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Original article

Impact of Imatinib on reducing the painful crisis in patients with sickle cell disease

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Introduction: Sickle cell disease (SCD) is a common hemoglobinopathy worldwide that causes painful crises and hospitalization of patients. These attacks decrease survival and cause chronic end-organ damage in these patients. *Hypothesis*: For this reason, finding new treatment approaches could be helpful. *Method*: In this study, Imatinib was applied as a mast cell inhibitor to reduce pain crises in these patients. Seven patients resistant to hydroxyurea and folic acid treatment and who had at least four painful crises per year with hospitalization were enrolled in this study with treatment with Imatinib (100 mg, twice daily). Subsequently, the number and duration of hospitalizations, analgesic requirement, the severity of chronic pain, and changes in the hematological parameters of these patients were evaluated before and after the treatment. *Results*: The data showed that the total number of hospitalizations and the entire duration of hospitalizations were reduced 16 times after treatment with Imatinib, without apparent changes in hematological parameters. Also, the demand for pethidine, tramadol, and nonsteroidal anti-inflammatory drugs (NSAIDs) was reduced in all patients. The average reduction in chronic pain was over 70%. *Conclusion*: This study demonstrates that treatment with Imatinib in patients with SCD or sickle cell anemia (SCA) may be a suitable therapeutic option for reducing painful crises.

Introduction

Sickle cell disease (SCD) is a hereditary disorder characterized by abnormal red blood cells (RBCs). It is caused by a point mutation in the β-globin chain of hemoglobin (Hb), which leads to the replacement of glutamic acid (a hydrophilic amino acid) with valine (a hydrophobic amino acid) at the sixth position.[1-3] The pathophysiology of sickle cell disease is complex and consists of several mechanisms, including the Hb polymerization,[4] cell dehydration,[5] decreased nitric oxide,[6] abnormal cell adhesion,[7] inflammation,[8] damage caused by ischemia-reperfusion injury,[9] activation of the coagulation system[10] and chronic vasculopathy.[8-11] The prevalence of sickle cell disease reached 1 to 2% in some regions of Africa in 2010.[12]

One of the most important molecules involved in sickle cell disease is the platelet-derived growth factor (PDGF). It has been reported that PDGF isoforms (AA, AB and BB) have vital

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roles in the regulation of vascular tone and elasticity and the capillary cell wall.[13] Patients with sickle cell disease have increased levels of PDGF-AB and PDGF-BB and an increased level of PDGF-AA has been directly associated with stroke and severe anemia.[14] On the other hand, the most common complication of sickle cell anemia (SCA) is vascular occlusion, leading to acute pain and end-organ ischemia.[15] Pain is usually the major factor that is used to determine the quality of life in patients with sickle cell disease.[16] Recurrent painful crises, more than three times per year, require hospitalization and correlate with decreased survival in adults. Additionally, it has been reported that these attacks are associated with chronic injury of the distal extremities.[17] Painful crises are treated with fluid therapy, supplemental oxygen and analgesics.[18]

The acute pain in patients with sickle cell anemia is produced by the vast-occlusive crisis (VOC), impaired oxygen supply, and infarction-reperfusion tissue injuries, a process in which inflammatory cytokines play a critical role. Chronic pain is initiated due to the prolonged hyperalgesia after a VOC and central sensitization. Neuropathic pain is induced due to central or peripheral nerve injury and the pain seems to be generated by protein kinase C.[19] Moreover, studies on murine models have reported that the activation and degranulation of mast cells are involved in the pathophysiology of sickle pain. Consequently, substance P is released into the skin and dorsal root ganglion (DRG), which induces neurogenic inflammation and activates nociceptors.[20]

Imatinib is a drug that inhibits tyrosine kinase and is administered orally. It blocks the activity of the breakpoint cluster region-Abelson (BCR-ABL), an oncoprotein, and the c-kit tyrosine kinase cell surface receptors. Furthermore, several studies discovered that Imatinib could attenuate inflammation by inhibiting or modulating the production of pro-inflammatory cytokines.[21-23] In addition, imatinib has the potential to inhibit the platelet-derived growth factor receptor (PDGFR) kinase, as well as mast cells.[24] Cerny-Reiterer *et al.* reported that, in patients with chronic myeloid leukemia (CML) who were treated with imatinib, the imatinib could effectively suppress the production of both *in vitro* and *in vivo* mast cells.[25] Therefore, targeting mast cells with imatinib might be a suitable approach to decrease pain in patients with SCA and possibly treat the disorder.

