Scholars LITERATURE

La Prensa Medica Argentina

Research Article

DOI: https://doi.org/10.47275/0032-745X-424
Volume 110 Issue 5

Isolation of Pathogenic Microorganisms in Oral Cavity of Children with Cancer in Basrah Pediatric Oncology Center

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Abstract

Background: Oral hygiene has been essential to improved oral and general health status of infant and children in the pediatric cancer and critical ill children, because of poor oral hygiene associated with dental plaque accumulation, bacterial colonization in oropharyngeal area and higher nosocomial infection.

Method: A case control study has been carried out on 62 children, their age ranged from 1 - 15 years, with newly diagnosed malignancy (33 males, and 29 females) admitted to Basrah pediatric oncology center from 1st of January till the end of October 2020, and 108 healthy children (56 males, and 52 females). This study has been done to look for the frequency and types of pathogenic microorganism in oral cavity of children with malignancy at time of diagnosis on day zero and during induction phase of chemotherapy on day 14 - 21.

Result: The study show Gram positive species (G+ve) were the most common microorganism in both control group and patient with cancer dominated by oral *Viridians streptococci*, and there is shifting and modification of oral microflora to more pathogenic and opportunistic Gram negative species (G-ve) in patients with cancer before induction (11), during induction (29) in comparison to control group, p value statistically significant 0.024, and most common G-ve isolated were *Pseudomonas* species, *Klebsiella Pneumonia, Neisseria cataralis, Enterobacter cloaca,* and *Escherichia coli. Candida* species especially *Candid albicans* was more common fungi isolated, and there is increased risk of oral colonization with fungal microorganism, before chemotherapy (53), and more increment during induction of chemotherapy (66%) compared to control groups (34%) p value statistically significant 0.023. Infection with G-ve has been increased during induction of chemotherapy in moderate to severe neutropenia (p = 0.049), in addition G-ve increased with severity of mucositis (60%), but *Candida* species were more with mild mucositis (82.8%). Regarding type of malignancy, G-ve and *Candida* species were more isolated from patients with solid tumor while G-ve were more with lymphohematopoietic malignancy.

Conclusion: From this study can be concluded, that there is great variation in proportion and types of oral microflora, modification and shifting of microorganism to more pathogenic and opportunistic negative species in patient with cancer, these will affect the health status of children especially those with neutropenia and mucositis.

Keywords: Pathogenic microorganisms, Oral cavity, Cancer, Basrah pediatric oncology center

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Citation: Hasan JK, Hasan J, Ali TZ (2024) Isolation of Pathogenic Microorganisms in Oral Cavity of Children with Cancer in Basrah Pediatric Oncology Center. Prensa Med Argent, Volume 110:5. 419. DOI: https://doi.org/10.47275/0032-745X-424

Received: July 01, 2024; **Accepted:** September 12, 2024; **Published:** September 16, 2024

Introduction

Cancer is predominantly a disease of ageing and is very rare in childhood, in western populations; only around 0.5% of all cancers occur in children aged less than 15 years [1]. Lymphohematopoietic cancer (acute leukemia and lymphomas) accounts for approximately 40% [2]. Acute lymphoblastic leukemia (ALL) accounts for 75% of cases, the various subtypes of acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) account for 15%, 5% respectively [3]. The incidence of solid tumors is age-dependent, they make up to more than 80% of all malignancies in infants; the solid tumors to leukemia ratio are 2:1 in children aged 1 - 14 year but 5:1 in infants less than 1 year [4]. Oral hygiene has been essential to improved oral and general health status of infant and children in the pediatric cancer and critical ill children, because of poor oral hygiene associated with dental plaque accumulation, bacterial colonization in oropharyngeal area and higher nosocomial infection [5].

Methods

The study was conducted in Basrah children's specialty hospital of Basrah Governorate, over 10 months; from 1st of January till the end of October 2020.

