Peer Review File

Article Information: https://dx.doi.org/10.21037/apm-22-797

Round 1:

Reviewer A

I commend the authors for the work. However, I could not appreciate novel thing in this paper. Anything new finding would make this paper better. Minor comments below.

1. Abstract: Typo in line 22: 0.8%, carotid endarterectomy carotid artery stenting?

Reply 1: Thank you for noticing and help us improve our manuscript. We fixed the typographical error.

myocardial infarction (n=1, 0.8% [carotid artery stenting]; n=1, 0.9% [carotid endarterectomy]; p=0.899)

Changes in the text: See page 4, line 16 of abstract

2. Result: Page 5, line 9) Any difference observed between groups in asymptomatic patients?

Reply 2: Thank you for the interesting question. We merged the previous Tables 3 and 4 into a revised Table 3. Table 4 compared asymptomatic patients; in addition, a table comparing patients over 70 years of age was added. There was no significant difference between the two groups in asymptomatic patients. The following are the revised parts in the updated version of the manuscript:

Results

There were 164 symptomatic patients, 80 in the CEA and 84 in the CAS group. No significant difference was observed in outcomes between the two groups in symptomatic patients. Moreover, no significant difference was found in outcomes of symptomatic patients > 70 years old (Table 3). There were 71 asymptomatic patients, 27 in the CEA and 44 in the CAS group. In asymptomatic patients, there was only one case of 30-day postoperative CI in the CAS group, and no other major complications occurred. There were no 30-day postoperative MI, 30-day postoperative CI, and in-hospital postoperative death in the asymptomatic patient group over 70 years of age (Table 4).

Discussion

According to the second Asymptomatic Carotid Surgery Trial (ACST-2) (14), overall, 1% of patients had disabling stroke or death procedurally (15 allocated to CAS and 18 to CEA) and 2% had non-disabling procedural stroke (48 allocated to CAS and 29 to CEA). In this study, there was one case (1.4%) of 30-day postoperative CI among asymptomatic patients, and it occurred among the patients who underwent CAS. There was no in-hospital postoperative death (Table 4). Also, there was no 30-day postoperative MI, CI, and in-hospital postoperative death following either CAS or CEA in the asymptomatic patient group over 70 years of age.

Changes in the text: Please refer to Table 4. See the resulting amended main text on page 11 (results), lines 4-11, and page 13 (discussion), lines 10-16.

3. It is not mentioned the risk of cerebral infarct after 30 days of the surgery. If the total follow-up duration is 34 ± 29, I would like to know the cerebrovascular accidents rates after CEA/ CAS.

Reply 3: Thank you for the valuable comment. We have added the following parts in the manuscript:

(results)

During the follow-up period (34±29 months), CI occurred in three patients (1.3%) of 235 patients after postoperative day 30. There was one case (0.8%) in the CAS group and two cases (1.9%) in the CEA group, with no significant difference (p =0.53). Information on three patients is presented in Table 5.

(discussion)

In this study, ipsilateral CI (excluding the perioperative period) after postoperative day 30 occurred in all symptomatic patients, one case (0.8%) in the CAS and two cases (1.9%) in the CEA group. According to the Asymptomatic Carotid Trial (ACT I), the 5-year incidence of ipsilateral stroke was 2.2% in CAS and 2.7% in CEA (15). In CREST, symptomatic and asymptomatic patients were cohort mixed, and the rate of 10-year ipsilateral stroke (excluding the perioperative period) was 6.9% in CAS and 5.6% in CEA (7). Since the follow-up duration of our study was on average 34±29 months, which was shorter than that of both the abovementioned studies and not all individuals were followed up for a long period of time, our results cannot be compared with those of ACT I and CREST. However, ipsilateral CI did not

occur during the follow-up period (excluding the perioperative period) in asymptomatic patients, and longer-term results are necessary to confirm this finding.

Changes in the text: See page 11, lines 12-15, and page 13, line 17 up to page 14, line 2.

4. How were the other kinds of common complications such as hyperperfusion and intracerebral hemorrhage. None?

Reply 4: Thanks for the valuable comments and for raising this interesting question. As an answer to that, the following content has been added to the results section:

There were no patients with hyperperfusion syndrome in either group.

