Impact of vitamin C on the reduction of opioid consumption after an emergency department visit for acute musculoskeletal pain: a double-blind randomised control trial protocol

Raoul Daoust,1,2,3 Jean Paquet,2 Jean-Marc Chauny,1,2 David Williamson,4,3,4 Vérlilbe Huard,1,2,3 Caroline Arbour,5,3 Marcel Emond,6 Dominique Rouleau,3 Alexis Cournoyer1,2

ABSTRACT

Introduction Recent evidence has shown that vitamin C has some analgesic properties in addition to its antioxidant effect and can, therefore, reduce opioid use during recovery time. Vitamin C analgesic effect has been explored mostly during short-term postoperative context or in disease-specific chronic pain prevention, but never after acute musculoskeletal injuries, which are often seen in the emergency department (ED). The protocol’s primary aim is to compare the total morphine 5 mg pills consumed during a 2-week follow-up between patients receiving vitamin C or a placebo after ED discharge for an acute musculoskeletal pain complaint.

Methods and analysis We will conduct a two-centre double-blind randomised placebo-controlled trial with 464 participants distributed in two arms, one group receiving 1000 mg of vitamin C two times a day for 14 days and another one receiving a placebo. Participants will be ≥18 years of age, treated in ED for acute musculoskeletal pain present for less than 2 weeks and discharged with an opioid prescription for home pain management. Total morphine 5 mg pills consumed during the 2-week follow-up will be assessed via an electronic (or paper) diary. In addition, patients will report their daily pain intensity, pain relief, side effects and other types of pain medication or other non-pharmacological approach used. Three months after the injury, participants will also be contacted to evaluate chronic pain development. We hypothesised that vitamin C, compared with a placebo, will reduce opioid consumption during a 14-day follow-up for ED discharged patients treated for acute musculoskeletal pain.

Ethics and dissemination This study has received approval from the Ethics Review Committee from the ‘Comité d’éthique de la recherche du CIUSSS du Nord-de-l’île-de-Montréal (No 2023−2442)’. Findings will be disseminated through scientific conferences and peer-reviewed journal publication. The data sets generated during the study will be available from the corresponding author on reasonable request.

Trial registration number NCT05555576 ClinicalTrials. Gov PRS.

INTRODUCTION

Opioids remain an important part of the treatment for moderate to severe acute pain in the emergency department (ED) and are frequently prescribed for home pain management after ED discharge.1 2 However, even short-term opioids’ use after an ED visit can cause undesirable side effects like constipation, nausea/vomiting, drowsiness, weakness and can also produce more severe adverse events like respiratory depression.4 It can also lead to long-term use,6 opioid use disorders,7 overdose and death.8 9 Furthermore, larger quantity of opioid consumed is associated with a higher prevalence of opioid-related adverse events.10 Therefore, reducing opioid consumption for acute pain without compromising the patients’ home pain management is a constant challenge for clinicians.11

Currently, the main strategy employed to reduce opioid consumption is to limit the
rate and/or the quantity of opioids prescribed for acute pain.12-15 The efficacy of this approach to reduce the quantity of opioid prescribed remains low and studies rarely report patient-centred outcomes such as pain relief or patients’ satisfaction.16 Yet, using adjunct analgesia was associated with less pain and opioid use.17 Non-steroid anti-inflammatory drugs (NSAIDs) are frequently suggested as adjuvants to reduce opioid consumption but are known to contribute to gastrointestinal, cardiovascular, musculoskeletal (MSK) and renal adverse effects.18 19 Recent evidence showed that vitamin C (ascorbic acid) has analgesic properties by adding, through an unknown mechanism, an antinociceptive action to its antioxidant effect.20-22 One potential mechanism is to reduce free radicals’ production, which helps protect tissues (including nerves) from irreversible damage.23 24 The advantages of using vitamin C as adjuvant to opioids in acute pain management remain its low toxicity and low side effects, also in addition to performing well in different types of pain disorders.25

