99:475-485. 1997

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ANATOMIC DIMENSIONS OF THE SCAPULAR SPINE AMONG FILIPINOS BASED ON CADAVER DISSECTION*

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ABSTRACT

Objective
General: This study aims to measure the dimensions of the spine of the scapula in Filipino cadavers.
Specific: To measure the length of the spine of the scapula, with and without the acromion process; to measure the greatest height of the scapular spine, and; to measure the thickness of the scapular spine.
Design: Descriptive Study (Anatomic Dissection)
Setting: Laboratory of Human Anatomy, Department of Anatomy, College of Medicine, Pamantasan ng Lungsod ng Maynila
Subjects: Cadavers (10 males and 5 females)
Results: The male spines of scapula have a mean length, without the acromion, of 7.2 cm and 12.1 cm when the acromion was included. The greatest height has a mean of 3.3 cm and an average thickness of 1.0 cm. The female spines of scapula have a mean length, without the acromion, of 6.2 cm and 10.5 cm when the acromion was included. The greatest height has a mean of 2.8 cm and an average thickness of 0.9 cm.
Conclusion: The mean dimensions of the Filipino scapular spine, as measured by cadaver dissection consisting of 10 males and 5 females, are as follows: length, without the acromion, of 6.9 cm and 11.5 cm when the acromion was included; greatest height of 3.2 cm and a thickness of 1.0 cm. The dimensions of the spine of the scapula in Filipino cadavers presented in the study can serve as a guide in the use of the trapezius osteomyocutaneous flap with the scapular spine for mandibular defects.

INTRODUCTION

Reconstructive techniques for surgical defects in the head and neck have made significant advancements in the past decades. Collective surgical experience has shown that the goal of margin-free tumor excision and primary one-stage reconstruction is feasible and successful. Large lesions of the lower face and neck can now be resected and reconstructed to the patient and physician's satisfaction (1).

As more radical surgeries are performed for head and neck tumors, an increasing variety of flaps have been developed for reconstruction of surgical defects. The more common myocutaneous flaps for large defects are the pectoralis major, trapezius and latissimus dorsi flaps. For large bony defects, such as those secondary to mandibulectomy, osteomyocutaneous flaps, which include bone from the scapula, sternum, ribs, or iliac crest are utilized. Other alternatives for reconstructing mandibular defects are plating techniques and microvascular free flaps.

Reconstruction of the mandible following ablative surgery is a difficult problem. Traditional nonvascularized bone-grafting techniques often fail because of irradiated or bacterial contaminated tissue recipient beds, often in patients with poor nutritional status. More recently, free flaps incorporating bone have been used, but they suffer the disadvantages of requiring prolonged operative time, a large number of operative personnel, and microvascular techniques. Postoperatively, when compared with island flaps, the anastomotic patency rate of free tissue transfers decreases with exposure to large salivary fistulas and oral flora contamination (2).

In 1976, Demergasso was the first surgeon to describe the trapezius myocutaneous flap for reconstructive surgery. He designed a transverse flap over the acromioclavicular angle,

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SECOND STAGE VOICE RECONSTRUCTION AMONG POST LARYNGECTOMY PATIENTS*

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ABSTRACT

OBJECTIVE: To present a surgical technique on second stage voice reconstruction using the Tracheoesophageal (TEF) Technique in five post-laryngectomy patients.
DESIGN: Surgical Innovation
SETTING: Tertiary Hospital
PATIENTS: Five post-laryngectomy patients who underwent second stage voice reconstruction using the Tracheoesophageal fistula (TEF) technique.
RESULTS: Four out of the five cases were classified as S3 while one case was classified as S2. Four out of the five cases were G1 while one case was classified as G3 to whom a Blohm-Singer prosthesis was inserted. The fifth case was able to produce voice 10 weeks after the procedure, right after being inserted with the prosthesis.
CONCLUSION: The secondary voice reconstruction is a good option for post-laryngectomy patients who may or may not require head and neck reconstruction. Wound dehiscence may be a risk during concomitant head and neck reconstruction.

INTRODUCTION

Laryngeal carcinoma has been one of the increasing problems encountered by the head and neck surgeon. Although it is not as common as cancer of other organ systems, patients with laryngeal cancer suffer the devastating consequences of the disease and its outcome.

Surgical resection of laryngeal tumor has been one of the mainstays in the management of laryngeal cancer. Prognosis is good once diagnosed early and managed accordingly [1].

However, surgery imparts serious consequences which permanently disables the patient. The presence of a permanent tracheostoma limits the activity of the patient not only in terms of social interaction but also the recreation facets of his lifestyle such as swimming and playing active sports.

Loss of voice from removal of the larynx is believed to be one of the most crucial problem among laryngectomees. Almost all patients who undergo surgical resection of the larynx become depressed and tend to shy away from friends and family. They also become frustrated in communicating with their partners and loved ones.

The surgeon has the responsibility of eradicating and controlling spread of tumor. However, he should also be responsible for the recovery and over all well-being of the patient.

With the advent of new techniques in the management of laryngeal cancer, one of the options that can be given to the patient is voice restoration. The skilled surgeon can add another dimension to the completion of the rehabilitation of the laryngectomized patient.

Voice restoration procedures have been developed since the middle of the last century. Authors such as Briani (1952), Conley (1958), Asai (1960), Calcaterra (1971), Arslan & Serafini (1972), Staffierri (1972), Iwai & Koike (1975) have all developed different techniques for voice restoration with varying results [3].

Voice restoration technique by Amatsu was pioneered in the Philippines in the 1980's by Jamir, et.al. However, aspiration through the neoglottis was a consistent problem noted among the patients prompting the other surgeons to abandon the technique [2].

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THE USE OF COTTON IN PATCH TEST*

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ABSTRACT

Cotton is used as a patch material over the traditional cigarette paper mainly because it provides easier handling/ manipulation and at the same time causes less discomfort to patients. The efficacy of cotton patch was tested in sixteen subjects with perforated tympanic membrane. Pre-operative audiogram, patch test audiogram, and post tympanoplasty audiogram were presented and analyzed. It was noted that the use of cotton as patch material can be applied with ease and it occluded the whole rim of the perforation leading to improved hearing threshold as seen in the audiogram. Its values were tested against post tympanoplasty audiogram and were found to almost simulate the hearing threshold of the latter.

INTRODUCTION

In the early days of tympanoplasty, it was a common practice to patch the perforation of the tympanic membrane with cigarette paper to demonstrate the improvement in hearing that could be achieved by permanent closure. The paper disc, moistened on one side with a solution of 1 percent phenol in glycerine to make it adhere, is introduced with a small alligator-type forceps and teased into place with a tiny blunt ear hook.[1] This procedure requires skill of the surgeon and constant practice is of importance to entail the success of the maneuver. One disadvantage observed is that the placement of paper into the perforation may cause discomfort to the patient. Also, placement of paper maybe difficult especially in patients with total perforation of the tympanic membrane. With the disadvantages mentioned, an attempt to find an alternative material was done that would facilitate easier application of the patch. The attempt to use cotton as a substitute for paper achieved the same purpose and gave the same expected results.

DISCUSSION

In this study, we opted to use cotton instead of paper to patch the perforation because of its softness thus easier handling as noted in its ability to occlude the whole perforation. (See figure 3 & 4). Application of cotton was less time consuming too.

Baseline audiogram was obtained in sixteen subjects with perforated tympanic membrane. The patients were surgically prepared prior to the placement of cotton patch. Placement of cotton patch was performed under microscopic or otoscopic guidance and audiogram was repeated. The baseline audiogram, cotton patch, and post tympanoplasty audiogram were then compared. It was noted that there was a marked hearing improvement with the cotton patch. A similar hearing improvement was also noted with tympanoplasty. (See tables 1- 6)

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EFFECTS OF CHITOSAN ON THE HEALING OF TYMPANIC MEMBRANE PERFORATION IN RABBITS*

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NORBERTO V. MARTINEZ, MD***
GLORIA C. BERNAS, PhD****

ABSTRACT

OBJECTIVES: To determine the effectiveness of chitosan in the closure of tympanic membrane perforations in rabbits and to describe the histologic changes in tympanic membranes applied with chitosan.
DESIGN: Animal Experiment, Independent t-test 1 tailed, chi square.
SUBJECTS: 18 healthy adult rabbits.
OUTCOME MEASURES: Proportions of rabbit tympanic membranes that closed 2 weeks after perforation and thickness of tympanic membranes.
RESULTS: There were no differences in proportions of tympanic membrane closure among chitosan treated and untreated rabbits after two weeks. Chitosan treated tympanic membranes had significant epithelial and fibrous layer formation.
CONCLUSION: Chitosan application may have no significance effect on the closure of tympanic membrane perforations. However, tympanic membranes of the chitosan treated group showed an increase in the thickness of the epithelial and fibrous layers.

