

Oral Iron Therapy with Polysaccharide-Iron Complex May be Useful in Increasing the Ferritin Level for a Short Time in Patients with Dilated Cardiomyopathy

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Abstract

Background: Iron deficiency (ID) is one of the most common comorbidities in patients with heart failure (HF). The preferred form of iron supplementation is intravenously. Polysaccharide-iron complex (PIC) is an oral iron supplement that has a bioavailability of 100%; gastrointestinal complaints are absent or less frequent with PICs.

Objectives: In this study we aimed to investigate if oral PIC was effective at increasing the ferritin level over 12 weeks in dilated cardiomyopathy patients with an absolute iron deficiency and to determine the incidence GI side effects with this type of treatment.

Methods: Thirty patients with a diagnosis of non-ischemic dilated cardiomyopathy (left ventricular ejection fraction (LVEF) < 35%) and absolute iron deficiency (serum ferritin level < 100 mcg/L) were recruited. For all study participants, one capsule of Feramax-150 was prescribed on a daily basis for 12 weeks. All patients were asked to report any GI side effects, including heartburn, abdominal pain, nausea, vomiting, diarrhea, constipation, and bloating.

Results: The mean (SD) age was 43.2 (13.4) years. The mean LVEF was 23%. The mean (SD) ferritin level was 48.8 (27.7) at baseline. After 12 weeks of treatment with Feramax-150, the mean (SD) ferritin level had increased to 69.9 (42) ($P < 0.001$). No patients reported any gastrointestinal side effects.

Conclusions: PICs could be a good and well-tolerated medicine in the treatment of iron deficiency in patients with heart failure. It is recommended that PICs be prescribed to maintain body iron stores after IV iron therapies in HF patients.

Keywords: Iron Deficiency, Heart Failure

1. Background

Iron deficiency (ID), one of the most common comorbidities in patients with heart failure (HF), is seen in up to 60% of these patients (1-4). ID is more prevalent in patients with more severe HF, including those with a New York heart association (NYHA) functional class of III and higher NT-proBNP levels. However, it is estimated that more than 30% of patients with an NYHA functional class of I or II suffer from ID. Regardless of the presence of anemia or the severity of heart failure, ID is significantly associated with a higher mortality in patients with heart failure even after adjustment for other risk factors, such as the NYHA functional class and NT-proBNP level (2-6).

According to the European society of cardiology (ESC) guidelines for heart failure (2012), patients with HF may have absolute ID (defined as a ferritin level equal to or less than 100 mcg/L) or functional ID (a ferritin level less than 300 mcg/L with a transferrin saturation of less than 20%). These values are considered valid regardless of the hemoglobin level (1, 5, 7).

It has been shown that iron therapy improves symptoms, exercise capacity, and quality of life in HF patients with a reduced ejection fraction (HFrEF). Therefore, the ESC guidelines recommend iron therapy in all patients with HFrEF who have ID regardless of the presence of anemia (1-3, 5, 6, 8).

Oral iron supplements are widely used and are relatively inexpensive. The most frequently administered form of oral iron is ferrous sulfate. However, the absorption of this type of iron is relatively low, and up to 60% of patients develop gastrointestinal (GI) side effects, such as constipation, dyspepsia, nausea, diarrhea, and heartburn, which leads to poor compliance (5, 9-11).

On the other hand, evidence suggests that ferrous sulfate can provoke oxidative stress locally in the GI system, especially at higher doses, which produces adverse consequences, including lipid peroxidation, disruption of the cell membrane, and DNA damage. Therefore, oral iron therapy is unlikely to be effective if rapid iron replacement is required and would not be suitable for patients who cannot tolerate the drug or who show poor compliance (9-12).

Using intravenous (IV) iron preparations instead of oral iron is one solution for the adverse effects of oral iron therapy with ferrous sulfate. IV iron is generally safe and has considerable efficacy; unfortunately, there are some limitations, including the requirement of hospital facilities for its administration, higher costs, and risk of hypersensitivity with some types of IV iron preparations, including Venofer (2, 3, 5, 13).

