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Original article

Caregiver Burden: Prevalence and Effect on Productivity among Adult Informal Caregivers of the Elderly in Klang Valley, Malaysia

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Abstract

Background: Caregiver burden refers to the physical, financial and psychosocial hardships of caring for a loved one. Informal caregivers, typically adult children who look after their elderly parents, shoulder an unspoken degree of stress from this filial responsibility. They report having to make major life changes and personal sacrifices. High degree of caregiver burden among working adults potentially affects their productivity at work. This study aimed to identify the prevalence of caregiver burden among adult family caregivers of elderly in Klang Valley, Malaysia and to determine the effect on work productivity. **Methods:** This cross-sectional study was performed on 281 adult family caregivers using a self-administered questionnaire. A short version of Zarit Burden Interview (ZBI-12) was employed to measure caregiver burden. Work Productivity and Activity Impairment as adapted for caregiving (WPAI: CG) was used to measure work productivity as well as regular activities. **Results:** Adult caregivers in Klang Valley reported experiencing moderate level of burden (ZBI-12 score =15.30) in providing care to their elderly. Employed caregivers reported an overall work productivity loss of 57.2% due to caregiver burden. The study subjects experienced 35.2% loss of regular activity productivity

and it significantly correlated with the degree of caregiving burden ($r = 0.499$, $p < 0.05$). Factors affecting caregiving burden include ethnicity of caregivers ($p<0.05$) and care recipients ($p < 0.05$), education level of caregivers ($p = 0.003$), overall health status of caregivers ($p = 0.006$) and care recipients ($p = 0.047$), family relationship of caregivers with the elderly ($p = 0.002$) and living arrangement of the elderly ($p = 0.005$). **Conclusion:** Informal adult caregivers of the elderly in Klang Valley experienced moderate level of caregiver burden and it significantly affected their work productivity.

Keywords: caregiver burden, stress, elderly, work productivity.

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Introduction

According to the Fifth Malaysian Population and Family survey, 95.3% of community-dwelling elderly receive care support from their family[1]. Family members are often the primary caregivers providing informal care to their elderly parents on a voluntary basis[2]. They are not formally trained nor have contract responsibility as in the case of housemaid and nurses. They perform a wide range of care tasks without time limit, including personal care, household chores and emotional support. With these filial duties, informal caregivers are very likely to encounter hardships in elderly caregiving and be subjected to stress. The duty of elderly caregiving is much more difficult for adult

caregivers who are employed as they are forced to juggle multiple roles at the same time.

Caregiver burden is described as an 'illness' for informal caregivers with imbalance of emotional, physical and financial demands [3]. The concept of caregiver burden is multi-dimensional and can be characterised as subjective and objective[4]. Subjective burden deals with the ways the caregivers perceive the care, which is related to their physical and psychological well-beings[4]. Zarit Burden Interview (ZBI) is the most frequently used instrument to measure subjective burden among informal caregivers of the elderly [5]. The 12-items short version ZBI (ZBI-12) was developed by Bédard et al.[6] with improved internal consistency compared to the original version.

A recent study by Ciccarelli and Van Soest[7] noted that caregiving negatively affected the employment status and work performance of caregivers. Longacre et al.[8] reported 39.8% of unemployed caregivers of older adults quit or retired early from their workforce and 52.4% employed caregivers experienced work interference due to caregiving responsibility. The study subjects also reported higher levels of emotional stress. Work productivity can be quantitatively described in terms of 'presenteeism' and 'absenteeism' [9]. Absenteeism refers to the time missed from work due to certain contributing factors. Meanwhile, presenteeism is the estimation of 'productive output' of an individual under the same exposure of those factors [9]. Work Productivity and Activity Impairment adapted for caregiving (WPAI: CG) is the first validated instrument to study the impacts of caregiving on work productivity and regular activity. It is duly validated among informal caregivers of chronically ill older adults.

This study aimed to identify the prevalence of caregiver burden among adult informal caregivers of the elderly in Klang Valley, Malaysia as well as to study the effect on both work productivity

and regular activities. We also analysed the association between caregiver burden and socio-demographics of informal caregivers, care recipients as well as characteristics of informal care situation respectively.

Materials and Methods

Study Design: This is a cross-sectional study using self-administered questionnaire. The inclusion criteria are adult informal caregivers aged between 18 to 64 years old, staying in Klang Valley, Malaysia and provided informal care to at least one elderly in their family on voluntary basis. This study excluded paid caregivers, including housemaids and nurses (i.e. formal caregivers). If the study respondents had more than one care-recipients, only one elderly they cared for the most was considered in this study.

Study Instrument

The survey instrument comprised of two parts, the validated ZBI-12 and WPAI:CG questionnaires. Scores on the ZBI-12 were used to classify the degree of burden by quartiles: no burden (scores between 0 to 3), mild burden (scores between 4 to 9), moderate burden (scores between 10 to 16) and high burden (score of 17 or above, up to 48) [6].

WPAI:CG instrument was used to measure four aspects of productivity (i.e. absenteeism, presenteeism, overall work productivity loss and regular activity productivity loss) [10]. Employed caregivers, including those who were self-employed, recalled the number of hours they missed from work for the past seven days due to caregiving and other reasons such as sick day. They also rated how caregiving affected their productivity on a scale of '0' to '10', with '0' referring to caregiving had no effect on work, and '10' referring to caregiving completely prevented them from working. The regular activity productivity loss of respondents was also scored on a scale of '0' to '10', with '0' referring to caregiving had no effect on regular activities, and '10'

referring to caregiving completely prevented them from performing regular activities [10]. The unemployed caregivers were asked whether they had to quit or retire from their job due to caregiving.

The questionnaire was designed in three major languages, e.g. Malay, Chinese and English to increase response rate and reduce potential reporting bias in data collection.

Sampling Method and Setting

Based on the Cochran's formula, the estimated sample size was 270 subjects with 90% confidence interval.

Random cluster sampling was employed to collect samples from ten municipalities of Klang Valley, i.e. Kuala Lumpur, Putrajaya, Shah Alam, Klang, Petaling Jaya, Subang Jaya, Ampang Jaya, Kajang, Sepang and Selayang. Subjects were approached in public places such as shopping malls, open markets, recreational parks and office areas. The questionnaires were then distributed if they consented to take part in the study. Nearly equal number of samples were collected from each cluster to ascertain fair representation of the population.

A total of two hundred and eighty-one subjects were included from August 2018 to September 2018.

Data Validity and Reliability

All three versions of ZBI-12 and WPAI: CG have officially been validated and approved to be used in this study. The English version of ZBI-12 is available from the published article by Bédard et al.[6]. The validated Malay version of ZBI was obtained from the original author with permission [11]. The validated Chinese version of ZBI-12 was adopted from the published article by Ko et al.[12]. WPAI-CG instrument adapted in this study was originally developed by Giovannetti et al.[10] in English. Chinese and Malay version of WPAI: CG were adopted from their official versions of WPAI: GH (General Health) [13,14].

A pilot study consisting of 30 randomly chosen respondents was conducted prior to the index study that yielded a Cronbach's alpha value of 0.782. The reliability test conducted on a sample size of 270 respondents achieved a good internal consistency with a Cronbach's alpha value of 0.885 [15].

Statistical Analysis.

Standard descriptive analysis was performed to summarise the demographic profile of study respondents and care-recipients. The prevalence of caregiver burden was computed as mean total ZBI-12 score. Presenteeism, absenteeism, overall work productivity loss and regular activity productivity loss of the respondents were calculated based on the formulae adopted from Giovannetti et al.[10]. Overall work productivity loss of employed caregivers was calculated from absenteeism, presenteeism and percentage of hours actually worked in seven days preceding study participation [10].

Spearman rank-order correlation analysis was conducted to determine the associations between total ZBI-12 score and absenteeism, presenteeism, overall work productivity loss and regular activity productivity loss of study respondents. This analysis was also applied to determine the relationship between total ZBI-12 score and socio-demographics of caregivers (i.e. age, overall health rating), overall health rating of care-recipients, duration of care and intensity of care. Mann-Whitney and Kruskal-Wallis tests were performed to compare the total ZBI-12 score across various characteristics of caregivers (i.e. gender, employment status, types of employment, nationality, ethnicity, highest education level, marital status), care-recipients (i.e. gender, ethnicity, relationship with caregivers) and living arrangement of care-recipients.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Version 22.0. For all analyses, a P

value of less than 0.05 was considered to indicate statistical significance.

Ethics Approval

This study was approved by the SEGi University Ethics Committee (Approval Code: SEGi/RIMC/FOP/18/2018). Written informed consent was obtained from all study participants prior to survey enrolment.

Results

Demographic of Respondents, Care Recipients and Informal Care Situation

A total of 281 subjects were included in the study. Majority of respondents were female (58.4%), Malaysian (99.3%) and of Bumiputera ethnicity (52.7%). Of the 179 employed respondents (63.7%), 48% were working full-time (N=135), 12.1% self-employed (N=34) and 3.6% were employed part-time (N=10). Among 102 respondents who were not working, 11.8% quit or retired early from their previous job due to caregiving. The study respondents rated their own health status with an average of 7.9 (SD = 1.68) on a scale of ten.

The demographics of the elderly receiving care was vastly skewed towards female (67.3%) of Bumiputera background (53.0%). At the time of the survey, the respondents rated the health status of their elderly (i.e. parents, grandparents, spouse, other relationships) a low score of 4.53 on a scale of ten.

The study respondents reported to have spent an average of 59 months (SD=78.65) rendering informal care to their elderly, clocking in about 7.7 hours per day (SD=6.31) for caregiving.

Table 1: Demographic of respondents, care recipients and informal care situation.

Characteristics	N	Percentage (%)	Mean ± SD	Median (IqR)

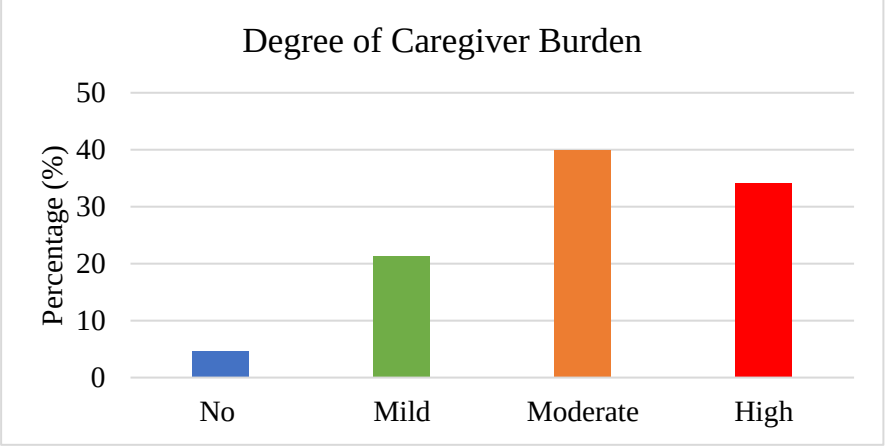
Caregiver gender				
Male	117	41.6	NA	NA
Female	164	58.4		
Caregiver age	281	NA	35.5 ±12.05	34 (19)
Caregiver ethnicity				
Bumiputera	148	52.7		
Chinese	96	34.2	NA	NA
Indian	35	12.5		
Others	2	0.7		
Caregiver nationality				
Malaysian	279	99.3	NA	NA
Non-Malaysian	2	0.7		
Caregiver educational level				
Primary school	16	5.7		
Secondary school	109	38.8		
Pre-university education	57	20.3	NA	NA
Undergraduate education	80	28.5		
Postgraduate education	17	6.0		
Others	2	0.7		
Caregiver marital status				
Never married	115	40.9		
Married	160	56.9	NA	NA
Others	6	2.1		
Caregiver current employment status				
Working	179	63.7	NA	NA
Not working	102	36.3		
Types of employment status				

Employed, full time	135	48.0		
Employed, part time	10	3.6		
Self-employed	34	12.1	NA	NA
Unemployed	38	13.5		
Student	54	19.2		
Retired	8	2.8		
Others	2	0.7		
Quit or retire early due to caregiving				
Yes	12	11.8	NA	NA
No	90	88.2		
Overall health rating of caregiver	281	NA	7.9 ± 1.68	8 (3)
Care recipient gender				
Male	92	32.7	NA	NA
Female	189	67.3		
Care recipient ethnicity				
Bumiputera	149	53.0		
Chinese	94	33.5	NA	NA
Indian	36	12.8		
Others	2	0.7		
Family relationship of caregivers with care recipients				
Parents	154	54.8		
Spouse	5	1.8	NA	NA
Grandparents	112	39.9		
Others	10	3.6		
Overall health rating of care recipient	281	NA	4.5 ± 2.25	5.0 (3.0)
Living arrangement of elderly				
Live along with caregiver	167	59.4	NA	NA
Live apart from caregiver	114	40.6		

Duration of care (months)	281	NA	59.0 ± 78.65	24.0 (66.0)
Intensity of care (hours per day)	281	NA	7.7 ± 6.31	5.0 (6.5)

Note. N = Frequency. SD = Standard deviation. IqR = Interquartile range. NA = Not applicable.

