



Glucocorticosteroid Induced Bradycardia in Children Receiving Induction Chemotherapy for Acute Lymphoblastic Leukaemia-an Unrecognised Phenomenon

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Authors' contributions

This work was carried out in collaboration among all authors. Author YK wrote the protocol and did the literature search of the manuscript. Author SG analysed the data and made the first draft of the manuscript. Author UVS did the statistical analysis mentioned in the study. Author PSS corrected and redrafted the final study. All authors have read and approved the final manuscript.

Article Information

Editor(s):

- (1) Dr. Sri Lakshmi Hyndavi Yeruva, Hershey Medical Center, USA.
(2) Dr. Ramesh Gurunathan, Sunway Medical Center, Malaysia.

Reviewers:

- (1) Ronit Sionov, The Hebrew University of Jerusalem, Israel.
(2) Ahmed Mohamed Fathi Salama, Benha University, Egypt.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/66047>

Original Research Article

Received 28 December 2020

Accepted 02 March 2021

Published 15 March 2021

ABSTRACT

Introduction: Glucocorticoids are an integral part of the treatment protocols of acute lymphoblastic leukaemia. Bradycardia is an under recognised cardiovascular side effect of steroids in children. Though there is published data from the west on this phenomenon, there is very little data on the same in Indian children. We did an analysis to determine the characteristics of bradycardia in our children with acute lymphoblastic leukaemia receiving induction chemotherapy with steroids. The results were compared with the available published western data.

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Materials and Methods: All children less than 18 years diagnosed to have Acute Lymphoblastic Leukemia, between January 1, 2018 and December 31, 2019 and received induction chemotherapy with steroids were retrospectively analysed for various parameters of bradycardia. Bradycardia was defined as heart rate less than 110 beats/min, 100 beats/min, 80 beats/min, 70 beats/min and 60 beats/min in the age group of 0-3months, 4-11 months, 1-4 years, 5-11 years and more than 12 years respectively as defined by the PEWS chart. The statistical analysis in the study was done using SPSS 26.0.

Results: Majority of the patients out of a total of 44 children developed decrease in heart rate (HR) after initiation of steroids. Bradycardia was seen in 21 out of 44 (47.7%) children analysed. The mean HR in patients who developed bradycardia was 63 beats/min. (Range-50-78). The mean decrease in HR was 41 beats/min. The mean day of onset of bradycardia in our cohort of children was 3.95 days (Range-3-6) and the mean week of recovery was 3 weeks(Range-2-5).

Conclusion: We could demonstrate a decrease in heart rate in our children receiving steroids as a part of our institutional induction regimen. The bradycardia usually occurred in the first week of initiation and recovered by the third week of the protocol treatment.

Keywords: Glucocorticoids; bradycardia; acute lymphoblastic leukaemia; steroids.

1. INTRODUCTION

Glucocorticoids have been an integral part of the treatment protocols in various disorders especially rheumatological, neoplastic, immunological and renal; since decades. The most commonly encountered side effects include hypertension, hyperglycaemia, infections, psychosis etc. Though poorly understood, adverse effects on the cardiovascular system have been described in literature like increased risk of myocardial infarction, heart failure and the uncommon risk of atrial fibrillation or flutter [1,2]. Another less described entity is steroid induced bradycardia [3]. Glucocorticosteroid related bradycardia has been described in adults and children who were administered steroids for various non malignant causes like autoimmune disease from the later half of the 20th century [4]. Later, a detailed account of the changes in heart rate (HR) of children with acute lymphoblastic leukaemia (ALL) on steroids was published by van der Gugten et al [5]. We performed a retrospective analysis to determine the characteristics of bradycardia in our children with acute lymphoblastic leukaemia receiving induction chemotherapy with steroids.

