Comparing patient-based outcomes related to neutral zone and conventional mandibular dentures: a systematic review.

SADJ May 2017, Vol 72 no 4 p284 - p289

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SUMMARY
Introduction: neutral zone mandibular dentures are considered to be superior to conventional complete dentures.

Aim
To synthesize evidence regarding patient-based outcomes of treatment with complete mandibular dentures following static or dynamic methods of establishing denture shape.

Objective
To answer the question: “In edentulous patients, what is the effect of neutral zone dentures on oral health-related quality of life and preference as compared with conventional dentures?”

Methods
Medline, Wiley, Cochrane Central Register of Controlled Trials, Proquest, Elsevier, Trip and Science Direct databases were searched for clinical studies, using a specific search strategy.

Results
From a total of 103 records, 9 studies (participants n=270) were included in the review, based on specific selection criteria. Reports on oral health-related quality of life and preference produced conflicting results. Most patients reported improvement in retention, stability, comfort, chewing, speech with fewer recall visits for neutral zone dentures. High level of heterogeneity in study design, patient-based outcomes, instruments and statistical analysis was encountered, preventing meta-analysis. Quality of most studies was low, with small sample sizes (range: n=5-128), short follow-up periods (5 days-2 months), and high level of selection, performance and detection bias.

ACRONYMS:
CD: complete dentures
NZ: neutral zone method
OH-RQoL: oral health-related quality of life
PBOs: patient-based outcomes
RoBm: risk of bias

Conclusion
Results should be interpreted within the context of little and low-level scientific evidence.

INTRODUCTION
Conventional complete dentures (CD) have been the most common and only treatment modality for rehabilitation of edentulousness until the introduction of dental implants. Implant-retained or implant-supported prostheses have been proven to be superior to conventional CDs in terms of patient-based outcomes (PBOs). However, implant therapy may be out of reach of patients due to a variety of reasons. This group of patients is and will continue to be dependent on traditional CDs to restore form and function. It is assumed that these patients would benefit if dentures were made to be as stable and comfortable as possible.

The neutral zone (NZ) concept has been defined as “the potential space between lips and cheeks on the one side, and tongue on the other side; that area or position where forces between tongue and cheeks and lips are equal.” As early as 1746, Fauchard advocated that the inside and outside form and shape of dentures should be considered carefully in order to avoid conflict with lips, cheeks and tongue (in: Lott and Levine, 1966). Today, there is a high level of international consensus that teeth should be arranged in a neutral position and that arch form should assist stability during function.

While experts may agree, there appears limited scientific evidence based on patient feedback on the clinical benefits of CDs made according to a dynamic NZ method (NZD) over a biometric, static method of determining arch form and shapes of dentures. To date, no systematic review of clinical studies comparing PBOs of the mandibular NZD versus a conventional mandibular CD has been done. Therefore, the efficacy of NZDs compared with CDs has yet to be established.

The aim of this systematic review was to synthesize scientific data related to PBOs of mandibular CDs fabricated according to the NZ concept as compared with conventional methods.

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The objectives of this systematic review were:
1. To identify clinical studies comparing PBOs of mandibular NZDs versus conventional CDs
2. To extract and compare data based on PBOs of both types of dentures from studies included in the review
3. To perform a meta-analysis should the nature of the data identified from the clinical studies allow this to be done.

