APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE

IMPACT FACTOR 2.595

Peer Review File

Article Information: https://dx.doi.org/10.21037/apm-22-133

Review Comments (First round)

Thank you for taking the time to review this study. Please find all comments addressed below. Please let us know if any further corrections should be made.

In general, this is a good review of the clinical trials in recent years. I would have liked more content about what they are studying apart from cranial stimulation, such as medications and therapies. This would make the paper more complete and clinically interesting. Also, the authors should employ a good writing technique to examine the need (or as most often is the case, lack of need) for adverbs. They are overused throughout the paper. Things like notably, importantly, in short, etc. Also, I am surprised at the number of errors you left in a paper that you are submitting for publication. Better attention to grammar, spelling, and acronyms should be done in the future to improve your chances of publication.

In line 31: In a 2018 paper revising the criteria and treatments of Disorders of Conciousness, persistent VS was renamed chronic vegetative state (CVS), since there are very rare documented late recoveries. Giacino, J.T., et al., Practice guideline update recommendations summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Neurology, 2018. 91(10): p. 450-460. You should use this most recent terminology throughout the paper.

Reference added and terminology changed throughout.

Line 52: I would include a table at the end with the diagnostic criteria of MCS, since this is the subject of your paper. It is too nuanced for a one sentence definition. Giancino has a 2009 paper in Neurology with a good table of characteristics you can include and reference. Especially since you bring up the diagnostic criteria in Line 57- they should be easily referenced in a table for the less familiar reader.

Reference added and table 1 also added.

Lines 52-56: This sentence is too long, and awkward, and a very important point in the paper. Probably better to divide into two, stating that MCS differs from both Coma and CVS which are marked by inability to interact with the outside world or respond to environment. Coma and CVS differ in that CVS has periods of wakefulness (eyes open), while Coma does not have any wakefulness (eyes closed unconsciousness).

This was addressed lines 133-137:

"Importantly, MCS differs from both coma and CVS which are marked by the inability to interact with the outside world or spond to the environment (3). Coma and CVS differ in that CVS has periods of wakefulness (eyes open), while coma does not have any wakefulness (eyes closed unconsciousness) (4). Diagnostic criteria for these patients are found in Table 1 (5)."

Lines 62-67: This is not worded well. Emotional suffering of whom? The patient or the family? I would change it to read something like: Misdiagnosis of MCS as CVS could result in missed opportunity for early intervention and therapy associated with improved outcomes, or even premature cessation of life sustaining therapies.
What makes this distinction so important (especially to readers of this Journal), and is not mentioned in the paper, is that by definition, MCS patients can and do experience pain and suffering, whereas CVS patients cannot. Thus, it is vital to distinguish between the two correctly. See reference below.
Boly, M., et al., Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol, 2008. 7(11): p. 1013-20.

This was addressed lines 143- 146:

"Misdaignosis of MCS as CVS could result in a missed opportunity for early intervention and therapy associated with improved outcomes, or even premature cessation of life sustaining therapies. Patients with MCS also experience pain and suffering, whereas patients with CVS cannot (13)."

Line 70-I would change the word mental to emotional.

Corrected line 174.

Line 128- This is an error. This scale is called the Nociception Coma Scale-Revised (not score) and is abbreviated NCS-R.

Corrected line 285.

Line 138- typos: being is misspelled. I suspect you mean in not is.

Corrected line 331.

Line 149: It should be stated that these were patients who experienced a traumatic brain injury at least one year previously and were in a Chronic state of impaired consciousness. They specifically excluded patients where the state was not brought on by trauma. This is important because causality is important in prognosis. I would also say that you cannot conclude much from a trial that is so small.

This was addressed lines 324-326:

These were patients that experienced a trumatic brain injury at least one year prior and were in a chronic state of impaired consciousness, thus excluding patients without trauma. In addition, the sample size was small with only 4 patients limiting its conclusions.