INTRODUCTION

The tympanic membrane is found in the end of the osseous external auditory meatus and forms the lateral wall of the tympanic cavity. It is composed of three layers, a lateral epidermis continuous with the skin of the external auditory meatus, a middle layer or lamina propria and middle mucosal layer continuous with the mucosa of the tympanic cavity[2].

Tympanic membrane perforation may be of traumatic origin or ifection. Trauma that leads to a permanent perforation of the tympanic membrane may be the result of sudden or explosive alterations in air pressure in the external meatus, or of hot water, slag, or acid entering the meatus.

Trauma may follow a lightning stroke or skull fracture. Perforations heal by reepithelialization, and fibrous layer proliferation. Closure of the tympanic membrane perforations restores the vibratory area of the membrane and affords round window protection. Closure also lessens the susceptibility of the middle ear mucosa for infection via the eustachian tube and external auditory meatus[8]. These problems led to the study of several grafts for possible use in the closure of tympanic membrane perforation. Some materials used today are fascial grafts, perichondrium, skin and fat.

Chitosan is a deacetylated chitin of animal cellulose, which is the major biochemical component of the shells of crustaceans. It is an insoluble polysaccharide that gives the shell its flexible toughness. Chitosan belongs to a class of biopolymer called hydrocolloids. It is polycationic positively charged at biologic pH values. Another advantage of chitosan is its anti microbial activity[1]. These properties therefore, make chitosan a very attractive alternative as a wound coverage material. Chitosan was also found to form ionic complexes with glycosaminoglycans,

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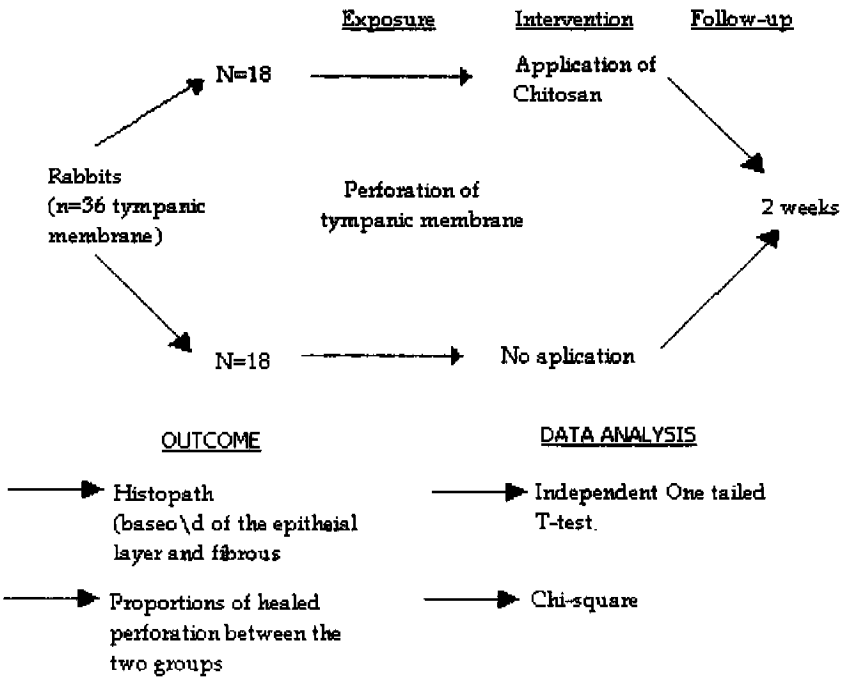

thereby acting as scafolds in tissue engineering.

Whether chitosan exert similar effects on the healing of tympanic membrane perforations have not yet been determined.

OBJECTIVES

1. To determine effectiveness of chitosan in the closure of tympanic membrane perforation in rabbits.
2. To describe the histologic changes in tympanic membranes applied with chitosan.

METHODOLOGY

I. Study Design

II. Conduct of study

Preparation of chitosan biofilm:

Shells of Penaeus monodon, commonly known as giant tiger prawn, were cleaned by washing and scraping under running water. The washed shells were dried in a vacuum oven at 50°C. The clean, dried shells were ground and soaked for three days in 10% oxygen - free sodium hydroxide solution at room temperature. The alkaline solution was changed everyday. The deproteinized particles were then washed with water until the filtrate was colorless, and then 95% ethanol was added. The particles were further titrated with acetone, 95% ethanol, and ether in small portions and filtered. The nearly colorless particles were then dried under reduced pressure, and later put into 37% hydrochloric acid at -20°C. The mixture was kept for 4 hours at this temperature. The swollen particles were separated by centrifugation t 0°C until the washings were acid free. After washing with several changes of 95% ethanol and ether in that order, and dried under reduced pressure; the acid treatment, washings, and drying were repeated. Further purification was accomplished by dissolving the isolated chitin in cold 40% hydrochloric acid and precipitated by dilution of the solution with cold water.

The purified chitin was treated with 40% aqueous sodium hydroxide solution at 115°C for six hours, with exclusion of air. The cooled mixture was filtered and washed with water until the washings were neutral to phenolphthalein, the crude chitosan was purified as follows. It was dispersed in 10% aqueous acetic acid. The mixture was centrifuged after 24 hours, and 40% aqueous sodium hydroxide solution was added dropwise to clear supernatant. The white flocculent precipitate formed at pH 7 was recoverd by centrifugation and then washed repeatedly with water, ethanol and ether and then dried, obtaining 82% deacetylated product. Further deacetylation of the product to 97% was achieved by the treatment of the dried product again, with 40% sodium hydroxide heated for 90°C for 1 hour, centrifuged and washed as before. A 90% yield

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MANDIBULAR SWING AND LATERAL PLATE PTERYGOIDECTOMY AS AN ALTERNATIVE APPROACH TO THE MANAGEMENT OF NASOPHARYNGEAL CARCINOMA*

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ABSTRACT

The nasopharynx is one of the most difficult areas to reach and manipulate surgically. Surgical access to the area is usually associated with morbidities and incomplete tumor control because of the limitation of exposure. It is for this reason that a combined neck dissection, mandibular swing and lateral pterygoid plate excision was conceived. This approach facilitates operating on a single field, provides exposure of all important neurovascular structures for surgical safety and adequate resection of localized nasopharygeal tumors, including neck metastasis. This approach seeks to augment our surgical armamentarium and does not aim to replace present protocols of NPCA management.

Objective: To surgically access the nasopharynx with less morbidity and better exposure.
Specific objective: To control the primary nasopharyngeal carcinoma and its neck node metastasis using this surgical approach, with or without chemotherapy or radiotherapy or without.
Study Design: Surgical innovation, prospective study
Size of Samples: Series of nine (9)
Study setting: A tertiary hospital
Inclusion criteria:
1. No distant, intracranial, internal carotid or cavernous sinus invasion
2. Medical clearance for surgery
3. At least three months post radiotherapy course
4. Good nutritional status preferred

Limitation of Study and technique:
1. Small sample size and lack of long term follow-up. This surgical innovation shall formally be subjected to a prospective study in regards to prognostication of treated patients.
2. Surgical approach not feasible for intracranial and cavernous sinus tumor extent.

INTRODUCTION

Cutting edge technology has enhanced prognoses and diminished unpleasant and lengthy hospital stays in the treatment of skull base disorders. In the past, such tumors presented difficult treatment challenges. However, in recent years, medical breakthroughs have continually improved the surgeon's ability to access and successfully treat these lesions and associated cranial nerve disorders. The evolution of an interdisciplinary, team approach to surgery and treatment has been an important development.

Considerable advances made in the areas of diagnostic imaging, interventional radiology, surgical approaches and techniques, and electrophysiologic monitoring also have fostered successful treatment of skull base tumors and disorders. This study shows surgical access to the nasopharynx, parapharyngeal space and skull base through a mandibular swing and lateral plate pterygoidectomy technique in treating nasopharyngeal carcinoma.

