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ORIGINAL ARTICLE

To determine the effect of parenteral iron in the management of symptoms related to restless leg syndrome in patients with iron deficiency anemia

Bughdad Khan[1], Bilal Zeb Qureshi[2], Fahad Naim[1], Nizamuddin[3*], Tariq Mahfooz Khawaja[4] and Syed Hasnain Ali Shah[4]

[1] Khyber Teaching Hospital Peshawar, [2]Kuwait Teaching Hospital Peshawar, [3] Khyber Medical College Peshawar, [4]Kabir Medical College Peshawar

ABSTRACT

Background: The current study aimed to determine the frequency of restless leg syndrome (RLS) in patients with iron deficiency anemia (IDA) presenting to Khyber Teaching Hospital (KTH) and Khushal Medical Center (KMC) Peshawar and to see the effect of parenteral iron therapy on RLS with IDA.

Methods: This prospective cohort study enrolled 110 patients of either gender with IDA from September 2022 to December 2023. All patients were interviewed and data was recorded for restless leg syndrome as per operational definition. The diagnosed RLS patients were given 500mg iron carboxymaltose in 100ml normal saline (NS) over a period of 15 minutes stats and 500mg after two weeks and treatment response was assessed four weeks after the treatment. Clinical symptoms including pain, fatigue and sleep quality were recorded before and after the iron therapy. All the data were analyzed using SPSS version 22.0.

Results: RLS was observed in 35.5% patients with IDA. The mean age was 48.70±8.0 years. Male gender was 54.5% while female gender was 45.5% in our study. The levels of hemoglobin (Hb) were significantly improved with iron carboxymaltose (p-value <0.001). The symptoms related to RLS including pain, fatigue and quality of sleep were 90.1% improved after iron therapy. T-test reveals significant improvement in pain, fatigue and sleep quality before and after iron therapy with p-value <0.001. There was no statistical significant association between gender and improvement of symptoms related to RLS (p-value >0.05).

Conclusion: RLS was highly prevalent in patients with IDA in our population. Management of IDA with parenteral iron carboxymaltose not only improves the levels of Hb but provide immediate relief of symptoms related to RLS.

Keywords: Hemoglobin, Iron Carboxymaltose, Iron Deficiency Anemia, Iron Deficiency, Restless Leg Syndrome.

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Introduction

Iron is essential for the production of hemoglobin. The depletion of iron stores may result from blood loss, decreased intake, impaired absorption, or increased demand. IDA could arise from occult gastrointestinal bleeding (1). Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is a frequent neurological disorder whose recognition among neurologists is still low,

despite the typical symptoms reported by patients (2). Patients typically present with sensory symptoms and discomfort in their legs, an urge to move at rest above all in the evening, and consequently, sleep disturbances, but they are often undiagnosed and untreated for years (3). Early-onset RLS is often familial and has a slow progression of symptoms, while late-onset RLS may show a rapid evolution and is more frequently associated with comorbidities, above all iron deficiency (4). The deficiency of iron not only worsen the symptoms of RLS but also cause the disease (5). Iron is a cofactor of enzymes involved in dopamine synthesis and dopamine receptor regulation and its deficiency can cause RLS symptoms (6, 7). A historical paper published in 1953 where Nordlander (8) reported that patients having IDA and RSL symptoms greatly improved with parenteral iron. Following this, many reports published on the casual relationship between IDA and RLS (9, 10). However, the data is still scare based on ethnicity related to the symptoms of RLS as well as its association with IDA (10).

This study will provide the local estimate of prevalence of RLS in an IDA population and its response to parenteral iron in patients visiting KTH Peshawar.

CORRESPONDING AUTHOR

Dr. Nizamuudin
Department of Pharmacology, Khyber Medical College Peshawar
Email: drnizam99@yahoo.com

Methods

This prospective cohort study was initialed in Khushal medical center (KMC) and Khyber Teaching Hospital (KTH) Peshawar after ethical approval from KMC and data approval from KTH via letter no. KMC/EB01/023. The duration of study was one year started from September 2022 to December 2023. Total 110 IDA patients were enrolled upon their consent. Sample size was calculated with WHO sample size software, 95% confidence interval and 8% margin of error with expected frequency of restless leg syndrome by 23.9% in patients with iron deficiency anemia (9). After baseline investigation, all the IDA patients were interviewed and the diagnosis of RLS were made as per criteria defined previously by Allen et al (11) related do discomfort in legs followed by movement of legs and whether the movement worse or relive the unpleasant or discomfort in legs and whether these symptoms is worse during day or night, fatigue and quality of sleep. Patients not willing to participate in the study, ferritin levels >300µg/l, pregnant or lactating women or individual with metabolic disorders were excluded from the study. After the diagnosis of RLS, the patients were subjected to 500mg iron carboxymaltose slow intravenous in 100ml NS over a period of 15 minutes on day first and 500mg iron after two weeks. The RLS patients were re-interviewed after 4 weeks and response of the patients related to pain, fatigue and quality of sleep was recorded.

All the data was entered in SPSS version 22.0. Descriptive data were presented in mean ± SD and frequency (percentages). Paired sample t test was performed to see the improvement in Hb before and after therapy. Chi-square was done to see the level of significance between gender and symptoms related to RLS. Graphs were constructed using MS-Excel and p-value <0.05 was considered significant.

Results

This study enrolled total 110 IDA patients.

After thorough interview, 33 patients were diagnosed with RLS in which 54.5% were males and 45.5% were females. The mean age was 48.70±8.0 years. The level of Hb before therapy was 9.93±0.68 g/dl while it was improved to 12.91±0.73 g/dl after iron carboxymaltose therapy. The details are shown in table 1.