Search and Selection Strategy
Online searches were conducted for primary and ongoing studies to identify literature on the topic of NZ as a treatment strategy for edentulous adult patients. Two reviewers ([G] and [S]) independently and systematically searched for studies using the databases Medline, Wiley, Cochrane Central Register of Controlled Trials, Proquest, Elsevier, Trip and Science Direct, Medical subject headings (MeSH) terms were applied in databases which allowed this function. Key terms were combined using Boolean operators and search strategies were developed for each database using database specific functions. For PubMed, the search terms were: Neutral zone AND complete dentures and the following article types were selected: Case Reports, Clinical Study, Clinical Trial, Clinical Trial Phase I, Clinical Trial Phase II, Clinical Trial Phase III, Clinical Trial Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial. A similar search strategy was developed and modified according to the requirements of each database to ensure inclusion of all relevant studies. If databases allowed it, the following filters were applied: publication dates (1930-2017), species (human), ages (18+ years). No language filters were activated. Similar articles listed for each reference were also searched for possible inclusion. Based on titles and abstracts, a first selection of articles was done. Full texts of these selected articles were retrieved. Eligibility of these articles was determined using the customized eligibility tool. Reference lists of included studies were searched for additional records. Where full texts were unavailable, authors were contacted. Efforts were also made to obtain English versions of studies reported in other languages either by requesting them from the authors or using language experts to translate key findings. At every level of selection, consensus was reached between the two reviewers, adopting a lenient approach towards inclusion of records.

Data extraction
The two reviewers independently reviewed all included full-articles extracting the following data using the standardized data extraction sheet: authors, title, date, country, publication type, study method, estimate of bias, sample number, age, sex, interventions, outcomes, statistical analyses, results, conclusions, funding sources, ethics clearance, comments and correspondence required. Extraction sheets were compared. Differences were discussed until consensus was reached. Where more than one article reported different aspects of the same study, these were combined as a single study. Data from the included and excluded studies were summarized in tables of included and excluded studies respectively.

Qualitative analysis
The two reviewers independently evaluated the included studies for RoB using the Cochrane’s “Risk-of-bias assessment tool.” Risk of bias was assessed across the following components: Sequence generation and allocation concealment to prevent selection bias; Binding of participants, personnel and outcomes assessors to reduce performance bias; Incomplete outcome data to eliminate attrition bias; Selective outcome reporting to reduce selective outcome reporting bias; and other sources of bias, such as those related to specific study designs, early stoppage, fraudulent or extreme baseline imbalances. Risk of bias for each component was scored as ‘high’, ‘low’ or ‘unclear’. Bias was summarized in RoB graphs for each study in the Review Manager Software program.

Data synthesis and management
Results from the included studies were reported separately according to the interventions, controls, and reported outcomes. No imputation of missing data was carried out and as all outcomes were reported, authors were not contacted for these. Although a meta-analysis of outcomes across studies was anticipated, the included studies had different designs and reported outcomes differently. Hence, individual study results could not be pooled in a meta-analysis.
Table 1: Selection criteria for study eligibility

<table>
<thead>
<tr>
<th>Inclusion criteria (all criteria had to be present)</th>
<th>Exclusion criteria (any of the criteria present resulted in exclusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of study</strong></td>
<td>Clinical study (n=6)</td>
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<tr>
<td><strong>Type of participants</strong></td>
<td>Human Male and female ≥18 years of age Requesting replacement CD</td>
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<tr>
<td><strong>Type of interventions</strong></td>
<td>NZD with or without piezographically shaped flanges</td>
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<tr>
<td><strong>Type of comparisons</strong></td>
<td>PBOS from NZD and conventional CD, including patients’ existing dentures</td>
</tr>
<tr>
<td><strong>Type of PBOS</strong></td>
<td>Primary outcomes: OHQoL, preference, patient satisfaction Secondary outcomes: stability, retention, comfort, speech, chewing, need of recalls as reported by patients</td>
</tr>
<tr>
<td>CD = conventional mandibular denture</td>
<td></td>
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<tr>
<td>NZD = neutral zone mandibular denture</td>
<td></td>
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<tr>
<td>PBOS = patient-based outcomes</td>
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<tr>
<td>OHQoL = oral health-related quality of life</td>
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RESULTS

Results of the search are indicated in the PRISMA flow chart (Figure 1). One hundred and fifty-nine records were generated: 157 records from online search engines and two records found later on reference lists from included full-texts. A total of 56 duplicate records were removed, leaving 103 records which were assessed for eligibility. After reading titles and abstracts, a further 79 records were excluded. Full texts of the remaining 24 records were retrieved. A total of 10 articles, reporting results of 9 studies, were used for this review. There were no deviations from the protocol during the search.