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DESCRIPTION

Pre-op details:

1. complete history & physical examination including neurologic (cranial nerves) Findings on physical examination that reflect dysfunction of specific CNs include decreased elevation of the ipsilateral palate (ie, deviation of the uvula to the nonaffected side-CN X), decreased mobility/strength of the tongue (ie, deviation to the involved side upon protrusion- CN XII), decreased supraglottic sensation, pooling of secretions in the hypopharynx, ipsilateral vocal cord paralysis (CN X), and atrophy and paralysis of the sternocleidomastoid and trapezius muscles (CN XI).
2. A detailed assessment of the extent of tumor involvement
3. Transnasal biopsy and FNAB of neck nodes
4. Pre-op imaging : CT of the skull base & pharynx
5. Metastatic workup must be performed to exclude distant metastases
6. Planning and counseling with the family & the patient pre-op & post-op about the possibility of loss of cranial nerve function and the effects on speech and swallowing.
7. discussed with the patient the possibility of tracheostomy

METHODOLOGY
SURGICAL TECHNIQUE

Pre-operative preparation:

Anticipate the need for blood replacement. Administer wide-spectrum perioperative antibiotic prophylaxis with good penetration of the blood-brain barrier before the surgery, and continue it for 48 hours postoperatively.

Properly secure the endotracheal or tracheostomy tube. Pass and secure a nasogastric tube and Foley catheter. Position the head of the patient on the opposite the side of the lesion and place a shoulder roll on the side of the operation. Shave the scalp, following the planned incision line and infiltrate the incision line with a solution of lidocaine and epinephrine (1:100,000-1:400,000).

Operative Details:

Radical Neck Dissection is routinely done to clean the neck of metastasis. Upon reaching the mandible, the tendon of the medial pterygoid muscle is severed and part of the masseter cleared for mandibular osteototomy. Cutting the mandible in a stepwise manner behind the last molar is preferable to facilitate accurate re-approximation later.

The digastric tendon that joins the two parts is cut to medially widen exposure (tendon to be re-approximated later). The hypoglossal nerve is an easily identified nerve as it comes out from its foramen. Abduction of the ramus is done while the medial pterygoid muscle is medialized exposing the lateral pharyngeal space. (This maneuver may cause traction to the facial nerve so caution is observed). Branches of CN V like the lingual nerve and inferior alveolar nerve and their vascular counterparts from the internal maxillary artery are exposed. The blood vessels are ligated or cauterized while the nerves are retracted aside. Poke a finger inside and identify the lateral pterygoid plate.

Dissect carefully and identify the middle meningeal artery medial to the spine of the sphenoid. In some patients, chiseling of a protruding sphenoid spine is done. The middle meningeal artery is also ligated or cauterized. The pterygoid plate is chiseled out using a one-cm wide blade. At the lateral wall of the nasopharynx, a window is made. Traversing the buccopharyngeal fascia, the superior constrictor muscle and the nasopharyngeal mucosa. Using a base of skull retractor with blades measuring 2.5 x 5 cm made for this purpose, the nasopharynx is clearly visualized for further surgery.

During excision of the primary, which is commonly in the fossa of Rossenmuller, the origin of the levator and tensor veli palatini is taken out together with the tumor. The Eustachian tube opening is not closed but myringotomy with VT insertion in the ipsilateral ear is necessary. Sometimes, encapsulated submucosal primaries are removed without sacrifice of adjacent structures. As long as nasopharyngeal closure is ably done to prevent salivary leak into the wound, skin grafting is not routinely done to cover the mucosal defect. It was noted that the defects re-mucosalize.

Closure involves the re-approximation of the nasopharygeal window previously created and the re-approximation of the medial pterygoid muscle in its remaining tendon and rigid fixation of the mandible with intermaxillary fixation. A foley catheter with 30cc capacity is used as posterior nasal pack for three days. Negative pressure drain is used in the neck and an NGT is inserted for feeding.

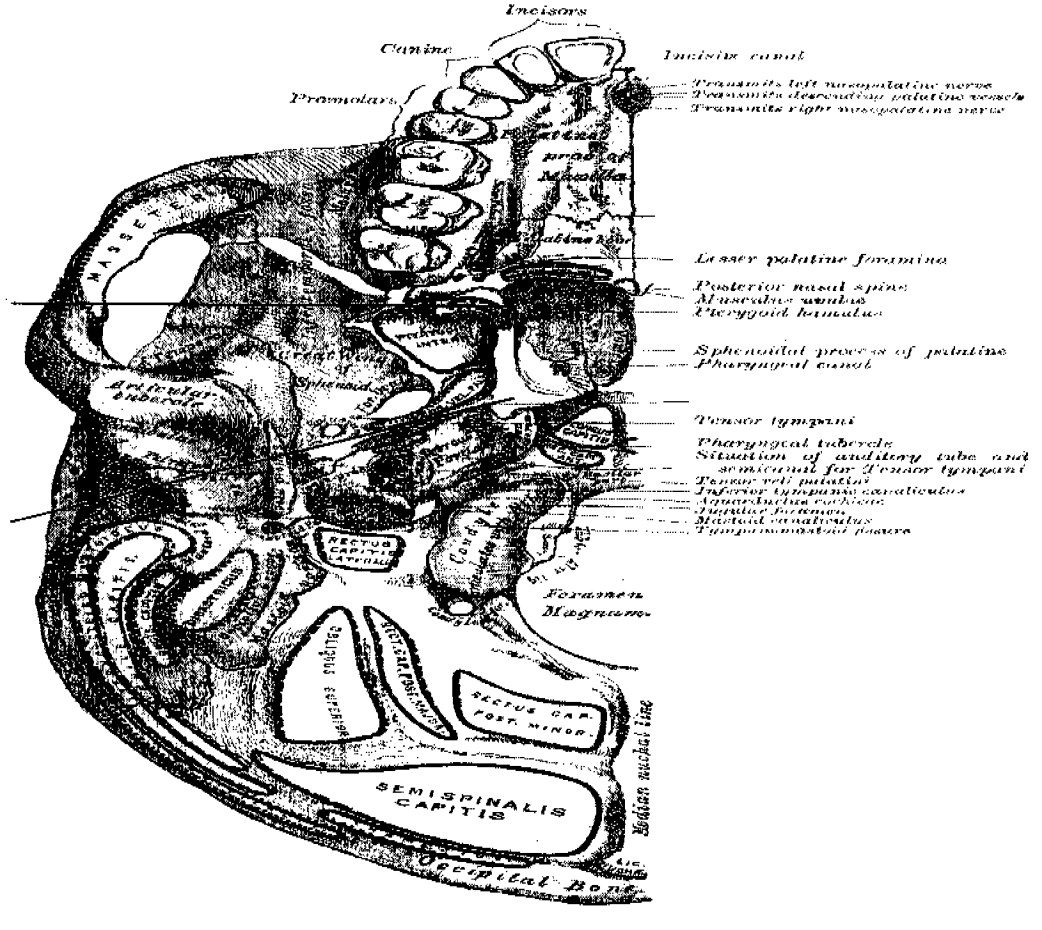
On the non-surgical aspect, the authors tried one dose of pre-op chemotherapy two weeks before surgery to theoretically sterilize the edges of the tumor and possible intravascular tumor

cells on virgin cases. Post-operative cases are encouraged to undergo a full course of radiotherapy after full bone healing.

4. should undergo routine follow-up, regardless of whether treatment is nonoperative or surgical. The frequency of follow-up examinations varies according to the tumor histology. Patients should be monitored for tumor growth and development or progression of symptoms.

ILLUSTRATION

FIGURE 1
Skull base approach
seen in between lines



CASE SERIES

The cases presented consist of our preliminary data. The first two cases were done because of patient's insistence to surgery and fear of chemotherapy or radiotherapy and parent's choice respectively. With an encouraging result, we tried two post-treated patients with massive tumors causing total trismus, nasal obstruction and CN VII paralysis. Surgery was very extensive necessitating segmental mandibulectomy and the use of adjacent flaps for reconstruction. Both required pre-op tracheostomy. Our first patient died after 13 months because of bleeding peptic ulcer but no recurrence was noted. The second is just 2 months post op but went home able to swallow in a month. We have a case of malaria post-op probably due to contaminated blood not detected by the blood bank. Our second stage IV patient had post-operative psychosis but was managed immediately.