In the CAS group, contrast-induced nephrotoxicity occurred in a patient with atrial fibrillation; stage 4 chronic kidney disease after CAS occurred in another case, in which hemodialysis was performed. There were five cases of hematoma at the puncture site, but no special treatment was required. In the CEA group, one patient with asthma had an asthma attack in the intensive care unit after surgery and underwent reintubation. After steroid intake, the patient improved and was discharged without any special problems. Three patients developed a postoperative hematoma, two patients were discharged without special treatment, and one patient used compression and hemostatic agents. However, there were no cases where reoperation was required owing to bleeding. After surgery, there was one case of vagus nerve injury and four cases of hypoglossal nerve injury. All five patients had improved symptoms before discharge and did not develop any disability.

Changes in the text: See page 10, lines 7-18

5. Discussion: Page 5, line 36) (Meta ≥70). What does this mean? Is this “meta” commonly used expression??

Reply 5: Thanks for noticing and highlighting this. It was due to an inconvenience caused by the automatically linked references. Thanks to your comment, we could amend the manuscript so that the content within parentheses has been corrected to “8”, and the rest of the reference information has also been adjusted. Now the text reads as follows:

The Carotid Stenting Trialists’ Collaboration analyzed outcomes in 4754 patients from 4 clinical trials. CEA was superior to CAS in these randomized controlled trials in patients aged ≥70–74 years (8).

8. Howard G, Roubin GS, Jansen O, et al. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomized trials. Lancet 2016;387:1305-11.
Changes in the text: See page 12, line 15, and page 19, lines 1-3 (reference 8)

6. Table 1: Age is written below the decimal point. It is not realistic to write age like 74.06. Please round the values. Same thing applies to other values such as operation time, length of hospital stay, etc.
Reply 6: Thanks for the very good point. Tables 1 and 2 have been modified according to your suggestion.
Changes in the text: See the revised Table 1 and Table 2.

7. Table 2: In CEA group, length of hospital stay was 15 ± 44. It seems longer for usual post-CEA patients to stay in the hospital for more than a week. Was there any kind of postoperative event that prevent them from being discharged?
Reply 7: Thanks for raising this issue. We ourselves were concerned about this fact, since there are practical issues with patient management in Korea that diverge from what is common practice in other countries. According to the Korean medical system, patients are discharged from the hospital after receiving rehabilitation rather than going to a rehabilitation hospital after surgery. For this reason, the length of hospital stay for symptomatic patients in our study includes post-surgery rehabilitation. In addition, there is a tendency not to leave the hospital if the wound is not completely healed after surgery because the economic burden is small, even that of a long hospitalization, according to the Korean medical insurance system. In addition, few out-of-hospital institutions can provide rehab after surgery, so patients often refuse to be discharged. Even after surgical treatment has been completely delivered, there is no way to forcibly discharge a patient, so the hospitalization period is inevitably longer than in other countries (in the case of discharge without complications, if Korea's national health insurance coverage is applied to the treating hospital, the insurance claim amount is about $ 6000, similar to the cost of both CEA and CAS, and the patient's co-payment is about $800. At least, this is the average amount at our hospital, not necessarily representative of the whole of Korea).

8. Please erase vertical lines unless specified by journal guidelines.

Reply 8: Thanks for flagging this. We amended our table layout.

Reviewer B

1. This is an excellent retrospective single-center study comparing the outcomes of carotid artery stenting with carotid endarterectomy.

I am not sure why the authors chose the Journal of Palliative Medicine for this study. I suspect it was rejected from every vascular journal it was submitted to, but I cannot be sure.

In any case, this pragmatic report presents an unbiased presentation of real-life results.

The Conclusion may need to be modified, the authors mention that "Future studies should include a multicenter randomized trial to account for the limitations present in this study design." CREST-2 and other trials are underway.

Reply 1: Thanks for the appreciative comments. We revised the results section, following your suggestion.

The publication of the results of CREST-2 and other multicenter randomized trials is highly awaited to provide clearer treatment criteria when selecting CEA and CAS.

Changes in the text: See page 15, lines 11 – 13.

Reviewer C

The retrospective study presented brings objective data on the postoperative outcome of carotid endarterectomy and carotid angioplasty from a single center.

