




## RESEARCH ARTICLE

**REVISED** A Comparison of Pain Before and After Transfusion in Adult transfusion-dependent thalassemia (TDT) Using BPI-SF [version 2; peer review: 2 approved, 1 approved with reservations]

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## Abstract

### Background

*Pain* is a complication in patients with transfusion-dependent thalassemia (TDT). There are several mechanisms underlying pain in people with thalassemia and low hemoglobin at the end of the transfusion cycle was the most etiology. Pain can develop into chronic pain and interfere with the quality of life. The Brief Pain Inventory Short Form (BPI-SF) can help identify pain in people with TDT. The present study aimed to compare pain before and after transfusion in adult TDT patients.





### Methods


It was an analytical observational study using a cross-sectional design on adult TDT patients with pain who came to the Haemato-Oncology Clinic of Dr. Hasan Sadikin Hospital Bandung. This study was conducted from December 2020 to July 2021. All subjects were assisted in filling out the Indonesian version of the BPI-SF questionnaire hemoglobin levels were examined and before and after transfusion, then paired test analysis was performed using the Wilcoxon Test.

### Results

## Open Peer Review

Approval Status 

	1	2	3
<b>version 2</b> (revision) 09 Aug 2024		 view	 view
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- Noor Syhareen Mohammed** , Sultanah Bahiyah Hospital, Alor Setar, Malaysia
- Donna Wall**, University of Toronto, Toronto, Canada

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This study is conducted on 60 adult TDT patients with symptoms of pain. The median value of pain intensity and pain interferes with life obtained from the Indonesian version of the BPI-SF score after transfusion decreased significantly compared to before transfusion (NRS 5 vs. 0 and 2.8 vs. 0;  $p=0.0001$ ).

## Conclusion

There is a significant difference in pain intensity and pain interfere with life in adults with TDT before and after transfusion. It is necessary to carry out pain assessments for thalassemia patients.

## Keywords

Thalassemia; hemoglobin; pain; transfusion; BPI-SF; quality of life; questionnaire; pain assessment; adults.

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**REVISED Amendments from Version 1**

There were several improvement that we made. We highlight about the aim of the study not only compare pain before and after transfusion, but also explain its role in underlying pain mechanism, increase awareness to detect, prevent and treat pain in adult TDT patients. We also explained more about methodology, such as consecutive sampling methods and the reason for selecting adult patients in our study. This age was chosen based on the criteria for adult patients at our hospital and the consideration that they able to express pain. The subjects had the same risk of experiencing pain because they had been diagnosed thalassemia for a long time, ranged from 3-50 years. The level of education and employment status of the sample were already mentioned in Table 1.

We mention the year of design of the BPI-SF questionnaire. We perform the BPI-SF questionnaire validity test in the Indonesian version in 2021 using Pearson's correlation. The validity test stages were done according to the questionnaire validation guidelines using the following steps as described in Figure 1.

In Discussion section, we explained more about the result of this study and comparison with the results of other studies. We explain several mechanisms underlying pain in thalassemia, not only due to low haemoglobin at the end of the transfusion cycle, but also other pain mechanism such as ineffective erythropoiesis, that may cause bone marrow hypertrophy, fracture due to osteoporosis, scoliosis and compression spinal cord.

The limitation this study were already mentioned such as the BPI-SF questionnaire were that it didn't assess the percentage and duration of pain relief and non medical methods use to relieve pain as mentioned in BPI long form and further studies with larger sample size were needed.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

*Pain* is an unpleasant sensory and emotional experience for everyone but is not as a chief complaint and ignored in daily examinations. Recent studies have shown increasing pain reports in patients with thalassemia.<sup>1,2</sup> Thalassemia is the blood disorder occurring due to decreased or lost synthesis of one or more globin chains.<sup>3</sup> This disease is hereditary autosomal recessive due to mutations in the globin-forming gene.<sup>4,5</sup> The spectrum of thalassemia syndromes is based on the requirements for blood transfusions for survival, including transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT).<sup>6</sup>