The nine studies were placed in three different groups according to NZ methodology. In Group 1, NZDs were made using a NZ impression including piezographically shaping of flanges. In Group 2, NZDs were made without piezographically shaping of flanges. Group 3 included methods of Groups 1 and 2. Because of the different NZ techniques followed for these studies, it was decided not to combine results from studies in different groups.

There were seven studies in Group 1, reporting on a total of 137 patients. 7-14 Their follow-up periods were 1, 2, 4, 8 (±2) weeks. Two studies did not report a follow-up period. Two studies reported on OHQoL using two different versions of the OHIP, with conflicting results. Geerts (2017) (OHIP-20, n=37) reported no significant

Table 2: Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Statistics</th>
<th>Participants</th>
<th>Intervention</th>
<th>PBOS</th>
<th>Results</th>
<th>Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fahmy &amp; Kharat (1993) Saudi Arabia Clinical study</td>
<td>Cross-over Follow-up 2 weeks post-insertion</td>
<td>No stats for preference</td>
<td>Total: 10 Gender: not reported Age: not reported</td>
<td>1. new conventional CD 2. new NZD (Group 1)</td>
<td>Preference</td>
<td>10/10 preferred NZ denture (better comfort and speech, none mentioned mastication as reason for preference)</td>
<td>No instrument given for preference</td>
</tr>
<tr>
<td>Ladh et al. (2014) India Clinical study</td>
<td>Cross-over Follow-up: 2 months for each denture</td>
<td>Kruskal-Wallis with non-parametric Mann-Whitney tests, p&lt;0.05</td>
<td>Total: 10 Gender: 1 Female Age group: 60-80 yrs. Advanced ridge resorption</td>
<td>1. old denture (A) 2. swallowing (SNZ) &amp; phonetic (PNZ) NZ (Group 1)</td>
<td>Satisfaction Aesthetics Stability Retention Comfort Speech Soreness Food entrainment</td>
<td>For mandibular denture: Satisfaction, retention, stability, speech, comfort, chewing, statistically better for SNZ and PNZ as compared to A. No difference between SNZ and PNZ. No difference for soreness among 3 groups. Statistical difference in food entrainment between A and SNZ. Preference: higher for SNZ</td>
<td>16-item questionnaire with VAS scale answers (5-point Likert scale 0-4)</td>
</tr>
<tr>
<td>Rehmann et al. (2016) Germany Clinical study</td>
<td>1 cohort Follow-up: 4 weeks of wearing denture</td>
<td>Sign test</td>
<td>Total: 21 Gender: 10 females Age: mean 71 +/- 19yrs</td>
<td>1. unsatisfactory “new” CD 2. NZD (Group 1)</td>
<td>Satisfaction Denture function Mastication Stability</td>
<td>Stat sign improvement in OHQoL for NZ Masticatory test: no sign, change. 18/21 patients reported improved general stability and stability with chewing. 14/21 patients reported improved stability during speech</td>
<td>OHIP-14 Scale: stability clearly improved, improved, unchanged, deteriorated</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Country</td>
<td>Design</td>
<td>Follow-up</td>
<td>Patients</td>
<td>Length</td>
<td>Outcomes</td>
<td>Comments</td>
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</tr>
<tr>
<td>Rehmann et al. (2012)</td>
<td>Germany</td>
<td>Clinical study</td>
<td>1 cohort</td>
<td>Follow-up not reported.</td>
<td>no</td>
<td>Total 5</td>
<td>Age: mean 65yrs. Gender: not reported</td>
</tr>
<tr>
<td>Walsh and Walsh (1976)</td>
<td>South Africa</td>
<td>Clinical study</td>
<td>1 cohort</td>
<td>Prospective Randomization not reported. Follow-up: 1 week.</td>
<td>no</td>
<td>Total 30</td>
<td>Age: not reported. Gender: not reported</td>
</tr>
<tr>
<td>Zaigham (2006)</td>
<td>Pakistan</td>
<td>Clinical study</td>
<td>2 Cohorts</td>
<td>(12 x 2) Comparative Duration: not reported</td>
<td>Student t-test</td>
<td>Total 24</td>
<td>Gender: not reported. Age: not reported</td>
</tr>
<tr>
<td>Raja and Saleem (2009)</td>
<td>Pakistan</td>
<td>Clinical study</td>
<td>4 Cohorts</td>
<td>Follow-up 40 days after insertion Randomized sampling</td>
<td>t-test, chi square, Fisher’s Exact Test (p&lt;0.05)</td>
<td>Total 128</td>
<td>Gender: 39 females. Age: mean for 4 groups = 55.8-58.3yrs</td>
</tr>
<tr>
<td>Stromberg and Hickey (1985)</td>
<td>USA</td>
<td>Clinical study</td>
<td>Cross-over Follow-up</td>
<td>5 days (3 measurements: day 1, day 3, day 6)</td>
<td>no</td>
<td>Total 36</td>
<td>Gender: 2 female. Age: not reported</td>
</tr>
</tbody>
</table>