As sickle cell anemia is a common hemoglobinopathy worldwide, as well as in Iran, in this pilot study, we aimed to determine the reduction of the sickle cell crisis in patients with sickle cell anemia who were resistant to treatment with hydroxyurea (HU), or were unable to tolerate hydroxyurea.

Materials and methods

In a prospective interventional pilot study, seven patients with sickle cell anemia (hemoglobin SS or Sβ^{-} thalassemia) were recruited from the Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, between November 2011 and July 2014. The clinical trial code in the Iranian Registry of Clinical Trials is IRCT201306015305N2. This study was approved by the Ethics committee of the Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.REC.1393.4092). The condition for all of these patients to enter this study was a pain crisis that could not be controlled with hydroxyurea (500 mg) with a time medication dose of 12 h (HU resistant). Moreover, they had a history of more than three hospitalizations per year (before taking imatinib). The duration of more than 4 h of admission at the hospital was considered as the hospitalization criteria. Written informed consent was received from all patients before enrollment in the study. The benefits and risks of imatinib were explained to each patient before administering the medication. The patients' mean age was 26 years (age range of 24 - 30). They were administered 100 mg. of imatinib (Sobhan Co.) twice a day, orally. During this study, the administration of HU was continued with the same dose as before (500 mg., BD) and folic acid (5 mg.) as a complementary drug alongside the twice-a-day administration of imatinib (100 mg.) for the duration of one year. One of the patients continued this treatment for two years. Patients were followed up with a checkup visit every six months. Demographic information was collected from all patients.

The main parameters that were evaluated in this study were the number of hospitalizations, duration of total hospitalizations, the average duration of each hospitalization, reduction in analgesic use, and reduction in pain intensity, which were measured with the Numerical Rating Scales (NRSs) in the value range of 0 to 10. In addition, the hematological variables included white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), and platelets, which were assessed before and after treatment with imatinib. Clinical and laboratory data were documented in an electronic spreadsheet prior to, and one year (twelve months) after, treatment with imatinib. Descriptive statistical analysis was performed with the SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL). As none of the data distribute normally, the non-parametric sign rank test was applied for all statistical analyses in the format of Median±SEM. A p-value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the demographic information of the patients enrolled in this study. There was no significant difference in the age of the patients. In addition, the number of male and female patients was approximately similar (the ratio of approximately 1:1). The effects of imatinib on the analgesic use, the number of hospitalizations, duration of total hospitalizations, and average duration of each hospitalization, before and after treatment, are presented in Table 2. The statistical analysis of the number of hospitalizations indicated that the number of hospitalizations was reduced after

Table 1 – Demographic information of the seven enrolled patients.

Variables		Value
Sex (number)	Male	4
	Female	3
Age (year)	Male	26.14 ± 3.2
	Female	26.75 ± 4.34
	Total	26.14 ± 1.24

Table 2 – Comparison of the number of times analgesics were used, as well as the number, total time, and mean time of hospitalization before and one year (twelve months) after treatment with imatinib.

Variables		Before treatment with imatinib	One year after treatment with imatinib	*p*-value
Number of times analgesics were used	Pethidine 50mg	10	0.5	
	Tramadol 100 mg	10	0	
	NSAIDs	20	5	
Number of hospitalization(times)		62	16	
The median number of hospitalization(times)		11(4 - 12)	2(0 - 5)	0.018
Total time of hospitalization duration(days)		213.25	26.25	
The median total time of hospitalization duration (days)		21.5(7.25 - 45)	0.75(0 - 4)	0.02

treatment with imatinib from 62 times to 16 times, with a *p*-value of 0.018, which means that using imatinib enabled a significant decrease in the number of patient hospitalizations. The median number of hospitalizations before treatment with imatinib was reduced from 11 times (in the range of 4 - 12 times) to 2 times (in the range of 0 - 5 times). Furthermore, the total days of hospitalization of all the patients tremendously decreased from 213 days before treatment with imatinib to 26.5 days after treatment with imatinib, with a *p*-value of 0.02. The median hospitalization duration was 21.5 days, with a range of 7.25 to 45 before treatment with imatinib, which was reduced to 0.75 days, with a range of 0 to 4 days, after treatment with imatinib.

