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Introducing the Tran Qol: A New Disease-Specific Quality of Life Measure for Children and Adults with Thalassemia Major

Robert J Klaassen[1]*, Shabbir Alibhai[2], Melanie Kirby Allen[3], Katherine Moreau[4], Manuela Merelles Pulcini[3], Melissa Forgie[5], Victor Blanchette[3], Rena Buckstein[6], Isaac Odame[3], Ian Quirt[7], Karen Yee[7], Durhane Wong Rieger[8] and Nancy L Young[9]

[1]*Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada*
[2]*Division of Internal Medicine and Geriatrics, University Health Network, Toronto, Canada*
[3]*Department of Pediatrics, Hospital for Sick Children, Toronto, Canada*
[4]*Research Institute, Children's Hospital of Eastern Ontario, Canada*
[5]*Department of Hematology, Ottawa Hospital, Ottawa, Canada*
[6]*Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada*
[7]*Princess Margaret Hospital, Toronto, Ontario, Canada*
[8]*Anemia Institute for Research and Education, Toronto, Canada*
[9]*Human Kinetics, Laurentian University, Sudbury, Canada*

Abstract

Background: Patients with thalassemia major require red cell transfusions for survival and have to deal with iron overload and chelation. Chelation is burdensome, traditionally involving nightly prolonged subcutaneous infusion therapy. We developed a disease-specific tool for these patients (TranQol) to measure their unique quality of life issues. Methods: Pediatric and adult thalassemia health care professionals and quality of life methodology experts generated 69 potential items. 74 further questions were generated through interviews with patients (pediatric and adult) and parents.

Results: 120 participants contributed: 16 healthcare workers, 31 children and 30 adults with thalassemia and 43 parents. Duplicate and infrequent questions were discarded leaving 58 items. Three self-reported questionnaires (child, parent and adult) and one child proxy-report for parents were developed. Questionnaire length ranged from 29 (child's) to 39 (parent's). Questions were grouped into four domains: physical health, emotional health, family functioning, and school and career functioning. A fifth category on sexual activity included only one item. Cognitive debriefing was done by interviewing additional children, parents, and adults. As a result, three items were added, one was deleted and 16 were modified.

Conclusion: The TranQol is a new disease-specific quality of life measure for thalassemia major patients developed using rigorous methodology.

Keywords: Thalassemia; Quality of life; Questionnaire; Health status indicators; Child; Adult

Introduction

Inherited hemoglobin disorders are the most common monogenic disease worldwide with an estimated 7% of the global population being carriers for such disorders [1-3]. One severe form of hemoglobin disorder is thalassemia major, which typically presents in the first year of life with severe anemia and requires life-long red blood cell transfusions every 3-4 weeks [4]. Thalassemia major is primarily due to homozygous β thalassemia, but is increasing due to hemoglobin E beta thalassemia as well as homozygous α^0 thalassemia. More than 40,000 babies are estimated to be born every year worldwide with this disease [2]. Iron overload develops after one to two years of transfusion and is ultimately fatal if not treated [4]. Because of this, in addition to regular transfusions these patients need to receive iron chelation therapy, with the conventional treatment being deferoxamine which is administered 5-7 days a week subcutaneously by overnight continuous infusion for 8-12 hours [4]. This puts a significant burden on these patients and caregivers, and can result in poor compliance with treatment. Deferasirox is the latest oral agent to be approved in Europe and North America, which has been found to have equivalent efficacy to deferoxamine and has become the clinical standard in the developed world [5]. Deferiprone is another available oral agent that is particularly effective at removing cardiac iron [6].

Currently there are no disease-specific tools available to accurately measure the overall impact of this unique disease. As newer chelating agents become available with increasing use of combination therapy, it will be important to have a precise assessment of the treatment burden as well as the disease-related complications facing these patients, to fully grasp the benefit (or lack thereof) of a particular therapeutic regimen.

One method of capturing the difficulties faced by these patients is by using a patient reported outcome measure, in particular assessing Quality of life (QoL). QoL has been defined by the World Health Organization as the "net consequence of life characteristics on a person's perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns" [7]. Health-related quality of life (HRQoL) often refers to the specific impact a disease or illness may have on overall QoL. However, in many instances, the terms QoL and HRQoL are used interchangeably. The key to measuring QoL and

***Corresponding author:** Robert Klaassen, Division of Hematology/Oncology, Department of Pediatrics, Children's Hospital of Eastern Ontario, 401 Smyth, Ottawa, Ontario, Canada, Tel: (613) 737-2393 2210; Fax: (613) 738-4828; E-mail: rklaassen@cheo.on.ca

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HRQoL is that they are subjective, reflecting present lifestyle, past experience, hopes for the future, dreams and ambitions [8]. HRQoL can also be summarised as the gap between our expectations of health and our experience of it [9].

