Early follow-up quality of life and mental health of patients with congenital vascular malformations cared for in a multi-disciplinary specialist center

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Short title: Early follow-up of quality of life in vascular malformations

Abstract

Objective

The study aimed to evaluate the early follow-up quality of life (QoL), pain and mental health of patients with congenital vascular malformation (CVM) from a variety of treatment options.

Methods

All patients with CVM who received care and had follow-up between February 1st 2018 and January 31st 2020 were included. The health-related QoL, pain, and mental health were assessed with RAND Health Care 36-Item Short Form Survey (SF-36), visual analogue score for pain (VAS-P) and Hospital Anxiety and Depression Scale (HADS). Paired t-test was used for all analyses. $P<0.05$ were considered significant.

Results

In total, 110 patients with a mean age of 36.9 years were included in this study. In all patients following care, significant improvement was found in the bodily pain domain of SF-36 and VAS-P (both $P = 0.01$). This was largely driven by high-flow vascular malformation patients who responded better to embolo-sclerotherapy, which revealed significant improvement in the bodily pain domain of SF-36 ($P=0.002$) and VAS-P ($P = 0.02$). Patients who received supportive treatment only reported significant improvement in mental health ($P=0.004$) and social functioning ($P=0.03$) domains of SF-36. Meanwhile, patients treated with embolo-sclerotherapy reported significant improvement only in VAS-P ($P=0.02$).

Conclusions

This study concluded that the effects of care on early follow-up QoL, pain and mental health of patients with CVM were heterogenous. Future research should therefore, include larger sample size and longer-term follow-up to understand the various factors that affect the QoL and mental health of these patients, as well as the holistic approaches to manage them.

Keywords

Quality of life, Mental health, Patient outcome assessment, Vascular malformations, Arteriovenous malformations, Vascular malformations treatment

Introduction

Congenital vascular malformations (CVM) are lesions derived from aberrant embryonic development of vascular channels and feature dysplastic abnormally formed vessels that consists of arteries, veins, capillaries or lymphatics or a combination of these vessels (1,2). Patient with CVMs may suffer from chronic debilitating symptoms including pain, swelling, disfigurement, ulceration, bleeding, thromboembolism, infection, and end-organ ischaemia and failure. As a result, patients with CVMs have been shown to report significantly poorer quality of life (QoL) compared with the general population including in our patient cohort (1).

CVMs are described and classified by the vessels involved and their flow characteristics. Haemodynamically, these lesions may demonstrate slow/low or fast/high fluid flow. Low-flow vascular malformations (LFVM) consist of capillary, lymphatic, venous whereas high-flow vascular malformations (HFVM) are any that contain an arterial component (3,4). In 2014 and 2018, the International Society for the Study of Vascular Anomalies (ISSVA) updated the existing classification with new information on the genetics and histology of vascular anomalies. This is a widely accepted classification system used by both clinicians and scientists in categorizing vascular malformations and vascular tumours. The understanding of molecular biology in vascular malformations has evolved over the years and has enabled a better understanding of the pathogenesis and molecular mechanisms underlying vascular malformations (2).

Venous malformations (VM) are the most frequent low-flow vascular malformations with an estimated incidence of around 1 in 10 000 (5) whereas arteriovenous malformations (AVM)

affect approximately 1 in 100 000 (6). VMs are typically managed conservatively with compression devices to prevent thrombosis and pain. However, symptomatic VMs require treatment with sclerotherapy regarded as the first line treatment option. AVMs represent the most aggressive form and have a high recurrence rate with a proximal AVM causing increase cardiac load resulting in congestive heart failure (7) and a distal AVM causing lower flow resulting in peripheral ischaemia (steal syndrome). Treatment of AVM is primarily embolization alone or in combination with surgical resection (8).