Some points need to be clarified:

1. Considering the size of the sample and the characteristics of the study, the objectives cannot be to evaluate the effectiveness of the treatment, but to present data from the service and compare them with other studies.

Reply 1: Thank you for your comment. We totally agree with your opinion. The background and introduction of the abstract have been modified as follows:

This study reports the results of CAS versus CEA in patients with symptomatic or asymptomatic carotid stenosis and compares them with other studies.

Changes in the text: See page 4, lines 6-9.

2. The number of patients with one treatment and another is very similar. Weren't the indications for angioplasty just for patients with anatomic restriction or high risk? The nomination criteria for one group or another could be further refined.

Reply 2: Thanks for the valuable comments. We believe that the study design as reported in the methods section includes what is mentioned.

Considering the patient's condition and risk of surgery, a neurologist, neurointerventionist, and cardiovascular surgeon consulted together to determine the treatment method. CAS was considered first in patients with severe comorbidities or challenging technical or anatomic factors. Severe comorbidities included class III/IV congestive heart failure or angina, left main coronary artery occlusive disease, coronary artery occlusive disease involving more than 2 vessels, ≥30% left ventricle ejection fraction, recent myocardial infarction, and severe lung or renal disease.

Challenging technical or anatomic factors included prior neck operation or neck irradiation, post-endarterectomy restenosis, and an extremely high lesion location (above the 2nd cervical vertebra).

Changes in the text: No changes done. Please see the highlighted passage from page 6, line 24 to page 7, line 9.

3. A table with data on asymptomatic patients would be interesting, as well as comments in the discussion about it.

Reply 3: Thanks for this constructive comment. We merged the existing Tables 3 and 4 into a revised Table 3. Table 4 compared asymptomatic patients. A table comparing patients over 70 years of age was also added. There was no significant difference between the two groups in asymptomatic patients.

There were 164 symptomatic patients, 80 in the CEA and 84 in the CAS group. No significant difference was observed in outcomes between the two groups in symptomatic patients. Moreover, no significant difference was found in outcomes of symptomatic patients > 70 years old (Table 3). There were 71 asymptomatic patients, 27 in the CEA and 44 in the CAS group.

In asymptomatic patients, there was only one case of 30-day postoperative CI in the CAS group, and no other major complications occurred. There were no 30-day postoperative MI, 30-day postoperative CI, and in-hospital postoperative death in the asymptomatic patient group over 70 years of age (Table 4).

Discussion

According to the second Asymptomatic Carotid Surgery Trial (ACST-2) (14), overall, 1% of patients had disabling stroke or death procedurally (15 allocated to CAS and 18 to CEA) and 2% had non-disabling procedural stroke (48 allocated to CAS and 29 to CEA). In this study, there was one case (1.4%) of 30-day postoperative CI among asymptomatic patients, and it occurred among the patients who underwent CAS. There was no in-hospital postoperative death (Table 4). Also, there was no 30-day postoperative MI, CI, and in-hospital postoperative death following either CAS or CEA in the asymptomatic patient group over 70 years of age.

Changes in the text: Please see the new Table 4. Please also see the revised main text, page 11, lines 4-11 and page 13 (discussion), lines 10-16.

4. The Conclusion needs to be redone considering that no analysis was performed on the number of strokes avoided or prevented. Only short-term postoperative data were analyzed.

Reply 4: Thanks for the useful comment. We revised the results section accordingly. Taking also into account the opinions of other reviewers on this topic, we have added the information on long-term results. The following are the changes done to the manuscript:

(conclusions)

The publication of the results of CREST-2 and other multicenter randomized trials is highly awaited to provide clearer treatment criteria when selecting CEA and CAS.

(results)

During the follow-up period (34±29 months), CI occurred in three patients (1.3%) of 235 patients after postoperative day 30. There was one case (0.8%) in the CAS group and two cases (1.9%) in the CEA group, with no significant difference (p =0.53). Information on three patients is presented in Table 5.