Difference in OHIP-scores between NZD and CD, while Rehmann et al. (2016) G-OHIP=14, n=21) found significant differences. Three studies (total n=71) reported on patient satisfaction. A total of 49 preferred NZDs, eight preferred CDs and 14 had no preference. Only one study had results statistically analyzed and found no significant difference in preference. This study was also the largest with the longest follow-up period (at least eight weeks as compared with two weeks and unknown). One study reported on satisfaction (n=10) with a significantly higher satisfaction for NZDs. Of the studies that reported on stability (total n=66), 50 out of 56 patients reported improvement for NZDs, and one study (n=10) reported a significant improvement for NZDs. Only one study (n=10) reported a statistically improved patient-reported retention, chewing, satisfaction, comfort, speech for NZDs. Walsh (1976) n=30) reported that nine patients needed recalls for NZDs, as compared with 21 for CDs. Group 2 had one study, reporting on 128 patients, with a follow-up period of 40 days. “Number of recalls” was used as a measurement for patient satisfaction. This study reported statistically less recalls for NZDs for patients who were edentulous for longer than two years. Group 3 also had one study, reporting on five patients, followed-up over five days, who all preferred manually formed flanges as compared with physiologically shaped flanges. The study characteristics of all included studies are summarized in Table 2. It must be noted that, regarding outcomes, only PBOs were extracted. Some studies also reported on clinician-based outcomes, but these outcomes are not reported since they fell outside the scope of the review. Excluded studies are recorded in Table 3, together with reasons for exclusion. For each included study, RoB was assessed as being ‘low’, ‘high’ or ‘unclear’ following Cochrane guidelines. Results are shown in a RoB graph and RoB summary (Figures 2 and 3). A detailed explanation of the results is as follows:

**ALLOCATION (SELECTION BIAS)**

Three of the nine studies were reported as randomized. For sequence generation: Three out of nine studies used some sequence to include patients into the study (Figures 2 and 3). One study drew lots, one used random tables and another used computer generated numbers. Where participants were asked to join the study or were included on the basis of their experiencing problems with old dentures, these were recorded as studies with a high risk of bias. Three of the studies used an allocation technique (directing the patient to a specific treatment group) eliminating selection bias. In two of the studies, allocation was unclear.

**BLINING (PERFORMANCE BIAS AND DETECTION BIAS)**

Blinding of either participants and/ or personnel was ensured in three of the nine studies (Figures 2 and 3). Blinding of participants only may thus be considered as in a single-blinded cross-over clinical trial. But this process was unclear in one of the studies. For all the included studies, the outcomes assessors were not blinded and these were all judged as having a high risk of bias.