2. MATERIALS AND METHODS

All children diagnosed to have Acute Lymphoblastic Leukemia between January 1, 2018 and December 31, 2019 at MVR Cancer Centre and Research Institute were included in this study. Records of all the children less than 18 years who received induction chemotherapy with steroids as a part of the induction regimen either in the newly diagnosed or relapsed setting

were retrospectively analysed. The demographic data and the regimen used with the details of the type and dose of steroids were recorded. Baseline cardiac workup done as a part of the institutional policy to know cardiac status before starting anthracyclines was retrieved from the case records. Since all children are given induction chemotherapy at our centre as inpatient admission, the vital parameters are monitored continuously during this period every 4 hourly and the Paediatric Emergency Warning Scores (PEWS) noted in the case records. The vital parameters recorded during initial 24 hrs were taken as baseline value for all parameters. Heart rate (HR), blood pressure (BP), oxygen saturation, respiratory rate and temperature at baseline were retrieved from the case records. The nadir HR after starting of steroids was obtained. Bradycardia was defined as heart rate less than 110 beats/min, 100 beats/min, 80 beats/min, 70 beats/min and 60 beats/min in the age group of 0-3months, 4-11 months, 1-4 years, 5-11 years and more than 12 years respectively as defined by the PEWS chart. Other parameters like day of induction from which the nadir HR occurred and the duration for which bradycardia was present were identified. The day on which the bradycardia resolved was also recorded. The presence of hypertension, hyperglycemia or ECG abnormalities were identified.

2.1 Statistical Analysis

Subject characteristics were summarised using median value for continuous variables and frequency and percent for categorical variables. Estimates of proportions were presented with a 95% confidence interval. Comparisons between

patient populations on categorical variables were conducted with χ^2 test. Pearson correlation was computed to quantify the association of heart rate before and after steroids. All statistical analysis were done using SPSS 26.0. This study was approved by Institutional Ethics Committee, MVR Cancer Centre and Research Institute.

3. RESULTS

3.1 Patient Characteristics

A total of 44 subjects with ALL were identified from the electronic medical records. The details of the patient characteristics is shown in Table 1. Majority (43.2 %) of patients were between the age of 1-5 years with a mean of 7 years. 41/44 (92.7%) of patients received either the BFM IC2009 protocol or the EsPHALL protocol which had prednisolone 60mg/m²/day in three divided doses for a period of 28 days along with chemotherapy drugs (vincristine, daunorubicin and L-asparaginase) which are started on day 8 after initiation of steroids. The other two regimens used had short pulses of high dose

dexamethasone. Out of the 44 patients analysed, 21 (47.7%) developed bradycardia. Various characteristics including age, sex, risk stratification, the type of steroids, protocol used were analysed in the patients who developed bradycardia and who had no bradycardia; and none attained statistical significance as shown in Table 1. None of the children studied were on any opioids beta blockers or any concomitant medications that are known to cause bradycardia.

3.2 Characteristics of Bradycardia

The HR before and after initiation of steroids in the population studied were plotted in a scatter diagram in a coupled data format (Fig. 1). Though majority of patients showed a decrease in HR, only 21 patients had a decrease in HR amounting to bradycardia. The various characteristics of bradycardia is shown in Table 2. The mean HR in patients who developed bradycardia after initiation of steroids was 63 beats/min with a mean decrease in HR of 41 beats/min.