Dysphagia was a common post-operative complaint except for a few. Since we also fracture the mandible in our approach, we routinely insert

an NGT for postoperative feeding, disallowing patients to masticate. After two weeks, when patients are able to swallow well, NGT's are removed and patients are discharged on blenderized feeding for 6 weeks to facilitate full recovery of the mandible. It is also after this time that radiotherapy or chemotherapy is started.

CNVII palsy is also a common complication due to traction of the facial nerve when the mandible is retracted laterally. Recovery of the temporo-orbital branch is noted as early as the first post-op day. In our two T4 cases with pre-op facial paralysis, the facial nerve was sacrificed with the tumor.

Numbness of the ipsilateral lower lip always follows the surgery but patients are able to adopt well after a few months. Ipsilateral facial swelling post-op is also common due to the elimination of lymph channels in the neck during RND. This subsides in a few months.

Bleeding has not been a problem because the major blood vessels are exposed and manageable. On the average, 1 liter of fresh whole blood is needed for the surgery, which lasts for an average of 9 hours.

Out of nine patients, three were fungating primaries, including the T4 patients. The rest were submucosal. The submucosal primaries explain the negative NP biopsy results even if guided by CT scan or by a fiberoptic scope. It is the positive neck node and the bulge in the nasopharynx that made us decide to operate. One of the T4 patients presented with histology of moderately differentiated SCCA. The rest were undifferentiated carcinomas.

DISCUSSION

The mandibular swing and lateral plate pterygoidectomy approach to access the nasopharynx in nasopharygeal carcinomas is a practical procedure. There is a gain of exposure with an average of 2.5 - 3.0 cms on the vertical and four cms on the horizontal dimension. Radical neck dissection is done to eliminate neck node metastasis and improve exposure at the same time in a single operating field. Almost all the blood vessels and cranial nerves that traverse the neck and the nasopharynx could be safely identified and preserved if not invaded by tumor. Transection of the lateral pterygoid plate to provide more exposure does not add morbidity. The mandibular osteotomy is managed according to

TABLE 1
Patient Profile

CASE SERIES	ID	Stage	Post-op morbidity	Adjuvant tx	present status
Case 1	*IM, 28m*	T1N2a	CN VII palsy	none	NED 6 years
Case 2	*CM, 6m*	T1N2b	dysphagia x 2 weeks	post-op chemo	NED 6 years
Case 3	*PV, 59m*	T4N3b	dysphagia x 1 year	post-op RadTx	dead in 13 months
Case 4	*BC, 68m*	T1N2a	dyshagia x 2 weeks	none	NED 2 years
Case 5	*DC, 33m*	T1N3a	wound dehiscence	none	LTF
Case 6	*GP, 43m*	T1N2a	Malaria	pre-chemo; post-opRadTx	NED 3 months
Case 7	*CM, 56m*	T4N3b	wound dehiscence; dysphagia x 1 month; psychosis	Pre-chemo-RadTx	NED 2 months
Case 8	*RT, 31m*	T1N2a	dysphagia x 2 weeks	Pre-chemo	NED 2 months
Case 9	*AC, 63m*	T1N2b	CN VII palsy	Pre-chemo	recent

Legend:
NED : *No evidence of Disease*
LTF : *Lost To Follow-up*

maxillofacial principles and malocclusion after bone healing is not a problem. With this approach, the surgeon can take out any visible and/ or palpable tumor from the nasopharynx to the neck with confidence and without fear because of exposure of the nerves and blood vessels.

The prognoses of patients done in this small series remain to be seen. A bigger sample size is needed and a 5 to 10 year follow-up is ideal. Pre-operatively, we counsel our patients about possible morbidity due to the treatment modalities and the importance of follow-ups. Treatment of co-morbidities and avoidance of identified etiologic factors is necessary like tobacco, eating of smoked meat, excessive alcohol intake and bettlenut chewing. The importance of a balanced diet is also emphasized and most of our patients are on multivitamin and mineral supplements.

To propose this approach as a first line treatment to NPCA is too early as non-invasive therapy has an average of 48% disease free three-year follow-ups. To patients who are afraid of radiotherapy or chemotherapy because of their side effects and to resistant cases, surgery with a controlled adjuvant therapy is an option. Afterall, for smaller tumors, post-operative morbidity is gone in two weeks at the earliest.

CONCLUSION

The mandibular swing - lateral plate pterygoidectomy in combination with radical neck dissection for nasopharyngeal carcinoma is a viable surgical option. It provides adequate exposure with lesser manageable post-operative morbidity. It can be used as a primary treatment in conjunction with other treatment modalities on a case to case basis. For radiotherapy and chemotherapy resistant cases of NPCA, it is an alternative safe surgical approach.

Related Literatures:

Treatment Modalities and other Surgical Approaches

Fee describes a transpalatal, transmaxillary, and transcervical approach. This approach to the nasopharynx provides excellent exposure to both sides of the nasopharynx with minimal morbidity to the patient. Isolation and protection of the internal carotid artery through the transcervical approach allow resection of the lateral nasopharyngeal wall with minimal risk to the internal carotid artery and cranial nerves. Disease that extends to the pterygomaxillary space can be exposed via a transmaxillary approach through the posterior wall of the maxillary sinus. Fee recently reported on his experience with 33 patients who had recurrent NPC and were monitored for 2-17 years after nasopharyngectomy. A 5-year local control rate of 67% with 5-year disease-free survival of 52% and an overall survival rate of 60% were achieved.

Fisch describes the infratemporal fossa approach, and Gros and Panje describe the lateral temporal approach. Both approaches provide excellent exposure of tumors extending into the infratemporal fossa and the parapharyngeal space. A major disadvantage of these approaches is that entry into the nasopharynx is performed on the side of the lesion, making complete excision difficult if the tumor extends to the contralateral nasopharynx. Furthermore, the morbidity may include sensorineural hearing loss, cerebrospinal fluid (CSF) leak, unilateral laryngeal paralysis, and facial nerve deficit.

Wei suggested an approach for exposure of the nasopharynx through the maxillary swing (facial translocation) approach. This approach involves a Weber-Fergusson incision. After achieving the necessary bone cuts, the entire osteocutaneous complex is swung laterally to provide exposure of disease in the ipsilateral pterygomaxillary and paranasopharyngeal space. However, the control of the internal carotid artery is less than optimum. Wei reported a local control rate of 42% at 3.5 years.

Biller and Krespi describe the transcervico-mandibulo-palatal approach. This approach provides a wide-field exposure of the nasopharynx and excellent protection of the internal carotid artery. Morton et al reported a 67% local control rate at 2 years with this approach. King et al recently reported on a series of 31 patients who were treated with a variety of surgical approaches followed by postoperative radiation. They reported a 5-year survival rate of 47% with a 5-year disease-free survival rate of 42%. This study focuses on the mandibular swing with resection of the Lateral pterygoid plate to access the nasopharynx & adjacent structures.

An Infratemporal approach is a complex procedure involving significant time, effort, and cost; therefore, under most circumstances, consider the procedure only as part of a "curative" therapeutic plan. It provides access for the resection of a tumor, or it may be adjunctive to other approaches, such as transcranial-subtemporal, Le Fort I, transmaxillary, or anterior subfrontal approaches. A preauricular approach also may be combined with other approaches to expose tumors that extend posteriorly or anteriorly. The preauricular approach, however, provides inadequate exposure for the resection of tumors that invade the tympanic bone and does

not provide adequate access to the intratemporal facial nerve or jugular bulb.

The postauricular approach is designed to expose and resect lesions that involve the temporal bone and that extend into the ITF.
The transfacial approach is best used to approach sinonasal tumors invading the ITF, the masticator space, or the pterygomaxillary fossa and for tumors of the nasopharynx extending into the ITF.

Transoral approach

The transoral approach has been described for the removal of small, benign neoplasms that originate in the prestyloid PPS (parapharynmgeal space) and present as an oropharyngeal mass. The limitations of this approach are limited exposure, inability to visualize the great vessels, and an increased risk of facial nerve injury and tumor rupture. This approach is best suited for small benign salivary tumors arising from minor salivary glands of the lateral pharyngeal wall. The transoral approach may be combined with an external approach to mobilize lesions with a significant oropharyngeal component. This is not the approach of choice for the majority of lesions of the PPS.