**INCOMPLETE OUTCOME DATA (ATTRITION BIAS)**

All studies did not report the analysis to be completed by the “intention-to-treat” principle, nor did any of the studies lose any patients, thus results were not negatively affected. Moreover, all pre-specified outcomes (even though these were not pre-specified as primary or secondary outcomes) were reported, thus all the studies were judged to have a low risk of bias as there was no missing data (Figures 2 and 3).
## Table 3: Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason/s for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afroz et al. (2012)</td>
<td>Patients had oral submucous fibrosis</td>
</tr>
<tr>
<td>Astorga et al. (2013)</td>
<td>Participants’ characteristics suggested this study be excluded</td>
</tr>
<tr>
<td>Barrenás and Odman (1989)</td>
<td>Not NZ impression – only piezographically generated polished surfaces</td>
</tr>
<tr>
<td>Comun and Semohano (2015)</td>
<td>Case report, which initially formed part of inclusion criteria, but this later changed</td>
</tr>
<tr>
<td>Darwish et al. (2015)</td>
<td>The study did not include the NZ as intervention or control, and patients had implants</td>
</tr>
<tr>
<td>Kursoglu et al. (2007)</td>
<td>The study was excluded on the basis of the NZ not being the intervention or control and the study type or design also not meeting the inclusion criteria</td>
</tr>
<tr>
<td>Liu et al. (2015)</td>
<td>The study had the specific design but the NZ not the intervention or control</td>
</tr>
<tr>
<td>Macomére (2004)</td>
<td>The conventional denture was not the control</td>
</tr>
<tr>
<td>Miller et al. (1998)</td>
<td>No patient-based outcomes</td>
</tr>
<tr>
<td>Mustafa (2015)</td>
<td>No NZs or patient-based outcomes</td>
</tr>
<tr>
<td>Patel (2010)</td>
<td>The study was excluded on the basis of the NZ, the intervention or control and the participants not meeting the inclusion criteria</td>
</tr>
<tr>
<td>Pilton et al. (1985)</td>
<td>The study did not meet the type or design criteria</td>
</tr>
<tr>
<td>Perlw et al. (2016)</td>
<td>The study met the design criteria but not having the neutral zone denture as the intervention or control suggests exclusion</td>
</tr>
<tr>
<td>Tambe et al. (2014)</td>
<td>The NZ and characteristics of participants ensured exclusion of this study.</td>
</tr>
</tbody>
</table>

NZ = neutral zone mandibular denture

### SELECTIVE REPORTING (REPORTING BIAS)

All included studies pre-specified and reported all outcomes, but only the Geers (2017) study pre-specified these as primary and secondary outcomes. Most of the studies were not registered or approved by a review board, but because these studies reported all the outcomes as specified in the protocol, these were still judged as having a low risk of bias.

### OTHER POTENTIAL SOURCES OF BIAS

Studies were judged as having a low risk of bias if there were no reason to suggest any other potential sources of bias. Four other studies were judged as having a high risk of bias due to the poor design, small sample sizes, no blinding and/or no randomization and because no ethical approval was obtained.

### DISCUSSION

This SR was developed to answer the question: "In edentulous adult patients, what is the effect of NZDs on OH-IRGQOL, patient satisfaction, and preference as compared with that of conventional mandibular CDs?" Following the search strategy, nine studies were included in an effort to answer the question. The nine studies showed high levels of heterogeneity in terms of study design, sample size, gender, type of PBOs, instruments used to measure PBOs and RoB. Therefore, the answer to the question is: There exists no strong evidence on the beneficial effects of NZDs over conventional CDs when analyzing PBOs.