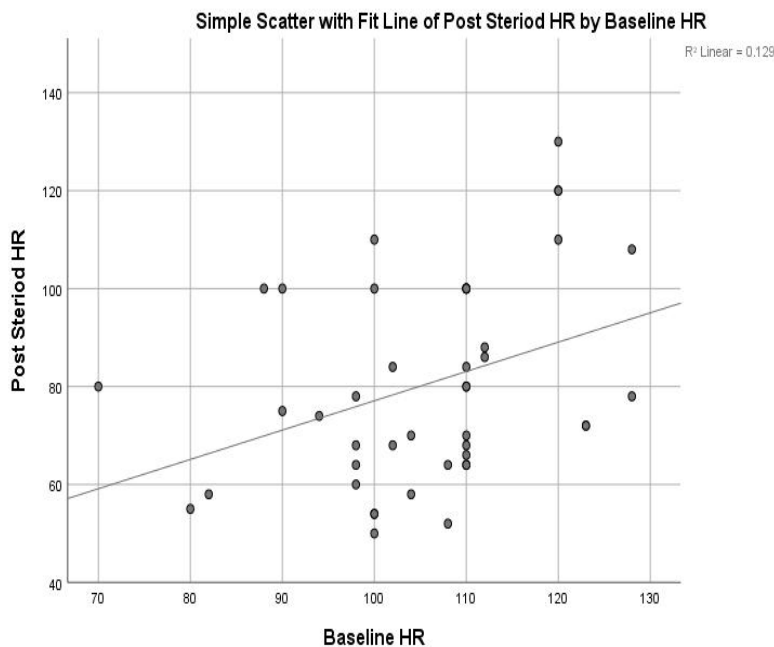


Fig. 1. The x-axis is HR before steroids (baseline HR) and y-axis is HR after steroid (post steroid HR), and each point represents a subject. The points below the diagonal line indicate HR decreased after treatment, and the further the data point from the diagonal line the bigger the decrease in HR. Pearson correlation 0.36, 95% CI (0.08, 0.60). HR indicates heart rate

Table1. Patient characteristics

	Patients who developed radycardia(n=21)	Patients who had no bradycardia (n=23)	Total	p value
Age				
1-5 years	7(33.3%)	12(52.2%)	19(43.2%)	0.89
6-10 years	6(28.6%)	6(26.1%)	12(27.3%)	
11-15 years	6(28.6%)	1(4.3%)	7(15.9%)	
>15 years	2(9.5%)	4(17.4%)	6(13.6%)	
Mean Age	8.61 ± 5.01	6.93 ± 5.61	7.73 ± 5.34	
Sex Male	13(61.9%)	13(56.5%)	26(59%)	0.78
Female	8(38.1%)	10(43.5%)	18(41%)	
Diagnosis				
Newly Diagnosed ALL	20(95.2%)	18(78.2%)	38(86.4%)	0.62
Relapsed ALL	1(4.8%)	2(8.7%)	3(6.8%)	
Lymphoblastic lymphoma	0(0%)	3(13.1%)	3(6.8%)	
Risk stratification				
Standard risk	6(28.6%)	9(39.1%)	15(34.1%)	0.67
Intermediate risk	12(57%)	13(56.5%)	25(56.8%)	
High risk	3(14.3%)	1(4.4%)	4(9.1%)	
Type of steroid				
Prednisolone 60mg/m2/day	19(90.4%)	18(78.3%)	37(84%)	0.85
Dexamethasone 20mg/m2 /day	1(4.8%)	2(8.7%)	3(6.9%)	
Dexamethasone 6mg/m2/day	1(4.8%)	3(13%)	4(9.1%)	
Protocol				
BFM IC 2009	18(85.7%)	21(91.2%)	39(88.7%)	0.79
BFM REZ 2002	1(4.8%)	1(0.4%)	2(4.5%)	
EsPHALL	2(9.5%)	0(0.0%)	2(4.5%)	
Hyper CVAD	0(0.0%)	1(0.4%)	1(2.3%)	
Hypertension				
Yes	2(9.5%)	3(13%)	5(11.4%)	0.91
No	19(90.%)	20(87%)	39(88.6%)	
Hyperglycemia				
yes	1(4.8%)	2(8.7%)	3(6.8%)	0.82
No	20(95.2%)	21(91.3%)	41(93.2%)	

The mean day of onset of bradycardia in the patients studied was 3.95 days and the mean time of recovery was 3 weeks after onset of bradycardia. All the children who developed bradycardia were asymptomatic. Electrocardiogram and Echocardiography were normal in all the subjects except for an incidental ventricular ectopic in a child which persisted even after stopping steroids. None of the children required any treatment during the episode of bradycardia. Two children required atropine during a short anaesthetic procedure for intrathecal therapy.

