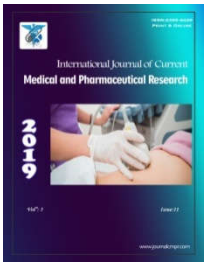
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 11(A); November 2019; Page No. 4686-4690
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201911776



Research Article

NEURODEVELOPMENTAL OUTCOME OF CHILDREN WITH CONGENITAL HYPOTHYROIDISM: RELATIONSHIP WITH THE TIME OF INITIATION OF TREATMENT

Ismot Ara Zannat[1], Mohammad Asaduzzaman[2], Suraiya Begum[3], Monira Hossain[4] and Roushan Jahan[5]

[1]Paediatric Hematology and Oncology Department, National Institute of Cancer Research & Hospital, Dhaka
[2]Medical Oncology Department, National Institute of Cancer Research & Hospital, Dhaka
[3]Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka
[4]Department of Paediatrics, Shaheed Suharawardy Medical College Hospital, Dhaka
[5]Neonatology Department, Dhaka Medical College Hospital, Dhaka

ARTICLE INFO

Article History:
Received 12th August, 2019
Received in revised form 23rd September, 2019
Accepted 7th September, 2019
Published online 28th November, 2019

Key words:
Congenital hypothyroidism; Neurodevelopment.

ABSTRACT

Background: Congenital hypothyroidism (CH) is one of the leading causes of preventable mental retardation in children. Normal neurological development can be achieved by early and effective treatment. The aim of the study was to assess neuro-developmental status of children with congenital hypothyroidism who were on treatment with oral levothyroxine and compare neurodevelopmental outcome in relation to time of initiation of treatment.

Methodology: This was a prospective observational study conducted in the Pediatric Endocrine Outpatient Department (OPD), BSMMU from March 2016 to February 2018. Fifty children aged 1 month to 48 months with congenital hypothyroidism who treated with levothyroxine during the study period were included in this study. Patients were divided into 4 groups on the basis of age at diagnosis and starting of treatment: Group I (started by one month of age), Group II (>1 months - 3 months of age), Group III (> 3 months - 12 months of age), Group IV (>12 months of age). Neurodevelopmental status in four domains such as gross motor, fine motor, cognition and language were assessed by Bayley Scales of Infant and Toddler Development (BSID III) during 3 months and 6 months follow up visit. Hearing screening was also performed during 3 months follow up visit.

Results: There were 12 patients in group I, 14 in group II, 14 in group III and 10 patients in group IV. Statistical significant differences in cognition and language were found during 3 months (p value < 0.05) and 6 months (p value < 0.01) follow up visit among four groups. Cognitive function was impaired 41% patients in group I, 50% in group II, 92.9% in group III and 90% in group IV and delayed language was observed 16.7% in group I, 50% in group II , 78.6% in group III and 70% in group IV during 3 months follow up visit. During 6 months follow up visit 25% patients in group I, 57.1% in group II, 92.9% in group III, 90 % in group IV had delay in cognitive function. However, 8.3% patients in group I, 28.6% in group II, 71.4% in group III and 60% in group IV had delay in language. Regarding hearing screening, gross motor and fine motor functions there were no significant differences among four groups of patients.

Conclusion: Patients who were started treatment early had favorable outcome in cognitive and language domains of development in comparison to patients with congenital hypothyroidism who had delay in starting treatment.

INTRODUCTION

Thyroid hormones are critical for growth and central nervous system (CNS) maturation from the early stage of fetal life to 2-3 years of age.[1] Congenital hypothyroidism (CH) is one of the leading causes of preventable mental and growth retardation, especially in underdeveloped and developing countries that do not routinely employ newborn screening (NBS).[2]The incidence of CH varies widely from 1:2,000 to 1:4,000 in different countries and has shown a consistent increase over the past several decades.[3]Nearly all screening programs report a female preponderance, approaching 2:1 female to male ratio.[4] One pilot study showed that the prevalence of congenital hypothyroidism in Bangladesh is about 1 in 2000 newborns.[5]Levothyroxine is the treatment of choice in CH.[6]The goals of treatment are to maintain the serum free T4 or total T4 in the upper half of the reference range for age with

