Stroke survivor attitudes toward, and motivations for, considering experimental stem cell treatments

David J. Unsworth, Jane L. Mathias, Diana S. Dorstyn and Simon A. Koblar

ABSTRACT

Purpose: Interest in stem cell treatments is increasing among some patient groups, but it is unclear whether this holds true for stroke survivors. This study examined stroke survivor attitudes toward stem cell treatments and identified a number of variables that may increase the likelihood that patients will consider these treatments.

Methods: Adult stroke survivors (N = 183) were recruited (stroke advocacy/support groups, outpatient register) for a cross-sectional study. Attitudes to stem cell treatments were surveyed, guided by the Theory of Planned Behavior. Demographic information was collected, and a number of self-report medical, cognitive and psychological measures completed.

Results: Twenty-five percent (n = 46) of respondents indicated they were considering undergoing stem cell treatments, although most were unsure about the safety/effectiveness and accessibility/affordability. Stroke survivors with positive attitudes toward stem cell treatments, longer post-stroke intervals, poorer physical functioning, younger age, longer post-stroke interval, poorer physical functioning, and perceived caregiver burden were more likely to be considered experimental treatments (odds ratios = 1.22, 1.08, 0.95, 0.96, 1.07; respectively).

Conclusions: Stroke survivors may consider undergoing experimental stem cell treatments despite uncertainty regarding the risks/benefits. Clinicians should be mindful of the factors that may increase the likelihood of patients considering these treatments and intervene, where appropriate, to clarify any misconceptions regarding the medical/financial risks.

IMPLICATION FOR REHABILITATION

- Stem cell treatments offer a new focus for reducing stroke-related disability, although their safety and effectiveness have yet to be established.
- Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, stroke survivors may still consider undergoing treatment in private, unregulated clinics.
- A number of factors, including younger age, longer post-stroke interval, poorer physical functioning, and perceived caregiver burden may place stroke survivors at an increased risk of considering these treatments.
- Clinicians should endeavor to educate stroke survivors regarding the risks and benefits of these experimental treatments and clarify any misconceptions, in order to reduce the likelihood that they will consider these as-yet unproven treatments.

Introduction

Over 15 million people suffer a stroke annually [1] and, despite improvements in acute care [2] and multidisciplinary rehabilitation [3], one in three patients experience ongoing physical disabilities, cognitive impairments [4], and/or emotional problems [5]. The extent to which a patient recovers is largely dependent upon the speed with which medical treatment is received, but is also contingent upon the type of stroke (ischemic, hemorrhagic), extent of the damage, and severity of the initial impairments; in addition to, the patient’s age, premorbid health/functioning, ongoing mental health, and level of social support [6]. Stem cell treatments (i.e., intracranial, intrathecal, intra-arterial, intravenous, or subcutaneous injections of stem cells/cell-related matter), are being examined as a potential means of reducing stroke-related disability, and preliminary data suggest that some treatments may improve neurological (motor, speech) and functional (mobility, self-care) outcomes, by augmenting endogenous repair processes and restoring damaged brain tissue [7–9].

However, the majority of data originate from early-phase clinical trials or observational studies, few of which controlled for placebo effects or tracked the injected cells. Moreover, treatment-related adverse events, including brain and spinal tumors, seizures, and further strokes have been observed [7–9]. Phase II/III clinical trials are currently being conducted (NCT02448641; NCT02961504; NCT03545607; NCT03004976; NCT01716481 [clinicaltrials.gov]) but, even if proven to be safe and effective, it will be some time before these treatments are approved for clinical use [10]. Thus, stem cell
treatments are not currently approved for use with stroke patients in the United States, United Kingdom or Australia.

Despite uncertainty regarding their risks and benefits, expensive (~US$100,000) experimental stem cell treatments are currently offered for stroke by private clinics throughout Asia, Russia and South America [11]. These treatments often involve unregulated, nonstandardized administration practices, non-disclosure of cell sources and manufacturing processes, and a lack of empirically-based treatment data [12]. Although research suggests that there is a growing interest in experimental stem cell treatments

Table 1. Survey questions exploring attitudes and expectations of stroke survivors concerning experimental stem cell treatments, together with summary findings (N = 183).