Transcervical approach

Most authors favor the transcervical approach as the preferred method for removal of most poststyloid PPS tumors. A transverse incision at the level of the hyoid bone, 2 fingerbreadths below the mandible is performed and the carotid artery and internal jugular vein identified. The digastric and stylohyoid muscles are retracted to allow access to the PPS. The submandibular gland can be retracted anteriorly for exposure or it can be removed if necessary.

Transcervical-transparotid approach

For tumors arising from the deep lobe of the parotid, the transcervical approach can be combined with a transparotid approach by extending the incision superiorly as for parotidectomy. The facial nerve is identified and dissected and superficial parotidectomy performed and the deep lobe portion of the tumor identified. The cervical incision allows access to the PPS component of the tumor.

Transcervical-transmandibular approach

The transcervical approach may be combined with mandibulotomy when improved exposure is required. Such situations include very large tumors, vascular tumors with superior PPS extension, malignancies in which improved exposure facilitates oncologic resection, and cases in which distal control of the carotid at the skull base is required. Mandibulotomy may be lateral or anterior (midline); an osteotomy anterior to the mental foramen is preferred for preservation of inferior alveolar nerve function. A lip-splitting incision is utilized to expose the mandible for midline osteotomy. After mandibulotomy, the incision is continued intraorally along the floor of mouth back to the level of the tonsil pillar and the mandible retracted laterally. Tracheostomy is required for airway management in the immediate postoperative period.

Infratemporal fossa approach

A preauricular infratemporal fossa approach, as described by Fisch, can be utilized for malignant tumors involving the skull base or jugular foramen. This approach can be combined with frontotemporal craniotomy for removal of tumors with significant intracranial extension. A parotidectomy incision with cervical extension as described above is extended superiorly into a hemicoronal scalp incision. The temporalis muscle is elevated to expose the glenoid fossa, which is removed laterally. The temporomandibular joint can be displaced inferiorly, or the mandible condyle can be transected for improved exposure. Orbitozygomatic osteotomies are performed and the infratemporal skull base and distal carotid exposed. The facial nerve and vascular structures in the neck are identified through the cervical and preauricular approaches.

Surgery is the mainstay of treatment for tumors of the PPS. The choice of surgical approach is dictated by the size of the tumor, its location, its relationship to the great vessels, and suspicion of malignancy. Unlike other head and neck cancers, NPC is known for continued risk of late recurrences, and long-term follow-up care is required. While the majority of recurrences occur within 5 years, 5-15% of recurrences may manifest between the 5th and 10th year. Therefore, monitor NPC patients for at least 10 years after treatment. Some authors have suggested that a 10-year, rather than the 5-year, survival rate is needed to assess the effectiveness of a particular treatment for NPC.

Other literatures says that radiation treatment is indicated for previously untreated nasopharyngeal carcinoma and nasopharyngectomy is reserved only for recurrent cases of typical NPC and unusual histologies such as adenocarcinoma or sarcoma.

Surgical complications can be divided into those associated with nasopharyngectomy and those associated with neck dissection. Since surgery usually is performed after a course of radical radiotherapy, complications from poor

wound healing commonly are observed. These complications include palatal fistula, nasopharyngeal wound infection, osteonecrosis, osteomyelitis of cervical vertebrae or skull base, nonunion or malunion of osteotomy sites, and wound edge or flap necrosis. Other complications include damage to the internal carotid artery or cranial nerves, dural violation at the skull base, and death.

The choice of treatment for local recurrence is another area of ongoing controversy. Fee concluded that the results of surgical resection probably are only slightly better than retreatment with radiotherapy. However, he believes that surgery is associated with fewer long-term complications when compared to re-irradiation.

None of the surgical approaches for resection of recurrent NPC is ideal. Due to the nature of the disease process, which involves an extremely complex anatomic region, the surgeon needs to be familiar with all of the surgical approaches. The operation performed must be tailored to the areas involved by the tumor and may involve a combination of approaches to allow maximal exposure while minimizing associated morbidity.

Unfortunately, the literature is conflicting regarding the role of chemotherapy in the treatment of advanced NPC. This discrepancy in the literature may result from differences in the proportion of NPC types, the use of chemotherapeutic agents, treatment schedules, and the number of various clinical trials. The significant improvement in survival with the addition of chemotherapy reported from the Intergroup Study may be due to the large proportion of patients with type 1 NPC in this study and the concurrent use of chemotherapy. Other large clinical trials, most notably from Asia, include a large proportion of patients with type 2 and type 3 NPC who received chemotherapy in the neoadjuvant or adjuvant fashion. Currently, several clinical trials that are testing concurrent chemoradiatotherapy for locoregionally advanced NPC are ongoing in Asia.

External beam radiation therapy is the primary mode of treatment for NPC, both at the primary site and in the neck. This fact mainly is due to the tumor's high degree of sensitivity to radiation and the anatomic constraints for surgical access to the highly complex nasopharyngeal region. Recent advances in imaging capabilities to more accurately define tumor volumes and improved radiotherapy techniques, such as brachytherapy and stereotactic radiotherapy boost, have helped to improve the locoregional control rate. At the same time, complications associated with radiation therapy have been reduced. Various sophisticated fractionation schema and boosting techniques have been advocated, with a minimum of 65-75 Gy of radiation delivered to the primary site.

While radiation therapy alone is a well accepted treatment for stage I and II NPC, the administration of chemotherapy adjunctive to radiotherapy in advanced NPC (ie, stage III, IV) has remained a controversial issue due to conflicting reports in the literature.

BIBLIOGRAPHY

1. Ho-Sheng Lin, Fee W, Jr, et al. Malignant Nasopharyngeal Tumors Department of Otolaryngology-Head and Neck Surgery, Wayne State University/Detroit Medical Center,Department of Surgery, Division of Otolaryngology, Stanford University Medical Center Oct 18, 2001

2. Parapharyngeal space tumors Christine G Gourin, MD, Jonas T Johnson, MD, FACSDepartment of Surgery, Division of Otolaryngology-Head and Neck Surgery, Medical College of Georgia Head/Neck Oncology and Immunology, Department of Otolaryngology, Ear & Eye Institute, University of Pittsburgh School of Medicine Sept 13, 2001

3. Skull base, infratemporal approach Ricardo L Carrau, MD, Amin B Kassam, MD, , Departments of Otolaryngology and Neurological Surgery, University of Pittsburgh Medical Center, Cranial Base Surgery Center, , Department of Neurological Surgery, University of Pittsburgh Medical Center June 6, 2002

4. Ayahao, F.D.,MD.; Mandibular Swing -Lateral Pterygoid Platectomy with Radical Neck Dissection Approach to NPCA: unpublished. Department of Otolaryngology-Head and Neck Surgery, Baguio General Hospital and Medical Center, Baguio City, Philippines

FIGURE 2
Stepwise osteotomy done between the body and the angle of the mandible. Posterior segment reflected laterally and superiorly to expose the lateral nasopharyngeal wall.

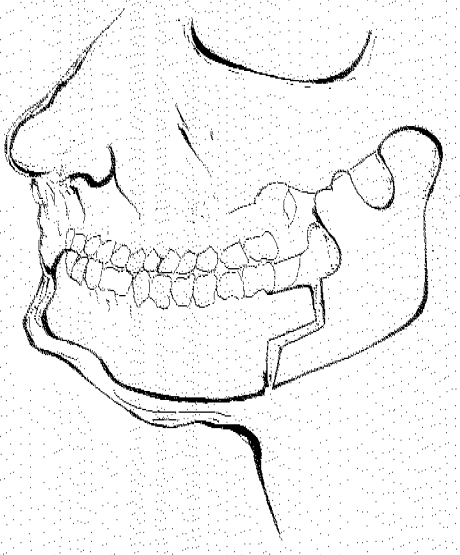


FIGURE 3
Actual picture showing access to the nasopharynx after mandibular swing. Large vessels also seen.

FIGURE 4
Another picture of the dissection showing the nasopharynx after mandibular swing.