Graph 1: Degree of caregiver burden



Caregiver Burden

The mean ZBI-12 score recorded among our study subjects was 15.3. This corresponds a caregiver burden of moderate intensity. Figure 1 shows the distribution of burden perceived by the study respondents.

Work Productivity and Activity Impairment

Employed caregivers of the elderly reported to experience various degree of work interference due to their filial duties, specifically 27.5% of absenteeism and 34% of presenteeism. This translates

to a substantial work productivity loss of 57.2% and an overall loss of regular activity productivity of 35.2%.

As shown in Table 2, spearman correlation tests showed positive correlation between ZBI-12 score and presenteeism ($r = 0.447$, $p < 0.05$), overall work productivity loss ($r = 0.335$, $p = 0.001$) as well as regular activity productivity ($r = 0.499$, $p < 0.05$).

Associations between Caregiver Burden and Characteristics of Caregivers, Care Recipients and Care Situation

Caregiver burden was inversely associated with the health status of the adult caregivers ($r = -0.148$, $p = 0.006$) and the elderly they were rendering care for ($r = -0.1$, $p = 0.047$). Caregivers with Chinese background reported the highest burden (ZBI-12 score = 17.00) and it was significantly different from those of Bumiputera caregivers (ZBI-12 score = 11.00, $p < 0.05$). Kruskal-Wallis test showed there were significant difference in caregiver burden sustained by caregivers of different educational backgrounds ($p < 0.003$).

Caregivers who were spouses of the elderly reported to experience statistically significant burden (ZBI-12 score = 34) compared to other family relationships. Respondents who were the children or grandchildren taking care of their elderly reported significantly lower burden ($p = 0.012$ and $p = 0.025$ respectively), compared to those who had other family ties with the care recipients (e.g. relatives).

Table 2: Spearman correlation between total ZBI-12 score and work productivity as well as regular activity productivity.

	r	*p*
Absenteeism	0.023	0.415
Presenteeism	0.447	<0.05

Overall Work Productivity Loss	0.335	0.001
Regular Activity Productivity Loss	0.499	<0.05

Note. r = correlation coefficient. *p* = significance

Table 3: Association between caregiver burden with socio-demographics of caregivers, care recipients and care situation.

	r	M	*p*
Overall health rating of caregiver	-0.148	NA	0.006
Caregiver ethnicity			<0.05
Bumiputera	NA	11.00	
Chinese		17.00	
Indian		12.00	
Others		7.00	
Caregiver highest education level			0.003
Primary education	NA	20.00	
Secondary education		11.00	
Pre-university education		12.00	
Undergraduate education		16.00	
Postgraduate education		13.00	
Others		21.50	
Overall health rating of elderly	-0.100	NA	0.047
Care recipient ethnicity			<0.05
Bumiputera	NA	11.00	
Chinese		17.00	
Indian		11.50	
Others		12.00	
Family relationship of caregiver to care recipient			0.002
Parent	NA	12.00	
Spouse		34.00	
Grandparent		13.00	
Others		27.50	

Living arrangement of elderly			0.005
Live along with caregiver	NA	14.00	
Live apart from caregiver		12.00	

Note. r = correlation coefficient. M = Median. *p* = significance. NA - Not applicable.

Discussion

In this cross-sectional community-based survey that directly analysed the prevalence of caregiver burden and its impact on work productivity, we found that the degree of caregiver stress experienced by employed caregivers in the metropolitan city of Klang Valley, Malaysia, was deeply concerning. Based on the self- administered Zarit Burden Interview (ZBI-12) questionnaire, the level of caregiver burden among the 281 study subjects was recorded to be of moderate intensity. Furthermore, this largely underrated stressor was also shown to significantly affect the work productivity of these employed caregivers. These findings concur with works of Longacre et al.[8] and Abu Bakar et al.[16] in their respective studies whereby caregiving was shown to negatively affect work performance of employed subjects leading to work-care conflicts.

As with many Asian societies, filial piety has a deep-rooted cultural significance in Malaysia [17,18]. With intergenerational co-residence being a very common yet integral attribute of Asian families [19], family members naturally shoulder the responsibility of caring for their elders.

Often unprepared and/ or inadequately trained, these informal carers take on a tough and daunting task of looking after their frail parents/ grandparents which could result in undue stress and anxiety. Over time, this could overspill into their work performance and affect their productivity at work.

In our study, the respondents acknowledged to an overall work

productivity loss of 57.2% exclusively due to their responsibilities of providing care to their elderly parents/ spouses in the household. This loss of work productivity was linearly associated with the degree of burden endured by the study respondents. In other words, the greater the burden of caregiving, the higher the loss of productivity at work.

Absenteeism [20,21], crudely defined as habitual absence from scheduled work, due to caregiving was calculated to be 27.5%. Although there was a weak correlation between absenteeism and the degree of caregiver burden, it was not statistically significant. On the other hand, presenteeism, a more complex variant of unproductivity, was recorded at 34%. Not surprisingly, presenteeism was positively associated with the level of caregiver stress in our study.

Presenteeism is characterized by employees not being fully functional in the workplace despite coming to work, due to impaired physical or psychological health issues [22]. In the case of informal caregivers, caring for their loved ones understandably takes a toll on their emotional wellbeing, which in turn could have an adverse impact on their presence of mind and hence, poor efficiency at workplace.

These staggering numbers are a serious cause for concern and acutely reflect an unmet need of our working adults who are clearly overwhelmed juggling between work and rendering care to their elderly. The economic repercussions of these statistics would be an interesting facet to explore to accurately valuate and monetise these intangible costs of informal care provision.

Our results are consistent with the findings by Wolff et al.[23] wherein caregiving had no significant effect on absenteeism but greatly reduced the overall work productivity and performance while at work of those employed caregivers.

Elsewhere, studies have also shown that care provision in a family negatively influences the employment experience and income of employed caregivers with lesser chance of job promotion [16].

Caregivers require time and energy to care for their loved ones. However, when they are at work, they are unable to fulfil their responsibility adequately. As a result, some caregivers are forced to quit or retire early from their job and focus more on caregiving. In our study, 11.8% of the unemployed respondents admitted to leaving their career due to their filial duties. The socioeconomic security of these caregivers as well as the care-recipients remains to be evaluated.

It is interesting to note that there was a significant difference in the caregiver burden perceived by the various ethnic groups in this country, with the Chinese reporting highest level of burden and the Bumiputera carers the lowest. This could in part be explained by the cultural differences between these two societies. Most of the Bumiputera in this country are Muslims and one of the principle teachings in Islam is to be respectful, patient and tolerant when dealing with the elderly [24]. This underpins a strong filial piety whereby they faithfully accept caring for their elderly as a responsibility, and thus see it as less of a burden.

Elsewhere, Ting and Woo[25] had noted that there is an increase in nuclear families among the Chinese which may have weakened the traditional extended family support. Changes in family values between younger and older generations could also contribute to the waning traditional Chinese culture of filial propriety.

The health status of the caregivers as well as the care-recipients had a significant correlation with the perceived burden of care. The poorer the health status of the carers or their recipients, the

greater the burden of care. The finding echoes the premise that the physical and mental health of the caregivers affect their competency in providing the necessary care for their elders [26]. This could serve as a focus area in implementing strategies to alleviate the burden of caring for their elderly.

Similarly, the health condition of the care recipients is also an invariable stressor that compounds the degree of burden borne by the carers [27]. In a study among caregivers of the elderly with chronic illnesses, Ghazali et al.[28] reported that caregiving for elderly with greater functional dependence was seven times more burdensome.

In our study, spousal caregivers experienced the greatest caregiving burden among all because they are considered as the primary caregiver in a family. They tend to perform more care tasks and spend longer time for caregiving without pressuring their children[29]. As observed by Giovannetti et al.[10], co-residing caregivers experienced a greater reduction in work productivity compared to those who lived apart from their care recipients. This is because they are engaged more in the caregiving duties thus affecting their work hours[30].

Elderly caregiver burden could escalate to a serious socioeconomic issue if it is not addressed in a timely manner. Prolonged mental strain endured by these caregivers could lead to chronic stress and eventually burnout. It is therefore imperative that social programmes are put in place to raise awareness about caregiver burden and strategies are individualised to educate the carers on appropriate coping mechanisms.

The strengths of this study include a community-based design with adequate sample size, using validated survey instruments. To our knowledge, this is the maiden study in Malaysia that

directly assessed the prevalence of caregiver stress of the elderly and the impact on productivity at work.

Several limitations need to be acknowledged. The possibility of confounding by unmeasured or unknown factors cannot be excluded. Also, our study may not be generalisable to the entire Malaysian population as it was conducted within Klang Valley.

Conclusion

In conclusion, informal caregivers of elderly in Klang Valley, Malaysia reported to experiencing moderate level of caregiver stress, that was significantly associated with overall work productivity and regular activity productivity loss. The prevalence of absenteeism and presenteeism was recorded at 27.5% and 34%, respectively with the latter having significant correlation with the degree of caregiver burden. The welfare of informal caregivers in this country needs to be addressed via social or individually tailored programmes as to safeguard the socioeconomic health of our nation.

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References

1. National Population and Family Development Board (NPFDB). Report on Key Findings of the Fifth Malaysian Population and Family Survey (MPFS-5). National Population and Family Development Board *(NPFDB)*. 2014:1-92.

2. Hoefman R, Van Excel N, Brouwer W. IMTA Valuation of Informal Care Questionnaire (IVICQ). Erasmus Universiteit Rotterdam. 2011;Vol 1.1. https://www.imta.nl/questionnaires/. Accessed June 30, 2018.

3. WHO Centre for Health Development. A Glossary of Terms for Community Health Care and Services for Older Persons. Kobe, Japan: WHO Centre for Health Development; 2004. http://apps.who.int/iris/handle/10665/68896. Accessed October 26, 2018.

4. Flyckt L, Fatouros-Bergman H, Koernig T. Determinants of subjective and objective burden of informal caregiving of patients with psychotic disorders. Int J Soc Psychiatry. 2015;61(7):684-692. doi:10.1177/0020764015573088

5. Whalen KJ, Buchholz SW. The reliability, validity and feasibility of tools used to screen for caregiver burden: a systematic review. JBI Libr. Syst. Rev. 2009;7(32):1373-1430.

6. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview: a new short version and screening version. Gerontologist. 2001;41(5):652-657. doi:10.1093/geront/41.5.652

7. Ciccarelli N, Van Soest A. Informal Caregiving, Employment Status and Work Hours of the 50+ Population in Europe. Economist. 2018;166(3):363-396. doi:10.1007/s10645-018-9323-1

8. Longacre ML, Valdmanis VG, Handorf EA, Fang CY. Work Impact and Emotional Stress Among Informal Caregivers for Older Adults. J Gerontol B-Psychol. 2017;72(3):522-531. doi:10.1093/geronb/gbw027

9. Despiégel N, Danchenko N, François C, Lensberg B, Drummond MF. The use and performance of productivity scales to evaluate presenteeism in mood disorders. Value

Health. 2012;15(8):1148-1161. doi:10.1016/j.jval.2012.08.2206

10. Giovannetti ER, Wolff JL, Frick KD, Boult C. Construct validity of the Work Productivity and Activity Impairment questionnaire across informal caregivers of chronically ill older patients. Value Health. 2009;12(6):1011-1017. doi:10.1111/j.1524-4733.2009.00542.x

11. Shim VK, Ng CG, Drahman I. Validation of the Malay Version of Zarit Burden Interview (MZBI). Malaysian Journal of Psychiatry. 2017;26(2):3-18. https://www.mjpsychiatry.org/index.php/mjp/article/view/443. Accessed October 4, 2019.

12. Ko K-T, Yip P-K, Liu S-I, Huang C-R. Chinese version of the Zarit caregiver Burden Interview: a validation study. Am J Geriat Psychiat. 2008;16(6):513-518. doi:10.1097/JGP.0b013e318167ae5b

13. RWS Life Sciences. WPAI: GH Version 1.0 (Simplified Chinese). 2018. http://www.reillyassociates.net/WPAI-GH__Chinese-Simplified-China_.pdf. Accessed September 28, 2018.

14. RWS Life Sciences. WPAI: GH Version 2.1 (Malay). 2018. http://www.reillyassociates.net/WPAI-GH_V2_1-Malay-Singapore-13OCT2014-final-debriefed.docx. Accessed September 28, 2018.

