Subcortical Vascular Dementia: Survey of Treatment Patterns and Research Considerations

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ABSTRACT: *Background:* Since few studies have examined the effectiveness of therapies for subcortical vascular dementia, treatment guidelines are not available. Current patterns in the treatment of such dementias have not been studied. *Objective:* To determine the practice patterns of Canadian specialists for the treatment of subcortical vascular dementia, and to survey their opinions regarding issues which are important in the design of a randomized controlled trial (RCT) in this field. *Design:* National survey of all specialists certified in Neurology or Geriatric Medicine. *Results:* Of responding physicians (78%) prescribed antithrombotic therapy for patients with vascular dementia. Most begin treatment with aspirin 325 mg daily (64%). The next three most common initial treatments were; no pharmacotherapy (12%), aspirin 650 mg daily (11%), and aspirin 1300 mg daily (11%). If the dementia continued to progress despite initial therapy, the treatment options were more varied. Most specialists (69%) believed that an RCT to assess the efficacy of aspirin in vascular dementia is warranted. The majority (69%) also felt that serial neuroimaging would be required for participants in such a trial, with magnetic resonance imaging being cited most frequently (41%). The majority of specialists considered three years as the minimum duration for such a trial. *Conclusions:* Specialist physician practice patterns vary significantly for the treatment of patients with subcortical vascular dementia. Most physicians believe that an RCT testing the efficacy of aspirin in this condition is required. However, before such a trial can be conducted, many methodological difficulties need to be addressed.

RÉSUMÉ: Démence vasculaire sous-corticale: étude des modalités de traitement et considérations sur la recherche. *Introduction:* Comme peu d'études ont examiné l'efficacité des traitements de la démence vasculaire sous-corticale, il n'existe pas de lignes directrices pour le traitement de cette condition. Le traitement courant de ces démences n'a pas été étudié. *Objectifs:* Nous voulons déterminer quel est le traitement prescrit par les spécialistes canadiens dans la démence vasculaire sous-corticale et enquêter sur leurs opinions au sujet d'aspects qui sont importants dans la planification d'une étude contrôlée, randomisée (ECR) dans ce domaine. *Plan de l'étude:* Il s'agit d'une enquête auprès de tous les spécialistes certifiés en neurologie ou en gériatrie. *Résultats:* 78% des répondants prescrivent une thérapie antithrombotique chez les patients atteints d'une démence vasculaire. La plupart (64%) commencent le traitement par de l'aspirine à la dose de 325 mg i.d. Les trois autres traitements initiaux les plus fréquents étaient: aucune médication (12%), de l'aspirine à la dose de 650 mg i.d. (11%) et de l'aspirine à la dose de 1300 mg i.d. (11%). Si la démence continuait à progresser malgré ce traitement, les options de traitement étaient plus variées. La plupart des spécialistes (69%) croyaient qu'une ECR pour évaluer l'efficacité de l'aspirine dans la démence vasculaire est justifiée. La majorité (69%) croyaient également qu'une évaluation des patients participant à une telle étude par imagerie neurologique sériée serait nécessaire. La technique la plus fréquemment (41%) citée était la résonance magnétique. La majorité des spécialistes considérait que la durée minimum d'une telle étude devait être de 3 ans. *Conclusions:* Les modes de traitement des spécialistes varient beaucoup quant au traitement des patients atteints de démence vasculaire sous-corticale. La plupart des médecins croient qu'une ECR évaluant l'efficacité de l'aspirine dans cette maladie est nécessaire. Cependant, avant d'entreprendre une telle étude, plusieurs difficultés méthodologiques doivent être résolues.