The World Health Organization or WHO states that about 7% of the world's population has the thalassemia gene, the highest incidence of up to 40% cases in Asia.  $\beta$ -thalassemia is found in Mediterranean countries, Central Asia, India, Southern China, North Africa and South America. Indonesia is included in the world's thalassemia belt area with the carriers incidence of thalassemia traits ranging from 6-10%.<sup>7</sup> There were more than 10.531 thalassemia patients in Indonesia according to the data from the Ministry of Health of the Republic of Indonesia in 2019. Dr. Hasan Sadikin Hospital Bandung is a referral hospital for West Java Province with the highest thalassemia cases in Indonesia reaching 40 percent of the national figure.<sup>8</sup>

There are several mechanisms underlying pain in people with thalassemia. Low hemoglobin at the end of the transfusion cycle can cause pain in 45% cases and decrease after transfusion.<sup>9</sup> Low hemoglobin in thalassemia causes hypoxia and releases reactive oxygen species (ROS) through inhibition activity of oxygen-sensitive prolyl hydroxylases (PHDs), then causes activation of transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1).<sup>10,11</sup> This protein activation will release substance P which plays a role in pain sensitization.<sup>12</sup> Transfusion can improve anemia, suppress erythropoiesis, and inhibit iron absorption in the gastrointestinal tract. Maintaining hemoglobin levels above 10 g/dL can prevent hyperplasia and bone marrow expansion, thereby preventing the development of skeletal abnormalities.<sup>4,13</sup>

The pain effect in daily activities needs to be assessed using a pain screening tool. The Brief Pain Inventory (BPI) is the recommended pain screening tool to assess pain intensity and pain interfering with life.<sup>14</sup> The advantage of this questionnaire is available in a short form and easier to apply. This questionnaire can evaluate pain treatment and the pain impact on the patient's life quality with the sensitivity of 79.4%.<sup>15-18</sup>

Pain in thalassemia needs to be identified because it can develop into chronic pain which can interfere the patients' life quality. Pain management in thalassemia depends on the pain assessment accuracy. This study aims to compare pain before and after transfusion in adult TDT patients and its role in underlying pain mechanism, increase awareness to detect, prevent and treat pain in adult TDT patients.

## Methods

### Sample size

This study inclusion criteria was  $\geq 18$ -year-old patients diagnosed with  $\beta$ -thalassemia with pain who underwent routine transfusion at the Hemato-Oncology Internal Medicine Clinic in Dr. Hasan Sadikin Hospital Bandung and was willing to participate in the research. This age was chosen based on the criteria for adult patients at our hospital and the consideration that they able to express pain. Transfusion is initiated if the thalassemia diagnosis is confirmed based on severe anemia (hemoglobin level  $< 7$  g/dL for more than two weeks, excluding other anemia causes or hemoglobin level  $> 7$  g/dL with a facial deformity, impaired growth, presence of bone marrow expansion, and hepatosplenomegaly). The target for hemoglobin after transfusion is 13-14 g/dL; therefore, the transfusion frequency is every 2-4 weeks to achieve the hemoglobin target. The patient received 1-2 units of blood transfusion depending on the hemoglobin level before transfusion. The procedure was done in 3-4 hours. This adult selection as the subject (It ranges from the age of 18 in our hospital) was done since they were expected to be able to express pain more. Exclusion criteria was patients who had confirmed pain due to fractures or other diseases and had been diagnosed with anemia due to other causes.