Among the children who developed bradycardia, 8/21(38.1%), 7/21 (33.3%), 5/21 (23.8%) and 1/21(4.8%) children developed the same on day 3,4,5 and 6 respectively after initiation of steroids. Similarly 4/21 (18%) and 14/21(66.7%) children had recovery of bradycardia on Week 2 and Week 3 respectively while still on steroid therapy; while 3/21 (14.3%) had recovery only after stopping steroids. (Fig. 2)

The mean post steroid HR in patients who developed bradycardia was compared to those who had no bradycardia and found to be statistically significant as shown in the box plot in Fig. 3.

4. DISCUSSION

Sinus bradycardia with glucocorticoid therapy has been described in literature from the 1980's. The first case series was described by Tvede et al. [4] in adults on treatment for rheumatoid arthritis with methyl prednisolone. All the initial reports in children were neonates treated with steroids for respiratory distress [6,7,8]. Reports of the same phenomenon in children treated for glomerulonephritis and rheumatological disorders have been published in literature [3,9].

The earliest reports of a significant drop in heart rate in children on treatment for acute lymphoblastic leukaemia receiving high dose of glucocorticoids was described from Netherlands by van der Gugten et al. [5]. This retrospective study showed a consistent drop in pulse rate, a rise in diastolic blood pressure and decrease in temperature in 61 children undergoing treatment with steroids for several immunological and malignant disorders using a mixed effects regression model. The authors describe an average decrease of 16.8 beats /min within the first 16 hours of start of treatment and a drop of 30.9 beats /min at 72 hours.

There have been two case series from the United Kingdom and United States of America to determine the frequency and characteristics of glucocorticoid induced bradycardia in children with ALL [10,11]. The Canfield et al. [10] study in which the bradycardia was defined as more than 30% decrease in heart rate; 47 out of the 60 (78.3%) children who received steroids with either prednisolone or dexamethasone was found to have bradycardia. Mean reduction in the study with various steroid preparations varied from 36-48 %. Duffy et al. [11] also demonstrated the decrease in the mean heart rate with steroids and among the 150 patients, 90 (59%) had bradycardia which was defined as less than 1st percentile for the age. In our study only 47.7% of our population developed a bradycardia during the observed period (Table 3).

The authors who have published data have mentioned the asymptomatic nature of the bradycardia and none of the children required treatment for the same [10,11]. In our study also none of the children were symptomatic and no treatment was initiated during the episodes except for 2 children who required atropine during a short anaesthetic procedure for intrathecal chemotherapy.

The cardiac side effects of glucocorticoids are postulated to be due to increased systemic vascular resistance, increased extracellular volume and increased cardiac contractility. The exact mechanism for the occurrence of bradycardia is not clear. Out of the many reasons described are excretion of electrolytes in urine following volume expansion, elevated blood pressure leading to reflex bradycardia and lowered sensitivity of myocardium to catecholamines. It is a well described fact that steroids induce changes in electrolytes and water balance and most authors believe that this might be the major factor for bradycardia. But this has never been clinically proven by biochemical evaluation. Left ventricular free wall rupture due to delayed myocardial scar formation has also been described even leading to sudden cardiac death [3,12,13].

Hypertension and hyperglycaemia are well known side effect of steroids [14]. In our study, 11.4% of children had hypertension during induction and all children required antihypertensives for control; but only 2 out of 5 children had bradycardia. In the study by van der Gugten et al. [5], there was a significant rise in the diastolic blood pressure with a mean arterial pressure rise from 77 mmHg to 82 mmHg. 15%

and 10% of the children in the Duffy et al. [10] study developed hypertension and hyperglycaemia respectively after steroid initiation. In our series of children, 3/ 44 (6.8%) had requirement of insulin during induction for hyperglycaemia.

In the case reports in adult patients, the onset of bradycardia ranged from 1-7 days and this silent bradycardia has been described to be responsible for the sudden cardiac deaths in pulsed corticosteroid treatment [13,15]. In the study from the United States, the nadir heart rate was reached after 7 doses of steroids and 79.1 hours after initiation [11]. In the study from the Netherlands, a significant drop of heart rate was

seen at 72 hours time period [9]. In our centre, nadir heart rate was seen at 3.95 days with a range of 3-6 days.