(discussion)

In this study, ipsilateral CI (excluding the perioperative period) after postoperative day 30 occurred in all symptomatic patients, one case (0.8%) in the CAS and two cases (1.9%) in the CEA group. According to the Asymptomatic Carotid Trial (ACT I), the 5-year incidence of

ipsilateral stroke was 2.2% in CAS and 2.7% in CEA (15). In CREST, symptomatic and asymptomatic patients were cohort mixed, and the rate of 10-year ipsilateral stroke (excluding the perioperative period) was 6.9% in CAS and 5.6% in CEA (7). Since the follow-up duration of our study was on average 34±29 months, which was shorter than that of both the abovementioned studies and not all individuals were followed up for a long period of time, our results cannot be compared with those of ACT I and CREST. However, ipsilateral CI did not occur during the follow-up period (excluding the perioperative period) in asymptomatic patients, and longer-term results are necessary to confirm this finding.

Changes in the text: See page 15, lines 11 – 13. See page 11, lines 12-15, and page 13, line 17 up to page 14, line 2.

Reviewer D

This manuscript describes a single-center retrospective study comparing outcomes for patients undergoing CEA vs. CAS for carotid stenosis. Strengths of this study include a clear description of the design, and high potential for clinical application. I have a few comments on the current draft which I think should be addressed.

1. Given the low rate of mortality or serious complication in either group, the study would need to have a much larger sample size to have the statistical power to be able to detect a difference in these outcomes. While I think there is still a great deal of value in publishing this paper, I also think that this point needs to be made in the discussion section. The lack of difference between the two groups should not be interpreted to imply that they are equal on these outcomes, because the sample size cannot support that conclusion.

Reply 1: Thank you very much for your comments. We have changed the conclusions section in the revised manuscript. As mentioned when examining our study's limitations, this study only included cases from a single institution with a small number of patients. However, the minimum sample size was satisfied. This study's sample size was calculated for a large effect size and for alpha=0.05 and beta=0.80, using the G-Power 3.1.9.7. As a result, at least 132 samples were calculated (two groups of 66, respectively). Moreover, we would like to draw attention to a published study with a similar research design and comparable numbers of participants reported by Pasqui et al. (17). That study's total sample size was 234 (98 CEA and

136 CAS), and the data were retrospectively analyzed from a prospectively compiled single-center database.

We have changed this paragraph in the revised manuscript, as follows:

(discussion)

Nevertheless, the minimum sample size was satisfied. This study's sample size was calculated for a large effect size and for alpha=0.05 and beta=0.80, using the G-Power 3.1.9.7. As a result, at least 132 patients were calculated (two groups of 66, respectively). Moreover, we would like to draw attention to a published study with a similar research design and comparable numbers of participants reported by Pasqui et al. (17). That study's total sample size was 234 (98 CEA and 136 CAS), and the data were retrospectively analyzed from a prospectively compiled single-center database.

(conclusion)

In elective surgery, CAS and CEA had a similar effect on preventing cerebral infarction, and there were no differences in postoperative complications.

(references)

17. Pasqui E, De Donato G, Alba G, et al. Early and long-term outcomes of carotid stenting and carotid endarterectomy in women. Front Surg 2021;8:646204.

Changes in the text: See Page 15, lines 1-8 and 10-11; page 20, lines 4-5.

2. On the other hand, it is worth noting that a significant difference was detected between groups for procedure length and length of stay. These are metrics that have at least indirect implications for patient well-being (particularly length of stay), since they would be expected to be related to a more rapid recovery time as well as less opportunity for developing certain types of complication (e.g., hospital-acquired infections). Both of these outcomes also relate directly to cost of care. Assuming that there are no clinically significant differences in morbidity and mortality (and acknowledging as described above that the sample size in this study is too small to draw definitive conclusions in that regard), this would then provide evidence in support of CAS over CEA. With a mean procedure time nearly half as long as CEA, and a mean LOS nearly one third as long, that would suggest substantial likely benefits in terms of increasing availability of healthcare resources and reducing costs. This could be addressed in the discussion.

Reply 2: Thank you very much for your comments. The following content has been added to the discussion.