Line 151-152-Did you mean all the trials above, or just NCT02025439? Since the line is included in the paragraph with the discussion of NCT02025439 it seems like it applies to this trial, but the sentence says “trials” (plural). Do you mean this trail found....singular? If you mean all the mentioned trials above, you should make that its own paragraph or put it in the next paragraph.

This was made its own paragraph lines 337-338:

All the three aforementioned clinical trials found 0% mortality and no serious adverse events in the cohorts.

Line 178- It is unclear what you mean here. Do you mean only 41 trials that were discoverable using the search term MCS? I think you might mean with instead of while. Please reword this and make clear what you are trying to say. I would also include in this paragraph that the definition of MCS is now 20 years old, and to design a clinical trial that does not distinguish this state from CVS clearly is a poorly designed trial, since the disorders have very different prognoses. Also, it should be noted that MCS is ten times more common than CVS, thus its study is even more important.

This was addressed 372- 377:

"With only 41 studies being registered on ClinicalTrials.gov for MCS, it is likely that many trials evaluating CVS or comma have misclassified patients and included patients in their study with MCS. The definition of MCS is now 20 years old, therefore designing a trial that does not distinguish MCS from CVS is a poorly designed trial, since these disorders have very different prognoses. MCS is also ten times more common than CVS, thus its study is even more important."

Line 213-I think it would be valuable to know what other medications are being trialed, and the results. Though much attention is given to types of electrical stimulation, there is no mention of medications other than amantadine. If the point is to review what is going on in these trials, I would include that here.

Added in lines 281- 282:

Among the pharmaceuticals studied were apomorphine, dexmedetomidine, midazolam, acetaminophen, ibuprofen, diclofenac, tramadol and oxycodone.

Added in lines 490-501:
"Pharmaceutical interventions included mainly dopamine promotors, analgesics and sedatives. The dopamine promotor being tested is apomorphine which is thought to improve behavioral effects in patients with MCSs. Analgesics were also studied to assess the relationship of analgesic potency with NCS-R scores in patients with MCSs. This trial is evaluating whether opiate pain control improves NCS-R scores more than pain control with NSAIDs or acetaminophen. Sedatives are being evaluated including dexmedetomidine and midazolam. These are being evaluated for their use in regional anesthesia."

Line 223: I assume this is another typo-It has been CRS-R up until this line, and that is how this scale is abbreviated. Since you mention this scale several times, I think you should include a brief line after its first mention to explain what clinical parameters it assesses or include it as a table at the end.

This was addressed in lines 240-244 and table 2 was added:

"The CRS-R is a 23 point system where patients can achieve 4 points for auditory functions, 5 points for visual functions, 6 points for motor functions, 3 points for oromotor functions, 2 points for communication functions, and 3 points attributed to arousal (17). A higher score is associated with a higher level of consciousness (Table 2)."

Corrected line 506.

Line 227: I assume you mean MCS?

Corrected line 510.

Line 246: should be have, not had (definition and criteria have)

Corrected line 541.

Line 247: I would say remain closely associated despite evidence (you don't need a comma here)

Corrected line 542:

"…these two conditions remain closely associated despite evidence of different patient outcomes and treatment options."

Line 255: This is misleading, implying that most patients eventually recover. In reality the prognosis after 3 months for non-traumatic, and 6-12 months for traumatic brain injuries is very poor. I would say something like "MCS is a condition with no clear timeline, and variably little improvement with current treatments."

Corrected Lines 549-550:

This is important since MCS is a condition with no clear timeline, and variably little improvement with current treatments.

RE-review Comments (Second round)

The paper in it's current form is good. There are still some typos and one confusing thing that should be fixed.
Please eliminate the sentence in line 109 "This Challenge....life sustaining care." It is sufficiently addressed and better explained in the following two sentences.
There are still several typos in the paper that should be fixed:
Line 103 spond should be respond
Line 111 misdiagnosis is mispelled
Line 203 traumatic is mispelled
Line 194 when is written twice.
Once these minor things are corrected, it will be ready for publication, in my opinion

APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE
IMPACT FACTOR 2.595

We have made all of these modifications as specified, with track changes.

AME Publishing Company