A case control study has been carried out on children with newly diagnosis cancer. The subjects studied comprised two groups of children, patients, and control groups. The patient group included 65 patients with cancer, aged 1 - 15 year, 33 males and 29 females, three of them died: one with sacrococcygeal teratoma and renal failure and two with AML and septicemia. Control group included 108 healthy children; 56 male 52 female free of systemic and oral pathology, obtained from primary health care center for routine checkup and vaccinations, their age and sex matched with patients' group. And subject age groups are divided into 3 groups: ≤ 5 years, 5 - 10 years, and 10 - 15 years.

In exclusion criteria any patient received drugs other than

chemotherapy may be used in patient with cancer example: antiemetic agents, antihistamines, tricyclic antidepressant, benzodiazepines and opioid, these drug cause hyposalivation or xerostomia and increase the risk and severity of mucositis [6, 7].

Data for each case included in this study have been collected using a special questionnaire designed for the purpose of the study. Clinical observation of oral cavity was done before and during chemotherapy made by one investigator and conditions of mucosa, type of lesions and grading of mucositis were all recorded. Mucositis produced during induction of chemotherapy were divided into five grades; (grades 1 and 2) were considered as mild mucositis, (grades 3 and 4) as sever mucositis [8] and (grade 0) no mucositis. Investigation was done in this study CBP monitored every other day during chemotherapy, neutropenia was estimated from absolute neutrophile count. Sever neutropenia < 500, moderate neutropenia 500 - 1000, and mild neutropenia 1000 - 1500 [9]. Significant thrombocytopenia was regarded when platelet countless 20000, the risk of mucosal petechiae and spontaneous oral hemorrhage increases significantly [6].

All patients were sampled on day zero (before chemotherapy) and on day 14 - 21 (during induction of chemotherapy), sampling was done approximately 1 h after breakfast for each patient the specimen was collected from oral cavity (soft palate, buccal mucosa, tongue, subgingival, supragingival plague of teeth, and lips) with a sterile collection swab called Amies transport medium and all specimens were processed within following 2 h all mouth swabs were cultured from amies transport medium on the following agar (blood agar, chocolate agar, sabourauds agar, and MacConkey's agar), the sample cultured on these four media were then incubated for 1 - 2 days at 37˚C. Colony identification was accomplished using the standard technique which included (Gram's stain, tests based on the presence of metabolic pathways, catalase test, oxidase test, coagulase test, urea's test, and germ tube test).

Results

A total of 62 children with newly diagnosed malignancy and 108 children of control group were included in this study their ages ranged from 1 - 15 years. and distribution of age and sex are shown below, and there is no statistically significant difference in age and sex distribution between patients with cancer and control group (Table 1).

Show that ALL is the most common diagnosis of all types of malignancies, while neuroblastoma is the most common solid tumors (Table 2).

This study show the frequency of G+ve, G-ve and candida infection isolated from patients before induction are significantly high percentage in compare to control group and percentage of G+ve species before induction of chemotherapy is significant higher than during induction ($p < 0.05$), while the percentage of G-ve and *Candida* species during induction of chemotherapy are higher than before induction of chemotherapy ($p < 0.05$) (Table 3).

Table 1: Age and sex distribution of patients and control group.

Age (year)	Patients no. (%)	Control no. (%)	p value
≤ 5	36 (58.1)	66 (61.1)	0.844
< 5 - 10	15 (24.2)	22 (20.4)	
> 10 - 15	11 (17.7)	20 (18.5)	
Sex			
Male	33 (53.2)	56 (51.9)	0.875
Female	29 (46.8)	52 (48.1)	
Total	62 (100)	108 (100)	

Table 2: Types of malignancy reported among patients.

Type of malignancy	Patient no. (%)
Lymphohematopoitic malignancy	41 (66.1%)
ALL	24 (38.7%)
AML	7 (11.3%)
Non-Hodgkin lymphoma	8 (13%)
Hodgkin lymphoma	2 (3.2%)
Solid tumors	21 (33.9%)
Neuroblastoma	8 (13%)
Wilms tumor	2 (3.2%)
Nasopharyngeal carcinoma	2 (3.2%)
Ewing sarcoma	1 (1.4%)
Langerhans cell histiocytosis	1 (1.6%)
Rhabdomyosarcoma	3 (5%)
Retinoblastoma	2 (3.2%)
Astrocytoma	2 (3.2%)
Total	62 (200%)

Table 4 reveals no statistically significant difference in frequency of different species among different age groups.