Supportive therapy and reassurance are often sufficient for patients with asymptomatic or minimally symptomatic lesions. However, some patients especially those with significant symptoms or complications from their CVMs may require interventions such as embolo-sclerotherapy (EST) and open surgery. Targeted pharmacological therapies, such as sirolimus, trametinib and thalidomide, are also increasingly being used for very selective patients with CVMs. Some of these treatment options have been shown to improve QoL of patients with CVM but the overall literature remains scarce and features a relatively small population size (9,10). Increased understanding of the effectiveness of treatment on the QoL and mental health of these patients will help clinicians to provide more holistic care. Therefore, the aim of this study was to evaluate the early follow-up QoL and mental health of patients with CVM receiving care in a single multi-disciplinary specialist center which offered a variety of treatment options. Early-follow-up was defined as a period between 6-12 months from pre-treatment questionnaire to post-treatment questionnaire.

Methods

This study was approved by the local clinical audit and governance committee and informed consent was obtained.

Study design and participants

This was a two-year prospective observational study of patients with CVMs cared for at a multi-disciplinary center for vascular anomalies. All patients with CVMs referred to the tertiary specialist center underwent evaluation by a multi-disciplinary team consisting of vascular surgeons, interventional radiologists, and a clinical nurse specialist, which subsequently directed decisions on care options including supportive treatment, EST, open surgery, and targeted pharmacological therapy. There is no algorithm or guideline that is used to direct modality of care. However, upon review of patients, including clinical history, physical examination and radiological imaging, treatment option is offered based on a multi-disciplinary decision, as described below. All patients who attended our out-patient clinics were routinely assessed for health-related QoL (HRQoL), pain, and anxiety and depression scores with validated questionnaires that were filled in by paper, as part of the department's usual patient review. It should be noted that the QoL tools used in this study are non-specific, nor validated in patients with CVMs. Rather the HRQoL measuring tools used were generic and developed for other patient populations. At the time of filling out the questionnaires some patients maybe taking concomitant medication such as analgesia or anxiolytics, and it was unknown whether these medications are for other co-morbidities or related to the vascular malformation. However, these medications were not initiated by the multi-disciplinary team and to the best of our knowledge no patients were on any analgesia or anxiolytics. Pre-treatment cross-sectional imaging i.e.

computed tomography (CT) and/or magnetic resonance (MR), with or without duplex ultrasonography were performed on all patients to aid planning. Patients who were asymptomatic or minimally symptomatic were mainly offered supportive treatment only such as compression, pain management, physiotherapy, counselling and reassurance. Patients with or at risk of developing significant symptoms and complications from their CVMs were often treated with interventional therapy such as EST and/or surgery; with the former being our mainstay treatment. Patients' risk was stratified according to multi-disciplinary clinical assessment and judgement based on clinical history, physical examination and radiological imaging. All EST were performed under fluoroscopic guidance and general anaesthesia with HFVMs treated with selective catheter angiography and direct injection, and LFVMs treated with direct injection only. Fluoroscopy guidance with digital subtraction angiography were performed to confirm the accurate position of the catheter and/or needles, and to assess the flow; either in a vascular hybrid theatre with a floor mounted C-arm or standard operating theatre with a mobile C-arm. Under guidance, the sclerosant agent is injected until either the lesion is filled or there is visualization of the sclerosant in the immediate draining vein. The EST agents used included foam sodium tetradecyl sulfate (STS) 3% (mixed with air in a 1:4 ratio), ethanol, and coils, as well as steroid injections at times. The choice and quantity of agent used were at the discretion of the operators at the time of each procedure. Our preferred EST agent was foam STS 3% and this was purely from our own experience. Ethanol and coils were only occasionally used, often in combinations, and for HFVM where lesions were perceived to be more aggressive by the operator. The majority of the EST were carried out as day cases. Meanwhile, open surgery included excision and debulking of lesions. Post-operatively, patients were followed up in the out-patient clinic at six to eight weeks. The targeted pharmacological therapies offered and used

in the center were thalidomide and sirolimus. These agents are considered as immunomodulatory, by working through a number of mechanisms such as decreasing TNF-α production. . The off-label use of these targeted pharmacological therapies were limited to very selective patients whose CVMs were too diffuse and extensive, located in challenging anatomical sites for surgical and EST access, and/or resistant to other interventions.

All patients who attended the out-patient clinics between February 1st 2018 and January 31st 2020 were recruited with the following inclusion and exclusion criteria. Other inclusion and exclusion criteria were as follows.

Inclusion criteria:

- Male and female of age 16 years old and above.
- Patients with a clinical and/or radiological (duplex ultrasonography and MRI and/or CT) diagnosis of CVM.
- Patients who were initiated on treatment.
- All patients who presented with complications related to vascular malformations such as localized intravascular coagulopathy or phleboliths.

Exclusion criteria:

- Any patients whose CVM involved the central nervous system.
- Patients who declined or were unable to answer the study questionnaires, e.g. patients with limited understanding of English, learning disability and blindness.
- Patients who were already on treatment outside the study period frame.

The baseline HRQoL, pain score, anxiety and depression scores of the cohort of patients with CVMs attending the specialist center during the study period has been published previously (11). In this study patients who received care and were followed up during the study period and therefore, re-evaluated with follow-up HRQoL, pain score, and anxiety and depression validated questionnaires following care given were included. The follow-up period was two to six months and post-treatment questionnaire was completed at this time after the patient's first intervention. Any subsequent treatment, if any, did not form part of the statistical analysis.

Data collection and analysis

Patient demography, clinical data including the anatomical locations and types of vascular malformation, types of treatment, pain score, and HRQoL, anxiety and depression scores were analyzed. CVMs were classified as either LFVM or HFVM where the former was defined as lesions that consist of either veins, capillaries, lymphatics or a combination, without any arterial component. Meanwhile, the latter were vascular malformations involving arterial component Care given was divided into four groups: (1) supportive treatment only, (2) open surgery, (3) targeted pharmacological therapy, and (4) EST. The anatomical location of the CVMs was categorized into (1) torso (chest, abdomen, pelvis and back), (2) head and neck, (3) lower limbs, and (4) upper limbs.

HRQoL assessments

<u>RAND Health Care 36-Item Short Form Survey (SF-36)</u>

The SF-36 measured eight scales: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health. Scoring was calculated

using the recommended guidelines from the RAND Health Care (12,13). Briefly, all 36 items were scored on a 0 to 100 range; items in the same scale were then averaged together to create the eight scale scores.

Visual analogue score for pain (VAS-P)

Pain was assessed using the VAS-P. The score was determined by measuring on the 100 mm line between 'no pain' and the patient's mark, providing a range of scores from 0 - 100. A higher score indicated greater pain intensity.

Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression were assessed using the HADS. The questionnaire was comprised of seven questions for anxiety (HADS-Anxiety) and seven questions for depression (HADS-Depression), which were rated on a four-point (0 - 3) Likert scale. A total of 21 points for each section with cut-off scores available for quantification i.e. ≥8 points was defined as clinically relevant for both anxiety and depression. The HADS questionnaire had been validated in many countries and settings (14–16). It was one of the National Institute for Health and Care Excellence (NICE) recommended tools for diagnosis of anxiety and depression (19,20).

Handling of missing items in SF-36 and HADS

Not all patients filled the SF-36 and HADS questionnaires completely leading to missing items. Our handling of missing items within the SF-36 questionnaire in this study followed the SF-36 manual. The manual suggested that missing items could be estimated by item mean imputation if respondent answered at least half of the items in a multi-item scale. If more than half of the items were missing, then the scale could not be calculated and would be regarded as missing (19). A

total of 16 patients (14.5%) questionnaires were incompletely filled but the missing responses were random.

Statistical analysis

All statistical analysis was performed using StataCorp2017 (*Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). The outcome measures were variables of SF-36, HADS and VAS-P scores; all of which were measured on a continuous scale and presented as mean and standard deviation. The changes of these variables from pre- to post-care were presented as mean and 95% confidence interval (CI) The outcome measures were analyzed to determine any changes for pre- and post-treatment treatment in all the study patients with CVMs as a whole and in subgroup of patients. An examination of the distribution of the outcomes suggested that changes from pre- to post-treatment were approximately normally distributed for all outcomes. As a result, the paired t-test was used for all analyses. $P<0.05$ were considered significant.

Results

Patient demography and type of care

A total of 284 questionnaires were filled out of which , 110 were included following the inclusion/exclusion criteria.. Table 1 summarizes the demographic characteristics of and type of care received by the study patients. Only supportive treatment showed a significant difference ($P<0.05$) between LFVM and HFVM. No side effects were documented on patient records who received treatment and only one patient (7.7%) from the HFVM EST group received ethanol as a sclerosant agent.

Pre- and post-care changes

All patients

Table 2 summarizes the pre- and post-care SF-36, VAS-P and HADS scores for all the patients receiving all types of care. Significant improvement was found in the bodily pain domain of SF-36 and VAS-P (both P = 0.01) following care in all patients. No other significant changes from pre- to post-care were observed for the other outcome variables.

LFVM and HFVM subgroups

Table 3 summarizes the pre- and post-care SF-36, VAS-P and HADS scores of patients with LFVM and HFVM receiving all types of care. Only patients with HFVM reported significant improvement in the bodily pain domain of SF-36 (P=0.002) and VAS-P (P = 0.02) following care in all patients. No other significant changes from pre- to post-care were observed for the other outcome variables although there was a non-significant improvement in pain, both for SF-36 and VAS-P in patients with LFVM.

Type of care

a. Open surgery

No statistical analysis was carried out on open surgery subgroup due to insufficient number of patients (n=2).

b. Supportive treatment only

Table 4 shows the pre- and post-care SF-36, VAS-P and HADS score of all patients who received supportive treatment only (n= 25). This group of patients reported significant improvement in mental health (P=0.004) and social functioning (P=0.03) domains of SF-36. There was also a non-significant improvement in vitality. Further subgroup analysis of LFVM and HFVM separately, only showed significant improvement in mental health domain (P=0.002) of SF-36 in the former who received supportive treatment only (Supplementary Table 1). No other significant changes in the SF-36 domains, VAS-P and HADS were found for both LFVM and HFVM.

c. Targeted pharmacological therapy

There were no significant changes reported in all the domains of SF-36, VAS-P and HADS score pre- and post-care for all patients who received targeted pharmacological therapy i.e. thalidomide or sirolimus (n = 22), as well as when they were sub-grouped into LFVM and HFVM (Supplementary Table 2 and 3, respectively).

d. Embolo-sclerotherapy

Table 5 shows the pre- and post-care SF-36, VAS-P and HADS scores of all patients received who EST (n= 61). There was a significant improvement in VAS-P (P=0.02) but not in any of the SF-36 domains and HADS. Further subgroup analysis showed significant improvement in pain score, both bodily pain domain in SF-36 and VAS-P, were only reported in patients with HFVM who had EST (Supplementary Table 4).

Anatomical locations

Table 6 summarizes the changes to the SF-36, VAS-P and HADS score pre- and post-care for all patients receiving all types of care based on the anatomical location of the CVMs. Patients with CVM in the torso reported significant improvement in the mental health (P=0.04) and bodily pain (P=0.01) domains of the SF-36, and for depression scores (P=0.01). Meanwhile, patients with lesions in the lower limbs reported significant improvement in vitality (P=0.02) and bodily pain (P=0.01) domains of the SF-36 score, and for the VAS-P (P=0.003) and depression scores (P=0.02). Patients with CVMs in the head and neck, and upper limbs did not report any significant changes in all SF-26 domains, VAS-P and HADS in their follow up.

Discussion

This study demonstrated heterogeneity in early follow-up changes to the early QoL, pain and mental health of patients with CVM cared for in a multi-disciplinary specialist setting. Early improvement in some domains of QoL, pain and mental health were noticed in some groups of patients, but not all, depending on factors including the type and anatomical location of the CVM, and treatment modality. For example, early improvement in pain was reported by patients who had EST especially those with HFVM; suggesting that such treatment was important for pain management. Only general health domain of the SF-36 scored lower post-treatment compared to pre-treatment. However, this was not statistically significant. Furthermore, our study suggested that patients with LFVM seemed to report better early response to supportive treatment only than those with HFVM. In particular, patients who received supportive treatment only reported significant early improvement in mental health and social functioning domains of the SF-36. This could be due to the

reassurances from such therapy, and further emphasizing the importance of supportive treatment to these patients. In our study, targeted therapy (i.e. thalidomide and sirolimus) were administered orally. Thalidomide is an anti-angiogenic agent which was used to treat selective patients with HFVM. Sirolimus is an allosteric inhibitor of mTOR which has been shown to be efficacious to selective vascular malformations, especially LFVM through the inhibition of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian Target of Rapamycin (mTOR) pathway (21,22). Patients with CVMs in the lower limbs and torso in this study seemed to respond better to overall care given than those with lesions in the head and neck, and upper limbs although the reasons behind this remain unclear. The reasons could be related to the head and neck, and upper limbs were generally more sensitive to pain, cosmesis and functions than the lower limbs and torso. To the best of our knowledge , at the time of the study, no patients presented with complications such as localized intravascular coagulopathy or phleboliths and therefore were not receiving current treatment such as counselling, psychiatry/psychology input, low molecular weight heparin, analgesia or anxiolytic medications. Furthermore, as questionnaires were part of the department's routine patient review, there is a reduced chance that the patients reported improved QoL based on the fact they were being studied.

We have previously published a snapshot of the baseline QoL, pain and mental health of patients with CVM attending our multi-disciplinary specialist center during the same period as this study (5). Our previous study concluded that patients with CVM reported worse QoL compared with the United Kingdom general population. This study was an extension of the previous one to assess the early changes of QoL, pain, and mental health of the subgroup of patients from the same cohort who had early follow-up following care given. Therefore, the majority of the patients who were in our

previous study but not in this study were likely to be those with relatively stable condition that did not require early follow-up. The results from this study are encouraging as it has shown following care given, there is general overall improvement in QoL, which was previously significantly impaired in our previous study. It is also important to point out that we could not extend the duration of follow-up from this cohort of patients due to the emergence of the Covid-19 pandemic which limited and changed our clinical activities significantly in March 2020.

To the best of our knowledge, no similar studies have assessed the changes to QoL, pain and mental health including comparing pre- and post-treatment amongst patients with CVMs who received various care modalities in a multi-disciplinary setting, as well as the potential affecting factors. Even though early follow-up has led to most patients only received one treatment modality when analyzed in this study, these patients are likely to have been treated with multiple modalities in future. Therefore, it would be interesting to assess the changes of the QoL, pain and mental health of these patients in future. Furthermore, previous studies tended to look at specific treatment modality such as sirolimus (23–26) and EST (27–31) rather than in a wider context when compared to this study. Rautio *et al* (11) assessed the QoL in 20 patients after endovascular treatment of venous malformations in the face and neck. The study showed that most patients did well after endovascular treatment. However, QoL was significantly poorer after treatment in patients who had malformations involving the tongue. Unfortunately, in this study the authors did not conduct a measurement of QoL before treatment to make comparisons. Weitz-Turoretmaa *et al* (12) evaluated the QoL in 41 patients after endovascular sclerotherapy of LFVM. Results showed that the majority of patients responded well after polidocanol sclerotherapy. In addition, the location of the malformation did not affect the outcome of post-treatment QoL.

It is important to emphasize that this study only evaluated the early QoL, pain and mental health i.e. in the first two to six months following care. This period might not be sufficient for the full benefits of some of the treatment modalities on the QoL, pain and mental health to take effect. Patients who received targeted pharmacological therapy might require longer duration to appreciate their benefits or side effects, while some patients who were treated with EST might still be recovering from their intervention to fully recognizing the treatment outcomes. Furthermore, it is known that more than one EST session would be needed in some cases to achieve clinical benefits (32). Interestingly, patients who had supportive treatment only demonstrated significant improvement in mental health and social functioning in the early period, demonstrating that simple measures including information giving, counselling, compression, pain management and reassurance were important to these patients. We recommend that all patients should be treated with a multi-disciplinary approach. As a baseline, all patients should receive supportive treatment (compression, pain management, physiotherapy, counselling and reassurance). EST should be the main interventional therapeutic tool and medical therapy should be reserved for patients where EST is deemed too high risk, contraindicated and/or refractory to interventional therapy (EST and/or surgery).

CVM is often a chronic condition which affects the patients for a significant part of their lives. Understanding the various factors that affect their QoL and mental health at different time-points, as well as the care that they receive is vital for the care of these patients. Our study clearly showed that research and effort are still needed to help improve all areas of the QoL and mental health of patients with CVMs as the current treatment modalities, seemed to only help one or two domains significantly, at least in the short term. We have highlighted the importance of subgroup analysis of QoL in relation to different types of CVMs (i.e. low-flow and high-flow), anatomical location and

type of management. (34)This enables enhanced understanding of outcomes according to different variables and hence improve holistic treatment to patients. However, the extent of the CVM was not analyzed, and would have been a potential important factor affecting QoL. The distinguishment between LFVM and HFVM is essential as the disease progress, prognosis and treatment are vastly different. HFVM can produce potentially life- or limb-threatening complications such as ischaemia, mass pressure effect and congestive cardiac failure (33). Therefore, assessment should prioritise this and hence early treatment of AVM is recommended (34). On the contrary, LFVM is seldom life- or limb-threatening and patients commonly present with symptoms such as pain and swelling and hence these could remain leading issues on evaluation as an indication for treatment. It is imperative to recognise the differences between the two as inappropriate treatment strategy can stimulate HFVM lesions into a proliferative state, resulting in aggressive growth and uncontrollable complications (34). Therefore, to address these issues future research should therefore, include larger sample size and longer-term follow-up to understand the various factors that affect the QoL and mental health of these patients, as well as the holistic approaches to manage them. An approach could be a multi-center study including a joint prospective database with longer term data on 3- and 5-year analyses. The outcomes from our study could certainly provide the platform to design the scope of this multi-center study focusing on the common type of CVMs and different treatment modalities (e.g. supportive, medical, interventional).

There were several limitations in this study. Firstly, the relatively small patient sample size and short follow-up period were not sufficient to evaluate the heterogeneity of CVMs. However, our study remained relatively large when compared to those in the literature. Secondly, we did not subcategorize the CVMs into the vessel type affected e.g. venous, capillary and lymphatic

malformation. However, with the already small sample size it would not have been practical to further subcategorized them as no meaningful statistical analysis would be possible. Thirdly , the QoL tools used in this study were non-specific for patients with CVMs and therefore lacked concept elicitation hence other domains of QoL that are affecting these patients may have been overlooked. In addition, patients with learning disability, not able to consent, as well as those under the age of 16 years were also excluded from the study partly due to the SF-36 not being designed for this age group. However, the SF-36 was considered a promising measure for HRQoL of adult patients as it is well investigated in diseases that are clinically similar to vascular malformations such as vascular or lymphatic diseases and benign tumors (34). Finally, our cohort of patients who attended a tertiary referral center could be presumed to suffer with more symptoms and signs, complicated and serious condition than the general cohort of patients with CVMs. Therefore, they might not be fully representative, their baseline QoL was presumably lower, and any form of treatment might potentially demonstrate more obvious beneficial effects than those who were not managed in tertiary referral center with potentially milder condition. Furthermore, patients who received EST would appear to be a 'higher risk' cohort of patients and therefore may not be a representable comparison to a 'lower risk' population and hence a heterogenous effect. Future studies should aim to compare those with similar risk that may not wish to proceed with certain medical or EST compared to those who agree to medical of EST. In addition, no side effects or complications were recorded for patients following treatment. However, it should be noted that these may have influenced results. Moreover, patients with or at risk of developing significant symptoms and complications were often treated with interventional therapy such as EST and/or surgery and these individuals may not have been 'satisfied' due to a higher 'preconceived treatment

effect' that they were hoping for and therefore influenced the mental health and social functioning domains.

Conclusion

This study concluded that the effects of care on early follow-up QoL, pain and mental health of patients with CVM by a multi-disciplinary specialist setting that offered various treatment modalities were heterogenous. Early improvement in some domains of QoL, pain and mental health were noticed in some groups of patients, but not all, depending on factors including the type and anatomical location of the CVM, and treatment modality. Future research should therefore, include larger sample size and longer-term follow-up to understand the various factors that affect the QoL and mental health of these patients, as well as the holistic approaches to manage them.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest

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