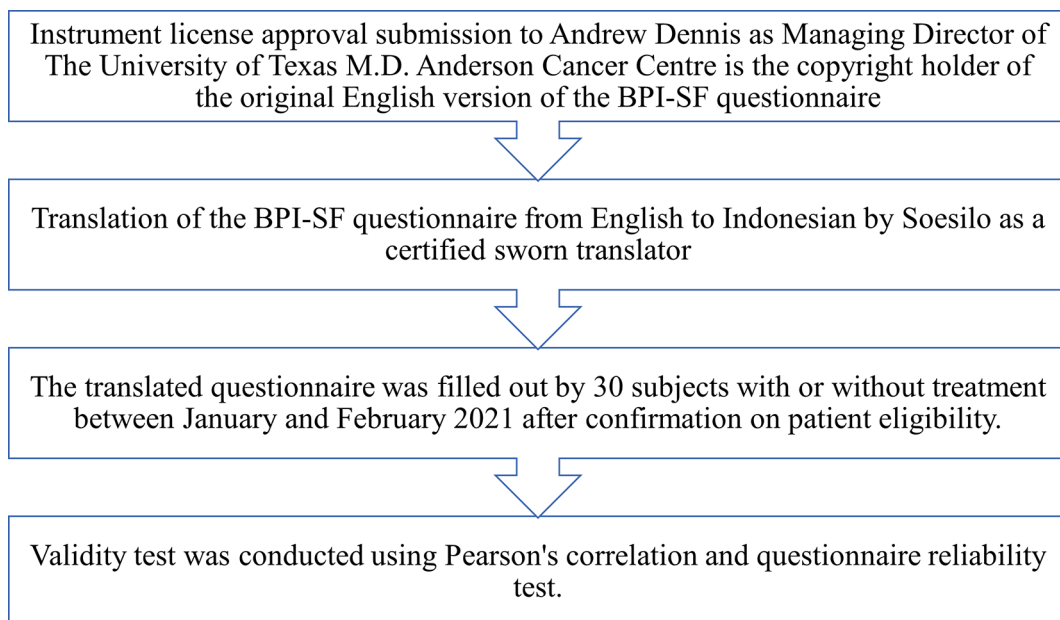
The sample size of this study consists of subjects testing the questionnaire validity and the sample size for paired test analysis. The sample size for questionnaire validation in this study was determined using a correlation analysis formula obtained from 30 subjects. Subjects filling out the questionnaire complained various types of pain such as low back pain, nerve entrapment pain, radiculopathy, joint pain, and facial pain. There were consecutive sampling with minimum sample size for paired test analysis is 46 research subjects. If 10% is added to anticipate data loss, the minimum sample size then is 51 research subjects. A total of 60 TDT patients were obtained according to the period of our research.

The written informed consent for this research was obtained from the patient and research ethics approval was obtained from the ethics committee of Padjadjaran University Bandung under the ethical clearance number of 198/UN6.KEP/EC/2021.

### Statistical analysis

This study was an analytical observation using a cross-sectional design conducted from December 2020 to June 2021. We perform the BPI-SF questionnaire validity test in the Indonesian version in 2021 using Pearson's correlation. The validity test stages were done according to the questionnaire validation guidelines using the following steps as described in [Figure 1](#).<sup>19</sup>

Sixty subjects meeting the inclusion criteria were explained about the study procedure and asked to sign an informed consent form if they were willing to participate; furthermore, demographic data collection and pain screening were carried out on the subject using the BPI-SF questionnaire. The Brief Pain Inventory (BPI) assessed pain intensity and pain



**Figure 1.** Flow of questionnaire validation.

interfering with life.<sup>14</sup> Patients were assisted before the transfusion and a maximum of one day after the transfusion in filling out the BPI-SF questionnaire in Indonesian version. Hemoglobin levels were examined before and after transfusion, and then a comparison test was performed with the Wilcoxon Test.

## Results

The validity test of this study uses Pearson's correlation. The results were obtained and processed using SPSS 24.0 software with a significance level ( $\alpha$ )=0.05 (5%). The questionnaire is considered valid if it is greater than the Pearson product-moment correlation coefficient. The table correlation number (r table) is 0.30 with the number of samples (n)=30 people. All question instruments on the questionnaire variable are valid because the r-count is >0.3. Reliability testing is carried out with internal consistency or the answers accuracy degree using *Cronbach's Alpha*. A measuring instrument is said to be reliable if the coefficient value of r is 0.7. All questionnaire variable instruments are reliable because of the r > 0.7 value.

This study was conducted to 60 people with thalassemia meeting the inclusion criteria and not included in the exclusion criteria. The subjects mean age was young adults,  $26.1 \pm 9.1$  years, and most of them were female (65%). The subjects had the same risk of experiencing pain because they had been diagnosed thalassemia for a long time, ranged from 3-50 years. The subjects demographic distribution is described in [Table 1](#).

### Pain characteristics of research subjects

The pain location is experienced mainly in the lower back followed by the knee while the others complained it in more than one location, as seen in [Figure 2](#).