Vascular dementia is the leading cause of cognitive impairment in Russia and Japan, and second only to Alzheimer's Disease in the western world.[1] It is reported that 24-48% of dementing illnesses worldwide are vascular in origin.[2] The precise prevalence of vascular dementia is difficult to determine because of the lack of consensus regarding diagnostic criteria.[3-5] Vascular dementia is a syndrome which encompasses three main subtypes; multi-infarct dementia (MID), strategic-infarct

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dementia (SID) and subcortical white matter dementia (SWMD).[6] Essentially, vascular dementia may be secondary to cortical and/or subcortical ischemia. Based on the efficacy of antiplatelet agents in the secondary prevention of stroke, treatment with aspirin or ticlopidine of dementia which includes a component of cortical cerebral ischemia is clearly justified.[7,8]

Unfortunately, the appropriate treatment of dementia which is due to subcortical ischemia (SWMD or MID solely due to lacunar infarcts) is much less clear. In this condition, the use of antithrombotic therapy (aspirin or ticlopidine) is based on three levels of supporting evidence; 1) extrapolation of the results of studies of antiplatelet therapies for the secondary prevention of strokes (most of which were cortical), 2) the subgroup analyses performed in two of these trials, and 3) studies performed by Meyer and colleagues.

Prior meta-analyses of platelet inhibitors for patients with vascular disease (a group including patients with transient ischemic attacks (TIA), strokes, angina and myocardial infarction) have demonstrated significant benefits of platelet inhibitors (including aspirin) in the prevention of strokes.[7,8] However, in an analysis including only patients with TIA or minor stroke of non-cardiac origin, the benefit of aspirin was more modest.[9] Extrapolation of these results to the treatment of subcortical ischemia is controversial. Only two trials provide evidence regarding patients presenting with lacunar infarcts but without cortical strokes. The AICLA trial[10] randomized 604 patients (of which 98 had probable lacunar stroke) to aspirin, aspirin plus dipyridamole, or placebo. For patients with lacunar stroke only, the annual incidence of recurrent stroke was 3% in the aspirin group compared with 9% in the placebo group. The CATS trial[11] randomized 1072 patients (of which 270 patients had lacunar stroke) to ticlopidine or placebo. Subgroup analysis suggested similar significant benefits for patients with lacunar stroke as those with cortical stroke. However, as neither trial was specifically designed to assess the efficacy of antiplatelet agents in patients with lacunar infarcts, their results must be considered promising exploratory data analyses.

Meyer et al.[12] performed a non-randomized, unblinded interventional study of 52 patients with multi-infarct dementia. Co-intervention was a problem in this study as many of the patients received carotid revascularization, improved control of their hypertension, and/or counseling for smoking cessation. These patients were compared with 15 age-matched normal controls and 15 age-matched controls with Alzheimer's disease. There was a non-statistically significant trend for patients taking aspirin to have improved cognitive scores. Meyer and colleagues[13] later performed the only randomized clinical trial testing a pharmacologic treatment for vascular dementia. Compared with control subjects, patients who received 325 mg of aspirin daily showed statistically significant improvements in cognitive scores. Finally, in 1995 Meyer et al.[14] compared the effect of multiple simultaneous interventions (blood pressure control, diabetic control, treatment for hyperlipidemia, smoking cessation, and aspirin or ticlopidine) in 22 patients with ischemic vascular dementia with 22 age-matched normal control subjects. Sixty-four percent (64%) of the patients with ischemic vascular dementia had improvement in their cognitive scores. Unfortunately, results for the control group were not reported. None of the three studies by Meyers were blinded, raising concerns of observer bias. Due to this and other design limitations (low

numbers of patients, multiple co-interventions, lack of control groups of patients with vascular dementia) these trials do not unequivocally prove that aspirin is efficacious in the treatment of subcortical vascular dementia.

The goals of our study were to: 1) determine the treatment stategies for subcortical vascular dementia currently employed by Canadian neurologists and geriatricians; 2) determine the perceived need for (and receptiveness to) a randomized controlled trial (RCT) in this area; and 3) survey opinion on key methodologic features which would be required for such a trial.

METHODS

A list of all geriatricians (N = 111) and neurologists (N = 476) certified by the Royal College of Physicians and Surgeons of Canada was obtained. These physicians were mailed a survey that included questions regarding their present treatment for subcortical vascular dementia, perceived need for an RCT in this area, and design features of such a trial. The survey took approximately five minutes to complete. The package was mailed in a University of Ottawa envelope and included a cover letter on university letterhead, a stamped self-addressed return envelope, and the questionnaire.

The survey was conducted from April to July 1997. Persons who did not respond were mailed a second and if necessary, a third copy of the survey. Mailings were separated by a 4 to 6 week response period. Survey design, mailout and data extraction were performed at the Division of Geriatric Medicine, Ottawa Civic Hospital. To preserve the confidentiality of the responding physicians, all surveys were identified by code numbers only.

Data analysis involved frequency analysis of responses using SPSS software.

RESULTS

Of the 587 physicians to whom a survey was mailed 362 (62%) responded. Of respondents, only the 281 physicians (78%) with clinical and/or research activities including patients with dementia completed the survey.

Present Treatment Patterns

Physician responses indicating their most common initial antithrombotic therapy for patients with subcortical vascular dementia are shown in Table 1. All treatment options they would consider for patients who continue to progress despite their initial therapy are also shown (Table 2). Only 2% indicated

Table 1: Initial antithrombotic therapy for patients with subcortical vascular dementia.

Management	Geriatricians (N = 80)	Neurologists (N = 201)	Both (N = 281)
1. No Antithrombotic Therapy	14%	11%	12%
2. Aspirin 80 mg/day	0%	1%	1%
3. Aspirin 325 mg/day	77%	58%	64%
4. Aspirin 650 mg/day	4%	14%	11%
5. Aspirin 1300 mg/day	4%	13%	11%
6. Ticlopidine	1%	1%	1%
7. Warfarin	0%	0%	0%

Table 2: All antithrombotic treatment options which physicians would consider employing (either initially or as the vascular dementia progressed). Each clinician could select more than one option.

Management	Geriatricians (N = 80)	Neurologists (N = 201)	Both (N = 281)
1. No Antithrombotic Therapy			
at any time	1%	3%	2%
2. Aspirin (any dose)	96%	96%	96%
80 mg/day (maximum)	0%	0%	0%
325 mg/day (maximum)	35%	24%	27%
650 mg/day (maximum)	18%	23%	22%
1300 mg/day (maximum)	42%	48%	46%
> 1300 mg/day (maximum)	1%	0%	0%
3. Ticlopidine	58%	65%	63%
4. Warfarin	33%	20%	24%

that they would not employ antithrombotic therapy at any time (i.e., initially or as the dementia progressed). However, 33% of respondents indicated that they would consider stopping all antithrombotic therapy if patient symptoms progressed despite their initial therapy.

Design features of a randomized controlled trial of aspirin in subcortical vascular dementia

Sixty-nine percent of respondents believed that a placebo-controlled RCT to assess the efficacy of aspirin for patients with subcortical vascular dementia is required. Less than one-third (31%) felt that such a trial is not appropriate citing reasons including; 1) it is unethical, 2) aspirin has already been proven to be effective, 3) the efficacy of aspirin is clinically insignificant, and 4) at the time of diagnosis, the disease is usually too advanced for aspirin to be effective.

Of physicians who believed that an RCT is appropriate, 94% felt that neuroradiological evidence of subcortical vascular lesions is an important requirement for inclusion into the study. Forty-seven percent (47%) indicated that computerized assisted tomography (CT) should be performed, while 39% and 8% indicated magnetic resonance imaging (MRI) and single photon emission computerized tomography (SPECT) respectively were more appropriate. Most respondents (69%) believed that patients enrolled in an RCT should be followed with serial neuroimaging. Of those who felt serial neuroimaging was required, 41% indicated a preference for MRI and 21% indicated CT.

With respect to an RCT, physician responses regarding preferences for diagnostic inclusion criteria are shown in Table 3. There was little agreement on the appropriate set of diagnostic criteria necessary for inclusion of patients into an RCT. There were also mixed responses from physicians when asked to select the single primary outcome for such a trial (Table 4). When asked to select which specific cognitive rating scale should be used, their responses were also varied (Table 5). All other cognitive rating scales (e.g., Mattis[15]) were selected by less than 2% of respondents.

Physician responses regarding the minimum acceptable trial length are shown in Table 6. It was assumed that persons indicating a certain duration would also consider a trial of longer duration acceptable. For instance, those who selected a one-year duration were also included in the two, three, four, and five year calculations.

Table 3: Diagnostic criteria for entry into a randomized controlled trial of aspirin in vascular dementia (physicians could select more than one option).

1. Hachinski Ischemic Score[26]	45%
2. DSM Criteria[27]	35%
3. NINDS-AIREN[28]	7%
4. ADDTC criteria[29]	1%

DSM = Diagnostic and Statistical Manual
NINDS-AIREN = National Institute for Neurological Disorders and Stroke - Association Internationale pour la Recherche et L'Enseignement en Neurosciences
ADDTC = (State of California) Alzheimer's Disease Diagnostic and Treatment Centres.

Table 4: Primary outcome of a randomized controlled trial assessing the efficacy of aspirin for the treatment of vascular dementia (respondents instructed to only select a single option - some selected more than 1 option accounting for the > 100% response).

1. Cognitive Status	52%
2. Functional Status	22%
3. Rate of New Strokes	16%
4. Clinician's Global Impression	12%
5. Caregiver's Global Impression	7%
6. Rate of Institutional Placement	4%
7. Mortality Rate	2%
8. Behavioural Rating	1%

Table 5: Cognitive scale to be employed in a randomized controlled trial.

1. Folstein MMSE[22]	54%
2. 3MS[23]	23%
3. ADAS[25]	15%

MMSE = Mini-mental State Examination
3MS = Modified Mini-mental State
ADAS = Alzheimer's Disease Assessment Scale.

Table 6: Duration of a randomized controlled trial which respondents would find acceptable.

1 year	27%
2 years	67%
3 years	84%
4 years	85%
5 years	98%

DISCUSSION

We surveyed all Canadian Royal College certified neurologists and geriatricians regarding their views on the treatment of patients with subcortical vascular dementia. Of the 372 who responded, 281 (78%) see patients with this condition during their clinical and/or research activities. Most (87%) consider aspirin the initial pharmacotherapy of choice, with only 12% believing that no pharmacotherapy should be prescribed initially. However, there is significant variation in the specific dose of aspirin that these physicians prescribe initially. For patients whose disease progresses despite initial therapy, many physicians would consider other therapies including ticlopidine and

warfarin. This level of treatment variation indicates the need for an RCT assessing the efficacy of aspirin in this condition. However, only 69% of respondents would support such a trial. Interestingly, of those who felt that an RCT is inappropriate, opinion was divided between those who felt that the efficacy of aspirin is proven, and those who felt that aspirin is ineffective. Furthermore, the widespread use of aspirin in the treatment of patients with vascular dementia also makes the feasibility of a placebo-controlled RCT unclear.

Given that there appears to be a relationship between vascular risk factors and Alzheimer's disease,[16] it may be justified to conduct a trial of acetylcholinesterase inhibition in patients with subcortical vascular dementia. A future trial might therefore compare aspirin, an acetylcholinesterase inhibitor, and/or a combination of both. If acetylcholinesterase inhibitors and other treatments (e.g., propentofylline, a xanthine derivative shown in preliminary trials to stabilize the cognition in both Alzheimer's Disease and vascular dementia patients[17]) are shown to be effective in this condition, the window of opportunity for a placebo-controlled trial of aspirin will disappear.

Many of the other questions posed in the survey will remain applicable to future vascular dementia studies. The responses indicating the most appropriate diagnostic criteria for an RCT (Table 3) revealed little agreement. This lack of agreement regarding appropriate criteria for subcortical vascular dementia is well known[2-6,18,19] and remains a significant barrier to research in this field. The optimal diagnostic criteria for vascular dementia will remain controversial until confirmatory clinical - neuropathological correlate studies are performed.