Polysaccharide-iron complex (PIC) is an oral iron supplement that allows ionic iron to be absorbed intact through the small intestine without coming into contact with the upper GI tract and then be delivered directly into the bloodstream. Oral PIC has been evaluated in a wide variety of medical conditions that present with ID, including patients undergoing dialysis. The bioavailability of PIC is 100%. PIC has been shown to be well accepted and tolerated by patients; GI complaints with PIC are absent or less frequent than those associated with oral iron supplementation. This type of iron replacement allows for a reduction in the number of doses required per day, particularly in patients who need higher amounts of elemental iron and who are taking numerous medications (9, 11, 14-21).

2. Objectives

In this study, we aimed to investigate whether oral PIC is effective at increasing the ferritin level over 12 weeks in dilated cardiomyopathy patients with an absolute iron deficiency and also to examine the incidence of GI side effects with this type of treatment.

3. Methods

In this case series study, 30 patients with a diagnosis of non-ischemic dilated cardiomyopathy (DCM) who had been referred to the heart failure and transplantation clinic of Rajaie cardiovascular medical and research center were recruited according to the following inclusion criteria: left ventricular ejection fraction (LVEF) equal to or less than 35%, NYHA functional class of I-III, and a serum ferritin level less than 100 mcg/L.

The study population was required to be on guideline-directed medical therapy for heart failure, which remained unchanged throughout the entire study duration (12 weeks) unless the patients developed decompensation and/or any condition in which a drug dosage adjustment was necessary. The exclusion criteria were comprised of the presence of decompensation, a need for drug adjustments, any inflammatory process at baseline or during the study period, a history of hemoglobinopathies, recent treatment with oral or IV iron supplements, malabsorption, a history of hypermenorrhea in premenopausal

women, any endocrine disorders including diabetes mellitus, and renal failure.

The study was approved by the institutional ethics and research committee, and informed consent was obtained from all patients.

After explaining the study's aim and methods to each patient, a thorough history and physical examination was obtained from all participants, and their NYHA functional class was recorded.

The NYHA functional class was evaluated by considering the severity of the patients' limitations regarding physical activity, where class I indicates no limitations, class II carries slight limitations, class III indicates significant limitations, and class IV includes symptoms of dyspnea when at rest (1).

The functional capacity was evaluated by 6-MWT according to the protocol of Guyatt and colleagues (22) at baseline and also after 12 weeks.

3.1. Laboratory Tests

The laboratory tests included a complete blood count, hemoglobin level, NT-proBNP as well as the iron profile (serum iron, total iron-binding capacity (TIBC), and ferritin level) and were measured at baseline and again after 12 weeks. All patients were determined to have normal renal function after testing the urea and creatinine levels at baseline.

3.2. Treatment With PIC

The Feramax-150 (Bio Syent Pharma, Inc.) was selected as the PIC used in this study. This drug is in the form of a capsule and contains 150 milligrams of elemental iron. For all study participants, one Feramax-150 capsule was prescribed daily for 12 weeks.

All patients were asked to report any GI side effects they experienced, including heartburn, abdominal pain, nausea, vomiting, diarrhea, constipation, and bloating.

3.3. Statistical Analysis

The IBM statistical package for the social sciences (SPSS) for Windows, version 19 (IBM Corp, Armonk, NY, USA), was used for all statistical analyses. One sample Kolmogorov Smirnov test was employed to assess the normal distribution of variables. Categorical variables were expressed as a number (percentage), while quantitative variables were expressed as mean (standard deviation) or median (interquartile range (IQR)) as appropriate. Student t-test and Mann-Whitney or Wilcoxon signed rank tests were used for comparisons and associations, as appropriate. $P < 0.05$ were considered statistically significant.