The operative times (128.69±30.66 min in CEA versus 75.79±26.03 min in CAS; p=0.000) and length of hospital stay (14.79±44.35 days in CEA versus 5.77±4.89 days in CAS; p=0.023) were significantly longer in the CEA group than in the CAS group. The cause of the difference in length of hospital stay is that CAS is performed immediately after transfemoral carotid angiography. However, in the case of CEA, since dual antiplatelet treatment is used in almost all patients before surgery, the procedure is performed 5–7 days after stopping one antiplatelet treatment. This period included, it seems that there was a significant difference in the length of hospitalization between the two groups. Another reason is that, according to Korea's medical insurance system, even if the length of hospital stay is long, it does not represent a substantial additional economic burden when compared with the costs of the surgical procedures. In addition, patients frequently refuse to be discharged from the hospital because very few out-of-hospital facilities can offer rehabilitation after surgery. There is no way to force a patient to be discharged even after treatment has been delivered, so the hospitalization period is inevitably longer than that in other countries. Moreover, according to the Korean medical system, patients are not discharged to go to a rehabilitation hospital following surgery: they are discharged at the end of the rehabilitation treatment. For this reason, the length of hospital stay for symptomatic patients includes rehabilitation.

Additional replies not included in the main text's body:
In the case of discharge without complications, if Korea's national health insurance coverage is applied to the treating hospital, the insurance claim amount is about $ 6000, similar to the cost of both CEA and CAS, and the patient's co-payment is about $800. At least, this is the average amount at our hospital, not necessarily representative of the whole of Korea.
Changes in the text: See Page 14, lines 3-19.

3. A minor issue; there are a few instances in which p-values are reported as .0000, but these should be given as < .0001.
Reply 3: Thank you very much for your suggestions. We have amended the manuscript according to this indication.
Changes in the text: See Table 2.

Reviewer E

A few comments:

1. You cannot really say in the conclusion of the abstract that the procedures prevented stroke if you only follow the patients for 30 days postoperatively. For asymptomatic patients, the standard quoted trials suggest benefit at 2-5 years which is much longer than your follow-up.

Reply 1: Thanks for the good point. We have added the following:

(results)

During the follow-up period (34±29 months), CI occurred in three patients (1.3%) of 235 patients after postoperative day 30. There was one case (0.8%) in the CAS group and two cases (1.9%) in the CEA group, with no significant difference (p =0.53). Information on three patients is presented in Table 5.

(discussion)

In this study, ipsilateral CI (excluding the perioperative period) after postoperative day 30 occurred in all symptomatic patients, one case (0.8%) in the CAS and two cases (1.9%) in the CEA group. According to the Asymptomatic Carotid Trial (ACT I), the 5-year incidence of ipsilateral stroke was 2.2% in CAS and 2.7% in CEA (15). In CREST, symptomatic and asymptomatic patients were cohort mixed, and the rate of 10-year ipsilateral stroke (excluding the perioperative period) was 6.9% in CAS and 5.6% in CEA (7). Since the follow-up duration of our study was on average 34±29 months, which was shorter than that of both the abovementioned studies and not all individuals were followed up for a long period of time, our results cannot be compared with those of ACT I and CREST. However, ipsilateral CI did not occur during the follow-up period (excluding the perioperative period) in asymptomatic patients, and longer-term results are necessary to confirm this finding.

Changes in the text: See page 11, lines 12-15, and page 13, line 17 up to page 14, line 2.

2. Were there any TCAR in your cohort?

Reply 2: Thank you for raising this question. No TCAR was included in this study.

3. You indicate in the methods that follow-up is for 30 days but then in the results you have 2 patients with restenosis that was treated at 13 and 51 months. Please clarify the follow-up.

Reply 3: Thanks for the valuable comment. Accordingly, we have added the following information to our manuscript:

One patient underwent further CAS owing to severe in-stent restenosis. Another patient had moderate to severe in-stent restenosis. However, he refused additional treatment because his life expectancy was not long owing to the terminal stage of small cell lung cancer.

Changes in the text: See page 10, lines 22-25.