| Interest in stem cell treatments | (1) Are you considering experimental stem cell treatments? |
|----------------------------------|----------------------------------------------------------|
| Yes                              | 46 (25.1%)                                               |
| No                               | 97 (53.0%)                                               |
| Unsure                           | 40 (21.9%)                                               |

| Familiarity with stem cell treatments and main sources of information | (2) How much do you know about stem cell treatments for stroke? |
|-----------------------------------------------------------------------|---------------------------------------------------------------|
| Nothing                                                               | 105 (57.4%)                                                 |
| A little                                                              | 64 (35.0%)                                                  |
| Quite a bit                                                           | 10 (5.5%)                                                   |
| A lot                                                                 | 4 (2.1%)                                                    |

| Perceived risks and benefits | (3) From what source have you heard about them most? |
|------------------------------|-----------------------------------------------------|
| Unsere                       | 114 (62.3%)                                         |
| Very safe                    | 6 (3.3%)                                             |
| Quite safe                   | 56 (30.6%)                                          |
| Quite unsafe                 | 6 (3.3%)                                             |
| Very unsafe                  | 1 (0.5%)                                             |

| Preferred treatment types and outcomes | (4) How many stem cell therapy information booklets have you read? |
|----------------------------------------|---------------------------------------------------------------------|
| Animals                                | 113 (64.9%)                                                         |
| Embryo/foetus                          | 87 (49.2%)                                                          |
| Other people’s                         | 63 (35.6%)                                                          |
| Your own                                | 24 (13.3%)                                                          |

| Perceived accessibility and affordability of stem cell treatments | (5) How safe do you think they are? |
|------------------------------------------------------------------|-------------------------------------|
| Unsure                                                           | 64 (35.0%)                          |
| Very difficult                                                   | 65 (35.5%)                          |
| Difficult                                                       | 36 (19.7%)                          |
| Easy                                                            | 14 (7.65%)                          |
| Very easy                                                       | 4 (2.2%)                            |

| Main concerns regarding stem cell treatments | (6) How effective do you think they are? |
|----------------------------------------------|------------------------------------------|
| Side effects / complications                 | 88 (48.2%)                               |
| Cost                                          | 46 (25.1%)                               |
| No improvement                                | 28 (15.3%)                               |
| Traveling overseas                            | 16 (8.7%)                                |
| No concerns                                   | 5 (2.7%)                                 |

| n (%) | n (%) |
|-------|-------|
| Yes   | 46 (25.1%) |
| No    | 97 (53.0%) |
| Unsure| 40 (21.9%) |
| Media | 88 (48.1%) |
| No source | 74 (40.5%) |
| Doctors/Nurses | 7 (3.8%) |
| Empirical research | 7 (3.8%) |
| Socially | 7 (3.8%) |
| None  | 165 (90.2%) |
| One or more | 18 (9.8%) |
| Unsure | 123 (67.2%) |
| Very effective | 15 (8.2%) |
| Moderately effective | 28 (15.3%) |
| Slightly effective | 14 (7.7%) |
| Not effective | 3 (1.6%) |
| Spinal Cord | 83 (46.1%) |
| Brain  | 73 (40.1%) |
| Artery | 41 (22.8%) |
| Stomach| 37 (20.9%) |
| Vein  | 32 (18.0%) |
| Physical | 118 (64.5%) |
| Cognitive | 45 (24.6%) |
| Psychological | 20 (10.9%) |
| Unsure | 57 (31.2%) |
| Not affordable | 78 (42.6%) |
| Potentially affordable | 34 (18.6%) |
| Affordable | 13 (7.1%) |
| Easily affordable | 1 (0.5%) |
| Yes   | 91 (49.7%) |
| No    | 32 (17.5%) |
| Unsure| 60 (32.8%) |

n: number.
*Item scores used to calculate stem cell treatment attitude score.
*Multiple responses permitted (percentage totals > 100%).
among people with multiple sclerosis, Parkinson’s disease and amyotrophic lateral sclerosis [13], it is not yet known whether stroke survivors show a similar interest in, and expectations of, these treatments. Moreover, little is known regarding why patients seek unproven stem cell treatments, with the limited data suggesting that being male, having severe long-term physical disabilities [14], and dissatisfaction with existing/available treatments [15,16] may increase the chance that a person will consider or undergo experimental stem cell treatments.

Given that the stroke sequelae differs from that of the neurodegenerative disorders that have been studied (e.g., sudden onset of severe, persistent disabilities), a number of additional variables may need to be considered when examining which patients are most likely to consider stem cell treatments [6]. Indeed, the stroke literature identifies multiple factors that contribute to physical disability; including age, time-post stroke, health-related quality of life, cognitive functioning, mental health, and social support [17]. In addition, the attitudes of a stroke survivor and their family/friends toward a treatment (i.e., the perceived risks/benefits/accessibility/affordability), may influence whether or not they consider it. This is consistent with the Theory of Planned Behavior model [18,19], an empirically validated socio-cognitive framework that has been used to predict treatment-seeking behaviors. Thus, stroke survivors who believe stem cell treatments are safe, effective, accessible and affordable, and whose family/friends support them, having these treatments, may be more likely to consider having them [20].

The current study, therefore, surveyed a group of Australian stroke survivors who had not previously undergone stem cell injections in order to: (1) evaluate how many were considering having stem cell treatments; (2) explore their attitudes toward, and expectations of, these treatments; (3) identify what demographic, medical, cognitive, psychological and attitudinal variables may increase the likelihood of a stroke survivor considering stem cell treatments; and (4) construct an integrated model to help identify which stroke survivors may be most likely/unlikely to consider such treatments.