Two meta-analysis reported the effects of vitamin C for immediate postoperative pain. One found a moderate-level evidence supporting the use of a 2g oral preoperative dose of vitamin C as an adjunct for reducing postoperative morphine consumption.26 The other showed significant reductions in pain scores and opioid requirements up to 24hours postoperative, suggesting the effectiveness of perioperative (on the day of the surgery or up to 30min after the surgery’s beginning) vitamin C use.27 One study using 500mg intravenously two times a day up to the third day after surgery also demonstrated less pain intensity and opioid consumption with vitamin C.28 Taking 200mg orally of vitamin C three times a day, for 10 days after tooth extraction, was associated with reduced postoperative pain. However, this small study did not find any difference between 600mg and 1500mg per day of vitamin C.29 The only study performed in a non-postoperative acute pain context showed that intravenous administration of vitamin C was effective in reducing the incidence of post-herpetic neuralgia.30

The efficacy of vitamin C to prevent specific types of chronic pain, notably in complex regional pain syndromes (CRPS), has been reported in a meta-analysis.31 Using a daily regimen of at least 500mg of oral vitamin C initiated immediately after extremity surgery or injury and continued for 45 to 50 days, all studies showed a significant decrease of CRPS incidence up to 90 days after the event. Two other meta-analyses showed that daily supplementation with 500mg of vitamin C for 50 days decreased the 1-year risk of CRPS after wrist fracture or limb extremity fractures.32 33 Taking 1g per day of vitamin C for 40 days after a total knee arthroplasty also reduces CRPS risk.34 Yet, a literature synthesis on the effect of vitamin C on CRPS after distal radius fracture found a decrease in efficacy in recent studies.35

Study rationale
The literature suggests that administration of vitamin C has an effect in reducing pain and opioid consumption in the context of immediate postoperative acute pain (24 to 72hours), which is similar to pain caused by trauma seen in ED. However, we could not find evidence on the effectiveness of vitamin C administration after an ED visit in the context of acute pain, notably in trauma injuries like fractures, bruises, sprains, strains, etc. Therefore, we propose to evaluate the efficacy of a 14-day regimen of vitamin C given to ED patients discharged with an opioid prescription for acute MSK pain on total opioid consumption after 2weeks. The 2-week period was chosen because it defines the usual acute pain timeframe,36 during which the need for analgesics including opioids is essentially resolved in most patients (88% of our previous study cohort).37 Since vitamin C is also associated with less postherpetic neuralgia and CRPS, we also propose to evaluate its impact on the incidence of chronic pain and CRPS at 3 months.

Study objectives
The primary aim of this protocol is to evaluate the effectiveness of vitamin C, compared with placebo (lactose), in reducing the total morphine 5mg pills consumed during a 2-week period following ED discharge for an acute MSK pain complaint.

The secondary aims are to compare the following between patients receiving vitamin C and patients receiving a placebo: pain intensity trajectories, average pain relief during the 2week, side effects, total morphine 5mg pills consumed after a 2-week follow-up for each type of MSK pain (fracture, contusion, cervical pain, lower back pain, MSK pain at other sites), global chronic pain incidence (including CRPS) at 3 months and for each type of MSK pain specifically, CRPS incidence for limb fractures and for wrist fracture at 3 months, and prevalence of opioid use at 3 months.

METHODS AND ANALYSES

Study design
We will conduct a double-blind, randomised, placebo-controlled trial performed in two tertiary trauma care university-affiliated hospitals located in Montreal and Quebec City (Québec, Canada) with an annual census of 60,000 and 67,000 visits, respectively. This parallel group randomised trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement for reporting parallel-group randomised trial.38 This protocol has been reported according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)(online supplemental file online 1).39

Participants and recruitment
Consecutive patients (from 8 hours to 20 hours every day) diagnosed with an acute MSK pain complaint ongoing for less than 2 weeks and discharged from the ED with an opioid prescription will be approached by the treating clinician to participate in the study and obtain their verbal

consent to be seen by a research assistant. The decision to prescribe opioids will be at the treating physician’s discretion. Based on our previous work, all included patients will receive an identical 20 pills of 5 mg morphine prescription. The research assistant will then verify the patient’s inclusion and exclusion criteria, explain the research protocol and obtain informed written consent.

Eligibility criteria
Patients will be included in the study when they satisfy all following criteria: (1) aged 18 and over, (2) treated in ED for acute MSK pain present for less than 2 weeks, (3) discharged with an opioid prescription, (4) French or English speaking.