4. Were any neurologic events after CAS on the contralateral side to the intervention?

Reply 4: Thank you for asking this question. It prompted us to add the following information: The cerebral infarctions (CI) that occurred within 30 days after CAS in all four patients were procedure-related multiple embolic infarctions and intracranial hemorrhage. Three of the four patients were symptomatic. One of the four patients who underwent CAS and developed 30-day postoperative CI developed ipsilateral procedure-induced CI. In two patients, bilateral hemorrhagic transformation with procedure-induced CI was observed on magnetic resonance imaging, but no surgical treatment was required. The other patient underwent craniectomy owing to bilateral intraventricular hemorrhage and surrounding intracerebral hemorrhage but died on the 28th postoperative day owing to infection and multiorgan failure. Cerebral infarction occurred within 30 days of CEA in an asymptomatic patient.

Changes in the text: See page 9, line 20 up to page 10, line 4.

5. Please indicate the criteria for choosing CAS or CEA in your center

Reply 5: Thank you for the good comment. We believe that the study design outline reported in the methods section includes what is requested.

Considering the patient's condition and risk of surgery, a neurologist, neurointerventionist, and cardiovascular surgeon consulted together to determine the treatment method. CAS was considered first in patients with severe comorbidities or challenging technical or anatomic factors. Severe comorbidities included class III/IV congestive heart failure or angina, left main coronary artery occlusive disease, coronary artery occlusive disease involving more than 2 vessels, ≥30% left ventricle ejection fraction, recent myocardial infarction, and severe lung or renal disease.

Challenging technical or anatomic factors included prior neck operation or neck irradiation, post-endarterectomy restenosis, and an extremely high lesion location (above the 2nd cervical vertebra).
Changes in the text: No changes done. Text is highlighted on page 6, line 24 up to page 7, line 9.

6. CREST already randomized CEA versus transfemoral CAS and those results are well known in terms of better stroke and death rates with CEA but lower MI rates with CAS. What does this study add to the literature that is unique?
Reply 6: Thank you for your comments and for raising this question. This study cannot be compared to large-scale randomized trials. However, we think that clinical results from centers that include regions and races that were not included in large, randomized trials also have some relevance for clinical practice and treatment.

Round 2:

Reviewer A

This paper became much more readable and better in quality. I appreciate the authors' effort in the revision. I also thank the authors for the courteous replies to the comments. I am glad to understand the medico-social environment in Korea, which explains the reason why the length of stay in patients after carotid endarterectomy is long. I think this paper should be ok to be accepted after managing the following minor points.

1. Page 9; line 20-21: "The cerebral infarctions (CI) that occurred within 30 days after CAS in all four patients" Page 10; line 1-3: "The other patient underwent craniectomy owing to bilateral intraventricular hemorrhage and surrounding intracerebral hemorrhage". Strictly speaking, cerebral infarction does not include intraventricular hemorrhage or intracerebral hemorrhage. The word "stroke" is a more accurate term rather than CI on page 9; line 20. Either stroke or cerebrovascular accidents. Stroke covers both cerebral infarct and intracerebral hemorrhage (including intraventricular hemorrhage).

Reply 1: Thank you for pointing this out. Accordingly, we have changed cerebral infarction (CI) to "stroke" throughout the revised manuscript.

The stroke that occurred within 30 days after CAS in all four patients were procedure-related multiple embolic infarctions and intracranial hemorrhage. Three of the four patients were symptomatic. One of the four patients who underwent CAS and developed 30-day postoperative stroke developed ipsilateral procedure-induced stroke. In two patients, bilateral hemorrhagic transformation with procedure-induced stroke was observed on magnetic resonance imaging, but no surgical treatment was required. The other patient underwent craniectomy owing to bilateral intraventricular hemorrhage and surrounding intracerebral hemorrhage but died on the 28th postoperative day owing to infection and multiorgan failure.

• Page 10, line 4-12

2. Page 10; line 4-5: "Cerebral infarction occurred within 30 days of CEA in an asymptomatic patient." Cerebral infarction was abbreviated as CI. Please use CI instead of cerebral infarction at this point. Based on Tables 3 and 4, it is a symptomatic patient, not an asymptomatic patient that had CI within 30 days of CEA.

Reply 2: Thank you for noticing this and helping us to improve our manuscript. We have changed the previous “Cerebral infraction” to “stroke,” and “Cerebral infarction” on line 12 to “Cerebral infarction (CI).” Moreover, we have changed “asymptomatic” to “symptomatic.” Cerebral infarction (CI) occurred within 30 days of CEA in a symptomatic patient.

• Page 10, line 12-13