Method
This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [21] (see Supplementary Material for STROBE checklist).

Participant eligibility and recruitment
Participants were eligible if they were adults (≥18 years) at the time of their stroke (ischemic or hemorrhagic), had not previously undergone experimental stem cell treatments, and could complete a paper-based, online or telephone survey (with or without assistance). Eight Australian stroke advocacy organizations and stroke support groups (see acknowledgments) promoted the survey among their members, which resulted in 114 responses. The Australian Stroke Clinical Registry, an outpatient registry, also mailed 500 paper-based surveys to members, from which 69 responses were received (13.8% response rate). Of the 183 responses that were received in total, 173 were completed via mail or online, and 10 were completed via telephone interview with the first author DJU. Informed consent was obtained from each participant prior to completion of the survey. Recruitment occurred from September 2016 to January 2018.

Stem cell treatment survey
A 14-question survey (see Table 1) was constructed to: (1) assess the number of stroke survivors who were considering experimental stem cell treatments (yes, no, or unsure) (item 1); and (2) explore respondents’ familiarity with, and main sources of information about, stem cell treatments (items 2–4), the perceived risks and benefits of stem cell treatments (items 5, 6), their preference for different treatment types (items 7, 8), their desired outcomes (item 9), the perceived accessibility and affordability of these treatments (items 10–13), and their main concerns (item 14). Stem cell treatments were defined as those that are unproven and experimental in nature, and that involve the injection of stem cells/cell-based materials sourced from the patient, other people, embryos/foetuses or animals, into the brain, spinal cord, vein, artery or stomach by an overseas clinic [12]. Prior to conducting the survey, the content was piloted with a separate group of 10 stroke survivors, who were sourced from Stroke SA, to ensure that the survey wording and length was acceptable.

Other self-report measures
A range of additional self-report measures were included in order to help identify the demographic, medical, cognitive, and psychological variables that may influence the likelihood that a stroke survivor would consider stem cell treatments.

Demographic variables
Respondents’ age, sex, and year of stroke were all surveyed, as was information pertaining to their type of stroke (ischemic/hemorrhagic), residential location, relationship status (married/partnered/single), work status (employed/unemployed due to health or age), years of education, and recruitment source.

Medical and cognitive variables
Physical independence was assessed using the Nottingham Extended Activities of Daily Living Scale [22], which measures the level of assistance required to perform 22 tasks in the past 2 weeks (4-point Likert scale: lower scores = greater physical dependence; range: 0–66). Health-related quality of life was evaluated using the pain, sleep and communication items from the Assessment of Quality of Life questionnaire (Version 4-D) [23]. Item scores range from 1 to 4; with lower total scores indicating poorer health-related quality of life (range: 3–12). The memory/thinking subscale of the Stroke Impact Scale [24] was used to evaluate cognitive functioning. Using a 5-point Likert scale, participants reported how difficult it was in the past week to perform seven tasks that required concentration, immediate and delayed recall, or executive functioning (lower scores = poorer cognition; range: 7–35).

Psychological variables
Treatment satisfaction was assessed using the Patients’ Satisfaction with Stroke Services Questionnaire [25] in which respondents rate 14 areas using a 4-point Likert scale (lower scores = less satisfaction; range: 14–56). Social support was evaluated using the 12-item Multidimensional Scale of Perceived Social Support (7-point Likert scale, lower scores = less social support; range: 12–84) [26]. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale [27], which
assesses how frequently (0 to 3) respondents experienced 14 symptoms during the past week (higher scores = greater anxiety/ depression; range: 0–21; scores ≥ 4 = clinically-significant levels of symptoms [28]). Participants who had an unpaid/informal caregiver (spouse/family/friend) additionally completed the 10-item Self-Perceived Burden Scale [29]; reporting how often (scale of 1–5) they felt guilty/worried/concerned about the demands placed on their carer (higher scores = greater concern; range: 10–50).

Attitudinal variables

Participant attitudes toward experimental stem cell treatments were measured using a five-item scale that was designed for this study. Specifically, respondents were asked to rate (5-point Likert scale) how safe, effective, accessible, and affordable they perceived stem cell treatments to be, and how likely it was that their family/friends would want them to have stem cell injections (see Table 1, items 5, 6, 10–12). Item scores were summed to create a composite score, with higher scores indicating more positive attitudes regarding experimental stem cell treatments (range: 5–25).

