Chapter 11

Discussion & Conclusions

The incidence of adjacent segment degeneration in motion preservation surgery

According to the evidence presented in chapter 2, literature review delivers the first remarkable finding of this thesis. Although the cervical disc prosthesis was introduced in anterior spine surgery to prevent adjacent segment degeneration (ASD), our literature review demonstrated that the occurrence of ASD was only studied marginally. In none of the publications concerning prosthesis evaluation in patients suffering exclusively from cervical radiculopathy, radiological evaluation on ASD was studied. In studies concerning prosthesis evaluation in mixed patient populations, radiological evaluation of ASD was performed only in a limited number of articles. And even if it was mentioned, the method to study ASD was repeatedly insufficient: intervertebral disc degeneration is deemed to be a physiological process[1-5], and therefore some extent of degeneration at the adjacent disc levels is expected to be already present at baseline. In order to radiologically identify pre-existing degeneration, it is essential to compare postoperative signs of degeneration (disc height and osteophyte formation) to baseline degeneration. Only six[6-11] of 38 mixed population studies adequately studied radiological ASD by comparing to baseline data. In these articles, at baseline, ASD was already present in a high percentage (50%)[6] of cases. This is to be expected since it concerns a population suffering from myelopathy which is degenerative by diagnosis. Literature demonstrates a tendency to more ASD in the fusion groups, but no statistically significant differences could be demonstrated.

Our study is thus the first to evaluate ASD in a cohort consisting only of radiculopathy patients. Evaluating ASD in the NECK and PROCON trial was done by studying the decrease of disc height and the severity of osteophyte formation on X-rays at baseline and postoperatively[4] at both the superior and the inferior level. We demonstrated that baseline ASD was present in 34% of patients, which was lower in comparison to the data that we found in our review. This is well attributable to the study population: the 50% baseline ASD was demonstrated in the mixed study population, as mentioned in the previous paragraph. ASD increased to 58% at two-year follow-up and we could not demonstrate a difference in the incidence and progression of ASD in patients who underwent cervical arthrodesis (ACD or ACDF) and patients who received a cervical prosthesis (Chapter 3). Therefore, the proclaimed advantage of implanting a prosthesis to prevent ASD could not be established.

However, one could argue that our power calculations were not aiming at finding a difference between the groups based on ASD since they were based on a finding a difference in NDI. Originally though, the power calculation was indeed based on a difference in symptomatically relevant ASD between the groups according to data provided by Robertson et al.[10]. In the original NECK trial protocol, the following was mentioned: 'the sample size was calculated according to the incidence of clinical ASD of 2% after ACDA and 7% after ACDF reported by Robertson et al.[10]. To this end, a total of 750 patients are needed in this study.' However, after a few years, it became obvious that it would need more than 15 years to accomplish the trial. Therefore, in the NECK trial, we subsequently changed the protocol and made new calculations using the neck disability index (NDI) as the primary outcome parameter to justify the clinically relevant benefit after ACDA. On the other hand, after a double check on the original full text, the incidence of symptomatic ASD in the ACDF group described by Robertson et al. is 0 rather than 2%. In their study, symptomatic ASD was defined widely, which is patients who manifested as neck, shoulder, and/or arm pain that required medical attention during the 24-month period, degenerative disc disease at the adjacent level, and the appearance of a ruptured cervical disc at the adjacent level. Moreover, they also reported that the incidence of radiological ASD was 35% in ACDF and 18% in ACDA, which was described as new anterior osteophyte formation or enlargement of existing osteophyte, increased or new narrowing of a disc space, and new or increased calcification. However, the correlation between symptomatic ASD and radiological ASD is not clear in this study. Since it is still debatable on the definition of symptomatic ASD as both the rate of reoperation at the adjacent levels and the development of new clinical symptoms corresponding to the adjacent levels can be used as the measurement, it would be interesting to evaluate the incidence of radiological ASD in the NECK trial as well.

