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Improved quality of life after XeCl excimer transmyocardial laser revascularisation: Results of a randomised trial

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This study assessed the QOL in a randomised clinical trial investigating TMLR as a treatment for severe refractory angina pectoris.

Thirty patients were randomised to receive either XeCl excimer TMLR in combination with maximal cardiac medication, or maximal cardiac medication alone. QOL was assessed at baseline, 1, 3, 6 and 12 months using three different questionnaires: The Medical Outcomes Study - Short Form 24 (MOS, 7 domains), the Seattle Angina Questionnaire (SAQ, 5 domains) and the EuroQol Standardised Questionnaire (5 domains and a Visual Analogue Scale, VAS). The MOS and EuroQol are general health questionnaires and the SAQ is a disease (angina) specific questionnaire. The primary outcome measure was the change in score between baseline and 12 months.

TMLR treated patients scored significantly better compared to medicated patients in the EuroQol usual activity domain, the EuroQol VAS, the MOS social functioning, energy, general health and bodily pain domains and in the SAQ physical limitation, angina frequency and disease perception domains.

In conclusion, QOL significantly improved after XeCl excimer TMLR compared to medication. These results are similar to the improvements in QOL that have been reported following CO₂ and Ho:YAG TMLR.
Introduction

For the growing number of patients with severe angina pectoris refractory to standard treatments, improvement in quality of life (QOL) is one of the most important therapeutic goals. For one of these therapies, TMLR, significant improvements in QOL has been reported in randomised studies using CO\textsubscript{2} or Ho:YAG lasers [71-74,77]. For the third clinically used laser, the XeCl excimer laser, uncontrolled studies have also reported promising clinical improvements [110,111,126,127]. In these studies laser parameters were used that were similar to ours (see below) or a shorter pulse (20-40 ns) with a lower pulse energy (9-15 mJ/pulse) was used at a higher repetition frequency (up to 240 Hz). Here we present the QOL results of the first randomised study comparing XeCl excimer TMLR with maximal anti-anginal medication.

Methods

The QOL study presented here was part of a randomised study comparing XeCl excimer TMLR with maximal anti-anginal medication (see chapter 5). A total of 118 patients were evaluated for inclusion in this study. Thirty patients with angina pectoris NYHA class III or IV refractory to conventional treatments (medication, balloon angioplasty, bypass surgery) and with detectable reversible myocardial ischaemia were included and randomised in pairs between stand-alone (i.e. without bypass surgery) XeCl excimer TMLR with maximal anti-anginal medication (treatment group) or maximal anti-anginal medication alone (control group). Maximal anti-anginal medication was defined as the maximally tolerable dosage of β-blockers, calcium-antagonists and long-acting nitrates. All patients received maximal anti-anginal medication prior to enrolment. At randomisation, patients assigned to continued maximal medication were offered the opportunity to undergo TMLR after one-year follow up. The hospital medical ethical committee approved the study and all patients gave written, informed consent. In TMLR-assigned patients a left-lateral thoracotomy was performed, the heart was exposed and in the ischaemic area (as identified by myocardial perfusion scintigraphy) one transmyocardial channel per cm\textsuperscript{2} was created with an ECG-triggered (100-120 ms after the R-wave) XeCl excimer laser (MAX-20, Medolas, Munich, Germany) with a wavelength of 308 nm. Using 37-40 mJ/pulse, a pulse duration of 110 ns and a pulse frequency of 40 Hz, a flexible 1 mm
flat-tipped fibre was manually advanced to perforate the myocardium in 3-4 triggered cardiac cycles (4-5 pulses/cycle). Complete transmyocardial penetration was confirmed by transoesophageal echocardiography.

Assessment of quality of life
Assessment of quality of life was performed during visits to the outpatient clinic at baseline and at 1, 3, 6 and 12 months follow up. At the end of each visit, patients were asked to fill out the three questionnaires described below. Baseline assessment was performed after randomisation. In this study, we aimed to assess QOL very extensively and therefore (validated) Dutch versions of three different questionnaires were used: The Medical Outcomes Study - Short Form 24 (MOS-SF24, which is derived from the MOS-SF36 [128]), the EuroQol Standardised Questionnaire [113], and the Seattle Angina Questionnaire (SAQ) [112]. The MOS-SF24 and the EuroQol are both non-disease specific questionnaires. Although some overlap exists, the specific domains are mostly different and thus provide different information. The SAQ is a disease-specific questionnaire, especially designed to evaluate QOL in patients with angina pectoris and can therefore be used to evaluate the effect of TMLR more specifically. Table 1 gives an overview of the questionnaires and their domains.