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USE OF A GREEN TEA-CAPSICUM SUPPLEMENT (CAPSIBIOL-T) AS ADJUVANT CANCER TREATMENT: CASE STUDY REPORTS*

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ABSTRACT

Objectives: To assess the effect of a decaffeinated green tea-capsicum supplement (CAPSIBIOL-T™) as adjuvant to standard chemotherapy, radiotherapy or both on overall survival time of stage III and IV unresectable metastatic head and neck and breast cancer patients.
Intervention: Administration of an herbal supplement together with conventional cancer treatment regimens of selected cancer patients.
Results: Over the course of treatment, patients exhibited tumor regression and/or survival way beyond the typical life expectancy of their disease state.
Conclusion: Significant improvements in therapeutic success and/or survival rate of cancer test subjects were observed with the concomitant administration of CAPSIBIOL-T™ and conventional cancer treatment. The cases presented are sufficiently encouraging to warrant further investigation.
Key Words: Green Tea catechins, *Capsicum*, CAPSIBIOL-T™, Cancer, Head & Neck Cancer, Compassionate Therapy, Survival

INTRODUCTION

There is reason from epidemiological and animal studies to associate health benefits of green tea in cancer protection with the principle green tea catechin (-)-epigallocatechin-3-gallate (EGCg). In addition to a high potential degree of efficacy from oral administration, EGCg is generally recognized as safe over a wide therapeutic range (equivalent to 10 to 20 cups of green tea). Much attention to tea catechins and health has focused on cancer (Dreosti, 1996); and drinking tea has been regarded traditionally in Asia as a generally healthful practice. Epidemiological studies show that cancer onset of patients in Japan who have consumed 10 cups of green tea per day was 8.7 years later among females and 3 years later among males, compared with patients who had consumed under three cups per day (Fujiki et al., 1999). Thus, a possible relationship between high consumption of green tea and the low incidence of prostate and breast cancer in some Asian countries has been postulated (Ahmad et al., 1997).

Health benefits of tea catechins in cancer have been broadly attributed to one of three areas: antioxidant properties, effects on intestinal micro flora and nutrient absorption, and effects on metabolism and metabolic enzymes and on growth, especially of cancer cells (Dreosti, 1996). Anticancer effects for tea are indicated both from animal *in vivo* studies (Ahmad et al., 1997; Chen et al., 1998; Fujiki et al., 1999; Liao et al., 1995; Gupta et al., 2001; Conney et al., 1999) and from human epidemiological observations (Fujiki et al., 1999; Katdare et al., 1998). A total of 31 studies and four reviews were examined by Bushman (1998), the majority of which showed an inverse association between tea consumption and cancer of the colon, urinary bladder, stomach, esophagus, lung and pancreas. A negative association between green tea consumption and cancer incidence, especially among females

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drinking more than 10 cups per day was reported (Imai et al., 1997). A large case-controlled study conducted in Shanghai, China, involving 2266 cancer patients and 1552 controls suggested that green tea consumption lowered the risk of cancer of the colon, rectum and pancreas by 18, 28 and 37%, respectively in men, and by 33, 43 and 47% respectively in women (Zhu et al., 2001). Previous studies by the same workers had suggested protective effects of green tea of similar magnitude against esophageal and stomach cancers (Guo et al., 1994). Other smaller studies have revealed a significantly reduced risk of colon cancer and of precancerous adenomas of the colon and rectum for tea drinkers (Ji et al., 1996; Kono et al., 1988). Five out of six cohort studies reported lower risks of pancreatic cancer among tea drinkers (Ji et al, 1997). There are few if any records of acute toxicity associated with the consumption of green tea as reported by the Office of Dietary Supplements (Botanical Fact Sheet, Green Tea 2001). The preliminary efficacy results of a Phase I-II clinical study from a cohort of non-cancer patients demonstrated no untoward side effects (Stoner and Mukthar, 1995). Also preliminary efficacy results of a Phase I clinical trial have demonstrated that after 12 weeks of treatment, patients treated at the highest dose of treatment, showed no discomfort (Fujiki et al., 1999).

In terms of a proposed mechanism of action, work at Purdue University has identified a cancer specific cell surface protein (tNOX) with NADH oxidase and protein disulfide-thiol interchange activity as the potential target for the anticancer action of cancer-fighting polyphenols and polyphenol mixtures such as the catechins found in green tea (Morré et al., 2000). This target was shown previously to be inhibited by *Capsicum* vanilloids such as capsaicin (Morré et al., 1995).

In synergistic studies in animals, oral administration of green tea to mice bearing implanted Ehrlich ascites carcinomas increased the efficacy of doxorubicin chemotherapy (Nakagawa and Miyazawa, 1997). Tea components also enhanced the antitumor activity of doxorubicin against M5076 ovarian carcinoma in mice (Suganuma et al., 1998). Development of mammary tumors in mice is inhibited completely by a combination of tamoxifen and green tea. Tamoxifen alone inhibited 50% and green tea alone was without effect (Fujiki et al., 1996). (-)-Epigallocatechin-3-gallate (EGCg) alone reduced lung metastases in mice bearing B-16-F3n melanoma cells. A combination of EGCg and docarbazine was more effective than EGCg alone and reduced the number of pulmonary metastases, reduced the number of primary tumor growths and increased the survival of the melanoma-bearing mice (Liu et al., 2001). Green tea was superior to (-)-epigallocatechin alone for cancer prevention in humans and was synergistic with Sulindac or Tamoxifen in the human cancer cell line PC-9 (Sugiyama and Sadzuka, 1998).

In general, these effects have been attributed to (EGCg) (Chen et al., 1998) but other catechins and polyphenols present in tea have been shown to act synergistically with EGCg in their anticancer properties (Morré et al., 2002). Subsequently, mixtures of catechins were found to be superior to EGCg alone and an addition of a capsaicin source to the catechin mixture was even more effective (Morré and Morré, 2003). As a result of this knowledge, a green tea-*Capsicum* (chili pepper) vanilloid mixture has been developed by Actibiol S.A. (Geneva, Switzerland) with the additional advantage of reducing the neurologic discomfort caused by the pungent principles, i.e. capsaicinoids. This mixture is 10 times more effective in inhibiting tNOX and the growth of cancer cells in culture than either green tea or *Capsicum* vanilloids alone (Morré and Morré, 2003). In this paper, we describe the course of treatment of selected cancer patients being given CAPSIBIOL-T™ together with their conventional cancer treatment regimen.

CAPSIBIOL-T™ is the registered Trade Mark of Actibiol S.A. Geneva. It is a mixture of decaffeinated green tea and red pepper (*Capsicum*), prepared according to a proprietary biotechnicological process at Actibiol S.A. (Geneva, Switzerland), from natural approved food sources using GMP providers (Morré and Morré, 2003). The study supplement was taken orally as 5 to 6 capsules a day in divided doses, for 6 months. Available capsule dose at the time was 650 mg/cap.

CASE REPORTS

Case Study 1

A.V., Age: 50 y/o male

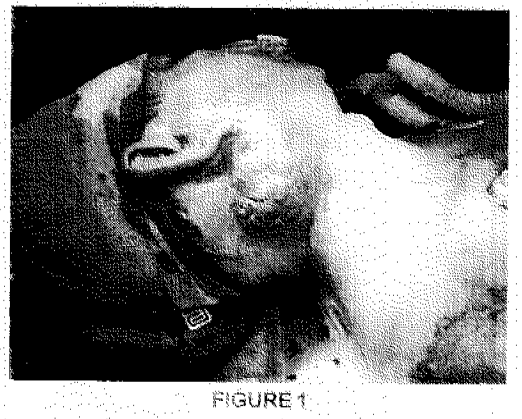

FIGURE 1

This patient was diagnosed via punch biopsy to have high grade mucoepidermoid carcinoma of the right parotid gland. His CT-scan shows invasion of the right jugular vein and carotid artery wall. The tumor also broke through the barrier of the skin of his neck (Fig. 1) CAPSIBIOL-T™ treatment was started a day before surgery.

Surgically accessible tumor mass was removed to allow for better penetration of the planned radiation treatment (Fig. 2). On palpation there were some smaller masses surrounding the periphery of the surgical defect. These were not removed because of ill-defined borders and the purpose of the surgery being palliative/debulking and not curative.

Three weeks later, the tumor which previously broke through healthy skin was not a factor in preventing healing of the advancement flap created to cover the defect (Fig. 2).