*Corresponding author: **Ismot Ara Zannat***
Paediatric Hematology and Oncology Department, National Institute of Cancer Research & Hospital, Dhaka

serum TSH optimally 0.5-2.0 mU/L. The recommended initial starting dose is 10-15 µg/kg/day for most term infants.[7]The dose and timing of thyroid hormone replacement and regular follow-up are important in achieving optimal growth and neurocognitive outcome. A delay in serum T4 normalization over one week can result in lower intelligence scores.[8] Several studies suggest that better outcomes may be achieved with earlier treatment and an initial high-dose of levothyroxine to more rapidly normalize thyroid function as well as closer monitoring.[9]There is scarcity of published data to find out the relationship of neurodevelopmental status and time of initiation of treatment in Bangladesh. For this reason this study was aimed to assess neurodevelopmental status in children with congenital hypothyroidism who are getting treatment with levothyroxine at different ages and to observe the relationship of neurodevelopmental outcome of children with time of initiation of treatment.

MATERIALS AND METHODOLOGY

It was a prospective observational study conducted in Paediatric Endocrine Outpatient Department (OPD), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March, 2016 to February, 2018. A total 60 children aged 1 month to 48 months with congenital hypothyroidism who were on treatment with levothyroixine were enrolled in this study. Congenital hypothyroidism associated with chromosomal disorders, birth asphyxia, cerebral palsy, neurometabolic disorder, other causes of mental retardation were excluded from the study. After enrollment, detailed history including age at start of levothyroxine treatment, initial dose of levothyroxine, duration of treatment, drug compliance was also be recorded in structured questionnaire. Patients were divided into 4 groups on the basis of age at diagnosis and starting of levothyroxine treatment.

- Group I (treatment started by one month of age);
- Group II (treatment started >1 months - 3 months of age);
- Group III (treatment started > 3 months - 12 months of age);
- Group IV (treatment started >12 months of age).

Follow up of the children was done 3 months and 6 months after initial enrollment. In each follow up visit neurodevelopmental status was assessed.FT4 and TSH level was also done in each follow up to adjust the dose of levothyroxine. Before neurodevelopmental assessment hearing screening was done during 1st follow up visit by an audiologist. For younger children Otoacoustic Emission Test or Behavioral Observation Audiometry was performed and for older children Pure tone audiometry was done. Neurodevelopmental assessment in four functional domains like gross motor, fine motor, cognition and language were evaluated by Bayley Scales of Infant and Toddler Development Screening test, third edition (BSID-III) in each follow up visit. Tests were performed with the help of developmental psychologist and was blinded to the group of the participant. Each test had been completed approximately in 60-120 minutes. Then evaluated by scoring and determine development for age of the child was normal or delayed.

Statistical analysis

Data were analyzed using SPSS version 22. Qualitative data was expressed as frequency and percentage. Statistical significant test in each group were analyzed by Chi-squared test. P values less than 0.05 was considered significant.

RESULTS

In this study initially total number of patients were 60.Four parents withdrew consent, 4 patients lost follow up during 3 months visit, 2 patients lost follow up in 6 months visit. Then total number of patients were 50.In the study population 24% patients were in group I, 28 % patients were in group II, 28% patients were in group III and 20 % patients were in group IV (Figure1).

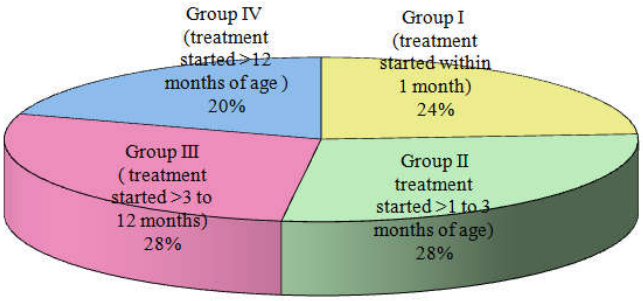


Figure 1 Pie diagram showing distribution of sample according to start of treatment (n=50)

This study showed homogenous distribution of patients among the four treatment groups with slight female preponderance in all the groups. Most of the patients were term in all four groups. Most of the parents monthly income were 10,000 taka to 20,000 taka. Family history of thyroid disorders were less common in all 4 groups (Table-I).

Table I Socio-demographic characteristics of the children with congenital hypothyroidism (n=50)

Parameters/ Characteristics	Group I (n=12) No.(%)	Group II (n=14) No.(%)	Group III (n=14) No.(%)	Group IV (n=10) No.(%)
Sex distribution				
Male	3(25.0)	6(43.0)	5(35.7)	3(30.0)
Female	9(75.0)	8(57.0)	9(64.3)	7(70.0)
Socioeconomic status (Taka/Month)				
Up to 10,000	3(25.0)	4(28.6)	7(50.0)	5(50.0)
10,001-20,000	8(66.7)	8(57.1)	7(50.0)	5(50.0)
20,001-30,000	1(8.3)	1(7.1)	0	0
30,001 and above	0	1(7.1)	0	0
Birth history				
Preterm	3(25.0)	3(21.4)	2(14.3)	3(30.0)
Term	9(75.0)	11(78.6)	12(85.7)	7(70.0)
Family history or thyroid disorder				
Present	4(33.3)	5(35.7)	0	1(10.0)
Absent	8(66.7)	9(64.3)	14(100.0)	9(90.0)

In all 4 groups serum TSH were high and Free T4 were low during initial diagnosis (Table-II). During study period FT4 and TSH level were maintained normal by adjusting the dose of levothyroxine. There were no significant differences in thyroid function status among 4 treatment groups after 3 months and 6 months follow up visit (Table- III, IV).

Table II Thyroid function level of the patients with congenital hypothyroidism at the time of diagnosis (n=50)

Group	Serum TSH (mIU/L) (Mean ± SD)	Serum FT4 (pmol/L) (Mean ± SD)
Group I (n=12)	47.0 ± 35.1	5.5 ± 2.1
Group II (n=14)	56.0 ± 39.8	6.0 ± 3.3
Group III (n=14)	88.0 ± 47.9	6.1 ± 3.5
Group IV (n=10)	77.5 ± 60.4	6.4 ± 3.6

Data were expressed as mean ± SD

Table III Thyroid function status of the patients with congenital hypothyroidism 3 months after enrollment (n=50)

Parameters/ Characteristics	Group I (n=12) No.(%)	Group II (n=14) No.(%)	Group III (n=14) No.(%)	Group IV (n=10) No.(%)	*P value*
TSH					0.342^{ns}
Normal	10(91.7)	11 (78.5)	10(71.4)	7(70.0)	
Abnormal	2(8.3)	3(21.5)	4(28.6)	3(30.0)	
FT_4					0.231^{ns}
Normal	11(91.7)	12(85.5)	10(71.4)	9(90.0)	
Abnormal	1(8.3)	2(14.3)	4(28.6)	1(10.0)	

Data were expressed as frequency and percentage and statistical analysis done by Chi-square test, ns = not significant

Table IV Thyroid function status of the patients with congenital hypothyroidism 6 months after enrollment (n=50)

Parameters/ Characteristics	Group I (n=12) No.(%)	Group II (n=14) No.(%)	Group III (n=14) No.(%)	Group IV (n=10) No.(%)	*P value*
TSH					0.283^{ns}
Normal	11(91.7)	11(78.6)	11(78.5)	8(80.0)	
Abnormal	1(8.3)	3(21.4)	3(21.4)	2(20.0)	
FT_4					0.404^{ns}
Normal	12(100.0)	12(85.7)	11(78.6)	9(90.0)	
Abnormal	0	2(14.3)	3(21.4)	1(10.0)	

Data were expressed as frequency and percentage and Statistical analysis done by Chi-square test, ns = not significant

Hearing impairment was observed in total 8% congenital hypothyroid children. Hearing screening were normal in group I patients and impaired 1 (7.1%) patient in group II, 2 (14.3%) patients in group III, 1 (10%) patient in group IV (Figure-II).There were no significant difference in terms of hearing impairment among four treatment groups (P value 0.601).