There is no statistically significant difference in frequency of different species among sex of patients (Table 5).

There is no statistically significant difference in the frequency of G+ve and *Candida* species in relation to neutropenic patients (Table 6). However, the frequency of G-ve species in areas significant with the severity of neutropenia.

There is no statistically significant difference in the frequency of G+ve species in relation to mucositis $p > 0.05$, but the frequency of G-ve species was significant high in sever mucositis, and *Candida* species was significantly high in mild mucositis both of them p value < 0.05 (Table 7).

Table 8 show that in spite of G+ve species are higher in lymphohematopoietic malignancies, however p value not statistically significant > 0.05, in contrast to G-ve and *Candida* species are higher in solid tumors, but p value is also statistically not significant > 0.05.

The symptoms that occur in oral cavity before and during induction of chemotherapy appeared that the frequency of soreness, difficulty in swallowing, dryness of mouth, oral thrush, and oral bleeding during induction of chemotherapy were higher than in compare before induction and there was statistically significant difference p value < 0.05 as shown in figure 1.

Discussion

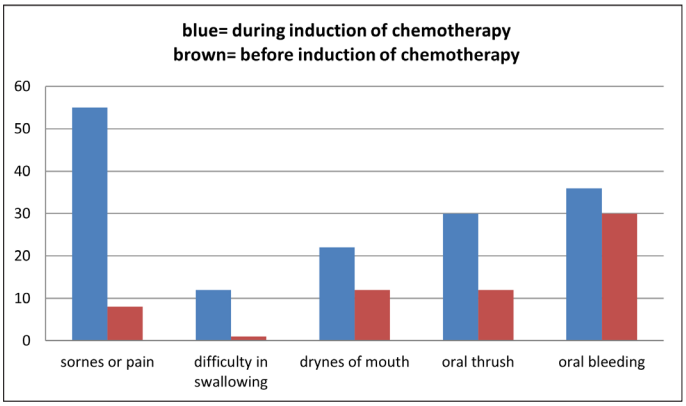

Figure 1: Oral symptoms before and during initiation of chemotherapeutic agents.

Table 3: Distribution of types of microorganism in patients and control groups.

Types of species	Patients		Control no. (%)
	Before no. (%)	During no. (%)	
G+ve			
Oral *V. streptococci*	54 (87.09)	45 (72.58)	94 (87)
Staphylococcus epidermidis	3 (4.83)	3 (4.83)	
Staphylococcus aureus	3 (4.83)	4 (6.45)	
S. aureus + oral *V. streptococci*	1 (1.61)	2 (3.22)	
S. epidermidis + *V. streptococci*	1 (1.61)	1 (1.61)	
Total	62 (100)	55 (88.7)	94 (87)
p = 0.002; p* = 0.013			
G-ve			
Pseudomonas fluorescence	2 (3.22)	3 (4.83)	0 (0.0)
Pseudomonas aeruginosa	0 (0.0)	3 (4.83)	
N. cataralis	1 (1.61)	2 (3.22)	
K. pneumonia	1 (1.61)	4 (6.45)	
E. cloaca	2 (3.22)	3 (4.83)	
E. coli	1 (1.61)	3 (4.83)	
Total	7 (11.3)	18 (29)	(0.0)
p* = 0.024			
***Candida* species**			
C. albicans	24 (38.70)	30 (48.38)	37 (34.25)
Candida tropicalis	9 (14.51)	11 (17.74)	0 (0.0)
Total	33 (53.2)	41 (66.1)	37 (34.25)
p = 0.023; p* = 0.20			

Note: p = value between patients before chemotherapy and control group; and p* = value between patients before induction and during induction of chemotherapy.