Patients will be excluded from the study if any of the following criteria apply: (1) opioid use 1 month prior to ED visit; (2) already taking vitamin C supplement; (3) active cancer; (4) treated for chronic pain; (5) treated for opioid use disorder; (6) unable to fill out diary or unavailable for follow-up; (7) any allergy, intolerance or sensitivity to milk or morphine; (8) treated with cyclosporine or warfarin; (9) pre-existing oxalate nephropathy or hemochromatosis; (10) pregnant or lactating (dosage >1800 mg not recommended). For women of childbearing age and sexually active in the past 3 months, urine pregnancy test will be performed.

Randomisation method and blinding
Eligible patients will be block randomised at the initial visit (via 1:1 ratio) to either 1 000 mg vitamin C taken orally two times a day or matching placebo (lactose) (figure 1), using a centralised randomisation web system. Allocation concealment will be in place to ensure that the investigator and the individual enrolling the subject into the study have no prior knowledge of group assignment. Since fractures are associated with more opioid consumption, randomisation will be a stratified by fracture (yes or no) and by centre. According to the centralised

Figure 1 Flowchart of patients’ enrolment in the study.
Studies on chronic pain management have typically used small dosages, recommended daily doses of vitamin C are larger. Our study will evaluate the impact of vitamin C in addition to an opioid prescribed for acute pain after an ED discharge. The current recommended dietary allowances specify 75 mg vitamin C for each of the morning and evening doses. Previous vitamin C dosage used for pain management.

Early withdrawal of subjects
At the time of consent, participants will be informed that their participation in this research is voluntary and that they may discontinue participation at any time.

Withdrawal of subject as the result of investigator decision
1. If an investigator terminates a subject’s participation in the trial, the investigator will explain to the subject the reasons for this action and, as appropriate, other treatment options.
2. If subjects were to have a serious adverse reaction to the medication, the investigator will recommend discontinuation of medication and provide aid for treatment.

Data collection and follow-up for withdrawn subjects
Data collected prior to participant withdrawal may be retained and used including Protected Personally Identifiable Information in a manner that is consistent with the study purpose and procedures as noted in this protocol and supplemental documents, unless a study participant notifies the primary investigator to remove all its information from the study.

Study drug
Vitamin C (ascorbic acid) is a vital nutrient; it helps form and maintain bones, skin and blood vessels and has antioxidant properties. It is not produced by the human body but occurs naturally in fruits, vegetables and other foods. It is also available as supplement over the counter in pharmacies, supermarkets, health supplement stores, and online.

Previous vitamin C dosage used for pain management
Our study will evaluate the impact of vitamin C in addition to an opioid prescribed for acute pain after an ED discharge. The current recommended dietary allowances of vitamin C are 90 and 75 mg/day for adult men and women, respectively. For anaesthetic or opioid sparing effects, recommended daily doses of vitamin C are larger. Studies on chronic pain management have typically used daily doses of 500 mg of vitamin C for 50 days to reduce by half the risk of CRPS within the first year. In postoperative context, studies generally administered only one dose of 2 g of vitamin C intravenously or 50 mg/kg orally just before or after anaesthesia induction and found significant reductions in opioid requirement and in pain severity within 24 to 72 hours. One of these studies used 500 mg intravenously two times a day up to the third day after surgery. The incidence of postherpetic neuralgia was lower after 8 weeks in the group of patients who received three daily doses of 5 g of vitamin C intravenously during the first 5 days of hospitalisation.

Dose rationale and risk/benefits
Levine and coworkers have shown that oral vitamin C uptake becomes less efficient as the dose increases due to transporter saturation. Although an oral dose of 200 mg vitamin C is completely absorbed, doses of 500 mg and 1250 mg vitamin C are only absorbed at <75% and 50%, respectively. Therefore, to maximise uptake and plasma concentrations of vitamin C, the chosen oral dose should ideally be administered in several smaller doses over the day. Vitamin C has low toxicity and is not believed to cause serious adverse effects at high intakes. The most common complaints are diarrhoea, nausea, abdominal cramps and other gastrointestinal disturbances due to the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract. A tolerable upper limit of 2000 mg per day of vitamin C has been established, and adverse events, including oxalate nephropathy or haemolysis in glucose-6-phosphate dehydrogenase-deficient patients, are reported for short course of vitamin C only with very high dosage (up to 60 g intravenous over 2 days) or solely for studies using lower dosages during to many months.

Considering dosages used in studies performed in acute postoperative and chronic pain context, adverse events reported with different dosages, and the absorption of vitamin C given orally, we will compare the effect of 1000 mg vitamin C taken orally two times a day (one in the morning and one in the evening) for a 14-day period after ED discharge for the treatment arm to a placebo for the control arm.

Subject compliance monitoring
All participants will be asked to complete a 14-day electronic or paper diary. Each day, participants will be asked whether they took both their study capsules and whether they started using a new vitamin or natural product. Reminders will be sent electronically to patients using the electronic diary, while phone calls will be used for patients completing the paper version. Results from our previous work suggest that nearly all patients fully understood how to fill out the diary and questionnaire and found them easy to complete.

Study procedures
After verifying all eligibility criteria, the research assistant will document the following initial data in REDCap: unique patient identifier, demographic variables (sex, gender, age and ethnicity), phone numbers, email address, complaint and pain location at triage, pain duration before ED visit, ED length of stay, final diagnosis (injury type and severity), history of opioid use or substance use disorder, analgesics received during ED stay, pain intensity at triage and discharge, pain medication prescribed at discharge, usual medication, vitamins and natural products, other non-pharmacological approach (ice, heat,
immobilisation, etc.), and if it was a work or motor vehicle-related incident. A pharmacist will dispense either active or placebo capsules and patients will be informed not to start consuming any other vitamin or natural products. All participating patients will be granted online access to an already validated 14-day electronic diary and questionnaire. An identical paper version (also previously tested) of the 14-day diary and questionnaire will be provided to patients without internet access or less familiar with smartphones. Patients will be instructed in person on how to use the electronic or paper diary and to start with acetaminophen and NSAID (if prescribed) before consuming opioids. Patients will also have phone access to research assistants should they require assistance.

Electronic questionnaires are generally favoured over phone interviews because they may be less affected by social desirability bias.52 This diary is used daily for real-time recording of quantity, date and names of all pain medications consumed, including vitamin C, related to the patient’s ED visit. At the end of each day, pain intensity will be assessed by one question: ‘What was your pain level throughout the day?’ measured on an 11-point numerical rating scale (NRS) from 0 to 10 (0 is no pain and 10 is worst pain imaginable) and, in general, if their pain had been relieved during the day (yes or no). Participants will be asked at the end of each day if they took their two study capsules (see paper version of the diary example in online supplemental file 1).

At the end of 2 weeks, patients will have a scheduled visit (in person or virtual depending on the patient’s preference), where they will bring all their medications. A series of questions will be asked regarding their actual pain intensity level as measured on an 11-point NRS from 0 to 10 (0 is no pain and 10 is worst pain imaginable), the frequency of their pain during a typical week, if they filled their initial opioid prescription (including partitioning), if they received additional opioid prescriptions (this will be verified with their pharmacy), their reasons for stopping or not taking any opioids (not enough or no pain, overly severe side effects, fear of addiction, other), unscheduled clinician visits related to their initial pain condition, if their medications were adequate for their overall pain management, and if they had any other treatment for their pain (surgery, physiotherapy, acupuncture, etc.). They will also report which of the following adverse reactions they experienced during the 14-day period: nausea, vomiting, constipation, dizziness, drowsiness, sweating, weakness or other side effects. If a serious unexpected adverse reaction is fatal or life threatening, the research team will notify as soon as possible the Natural Products Directorate no later than 7 days after the research team became aware of it, and no later than 15 days if the unexpected serious adverse reaction is neither fatal nor life threatening. They will be asked whether they started any other product to relieve pain (cannabis, alcohol, vitamins, other natural or over-the-counter products, etc.). As mitigation strategy, we will count the remaining morphine pills and study capsules, which will allow us to retrieve our main outcome for patients without (or incomplete) 14-day diary (see SPIRIT study design schedule in table 1).

At 3 months, patients will be contacted by phone to determine whether they suffer from chronic pain. A series of questions will be asked: their actual pain intensity level as measured on an 11-point NRS from 0 to 10 (0 is no pain and 10 worst pain imaginable), if they still consumed opioids in the last 2 weeks, medication used for pain, pain frequency during a typical week and to answer the Pain Disability Index (PDI) questionnaire.33 The PDI is made up of seven categories that are measured on a scale from 0 (no disability) to 10 (all of the individual’s normal activities have been totally disrupted or impossible because of pain). Family and household responsibilities, recreation, social activities, occupation, sexual activities, independence and life support activities make up the seven areas of the PDI. Subsequently, a total score is calculated by adding the responses to the seven items to give a PDI score, which can be between 0 and 70. The percentage obtained can correspond to five diagnoses: 0%–20% (minimal disability), 21%–40% (moderate disability), 41%–60% (severe disability), 61%–80% (infirm) and 81%–100% (bedridden). Chronic pain will be defined as at least moderate disability on the PDI. The 3-month follow-up period was chosen because pain is usually considered chronic when it persists or recurs for more than 3 months.54 Patients will also be asked whether their medications were adequate for their overall pain management. For patients with limb fractures who are still in pain, an in-person visit will be scheduled to evaluate the presence of CRPS defined by the Budapest criteria, which includes a physical examination (see box 1).55

Patients who had filled their initial opioid prescription will be contacted by phone 1 year after their initial visit and asked whether they consumed opioids in the previous 2 weeks. For patients who still consumed opioids, they will be asked to answer questions on opioid dependence using the rapid opioid dependence screen (RODS)56, as well as their reasons for consuming opioids. The RODS questionnaire is a newly validated56 measure of opioid dependence. This tool, composed of eight ‘yes/no’ questions, is designed to evaluate opioid dependence in clinical and research settings and is based on the Diagnostic and Statistical Manual of Mental Disorders V.IV. It takes 2 min to complete, and patients are considered as possibly opioid dependent if they answered positively to three or more of the eight items. This questionnaire has shown good internal consistency (α=0.92), fair inter-item correlations (0.66 to 0.87) and strong sensitivity (0.97) and specificity (0.76) when compared with a neuropsychiatric interview. Patients who meet the criteria for possible opioid dependency will be referred to an opioid use disorder clinic near their location.

Statistical analysis

Sample size determination
The effect of vitamin C on 24-hour postoperative opioid consumption was used to compute treatment effect size for our primary outcome (total morphine 5mg pills consumed after a 2-week follow-up). Two studies using oral route of vitamin C were reported, one by Kanazi et al.\textsuperscript{57} and one by Tunay et al.\textsuperscript{58} To be more conservative, we used the study with the smallest treatment effect (Tunay) and calculated an effect size of $d=0.32$. Anticipating a similar treatment effect, 190 participants in each arm are necessary to achieve a power of 0.90 with an alpha of 0.05 (PASS, V.11.0). Given the 18% lost to follow-up observed during a previous study using the same diary,\textsuperscript{37} a total of 464 patients will be recruited.

Previous studies made on the same population have shown an average recruitment rate of two participants per day at our study site.\textsuperscript{37} Therefore, an 8-month period will be necessary to enrol the initial sample. Accounting for the 3-month follow-up period and another 12 months for safety follow-up, a total of approximately 24 months will be required for recruitment and follow-up.

Analysis plan and statistical methods
We propose an intention to treat analysis with an additional per-protocol analysis. Mann-Whitney U test or t-test, depending on data distributions, will be used to compare the total morphine 5mg pills consumed after a 2-week follow-up between both arms. Although participants will be stratified by type of painful condition and randomised into the two arms, we will compare their distributions for potential confounding variables by calculating group-specific means and proportions, as appropriate.\textsuperscript{59} As a sensitivity analysis, we will use a multiple regression analysis to evaluate the effect of vitamin C on total 5mg pills consumed controlling for coanalgesic use, sex/gender, age, and ethnicity.