Generic HRQoL measures are available and certainly play an important role in allowing comparisons between disease groups. The Medical Outcomes Study short-form 36 (SF-36) has been administered in this population [10,11] with the results showing significantly decreased scores compared to controls [12]. As well, children with thalassemia were found to have significantly lower scores in the PedsQL compared to population norms [13]. The main limitation of using generic measures is they do not truly capture the unique aspects of the disease and treatment so that they tend to be less responsive to change [14].

New therapies need to be scrutinised with tools that can pick up subtle but important differences in HRQoL. The general consensus in the HRQoL community is that a combination of generic and disease-specific tools is the optimal method to capture disease burden in a population [15]. Disease-specific QoL measures allow for a more relevant, sensitive and complete assessment of the impacts of interventions in both the clinical and research settings and can facilitate informed choices among patients [15]. One disease-specific tool has been developed for chronically transfused patients including thalassemia patients – the "Satisfaction with iron chelation therapy" instrument (SICT), but is limited by focusing on chelation therapy and not on the other aspects of transfusion HRQoL. A tool encompassing all aspects of disease and treatment is needed to give us a complete picture.

The purpose of this study was to develop a disease-specific QoL measure to accurately capture the disease burden on transfusion-dependent thalassemia patients, in particular for use in future trials in this population.

Methods

The framework for measure development adhered to the guidelines published, in brief, potential items were generated using an extensive literature search, semi-structured interviews of patients, their families and health care workers. A draft measure was created using items that were frequently endorsed or particularly important to patients and families. This newly developed tool was then pilot-tested in a new group of patients and was further refined.

Conceptual Framework

The hypothesized conceptual framework for this new measure was to capture the full scope of health-related quality of life in children and adults with transfusion-dependent thalassemia as per Bianchi et al., including the domains of social, emotional, and physical wellbeing [9]. In addition, we intended to generate a separate tool to measure the impact of the disease on the parents of children with thalassemia. We hypothesised that generated items would be aggregated into separate domains, which would in turn would be aggregated into an overall TranQol score capturing the HRQoL for this group of patients and a measure of the burden of care for the parents. The anticipated result was three questionnaires to capture HRQoL: a child self-report; an adult self-report; a parent proxy-report; and a fourth questionnaire completed by the parents to capture the impact of the disease on the family.

Item Generation/Reduction and Development of the Initial Tool

The purpose of this phase of the study was to generate as many potential items for inclusion as possible, ensuring that all stakeholders had input so that no area of HRQoL was neglected. Two adult and two pediatric thalassemia comprehensive treatment centres participated in the study: the Children's Hospital of Eastern Ontario (CHEO) and the Ottawa Hospital (OH) in Ottawa, Canada; and the Hospital for Sick Children (HSC) and University Health Network (UHN) in Toronto, Canada. Initially the myelodysplastic syndrome treatment centres Sunnybrook Health Sciences Centre and Princess Margaret Hospital in Toronto participated but that group of patients was eventually excluded, as we found that their HRQoL issues were sufficiently different that they warranted a separate tool, which has now been separately developed and is called the Quality of Life in Myelodysplasia Scale (QUALMS-1). Approval from the local research ethics board of each institution was required prior to patient enrolment. Informed consent was obtained prior to participation and both parent consent and child assent were required for children enrolled in the study.

We began with an initial meeting of all the site investigators, representatives from nursing and social work from the various centres, and a representative from the national patient support group. A detailed literature review was presented to each attendee and a focus group discussion took place to identify potential items for the questionnaire. Participants were asked to write down relevant categories of potential concern and then asked to come up with one or two questions for each area. After that they were asked to look at other questionnaires and the literature and see if any of the items would be relevant to this population. A preliminary questionnaire was developed for use in semi-structured interviews with the patients and families.