15. Manerikar V, Manerikar S. Cronbach's Alpha. AWEshkar. 2015;19(1):117-120.

16. Abu Bakar SH, Weatherley R, Omar N, Abdullah F, Mohamad Aun NS. Projecting social support needs of informal caregivers in Malaysia. Health & Social Care in the Community. 2014;22(2):144-154. doi:10.1111/hsc.12070

17. Ishii-Kuntz M. Intergenerational Relationships Among Chinese, Japanese, and Korean Americans. Fam Relat. 1997;46(1):23-32. doi:10.2307/585603

18. Beh L, Folk JY. A study of filial piety practice in Malaysia: Relationship between financial well-being and filial piety. Afr J Bus Manag. 2013;7(38):3895-3902. doi:10.5897/AJBM10.424

19. Bongaarts J, Zimmer Z. Living arrangements of older adults in the developing world: an analysis of demographic and health survey household surveys. J Gerontol B-Psychol. 2002;57(3):145-157. doi:10.1093/geronb/57.3.S145

20. Harrison DA, Martocchio JJ. Time for Absenteeism: A 20-Year Review of Origins, Offshoots, and Outcomes. J Manage. 1998;24(3):305-350. doi:10.1177/014920639802400303

21. Johns G. Absenteeism and presenteeism: not at work or not working well. In: The Sage Handbook of Organizational Behavior. London: Sage; 2008:160-177.

22. Demerouti E, Blanc PM, Schaufeli W, Hox J. Present but sick: A three-wave study on job demands, presenteeism and burnout. Career Development International. 2009;14:50-68. doi:10.1108/13620430910933574

23. Wolff JL, Giovannetti ER, Boyd CM, et al. Effects of guided care on family caregivers. Gerontologist. 2010;50(4):459-470. doi:10.1093/geront/gnp124

24. Rosdinom R, Zarina MZN, Zanariah MS, Marhani M, Suzaily W. Behavioural and Psychological Symptoms of Dementia, Cognitive Impairment and Caregiver Burden in Patients with Dementia. Prev Med. 2013;57:67-69.

25. Ting G, Woo J. Elder care: is legislation of family responsibility the solution? Asian Journal of Gerontology and Geriatric. 2009;4(2):72-75.

26. Broese van Groenou MI, De Boer A. Providing informal care in a changing society. Eur J Ageing. 2016;13(3):271-279. doi:10.1007/s10433-016-0370-7

27. Poulshock SW, Deimling GT. Families caring for elders in residence: issues in the measurement of burden. J Gerontol. 1984;39(2):230-239. doi:10.1093/geronj/39.2.230

28. Ghazali SB, Abdullah KL, Aziz ABA, et al. Burden of caregivers of the elderly with chronic illnesses and their associated factors in an urban setting in Malaysia. Malaysian Journal of Public Health Medicine. 2015;15(1):1-9. https://ukm.pure.elsevier.com/en/publications/burden-of-caregivers-of-the-elderly-with-chronic-illnesses-and-th. Accessed October 4, 2019.

29. Friedemann M-L, Buckwalter KC. Family Caregiver Role and Burden Related to Gender and Family Relationships. J Fam Nurs. 2014;20(3):313-336. doi:10.1177/1074840714532715

30. Covinsky KE, Eng C, Lui LY, et al. Reduced employment in caregivers of frail elders: impact of ethnicity, patient clinical characteristics, and caregiver characteristics. J Gerontol A Biol Sci Med Sci. 2001;56(11):707-713. doi:10.1093/gerona/56.11.m707

Original article

Formulation and Evaluation of Acyclovir Oral Disintegrating Tablets

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Abstract

Background: Orally disintegrating tablets (ODTs) have recently gained attention as the substitute of conventional dosage form. Superdisintegrants, the main component in the ODTs, render fast disintegrating properties and facilitate the dissolution of active drug. **Aims:** In the present study, the main aims were to prepare acyclovir ODTs using superdisintegrants (sodium starch glycolate and croscarmellose sodium) by direct compression method and investigate the outcome of using various concentrations of superdisintegrant in single and combination formulations. **Materials and Methods:** Superdisintegrants incorporated in the formulations were croscarmellose sodium and sodium starch glycolate in single (F1, F2, F3 and F4) and binary combination (F5 and F6) and acyclovir tablets were directly compressed. Critical quality attributes investigated were uniformity of weight, thickness, hardness, friability, wetting time and water absorption ratio, in vitro disintegration time and in vitro dissolution study. One-way statistical ANOVA test and post hoc test were conducted by using Statistical Package for the Social Science (SPSS) software version 21. **Results:** The maximum acyclovir release rate was achieved in formulations F5 (90.09 ± 0.43%) followed by F2 (70.29 ± 0.07%) and F1 (61.33 ± 1.15%). Among the 7 formulations investigated, 1% w/w SSG and 5% w/w CCS in formulation F5 demonstrated shortest disintegration time (7.33 ± 0.246 seconds) and greatest dissolution rate (90.09 ± 0.43%). Such combination ratio provided synergism between mechanisms of action of two superdisintegrants (swelling and

wicking) thus resulted in excellent wetting properties and water absorption ratio ($p < 0.05$). **Conclusion:** From the present study, combination of superdisintegrants in ratio 1:5 did result in better disintegration and dissolution rate compared to ratio 1:1 and other single superdisintegrant formulations in terms of critical quality attributes investigated.

Keywords: Orally disintegrating tablets, acyclovir, superdisintegrants, sodium starch glycolate, croscarmellose sodium

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Introduction

Oral disintegrating tablets (ODTs) encountered significant recognition and focus to provide a more convenient drug delivery system. United States Food and Drug Administration (FDA) defines it as 'a solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue'[1].

Sodium starch glycolate (SSG) is a cross linked polymer of carboxymethyl starch. SSG is reported to undertake swelling mechanism where it can swell up to 7-12 folds in 3 dimensions within 30 seconds through fast water absorption. In a study of chlorpheniramine tablets formulated with different concentrations of SSG, it was found that when the concentration of superdisintegrant increased from 5% w/w and above, the disintegration time was reduced considerably[2]. However, it was reported that SSG of 8% w/w and above would lengthen disintegration time due to gel formation with increased viscosity[3].

Based on these studies, it is recommended to incorporate SSG at a concentration between 2-8%.

Croscarmellose sodium (CCS) is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking in CCS makes it insoluble and hydrophilic hence rendering to the superior swelling properties[4]. Its fibrous nature assists the great uptake amount of water and disintegrating by capillary action[5]. CCS has both swelling and wicking mechanism for good disintegrating properties and its concentrations usually ranged between 1-5% w/w in tablet formulations[6].

Acyclovir is an antiviral drug used in the pharmacological management of Herpes simplex virus infections, Varicella zoster (chickenpox) and Herpes zoster (shingles). Acyclovir will be converted to acyclovir triphosphate, which actively blocks viral DNA polymerase and destroys the growing viral DNA chain. It is belongs to Class III Biopharmaceutics Classification System (BCS) as it has high solubility and low permeability[7]**.** Oral route is generally safer as compared to intravenous route in terms of adverse effects[8].

Materials and methods

Materials

Acyclovir was the active ingredient in the formulation. Microcrystalline cellulose acted as diluent and binder (COMPRECEL M102D+) and magnesium stearate was purchased from ACROS ORGANICS. Sodium starch glycolate and potassium dihydrogen phosphate anhydrous were purchased from CHEMSOLN. Parteck ODT® which contained 95% croscarmellose sodium and 5% mannitol were used as superdisintegrant.

Equipments

List of equipments involved Mettler Toledo Al204 Analytical Balance, Turbula Shaker Mixer, Mini Press-SF Tabletting Machine, Copley (TBF 1000) Tablet Hardness Tester, Electrolab EF-2 Friabilator, Electrolab ED-2AL Disintegration Tester, Electrolab TDT-08L Dissolution Tester and Beckman Coulter DU 730 Life Science UV/Vis Spectrophotometer

Methods

Formulation of acyclovir ODTs

Seven formulations containing acyclovir as active ingredient were formulated. Four formulations had single superdisintegrant (sodium starch glycolate) incorporated at 2% w/w, 4% w/w, 8% w/w and 10% w/w and one control formulation without superdisintegrant (F7). Two formulations had combination of superdisintegrants (sodium starch glycolate and crosscarmellose sodium) at the ratio of 1:5 and 1:1 as shown in Table 1. Acyclovir and the excipients were weighed and blended in turbula shaker mixer for 15 minutes at 45 rpm and accounted for pre-formulation studies. After that, the powder blends were tableted by direct compression using rotary punch tableting machine with compression force fixed at 600-800 N.

Table 1: Formulation composition of acyclovir ODTs

Ingredients (mg)	**Formulations (mg)**						
	F1	**F2**	**F3**	**F4**	**F5 (1:5)**	**F6 (1:1)**	**F7 (control)**
Acyclovir	50	50	50	50	50	50	50
Parteck ODT	-	-	-	-	10	10	-
MCC	144	140	132	128	136	128	148
SSG	4	8	16	20	2	10	-
Magnesium stearate	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200

Pre-formulation studies

Angle of repose

Angle of repose was employed to measure powder flow properties by using funnel method. The powder were poured and allowed to flow freely through the funnel onto the plane.

Angle of repose, $\tan \alpha = \frac{h}{r}$

h = Height (cm)

r = Radius (cm).

Carr's compressibility index and Hausner's ratio

$$\text{Bulk density} = \frac{\text{weight of sample (g)}}{\text{initial volume occupied by the sample (ml)}}$$

$$\text{Tapped density} = \frac{\text{weight of sample (g)}}{\text{volume occupied by the sample after tapping (ml)}}$$

Powder compressibility evaluates the ability of powder in forming a stable and intact compact mass after pressure is applied:

$$\text{Carr's compressibility index} = \frac{\text{tapped density} - \text{poured density}}{\text{tapped density}} \; x \; 100\%$$

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{poured density}}$$

Post-compression studies

Appearance

The appearance of the ODTs was recorded with respect to the components such as shape, colour, odour and surface texture.

Uniformity of weight

Twenty tablets were taken randomly from each formulation and weighed separately to determine the average mass by using Mettler Toledo Al204 Analytical Balance. The acceptance limit is no more than two tablets should be deviated by ± 7.5% and none of the tablets differ by exceeding two times of ± 7.5%.

Thickness

Ten tablets were chosen from each formulation and the average was reported in mm by using vernier calipers. Thickness of each tablet should be within ± 5% of variation.

Hardness

Ten tablets were picked from individual formulation at a random. Each tablet was positioned between the two plungers of the Copley (TBF-1000) Tablet Hardness Tester. The force needed to break down the tablet into two parts entirely was measured in terms of kg/cm^2.

Friability

For tablet with an individual weight equivalent to or lesser than 0.65 g, take a total mass as closely to 6.5 g. The tablets were rotated up to 100 revolutions in Electrolab Ef-2 Friabilator. After that, the tablets were removed for dedust and reweigh.

$$\% \text{ friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \; x \; 100\%$$

Wetting time and water absorption ratio

A petri dish containing 10 mL of Rhodamine B solution was prepared by dissolving Rhodamine B dye in distilled water. A tablet was selected at random from every formulation and positioned in the centre of the petri dish. The test was carried out in triplicates. Time required for solution to reach top of the tablets was noted.

$$R = \frac{W_b - W_a}{W_a}$$

where R = water absorption ratio

W_a = weight before (g)

W_b = weight after (g)

In vitro disintegration time

The test was performed using a USP tablet disintegration test apparatus (Electrolab ED-2AL Disintegration Tester). Six tablets were employed from individual formulation in distilled water maintained at 37 ± 0.5 °C. The time needed for tablet to be complete disintegrated from large fragment into small fragments is recorded.

In vitro dissolution study

In vitro dissolution study for acyclovir ODTs were performed using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The study was conducted at 50 rpm in 900 ml of phosphate buffer (pH 6.8) at 37 ^{0}C using Electrolab TDT-08L Dissolution Tester. Ten millilitre of the sample solution was withdrawn from every vessel at time intervals of 0, 1, 3, 5, 10, 15, 20, 30, and 40, 50 and 60 minutes. After each sampling, an equivalent volume of phosphate buffer was refilled into the medium to keep consistent volume. Amount of acyclovir release can be determined through regression equation (y= 0.0614x – 0.0139). Percentage of acyclovir release at every specific time was determined and plotted in graph. Dissolution studies were conducted in replicates of six. Tolerance requires not less than 80% of acyclovir should be released from the formulation at 45th minutes of dissolution study.

Analytical method validation

Linearity

Acyclovir stock solution was produced by dissolving 100 mg of acyclovir powder in 100 mL of phosphate buffer. Five different

concentrations (0.625, 1.25, 2.5, 5, 10 and 15 microgram per mL) were prepared from acyclovir stock solution to determine absorbance and plot calibration graph. When the square of the correlation coefficient, r^2 is equivalent to or greater than 0.98, linearity was fulfilled.

Specificity

Specificity test was conducted to determine the absorbance values of both placebo and active formulations. The maximum absorbance of acyclovir stock solution was determined at 250 nm using Beckman Coulter DU 730 Life Science UV/Vis spectrophotometer.

Accuracy

A tablet was dissolved in 100 mL of phosphate buffer. After that, the solution with dissolved tablet was tested by using Beckman Coulter DU 730 Life Science UV/Vis spectrophotometer at wavelength of 250 nm to get the readings of absorbance. The accuracy test was performed in triplicates for each formulation studied.