Furthermore, the necessity for the use of the analgesics pethidine 50 mg, tramadol 100 mg. and nonsteroidal anti-inflammatory drugs (NSAIDs) was reduced by 93.5% (in four patients), 100% (in one patient) and 75% (in one patient), respectively. Moreover, the amount of subjective reduction in chronic pain was 70%, based on the pain rating scale (range 0 - 10). Our analysis demonstrated that the administration of pethidine, tramadol, and NSAIDs as analgesic drugs was significantly higher before treatment with imatinib ($p = 0.018$), compared to that after the administration of imatinib. The consumption of imatinib enabled the need of patients for all of these drugs to be reduced. Additionally, the analysis of hematological parameters was made before the consumption of imatinib and at one year (twelve months) after the administration of imatinib, showing that this drug did not cause significant changes in the WBC (*p*-value = 0.86), RBC (*p*-value = 0.13) and platelet (*p*-value = 0.93) counts, nor in the hemoglobin levels (*p*-value = 0.23) (Figure 1). The median, range, and statistical analysis of hematological parameters are presented in Table S1.

Discussion

Currently, hydroxyurea is highly recommended, as well as being the only FDA-approved drug, to treat sickle cell anemia. Previous studies have shown that HU use is associated with decreased episodes and severity of painful crises[26] and increased survival.[27] However, for some unknown reasons, HU did not show similar efficiency in patients with sickle cell disease in this study. Therefore, due to the high prevalence of SCD and some patients' resistance to HU, identifying an alternative agent for preventing complications caused by sickle cell disease, such as severe life-limiting pain and resultant end-organ damage, is urgently needed.[28] It has been reported that imatinib (a c-kit inhibitor) was capable of reducing chronic pain in mice with sickle cell anemia due to the inhibition of mast cells[29] and the blockage of the PDGFR activation, which are responsible for the analgesic tolerance.[30] Therefore, the effects of imatinib on painful crises and hematological features of patients with sickle cell disease were evaluated in this study.

Our data demonstrated that consumption of imatinib significantly reduced chronic pain without any significant changes in hematological variables. In addition, there was a significant reduction in hospitalized patients with sickle cell disease treated with imatinib. This may reduce the number of hospitalizations, the cost burden on health systems, and the costs imposed on patients and their families, as well as the analgesic requirements.[2] In addition, due to the high prevalence of sickle cell disease and some patients' resistance to HU, imatinib can help reduce painful crises and decrease the tolerance to pethidine, tramadol, and NSAIDs.

The use of imatinib in SCD is a new therapeutic strategy. To the best of our knowledge, there are only two previous reports on using imatinib in CML patients with SCD. They reported the resolution of vaso-occlusive crises with imatinib therapy.[28,31] Our findings on the efficiency of imatinib in reducing pain crises in patients with SCD align with these two reports. In the previous reports, two cases of patients with SCD and CML had received imatinib. Although there is probably no link between these two diseases, the association has been reported in 11 cases.[28,31-39] However, none of the seven patients in our study had CML while they were on therapy with imatinib.

Imatinib use presented a mild to moderate side effect, which is reversible by reducing or discontinuing its administration. The short-term toxicities of imatinib include superficial edema, muscle cramps, nausea, musculoskeletal pain, diarrhea, rash, fatigue, headache, abdominal pain, and joint pain in more than 10% of the patients. The long-term toxicities of imatinib consist of cardiac toxicities, secondary malignancy, myositis, multiple sclerosis, renal failure, dermatitis pancreatitis, hypophosphatemia, gynecomastia, hypogammaglobinemia, opportunistic infections, hepatotoxicity, pulmonary toxicities, skin hyper/hypopigmentation, and cerebral edema, which is observed in less than 1% of the patients.[40] Furthermore, it is also important to note that imatinib is categorized in the group D of drugs in pregnancy due to its evident disadvantages to the fetus. Therefore, its use in pregnant women is restricted to life-threatening conditions,