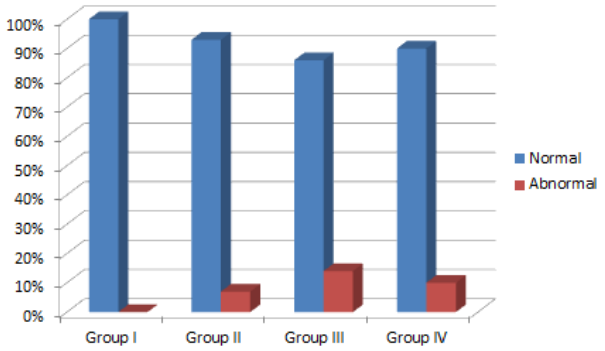


Fig 2 : Distribution of patients according to hearing screening 3 months after enrollment (n=50)

Neuro developmental status 3 months after enrollment showed that though gross motor and fine motor delay were present more patients in group III and IV than group I and Group II, but this differences were not statistically significant. But regarding cognition 5 (41.6%) patients in group I, 7 (50%) patients in group II, 13 (92.9%) patients in group III and 9 (90.0%) patients in group IV had impairment in cognitive function. In case of language 2(16.7%) in group I, 7(50%) patients in group II, 11 (78.6%) in group III and 7 (70%) patients in group IV had delayed language. There were statistical significant differences (P value <0.05) in cognition and language function among four treatment groups of patients (Table –V).

Neurodevelopmental status 6 months after enrollment found similar results as 3 months after enrollment (Table–VI). Neurodevelopmental status in gross motor and fine motor functions, there were no significant differences among four treatment group, but statistical significant difference were found in cognition and language. In group I,3(25%) patients, group II, 8 (57.1%) patients, group III 13(92.9%) patients, group IV, 9(90%) had delay in cognitive function. However 1(8.3%) patients in group I, 4 (28.6%) patients in group II, 10(71.4%) patients in group III and 6 (60%) patients in group IV had delay in language skills (Table-VI).

Table V Neurodevelopmental status of the patients 3months after enrollment by Bayley Scales of Infant and Toddler Development, 3rd edition (BSID III)

Parameters/ Characteristics	Group I (n=12) No.(%)	Group II (n=14) No.(%)	Group III (n=14) No.(%)	Group IV (n=10) No.(%)	*P value*
Gross motor					0.129^{ns}
Normal	10(83.3)	11(78.6)	8(57.1)	5(50.0)	
Delayed	2(16.7)	3(21.4)	6(42.9)	5(50.0)	
Fine motor					0.103^{ns}
Normal	11(91.7)	11(78.6)	8(57.1)	5(50.0)	
Delayed	1(8.3)	3(21.4)	6(42.9)	5(50.0)	
Cognition					0.016*
Normal	7(58.3)	7(50.0)	1(7.1)	1(10.0)	
Impaired	5(41.6)	7(50.0)	13(92.9)	9(90.0)	
Language					0.010*
Normal	10(83.3)	7(50.0)	3(21.4)	3(30.0)	
Delayed	2(16.7)	7(50.0)	11(78.6)	7(70.0)	

Data were expressed as frequency and percentage and statistical analysis done by Chi-square test, ns = not significant * = significant at P<0.05

Table VI Neuro developmental status of the patients 6 months after enrollment by Bayley Scales of Infant and Toddler Development,3rd edition (BSID III)

Parameters/ Characteristics	Group I (n=12) No.(%)	Group II (n=14) No.(%)	Group III (n=14) No.(%)	Group IV (n=10) No.(%)	*P value*
Gross motor					0.132^{ns}
Normal	11(91.7)	13(92.9)	10(71.4)	6(60.0)	
Delayed	1(8.3)	1(7.1)	4(28.6)	4(40.0)	
Fine motor					0.104^{ns}
Normal	12(100.0)	12(85.7)	11(78.6)	6(60.0)	
Delayed	0	2(14.3)	3(21.4)	4(40.0)	
Cognition					0.001**
Normal	9(75.0)	6(42.9)	1(7.1)	1(10.0)	
Delayed	3(25.0)	8(57.1)	13(92.9)	9(90.0)	
Language					0.005**
Normal	11(91.7)	10(71.4)	4(28.6)	4(40.0)	
Delayed	1(8.3)	4(28.6)	10(71.4)	6(60.0)	

Data were expressed as frequency and percentage and statistical analysis done by Chi-square test, ns = not significant, ** = significant at P<0.01

DISCUSSION

In this prospective observational study 50 patients of congenital hypothyroidism were enrolled and follow up were done at 3 months and 6 months after initial visit. This study showed female preponderance in all four study groups. Most of the study shows that the incidence of CH is twice as high in females than males.[10] Most of the parents monthly income

were < 20,000 taka in all four treatment groups. One study done in Sudan showed that 74.3% congenital hypothyroid patients came from low socio-economic class and 25.7% were from middle class.[11]Family history of thyroid disorder was present 33.3% patients in group I, 35.7% patients in group II, 10% patients in group IV, no family history of thyroid disorder was present in group III patients. Another study showed that family history of thyroid disorder was present in very few cases (6.7%).[12]

Hearing screening were normal in group I patients and impaired 7.1% patients in group II, 14.3% patients in group III, 10% patients in group IV 3 months after enrollment. No significant differences was observed among four treatment groups (p value 0.601). Study done by Hashemipour *et al*., they observed 3.2% CH patients had sensorineural hearing loss.[13]Another study done in Canada showed that 20% of CH patients had hearing impairment. In their study there was association between hearing loss and delay in initiating treatment. [14]

There were no significant difference in gross motor and fine motor functions among four treatment groups after 3 months and 6 months follow up visit. Gross motor delay was observed in 16.7%, 21.4%, 42.9% and 50% patients in group I, group II, group III and group IV respectively and fine motor delay was observed in 8.3%, 21.4%, 42.9%, 50% patients in group I, group II, group III and group IV respectively after 3 months follow up visit. After 6 months follow up visit 8.3% patients in group I,7.1% in group II, 28.6% in group III and 40% in group IV had gross motor delay, no patient in group I, 14.3% in group II, 21.4% in group III, and 40% patients in group IV had fine motor delay. Gulshan *et al*. reported that congenital hypothyroid children in early treatment group 10% presented impairment in gross motor skills, 13% in fine motor skills. In children getting treatment later stage 57% and 71% had delayedgross motor and fine motor skills respectively.[15] Frezzato *et al*. showed that statistical significant difference was observed in the gross motor and fine motor skills between the CH patients and the control group.[16]

Regarding cognition statistical significant differences were found among four treatment groups after 3 months (p value <0.05) and 6 months (p value <0.01) follow up visit. After 3 months follow up visit 41% patients in group I , 50% patients in group II, 92.9% patients in group III and 90% patients in group IV had impaired in cognitive function. After 6 months follow up visit 25% patients in group I, 57.1% patients in group II , 92.9% patients in group III , 90.0% in group IV had delay in cognitive function . Similar study done by Kumar *et al*., they categorized CH patients into 3 treatment groups according to age of onset of treatment, The 3 groups showed a statistically significant difference in mean IQ levels. Those children who were on treatment before one month (group 1) showed a mean IQ of 97.7, while 2nd group (treatment started between 1and 6 months) and 3rd group (treatment started after 6 months) showed IQ of 92.3 and 81.09 respectively.[12] Komur *et al*. stated that despite early and effective treatment in newborns with congenital hypothyroidism, retardation in neurological developmental has been detected. Cognitive, language and global motor scores in addition to receptive communication, expressive communication, fine motor and gross motor sub scores in children with congenital hypothyroidism were lower than those in the control which was significant (p value< 0.05).[17]

In case of language 16.7% patients in group I, 50% patients in group II, 78.6%patients in group III and 70% patients in group IV had delayed languageafter 3 months follow up visit. However 8.3% patients in group I, 28.6% patients in group II, 71.4% patients in group III and 60% patients in group IV had delay in language after 6 months follow up visit. There were statistical significant differences in language function among four treatment groups of patients both after 3 months(p value <0.05) and 6 months (p value <0.01) follow up visit.To assess language disorders in children Mohamed *et al*. included 60 children with CH and 20 age and sex matched control group. The study showed that the children with uncontrolled CH show delayed language, mental, social age, and intelligence quotient in comparison with children with controlled hypothyroidism and normal children. [18]

CONCLUSION

This study concluded that time of onset of treatment had a definite effect on neurodevelopmental outcome in case of congenital hypothyroidism. Comparison of initiation of treatment among different groups revealed that children who were started treatment early had favorable outcome in cognitive and language domains of development in comparison to children with congenital hypothyroid - dism who had delay in starting treatment.