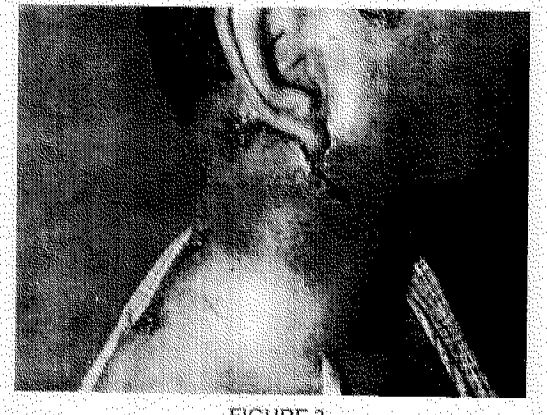

FIGURE 2

Furthermore, it seemed that the surrounding tumor masses previously palpated were now softer and smaller in size. Repeat CT-scan done before any radiation therapy, showed liquefaction in previous tumors, necessitating a reinsertion of a drain which can be seen in this picture (Fig. 2). Instead of blood, only greenish serous fluid was obtained from the drainage site.

Radiation treatment on a fully healed surgical flap was started six weeks after surgery. Two months after surgery, there seemed to be no trace of tumor left on his neck (Fig. 3)

Of interest is the fact that his sternocleidomastoid muscle on the right side seemed to be absent. This may have been atrophied by the radiation treatment or eaten away by the tumor. The patient survived his bout with cancer while he was taking Capsibiol-T. CAPSIBIOL-T™ intake however was stopped after six months as planned, and tumor recurrence was noted two months after. Patient expired four months after cessation of CAPSIBIOL-T™ despite initiating a second round of CAPSIBIOL-T™

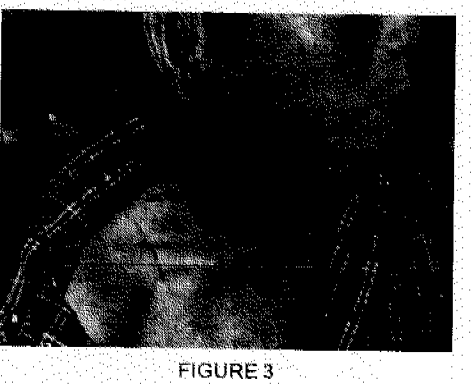

FIGURE 3

treatment once recurrence was noted. At this stage, patient compliance was questionable at best.

CASE STUDY 2

B.C., Age: 57 y/o male

This patient presented with a right sided neck mass with a history of conventional treatment failure. The mass was noted to be firm to hard in consistency (Fig. 4). Patient was diagnosed to have nasopharyngeal carcinoma based on a nasopharyngeal biopsy. The mass was also noted to be actively bleeding and needed constant pressure to control the hemorrhage. A trial of CAPSIBIOL-T™® was initiated with instructions for him to come back after a week.

After 12 days, this patient returned for follow up. The initial observation was that the mass had enlarged (Fig. 5). However, after

FIGURE 4

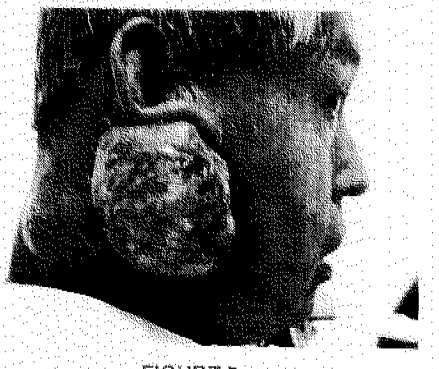

FIGURE 5

thorough evaluation, the following information was elicited: 1.) the mass no longer bled actively 2.) the tumor masses that could be palpated were now significantly softer as if necrotic, or liquefied inside. 3.) the base of the main mass was now smaller than its greatest diameter which seemed to indicate that the tumor was becoming more exophytic and less infiltrative. 4.) greenish, non-foul smelling liquid was oozing out from the main neck mass.

Two months later, the patient returned with his tumor size much reduced (Fig. 6). He had just started chemotherapy (Cisplatinum and 5-Fluorouracil) and was complaining of nausea and vomiting. This meant that the reduction in tumor size should be largely due to CAPSIBIOL-T™ since conventional chemotherapy had just started.

Patient compliance then became a problem. The patient failed to return to renew his supply of CAPSIBIOL-T™ and the mass became

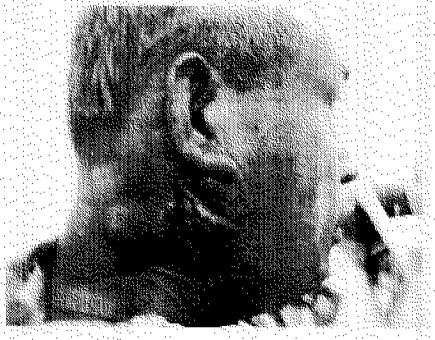

FIGURE 6

notably enlarged after 3.5 months without CAPSIBIOL-T™.

CASE STUDY 3:

C.B., Age: 44 y/o female

This is a case of recurring squamous cell carcinoma of the right cheek. Before referral, she had undergone surgical and/or radiation treatment at least 6 times in the last 2 years. At the time of consult she had recently undergone a repeat excision using a Weber-Fergusson approach with lower lip splitting (Fig.7). Histopathology revealed differentiated squamous cell cancer.

The patient was started on a CAPSIBIOL-T™ regimen of 5 capsules a day in divided doses. Treatment continued uneventfully for 6 months with no sign of recurrence. Unfortunately treatment was terminated after 6 months as planned.

Two and a half months after treatment had stopped; a recurrence of tumor mass was noted at the right temporal-zygomatic area (Fig. 8). She was then started on CAPSIBIOL-T™® once more but she subsequently moved to another country with little or no chance of follow-up.

CASE STUDY 4

D.S., Age: 53 y/o male

FIGURE 8

The patient was admitted with bilateral neck masses which obliterated the shoulder to neck angle. Open biopsy of neck masses and subsequent histopath diagnosis was delayed for 10 days due to various problems. This led to withholding of definitive treatment until definitive histopathologic diagnosis of lymphoma was made. In the meantime, the patient was slipping into stupor and became comatose. CAPSIBIOL-T™ treatment via nasogastric tube was initiated when he was comatose. The next day, the patient regained consciousness, histopath results (non-

FIGURE 7

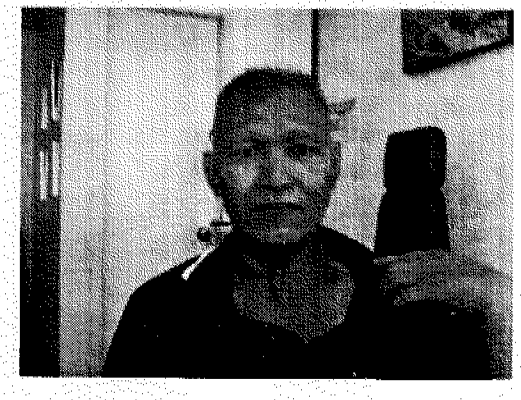

FIGURE 9

Hodgkin's lymphoma) became available and chemotherapy (Cyclophosphamide, Vincristine, Doxorubicin) was initiated. Patient was discharged with a normal sized neck after 9 days. Figure 9 shows the patient with a normal sized neck 3 months after CAPSIBIOL-T™ was started.

The dose of CAPSIBIOL-T™® was lowered to a maintenance dose of 3 capsules a day after the 6th month and the patient continues to be tumor free almost 13 months after treatment was started.

CASE STUDY 5

C.C., Age: 37 y/o male

This is a case of squamous cell carcinoma of the hard palate and upper gingival area (Fig. 10). The patient had a history of ill-fitting dentures which may have contributed to the condition.

The patient was placed on CAPSIBIOL-T™ treatment (5 capsules/day). Surgical

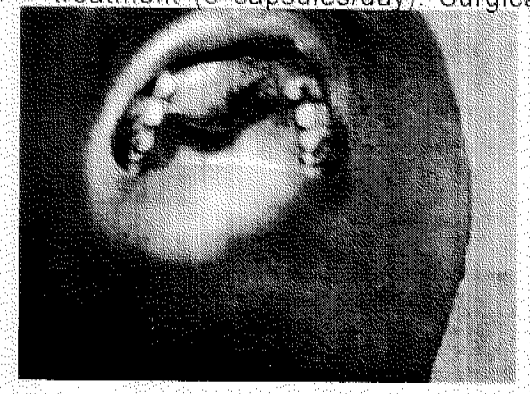

FIGURE 10

resection was also done with the goal of total resection in mind. The bony floor of the nasal cavity together with the lower portions of both maxillary sinuses was included in the resection. Despite this, the final histopathology report of the resected specimen showed the superior line of resection still positive for tumor. A wait and watch approach was adopted since the lines of surgical resection were now fully visible and accessible.