Precision

Intermediate precision was performed through dissolution test of the same formulation for 3 different days. Results were expressed as percentage of dissolution and the percentage of relative standard deviation (RSD) at the 60^{th} minutes of the study. Generally, a RSD of less than 2 % was required based on ICH guidelines.

$$\% \text{ RSD} = \frac{\text{Standard Deviation}}{\text{Mean}} \text{ x } 100\%$$

Robustness

Robustness test was performed by testing UV absorbance of standard stock acyclovir solution at 3 different wavelengths of 249 nm, 250 nm and 251 nm to obtain 6 replicates of readings for each wavelength by using Beckman Coulter DU 730 Life Science UV/Vis spectrophotometer.

Results and discussion

Pre-formulation studies

Table 2: Pre-formulation studies result of formulations F1 to F7.

Formulation	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's compressibility index (%)	Hausner's ratio
1	25.37	0.4387	0.5440	19.36	1.24
2	25.25	0.4508	0.5544	18.69	1.23
3	26.57	0.4495	0.5761	21.97	1.28
4	26.35	0.4389	0.5581	21.36	1.27
5	25.20	0.4262	0.5643	24.47	1.32
6	27.44	0.4464	0.5476	18.48	1.23
7	26.57	0.4447	0.5409	17.79	1.22

Angle of repose was in the range of 25° to 31°, showing powder blends suitable for manufacturing purposes. The compressibility index of all formulations was 17.79% to 24.47% while Hausner's ratio was observed to be between 1.22 to 1.32. With good powder flowabilty, the dies were filled with same amount every time during tableting process thereby the content uniformity for each tablet was assured.

FTIR Spectroscopy

Figure 1: FTIR results of formulations containing acyclovir, acyclovir with SSG, acyclovir with SSG and CCS and placebo

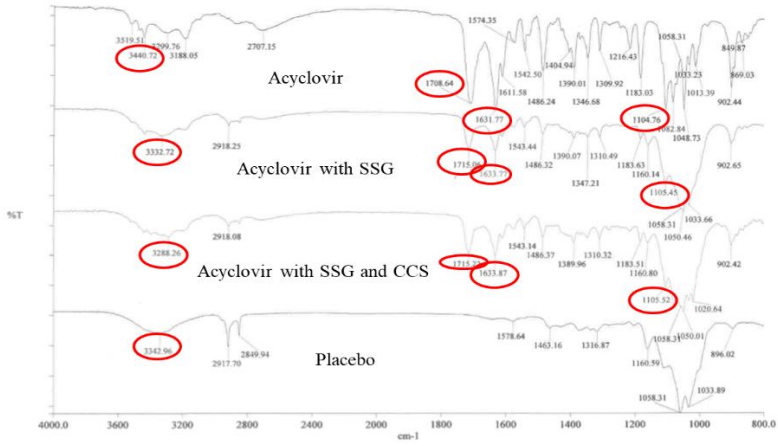

Table 3: FTIR results of formulations

Wave number	**Formulations**			
	Acyclovir alone	**Acyclovir with SSG (F2)**	**Acyclovir with SSG and CCS (F5)**	**Placebo (MCC and Mg stearate) (F7)**
N-H stretch	3440.72	3332.72	3288.26	3342.96
C=N stretch	1631.77	1633.77	1633.87	-
C=O stretch	1708.64	1715.06	1715.22	-
C-O-C stretch	1104.76	1105.45	1105.52	-

FTIR investigation of pure acyclovir, formulation F2 (acyclovir and SSG), formulation F5 containing (acyclovir, SSG and CCS) and control formulation F7 (MCC) were obtained. FTIR diagram of acyclovir demonstrated four particular peaks at 3440.72 cm^{-1} attributable to N-H stretch, 1631.77 cm^{-1} in view of C=N stretch, 1708.64 cm^{-1} owing to C=O stretch and 1104.76 cm^{-1} indicating C-O-C stretch. IR spectra of F2 and F5 demonstrated the characteristic pinnacles of the unadulterated drug acyclovir. Meanwhile, control formulation F7 showed peak at 3342.96 cm^{-1} which was possibly ascribed to the O-H bond in MCC structure. From the elucidation above, there was no shifting in the frequencies of functional groups mentioned earlier. Hence, there was no association between acyclovir and the excipients.

Post-compression studies

Physical evaluation of acyclovir ODTs

Figure 2: Physical appearance of acyclovir ODTs formulations F1-F7.

All the acyclovir ODTs were white, odourless and circular with smooth and shiny texture.

Performance evaluation of acyclovir ODTs

Table 4: Post compression evaluation results of acyclovir ODTs.

Formulation	Weight (g)	Thickness	Hardness	Friability (%)	Wetting time	Water absorption	In vitro disintegration

		(mm)	(kg/cm^2)		(sec)	ratio (%)	time (sec)
1	0.2304 ± 0.003	2.52 ± 0.012	6.70 ± 0.354	0.107	5.49 ± 0.176	75.46 ± 2.672	12.20 ± 0.243
2	0.2318 ± 0.003	2.52 ± 0.013	7.24 ± 0.325	0.117	2.80 ± 0.229	80.72 ± 1.843	9.07 ± 0.482
3	0.2420 ± 0.003	2.55 ± 0.020	6.66 ± 0.373	0.064	6.83 ± 0.405	63.81 ± 0.841	15.62 ± 0.816
4	0.2481 ± 0.003	2.63 ± 0.019	6.14 ± 0.332	0.549	6.74 ± 0.487	60.68 ± 0.508	20.80 ± 0.882
5	0.2422 ± 0.004	2.54 ± 0.011	6.50 ± 0.310	0.960	3.08 ± 0.772	82.13 ± 0.821	7.33 ± 0.246
6	0.2421 ± 0.007	2.57 ± 0.015	5.82 ± 0.120	0.170	8.99 ± 0.441	56.76 ± 0.569	17.66 ± 0.357
7	0.2337 ± 0.004	2.49 ± 0.016	7.51 ± 0.178	0.110	7.59 ± 0.331	41.14 ± 0.901	51.24 ± 0.993

All ODTs had complied with the uniformity of weight test as there was none of the single tablet which deviated from the average mass by ± 7.5% according to United State Pharmacopoeia (2014). The thickness for seven formulations was ranged 2.49 ± 0.016 mm to 2.63 ± 0.019 mm. Moving on to hardness, tablet hardness of all formulations was within the range of 5.82 ± 0.12 kg to 7.51 ± 0.178 kg. All formulations achieved the friability percentage in the range of 0.064% to 0.960 in accordance with the USP specifications which suggested that the tablets were mechanically stable and have the ability to resist abrasion in handling, packaging and transportation.

Formulation F5 showed the least wetting time followed by formulations F2, F1, F4, F3, F6 and F7 ($p < 0.05$). Control formulation F7 showed longest wetting time as it lacked of superdisintegrant in promoting the water uptake through swelling or wicking. The significantly longer wetting time observed in F3 and F4 was attributed to the disintegration mechanism of SSG which swells in contact with aqueous medium. Swelling in SSG was described to be occurred with gelling action and it may block the pores in the tablet to prevent water penetration into the tablet matrix thus wetting time increased. The incorporation of CSS to SSG formulations improved the wetting of the tablets due to its porous structure. However, formulation F6 comprising a binary superdisintegrants of SSG and CCS in ratio 1:1 had make an exemption as its wetting time was not critically shorter than formulations containing single superdisintegrant. It is possibly due to gelling effect of SSG contributing to the binding of tablet matrix and resulted in longer wetting time and limiting tablet disintegration[9].

Highest water absorption ratio was observed in formulation F5, which assumed to have swelled up to 82.13%. Formulations consisting superdisintegrants (F1-F6) showed greater water

absorption ratio than control F7 ($p < 0.05$). This was owing to the high water uptake and retention ability of superdisintegrants. Highly swelling materials (SSG and CCS) were able to absorb and maintain a larger amount of water whereas MCC showed low water uptake ability. Water uptake in MCC initiates in the pores accompanied by movement into the internal of the capillaries[10]. Without the incorporation of superdisintegrant, a tablet will not be able to retain the water after the maximum water uptake. Hence, the weight after wetting of a tablet is comparatively lower in formulation F7. Rojas et al. (2012) reported that SSG had high swelling ability and high water retention due to the amylopectin component of starch[10]. It was deduced that both SSG and CCS displayed swelling action and the capability of SSG to retain water depends on its concentration in the formulations. At optimal concentration of superdisintegrants, water uptake capacity improved with an increase in water absorption ratio.

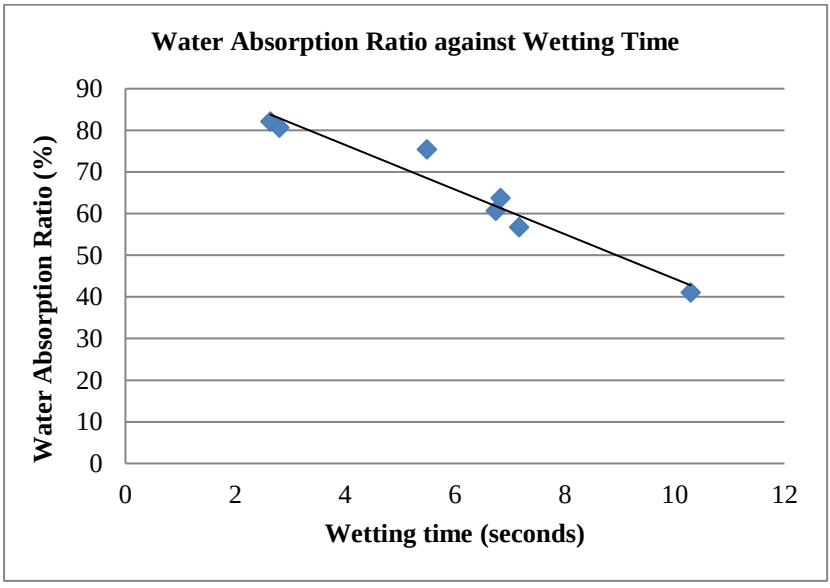

Figure 3: Correlation graph between wetting time and water absorption ratio.

F7 displayed longest disintegration time (51.24 ± 0.99 seconds) due to absence of superdisintegrant in the formulation. MCC did not replace the need for true superdisintegrants (SSG and CCS) in promoting fast disintegration[11]. Nevertheless, MCC lacks of swelling action which renders inadequate disintegration force and contributed to slower disintegration rate observed in formulation F7. In the matter of single superdisintegrant, both formulations F3 (8% w/w SSG) and F4 (10% w/w SSG) had longer disintegration time which indicated that SSG should not be used in the range of these concentrations. This was further supported by researches that reported when SSG concentration increases from and above 8% w/w of the formulation, it swells to a gel due to gelling and viscosity producing effect which blocks the pores in the tablet and prevent additional water uptake into the tablet[18]. According to the results, formulation F5 with combination of superdisintegrants had critically greater disintegration rate than F2 ($p < 0.05$). In formulation F5 comprised of a mixture of SSG and CCS, where water uptake was assisted by CCS and the swelling properties in SSG which promotes the disintegration rate with shortened disintegration time[12].

In vitro dissolution study of acyclovir ODTs (formulations F1, F2 and F5)

Table 5: Cumulative percentage of acyclovir release of formulations F1, F2 and F5.

Time (minutes)	**Cumulative percentage of acyclovir release (%)**		
	F1	**F2**	**F5**
1	9.63 ± 0.79	11.56 ± 2.22	17.35 ± 0.76

3	20.65 ± 1.43	22.62 ± 0.48	27.40 ± 0.68
5	27.22 ± 0.50	24.98 ± 0.90	30.13 ± 3.14
10	30.59 ± 1.26	30.70 ± 4.53	37.28 ± 3.28
15	35.46 ± 0.61	36.36 ± 4.37	51.34 ± 0.77
20	40.27 ± 0.56	45.97 ± 2.28	68.84 ± 2.64
30	45.04 ± 1.81	57.70 ± 1.00	78.93 ± 3.57
40	57.09 ± 2.23	65.69 ± 0.11	86.11 ± 0.67
50	60.45 ± 1.35	68.48 ± 1.00	87.99 ± 0.52
60	61.33 ± 1.15	70.29 ± 0.07	90.09 ± 0.43

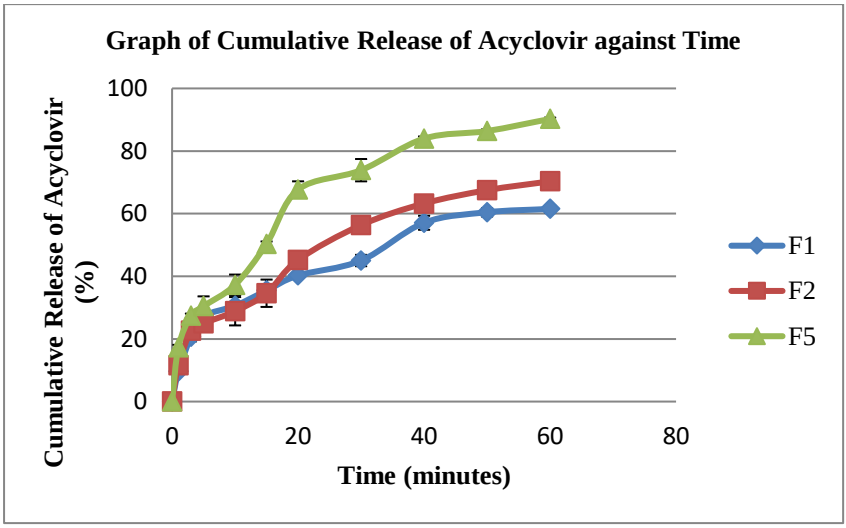

Figure 4: Graph of cumulative release of acyclovir against time.