Data preparation and statistical analysis

Summary results (means [SDs], frequencies [percentages]) were calculated, both for the full sample and for two subgroups (Considering stem cell treatment: Yes and No/Unsure). In the small number of cases (n = 6) where respondents were "unsure" of the timing of their stroke, the mean duration of 5.3 years was imputed (average of observed values) [30]. Where missing questionnaire items were identified, multiple imputations were performed for each respondent based on their mean item score. This method was selected because the number of respondents with missing data was less than 10% [31]. A multivariate logistic regression was conducted, using the Purposeful Selection of Covariates approach [32], to identify which demographic, medical, cognitive, psychological, and attitudinal variables increased the probability that a stroke survivor would consider experimental stem cell treatments (model 1). This analysis was repeated for respondents who had an unpaid/informal caregiver (n = 106) in order to determine whether perceived caregiver burden was an additional predictor (model 2). Exploratory univariate analyses were conducted (nominal/categorical data: Pearson χ² tests; continuous and ordinal data: Mann–Whitney U tests) to identify significant differences (p < 0.20).
between those who were considering stem cell treatments and those who were not or were unsure.

Odds ratios (ORs) and confidence intervals (95% CIs) were calculated for each of the predictors that were included in the final models (p < 0.05). An OR > 1 represented the increased odds of a patient considering stem cell treatment per unit increase in score on the corresponding measure (higher scores = higher odds) and an OR < 1 represented the decreased odds of a patient considering stem cell treatment per one unit increase in score (lower scores = higher odds) [32]. Bootstrapped beta-coefficient standard errors (SEs) and p values were used when assessing the statistical significance of the predictors (based on 1000 samples) to establish the internal validity of the respective models [33]. Likelihood ratio and Hosmer and Lemeshow tests assessed the quality and “fit” of the final models; respectively [32].

As an additional step, the ORs were also converted to predicted probabilities using the marginal standardization method (predicted probabilities summed to calculate a weighted average), so that the cumulative probability of an individual considering experimental stem cell treatments could be estimated based on their scores across multiple variables [34]. Probabilities ≥80%, ≥60% and <60% were categorized as likely, possible and unlikely to consider experimental stem cell treatments, respectively [35]; consistent with guidelines for the identification of “at risk” patients in clinical practice [34]. Statistical power was evaluated when the final N was known, based on a minimum event-to-predictor ratio of 5:1 [36]. All analyses were performed using IBM SPSS Statistics for Windows (version 24.0) [37].

**Results**

**Demographic and clinical details**

A total of 183 stroke survivors, aged between 26 and 96, completed the survey (see Table 2 for summary details). The post-stroke interval ranged from 1 to 36 years. Similar numbers of women and men responded, the majority of whom were married/partnered, had completed high school, and were unemployed/retired due to age or health. Ischemic strokes were more common than hemorrhagic strokes. Most respondents had received medical treatment and rehabilitation after their stroke, although only around one in three had also accessed psychological and/or psychiatric care.

On average, scores on the measures of physical independence (Nottingham Extended Activities of Daily Living Scale), health-related quality of life (Assessment of Quality of Life Scale) and cognition (Stroke Impact Scale) fell within the moderate-to-good range, as did the treatment satisfaction (Patient Satisfaction with Stroke Services Questionnaire) and social support (Multidimensional Scale of Perceived Social Support) scores. Conversely, 70% and 66% of the sample reported levels of anxiety and depression; respectively, that exceeded stroke guidelines (Hospital Anxiety and Depression subscale scores ≥4 [28]). Self-Perceived Burden Scale scores fell in the moderate range for those with a carer (n = 106).

---

### Table 3. Multivariate logistic regression analysis identifying potential predictors for stroke survivors considering experimental stem cell treatments.

| Model 1: Total sample (N = 183) | Predicted | Observed frequencies | % Correct |
|--------------------------------|------------|----------------------|-----------|
|                                | Yes        | No/Unsure            |           |
| Stem cell treatment attitude score | β | SE² | Wald's x² | df | p^ | OR (95% CI) |
| Time post-stroke | 0.202 | 0.10 | 7.92 | 1 | 0.008 | 1.22 (1.06–1.41) |
| Physical independence | 0.075 | 0.03 | 5.82 | 1 | 0.024 | 1.08 (1.01–1.15) |
| Age | −0.051 | 0.01 | 19.74 | 1 | 0.001 | 0.95 (0.93–0.97) |
| Constant | 0.626 | 1.30 | 0.23 | 1 | 0.673 | n/a |
| Model 1 evaluation | x² | df | p | |
| Likelihood ratio test | 40.62 | 4 | 0.000 |
| Hosmer and Lemeshow test | 7.61 | 8 | 0.472 |

| Model 2: Subgroup with caregivers (n = 106) | Predicted | Observed frequencies | % Correct |
|--------------------------------|------------|----------------------|-----------|
|                                | Yes        | No/Unsure            |           |
| Stem cell treatment attitude score | β | SE² | Wald's x² | df | p^ | OR (95% CI) |
| Time post-stroke | 0.262 | 0.09 | 8.42 | 1 | 0.004 | 1.30 (1.09–1.55) |
| Physical independence | 0.092 | 0.04 | 5.38 | 1 | 0.010 | 1.10 (1.01–1.19) |
| Perceived burden | 0.066 | 0.03 | 6.82 | 1 | 0.019 | 1.07 (1.02–1.12) |
| Constant | −6.434 | 1.62 | 15.74 | 1 | 0.001 | n/a |
| Model 2 evaluation | x² | df | p | |
| Likelihood ratio test | 17.23 | 3 | 0.001 |
| Hosmer and Lemeshow test | 4.68 | 8 | 0.791 |