Inclusion criteria included: signed consent; age 2.0 to 17.99 years for the pediatric group (under 7.0 years only the parent was enrolled), 18 and older for the adult group; thalassemia major (homozygous beta thal, Hb E beta thal and four gene deleted alpha thal) requiring regular transfusions; and all participants needed be able to communicate in English with no significant cognitive impairments. Patients were excluded if they had: thalassemia intermedia requiring transfusions less than 6 times per year; or significant comorbidity unrelated to thalassemia that was associated with moderate or severe symptoms or associated with functional disability (e.g. stroke with hemiparesis, cancer requiring active therapy, moderate coronary artery disease). Patients with stable chronic medical conditions that were asymptomatic or mildly symptomatic (e.g. hypertension, mild osteoarthritis) were included.

Two clinical research associates (CRA) conducted all of the interviews - KM (Ottawa) and MM (Toronto). Detailed training was undertaken to ensure methodologic uniformity. Children age 7.0 and older were asked to participate with one of their parents/guardians, whereas only the parent/guardian participated for the younger children (< 7 years). Most of the interviews were done while the patient received their regularly scheduled red blood cell transfusion. Because of this unique clinical setting, all of the interviews were done in person with individuals since focus groups were not conducive to that environment. Arrangements were made to ensure adequate privacy and avoid interruptions. The purpose of the interviews was to generate as many potential items as possible to develop as comprehensive a tool as possible.

The interviewers started with open-ended questions with explicit

instructions to use neutral terms where possible. The preliminary questionnaire from the health care focus group was subsequently used as a prompt to generate further items. Interviews were continued until a minimum of 15 patients in each group was carried out and saturation occurred, with no new items generated in five consecutive interviews. The CRAs wrote the suggestions verbatim to capture the words and phrasing used by the interviewee. The CRAs independently synthesized the interviews, eliminating duplicate items and summarized the generated items. The items were then summarised and listed, with any duplicates discarded.

To allow for item reduction, each participant was asked to write the previously generated items on cards and independently divide the cards into three piles: 1) extremely important 2) somewhat important and 3) not very important. Children 12 years and older and adult participants also ranked the items in each pile. Items rated extremely important by any of the participants, or with a high ranking in the somewhat important category by multiple participants were retained for use in the questionnaire. Items consistently categorized as not very important or having a low ranking in the somewhat important category were discarded. A subsequent meeting of the investigators and initial health care participants occurred to review the summaries generated by the research assistants and the initial measure was created.

Cognitive Debriefing of the Developed Measures

The purpose of this phase of the study was to pilot test the new measure to see if the participants had a common understanding of the questions and responses, and to confirm the face validity of the instrument as well as determine if less important items could be removed.

The local CRA contacted new patients from each patient group at the participating sites during a routine clinic visit. Similar inclusion and exclusion criteria were used and again signed consent was required. The cognitive interview was carried out using a method based on Jobe's framework for assessing cognitive and social-motivational processes. The analysis was qualitative in nature and was limited to content analysis of the notes and collective experiences of the CRAs. There was no attempt to generate deeper meaning from the data. The purpose of this phase was to provide a clearer understanding of the participants' comprehension of questions and response options.

The information collected from the interviews of each respondent was summarised by the CRAs based on their field notes and follow-up notes. These notes formed the basis for an Expert Consensus meeting. The members of the meeting included the investigators and representatives of the chronic transfusion community as well as the interviewers. Each centre's information was summarised on a single page per question. The summary began with a synopsis of the most common meaning of each question, followed by problems in interpretation with details of the characteristics of what types of participant experienced problems. The panel determined what if any items required modifications based on this information and agree upon the final formatting of the questionnaire. Following the meeting the questionnaires were formatted by a study coordinator.

Data Analysis

Data checks and cleaning was performed on all data. Summary statistics (means, standard deviations and ranges) were calculated using Microsoft Excel 2003.

Results

A total of 120 participants contributed to the development of the TranQol: 16 health care workers; 31 children with thalassemia and 43 parents; and 30 adults with thalassemia. The participant flow is outlined in the Figure 1.

Item generation/Reduction and development of the initial tool

An initial meeting of pediatric and adult thalassemia and quality of life methodology experts, which included 3 hematologists, 4 hematology nurses, 2 social workers, 1 methodology expert, 1 CRA and a representative from the national patient support group generated 69 potential items. A further 74 possible items were generated through interviews with 16 children with thalassemia (mean age 10.3 yrs; range 6, 17), and 21 parents (child's mean age 7.8 yrs; range 2, 17), as well as 15 adults with thalassemia (mean age 29.8 yrs; range 18, 41). Top ranked items by participant are listed in Table 1. Both the children and adults with thalassemia ranked a question concerning the impact of the disease on their family as the most important item. Parents ranked a question about their child's future as their number one issue.