Adjacent segment degeneration and range of motion

Hypothetically, it is thought that maintaining range of motion (ROM) at the target level will result in prevention from ASD and subsequently in better functional outcome in the long term. We thus studied whether ROM was maintained at the target level. In the majority of patients, ROM was indeed preserved after implanting a cervical prosthesis, and not preserved after ACD or ACDF. However, maintaining motion did not correlate to the incidence or positive progression of ASD at two years after surgery. We also studied the correlation between ROM of the whole cervical spine and ASD and could not demonstrate a correlation either.

We did notice however that ROM at the index level was not consequently absent in the ACD and ACDF group and was not consequently maintained in the ACDA group. In the present study, it was demonstrated that 63% of patients with ACDA had radiologically preserved ROM (>4 degrees) versus 37% that did not at two-year follow-up. We therefore additionally evaluated the correlation between ASD and ROM on the basis of preservation of ROM. Again, no correlation could be established between preserved ROM and the absence of ASD. Furthermore, this correlation was studied in all patients irrespective of the surgical method. We demonstrated that the percentage of patients with the presence of ASD and patients with positive progression of ASD was not significantly higher in patients with loss of ROM than in those with motion preservation at two-year follow-up.

It is generally presumed that the development of ASD is a slow process, and that therefore long-term follow-up periods are essential in order to properly judge the occurrence of ASD. However, an increase of approximately 20% of ASD (or 20% of patients with positive progression of ASD) within the first two years after surgery, justifies the conclusion that ASD is not significantly dependent on the preservation of motion at the index level.

Therefore, no advantage of a cervical disc prosthesis was demonstrated. Considering the higher costs and the longer operating time, it is not recommended to implant a prothesis in patients with singe-level cervical radiculopathy.

Does cervical sagittal alignment correlate with adjacent segment degeneration?

The cervical spine has a crucial role in compensating a distorted global spinal balance. In order to maintain horizontal gaze, the cervical spine will compensate[12]. Regularly, global sagittal imbalance, if present at all, will only be present in a very mild form in the average patient with cervical radiculopathy. Surgical interventions can however possibly interfere with cervical sagittal alignment. Subsequently, even minor cervical spine balance compensation mechanisms may cause accelerated degeneration of the cervical spine segments. Therefore, an acquired sagittal imbalance by anterior discectomy may influence ASD.

In Chapter 5, cervical sagittal alignment was demonstrated not to be altered by anterior discectomy at two-year follow-up. The alleged superiority of maintaining cervical sagittal alignment in arthroplasty was not confirmed. The occipito-cervical angle measured by occipital cervical inclination (OCI), being crucial in maintaining horizontal gaze, was identified as an important factor associated with radiological ASD.

OCI is a relatively new radiological parameter of the angle between the occiput and the cervical spine proposed by Yoon et al.[13] in 2017. Theoretically, the occipito-cervical angle is dictated by horizontal gaze, and if this angle is imbalanced it may well lead to compensation of subaxial cervical curvature, which will eventually lead to accelerated degeneration of the cervical spine[14,15]. This could explain the strong correlation of OCI with ASD detected in the current study. Notably, although there was significantly more ASD in patients with a higher OCI, the postoperative OCI angle did not change. Therefore, the result of this study suggests that accelerated degeneration of the cervical spine is dictated by the OCI angle. Thus, ASD of the cervical spine can be predicted if the OCI is known. Ideally a cut-off point of the OCI would be available. ASD is determined in this study in three ways and therefore three different values are available: for non ASD an angle of 102 to 104 degrees was measured, and for ASD angles varying between 108 and 113 degrees were observed. Yoon et al.[13] evaluated 200 normal, sagittally balanced patients (for both the whole spine and cervical spine) who were with no instability, spondylosis, degenerative change, deformity, or fracture. It was demonstrated that OCI was 103 degrees for male patients and 102 degrees for female patients, which is in agreement with the OCI value of non ASD patients reported in the current study. This suggests that an OCI angle of 102 to 104 degrees may indicate a sagittally balanced cervical spine, while the angle with higher degrees would have a risk to occur cervical disc degeneration, especially for those patients with more than 108 degrees. However, this 'normal' OCI value needs to be validated in healthy people with a large population. The cut-off value for OCI needs to be more accurate as well since the current study only shows a six to nine degrees difference between patients with and without ASD, which is not practical in the daily practice.