---

Cl: confidence interval; df: degrees of freedom; N: number; OR: odds ratio; p: p values; SE: standard error.

Predicted frequencies were calculated using 0.50 cutoff.

Values based on 1000 bootstrapped samples.
**Stem cell treatment survey responses**

Summary findings from the stem cell treatment survey are provided in Table 1. In total, 46 respondents (25.1%) indicated that they were considering experimental stem cell treatments, the remainder were not (n = 97, 53.0%) or were unsure (n = 40, 21.9%). Most respondents (57.4%) indicated that they knew nothing about such treatments. The media was the main source of people’s information (48.1%); far less had discussed stem cell treatments with doctors/nurses (3.8%) or read empirical research (3.8%), and only 18 respondents had previously accessed a patient information booklet. Most respondents were unsure about the risks (62.3%) and benefits (67.2%) associated with experimental stem cell treatments.

A large proportion said they would not consider treatments that used stem cells from animals (64.9%) and human embryos/foetuses (49.2%), or involved injections to the spinal cord (46.1%) and brain (40.1%). In terms of preferred treatment outcomes, the majority wanted physical (64.5%), rather than cognitive (24.6%) or psychological (10.9%), improvements. Most indicated that it would be difficult/very difficult to locate/attend a stem cell clinic (55.2%) or to afford treatment (42.6%), and few indicated that their family and friends would want them to do so (15.9%). However, 91 respondents (49.7%) indicated that they would consider stem cell treatments if they were available domestically. Respondents were mainly concerned about treatment-related side-effects (48.2%) and treatment costs (25.1%). The mean score for stem cell treatment attitude fell in the mid-range (see Table 2), suggesting a high level of uncertainty and ambivalence about the safety, effectiveness, accessibility, and affordability of these experimental stroke treatments.

**Characteristics of those considering experimental stem cell treatments**

The sample of 183 respondents was divided into two groups to enable a comparison of those who were considering experimental stem cell treatments (Yes: n = 46) with those who were not or were unsure (No/Unsure: n = 137). Descriptive statistics and the results of the univariate analyses are provided in Table 2. The multivariate regression models are provided in Table 3. Model 1 (full sample) indicates that stroke survivors who had positive attitudes towards stem cell treatments (OR: 1.22, \( p = 0.008 \)), longer post-stroke intervals (OR: 1.08, \( p = 0.024 \)), lower levels of physical independence (OR: 0.95, \( p = 0.001 \)) and younger ages (OR: 0.96, \( p = 0.003 \)) were more likely to be considering experimental stem cell treatments. In model 2 (respondents with positive attitudes towards stem cell treatments (OR: 1.30, \( p = 0.004 \)), longer post-stroke intervals (OR: 1.10, \( p = 0.010 \)) and greater self-perceived caregiver burden (OR: 1.07, \( p = 0.029 \)) were more likely to be considering experimental stem cell treatments. Likelihood ratio tests confirmed that the final models were better than intercept-only/null models at predicting which respondents were at risk of considering experimental stem cell treatments. Hosmer and Lemeshow tests indicated the “goodness-of-fit” for each model was fair (see Table 3). Each model predicted 70% to 80% of overall cases correctly; although both models identified those who were not considering experimental stem cell treatments with greater accuracy (see Table 3). Residual plots were inspected for potential outliers and influential cases, but all data were retained [38].

The probability that a stroke survivor would be likely, possibly, or unlikely (≥80%, ≥60%, <60%; respectively) to consider experimental stem cell treatments were calculated, based on the variables identified by models 1 and 2. As shown in Figure 1, the cumulative probability estimates for model 1 indicate that stroke survivors who: had high scores (i.e., positive responses) on the questions relating to stem cell treatment attitudes, were ≥10 years post-stroke, had low levels of physical independence (e.g., were unable to walk around outside, feed themselves, socialize without assistance; Nottingham Extended Activities of Daily Living Scale scores ≤10), and were aged ≤40 years, were more likely to consider experimental stem cell treatments. If they had a carer, model 2 indicates that stroke survivors who: had high scores (i.e., positive responses) on the questions relating to stem cell treatment attitudes, were ≥10 years post-stroke, and had strong concerns regarding their burden on caregivers (Self-Perceived Burden Scale scores ≥50) were more likely to consider experimental stem cell treatments (see Figure 2).
This study surveyed Australian stroke survivors to examine their level of interest in, and attitudes toward, experimental stem cell treatments. Overall, one in four (25%) respondents reported that they were considering experimental stem cell treatments, which is lower than a previous South Korean study (46%) [14], possibly reflecting cultural differences in attitudes and/or knowledge relating to experimental medical treatments [39]. Consistent with studies conducted in Asia [14] and Europe [40], this study found that the majority of respondents knew very little about the risks and benefits of stem cell treatments, with most relying on the media (e.g., radio, newspapers, internet) for health information. This is concerning, given that media reports – particularly those found online – tend to exaggerate the positive aspects of experimental stem cell treatments, without disclosing financial interests [41].