References

1. Najmi SB, Hashemipour M, Maracy MR, Hovsepian S, Ghasemim M. Intelligence quotient in children with congenital hypothyroidism: The effect of diagnostic and treatment variables. *J Res Med Sci*. 2013; 9:395-400.
2. Dayal D, Prasad R. Congenital hypothyroidism: current perspectives. *Research and Reportsin Endocrine Disorders*. 2015; 5: 91-102.
3. Viet G, Deladoey J. Disorders of the Thyroid in the Newborn and Infant. In: Sperling M, editors. Paediatric Endocrinology.7th ed. Vol. Philadelphia: Elsevier; 2014.pp. 186-208.
4. La Franchi SH. Hypothyroidism. PediatrClin North Am.1979; 26:33-51.
5. Hasan M, NaharN, Fauzia M, Begum N. Newborn screening in Bangladesh. Ann Acad Med Singapore. 2008; 37: 111-113.
6. Kelnar J, Butler G, Christopher JH. Endocrine Gland Disorder and Disorders of Growth and Pubert. In: Campbell A, Mcintosh editors. Forfar & Arneil'S Textbook of Pediatric., 7th ed. Churchill Livingstone: Elsevier; 2008. P. 465-471.
7. Stephen H, LaFranchi SH, Stephen A. Hypothyroidism. In: In Kliegman, RM, Stanton, BF, Geme, JWE, Schor, NF and Behrman, RE editors. Nelson Textbook of Pediatrics. 20thed.New Delhi: Elsevier; 2016.p. 2665-2672.
8. Schokking B, Schrama SM. Influence of timing & dose of thyroid hormone replacement on mental, psychomotor and behavioral development in children with congenital hypothyroidism. *J Pediatr*. 2005; 147: 768-774.
9. Jones JH, Gellen B, Paterso WF, Beaton S, Donaldson, MDC. Effect of high versus low initial doses L-thyroxin for congenital hypothyroidism on thyroid function & somatic growth. Archive of Disease in Children. 2008; 93: 940-944.

10. LaFranchi SH, Austin J. How should we be treating children with congenital hypothyroidism?. *J Pediatr Endocrinol Metab*. 2007; 20(5): 559-578.
11. Mukhtar N, Elshibli M, Abdelmonein H, Abdullah M, Elmula I. Demographic and Clinical Aspects of Congenital hypothyroidism. *Sudan Journal of Medical Sciences*. 2015; 10:1-7.
12. VijayaKumar M, Sabitha S, Raju V. Intellectual and academic performance of children with congenital hypothyroidism in relation to time of diagnosis. *J. Evid. Based Med. Healthc*. 2016; 3: 5592-5595
13. Hashemipour M, Hovsepian MD, Hashemi M, Amini M, Kelishadi R, Sadeghi S. Hearing Impairment in Congenitally Hypothyroid Patients. *Iran J Pediatr*. 2012; 22: 92-96.
14. Rovet J, Walker W, Bliss B. Long term sequels of hearing impairment in congenital Hypothyroidism. *J Pediatr*. 1996; 128(6): 776-83.
15. Gulshan A, Tahmina B, Fouzia M, Mizanur R. Neurodevelopmental outcome of congenital hypothyroidism in children between 1-5 years of age. Bangladesh *Journal of Medical Science*. 2011; 10: 245-251.
16. Frezzato R, Santos D, Goto M, Dutra V, MarconiM, Lima. P. FineMotor Skills and Expressive Language: A Study with children with congenital hypothyroidism. CoDAS.2017; 29 :1-7
17. Komur M, Ozen S, Okuyaz C, Makharoblidze K, Erdogan S. Neurodevelopmental evaluation in children with congenital hypothyroidism by Bayley-III. Brain& Development. 2013; 5: 392-397.
18. Mohamed HM, Zaki E, AbdallAA, Gomaa MA, Abdel Wahab MM. Language disorders in children with congenital hypothyroidism. *Egypt J Otolaryngol*. 2017; 33: 685-690.

How to cite this article:

Ismot Ara Zannat *et al* (2019) 'Neurodevelopmental Outcome of Children with Congenital Hypothyroidism: Relationship with the Time of Initiation of Treatment', *International Journal of Current Medical and Pharmaceutical Research,* 05(11), pp 4686-4690.

****