In the current study, no correlation between clinical outcome and cervical sagittal balance parameters could be demonstrated. The C2-C7 sagittal vertical axis (SVA) and T1 slope did not change in follow-up of surgery, the C2-C7 lordosis only increased minimally, and they did not demonstrate a correlation with ASD. Therefore, an absence of correlation to the clinical outcome is not surprising. However, previous studies did demonstrate an association between sagittal alignment parameters to the quality of life[12,16-18]. Tang et al.[19] found that the C2-C7 SVA was negatively correlated with physical-component summary (PCS) derived from the SF-36 and positively correlated with NDI scores after multilevel cervical posterior fusion. Hyun et al.[20] found that C2-C7 SVA greater than 43.5 mm was corresponded to severe NDI (>25). Nevertheless, Jeon et al.[21] and Kwon et al.[22], which compared similar radiographic parameters with NDI and visual analogue scale (VAS), reported that no cervical sagittal alignment parameters were significantly correlated with clinical outcome after ACDF surgery with three levels and two levels, respectively, which are consistent with our results. It has to be noted though that these authors described different surgical approaches. Tang et al.[19] and Hyun et al.[20] reported on patients with posterior cervical fusion surgery. Jeon et al.[21] and Kwon et al.[22] reported on multilevel anterior fusion surgery of the cervical spine and demonstrated threshold values for C2-C7 SVA of 40 mm[19] and 43.5 mm[20] in contrast to the values that we reported in the majority of patients (mean value: 20.6-22.5 mm).

Do Modic changes correlate with cervical disc degeneration or clinical condition?

Literature is scarce on Modic changes (MCs) in the cervical spine. However, from the literature available a positive association of cervical MCs with the prevalence of neck pain or disability and with the prevalence of disc degeneration was demonstrated. It has to be noted though that there are large variations in patient populations in which MCs are studied and that this explains the huge variation of the presence of MCs that is reported in literature (5% to 40%). All of the included studies demonstrate that MCs type II are predominant in the cervical spine and that C5-6 is the most frequent level followed by C6-7 at which MCs are diagnosed. As the endplates of C5-C7 sustain more weight than the higher levels and vertebrae are less limited in their excursion, greater momentum on the vertebral endplates are transmitted.

With a high quality of evidence, disc degeneration was positively correlated with MCs in the cervical spine, suggesting that the patients with MCs have more severe cervical disc degeneration. The only result of non-correlation was described by Davies et al.[23], who studied a small number of discs (106 discs) in comparison to the other studies (studying 256 to 6138 discs). Nevertheless, this is the only study using a histological method to evaluate disc degeneration. Since histological evaluation of intervertebral disc tissue is deemed the most accurate and sensitive method of identifying disc degeneration[24,25], more studies are needed to clarify the correlation between cervical disc degeneration assessed by histological methods and MCs.

Our own results demonstrated that one fifth of patients were detected to have MCs, being predominantly type II. One year after cervical discectomy, the prevalence of MCs increased to 30%, and remained predominantly type II. If observing MCs at the target level, 9% of patients had preoperative MCs, and this increased to 23% at one-year follow-up.

Although literature revealed an association between the presence of MCs with neck pain in the cervical spine, our data did not support this finding. This may be due to the absence of a proper scoring system for neck pain in these papers. In the present study, using accurate and representative measures for neck pain, it was shown both at baseline and at one year after surgery, that patients with and without MCs reported disabling neck pain in a comparable proportion. Our finding that there is absence of a correlation between MCs and neck pain is in agreement with earlier findings in our group by El Barzouhi et al.[26], which did not demonstrate a correlation between back pain and MCs. In follow-up research by Djuric et al.[27] though, an MCs dependent correlation between back pain/leg pain and the presence of macrophages in disc tissue in patients operated for sciatica due to a herniated disc was demonstrated. It is very interesting to evaluate whether that correlation is also valid for the cervical spine. Future research in our group is focussing on that.