A second expert meeting was convened to refine the suggested items. In attendance were 6 hematologists, 3 hematology nurses, 1 social worker, 1 methodology expert and 2 CRAs. Duplicate and infrequently mentioned suggestions were discarded resulting in 58 unique items that were incorporated into three self-reported questionnaires (child, parent and adult) and one proxy-report for parents.

Cognitive debriefing and description of the developed measures

An additional 15 children (mean age 11.4 yrs; range 6, 16), 21

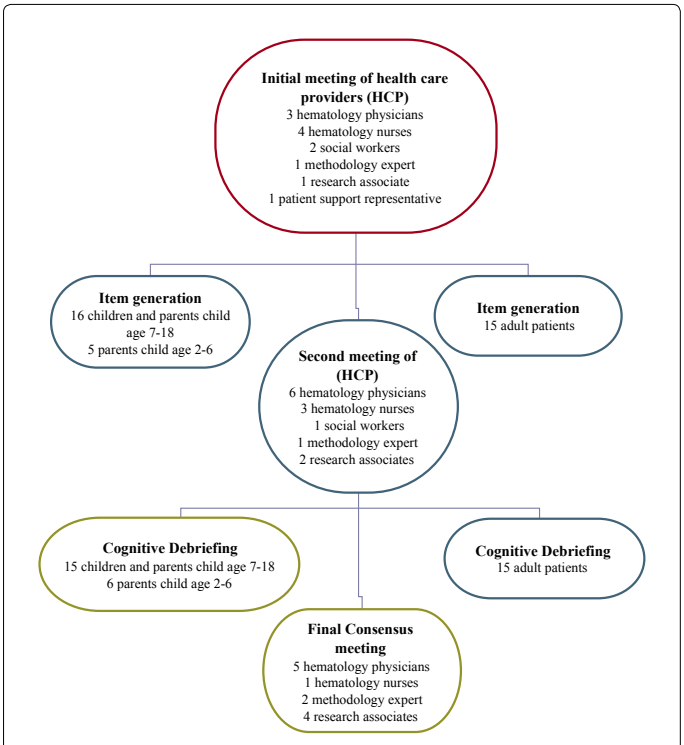

Figure 1: Participant flow diagram

parents (mean child age 9.8 yrs; range 2, 16), and 15 adults (mean age 26.3 yrs; range 19, 41) were interviewed as part of the cognitive debriefing of the new questionnaires. As a result, 3 items were added, one was deleted and 16 of the questions were modified to enhance clarity/understanding. Table 2 lists the items that were considered to be difficult to understand by 3 or more children. Parents and adults with thalassemia did not consistently identify any problems with item comprehension.

The number of items per report ranged from 29 for the child's questionnaire for children 7 years and older as well the parent proxy version mirroring the child version but for ages 2 to 18; 39 items for the parent version to assess their personal burden; and 37 for the adult self-report version. Each item was considered to have equal weight. The questions were grouped into 4 domains based on expert group consensus: physical health (2-10 items); emotional health (9-13 items); family functioning (6-10 items); school and career functioning (4-6 items). The parent and adult questionnaire included a fifth category on sexual activity which involves one question.

Discussion

Chronically transfused patients with thalassemia major have a unique set of concerns that are not adequately addressed by generic quality of life tools. The TranQol is a tool specific to this population that asks questions that came directly from patients and health care professional who have regular contact with these patients. Patients generated a significant number of items, emphasizing the importance of including patients when creating a new tool. Researchers and community members each bring their own expertise, backgrounds, and different knowledge base to the team so that a partnership between researchers and those affected by the issue being studied, promotes the voice of those being researched. As seen in Table 1 their top concerns are very different from other patient populations. Neither the PedsQL generic scale, a HRQoL tool commonly used in children, or the SF36, used in adults, ask questions related to the impact of the disease on the family. Not surprisingly, they also do not talk about the risk of infection from a blood transfusion, which was the second ranked concern of

Child
1. Are you satisfied with the support you receive from your family?
2. Do you worry about your future?
3. Are you worried about becoming sicker?
4. As a result of your condition are you able to participate in as many social events as you would like?
Parent
1. Do you worry about your child's future?
2. Do you worry about your child getting an infection from the blood they receive?
3. Do you think your child having Thalassemia may lead to an earlier death than if they did not have the disorder?
Adult
1. Thalassemia negatively/positively affected my family
2. Does your treatment (i.e. transportation to/from hospital, equipment, medication, parent/parents time off work) pose a financial strain for your family?
3. Thalassemia and its treatments affect my academic performance

Table 1: Top ranked items by respondent.