4. Results

In this case series, 30 patients (18 females) with a diagnosis of DCM were given Feramax-150 daily for 12 weeks. The mean (SD) age was 43.2 (13.4) years (range: 19 - 97 years). The mean LVEF was 23% (range: 10% - 35%), and 76% of patients had an NYHA functional class higher than II. All patients were on the maximum tolerable dosages of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor antagonists (ARB), beta-blockers, spironolactone, and diuretics.

The mean (SD) ferritin level was 48.8 (27.7), while the mean (SD) hemoglobin level was 13.4 (1.4) g/dL.

Table 1 depicts the general and clinical characteristics of the study population, while Table 2 shows a comparison of the study variables at baseline and also 12 weeks after treatment with Feramax-150.

4.1. Feramax-150 Treatment

As shown in Table 1, the mean (SD) ferritin level was 48.8 (27.7) $\mu\text{g/L}$ at baseline. After 12 weeks of treatment with Feramax-150, the mean (SD) ferritin level increased to 69.9 (42) $\mu\text{g/L}$, which was statistically significant ($P < 0.001$).

However, the ferritin level rose above 100 in only 4 patients, and no statistically significant changes were observed in the serum iron, TIBC, or hemoglobin levels.

There was a statistically significant increase in the 6 MWT (354 ± 83 meter at baseline versus 385 ± 84 meter, $P = 0.02$) and a decrease in the NT-proBNP level [median (IQR) at baseline = 1375 (range: 132 - 3292) versus 1035 (range: 98 - 2400), $P < 0.001$] after 12 weeks of treatment with Feramax-150.

A statistically significant improvement in the NYHA functional class was also noted in our study population after 12 weeks ($P = 0.04$).

4.2. Gastrointestinal Side Effects

During treatment with Feramax-150, the drug was well tolerated. All patients completed the treatment course, and no patients reported GI side effects, which are common during oral iron therapies and include GI upset and heartburn, nausea, vomiting, diarrhea, or constipation.

5. Discussion

In this case series, we showed that PICs were well tolerated in patients with HF and were useful in increasing the ferritin level in these patients. Iron deficiency is an important comorbidity in up to 50% of HF patients, and its complications are independent of any hematopoietic effects. A thorough diagnostic work-up for iron deficiency in

patients with HF was recommended by the ESC guidelines for heart failure in 2012, and treatment of iron deficiency is strongly recommended in these patients (1-4).

According to present evidence, the preferred form of iron supplementation is through an intravenous route. Oral iron preparations are poorly absorbed in patients with HF, and more than 50% of patients experience significant GI side effects, which lead to poor compliance (2, 3, 5, 7).

To our knowledge, there is currently no evidence of any clinical benefits of PICs in patients with HF, and the most experience with this type of oral iron supplementation has been in patients with chronic renal failure and patients who are being treated for postoperative anemia (14-18, 20, 21, 23-28). Kaufman et al. (29) showed that Niferex (PIC) is very effective in repleting and preserving the iron stores in end stage renal disease patients. In Feagan's study, a dose of 450 mg of PIC (3×150 mg) reduced the need for blood transfusions in patients undergoing hip arthroplasty (24), while McCluskey et al. (30) successfully used PICs to treat postoperative anemia. The present case series is the first study to use PICs in the treatment of iron deficiency in patients with HF. Although there was no change in the hemoglobin level after 3 months of treatment, the ferritin level had increased, and the NT-proBNP level decreased as well. In addition, the NYHA functional class and 6-minute walk test distance had also improved significantly.

The main limitation of oral iron supplementation is patient compliance due to unpleasant GI side effects (both diarrhea and constipation), particularly in patients with chronic diseases, such as HF. In this population, the prescription of additional medications may also exacerbate the GI side effects (10, 11, 23).