Table 4: Distribution of oral pathogens among patients according to age groups during induction of chemotherapy.

Type of species	Age			p value
	≤ 5 (36) no. (%)	> 5 - 10 (15) no. (%)	>10 - 15 (11) no. (%)	
G+ve	32 (88.9)	14 (93.3)	9 (81.8)	0.656
G-ve	13 (36.1)	3 (20)	2 (18.2)	0.35
Candida	27 (75)	8 (53.3)	6 (54.5)	0.221

Table 5: Distribution of oral pathogens among patients in relation to sex during induction of chemotherapy.

Type of species	Sex		p value
	Male (33) no. (%)	Female (29) no. (%)	
G+ve	28 (84.8)	27 (93.7)	0.432
G-ve	9 (27.3)	9 (31)	0.785
Candida	22 (66.7)	19 (65.5)	0.90

Table 6: Oral pathogens in relation to neutropenia during induction.

Type of species	Neutropenia				p value
	Non (23) no. (%)	Mild (8) no. (%)	Moderate (13) no. (%)	Sever (18) no. (%)	
G+ve	21 (91.3)	8 (100)	10 (76.9)	16 (88.9)	0.395
G-ve	3 (13)	1 (12.5)	6 (46.2)	8 (44.4)	0.049
Candida	11 (47.8)	5 (62.5)	10 (76.9)	15 (83.3)	0.88

The oral mucosa of cancer patients is colonized by a variety of potentially pathogenic microorganism especially G+ve, G-ve opportunistic bacteria and fungi; disturbed integrity of oral epithelial barrier, leucopenia, changes in salivary flow and composition cause shifting of oral microflora to abundance of G-ve bacteria especially in patients with periodontal disease and those on antineoplastic therapy [10].

Table 7: Relation of oral pathogens to mucositis during induction of chemotherapy.

Type of species	Mucositis			p value
	No mucositis 23 no. (%)	Mild mucositis 29 (grade 1 and 2) no. (%)	Sever mucositis 10 (grade 3 and 4) no. (%)	
G+ve	21 (91.3)	26 (89.7)	8 (80)	0.626
G-ve	2 (8.7)	10 (34.5)	6 (60)	0.008
Candida	9 (39.1)	24 (82.8)	8 (80)	0.003

Table 8: Oral pathogen in relation to types of malignancies.

Type of species	Cancer		p value
	Lymphohematopoitic tumor (41) no. (%)	Solid tumors (21) no. (%)	
G+ve	38 (92.7)	17 (81)	0.214
G-ve	10 (24.4)	8 (38.1)	0.376
Candida	26 (63.4)	15 (71.4)	0.583

This study show leukemia and lymphoma were common diagnosis together they form over 65% of all cases, ALL was most common type of all malignancies 38.7% and NB was most common solid tumor 12.9%, this is similar to study in United Arab Emirate by EL-Hayek et al. [11] which also has revealed that leukemia and lymphoma were common diagnosis together they represent over 60% ALL and NB were constitute (86%, and 8%) of all types of malignancies respectively [11].

In the present study, the G+ve species is the most common microorganism in both control and patients, dominated by oral *V.*

streptococci. In cancer patient on D zero there is variation in proportion and types of G+ve species, decrease proportion oral *V. streptococci* and appearance of another G+ve bacteria like *S. aureus* and *S. epidermidis*, this may be due to immunosuppression related to pathology itself and antibiotic treatment administered to these patient for frequent infection during weeks before diagnosis, this in agreement to study in France by Sixou et al. [12], but on D14-D21 there is increase complexity of microflora and more decrease in proportion of oral *V. streptococci* in contrast to study by Sixou et al. [12] which shown that there is increased proportion of oral *V. streptococci* and less complexity than control, this is might be due to use of chlorohexidine antiseptic mouth wash and highly selections of sample from supragingival plaque of the mouth, while in this study the children with cancer have poor oral care and none selection of samples [13].