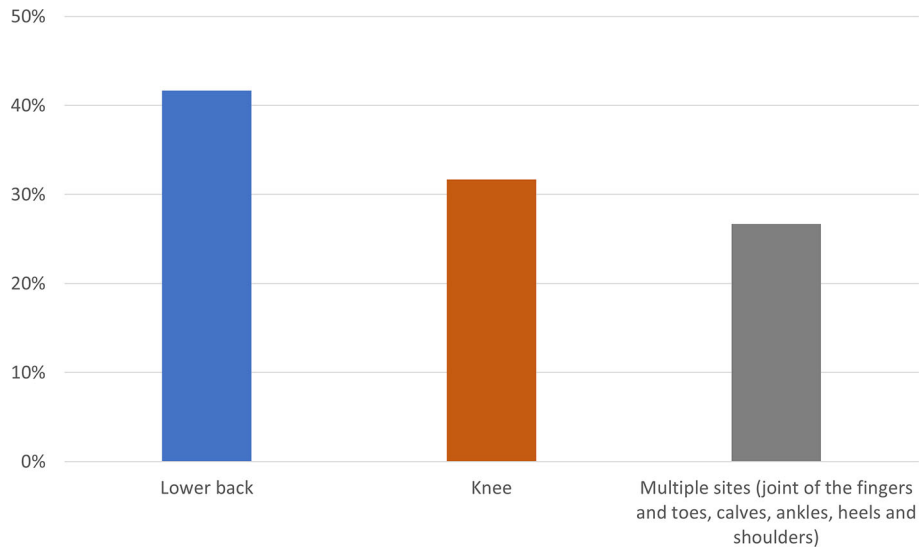
Most of the subjects have never been examined for their pain, so the cause of pain were not further assssesed. Based on the data of the study, the average pain intensity was moderate pain and disappeared after transfusion. The data can be seen in [Figure 3](#).

Questions in the BPI-SF questionnaire about the treatment taken by the patient and the pain treatment effect were not included in the scoring assessment. This study showed that most of the pain was reduced by transfusion in 20 (30%) patients with an effect of 40–100% pain reduction. Other treatments taken by the subjects are analgetics drugs, rest, traditional ointment, compress, and iron chelation. There is an increase in the average hemoglobin before transfusion from  $7 \pm 1.1$  g/dL to  $8.9 \pm 1.1$  g/dL.

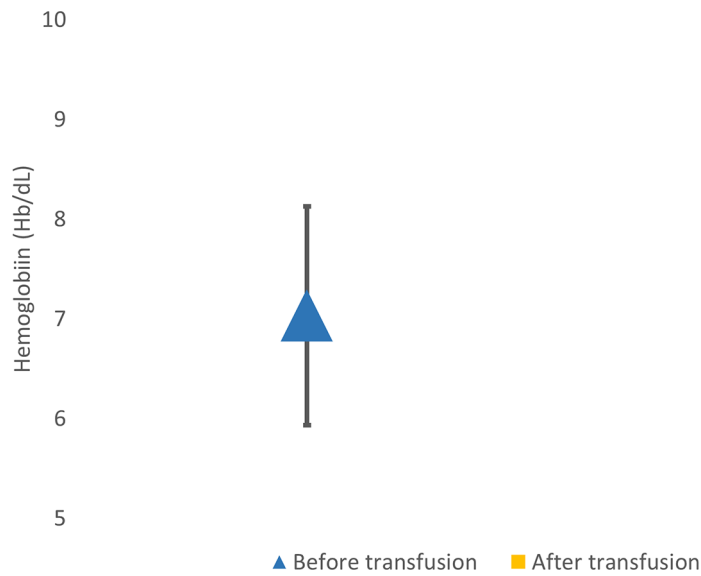
Pain intensity before transfusion had a median value of 5 while pain intensity after transfusion had a median value of 0. These numerical data were analyzed using the Wilcoxon test. The analysis results showed a significant difference in pain intensity before and after transfusion with  $p=0.0001$  (<0.05). A comparison of pain interfering with life obtained

**Table 1. Demographic characteristics of research subjects.**

Characteristics	N (%)
Age (years)	
Mean $\pm$ SD	26.1 $\pm$ 9.1
Gender	
Male	21(35)
Female	39(65)
Education	
Elementary school	7(11.7)
Junior high school	14(23.3)
Senior high school/Vocational school	32(53.3)
College	7(11.7)
Occupation	
Unemployed	49(81.7)
Employed	11(18.3)



**Figure 2.** Description of pain location.



**Figure 3.** Hemoglobin level before and after transfusion.

**Table 2.** Comparison of pain intensity and pain interfering with life using BPI-SF questionnaire before and after transfusion.