The main advantage of PICs is the lower incidence of GI side effects. In our study, no patients reported GI complications. In many other studies, PICs were very well tolerated in terms of GI side effects (11, 17, 20, 21, 27, 28). Johnson et al. reported a low incidence of adverse GI effects following treatment with PICs (16). Also, in Feagan's study, PICs were well tolerated; only 2% of patients discontinued their iron supplementation regimen due to GI side effects (24).

5.1. Study Limitations

The main limitation of this study were its small sample size and short-term treatment period. However, the careful selection of the included patients was a strength of this study.

In conclusion, PICs were a good and well-tolerated medication for the treatment of iron deficiency in patients with HF. Further studies should be designed to compare

Table 1. Demographic and Clinical Characteristics of the Study Population (n = 30)

Characteristics	Value
Gender (No. %)	
Female	18 (60)
Male	12 (40)
Age, y, mean (SD)	43.2 (13.4)
NYHA Class (No. %)	
I, I - II	7 (24)
II, II - III, III	23 (76)
LVEF, %, mean (SD)	23.2 (7.3)
Creatinine, mg/dL, mean (SD)	1 (0.3)
6-MWT, meter, mean (SD)	353 (83)
NT-proBNP, ng/dL, median (IQR)	1375 (132-3292)
Hemoglobin, g/L, mean (SD)	13.4 (1.4)
Ferritin, μg/L, mean (SD)	48.8 (26.7)
Iron, μg/dL, mean (SD)	87.2 (35.7)
TIBC, μg/dL, mean (SD)	344.5 (62)
Transferrin saturation, %, mean (SD)	21 (7)

Table 2. Comparison of the Study Variables at Baseline and 3 Months after Initiating oral Iron Therapy

Variable	Baseline	After 3 Months	P Value
NYHA Class			0.04
I, I - II	7 (24)	10 (33)	
II, II - III, III	23 (76)	20 (67)	
Hemoglobin, g/L, mean (SD)	13.4 (1.4)	13 (1.4)	0.4
Iron, μg/dL, mean (SD)	80 (20)	87.2 (35.7)	0.7
TIBC, μg/dL, mean (SD)	344 (62)	346 (47)	0.8
Ferritin, μg/L, mean (SD)	48.8 (26.7)	69.9 (42)	< 0.001
NT-proBNP, ng/dL, median (IQR)	1375 (132 - 3292)	1035 (98 - 2400)	< 0.001
6-MWT, meter, mean (SD)	354 (83)	385 (84)	0.02

the efficacy of PICs with intravenous iron supplementation. It is also recommended that PICs be prescribed to HF patients for the maintenance of body iron stores after IV iron therapy.

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Footnote

Authors' Contribution: Sepideh Taghavi: study design; Afsaneh Amiri: collecting samples, following up with the patients, and drafting the manuscript; Amirreza Ehsani: collecting samples; Ahmad Amin: study design; Majid Maleki: supervising the project; Nasim Naderi: concept of the study, study design, and final drafting and editing of the manuscript.