Items	
1. I had pain or discomfort...	Word problem, conceptual
2. My treatment (transfusion, pills, needles) prevented me from doing the things that I wanted to do…	Word problem, conceptual
3. I put off my treatment (transfusion, pills, needles)…	Word problem, conceptual
4. Thalassemia negatively (bad) affected my family…	Word problem, conceptual
5. Thalassemia positively (good) affected my family…	Word problem, conceptual

Table 2: Items rated as difficult to understand by 3 or more children with thalassemia

parents. The absence of these high priority items in generic HRQoL questionnaires supports the importance of including a disease-specific tool when assessing HRQoL in these patients.

The only other disease specific tool available for thalassemia patients, the SICT is limited by its focus only on iron chelation therapy (ICT). It has 28 items grouped into four domains: Perceived Effectiveness of ICT (six items), Burden of ICT (five items), Acceptance of ICT (five items), and Side Effects of ICT (three items). All of the questions refer to chelation with no reference to the impact of the disease itself or red cell transfusion. This limitation restricts the use of the SICT as a measure of HRQoL (which was not original intent of the developers) Cognitive debriefing of the TranQol significantly improved the tool, with important changes in wording and the addition of three more questions, including a question related to the feeling of helplessness that parents repeatedly noted was relevant to them. The children initially had problems with the wording of many of the questions, but this was quickly rectified so that the latter patients interviewed had no concerns. Parents and adults did not identify any problems with either the questions or the response options.

The main study limitation is geographic, as only two Canadian cities were involved in the tool development due to resource limitations. Additional items and different priorities might be found if this process was carried out in a different country or culture, in particular developing countries with different health care resources. We plan to test the validity of the TranQol in different languages and cultures to determine if this significantly affects the utility of this tool outside of North America. In addition, the rare nature of this disease also made it difficult to get large numbers of participants, although saturation was obtained, implying that the end result would not have significantly changed with a larger sample size.

The next stage of tool development is validation, which we have recently completed in six North America centres. The purpose of that study was to demonstrate the validity, reliability and responsiveness of the TranQol compared to other well-established generic HRQoL measures in adults, children and their parents with thalassemia major.

This research has relevance to several different audiences. From the perspective of researchers, this study establishes a new quality-of-life instrument for potential use in multi-centre trials. The instrument will provide invaluable supplemental information when examining disease outcomes. Use of the instrument may clarify issues to be considered in choosing management approaches. Patients and parents may be able to use the process of completing the questionnaires to enhance their ability to address the areas which most concern them and validate the importance of their voices in decision-making around the management of themselves or their child. Health Centre managers and funding sources may be able to benefit from the information obtained through

the use of the instrument to better understand management options chosen. For example, consistent low scores in the area of emotional health might indicate the need for increased psychology support for the clinic, conversely low scores in family functioning point to the need for social work intervention. Health care professionals may be able to glean insight into issues faced by patients receiving chronic transfusions and chelation, ultimately improving patient care.

Conclusion

The TranQol is a new disease-specific quality of life measure for thalassemia major patients. We have completed testing the validity of the measure in a multicentre study and the manuscript has been submitted for publication.

Acknowledgements

Robert J Klaassen is the principal investigator and supervised all aspects of the study including protocol development, attaining funding, REB approval, study implementation, data analysis and wrote the initial draft of the manuscript. Victor Blanchette is one of the senior investigators and was involved in protocol development, attaining funding, study implementation, and reviewed the manuscript. Katherine Moreau is the study coordinator and was involved in study implementation, REB approval, data analysis and entry and reviewed the manuscript. Manuella Merelles-Pulcini is the nurse coordinator for the study and was involved in protocol development, study implementation, REB approval, contract oversight and reviewed the manuscript. Melissa Forgie, Shabbir Alibhai, Melanie Kirby-Allen, Ian Quirt, Karen Yee, Rena Buckstein, Isaac Odame are site investigators for the study and were involved in the physician focus groups, arranging site contract and REB approval, local study implementation, patient recruitment and reviewed the manuscript. Durhane Wong-Rieger initiated the project and was essential for arranging for funding. Nancy L. Young is the other senior investigator and was involved in protocol development, study implementation, data analysis and wrote sections of the initial draft of the manuscript.

Disclosure

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