The nine selected studies were placed in one of three groups according to NZ technique used. In Group 1, four of the seven studies reported frequencies and/or ratios which were not statistically analyzed. Only two studies did a statistical analysis of some PBOs but used different instruments to measure these. Only two studies used validated instruments for measuring OH-IRGQOL, but reached conflicting results, with Geers (2017) reporting no difference in OH-IRGQOL between NZDs and CDs, while Rehmann et al. (2016) did identify differences. The reason might be that the study design differed, with Geers (2017) being a prospective cross-over study, while the Rehmann et al. (2016) study was a cohort study with the new NZD being compared with the patients’ existing dentures, made outside trial conditions. In the Ladhja et al. (2014) study, the main focus was comparing PBOs using a 16-item questionnaire using a 5-point Likert scale. This questionnaire was not provided. Hence, validity and reliability of the data could not be determined. Two different methods of making NZDs (swallowing and phonetics) performed statistically better than the CDS in satisfaction, retention, stability, comfort, speech and chewing hard food. However, they were compared with the patients existing dentures that were made outside the confines of the trial. Hence, for both the Ladhja et al. (2014) and Rehmann et al. (2016) studies, the fact that existing dentures were used as control may have caused bias towards a positive outcome for the NZDs. It has been reported that simply making new dentures already improves OH-IRGQOL, regardless of technique used. Another prospective single cohort study in Group 1 using the existing denture was by Walsh and Walsh (1976). The same argument can be used here to explain bias towards the positive results for NZDs as compared with CDs.

One study in Group 1 was prospective, using two cohorts, one receiving new CDs and one receiving new NZDs, but there was no other information on PBOs other than that all patients who received the NZDs preferred it (to the old dentures).

Groups 2 and 3 each had one study. The study in Group 2 was a prospective cohort with all patients receiving both a CD and NZD. However, the only PBO reported on was the number of recalls as a measure for satisfaction. The study in Group 3 was a cross-over study, but compared functionally shaped with manually shaped flanges. No literature could be found confirming a positive cause-effect relationship between number of recalls and patient satisfaction. The authors did not have a conventional denture as control – both dentures were NZ dentures. However, it was decided to include this study in the review for the following reason: Piezographically contoured flanges is one of the variables of the other two groups. This study showed that piezographically developed flanges did not influence retention as compared with manually shaped flanges, while all patients preferred the manually shaped flanges. This could be clinically relevant and should be investigated further because not having to dynamically shape flanges as part of the NZ procedures reduces clinical chair time.

Quality of the evidence of the research is dependent on several factors. By completing a RoB assessment, quality is evaluated and addressed. The quality of the evidence is an indication of the integrity of the study. The ethics in conducting a clinical study encompasses several aspects too, but the details of design and conducting the study and obtaining the expected data is equally important. It has been reported that developing a protocol and registering it with an Ethics review board or in trial registries and even publishing it, ensures rigor. The quality of the study is determined by the study design; and details must be such that...
results may be generalizable to larger populations. Randomised controlled trials and cross-over trials are of higher quality than cross-sectional and cohort studies. But if an RCT does not have all the steps such as ‘sequence generation,’ ‘blinding’ or ‘allocation concealment’ these may be downgraded and considered of poorer quality. The results may not be considered reliable and valid. Most of the included studies followed some guidelines to protect against bias even though not all the details were not reported. These were judged by using the Cochrane’s RoB tool. For example, completing power calculation to estimate sample size would reduce RoB. Sample sizes of the included studies ranged from five to 128, but only one study reported a power calculation.

The use of different study designs, methodologies, validated and unvalidated instruments and “results” not supported by data, prevented comparisons and the completion of meta-analysis among the studies. For example, Raja (2009) and Zaigham (2006) used subjective grading systems, also lacking calibration and reliability.

CONCLUSION
The nine studies incorporated in this SR showed a high level of heterogeneity in terms of study design, types of PBOs and instruments used to measure these PBOs.

The quality of the majority of clinical studies was low, with small sample sizes, short follow-up periods and presence of high level of selection, performance and detection bias.

Little high-level scientific evidence exists on the benefit of dynamic over static methods to determine mandibular CO form and shape.

Declaration
The authors received no funding for this research. The authors declare no conflict of interest.

References