Variable	Group		P-Value
	Before transfusion N=60	After transfusion N=60	
Pain intensity			0.0001**
Median	5	0	
Range (min-max)	1.8-7.5	0-7	
Pain interferes with life			0.0001**
Median	2.8	0	
Range (min-max)	0-8.1	0-7.4	

\*\*p<0.05 was considered significant.

from BPI-SF scores before and after transfusion using the Wilcoxon test obtained  $p=0.0001$  ( $<0.05$ ); accordingly, there is the significant difference in pain interfering with life before and after transfusion as listed in [Table 2](#).

## Discussion

This study showed that the subjects experienced improvement in the life quality after transfusion. Judging from the results of filling out the BPI-SF questionnaire by adults with TDT, 94.12% of the subjects experienced pain decrease after transfusion. It is found in [Table 3](#) that there are significant differences between pain intensity and pain interfering with life obtained from BPI-SF scores before and after transfusion. This study is in line with the previous studies that revealed pain in thalassemia is commonly associated with low hemoglobin at the end of the transfusion cycle relieved by transfusion.<sup>1</sup>

Most of the subjects did not disclose their pain to the doctor when they went to the Haemato-Oncology Clinic. There were only two subjects who checked for pain and carried out supporting examinations to determine the pain cause. Forty-nine other subjects were known to have pain based on the results of filling out the BPI-SF questionnaire. There are several mechanisms underlying pain in thalassemia. Low hemoglobin in thalassemia causes hypoxia and releases reactive oxygen species (ROS) through inhibition activity of oxygen-sensitive prolyl hydroxylases (PHDs), then causes the activation of transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1).<sup>10,11</sup> This protein activation will release substance P which plays the role in pain sensitization.<sup>12</sup>

TRPA1, a nonselective cation channel, is widely expressed in nociceptive C fibers, dorsal root ganglia (DRG) and trigeminal ganglia neurons.<sup>11</sup> Human nerve fibers are susceptible to free radicals such as ROS since it is high in phospholipids and mitochondria; furthermore, the neurons antioxidant defenses are weak. TRPV1 is a nonselective cation channel expressed mainly in unmyelinated C nerve fibers detecting and integrating pain stimuli. TRPV1 can be sensitized by exposure to hypoxia and can induce pain.<sup>10</sup> The role of TRPV1 and TRPA1 in thalassemia-related pain are thought to be associated with arthritis. These two molecules can be activated in sensory neurons, chondrocytes and synoviocytes.<sup>20</sup>

Other pain mechanism was ineffective eritropoiesis, that may cause bone marrow hipertrophy, fracture due to osteoporosis, scoliosis and compression spinal cord. Pain in thalassemia is associated with musculoskeletal involvement with a wide variety of symptoms.<sup>21</sup> The most common complaints of musculoskeletal pain are arthritis and low back pain.<sup>1,22,23</sup> The musculoskeletal pain primary location is in the lower back affecting 70-85% of the adult population.<sup>24</sup> Pain-sensitive structures in the lower back are involved in pain such as the periosteum of the bones, ligaments, facets, articular capsule, and paraspinal muscles.<sup>25-27</sup> The lower back anatomy has characteristics making this area more prone to pain than the other parts of the back. The foramina in the lumbar vertebrae are small, triangular, and narrow at the lateral angle at the L4-L5 vertebrae. The nerve roots are located in this lateral recess before exiting the intervertebral foramen more prone to compression. Each vertebra adjusts its shape and size as the reflection of the load it receives. The lumbar vertebrae has larger size than the other vertebrae, the load supported by the lower back is greater than the rest of the back and has more significant impact in trauma. The load received by the spine varies depending on the posture and external loads. The L3-L4 intervertebral discs in the sitting position receive higher load than when standing, the pressure is at the lowest when lying supine.<sup>26</sup>