Formulations F1, F2 and F5 were selected for dissolution study due to their performance in terms of critical quality attributes

investigated. Based on Table 5, formulation F5 has the highest acyclovir release rate of 90.09 ± 0.43%. Greatest cumulative percentage of acyclovir and fastest disintegration of acyclovir ODTs in formulation F5 was likely attributed to synergism in mechanism of action of two superdisintegrants (SSG and CCS). SSG was reported to have high swelling index accompanied by swelling and wicking action of CCS. The subsequent higher cumulative drug release was observed in formulation F2 which achieved 70.29 ± 0.07% and followed by 61.33 ± 1.15% in formulation F1. It can be explained by correlating the dissolution rate with the concentration of SSG in the formulations. When the SSG concentration increases, it swells rapidly upon contact with liquid hence dissolution rate will be greater provided the optimal concentration was not exceeded (< 8%).

Analytical method validation

Linearity

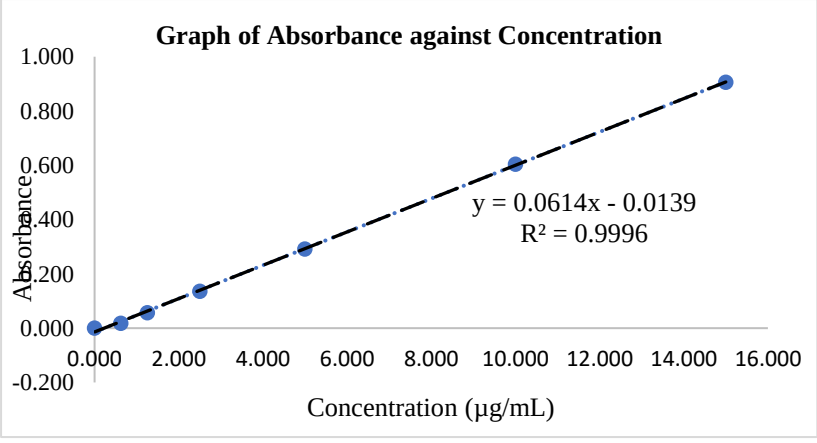

Figure 5: Calibration graph of acyclovir for linearity test.

The equation was determined as, y = 0.0614 + 0.0139x, where y is the absorbance, x is the concentrations of solution and y-intercept of 0.0614. The graph showed correlation coefficient, r^2

= 0.9996 which was greater than 0.98 hence linearity was established.

Specificity, Accuracy and Robustness

Table 6: Specificity, accuracy and robustness results of formulations F1, F2 and F5.

Formulation	**Specificity (absorbance)**		**Accuracy (Percentage of acyclovir released, %)**	**Precision (RSD, %)**		**Robustness (RSD, %)**
	Placebo	**Acyclovir**		**Intra-day**	**Inter-day**	
1	-0.001	0.614	91.33 ± 0.42	0.407	1.107	0.146
2	-0.078	0.601	98.13 ± 0.07	0.341	0.671	0.198
5	-0.002	0.748	98.87 ± 0.26	0.312	0.565	0.113

For specificity test, formulations F1, F2 and F5 containing acyclovir as active drug showed absorbance and peaks at wavelength of 250 nm. Meanwhile, placebo formulations showed no peak at wavelength of 250 nm which indicated the absence of acyclovir in placebo formulation. For accuracy test, the percentage of acyclovir released for formulations F1, F2 and F5 were 91.33%, 98.13% and 98.87% correspondingly hence formulations F2 and F5 were assumed to pass the accuracy test. The intra-day, inter-day precision and robustness results accomplished the acceptance limit as the (RSD) obtained were less than 2%.

Statistical Analysis

Data analysis was conducted by using the Statistical Package for the Social Science (SPSS) software version 21. One-way statistical ANOVA test and post hoc test were employed for analysis of data. A p-value of less than 0.05 was considered to be statistically significant.

Conclusion

In present study, acyclovir ODTs can be prepared using SSG and CCS as superdisintegrant through direct compression to enhance the disintegration and dissolution profile. All ODTs fulfilled the weight uniformity and friability test which complied with United States Pharmacopoeia (2014). All formulations had disintegrated within 51.24 seconds. Formulations F5 had shortest wetting time of 2.68 seconds which also showed shortest disintegration time of 7.33 seconds and greatest water absorption ratio of 82.13%. Formulation F5 containing 1% w/w SSG and 5% w/w CCS was the most preferred combination in formulating acyclovir ODTs. On account of its excellent wetting properties, it had the shortest disintegration time and greatest dissolution rate. In conclusion, the use of combination of superdisintegrants will fasten the onset of action and enhance the bioavailability of the drug.

Limitations of present study

Formulation F5 released more than 80% of acyclovir during 45 minutes of the dissolution test which complied with the acceptable limits. F1 and F2 containing SSG as the single superdisintegrant released only 61.33 ± 1.15% and 70.29 ± 0.07% of acyclovir. Such a low dissolution rate could be explained by the slower disintegration time of formulations F1 and F2. Despite the disintegration time obtained was lower than 12.20 ± 0.243 seconds, the tablets failed to disintegrate completely at the end of the dissolution test[27]. At 50 rpm, the

force of dissolution paddles was not as strong as the vertical movement of the disintegration apparatus to induce a whole breakdown of the tablets[28].

Recommendations for future study

In future study, it can be conducted by employing different combination ratio of superdisintegrants on the physical evaluation of acyclovir ODTs. Apart from that, flavour enhancers such as menthol and aspartame can be incorporated for taste masking. In contrast to MCC which was is insoluble in water, water soluble polyols such as mannitol and sorbitol are preferable as excipients for solid dosage forms that disintegrate in the oral cavity along with their pleasant mouth feeling, great mechanical properties and rapid dissolution[30].

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References

1. Research C for DE and. Orally Disintegrating Tablets [Internet]. U.S. Food and Drug Administration. 2019 [cited 2019 Jul 24]. Available from: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/orally-disintegrating-tablets

2. Oshi M. The effect of sodium starch glycolate concentration on physical effectiveness of chlorpheniramine tablets. J Pharm Educ Res. 2013 Apr 3;4:47–53.

3. Olah I, Lasher J, Regdon G, Pintye-Hodi K, Baki G, Sovany T. Evaluating superdisintegrants for their performance in orally disintegrating tablets containing lysozyme enzyme.

Journal of Drug Delivery Science and Technology. 2019 Feb 1;49:396–404.

4. Desai PM, Liew CV, Heng PWS. Review of Disintegrants and the Disintegration Phenomena. Journal of Pharmaceutical Sciences. 2016 Sep 1;105(9):2545–55.

5. Nagar PK. Superdisintegrants - Current Approach. 1. 2014 May 15;4(3):37–44.

6. Priyanka S, Vandana S. A review article on: Superdisintegrants. International Journal of Drug Research and Technology. 2017;3(4):11.

7. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm. 2004 Sep;58(2):265–78.

8. Arnal J, Gonzalez-Alvarez I, Bermejo M, Amidon GL, Junginger HE, Kopp S, et al. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Aciclovir. JPharmSci. 2008 Dec 1;97(12):5061–73.

9. Pabari R, Ramtoola Z. Effect of a Disintegration Mechanism on Wetting, Water Absorption, and Disintegration Time of Orodispersible Tablets. J Young Pharm. 2012;4(3):157–63.

10. Rojas J, Guisao S, Ruge V. Functional Assessment of Four Types of Disintegrants and their Effect on the Spironolactone Release Properties. AAPS PharmSciTech. 2012 Dec 1;13(4):1054–62.

11. Thoorens, G., Krier, F., Leclercq, B., Carlin, B., and Evrard, B. (2014) ‘Microcrystalline Cellulose, a Direct Compression Binder in a Quality by Design Environment—A Review’. International Journal of Pharmaceutics 473 (1), 64–72.

12. Desai PM, Er PXH, Liew CV, Heng PWS. Functionality of Disintegrants and Their Mixtures in Enabling Fast

Disintegration of Tablets by a Quality by Design Approach. AAPS PharmSciTech. 2014 Oct 1;15(5):1093–104.

13. Aguilar JE, Montoya EG, Lozano PP, Negre JMS, Carmona MM, Grau JRT. 6 - New SeDeM-ODT expert system: an expert system for formulation of orodispersible tablets obtained by direct compression. In: Aguilar JE, editor. Formulation Tools for Pharmaceutical Development [Internet]. Woodhead Publishing; 2013 [cited 2019 Dec 28]. p. 137–54. (Woodhead Publishing Series in Biomedicine). Available from: http://www.sciencedirect.com/science/article/pii/B9781907568992500062

14. Halder S, Anisul Islam M, Shuma Lata M, Bachar S. Development and evaluation of Water dispersible tablets of Acyclovir. International Journal of Advanced Research in Biological Sciences. 2014 Jun 1;1:17–24.

15. Heer D, Aggarwal G, Sl H. Recent trends of fast dissolving drug delivery system – An overview of formulation technology. Pharmacophore. 2013 Jan 1;4.

16. Kantharao CH, Swarna K, Leelakrishna J, Anusha J, Asha B, Bhavani B. Diclofenac Orodispersible Tablets: Formulation and In Vitro Evaluation. Annals of Clinical and Laboratory Research [Internet]. 2019 Feb 13 [cited 2019 Dec 24];7(1). Available from: http://www.aclr.com.es/abstract/diclofenac-orodispersible-tablets-formulation-and-in-vitro-evaluation-24055.html

17. Karpe M, Mali N, Kadam V. Formulation development and evaluation of acyclovir orally disintegrating tablets. Journal of Applied Pharmaceutical Science. 2012 Mar 1;2:101–5.

18. Kumar A, Saharan VA. A Comparative Study of Different Proportions of Superdisintegrants: Formulation and Evaluation of Orally Disintegrating Tablets of Salbutamol Sulphate. tjps. 2017 Apr 5;14(1):40–8.

19. Liew KB, Kok-Khiang P, Fung Tan YT. Orally disintegrating dosage forms: Breakthrough solution for non-

compliance. International Journal of Pharmacy and Pharmaceutical Sciences. 2013 Jan 1;5:4–8.

20. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res. 2017 May 1;34(5):890–917.

21. Pahwa R, Gupta N. Superdisintegrants in the development of orally disintegrating tablets: A review. International Journal of Pharmaceutical Sciences and Research. 2010 Nov 30;2.

22. Pr K, ps Mohanachandran, Saju F, Bini.K.B, Babu B, K.K S. Formulation and evaluation of mouth dispersible tablets of Amlodipine Besylate. International Journal of Applied Pharmaceutics. 2010 Apr 29;2:1–6.

23. R Gosai A, Patil S, Sawant K. Formulation and Evaluation of Oro Dispersible Tablets of Ondansetron Hydrochloride by Direct Compression using Superdisintegrants. Int J Pharm Sci Nanotechnol. 2008 Jan 1;26.

24. Rahane RD, Rachh PR. A Review On Fast Dissolving Tablet. 1. 2018 Sep 6;8(5):50–5.

25. Tanuwijaya J, Karsono. The Effects of Crospovidone and Croscarmellose Sodium as Superdisintegrants On the Characteristics Of Piroxicam Nanoparticles ODT (Orally Disintegrating Tablet). In 2013.

26. The United States Pharmacopoeia-National Formulary (USP 37-NF32). (2014) Vol 1.Rockville (MD) USA United States Pharmacopeial Convention

27. Vraníková, B., Pavloková, S., and Gajdziok, J. (2017) ‘Experimental Design for Determination of Effects of Superdisintegrant Combinations on Liquisolid System Properties’. Journal of Pharmaceutical Sciences 106 (3), 817–825

28. Zhao, N. and Augsburger, L.L. (2005) ‘Functionality Comparison of 3 Classes of Superdisintegrants in Promoting

Aspirin Tablet Disintegration and Dissolution'. AAPS PharmSciTech 6 (4), E634-640

29. Madgulkar A, Bandivadekar M, Shid T, Rao S. Sugars as solid dispersion carrier to improve solubility and dissolution of the BCS class II drug: clotrimazole. Drug Dev Ind Pharm. 2016 Jan;42(1):28–38.