References

- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012;**14**(8):803-69. doi: [10.1093/eurjhf/hfs105](https://doi.org/10.1093/eurjhf/hfs105). [PubMed: [22828712](https://pubmed.ncbi.nlm.nih.gov/22828712/)].
- Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2009;**361**(25):2436-48. doi: [10.1056/NEJMoa0908355](https://doi.org/10.1056/NEJMoa0908355). [PubMed: [19920054](https://pubmed.ncbi.nlm.nih.gov/19920054/)].
- Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail.* 2012;**14**(4):423-9. doi: [10.1093/eurjhf/hfs017](https://doi.org/10.1093/eurjhf/hfs017). [PubMed: [22348897](https://pubmed.ncbi.nlm.nih.gov/22348897/)].
- Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J.* 2010;**31**(15):1872-80. doi: [10.1093/eurheartj/ehq158](https://doi.org/10.1093/eurheartj/ehq158). [PubMed: [20570952](https://pubmed.ncbi.nlm.nih.gov/20570952/)].
- McDonagh T, Macdougall IC. Iron therapy for the treatment of iron deficiency in chronic heart failure: intravenous or oral?. *Eur J Heart Fail.* 2015;**17**(3):248-62. doi: [10.1002/ejhf.236](https://doi.org/10.1002/ejhf.236). [PubMed: [25639592](https://pubmed.ncbi.nlm.nih.gov/25639592/)].
- Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol.* 2008;**51**(2):103-12. doi: [10.1016/j.jacc.2007.09.036](https://doi.org/10.1016/j.jacc.2007.09.036). [PubMed: [18191732](https://pubmed.ncbi.nlm.nih.gov/18191732/)].
- Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;**36**(11):657-68. doi: [10.1093/eurheartj/ehu385](https://doi.org/10.1093/eurheartj/ehu385). [PubMed: [25176939](https://pubmed.ncbi.nlm.nih.gov/25176939/)].
- Gutzwiller FS, Pfeil AM, Comin-Colet J, Ponikowski P, Filippatos G, Mori C, et al. Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis. *Int J Cardiol.* 2013;**168**(4):3878-83. doi: [10.1016/j.ijcard.2013.06.045](https://doi.org/10.1016/j.ijcard.2013.06.045). [PubMed: [23870642](https://pubmed.ncbi.nlm.nih.gov/23870642/)].
- Cancelo-Hidalgo MJ, Castelo-Branco C, Palacios S, Haya-Palazuelos J, Ciria-Recasens M, Manasanch J, et al. Tolerability of different oral iron supplements: a systematic review. *Curr Med Res Opin.* 2013;**29**(4):291-303. doi: [10.1185/03007995.2012.761599](https://doi.org/10.1185/03007995.2012.761599). [PubMed: [23252877](https://pubmed.ncbi.nlm.nih.gov/23252877/)].
- Fei C. Iron Deficiency Anemia. 215.
- McDiarmid T, Johnson ED. Clinical inquiries. Are any oral iron formulations better tolerated than ferrous sulfate?. *J Fam Pract.* 2002;**51**(6):576. [PubMed: [12100787](https://pubmed.ncbi.nlm.nih.gov/12100787/)].
- Naude S, Clijns S, Naulaers G, Daniels H, Vanhole C, Devlieger H. Iron supplementation in preterm infants: a study comparing the effect and tolerance of a Fe²⁺ and a nonionic FeIII compound. *J Clin Pharmacol.* 2000;**40**(12 Pt 2):1447-51. [PubMed: [11185665](https://pubmed.ncbi.nlm.nih.gov/11185665/)].
- Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev.* 2012;**1**:007857. doi: [10.1002/14651858.CD007857.pub2](https://doi.org/10.1002/14651858.CD007857.pub2). [PubMed: [22258974](https://pubmed.ncbi.nlm.nih.gov/22258974/)].
- Bereman RD, Berg KA. The structure, size and solution chemistry of a polysaccharide iron complex (Niferex). *Inorganica Chimica Acta.* 1989;**155**(2):183-9.
- Coe EM, Bowen LH, Speer JA, Wang Z, Sayers DE, Bereman RD. The recharacterization of a polysaccharide iron complex (Niferex). *J Inorg Biochem.* 1995;**58**(4):269-78. [PubMed: [7500088](https://pubmed.ncbi.nlm.nih.gov/7500088/)].