The most common affected location in this study is the lower back in 22 (43.1%) patients. Low back pain is caused by osteophytes, facet hypertrophy, fractures and osteoporosis causing pain in the bones. Low back pain is also triggered by prolonged standing and heavy lifting and is mainly due to low hemoglobin which will improve after transfusion.<sup>28,29</sup>

The bone mass rapid turnover results from an imbalance between increased bone resorption and suppression of osteoclasts. This process is more common in the lumbar spine as a result of extramedullary erythropoiesis. The hemoglobin level before transfusion was 8.5-9 g/dL, it may be clinically tolerated by adults with thalassemia; nonetheless, the process of extramedullary erythropoiesis can continue to occur. It is recommended that the hemoglobin before transfusion be maintained at above 10 g/dL level to prevent extramedullary erythropoiesis in these patients' thalassemia. Decreased bone mass in thalassemia often occurs in the vertebral column and can manifest as spinal deformity, bone marrow compression, vertebral collapse, and intervertebral disc degeneration.<sup>30-32</sup> Matrix metalloproteinases can underlie the arthritis occurrence.<sup>33</sup> Pain in the lower back can also be caused by low bone density causing fractures and compression in the spinal cord.<sup>4</sup> The most common finding in the vertebrae MRI examination is the degenerative vertebral disc with the highest prediction for L4-L5 intervertebral discs.<sup>34</sup>

The second most common location is the knee while the rest complain the pain in more than one location in the body such as in the joints of the fingers and toes, calves, ankles, heels and shoulders. This condition is also known as thalassaemic osteoarthopathy.<sup>35</sup>

There is a role for Hypoxia Inducible Factor (HIF) in arthritis. HIF acts as the regulator of the adaptive response to hypoxia; hence, HIF is involved in the inflammation persistence and neovascular progression in arthritis. HIF has several target genes including erythropoietin (EPO) supporting the erythropoiesis. HIF is released under hypoxic conditions, yet it can also be released under normoxia by several inflammatory factors such as ROS, nitric oxide and proinflammatory cytokines such as IL-1 $\beta$  and TNF alpha.<sup>11,21</sup>

HIF-1 $\alpha$  hydroxylation is inhibited and accumulates in the cytoplasm under hypoxic conditions. This causes HIF-1 $\alpha$  to be phosphorylated and translocated to the nucleus, in which it binds to the HIF-1 $\beta$  subunit to form a complex [HIF- $\alpha$ /HIF-1 $\beta$ ]. This complex via HRE (Hypoxia Release Element) binds to a specific DNA sequence (5'TAGCGTGH3') in the promoter region of several genes such as including EPO (erythropoietin). HIF-2 $\alpha$  is the cartilage catabolism regulator working as a matrix-degrading enzyme and inflammation mediator (IL-1, IL-6, and TNF- $\alpha$ ), increasing the expression of proteolytic enzymes and MMPs (Matrix Metalloproteinases), accelerating cartilage destruction and causing chondrocyte hypertrophy, all of which play the role in the arthritis development.<sup>36</sup>

This study showed that the subjects experienced improvement in the life quality after transfusion. Judging from the results of filling out the BPI-SF questionnaire by adults with TDT, 94.12% of the subjects experienced pain decrease after transfusion. It is found in [Table 2](#) that there are significant differences between pain intensity and pain interfering with life obtained from BPI-SF scores before and after transfusion. This study is in line with the previous studies that revealed pain in thalassemia is commonly associated with low hemoglobin at the end of the transfusion cycle relieved by transfusion.<sup>1</sup>

### Strengths and limitations

This study emphasizes the importance of carrying out pain assessments for thalassemia patients. This study is the first to validate the BPI-SF tools into the Indonesian version and this questionnaire can be used in other studies as well related to chronic pain.

The following limitations are not further considered in this study. The examination was carried out to determine the pain etiology according to the fact that the subjects did not disclose their pain to the doctor when they went to the Hemato-Oncology Clinic. Most of the subjects knew their pain diagnose based on the results of filling out the BPI-SF questionnaire.