30. Ohrem HL, Schornick E, Kalivoda A, Ognibene R. Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? Pharm Dev Technol. 2014 May;19(3):257–62.

Review

Theories of tooth eruption: An update

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Abstract

The process for tooth eruption has been a matter of debate. Numerous theories of tooth eruption have been proposed. The understanding of recent advancements regarding the tooth eruption is needed as several types of cells and molecular factors that are believed to be responsible for the tooth eruption. This article reviews previously proposed eruption theories and the recent advances in the eruption mechanism.

Keywords: bone remodeling, dental follicle, tooth eruption

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Introduction:

Tooth eruption process has never been fully understood. But why is it be only hypothesized? And what forces push the teeth through the soft tissues? Each theory for eruption presents with a problem.[1, 2] The biological processes responsible for tooth eruption have long been a matter of debate. According to Massler and Schour, it can be defined as the movement of a tooth from its site of development within the jaws to its position of function within the oral cavity.[5] The eruption is necessary for the survival

of diverse species and is a continuous process. Which does not stop by reaching the occlusal plane rather continues throughout life. The scientific literature on mechanism of eruption in the field is extremely dispersed. Upon intensive research over the last 30 years, the specific mechanisms responsible for tooth eruption, are not understood. Numerous theories of tooth eruption have been proposed involving almost all tissues in or surrounding an erupting tooth. But none of them alone could review the focuses on human and other mammalian teeth eruption and also analyzes recent observations and experimental data. [3-5]

Movements of tooth are generally divided into three phases as: a) pre-eruptive b) eruptive c) Post-eruptive phases.

Many theories of eruptions were proposed [5, 6]

I] Theories that were not be considered as serious contenders like

- Pulpal pressure
- Pulpal growth, vascular pressure
- Blood-vessel thrust
- Traction by periodontal fibroblasts.

II] Theories that were considered as serious contenders:

- alveolar bone remodeling
- root elongation/periodontal ligament formation
- dental follicle theory

Theories of tooth eruption

A] Cushioned hammock theory:

It was proposed by Harry Sicher in 1942. This theory assumed that cushioned hammock ligament below the tooth is responsible for the eruption of the tooth but was not accepted, according to

Edward HF; it was an artifact in slide preparation, not a ligament.[6]

B] Bone remodeling theory:

Alveolar bone growth, tooth development, and eruption are interdependent. Formation of bone apical to developing teeth has long been proposed as one of the mechanisms for eruption, its programmed bone remodeling & the dental follicle is involved. The mutation of the parathyroid hormone receptor 1 gene is correlated with disturbances in bone remodeling and which leads to primary failure of tooth eruption. This primary failure of eruption is a non-syndromic eruption disturbance and not associated with defective osteoclasts which supports bone remodeling theory. [7]

C] Dental follicle theory:

The theory described as a factor decisive for the eruption process & is capable of inducing, bone resorption above the developing crown and bone apposition & enables the formation of an eruptive pathway. The molecular studies have shown that the eruption is regulated by inductive signals between the dental follicle, stellate reticulum, reduced enamel epithelium, and alveolar bone RANKL gene is a marker gene for bone resorption that shows higher expression in the coronal half of the dental follicle.[6] Bone morphogenetic protein-2 (BMP-2) gene is a marker for bone formation and higher expression in the basal half of the follicle. Eruption is a localized, & a bilaterally symmetrical event in an alveolar bone which is regulated by the dental follicle, a derivative of cranial ectomesenchyme. Recent developments, concerning the paracrine signaling function of the dental follicle in tooth eruption, interactions between the dental follicle, the Reduced enamel epithelium (REE) & stellate reticulum dental follicle recruits of monocytes, followed by bone resorption these apoptotic process have an influence on osteoclastogenesis as stellate reticulum cells releases the interleukin-1α.[6]

This interleukin-1α stimulates the expression of CSF-1 and monocyte chemotactic protein-1. Recently Nel S in 2015 proposed that tooth eruption should be regarded as a stages of tooth development.[4]

D] Periodontal ligament traction theory:

The most frequently cited are the root growth and pulpal pressure, other important causes are cell proliferation, increased vascularity, and increased bone formation around the teeth, and other possible causative agents include endocrine influence, vascular changes, and enzymatic degradation. Probably all these factors have an influencing role.[3] Although all the factors which are associated with tooth eruption are not yet known, elongation of the root and modification of the alveolar bone and periodontal ligament are thought to be the most important factors. These events are coupled with the changes overlying the tooth that produce the eruption pathway. Fibroblasts have traction power and they move incisally along the erupting tooth. The contraction of fibroblast generates significant force for the tooth eruption. Occlusal migration of these periodontal ligament fibroblasts has been said as main factors responsible for tooth eruption, possibly that the periodontal ligament (PDL) could play a role in the supra-osseous phase of the eruptive process in lifting the tooth into the occlusal plane.[4] Collagen synthesis, remodeling and the cells implicated in these processes can however not accepted as the only mediators of tooth eruption as a tooth without a periodontal ligament can still erupt.[1,6,9]

E] Innervation-provoked pressure theory:

According to this theory that tooth eruption depends on the space in the pathway of eruption, Pressure from below & the adaptation of the periodontal membrane. It assumes the existence that the root membrane acts as a glandular membrane. So, the innervation in this membrane causes pressure in the apical part of the tooth which results in tooth eruption.[10-13]

F] The equilibrium theory:

The theory postulates that once the functional plane is reached, the eruption of the tooth is balanced in response to the vertical growth of the mandible is controlled by forces impeding the eruption, as opposed to encouraging forces. These steady forces of masticatory function and the soft tissue pressures from the lips, cheeks, and tongue are the limiting factors of post functional occlusal eruption. The eruptive movement that occurs while the teeth are free of contact, supports the idea that eruptive control is based on the continuous force of the surrounding soft tissues.[6, 7, 13]

G] Neuromuscular theory or unification theory:

This theory of tooth eruption states that the synchronized forces of the orofacial muscles, under the control of the central nervous system (CNS) are responsible for the process. The molecular events prepared a pathway under the control of these forces by the coordinated neuromuscular forces & they are converted into electrical, electrochemical and biomechanical energies for the stimulation of cellular and molecular activities within and around the dental follicle. [5, 6, 14-20]

The probable mechanism for eruption of tooth may be: [22-24]

(i) Due to periodontal ligament or its precursor of the dental follicle, or a combination of fibroblast activity and vascular or tissue hydrostatic pressure.

(ii) It is multifactorial, involving the molecular and enzymatic activities.

Conclusion or confusion!

Tooth eruption is a biological process, which is still not fully understood, there is no theory to explain the generation of eruptive force which supported by sufficient experimental evidence, Many studies & systematic reviews were carried on animal tissues from its development in the bony crypt to its eruption till the occlusal level. Each of the eruption theories has a say to some portion of the eruption process and does not mention the etiology behind the eruption, some only state that it is unknown.

References

1. Avery J. K. Steele P. F, Essentials of Oral Histology and Embryology, Mosby Year Book, 1992.
2. Bath-Balog M. Fehrenbach M. J, Dental Embryology, Histology, and Anatomy, Elsevier Saunders, 2006.
3. Kjær I, Mechanism of Human Tooth Eruption: review article including a new theory for future studies on the eruption process Scientifica 2014, Article ID 341905, http://dx.doi.org/10.1155/2014/341905
4. Nel S, Hendrik HD, Boy SC, Raubenheimer EJ. Recent perspectives vis-à-vis the biological basis of tooth eruption SADJ 2015; 70 (6): 238 – 241.
5. Marks Jr S. C. Schroeder H. E, "Tooth eruption: theories and facts," The Anatomical Record, 1996; 245 (2):374–393.
6. Rabea A A. Recent advances in understanding theories of eruption Future Dental Journal 2018;4: 189–196.
7. Frazier-Bowers SA, Hendricks HM. Failure of tooth eruption: diagnosis and management. In: Wright JT. Craniofacial and dental developmental defects: diagnosis and management. Springer; 2015.
8. Becktor KB, Nolting D, Becktor JP, Kjaer I. Immunohistochemical localization of epithelial rests of Malassez in human periodontal membrane. Eur J Orthod 2007;29(4):350–3.

9. Brin I, Zilberman Y, Galili D, Fuks A. Eruption of rootless teeth in congenital renal disease. Oral Surg Oral Med Oral Pathol 1985; 60:61–4.
10. Kjær I, Kocsis G, Nodal M, Christensen LR. Aetiological aspects of mandibular tooth agenesis-focusing on the role of nerve, oral mucosa, and supporting tissues. Eur J Orthod1994; 16(5):371–5.
11. Becktor KB, Hansen BF, Nolting D, Kjaer I. Spatiotemporal expression of NGFR during pre natal human tooth development. Orthod Craniofac Res 2002; 5(2):85–9.
12. Bille ML, Thomsen B, Kjær I. Apoptosis in the human periodontal membrane evaluated in primary and permanent teeth. Acta Odontol Scand 2011; 69(6):385–8.
13. Proffit WR. Contemporary orthodontics. Fifth ed. Elsevier; 2013.
14. Bille ML, Thomsen B, Kjær I. Apoptosis in the human periodontal membrane evaluated in primary and permanent teeth. Acta Odontol Scand 2011; 69(6):385–8.
15. Loto AO. Tooth eruption: a neuromuscular theory, part one. J. Craniomax. Res. 2017; 4(1):278–83.
16. Wise GE, King GJ. Tooth movement. J Dent Res 2008; 87:414–34.
17. Ruta A, Irena B, Janina T. Factor's influencing permanent teeth eruption. Part one general factors. Stomatologija. Baltic Dental and Maxillofacial Journal 2010; 12:67–72.
18. Ash MM, Nelson SJ. Wheeler's dental anatomy, physiology, and occlusion. Ninth ed. Elsevier; 2003.
19. Kiliaridis S. The importance of masticatory muscle function in dentofacial growth. Semin Orthod 2006; 12 (2):110–9.
20. Wise GE. Cellular and molecular basis of tooth eruption. Orthod Craniofac Res 2009; 12 (2):67–73.
21. Koch G. and Poulsen S., Pediatric Dentistry. A Clinical Approach, Wiley-Blackwell, page 198.2009.

22. Bath-Balog M. and M. J. Fehrenbach, Dental Embryology, Histology, and Anatomy, Elsevier Saunders, 2006
23. Berkowitz B. K. B., Holland G. R., and. Moxham B. J, Oral Anatomy, Histology and Embryology, Mosby, Elsevier, 2009.
24. Kjær I. Mechanism of human tooth eruption: review article including a new theory for future studies on the eruption process. Sci Tech Rep 2014; 2014:1–13.

Case report

Compound odontoma associated with impacted maxillary central incisor: A case report

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Abstract:

Odontomas are the most common benign odontogenic tumors. The exact etiology is still unknown, however, local trauma, infection, inheritance, and genetic mutation play a role in the pathogenesis of this condition. The majority of these lesions are asymptomatic and are often detected during routine radiographic examination. Infrequently, few odontomas cause expansion of the cortical plates and facial asymmetry. Morphologically they are classified as complex, when present as irregular masses containing different types of dental tissues, or as compound if they have anatomic similarity to the teeth. Here, we report a case of a compound odontoma associated with impacted maxillary central incisor and retained deciduous central incisor in a 19-year-old patient.

Key words: Compound, Maxilla, Odontoma, Tooth

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Introduction

Odontomas are the most common benign odontogenic tumors mainly composed of an abnormal mass of calcified dental tissue. The term odontoma was first coined by Broca (1866); he defined it as a tumor formed by an overgrowth of complete dental tissues.[1] Based on gross, radiographic, and microscopic features, they are classified into complex odontoma and compound odontoma. Few researchers consider odontomas as hamartomas or malformations rather than true neoplasms due to its composition and behavior. These lesions display slow growth and non-aggressive behavior, moreover, they do not develop further once fully calcified. [2,3] According to the World Health Organization (WHO), a compound odontoma is defined as "A malformation in which all dental tissues are represented in a more orderly pattern than in the complex odontoma, so that the lesion contains many teeth-like structures. Most of these structures do not morphologically resemble the teeth in the normal dentition; however, enamel, dentin, cementum, and pulp are arranged as in the normal tooth.[4]

Odontomas are considered as mixed odontogenic tumors, as they are composed of both epithelial and mesenchymal elements. These cells and tissues can appear either normal or be a deficit in structure. The level of differentiation may vary, creating various formations of dental tissues such as enamel, dentin, cementum, and pulp. They may occur at any age, and in any location of the dental arch.[5], The mean age of detection on an average is 14.8 years, with the prevalent age being the second decade of life. There is a slight predilection for occurrence in males (59%) compared to females (41%). The compound odontoma is known to occur more commonly in the maxilla (67%) as compared to the mandible (33%), with a marked predilection for the anterior maxillary region (61%).[5] Here we present a case of a compound odontoma associated with impacted maxillary central incisor.