Additionally, we studied the correlation between MCs and radiculopathy. MCs were hypothesized to represent an inflammatory process involving low virulent anaerobic bacteria[28], which may influence the spinal root and thus influence pain in the arm. The correlation of MCs with disabling arm pain was however not confirmed in the present study. This is consistent with a previous report from Kressig et al.[29], which studied 44 patients with cervical radiculopathy and which reported arm pain with the numerical rating scale.

Does the size of cervical disc herniation affect clinical condition?

Cervical radiculopathy is diagnosed based on anamnestic details and physical examination. Imaging of the cervical spine can reveal whether the radiculopathy is caused by compression of the spinal root, for instance by a herniated disc. Size and contour of disc herniations can be measured and identified on magnetic resonance image (MRI), as can the size and proportions of the spinal canal[30], Our data could not find a correlation between the size of disc herniation measured on MRI and the clinical condition at baseline. Neither did the size of the disc herniation correlate to outcome and this is thus not predictive for clinical outcome after surgical treatment at two-year follow-up.

Regarding the patients with cervical radiculopathy, roughly 80-88% of them will improve within four weeks of nonoperative management[31,32]. If severe symptoms persist, spinal surgery as a treatment modality is considered, and it would be of significance if the size of the herniation would correlate to the clinical burden. This cannot be confirmed in the current study. Thus, not only is the presence of a disc herniation on MRI not distinctive for the presence of clinical signs, neither is the size of the hernia indicative for the severity of complaints.

Similarly, the correlation between the size of disc herniation and clinical symptoms was also absent in lumbar spine: el Barzouhi et al. demonstrated that the predictive value of the size of disc herniation at baseline in decision making for lumbar disc surgery is absent[33], and that the size of disc herniation at baseline measured on MRI did not correlate to outcome at one-year follow-up[34]. Eventually, the MRI performed at one-year follow-up in patients with surgical treatment did not distinguish between those with a favourable outcome and those with an unfavourable outcome[35].

These data indicate that the value of MRI for patients with cervical radiculopathy that do not require surgery at that point is minimal. An MRI can only be helpful if the treating physician wants to exclude another compressing cause for the radiculopathy like a tumour for instance. However, literature does not provide evidence that tumours are demonstrated on MRI if other alarm symptoms (loss of body weight, tiredness etc.) are absent. It may be that the patients need reassurance and that an MRI can be helpful in that process. Furthermore, it is debatable whether society should bear those costs. It would be interesting to find out how much the patient would be willing to pay for this reassurance by an MRI.

Does heterotopic ossification in cervical arthroplasty affect clinical outcome?

As one of the major complications after receiving ACDA, which may counteract the ROM of the cervical spine, the incidence of heterotopic ossification (HO) was reported with huge variation, from 17.8% to 94.1%[36]. The published results of HO from randomized controlled trails (RCT) are scarce and of very low evidence[37].

It was demonstrated in chapter 9 that high grade HO is present in half of patients at the index level at two years after surgery. However, only in two thirds of these patients that led to the absence of motion at the target level. Moreover, ROM at the index level could not be maintained in 14% of patients that did not demonstrate HO.

The occurrence of HO varied in previous studies. Pimenta et al.[38] reported only one patient with grade I HO among 229 prosthesis implantations at one-year follow-up (PCM prosthesis). However, these are results from an observational study on the device, being industry sponsored. Mummaneni et al.[39] described a similar result that one case of HO was detected among 276 patients in a multicentre RCT with follow-up of two years (Prestige prosthesis). Although this was a comparative study, it was also industry sponsored. Nevertheless, several authors disputed this extremely low occurrence of HO, and reported percentages varying from 7.8% to 94.1%[40-45]. Partially, this considerable difference can be explained due to the dynamic nature of HO, which has a progressive pattern[46]. Leung et al.[42] presented 17.8% of HO occurrence in patients at 12-month follow-up (Bryan prosthesis), and Suchomel et al.[44] demonstrated 88% patients experienced HO at a mean follow-up period of four years (Prodisc-C prosthesis). In the study of Park et al.[45], the occurrence of HO increased from 78.8% (one year) to 94.1% (two years; Mobi-C prosthesis).