Studies in adults have shown resolution of bradycardia within 3-10 days of stopping steroids [16]. In our analysis, majority of children had resolution of bradycardia by the third week while on steroids. A similar finding has been demonstrated in both of the Akikusa et al. [3] and Duffy et al. [11] study as against the normal perception of resolution of bradycardia after stopping the drug implicated. It is postulated that this phenomenon is due to the compensatory mechanisms which try to maintain peripheral perfusion.

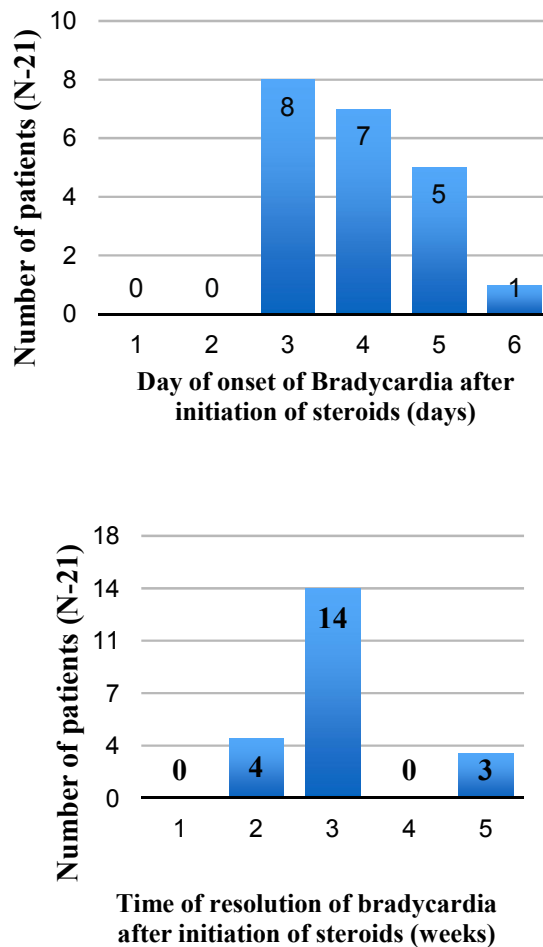


Fig. 2. Bar diagram showing the time of onset and resolution of bradycardia in children who developed bradycardia

Table 2. Characteristics of bradycardia

Parameter	Values	
Frequency of bradycardia	21 (47.7%)	
Mean HR in patient developing bradycardia after steroids (mean +SD) Range	63.29 ± 7.57 beats/min 50 – 78 beats /min	
Mean decrease in HR in patient developing bradycardia after steroids (mean +SD) Range	41.76 ± 8.78 beats/min 25 - 56 beats/min	
Mean Day of Onset of bradycardia (Range)	3.95 ± 0.92 day (3-6 days)	
Mean week of recovery of bradycardia (Range)	3.09 ± 0.89 (2-5weeks)	
	Having bradycardia	No bradycardia
Baseline HR (mean ±SD) Range	105.05 ± 11.63 (80bpm – 128bpm)	105.83 ± 13.28 (70bpm – 128bpm)
Post steroid HR (mean +SD) Range	63.29 ± 7.57 (50 bpm – 78bpm)	95.96 ± 15.70 (74 – 130)

Table 3. Comparison of characteristics of bradycardia in various studies

Characteristics	Duffy et al.	Gugten et al.	Our study
Children with bradycardia (%)	59	63.9	47.7
Mean HR after initiation of steroids (beats / min)		81.54	63.29
Mean decrease in HR after initiation of steroids beats / min(Range)	23(12.5-32)	31(23-38.7)	41.74(25-56)
Mean time to HR nadir days (Range)	3.3(2.3-4.5)	3	3.95(3-6)
Mean time of recovery of bradycardia (weeks)	> 1	NA	3.09(2-5)
Hypertension (%)	15%	NA	11.4%
Hyperglycemia	10%	NA	6.8%

Some studies have looked at the association of the type and dose of steroids and the incidence of bradycardia. As against the incidence of bradycardia which was initially described with high dose short pulses of steroids, authors have now described a higher occurrence of bradycardia with low dose oral steroids administered over a prolonged period of time [4]. In the Duffy et al study, higher rates of low HR was seen with the usage of dexamethasone than prednisolone. In our study, 25% and 33.3% of children had a decrease in HR while on low dose dexamethasone and high dose short pulse of dexamethasone respectively; though the numbers are too small to reach a conclusion.