To compare pain intensity trajectories between both groups, group-based trajectory modelling (GBTM) will be used. GBTM is a statistical tool that identifies groups of patients with similar behavioural evolution over time without assuming the existence of a specific trend or number of groups.\textsuperscript{60} This new tool offers a more flexible approach of identifying linear or non-linear trajectories of pain evolution.\textsuperscript{61} Complete description of the modelling
Box 1 Budapest clinical diagnostic criteria for complex regional pain syndrome

1. Continuing pain, which is disproportionate to any inciting event.
2. Must report at least one symptom in three of the four following categories:
   - Sensory: reports of hyperesthesia and/or allodynia.
   - Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
   - Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry.
   - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement).
   - Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry.
   - Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry.
   - Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
4. There is no other diagnosis that better explains the signs and symptoms

was reported in a previous work. A $\chi^2$ test will be used to compare the proportion of patients within each trajectory between each arm.

Proportion of participants with pain relief, and side effect during the 14-day follow-up, opioid use, chronic pain and CRPS at 3 months will be tested using $\chi^2$ tests. Multiple comparison adjustments using false discovery rate are planned to control for inflated alpha error rate. Results will be presented using effect size with their 95% CIs. No interim analysis is planned and consequently the study will not be terminated earlier.

Missing outcome data

Missing data and dropouts will be assessed monthly by the data manager. Remedial measures, including staff retraining, will be used as needed to minimise missing data and patients lost to follow-up. For statistical analysis, potential missing data will be estimated using multiple imputation approach based on previous identified predictors if data are missing at random. It creates several different plausible imputed data sets and appropriately combining results obtained from each of them.

Patient and public involvement

A patient partner was involved in the study design and in the paper and electronic version of the pain medication diary that will be used in this study.

ETHICS AND DISSEMINATION

Ethics approval

This study has been granted ethics approval from the local Ethics Review Committee. Any protocol deviations will be submitted to the Ethics Review Committee for review.

Data management

Confidential and informed consent will occur in a private room. Every precaution will be taken to ensure data confidentiality. Only research team members will have access to both the paper and electronic data. Subjects will be assigned a unique study ID that will be used on all case report forms and database reporting. The database will be REDCap, which is HIPAA compliant, encrypted and password protected. Electronic data files will be accessible only on password-protected computers. Any hard copies will be maintained in a locked cabinet in a locked office by a member of the research team. There will be strict adherence to data management protocols. All source documents and trial documentation will be kept in a secure location by the investigators for 15 years.

The study investigators will have full access to and ownership of all data. Deidentified data will be made available to other interested investigators for additional analyses, on reasonable request, following reports of primary outcomes and with appropriate data use agreement.

The trial steering committee, who will also act as the data safety committee and will be composed of six members: principal investigator, project manager, research coordinator, biostatistician, clinical pharmacist and one ED clinician. It will oversee all study progress aspects and ensure participants safety, monitor recruitment, data collection and quality. Monitoring will be done monthly while any serious adverse events will be reported immediately to the committee, which will notify the REB and the Natural Health Products Directorate.

Dissemination plan

We plan to use the study data to write a manuscript for publication in a respected peer-reviewed journal in a timely fashion. Journal choice will be dependent on study findings but will likely be related to the fields of pain and emergency medicine. The principal author is a member of national/regional committees on pain management/opioid use, and part of a Canadian research network which will facilitate knowledge transfer. Results will likely be presented at national and international conferences.

Author affiliations

1Département de Médecine Familiale et de Médecine d’Urgence, Université de Montréal, Montreal, Quebec, Canada
2Study Center in Emergency Medicine, Hopital du Sacre-Coeur de Montreal Centre de Recherche, Montreal, Quebec, Canada
3Centre de Recherche, Hopital du Sacre-Coeur de Montreal, Montreal, Quebec, Canada
4Faculté de Pharmacie, Université de Montréal, Montreal, Quebec, Canada
5Faculté des sciences infirmières, Université de Montréal, Montreal, Quebec, Canada
6Department of Family and Emergency Medicine, Universite Laval, Quebec, Quebec, Canada
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ORCID iDs
Naol Daoust http://orcid.org/0000-0001-6507-0198
David Williamson http://orcid.org/0000-0003-3360-4831
Caroline Abour http://orcid.org/0000-0002-9952-0589

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