Most respondents also indicated that they would not consider treatments that involve injections into the spine (intrathecal) or brain (intracranial) but would consider having stem cell injections into a vein (intravenous) or the abdomen (subcutaneous). These findings are noteworthy because the only large-scale clinical trial currently being conducted for patients in the chronic phase of stroke involves intracranial injections (NCT02448641), which suggests that stroke survivors may be reluctant to have this form of treatment even if it were to become publicly available. Moreover, the findings also suggest that stroke survivors may be more likely to seek out stem cell treatments that they perceive to be safer (i.e., intravenous, subcutaneous injections), despite evidence suggesting that the cells do not reach damaged brain tissue and are, therefore, less effective [8,9]. In addition, approximately one third of respondents reported that, if they were to have stem cell injections, they would prefer improvements in their cognitive (i.e., executive functioning, memory) or psychological functioning (i.e., reduced depression and anxiety), rather than their physical capabilities; however, neither of these areas have been routinely examined by current stem cell research [7,8].

Lastly, although most respondents thought it would be difficult to locate or attend a private clinic and to afford stem cell treatments, approximately half indicated that they would consider having them if they were available domestically. This is concerning because private clinics that offer adipose (stomach fat, bone marrow) stem cell injections, primarily for chronic pain conditions (i.e., osteo/rheumatoid arthritis), have begun operating throughout the United States, United Kingdom, and Australia, without the need for regulatory approval [42,43]. Given chronic pain is also common after a stroke, the findings from this study suggest patients may seek treatment from these clinics, despite only two Phase I clinical trials currently being conducted to establish the safety and tolerability of adipose stem cell injections for stroke (NCT03570450; NCT02813512 [clinicaltrials.gov]).

The present study also highlighted a number of potential factors that may influence whether a stroke survivor considers experimental stem cell treatments. In each of the groups that were examined (i.e., full sample and respondents with carers), positive attitudes regarding the safety, effectiveness, accessibility, and affordability of stem cell treatments appeared to be the most important factors. These findings are consistent with the Theory of Planned Behavior [19] and suggest that educational interventions – which are designed to improve stroke survivors and their family/friends’ understanding of the risks and benefits associated with experimental stem cell treatments – may assist in reducing the likelihood that patients will consider having these treatments. However, given that only 10% of respondents indicated that they had previously read an online patient-information booklet, more appealing and interactive methods of communicating this information (e.g., telephone advice lines, stroke community events) may prove to be more effective [44]. Moreover, the responses provided in the current study suggest that, by making it more difficult to access private clinics (i.e., via increased local and international regulation), fewer stroke survivors may consider undergoing experimental treatments. However, it is also important to note, that, despite ongoing attempts to regulate and/or close stem cell clinics that offer non-evidence based treatments, progress has been slow, particularly in non-Westernised countries [11,43].

The findings from this study also suggest that the longer an individual continues to live with stroke-related disabilities, the more likely they may be to consider stem cell treatment. This result was particularly evident amongst respondents who were also physically dependent on others; a source of frustration for many patients [14,15]. Younger stroke survivors may also be more
likely to consider experimental stem cell treatments, possibly reflecting lower risk aversion and a greater focus on treatment benefits, rather than risks [45]. Lastly, stroke survivors who are concerned about the burden they place on their caregivers (i.e., a spouse or family member) may be more likely to consider experimental stem cell treatments. Rehabilitation interventions to help patients and their caregivers prepare for and adjust to, the physical, cognitive, and emotional difficulties that commonly arise after a stroke are important in this respect [46,47]. Lastly, the cumulative probability estimates provide valuable information for treatment planning, by highlighting the importance of interdisciplinary interventions that aim to maximize physical functionality, in addition to supporting patient mental wellbeing, and patient-caregiver communication.