CAPSIBIOL-T™ was continued for 6 months with no further additional measures. The dose was lowered to 3 times a day on the 7th month and no sign of recurrence is noted more than 8 months after the resection (Fig. 11).

DISCUSSION

These case-reports represent the first attempts at compassionate intervention with potentially therapeutic doses of CAPSIBIOL-T™. Preliminary results demonstrate the potential benefit of this catechin-*Capsicum* (green tea-chili pepper) supplement in cancer management. Its mechanism of action has been shown to be the inhibition of the cancer specific marker protein, tNOX (Chueh et al., 2002a, b), followed by growth stasis of the cancer cells and the resultant induction of apoptosis as demonstrated in vitro (Morré et al., 2000). Other mechanisms may be at work however, making for an even more important issue for further research.

Of additional interest is the incidence of tumor recurrence only after cessation of CAPSIBIOL-T™. A follow up study will certainly have to consider what the optimum treatment duration should be and/or whether intake should be lifelong at maintenance dose after an initial intensive phase. Monitoring the blood for tNOX activity, the targeted molecule of the catechin-*Capsicum* mixture, is expected to help clarify this area of concern.

The results so far seem to indicate a positive role of this herbal mixture in clinical use as an aid for the prevention and control of cancer growth, metastasis and/or recurrence.

CONCLUSION

The use of CAPSIBIOL-T™ as an adjunct with conventional cancer treatment was indicative of survival benefits both for cancer protection and for slowing the growth and metastatic spread of established cancers for as long as it was being taken. This preliminary result demonstrates a potential benefit of a decaffeinated catechin-*Capsicum* (green tea-chili pepper) supplement in the treatment of cancer patients. The presented cases although few in number are sufficiently encouraging to warrant further clinical trials to determine a definitive role in cancer therapy.

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BIBLIOGRAPHY

1. Ahmad, N., Feyes, D. K., Nieminen, A. L., Agarwal, R. and Mukhtar, H. (1997) Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. J. Natl. Cancer Instit. 89:1881-1886.
2. Bushman, J. L. (1998) Green tea and cancer in humans: A review of the literature. Nutr. Cancer 31: 151-159.
3. Chen, Z. P., Schell, J. B., Ho, C. T. and Chen, K. Y. (1998) Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Can. Lttr. 129:173-179.
4. Chueh, P., Kim, C., Cho, N., Tang, X., Morré, D. M. and Morré, D. J. (2002a) Molecular cloning and protein expression of a unique hydroquinone (NADH) oxidase (tNOX) of the cancer cell surface. Biochemistry 41:3732-3741.
5. Chueh, P.-J., Morré, D. M. and Morré, D. J. (2002b) A site-directed mutagenesis analysis of tNOX functional domains. Biochem. Biophys. Acta. 1594:74-83.
6. Conney, A. H., Lu, Y.-P., Lou, Y.-R., Xie, J.-G., and Huang, M.-T. (1999) Inhibition effect of green and black tea on tumor growth. Proc. Soc. Exper. Biol. Med. 220:229-233.
7. Dreosti, I. E. (1996) Bioactive ingredients: antioxidants and polyphenols in tea. Nutr. Rev. 54:S51-S58.
8. Fujiki, H., Suganuma, M., Okabe, S., Sueoka, N., Imai, K., Nakachi, S. and Kimura, S. (1999) Mechanistic findings of green tea as cancer preventive for humans. Proc. Soc. Expr. Biol. Med. 220:225-228.
9. Fujiki, H., Suganuma, M., Okabe, S., Komori, A., Sueoka, E., Sueoka, N., Kosu, T. and Sakai, Y. (1996) Japanese green tea as a cancer preventative in humans. Nutr. Rev. 54:567-570.
10. Guo, Y. T., McLaughlin, J. K., Blot, W. J., Ji, B. T., Dai, Q. and Fraumeni, J. R., Jr. (1994) Reduced risk of esophageal cancer associated with green tea consumption. J. Natl. Can. Inst. 86:855-858.
11. Gupta, S., Hastak, K., Ahmad, N., Lewin, J. S. and Mukhtar, H. (2001) Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. Proc. Natl. Acad. Sci. USA 98:10350-10355.
12. Imai, K., Litt, O., Suga, K. and Nakachi, K. (1997) Cancer preventative effects of drinking green tea among a Japanese population. Prevent. Med. 26:769-775.
13. Ji, B.-T., Chow, W.H., Yang, G., McLaughlin, J. K., Gao, R. N., Zheng, W., Shu, X.-O., Jin, M. F., Fraumeni, J. F., Jr. and Gao, Y. T. (1996) The influence of cigarette smoking, alcohol and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. Cancer 77:2449-2457.
14. Ji, B.-T., Chow, W. H., Hsing, A. W., McLaughlin, J. K., Dai, Q., Guo, Y. T., Blot, W. J. and Fraumeni, J. F., Jr. (1997) Green tea consumption and the risk of pancreatic and colorectal cancers. Int. J. Cancer 70:255-258.
15. Katdare, M., Osborn, M. P. and Telang, N. T. (1998) Inhibition of aberrant proliferation and induction of apoptosis in pre-neoplastic human mammary epithelial cells by natural phytochemicals. Oncol. Repts. 5:311-315.
16. Kono, S., Ikada, M., Tokudome, S. and Kuratsune, M. (1988) A case control study of gastric cancer and diet in Northern Kyishu, Japan. Jap. J. Cancer Res. 79:1067-1074.
17. Liao, S., Umekita, Y., Guo, J., Kokontis, J. M. and Hiipakka, R. A. (1995) Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate. Can. Lttr. 96:239-243.
18. Liu, J. D., Chen, S. H., Lin, C. L., Tsai, S.H. and Liang, Y. C. (2001) Inhibition of melanoma growth and metastasis by combination with (-)-epigallocatechin-3-gallate and dacarbazine in mice. Cell. Biochem. 83:631-642.
19. Morré, D. J. and Morré, D. M. (2003) Synergistic *Capsicum*–tea mixtures with anticancer activitity J. Pharm. Pharmacol. 155: 987-994.
20. Morré, D. J., Chueh, P. –J. and Morré, D. M. (1995) Capsaicin inhibits

preferentially the NADH oxidase and growth of transformed cells in culture. Proc. Natl. Acad. Sci. USA 92: 1831-1835

21. Morré, D. J., Bridge, A., Wu, L.-Y. and Morré, D. M. (2000) Preferential inhibition by (-)-epigallocatechin-3-gallate of the cell surface NADH oxidase and growth of transformed cells in culture. Biochem. Pharmacol. 60:937-946
22. Morré, D. J. and Morré, D. M., Sun, H., Cooper, R., Chang, J. and Janle, E. (2002) Tea catechin synergies in inhibition of cancer cell proliferation and of a cancer cell-specific ECTO-NOX activity. Pharmacol. Toxicol. 92:234-241.
23. Nakagawa, K. and Miyazawa, T. (1997) Absorption and distribution of tea catechin, (-)-epigallocatechin-3-gallate, in the rat. J. Nutr. Sci. Vitaminol. 43:679-684.
24. Stoner, G. D. and Mukhtar, H, (1995) Polyphenols as cancer chemopreventive agents. J. Cell. Biochem. 22 (suppl.) 169-180.
25. Suganuma, M., Okabe, S., Kai, Y., Sueoka, N. Sueoka, E. and Fujiki, H. (1999) Synergistic effects of (-)-epigallocatechin gallate with (-) epicatechins, Sulindac or Tamoxifen on cancer-preventive activity in the human lung cancer cell line PC-9. Cancer Res. 59:44-47.
26. Sugiyama, T. and Sadzuka,Y. (1998) Enhancing effect of green tea compounds on the antitumor activity of adriamycin against M5076 ovarian sarcoma. Can. Lett. 133:19-26.
27. Zhu, M., Chen, Y. and Li, R. C. (2000) Oral absorption and bioavailability of tea catechins. Planta Med. 66:444-447.