The limitation of BPI-SF questionnaire were that it didn't assess the percentage and duration of pain relief and non medical methods use to relieve pain as mentioned in BPI long form.

Further studies with larger sample size are needed to determine the pain etiology in adults with TDT, especially those related to low back pain and arthritis as the most common pain causes in adults with TDT using the cross-sectional approach.

### Conclusion

The conclusion of this study is that the pain can occur in thalassemia patients due to low hemoglobin level and can be relieved with transfusion. There is the significant difference between pain intensity and pain interfering with life before and after transfusion.

### Data availability

F1000 Research: Data set 1. The data for BPI-SF validation per item question. <https://doi.org/10.6084/m9.figshare.16984870>

Data set 2. Demographic data of adult TDT patients. <https://doi.org/10.6084/m9.figshare.17032340>

Data set 3. The data of BPI-SF score and the hemoglobin level of adult TDT patients before and after transfusion. <https://doi.org/10.6084/m9.figshare.17032361>

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# Open Peer Review

Current Peer Review Status:



Version 2

Reviewer Report 20 September 2024

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**Donna Wall**

University of Toronto, Toronto, Canada

The main focus of this manuscript is exploring the use of the Brief Pain Inventory - short form in the setting of a referral program that provides care for patients with transfusion-dependent thalassemia.

The group first validated a version of the BPI-SF that had been translated into Indonesian and applied to a test group. They then studied 60 consecutive patients prior to and post transfusion of a single unit of red cells (hemoglobin avg went from 7 to 8.9 g) and repeat questionnaire was performed within 24 h of transfusion.

The major observation was that pain was a common problem and not reported by the patients at their visits - perhaps because it is such a pervasive/chronic issue. The response to even a modest change in hemoglobin was striking and in followup it would be interesting to understand the duration of improvement. The cohort had a low pre-transfusion hemoglobin level for a chronically transfused cohort - this raises the question of whether the degree of improvement would also be seen in a cohort where pre-transfusion hemoglobins were higher.

While the discussion of pathophysiology of pain in patients with thalassemia is interesting, the focus of the paper is the development/application of the BPI-SF to clinical care. Does the research team have recommendations on how this patient reporting tool could/should be integrated into the clinical practice - perhaps helping with targeting transfusion frequency or targets for trough hemoglobin? A brief exploration of applicability to practice would strengthen the impact of the results.

Including patient reporting is an under appreciated care tool and this study has demonstrated the ability to apply it to a practice in a thalassemia clinic in Indonesia.

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** hematology and bone marrow transplant with a focus on hemoglobinopathies

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 09 September 2024

<https://doi.org/10.5256/f1000research.170012.r312730>

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**Noor Syahireen Mohammed** 

Clinical Research Centre, Sultanah Bahiyah Hospital, Alor Setar, Kedah, Malaysia

No further comments

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Yes

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health system policy

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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**Version 1**

Reviewer Report 06 February 2024

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**Noor Syahireen Mohammed** 

Clinical Research Centre, Sultanah Bahiyah Hospital, Alor Setar, Kedah, Malaysia

The study provides a significant contribution to the understanding of pain experienced by thalassemia patients. The research's focus, methodology, significant results, and plausible findings are noteworthy. However, the study has certain limitations that restrict the generalizability of the findings. These limitations must be addressed as this would enhance the study's conclusions and help in developing better pain management strategies for thalassemia patients.

In detail, some of the strong points are:

- Clearly defined research question: The study investigates a relevant issue – pain management in adult TDT patients – with a specific and focused question about the impact of blood transfusion.
- Appropriate sound methodology: The study utilizes valid inclusion and exclusion criteria, an appropriate sample size for paired data analysis, and established pain assessment tools with proper validity and reliability testing.
- Statistically significant results: The observed decrease in pain intensity and interference following transfusion is statistically significant, supporting the main hypothesis.
- Plausible explanation: The discussion provides a scientific explanation for the findings, linking pain reduction to improved haemoglobin levels and reduced activation of pain receptors.
- Well-written and informative: The study is clearly presented and easy to understand, using appropriate language and structure.