Study limitations

There are a number of limitations that should be taken into account when considering these results. First, the current study was underpowered, having a 4:1 event-to-variable ratio (i.e., 46 “Considering stem cell treatment: Yes” cases; 12 predictors) [36]. Although a reduction in the number of variables would have improved this ratio, one of the main aims of the study was to identify a list of potentially useful predictors. Therefore, all variables were examined using conservative statistical techniques (e.g., 95% CIs, bootstrapped beta-weight SEs and p values). Second, the generalisability of these findings to other countries remains to be determined, due to demographic, clinical, treatment [1], and attitudinal differences [39]. Third, stroke survivors who were considering stem cell treatments may have been more likely to participate in the online survey (i.e., selection bias) and, those who were not, may have been less likely to have responded to the mailed surveys (i.e., non-response bias). Consequently, stroke survivors who were considering stem cell treatments may be over-represented in the current sample. Fourth, some of the variables that were identified (physical dependence, age) only marginally increased the odds of considering stem cell treatment, therefore predictions based upon multiple variables were provided. Lastly, the current study did not collect specific information about the respondents’ strokes (e.g., size and location of the infarct), premorbid health/functioning, or current health (e.g., blood pressure, blood gas levels), nor did it examine a number of potentially important variables (e.g., history of overseas travel, prior experimental treatments for other conditions). Future research should examine these additional variables, preferably within the context of a large international study, in order to extend the current findings.

Conclusions

The current survey suggests that some stroke survivors may consider having experimental stem cell treatments, despite the significant costs and ongoing uncertainty regarding the medical risks and benefits. Having to travel overseas for treatment may have previously acted as a deterrent; however, clinics offering adipose stem cell treatments for related conditions (e.g., chronic pain) are now operating in the United States, United Kingdom, and Australia, which may result in more patients undergoing these experimental treatments for their ongoing stroke-related symptoms. Consequently, health professionals working with stroke survivors need to be aware of the factors that may potentially increase the likelihood of patients considering these risky, experimental and unproven treatments. By clarifying misconceptions regarding the safety and effectiveness of experimental stem cell treatments, and educating families to help them prepare for, and adjust to the difficulties arising after a stroke, treating clinicians may help stroke survivors and their caregivers to make more informed decisions regarding their treatment options.

Acknowledgments

The following organizations assisted with recruitment: Stroke Foundation, Australian Clinical Stroke Registry (AuSCR), Stroke Association of Qld, Stroke Association of Victoria, Stroke Recovery Association of NSW, Young Stroke Group, Young Queensland Stroke Support Group, Young Victorian Stroke Support Group, Australian Aphasia Association. Advice regarding the data analyses was provided by Dr Stuart Howell, Senior Statistician, Data, Design and Statistics Service, University of Adelaide.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

David J. Unsworth http://orcid.org/0000-0002-2167-9409
Diana S. Dorstyn http://orcid.org/0000-0002-7799-8177

References

[1] Thrift AG, Cadilhac DA, Thayabaranathan T. Global stroke statistics. Int J Stroke. 2014;9:96–18.
[2] Wang Y, Wang Y. Stroke research in 2017: surgical progress and stem-cell advances. Lancet Neurol. 2018;17:2–3.
[3] Anderson E, Fernandez S, Ganzman A, et al. Incorporating nonphysician stroke specialists into the stroke team. Stroke. 2017;48:e323–e325.
[4] Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133:447–454.
[5] Hackett ML, Köhler S, O’Brien J, et al. Neuropsychiatric outcomes of stroke. Lancet Neurol. 2014;13:525–534.
[6] Richards CL, Malouin F, Nadeau S. Stroke rehabilitation: clinical picture, assessment, and therapeutic challenge. Prog. Brain Res. 2015;218:253–280.
[7] Unsworth DJ, Mathias JL, Dorstyn DS. Safety and efficacy of cell therapies administered in the acute and subacute stages after stroke: a meta-analysis. Regen Med. 2016;11:725–741.
[8] Unsworth DJ, Mathias JL, Dorstyn DS. Cell therapies administered in the chronic phase after stroke: a meta-analysis examining safety and efficacy. Regen Med. 2017;12:91–108.
[9] Nagpal A, Choy FC, Howell S, et al. Safety and effectiveness of stem cell therapies in early-phase clinical trials in stroke: a systematic review and meta-analysis. Stem Cell Res Ther. 2017;8:13.
[10] Jollkonen J, Kwakkel G. Translational hurdles in stroke recovery studies. Transl Stroke Res. 2016;7:331–342.
[11] Sipp D, Caulfield T, Kaye J, et al. Marketing of unproven stem cell–based interventions: a call to action. Sci Transl Med. 2017;9:1–5.
[12] Srivastava A, Mason C, Wagen E, et al. Part 1: defining unproven cellular therapies. Cytotherapy. 2016;18:117–119.
[13] Mikati T, Griffin K, Lane D, et al. International travel patterns and travel risks for stem cell transplant recipients. J Travel Med. 2015;22:39–47.

[14] Kim YS, Chung DI, Choi H, et al. Fantasies about stem cell therapy in chronic ischemic stroke patients. Stem Cells Dev. 2013;22:31–36.