Table 1: demographics of participants

Variable	Mean	SD
Gender (m/f)	18(54.5%)/ 15 (45.5%)	-
Age (years)	48.70	8.0
Hb before treatment (g/dl)	9.93	0.68
Hb After therapy (g/dl)	12.91	0.73

The symptoms related to RLS including pain, fatigue and sleep disturbance before and after iron therapy is shown in table 2.

Table 2: RLS symptoms before and after iron therapy

RLS variables	Before iron therapy N 33(%)	After iron therapy N 33(%)	Overall improv-ement	p-value
Pain m/f	18/15 (100%)	2/1 (9.1%)	90.1%	<0.001
Fatigue m/f	16/14 (90.9%)	2/1 (9.1%)	90.1%	<0.001
Disturbed sleep m/f	16/11 (81.8%)	1/2 (9.1%)	90.1%	<0.001

Abbreviations: RLS, restless leg syndrome; m, male gender; f, female gender

Initially, pain was 100% prevalent, fatigue was present in 90.9% RLS patients while disturbed sleep was found in 81.8% patients, after iron therapy, all the symptoms related to RLS was improved by 90.1% in all patients. To find the impact of gender in RLS improvement, chi-square test was done which shows no statistical significant impact of gender on RLS improvement (p-value >0.05). The details are summarized in table 3.

Table 3: Association of gender with RLS improvement

RLS variables	Male	Female	p-value
Pain after therapy (improved/not improved)	16/2	14/1	0.57
Fatigue after therapy (improved/not improved)	15/3	13/2	0.59
Sleep quality after therapy (improved/not improved)	17/1	13/2	0.43

There was statistical significant improvement observed in Hb. The level of Hb before therapy was 9.93±0.68 g/dl while it was improved to 12.91±0.73 g/dl after iron carboxymaltose therapy with p value <0.001. This is graphically shown in figure 1.

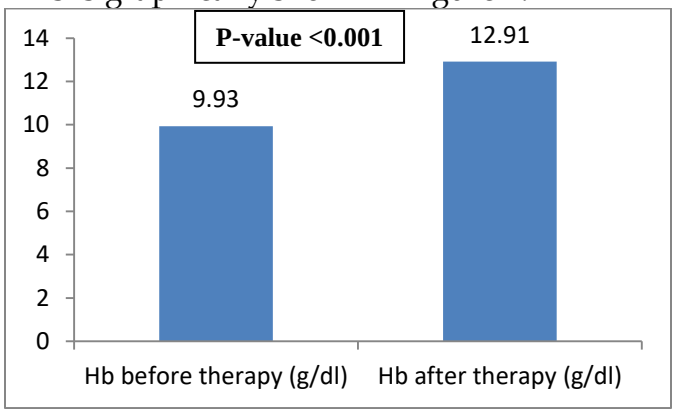

Figure 1: Hb improvement with iron therapy

Discussion

This study documented a high prevalence (35.5%) of RLS among patients with IDA in our population. In consistent with our findings, a study published in United States by Allen et al reported 31.5% prevalence of RSL in patient with IDA (9). A study published in Korea by Bae et al reported a much higher prevalence of RSL which was 40.3% in IDA patients (10).

In our study, the mean Hb level before therapy was 9.93±0.68 g/dl while after iron carboxymaltose therapy; it was improved to 12.91±0.73 g/dl. The improvement in Hb was highly statistical significant with p-value <0.001. Similar findings were also published

in the past in consistent with our results. A systematic review published by Rognoni et al shows significant improvement of Hb and ferritin level with iron carboxymaltose in patient with IDA (12). Significant improvement in the management of IDA with iron carboxymaltose was also observed in a report published by Koduru et al (13), which is in line with our findings. Furthermore, Rognoni et al also reported the safety and better efficacy of iron carboxymaltose in the management of IDA as compared to other iron preparations available (12).

The symptoms of RLS including sleep disturbances, pain and fatigue were positive in all RLS patients with IDA in which pain was 100% prevalent followed by fatigue and sleep disturbances. Certain studies reported as the disturbances of sleep more prevalent in patient with RLS (10). In our study, gender does not affect the severity or symptoms related to RLS as the distribution were similar in both males and females (p-value >0.05) as reported by Bae et al in his report also (10).

With parenteral iron carboxymaltose, the symptoms of RLS improved by 90.1% in our study. These symptoms including pain, fatigue and sleep disturbances which were significantly improved with iron therapy (p-value <0.001). According to a meta-analysis published in 2019 by Avni et al also found significant improvement of RLS symptoms with iron supplementation (14). Similar improvement of symptoms related to RLS was also reported in a meta-analysis of randomized control trials published by Bae et al in 2023 (15).

Our study showed a high prevalence of RLS among patients with IDA, and the symptoms related to RLS was greatly improved with parenteral iron carboxymaltose. Furthermore, it also provides an insight of the use of iron carboxymaltose in the management of IDA as compared to other preparations as it provide efficient improvement in the levels of Hb.

Conclusion

RLS was highly prevalent in patients with IDA in our population. Management of IDA with parenteral iron carboxymaltose not only improves the levels of Hb but provide immediate relief of symptoms related to RLS.

Limitation of the study

A cohort of larger RLS patients in multiple centers needs to enrolled with a larger period of time to achieve better results but due to limitation of funds and difficulty in follow-up we limit our study to only two centers with a month follow-up.

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Conflict of interest: None.

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All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed.