

Publicly-funded clinical trials on endovascular treatment of multiple sclerosis? The views of a citizens' council

EXECUTIVE SUMMARY

Background: There is controversy in Canada about treating multiple sclerosis with venoplasty, the so-called 'liberation procedure.' In August 2010, an expert panel sponsored by the Canadian Institutes of Health Research and the MS Society of Canada recommended against conducting clinical trials on this procedure because of insufficient evidence that MS is associated with venous abnormalities. Because of the continuing public debate, we elicited the views of informed members of the public on this issue.

Methods: In November 2010, nineteen members of the *Toronto Health Policy Citizens' Council (THPCC)* deliberated about whether there should be immediate, publicly-funded clinical trials of venoplasty as a treatment for multiple sclerosis. During a two-day session, council members heard from and questioned experts with different perspectives about whether a clinical trial should proceed. Through small group discussions and deliberations of the full council, members developed recommendations.

Results: Most citizens believed there should be an option for MS patients to access endovascular treatment in Canada. A majority (14/19, 74%) felt that a clinical trial should start immediately as long as the frequency of serious side-effects is low, and that the trial should stop if ongoing observational studies show there is no connection between MS and venous abnormalities. Of the group that supported an immediate clinical trial, most (12/14, 86%) thought the trial ought to be publicly funded. All council members felt that follow-up care should be provided for patients who had the procedure performed outside of the country.

Interpretation: The citizens' council's deliberations suggest that while members of the public have different views about endovascular treatment of MS, a majority of informed citizens believe a trial should start now. The controversy about endovascular therapy for MS also raises important questions about the role of public engagement in setting medical research priorities.

INTRODUCTION

In 2006, Dr. Paolo Zamboni, an Italian vascular surgeon, hypothesized that multiple sclerosis (MS) is caused by abnormalities in the cerebrospinal venous system, a condition he called chronic cerebrospinal venous insufficiency (CCSVI).¹ He proposed that the symptoms of MS can be improved by venoplasty to unblock the affected veins.² Dr. Zamboni's hypothesis, and the quality of the evidence supporting it, has been criticized by the majority of those involved in MS clinical care and research.³ Despite this, endovascular treatment of MS is available in many countries, but not in Canada. Access to the procedure is a subject of vigorous public debate in Canada, with extensive coverage in the media and advocacy from patients with MS.⁴

In August 2010, the Canadian Institutes of Health Research (CIHR), in collaboration with the MS Society of Canada, convened a panel of invited experts to identify research priorities for MS, with a particular focus on vascular treatments for the disease. The panel recommended that no interventional clinical trials studying the use of venoplasty as a treatment for MS should be funded until it has more clearly been shown that there is an association between CCSVI and MS.⁵ Both the MS Society of Canada and the National MS Society in the United States announced funding in June 2010 for seven research projects investigating this association.⁶ The MS Society of Canada also set aside \$1 million to fund a future clinical trial, if one is warranted.

Expert opinions about the likely benefits and risks of endovascular therapy are clearly important when deciding whether to expose MS patients to the risk of an interventional clinical trial, but the level of patient and public interest about endovascular therapy suggests that informed and deliberative public engagement on the topic is warranted. Therefore, in November 2010, we devoted a session of the Toronto Health Policy Citizens' Council (THPCC)⁷ to the question of whether public funds should be used to support a clinical trial to evaluate endovascular treatment for MS.

METHODS

The purpose of THPCC is to have citizens who do not have vested interests deliberate about important, value-sensitive health care issues. The THPCC has twenty-four members who were randomly selected by an independent third-party to reflect the diverse age, gender, cultural and socio-economic backgrounds of Torontonians. For the session on endovascular treatment of MS, only 19 members were able to attend. None of the council members are MS patients, their caregivers, nor employed in health-related occupations.

On November 13-14, 2010, the THPCC deliberated about the following question: Should Canadian governments now fund clinical trials of the liberation procedure for multiple sclerosis?

The session began with four presentations. First, a member of the research team (AL) gave a general overview of how the efficacy of new medical treatments and diagnostic tests is usually determined. The next three presentations focused specifically on endovascular treatment of MS. In order to allow council members the opportunity to hear a range of perspectives on the topic, we invited the MS Society of Canada and the Reformed MS Society of Canada⁸ (which actively advocates for expanded access to venoplasty) to each identify one expert to present their views about the issue.

Mr. John Temme, who at the time was the Senior Vice President of Research and Programs for the MS Society of Canada, spoke first. He briefly reviewed the nature of MS, explained that studies had not yet conclusively shown that people with MS have a higher frequency of venous abnormalities than those without MS, and that it can be difficult to determine the impact of a new therapy for MS, given the relapsing and remitting nature of some forms of the disease. He also stated that the MS Society would move quickly to support an interventional clinical trial, but only if an association between CCSVI and MS is established. He indicated that the MS Society was the first funding agency in the world to call for CCSVI-specific research proposals, and in June 2010 had announced funding for seven research studies to determine whether there is an association between CCSVI and MS.⁹

The Reformed MS Society brought two, rather than one, representative to the council meeting. Dr. Sandy McDonald, a vascular surgeon from Barrie, Ontario, spoke in support of endovascular therapy for MS, provided an overview of the procedure, described some patients who had very positive outcomes, and indicated that the procedure could be performed in Canada at a much lower price than patients were paying abroad. Mr. Steven Simonyi-Gindele, founder and president of the Reformed Multiple Sclerosis Society of Canada then told the council that between 3,000 and 4,000 people have had the procedure performed worldwide, with a significant number showing improvement, a few having no improvement, and an even smaller number suffering adverse effects. He also shared a personal story about a close family member who had undergone the procedure with positive results.

The citizens' questions focused on the cost of the procedure, the risk of adverse events, the ultrasound technique used, how long the effects of the procedure last, and current issues concerning access in Canada. The council asked why the MS Society had not brought a physician to speak in support of its position. In order to be fair to both sides of the issue, the research team, at the request of the council, arranged for a teleconference the following morning with Dr. Paul O'Connor, a neurologist from Toronto, Ontario, who treats MS patients and conducts MS research. Dr. O'Connor described how 26 of his patients had undergone the procedure, with none showing benefit on neurological examination, although a number had reported an improvement in fatigue. He also listed other reasons he was skeptical about the benefits of the liberation therapy, which included his belief that it is biologically unlikely that MS is related to vascular problems, Zamboni's studies were of poor scientific quality, other researchers had not been able to replicate Zamboni's results, and MS is a disease for which many unusual cures have been proposed in the past which have turned out to be ineffective.

After the expert presentations, the council members were randomly divided into three small groups to discuss the question presented to them. They were asked to respectfully discuss and debate their views, but there was no attempt to force consensus. Each group was moderated by a member of the research team. At the end of the second day, the entire council met to hear the results of the deliberations of the three small groups, to further debate the issues and develop recommendations. The process is outlined in Table 1. All of the citizens' deliberations were recorded, transcribed and analyzed by two members of the research team (KB, RC). A draft of the findings was sent to all of the council members to verify that they accurately reflected the deliberations and final recommendations of the council.

Table 1. Citizens' Council Process
<p>Day 1 (6 hours)</p> <ol style="list-style-type: none"> 1. Introduction to the topic 2. Presentation by Research Team Member (AL) 3. Presentation by Representative of the MS Society of Canada 4. Presentation by Representative of the Reformed MS Society of Canada 5. Presentation by a vascular surgeon invited by the Reformed MS Society of Canada 6. Question and answer between experts and council members 7. Small group discussion (three groups) <p>Day 2 (4.5 hours)</p> <ol style="list-style-type: none"> 8. Small group discussion (continued) 9. Teleconference with neurologist 10. Full group discussion 11. Recommendations drafted

RESULTS

The THPCC process allows council members to explore issues related to, but slightly different from, the question posed to them, if the citizens think these issues are important. The small group discussions focused on three main questions: 1) whether endovascular treatment for MS should be made available in Canada; 2) whether a clinical trial should start immediately or wait until the studies funded by the Canadian and American MS societies are complete; and 3) whether clinical trials should be supported by public funds.

Access to endovascular treatment and follow-up care in Canada

All of the citizens were sympathetic to the plight of MS patients. Given the dramatic reports of improvement after endovascular treatment, most understood why some patients had traveled abroad for the procedure at considerable personal expense. The council felt that having the procedure overseas likely posed more risks to patients than having the procedure in Canada, and that valuable information about the outcomes could be better captured if the procedure is performed in Canada. Although some severe adverse events after endovascular therapy had occurred, all of the individuals who presented to the council expressed the view that severe adverse events appeared to be fairly uncommon. Based on these considerations, the vast majority of the council felt that there should be options to access the procedure in Canada. The council felt the procedure should be performed in private clinics because it is still experimental, and the current level of evidence for it is such that it should not divert funds from other parts of the public health care system.

One of the council members had seen a news report about patients complaining that they were denied care for complications resulting from endovascular treatment when they returned to Canada. Some citizens were concerned that lack of expertise with this procedure could be a reason some clinicians appeared unwilling to provide after-care in Canada. The citizens were not sure how accurate these stories were, but felt that Canadian health care providers must provide care to patients who require follow-up care after undergoing endovascular care outside of Canada.

An immediate trial of endovascular treatment?

There were numerous points of disagreement among the citizens about whether a clinical trial should start immediately. The first related to whether a trial of endovascular therapy should be delayed until the association between CCSVI and MS is more definitively established. The representative from the MS Society had stated that the results of the seven studies supported by the Canadian and US MS Societies would likely be available within 18 months. Some citizens felt that waiting for the results of those studies was sensible, as long as the results were available in that time frame. As one citizen said, “after two years... hopefully you’ll be in a position to decide whether or not a clinical trial is warranted, but if it’s going to take ten years I wouldn’t support that. I would say we need to start something sooner than that.” The citizens also debated the possible impact of the results of the current observational studies, when they become available. One citizen asked, “What is the probability that in two years, with the studies that are presently going on, we would be able to have enough of a consensus about a standard that we would be able to do a clinical trial?”

The issue of fairness was raised by council members both for and against an immediate trial. Supporters of immediate clinical trials said it was unfair to make MS patients suffer while they wait for the ongoing observational studies to conclude. Other citizens

countered that patients are not suffering by denying them a procedure that has not yet been established to improve outcomes. They felt that it would be unfair to direct research funding to the evaluation of this new procedure largely on the basis of extensive advocacy and media attention. If limited public funds for research are used to study treatments that have a more established biological rationale, there would be a better likelihood of success, and more patients would likely benefit.

The citizens also gave different weight to the reports of patients who had the procedure performed. Supporters of immediate clinical trials were more likely to accept these first-hand accounts as evidence that the procedure was effective. Those opposed to immediate clinical trials were more likely to see these reports as anecdotal and not convincing evidence of effectiveness.

In the end, the citizens did not come to consensus about whether a therapeutic clinical trial should start immediately. Five council members felt that a trial should start immediately, with no conditions. Two council members felt that a trial should be started immediately but should be stopped if the ongoing studies funded by the North American MS societies find no correlation between CCSVI and MS. Seven other council members supported immediate clinical trials, but only if the procedure is shown to be of small risk to patients. Thus, 14 of the 19 (74 %) council members supported immediate clinical trials under some conditions. The remaining five council members felt that a decision about the need for a therapeutic trial should await the conclusion of the studies already under way to determine the association between CCSVI and MS.

If an immediate trial is done, who should pay for it?

Of the citizens' who supported an immediate clinical trial, 12/14 (86%) felt that it should be publicly funded. The remaining two citizens felt that because the evidence for the association between MS and CCSVI was still weak, public funds should not be diverted from other research projects to support the trial, and that private funds should be used instead. The citizens did not explore how this private funding option would be structured.

Schisms within the MS community

The council members were surprised and concerned by the deep schisms that appear to have arisen within the Canadian MS community (patients, physicians, the MS Society, CCSVI advocacy groups and others) over endovascular treatment. Having previously deliberated about nine potentially contentious issues, the citizens remarked that none of groups involved in the previous sessions had exhibited the same level of discord. For example, the Reformed MS Society was formed because of its strong opposition to the MS Society on this issue, which was evident during the expert presentations. The council members recommended that the two sides need to attempt to find common ground and remember that they have shared interests in the well-being of MS patients, regardless of their disagreement over CCSVI. One area the citizens thought the two groups could work on is to develop a shared framework for evaluating endovascular procedure going

forward. Even if they disagree about the timing of a clinical trial to prove or disprove the effectiveness of endovascular treatment as a treatment for MS, perhaps they could work together and agree on the design of such a study.

DISCUSSION

The debate about endovascular treatment of MS is noteworthy for a number of reasons. The coverage of this issue by Canadian conventional and social media has been exceptionally intense⁴, as has the amount of attention from politicians.⁹ The demand for access to endovascular treatment from many patients has been in marked contrast to the more cautious and skeptical views of MS clinicians and researchers, creating an unusual degree of tension between patients and physicians. The August 2010 recommendations of a scientific expert panel against an immediate clinical trial were greeted with responses ranging from support for its scientifically-based approach, to criticism for ignoring the wishes of patients. Canadian governments have responded differently to the expert panel's recommendation, with the Ontario government indicating that it will follow the recommendations against an immediate trial of endovascular treatment, Newfoundland having established a registry for patients who have had the procedure performed outside of the country, and the governments of Saskatchewan and Manitoba issuing requests for proposals for randomized trials. Finally, there has been a split among MS patients and their supporters, with some forming new organizations because they do not feel that the MS Society of Canada is advocating aggressively enough for access to CCSVI in Canada.

Deliberative citizens' councils are an effective means of obtaining informed public input on complex, ethics laden health policy issues, such as the controversy about CCSVI and MS.¹⁰ After two-days of deliberation, the members of the THPCC were divided about whether there should be immediate publicly-funded clinical trials, and when such trials should begin. One area of agreement was that almost all of the citizens thought MS patients should be able to access an endovascular procedure in Canada, although most felt the procedure should be paid for privately. The citizens seemed to be willing to accept a lower level of evidence to decide that a procedure should be available to patients if they pay for it themselves, than when committing public funds. The belief that strong evidence needs to be available before a new medical procedure should be publicly funded is consistent with the results of the council's previous deliberations about the introduction of positron emission tomography (PET) in Ontario.¹¹

This study has limitations. The council's membership was composed of a relatively small number of citizens from the Toronto area. There was not sufficient time to fully explore the practicality and legality of some of the citizens' recommendations, such as a privately funded access to endovascular treatment in Canada or a privately funded clinical trial. The council also did not fully explore the implications on funding of other unconventional medical treatments if access to endovascular treatment for MS was permitted. Nonetheless, the THPCC's deliberations provide important insights into citizens' considered views about the intersection between the wishes of scientists to proceed in an evidence-based fashion, the desire of clinicians to protect patients from what they perceive as a risky and unproven therapy, the wishes of patients to have access

to what they perceive as a promising new treatment, and the desire of governments to manage the costs of healthcare while at the same time responding to the wishes of the public.

In June 2011, six months after our citizens' council's meeting, the CIHR expert panel released "highlights" from its second meeting during which it considered the results of an unpublished systematic review of studies that have evaluated the association between CCSVI and MS, and updates on the progress of the seven on-going North American studies funded by the Canadian and American MS societies that are studying the same issue.¹² The panel recommended that the CIHR should fund a "phase I/II interventional trial", but did not indicate what had caused it to change its recommendation regarding the indications for a trial. We believe that the citizens' council's deliberations about research funding and provision of clinical services regarding a controversial therapy continue to be relevant, even though the CIHR panel changed its views after the citizens' council met.

This council session also raises questions about the role of the public in setting medical research priorities. This is an important issue for the research community to address, because in the era of social media and patient advocacy we suspect there will be similar controversies in the future, and greater demands from patients and the public to be part of that discussion. There are numerous questions which still need to be answered. For example, should experts and the public work together on the same panel or separately? New models for engaging the public in setting research priorities are being developed. For example, the UK James Lind Alliance brings patients and clinicians together to identify questions that they feel have not received adequate attention from industry or academia.¹³ Much more work still needs to be done. Controversies like the one regarding endovascular treatment of MS do not only call for informed public input, but also offer excellent opportunities for testing various approaches to involving the public.

Declarations of conflict of interest:

Dr. Laupacis is a Data Safety Monitoring Board member for studies of two drugs for patients with multiple sclerosis, funded by Novartis Pharmaceuticals. He is also the principal investigator of the systematic review of published studies evaluating the association of CCSVI with multiple sclerosis, funded by the Canadian Institutes of Health Research, the results of which were presented to the CIHR expert panel at its June 2011 meeting.

Acknowledgements:

We would like to thank Dr. Arthur S. Slutsky, from St Michael's Hospital, Toronto, and King Saud University, Riyadh, Saudi Arabia, for his comments on a previous draft of this report.

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