[15] Petersen A, Seear K, Munsie M. Therapeutic journeys: the hopeful travails of stem cell tourists. Sociol Health Illn. 2014;36:670–685.

[16] Rachul C. "What have I got to lose?" An analysis of stem cell therapy patients’ blogs. Health Law Rev. 2011;20:5–12.

[17] Stucki G. International Classification of Functioning, Disability, and Health (ICF): a promising framework and classification for rehabilitation medicine. Am J Phys Med Rehabil. 2005;84:733–740.

[18] Sheeran P, Maki A, Montanaro E, et al. The impact of changing attitudes, norms, and self-efficacy on health-related intentions and behavior: a meta-analysis. Health Psychol. 2016;35:1178–1188.

[19] Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Processes. 1991;50:179–211.

[20] Seow AN, Choong YO, Moorthy K, et al. Intention to visit Malaysia for medical tourism using the antecedents of Theory of Planned Behaviour: a predictive model. Int J Tourism Res. 2017;19:383–393.

[21] Von Elm E, Altman DG, Egger M, et al. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bmj. 2007;335:806–808.

[22] Nouri FM, Lincoln NB. An extended activities of daily living scale for stroke patients. Clin Rehabil. 1987;1:301–305.

[23] Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. Qual Life Res. 1999;8:209–224.

[24] Duncan PW, Wallace D, Lai SM, et al. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke. 1999;30:2131–2140.

[25] Pound P, Gompertz P, Ebrahim S. Patients’ satisfaction with stroke services. Clin Rehabil. 1994;8:7–17.

[26] Zimet GD, Dahlem NW, Zimet SG, et al. The multidimensional scale of perceived social support. J Pers Assess. 1988;52:30–41.

[27] Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes. 2003;1:29–33.

[28] Sagen U, Vik TG, Moum T, et al. Screening for anxiety and depression after stroke: comparison of the Hospital Anxiety and Depression Scale and the Montgomery and Åsberg Depression Rating Scale. J Psychosom Res. 2009;67:325–332.

[29] Cousineau N, McDowell I, Hotz S, et al. Measuring chronic patients’ feelings of being a burden to their caregivers: development and preliminary validation of a Scale. Med Care. 2003;41:110–118.

[30] Horton NJ, Kleinman KP. Much ado about nothing: a comparison of missing data methods and software to fit incomplete data regression models. Am Stat. 2007;61:79–90.

[31] Eekhout I, de Vet HC, Twisk JW, et al. Missing data in a multi-item instrument were best handled by multiple imputation at the item score level. J Clin Epidemiol. 2014;67:335–342.

[32] Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression. NJ: John Wiley & Sons; 2013.

[33] Steyerberg EW, Harrell FE. Prediction models need appropriate internal, external–external, and external validation. J Clin Epidemiol. 2016;69:245–247.

[34] Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. Int J Epidemiol. 2014;43:962–970.

[35] Zipkin DA, Umscheid CA, Keating NL, et al. Evidence-based risk communication: a systematic review. Ann Intern Med. 2014;161:270–280.

[36] Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165:710–718.

[37] IBM Corp. IBM SPSS Statistics for Windows, Version 24.0. NY, IBM Corp; 2012.

[38] Sarkar SK, Midi H, Rana S. Detection of outliers and influential observations in binary logistic regression: an empirical study. J of Applied Sciences. 2011;11:26–35.

[39] Yu JY, Ko TG. A cross-cultural study of perceptions of medical tourism among Chinese, Japanese and Korean tourists in Korea. Tour Manag. 2012;33:80–88.

[40] Aked J, Delavaran H, Lindvall O, et al. Attitudes to stem cell therapy among ischemic stroke survivors in the Lund Stroke Recovery Study. Stem Cells Dev. 2017;26:566–572.

[41] Petersen A, Munsie M, Tanner C, et al. Stem cell tourism and the political economy of hope. London (UK): Springer; 2017.

[42] McLean AK, Stewart C, Kerridge I. Untested, unproven, and unethical: the promotion and provision of autologous stem cell therapies in Australia. Stem Cell Res Ther. 2015;6:33–41.

[43] Kneebone II. A framework to support cognitive behavior therapy for emotional disorder after stroke. Cogn Behav Pract. 2016;23:99–109.

[44] Sparrow EP, Spaniel J. Age-related changes in decision making. Curr Behav Neurosci Rep. 2016;3:285–292.

[45] Knoepfler PS. Too much carrot and not enough stick in stem cell therapies in Australia. Stem Cell Res Ther. 2015;6:332–332.

[46] Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes. 2003;1:29–33.

[47] Horton NJ, Kleinman KP. Much ado about nothing: a comparison of missing data methods and software to fit incomplete data regression models. Am Stat. 2007;61:79–90.