However, some improvements can be made on these points or addressed by author:

**Introduction:**

- Lacks a clear opening statement to capture the reader's attention and set the stage for the research.
- Could benefit from a stronger connection between the background information and the research question.
- Mentions only one potential cause of pain (low haemoglobin) without acknowledging other possible contributors.
- Doesn't explicitly state the hypothesis or main argument of the study.

**Methodology:**

- Limited information on sampling technique (random vs. convenience etc.)
- Potential for bias in data collection due to self-reporting through telephone interviews.
- Limited information on pain assessment methods beyond BPI-SF
- Lack of consideration for potential confounding variables (e.g., medication use, psychological factors).

**Results:**

- Limited generalizability due to potential bias and reliance on self-reported data.
- No analysis of other potential causes of pain besides low haemoglobin.

**Discussion:**

- Limited exploration of alternative explanations for pain beyond low haemoglobin and musculoskeletal involvement.
- Offers limited explanation for the potential variation in individual responses and treatment effectiveness.
- Doesn't discuss the limitations of pain assessment tools like BPI-SF in this context.

In conclusion, this study provides very useful information on pain management for Thalassemia patients. However, the study has some limitations that need to be addressed, such as the sampling technique, the potential for bias, and a need for a more comprehensive investigation into pain mechanisms. Addressing these limitations would help strengthen the conclusions and lead to more generalizability of the methodology to help with policymaking.

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health system policy

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 04 Aug 2024

**Uni Gamayani**

Thank you for your review. I have revised my article and I sent it as version 2 article.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 08 January 2024

<https://doi.org/10.5256/f1000research.79898.r232559>

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**Xuemei Zhen**

Shandong University, Jinan, Shandong, China

**Introduction:**

1. Need to describe what is known about the issue based on current literature.
2. Mention your study innovation.
3. Need to state what the gap in the literature is and how this study helps to fill the gap in knowledge.
4. Why choose adult patients? State what problems adult TDT patients have that impose more pain.
5. The fourth paragraph should be mentioned in the Method section.
6. The purpose of the study needs to be modified. The objective is not clearly stated or specific.

**Method:**

1. Please describe each instrument separately in the data collection section.
2. The sample size formula should be mentioned and the calculation process should be explained to ensure that the sample size was sufficient for this study.
3. What variables and data were collected?
4. Validity and reliability of the instrument should be mentioned. If you used the Indonesian

- version of the instruments, please mention the references.
5. Please describe each instrument more specifically and in detail.
  6. Mention the year of design of the BPI-SF questionnaire.
  7. Explain better why it was not possible to include a larger sample.
  8. In the statistical analysis, you mentioned "the data was obtained by telephone interview". How were the interviews conducted? Is there a risk of bias in this situation?
  9. Please provide evidence of applying any measures of quality control such as "cherries survey checklist" or any other publicly available quality control measures.

**Result:**

1. In the first paragraph, the presentation of the analytical methods and tools used should be contained in the Method section.
2. In the second paragraph, "the duration of being diagnosed with thalassemia" needs to be mentioned in Table 1, as well as "other treatments taken".
3. Describe the educational level and employment status of the sample.

**Discussion:**

1. First paragraph should include the most important findings of the study.
2. In the third and fourth paragraph, the portion describing the lower back pain should be grouped into one paragraph.
3. Please explain more about the comparison with the results of other studies rather than describing the principles that lead to pain.
4. The discussion has not adequately compared the current study with other new studies. Many new studies have been conducted in the field of thalassemia patients in different countries. While the authors have used old references.
5. Various variables have been examined in the study, but these variables have not been examined in the discussion. For example, the different demographic variables.

**Strengths and limitations**

1. Sample size should be one of the limitations.

**Conclusion**

1. Mention the application of your findings in the fields of education, research, and clinical practice.

**References**

1. The references are very old and not acceptable at all. At least 50% of the references should be from the last 5 years.

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Partly

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Partly

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** My area of research is social medicine, health economic and policy.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 04 Aug 2024

**Uni Gamayani**

Thank you for your review. I have revised my article and I sent it as version 2 article.

**Competing Interests:** No competing interests were disclosed.

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