Almost all specialists believe that neuroimaging is required for entry into an RCT, with CT scanning being the most frequently cited choice. The majority also felt that serial neuroimaging for patients in the trial is required, and that MRI is the scan of choice. In order to permit comparable information on follow-up scanning, it can be argued that the diagnostic and serial neuroimaging modality should be the same. However, since some doubt exists regarding the merits of MRI compared with CT in detecting significant strokes (i.e., those that contribute to cognitive impairment), future trials need to compare CT and MRI. Ideally these studies would be performed after the optimal diagnostic criteria have been determined.

There was important disagreement regarding the most appropriate primary outcome measure and cognitive scale for such a trial. There was no single selection for either which would satisfy much more than half of the respondents. In keeping with the recommendations of the Consortium of Canadian Centres for Clinical Cognitive Research (C5R),[20] dementia research must employ outcomes from multiple domains (cognitive, functional, behavioural and global clinical impression). In order to avoid the array of outcome scales encountered in studies examining the efficacy of Tacrine for patients with Alzheimer's Disease, groups such as the C5R must continue to work towards achieving consensus on the most appropriate outcome measures within each domain. Only once this is accomplished can there be progression with other important research questions including establishment of the minimal clinically important difference of these scales.

The results of this survey indicate that the rate of new strokes as determined by serial neuroimaging is another outcome that should be considered in vascular dementia studies. While most respondents indicated MRI or CT scanning as the most appropriate diagnostic test to assess this, some (8%) mentioned SPECT scanning. Considering that the ability of SPECT scanning to differentiate vascular causes of dementia from Alzheimer's Disease is poor,[21] its value for serially following patients with subcortical vascular dementia is unclear.

Most respondents (54%) indicated that the Mini-mental State Examination[22] (MMSE) was the most appropriate scale to serially measure the cognitive function of patients enrolled in an RCT. However, the sensitivity of the MMSE to measure changes in cognitive function over time in patients with vascular dementia is questionable. The Modified Mini-mental State Examination[23] (3MS) may be more sensitive than the MMSE to detect this change.[24] Other cognitive scales (e.g., Alzheimer's Disease Assessment Scale[25]) used in clinical trials of patients with Alzheimer's Disease have not been validated for patients with vascular dementia. Determination of the most appropriate scale to measure cognitive function in an RCT for patients with vascular dementia awaits further research.

A majority of respondents believed that an RCT should be of at least three years duration. A trial of five years duration would be acceptable to almost all physicians. Unfortunately, the median survival of patients with vascular dementia is 5.2 years.[2] If other reasons for patient dropout or cross-over (e.g., patients developing conditions for which aspirin is indicated) are considered, a five year trial appears unfeasible. Determination of the appropriate length of a trial is also complicated by unknown factors such as the natural progression of subcortical vascular dementia, and the time period necessary for outcome measures to be able to detect change.

A limitation of our study is that we did not gather information regarding the diagnostic criteria for vascular dementia used by respondents to select patients for treatment in their daily clinical practice. These criteria may be significantly different from those clinicians believe are appropriate for an RCT. Ideally, in order to enhance the generalizability of the results of a future RCT, its designers should consider surveying clinicians for this information.

In summary, present evidence to support the routine use of aspirin in the treatment of subcortical vascular dementia is lacking, and thus clinical uncertainty about appropriate treatment of this condition exists. While most respondents felt that a placebo-controlled RCT is warranted, use of a placebo will become increasingly difficult to justify. Regarding the conduct of such a trial, several points can be made. There is little or no agreement on appropriate diagnostic criteria for study entry. This problem will not be resolved until neuropathological validation studies are performed. Neuroimaging at trial entry and in follow-up appear to be necessary. MRI is the scanning modality which most specialists find acceptable. A trial duration of three years appears to be optimal. This will balance physician satisfaction with the significant dropout rate that can be anticipated. Finally, there is no agreement on primary outcome measures or the cognitive scale to employ in such a trial. The approach of studying multiple domains appears to address this. Nevertheless, consensus on the appropriate measurement scale to use within each domain must be achieved before an RCT can be initiated.

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