Case history

A 19-year-old male patient reported to the clinic with the complaint of retained deciduous tooth in the upper front region of jaw since childhood. His past medical, dental, and family history was unremarkable. On extraoral examination, lymph nodes and TMJ revealed no abnormalities. Intraoral examination of hard tissue examination revealed a missing left upper permanent central incisor and retained deciduous central incisor [Figure1]. The maxillary anterior occlusal radiograph was taken which showed irregular three radiopaque tooth-like structure with a uniform radiolucent band and horizontally impacted maxillary left permanent central incisor [Figure 2]. The tube shift technique was adapted which revealed that the tooth-like structure was positioned on the labial side and impacted central incisor was placed palatal aspect.

A final diagnosis of compound odontoma with a horizontally impacted central incisor was made. The patient was advised for surgical removal of the odontoma along with the extraction of the impacted central incisor. Under general anesthesia [Figures 3 & 4], odontoma and impacted central incisor were removed. A postoperative intraoral periapical radiograph revealed the complete removal odontoma along with the extraction of deciduous and permanent central incisor [Figures 5 & 6]. The histopathological examination surgical specimen confirmed the clinical diagnosis.

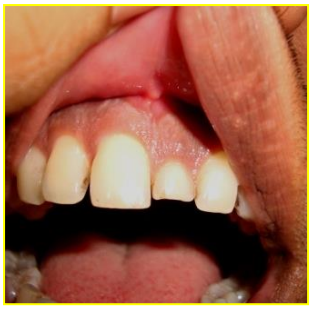

Figure 1: Clinical photograph showing retained 61 and missing 21

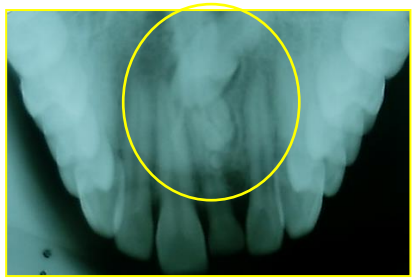

Figure 2: Maxillary true occlusal radiograph showing retained deciduous central incisor, Compound Odontoma and impacted permeant central incisor

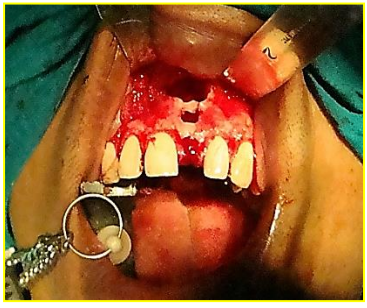

Figure 3: Surgical removal of Odontoma and impacted central incisor

Figure 4: Surgical specimen showing Odontoma attached to the impacted central incisor

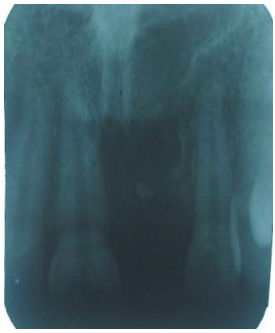

Figure 5: Postoperative intraoral periapical radiograph

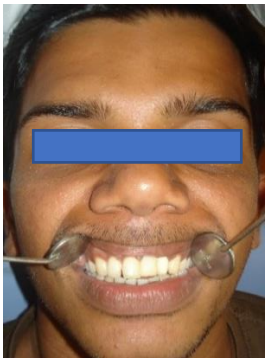

Figure 6: Postoperative prosthetic placement

Discussion

Odontomas are the most frequent odontogenic tumors accounting for 22–67% of all maxillary tumors.[6] Generally, they occur in younger individuals, however, less than 10% of cases are found in patients over 40 years old. Some studies have reported a correlation between patient age and the type of odontoma, Compound lesions are frequent in younger patients and maxillary anterior region; this was in accordance with our case. The majority of these cases detected during the radiographic investigation of a non-erupted permanent or retained primary tooth. Common clinical signs include a retained deciduous tooth or an impacted tooth. In the 26 cases of odontomas as analyzed by Iatrous *et al*., found that 80.7% of theses lesions are had the impaction of permanent teeth.[7] Similar findings were noted in our case.

Considerable controversy exists over the gender distribution as few studies consider odontomas to be more common in females

than in males, others consider that these lesions are distributed equally between both genders. On the contrary, Iatrous *et al*.,[7] and Yadav *et al*., [5] found a male prediction. A similar observation was made in the present case.

Clinically and radiographically, ameloblastic odontoma and ameloblastic fibro odontoma resemble odontomas, hence it is suggested to have a microscopic examination for definitive diagnosis. The exact etiology of an odontoma is still unknown however trauma during primary dentition, inflammatory and infectious processes, hereditary anomalies (Gardner syndrome, Hermann's syndrome), odontoblastic hyperactivity and alteration in the genetic components responsible for controlling dental development play a role in the development of odontomas.[7] In our case no syndromes were evident and no episode of previous trauma was reported by the patient.

Complete surgical removal is the treatment of choice for odontomas. But for surgeons, it might be challenging, as most odontomas are associated with normal adjacent tooth structures. Small and localized odontomas are easy to remove, but large odontomas require a complex treatment approach such as osteoplasty, reconstruction of soft tissue, and dental prosthesis.[8] In children and adults, the impacted permanent teeth, depending on the age and the tooth development, may be left to erupt spontaneously, or they may be guided to occlusion via orthodontic traction. In the present case, the surgical removal of odontoma and extraction impacted and retained deciduous teeth was performed.

Conclusion

We present a case of a compound odontoma associated with impacted and retained teeth in the maxillary anterior region. There is a high association between odontomas and permanent

teeth impaction. In order to prevent the adverse effects of disturbances in tooth eruption, the authors stress the importance of routine use of radiographs for early detection of such silent dental abnormalities.

References

1. P. Broca, TraiteV Des Tumeurs, P. Asselin, France, 1866.
2. Vengal M, Arora H, Ghosh S, Pai K. Large erupting complex odontoma: a case report. J Can Dent Assoc 2007; 73:169–723. 6.
3. Ragalli CC, Ferreria JL, Blasco F. Large erupting complex odontoma. Int J Oral Maxillofac Surg 2000; 29:373–4.
4. Philipsen, Richart PA. Revision of the 1992 edition of the WHO histological typing of odontogenic tumors –A suggestion. J Oral Pathol Med 2002; 31:253–8
5. Yadav M, Godge P, Meghana SM, Kulkarni SR. Compound odontoma. Contemp Clin Dent. 2012;3:S13-5.
6. Serra-Serra G, Berini-Aytés L, Gay-Escoda C. Erupted odontomas: a report of three cases and review of the literature. Med Oral Patol Oral Cir Bucal. 2009;14:E299–303.
7. Iatrous I, Vardas E, Theologie-Lygidakis N, Leventis M. A retrospective analysis of the characteristics, treatment, and follow-up of 26 odontomas in Greek children. J Oral Sci. 2010;52:439–47

8. Syed MR. Bilateral complex odontomas in mandible. J Oral Maxillofac Pathol 2006;10:89-91.

Case Report

A case report of a bony swelling in the mandible of a young female patient

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Abstract: Ameloblastoma is a benign odontogenic tumour having the tendency to occur in the posterior mandible. It is speculated to be of epithelial in origin. Although it is slow growing in nature but it can slowly infiltrate into the surrounding tissues thereby causing the extensive damage to the jaw bones. Ameloblastoma is considered to be the lesion primarily occurring in elderly male patients. This article presents a case of multicystic ameloblastoma occurring in a young girl highlighting the typical radiographic features of this extensive lesion. Surgical en bloc resection was done for the patient over the right side of the mandible and reconstruction was done using the iliac graft.

Keywords: Odontogenic, Benign, Ameloblastoma, Multilocular, Radiolucency.

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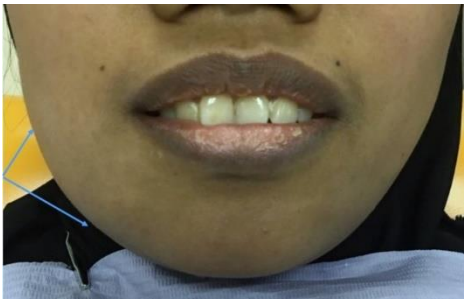
Introduction: Ameloblastoma is be the most common benign odontogenic tumor occurring in the jaws. It arises from the remnants of the enamel organ without the formation of enamel. This tumor is characterized by its locally invasive nature and causing the disfigurement of the face. It was defined as "unicentric, nonfunctional, intermittent in growth, anatomically benign and clinically persistent" by Robinson. This tumor has the predilection in 3^{rd} -4^{th} decade of life, commonly seen in the males. It is associated with the painless, unilateral swelling of the jaws with mobility and displacement of the teeth. It is also occasionally seen in association with the impacted teeth. [1]

Case Report: A 19 year old Indonesian female reported to the SEGi Oral Health center with the complaint of persistent swelling over her right side of face since many years. Her history of present illness revealed that the swelling was gradual in onset, not associated with any pain since 3-4 years. There was no history of trauma given. Patient revealed that the tooth on the right lower jaw became mobile and she got it removed from the govt. clinic 2 years ago. There was no significant medical history. All her vitals were with in normal range. There was an obvious facial asymmetry. A solitary swelling was seen over the right side of the face involving the lower border of the mandible, with diffused borders (Fig. 1). On palpation, swelling was non tender and hard in consistency. Swelling was non mobile and non-fluctuant. There was no local rise in the temperature.

Intraoral examination revealed clinically missing 16, 36, and 46. There was grade 1 mobility irt 44, 45. Significant vestibular obliteration was seen in 46 region. Overlying mucosa showed secondary ulcerations irt 46 region, due to traumatic occlusion from the upper molar. On palpation, swelling was bony hard and non-mobile.

There was buccal and lingual cortical plate expansion irt 46 region. (Fig. 2)



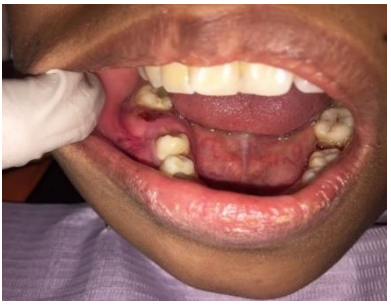


Figure 1: Extra oral Photograph Figure 2: Intraoral Photograph

Provisional diagnosis of Odontogenic Keratocyst was made based on the patient's age and location of the lesion. An OPG was taken for the patient. The radiograph revealed well defined multilocular radiolucency in left lower side of the mandible. Radiolucency was seen extending from the apical region of 44 to the distal third of the root of 48. Internally, multiple septae were seen with in the radiolucency giving it a soap bubble appearance. Lower border of the mandible appeared to be scalloped. There was mesial migration of 45 and distal migration of 47, with missing 46. Root resorption was seen irt 45 in the apical region. (Fig. 3)

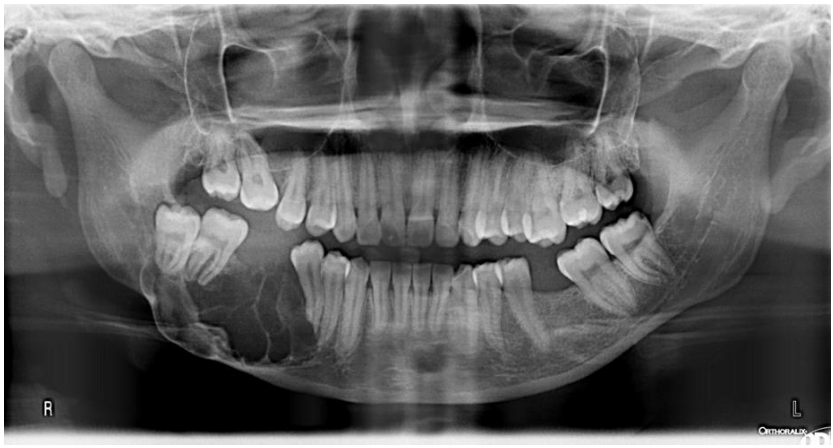


Figure 3: Pre-operative panoramic radiograph of the patient

Radiographic diagnosis of Ameloblastoma was made for the patient. The Odontogenic Keratocyst, Giant cell granuloma, Odontogenic Myxoma, and Ossifying fibroma can be considered in the radiographic differential diagnosis.

Patient was referred to higher center for biopsy and other investigations. Hematological investigations were insignificant. Biopsy confirmed the case as Follicular Ameloblastoma. Patient went back to her home country for the treatment of the lesion. CT scan was done before the surgical removal of the lesion. En Bloc resection of the right side of the mandible was done and reconstruction of mandible was done using iliac crest graft. After 6 months of the surgery, OPG was taken for the patient. (Fig. 4) Patient had the regular appointments with the speech therapist and removable prosthesis on the right side of the mandible (Fig. 5) was planned. Patient is still under the follow up.