The findings on the activC and Bryan prostheses demonstrate results that do fit into the presented ranges of HO. However, in the present study, HO was correlated to ROM, which was not presented by the other authors. Remarkably, the prevalence of HO does not consequently lead to preservation or absence of motion. Therefore, judging HO only on lateral x-rays evaluating overgrowth of bone, according to the McAfee-Mehren scale, seems not to be sufficient. However, no correlation to clinical outcome could be demonstrated, in accordance with Zhou et al.[47] and Sundseth et al.[48]. Therefore, there are no practical implications of this finding. In studying maintenance of motion of the cervical spine after arthrodesis from an academic point of view though, evaluation of ROM should not be omitted.

Since the difference of architecture of the cervical disc prosthesis may affect development HO, in the Chapter 10, the incidence of HO were compared between activC and Bryan prostheses. It was demonstrated that the phenomenon of HO was independent of the type of implant used. However, the occurrence of HO had no detrimental influence on clinical outcome.

A difference in architecture between the activC and the Bryan prosthesis is the presence of a keel in the activC prosthesis. The purpose of a keel is to affirm the prosthesis tot the end plate in a solid way. However, a keel violates the cortical surface of the end plate and this can hypothetically result in overgrowth of bone, and thus in HO[41]. In the present study, the presence or absence of a keel did apparently not influence the formation and progression of HO. Although the ROM of the total cervical spine was larger in the Bryan prosthesis group, this did not affect clinical outcome. A larger ROM in the Bryan prosthesis group may (partially) be explained by the lower proportion of patients with severe HO in the Bryan group. The absence of a correlation between a ROM and clinical condition corresponds with our previous result demonstrating that there is no correlation between ROM and clinical outcome after cervical discectomy[49].

In conclusion, HO occurs in an unexpected high percentage at two years after surgery. The correlation to loss of motion is not as strong as thought before, but neither could the clinical relevance of HO be demonstrated.

Current status and future perspective

The role of cervical prosthesis in patients with single-level radiculopathy should be rethought. The results of this thesis counteract the intuitive feeling of the advantages of implanting a prosthesis after anterior cervical discectomy. A limitation is the relatively short follow-up of two years. We are currently evaluating the five-year follow-up data, and this may lead to even more convincing data. The absence of a correlation between motion preservation and the presence of ASD from the two-year data are however so strong, that we would be surprised if other conclusions would be revealed.

Another limitation is the analysis of ASD in which we focused on radiological ASD. Clinically relevant ASD would be represented by invalidating radicular symptoms due to degeneration at the adjacent level(s). If these complaints would be significantly invalidating, subsequent surgery would follow. The number of reoperations in the three groups for this diagnosis, would therefore be a suitable measure for clinical ASD. However, the number of reoperations in the NECK trial are too small to draw meaningful conclusions. Therefore, in evaluating the five-year follow-up data, the reoperation data will be combined with the long-term follow-up data of the PROCON trial, focusing on reoperations. We aim to further elucidate the correlation between clinically relevant ASD and preserved ROM.

The presence of MCs was correlated to radiological degeneration at the global cervical spine at baseline. However, this correlation could not be confirmed in the analysis considering only the target level and disappeared at one year after surgery. The absence of such correlation at one-year follow-up may be due to the lower number of MRIs that were available. Furthermore, it would have led to stronger results if the VAS neck pain was assessed for the patients in the PROCON study too. Finally, the prosthesis lacks proper evaluation of MCs at the adjacent levels, which lowered the number of patients in which MCs could be studied even more. Future studies are needed to investigate the change of the prevalence of MCs between the pre- and post-operative condition.

MCs are believed to represent the inflammatory and degenerative condition of the endplates. In our research group, it was found that an MCs dependent correlation between back pain/leg pain and the presence of macrophages in disc tissue in patients operated for sciatica due to a herniated disc is present. Future research will be focussing on whether that correlation is also valid for the cervical spine.

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