Oral *V. streptococci* is the most common G+ve species isolated from oral cavity on D0, D14, and D21, this is in contrast to study in Brazil by Soares et al. [14], which reported that coagulase negative staphylococcus were most frequent microorganism isolated from oral from oral mucosa of children with ALL and after developing mucositis during chemotherapy, this is due to possible relationship between *Coagulase negative staphylococcus* and development of oral mucositis [11].

The current study reveals that there is an increase in the frequency of opportunistic and pathogenic G-ve species isolated from oral mucosa (before and during induction of chemotherapy) in comparison to control groups like *Pseudomonas* species*, and K. pneumonia. E. Coli, E. cloaca*, and *N. cataralis*, this is in agreement with study in United State by Galili et al. [13]. This may be related to immunosuppression properties of disease itself or antiplastic therapy and bad oral conditions, and in contrast to study in Brazil by Soares et al. [14], which showed low frequency of G-ve bacteria in oral cavity, this is explained by prophylactic use of chlorhexidine in combination with daily oral hygiene care [14].

In this study also isolate *Candida* species, in control groups *C. albicans* only and in disease patients *C. albicans* and *C. tropicalis* and there is an increased risk of oral colonization's with fungal microorganism before chemotherapy and more increment during induction of chemotherapy, this is in agreement with study in USA by Lalla et al. [15] which reported that prevalence of oral colonization with fungal organism before chemotherapy during chemotherapy [15].

This study revealed that G-ve species and to a lesser extent fungi have been observed in oral cavity during chemotherapy in moderate to severe neutropenia, this in agreement to study in Baltimore by Peterson et al. [16], which show granulocytopenic patients with leukemia in mid-chemotherapy at subgingival site colonize with opportunistic microorganism like *E. cloaca* and G-ve genera such as *Pseudomonas* species*, Neisseria* and *Vionella* species ($p < 0.05$) [16]. This add an aerobic G-ve species were the predominant cause of infection in oral cavity of neutropenic patients.

Also oral mucositis are associated with changes in oral microflora, and study revealed that bacteria particularly G-ve species were more in severe mucositis and *Candida* species more in mild mucositis, this in agreement to study in India by Aniradhan et al. [8], which show that bacteria in severe mucositis (27.3%) and in mild mucositis (20.8%), while fungi in mild mucositis (38.8%) and in severe mucositis (36.4%) [8]. The explanation for these results is that severe mucositis, disturbed integrity of oral epithelial barrier, neutropenia, advance stage malignancy and bad oral hygiene are associated with increase of G-ve species in oral cavity [17] and *Candida* species are not primarily involved in oral mucositis.

Regarding age and sex, the study reveals G-ve species were more isolated from oral mucosa of younger age group < 5 year and females, this might be due to younger patients appear to have a greater risk of chemotherapy-induced stomatitis, females to a more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors [18]. G+ve more in 6 - 10 years and Candida slightly more in male, both age and sex are no significant difference p value > 0.05.

This study revealed stomatoxicity of oral mucosa due to disease itself or chemotherapeutic agents results in soreness or pain, difficulty of swallowing, dryness of mouth, oral thrush (clinically observe of candidiasis) and oral bleeding (especially when platelet less than 20000), these oral conditions were more in patients undergoing chemotherapeutic treatment than in patient with pathology only and there is significant differences p value < 0.05.

Conclusion

The G+ve species, particularly oral *V. streptococci* were the most common oral bacteria isolated from oral cavity of children with cancer, and there was some variation in proportion and types of G+ve species among patients before and during chemotherapy. Also, there is shifting and modification of oral microorganisms to more pathogenic and opportunistic G-ve species especially *Pseudomonas* species*, K. pneumonia, E. coli, E. cloaca,* and *N. cataralis* in children with malignancies and during chemotherapy. In addition to that increase frequency of *Candida* species especially *C. albicans* among disease patients and especially during chemotherapy. There was a significant association between G-ve and *Candida* species with oral mucositis and severity of neutropenia during induction phase of chemotherapy.

Acknowledgements

None.

Conflict of Interest

None.

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