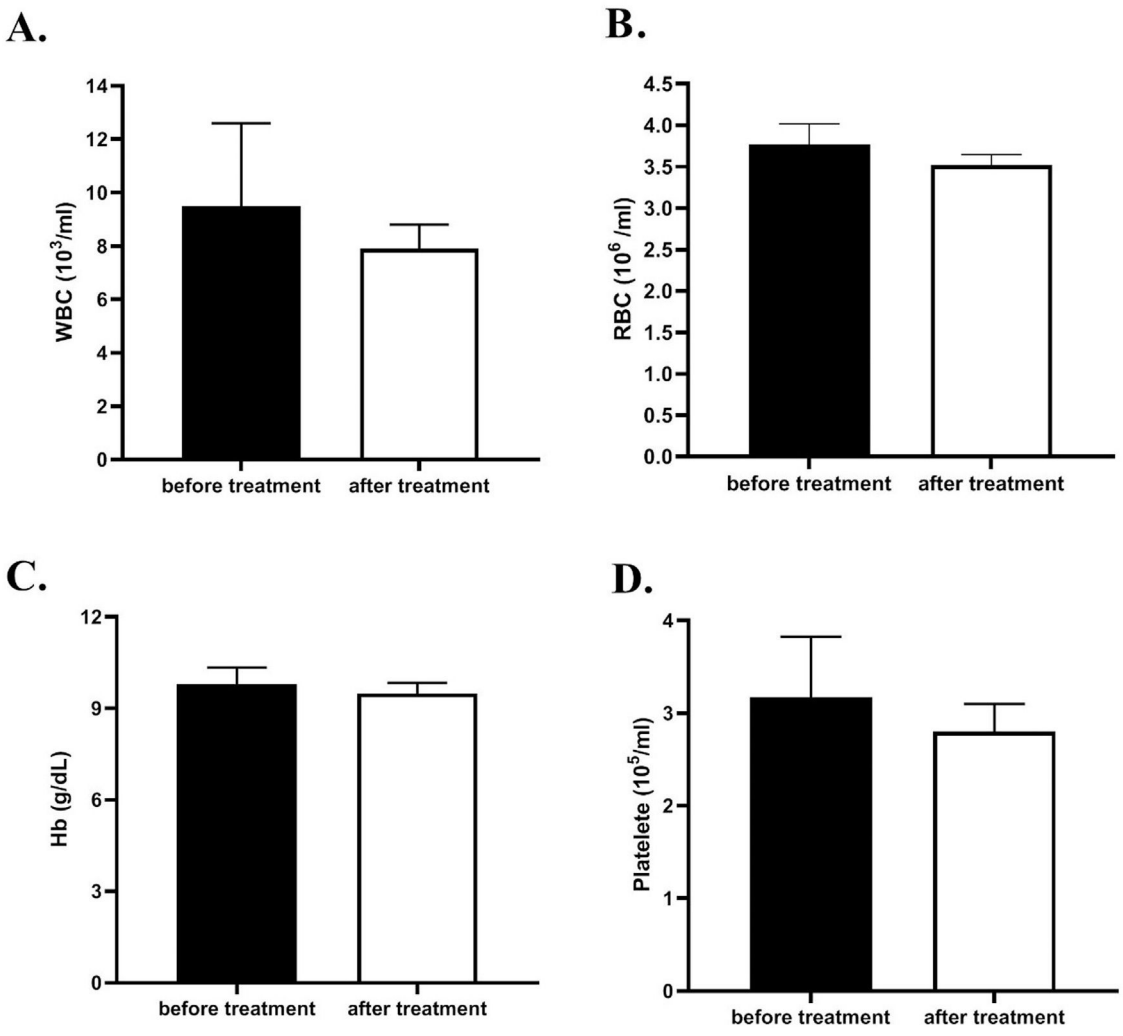

Figure 1 – The statistical analysis (Median±SEM) of the hematological parameters of the studied patients with sickle cell diseases before and after treatment with imatinib (p-value < 0.05). The results did not show significant changes in the red blood cell (RBC) count, white blood cell (WBC) count, platelets, and hemoglobin (Hb) values before and after treatment with imatinib.

and neither should it be used during breastfeeding.[41] In the current study, mild muscle cramps and edema were reported in some of the patients during the administration of imatinib and its dosage was reduced for these patients intermittently.

This study has some limitations. The sample size of this study is small and limited to seven patients. In addition, imatinib was added to the patients' standard treatment and was not studied as a single therapeutic option. Therefore, further studies with larger sample sizes are required to investigate and confirm the effects of imatinib on the painful crises of sickle cell disease.

Conclusion

In summary, our study demonstrates a significant reduction in the number of hospitalizations caused by painful crises, decreased length of hospitalization durations, and reduced duration of each hospitalization after initiating the imatinib therapy. In addition, chronic pain, opioid use, and analgesic consumption were reduced in these patients without any significant effects on hematological parameters. However, further investigations with higher sample sizes and different therapeutic procedures are required and highly recommended.

Authors' contributions

All authors passed the four criteria items for authorship contribution based on the recommendations of the International Committee of Medical Journal Editors.

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Ethical statements

This study was approved by the Ethics committee of the Shiraz University of Medical Sciences (IR.SUMS.REC.1393.4092). Written informed consent was obtained from the studied patients.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no competing financial ties or conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.htct.2023.06.007.

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