Another observation seen in our cohort was a higher incidence of bradycardia in children less than 5 years of age, but the analysis of correlation to age did not attain statistical significance. Though it is known that most side effects of steroids are seen in younger children, the association with age needs further study with larger number of patients [17].

Limitation of our study is that it is a retrospective series, having small number of patients. During induction chemotherapy a lot of confounding factors may also be associated with the vital parameters of children, which were not evaluated.

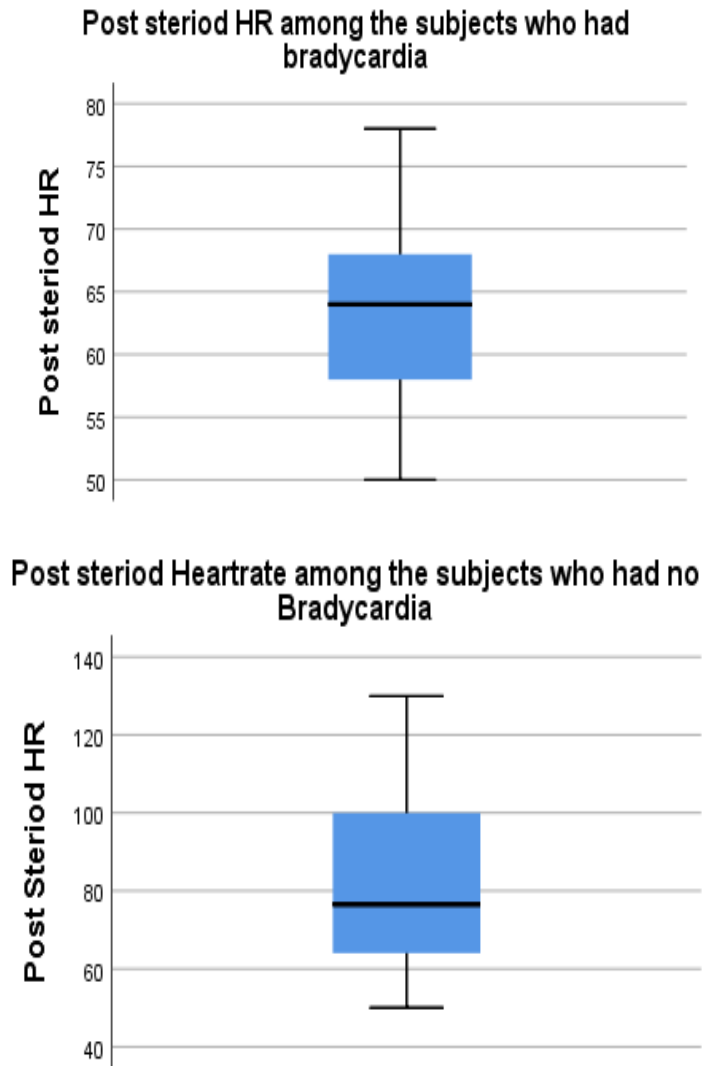


Fig. 3. Box diagram: Post steroid heart rate among the subjects
p value: 0.04

5. CONCLUSION

Glucocorticoid induced bradycardia is an under-recognised phenomenon when compared to the common side effects of steroids. In our retrospective data we could demonstrate a significant decrease in HR in our children with acute lymphoblastic leukaemia undergoing induction chemotherapy with steroids. The bradycardia usually occurred in the first week of initiation and recovered by the third week of the protocol treatment. Further large cohort studies are needed to analyse the other factors involved in the development of bradycardia.

ACKNOWLEDGEMENTS

The authors have no acknowledgements to disclose and the authors have not received any funding for the conduct of the study.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

This study was approved by Institutional Ethics Committee, MVR Cancer Centre and Research Institute.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

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