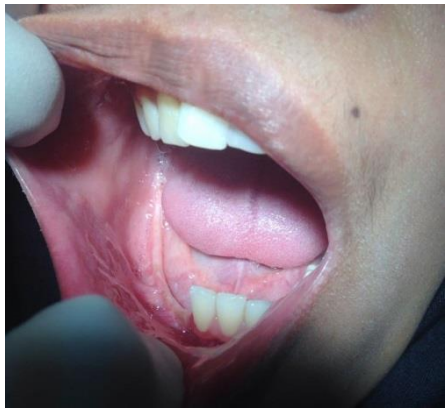


Figure 4: Post-operative intraoral photograph of the patient.

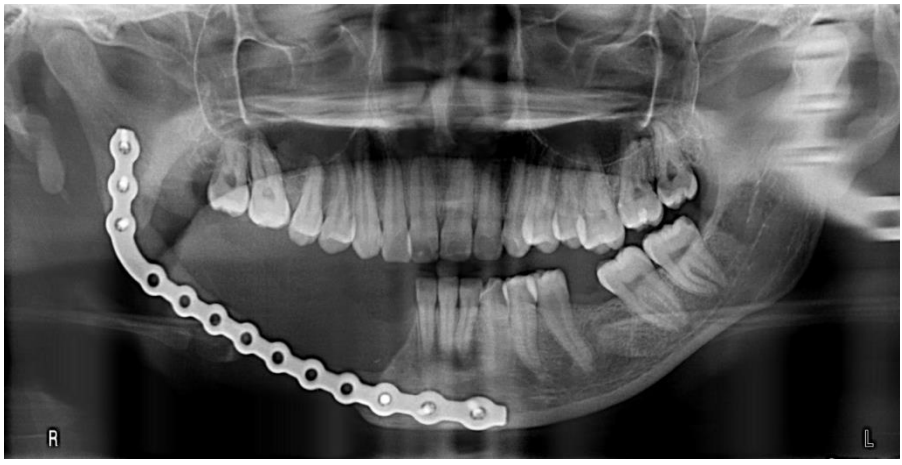


Figure 5: Post-operative panoramic radiograph of the patient

Discussion: Odontogenic tumours are the large heterogenous group of lesions involving the jaw bones, arising from the epithelial or ectomesenchymal tissues or both. Odontogenic tumours were first classified by WHO in 1971 following which, many modifications were done in the classification. Ameloblastoma was categorized as the epithelial odontogenic tumor in 1992 by WHO. Latest update on the classification was done in 2017. According to the latest classification

ameloblastoma is divided into four categories; conventional, extraosseous / peripheral, unicystic, and metastasizing ameloblastoma. WHO 2017 classification of odontogenic tumours is summarized in Table 1.[1]

Ameloblastoma has been derived from the Greek word 'amel' which means enamel and 'blastos' which means germ. It was first described by Cusack in 1827. In 1937, Robinson described this as a benign tumor that is usually "unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent." The word ameloblastoma was first coined by Ivey and Churchill in 1939.[2]

Global incidence of occurrence of ameloblastoma is 0.5 cases per 5 million persons per year. Ameloblastoma accounts for 1% of all the tumours and cysts of the jaws and 9%-10% of the odontogenic tumours.[3, 4]

It is a slow growing but locally invasive tumor having the tendency to erode the bone and invading the adjacent structures. Ameloblastoma has the propensity to grow in both the jaws, but most commonly it occurs in the mandible (80%) according to the published literature. It tends to occur in the posterior region of the mandible involving either body or ascending ramus of the mandible, but it can occur anywhere in the either of the jaws.[5]

2017 WHO Classification			
Benign			Malignant
Epithelial	Mixed	Mesenchymal	
• Ameloblastoma • Ameloblastoma, unicystic type	• Ameloblastic fibroma • Primordial odontog	• Odontogenic fibroma • Odontogenic myxoma/ myxofibroma	**Odontogenic carcinomas** • Ameloblastic

• Ameloblastoma, extraosseous/ peripheral type • Metastasizing (malignant) ameloblastoma • Squamous odontogenic tumor • Calcifying epithelial odontogenic tumor • Adenomatoid odontogenic tumor	enic tumor • Odontoma, Complex type • Odontoma, Compound type • Dentinogenic ghost cell tumor	• Cementoblastoma • Cemento-ossifying fibroma	carcinoma • Primary intraosseous carcinoma, NOS • Sclerosing odontogenic carcinoma • Clear cell odontogenic carcinoma • Ghost cell odontogenic carcinoma **Odontogenic carcinosarcoma** **Odontogenic sarcomas**

Ameloblastoma can involve any of the age groups, but peak incidence is reported to occur in 3rd-4th decade of life.[6] Some authors have noticed the peak age of occurrence of ameloblastoma in 2nd and 6th decade of life.[7]

The present case of Ameloblastoma happened to occur in a young female, which makes this case report quite rare. Variable male to female predilection has been reported by some of the authors.[5, 8]

WHO in 2003 classified ameloblastoma as: [9]

- Solid/Multicystic variant
- Unicystic variant
- Peripheral/Extraosseus
- Desmoplastic Ameloblastoma

Recently, it has been proposed that all the conventional lesions present with cystic degeneration both micro/macroscopically. Hence, the term of solid, multicystic ameloblastoma should be discarded and conventional lesions should be appropriately termed as "conventional ameloblastoma".[10]

The most common variant of the ameloblastoma is conventional ameloblastoma, accounting for approximately 90% of all the cases of ameloblastoma. This type of the tumor runs a benign course and slowly expands causing the disfigurement of the face.[11]

This tumor has the propensity to occur in young individuals, with no sex predilection. The mean age of the diagnosis of this lesion is around 3rd decade of life. This occurs most commonly in the mandibular posterior region and slowly infiltrates in the adjacent structures and erode the bone. There can be egg shell crackling effect also. Displacement and mobility of the teeth is often reported along with this tumor. Becelli et al have reported that 13% of cases of mandibular ameloblastoma tend to have paresthesia of the area innervated by mandibular nerve. Recurrence rate is around 60-80%.[4, 12]

The second most common type of ameloblastoma is the unicystic variant. It accounts for approximately 5-15% of all cases of ameloblatoma. This tumor occurs in relatively younger individuals, diagnosed usually in 2nd decade of life and presents as asymptomatic swelling in the mandibular posterior region. Most common clinical differential diagnosis of unicystic ameloblastoma is dentigerous cyst, as both the lesions occur around the crown of the impacted tooth.[13]

Peripheral variant of ameloblastoma (PA) is usually seen as sessile or pedunculated growth over the gingiva. PA has slight elderly male predilection, commonly involving the mandibular posterior region. 30 % of PA happens to occur in the mandibular premolar area. This variant is usually restricted to the soft tissues of the oral cavity and doesn't erode the underlying bone and is often mistaken for pyogenic granuloma. Other lesions with the similar clinical appearance are fibroma, peripheral giant-cell granuloma or peripheral ossifying fibroma.[14]

Desmoplastic ameloblastoma (DA) accounts for 4-14% of all the ameloblastoma cases. It was first described by Eversole et al.in 1984. DA is usually diagnosed after histopathological confirmation. It commonly occurs in 4th decade of life with equal sex predilection. DA is commonly seen in the anterior region of the jaws and is relatively smaller in size as compared to the other variants of ameloblastoma. It usually presents as the painless swelling of the jaw bones leading to the displacement of the teeth.[16]

Histopathologically, solid/multicystic ameloblastoma have six subtypes: follicular, plexiform, acanthomatous, basal cell, granular and desmoplastic. The follicular type of ameloblastoma have proliferating odontogenic epithelial cells arranged in islands, while plexiform type have epithelial cells arranged in continuous anastomosing strands.[11]

Wright et al, 2014 described two main histopathological variants of unicystic ameloblastoma as the luminal and mural type. Peripheral ameloblastoma have similar histopathological features as multicystic ameloblastoma. DA consists of islands of odontogenic epithelium in varied shapes with highly collagenous CT.[10]

Radiographically, ameloblastoma can present either as unilocular or multilocular radiolucencies with the corticated and scalloped borders. Typical radiographic appearance of ameloblastoma can vary from soap bubble to tennis racket or honey comb appearance because of the numerous internal septae. Ameloblastoma has the tendency to cause the buccal or lingual cortical plate expansion. Displacement of the adjacent teeth with the resorption of the roots is a quite common feature.[16]

DA have diffused borders unlike other variants expressing its infiltrative nature in adjacent bone marrow spaces according to Philipsen et al. This feature of DA makes it appear like a fibro-osseous lesion.[17, 18]

Conventional radiography is the initial diagnostic tool for the smaller lesions but the true extent of the large ameloblastoma can be assessed only by 3-dimensional imaging like CT, CBCT, PET or MRI.[19]

Major treatment modalities for the diagnosed cases of ameloblastoma are: surgical enucleation, marsupialization and wide surgical enbloc resection based on the type and size of the lesion.

Our case was diagnosed as the follicular type of conventional ameloblastoma, so the wide surgical enbloc resection was done for the tumorous lesion.

Conclusion: Ameloblastoma is a slow growing yet devastating tumour of the jaws. Early diagnosis of this tumour is crucial considering that it can occur even in the young individuals, as in our case. So, complete examination with proper diagnostic imaging modalities are important in the early diagnosis correlating the clinical and radiological findings with the histopathological report.

Conflict of Interest: There is no conflict of interest.

References:

1. El-Naggar, Chan JKC, Grandis JR, Takata T, Slootweg P, editors. WHO classification of Head and Neck Tumours. Chapter 8: Odontogenic and maxilofacial bone tumours. 4th ed., IARC: Lyon 2017, p.205-260.
2. K M K. Masthan, N Anitha, Jayasri Krupaa, Sudha Manikkam. Ameloblastoma. J Pharm Bioallied Sci. 2015 Apr; 7(suppl 1): S 167-170.
3. Brown NA, Betz BL. Ameloblastoma: a review of recentmolecular pathogenetic discoveries. Biomark Cancer 2015; 7:19–2.
4. Becelli R, Carboni A, Cerulli G, Perugini M, Iannetti G. Mandibular ameloblastoma: Analysis of surgical treatment carried out in 60 patients between 1977 and 1998. J Craniofac Surg. 2002; 13: 395–400.
5. Krishnapillai R, Angadi PV. A clinical, radiographic, and histologic review of 73 cases of ameloblastoma in an Indian population. Quintessence Int. 2010; 41: e90–100.
6. Adekeye EO, Lavery KM. Recurrent ameloblastoma of the maxillo-facial region: clinical features and treatment. J Maxillofac Surg. 1986; 14: 153–157.
7. Oomens MA, van der Waal I. Epidemiology of ameloblastomas of the jaws; a report from the Netherlands. Med Oral Patol Oral Cir Bucal. 2014; 19: 0.

8. Varkhede A, Tupkari JV, Mandale MS,et al. Plexiform ameloblastoma of mandible—case report.J Clin Exp Dent2010; 2: e146–8.
9. McClary AC, West RB, McClary AC, et al. Ameloblastoma: a clinical review and trends in management. Eur Arch Otorhinolaryngol. 2016; 273: 1649–1661.
10. Wright JM, Odell EW, Speight PM, Takata T (). Odontogenic tumors, WHO 2005: where do we go from here? HeadNeck Pathol 2014; 8: 373–382.
11. OA Effiom1, OM Ogundana1, AO Akinshipo1, SO Akintoye. Ameloblastoma: current etiopathological concepts and management. Oral Diseases 2017.
12. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Lyon, France: IARC Press; 2005. World Health Organization Classification of Tumours: Head and Neck Tumours.
13. Bansal S, Desai RS, Shirsat P, Prasad P, Karjodkar F, AndradeN. The occurrence and pattern of ameloblastoma in children and adolescents: an Indian institutional study of 41 years and review of the literature. Int J Oral MaxillofacSurg 2015; 44: 725–731.
14. Philipsen HP, Reichart PA, Nikai H, Takata T, Kudo Y. Peripheral ameloblastoma: biological profile based on 160 cases from the literature. Oral Oncol. 2001; 37(1):17-27.
15. Zhi-Jun Suna, Yan-Ru Wub, Ning Chengb, Roger A Zwahlenc, and Yi-Fang Zhaoa. Desmoplastic ameloblastoma – A review. Oral Oncol. 2009; 45(9): 752–759.
16. Dunfee BL, Sakai O, Pistey R, Gohel A. Radiologic and pathologic characteristics of benign and malignant lesions of the mandible. Radiographics. 2006; 26(6):1751-58.
17. Philipsen HP, Ormiston IW, Reichart PA. The desmo-and osteoplastic ameloblastoma. Histologic variant or clinicopathologic entity? Case reports. Int J Oral Maxillofac Surg. 1992; 21(6):352–7.

18. Manuel S, Simon D, Rajendran R, Naik BR. Desmoplastic ameloblastoma: a case report. J Oral Maxillofac Surg. 2002; 60(10):1186-8.
19. Hertog D, Van der Waal I. Ameloblastoma of the jaws: a critical reappraisal based on a 40-years single institution experience. Oral Oncol. 2010;46:61-4.

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