- Johnson C, Rosowski E, Zimmerman S. A prospective open-label study evaluating the efficacy and adverse reactions of the use of Niferex-150 in ESRD patients receiving EPOGEN. Advances in peritoneal dialysis Conference on Peritoneal Dialysis. .
- Johnson DW. Intravenous versus oral iron supplementation in peritoneal dialysis patients. *Perit Dial Int.* 2007;**27** Suppl 2:255-60. [PubMed: [17556315](https://pubmed.ncbi.nlm.nih.gov/17556315/)].
- Liu TC, Lin SF, Chang CS, Yang WC, Chen TP. Comparison of a combination ferrous fumarate product and a polysaccharide iron complex as oral treatments of iron deficiency anemia: a Taiwanese study. *Int J Hematol.* 2004;**80**(5):416-20.
- Piccinni L, Ricciotti M. Therapeutic effectiveness of an iron-polysaccharide complex in comparison with iron fumarate in the treatment of iron deficiency anaemias. *Panminerva Med.* 1982;**24**(3):213-20. [PubMed: [717687](https://pubmed.ncbi.nlm.nih.gov/717687/)].
- Yao L, Fan Q, Bo XL. Observation on the curative effect of polysaccharide iron complex (Niferex) to treat patients with iron deficiency anemia. *J Xinjiang Med Uni.* 2009;**11**:016.
- Zhang ZS, Wang XM, Han ZP, Yin L, Zhao MX, Yu SC. Physicochemical properties and inhibition effect on iron deficiency anemia of a novel polysaccharide-iron complex (LPPC). *Bioorg Med Chem Lett.* 2012;**22**(1):489-92. doi: [10.1016/j.bmcl.2011.10.100](https://doi.org/10.1016/j.bmcl.2011.10.100). [PubMed: [22153938](https://pubmed.ncbi.nlm.nih.gov/22153938/)].
- Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW. The 6-minutewalk: a new measure of exercise capacity in patients with chronic heart failure. *Canadian Med Assoc J.* 1985;**132**(8):919.
- Bayraktar UD, Bayraktar S. Treatment of iron deficiency anemia associated with gastrointestinal tract diseases. *World J Gastroenterol.* 2010;**16**(22):2720-5. [PubMed: [20533591](https://pubmed.ncbi.nlm.nih.gov/20533591/)].
- Feagan BG, Wong CJ, Kirkley A, Johnston DW, Smith FC, Whitsitt P, et al. Erythropoietin with iron supplementation to prevent allogeneic blood transfusion in total hip joint arthroplasty. A randomized, controlled trial. *Ann Intern Med.* 2000;**133**(11):845-54. [PubMed: [11103054](https://pubmed.ncbi.nlm.nih.gov/11103054/)].
- Hudson JQ, Comstock TJ. Considerations for optimal iron use for anemia due to chronic kidney disease. *Clin Ther.* 2001;**23**(10):1637-71. [PubMed: [11726002](https://pubmed.ncbi.nlm.nih.gov/11726002/)].
- Mohie-Eldin MY, Frankel RB, Gunther L. A comparison of the magnetic properties of polysaccharide iron complex (PIC) and ferritin. *J Magnetism Magnetic Material.* 1994;**135**(1):65-81.
- Sanders JF. Clinical response to iron-polysaccharide complex in geriatric patients with iron-deficiency anemia. *Mich Med.* 1968;**67**(11):726-7. [PubMed: [5655937](https://pubmed.ncbi.nlm.nih.gov/5655937/)].
- Wingard RL, Parker RA, Ismail N, Hakim RM. Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin. *Am J Kidney Dis.* 1995;**25**(3):433-9. [PubMed: [7872321](https://pubmed.ncbi.nlm.nih.gov/7872321/)].
- Kaufman JS, Reda DJ, Fye CL, Goldfarb DS, Henderson WG, Kleinman JG, et al. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. *N Engl J Med.* 1998;**339**(9):578-83. doi: [10.1056/NEJM199808273390902](https://doi.org/10.1056/NEJM199808273390902). [PubMed: [9718376](https://pubmed.ncbi.nlm.nih.gov/9718376/)].
- McCluskey SA, Karkouti K, Ghannam M. Treatment of Post Operative Anemia: Intravenous Iron Compared to Intravenous Iron and Erythropoietin. *Anesthesiol.* 2005;**103**(454).