The MOS-SF24 consists of 24 multiple-choice questions, which are subdivided in seven different health domains: Physical functioning, role functioning, social functioning, mental health, energy, general health and bodily pain. For each domain, the specific question scores are calculated into a domain score (from 0-100%) [128]

The EuroQol is composed of two parts. The first part consists of five multiple-choice questions, one for each of the following domains: Mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each question can be scored as: Having no problems (score = 3), some problems (score = 2) or severe problems (score = 1). Per domain question, we subtracted the baseline scores from the 12-month scores, resulting in a ‘change-score’ per domain per patient (a positive score indicates less problems at 12 months). The second part of the EuroQol consists of a Visual Analogue Scale (VAS). The VAS is a line that runs from 0% (worst imaginable health) to 100% (best imaginable health) on which patients directly score their perceived health status [113].

The SAQ consists of 19 multiple-choice questions which are subdivided in 5 domains: Physical limitation, anginal stability, angina frequency, treatment satisfaction and disease perception / quality of life. Again,
individual domain scores (from 0-100%) are calculated from the scores of the specific questions [112].

As shown in table 1, in general, higher MOS-SF24, SAQ and EuroQol domain scores indicate better physical, mental or social health. For the SAQ-physical limitation and SAQ-angina frequency domains higher scores respectively indicate less physical limitation and less frequent angina (which also corresponds to better health). The only exception is the MOS-bodily pain domain, where a higher score indicates more pain.

**Outcome measure, statistics and missing data analysis**

The primary QOL outcome measure was the change in score between baseline and 12 months. Thus, for each of the 18 MOS-SF24, SAQ and EuroQol domains and for the EuroQol VAS, this change was compared between the TMLR and control group. Furthermore, comparison of the average baseline domain scores was performed between the TMLR and control group. All comparisons were performed with two-tailed independent-sample t-tests (with Statistical Programme for Social Sciences (SPSS) software, version 11.0). Results are presented as mean ± SD.

In both groups, missing QOL scores were substituted using linear interpolation, except when the one-month follow up was missing in the TMLR group. Then, the average (TMLR) group changes were used to
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calculate substitutes for the missing values. In case of missing data due to mortality, the last observations obtained before death were used as input for the remaining follow up moments (‘last observation carried forward”).

Results

The baseline patient characteristics are shown in table 2. During TMLR, on average 46 ± 10 channels were created per patient. One patient died in the TMLR group (1 day after the operation due to a myocardial infarction), none in the control group. None of the patients were lost to follow up. At baseline and 12 months, no data were missing for both groups. At 1 month follow up, 3 patients in the TMLR group vs. 2 controls did not complete their questionnaires. At 3 and 6 months FU, this was the case for 3 vs. 0 and 2 vs. 1 patient respectively.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TMLR (n = 15)</th>
<th>Maximal medication (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>62.7 ± 7.6</td>
<td>58.1 ± 7.6</td>
</tr>
<tr>
<td>Men : women</td>
<td>13:2</td>
<td>14:1</td>
</tr>
<tr>
<td>Average NYHA angina class (mean ± SD)</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>LVEF (% , mean ± SD)</td>
<td>55 ± 9</td>
<td>56 ± 6</td>
</tr>
<tr>
<td>Previous bypass surgery (n)</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Previous coronary angioplasty (n)</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2. Baseline patient characteristics. LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

Medical Outcomes Study (MOS)

The results of the MOS-SF24 domains are presented in figure 1. There were no baseline differences between the TMLR and the control group except for the physical functioning domain where the TMLR group scored significantly higher than the control group. Social functioning, energy and general health were significantly more improved between baseline and 12 months in the TMLR group than in the control group (see figure 1 for p-values). Bodily pain was significantly more decreased between baseline and 12 months in the TMLR group compared to the control group. In the remaining domains (physical functioning, role functioning and mental health) no significant differences between the TMLR and the control group were observed.
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**EuroQol**

Results of the 5 EuroQol domains are presented in table 3. Only the improvement in the ‘usual activities’ domain 12 months after TMLR was significantly higher in the TMLR group than in the control group. The EuroQol VAS scores were significantly more improved between baseline and 12 months in the TMLR group than in the control group (figure 2).

<table>
<thead>
<tr>
<th>Domain</th>
<th>TMLR Baseline</th>
<th>TMLR 12 months</th>
<th>Maximal medication Baseline</th>
<th>Maximal medication 12 months</th>
<th>p-change baseline vs. 12 m†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>2.3 ± 0.4</td>
<td>2.3 ± 0.5</td>
<td>2.1 ± 0.3</td>
<td>2.3 ± 0.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Self care</td>
<td>2.7 ± 0.5</td>
<td>2.9 ± 0.4</td>
<td>2.7 ± 0.5</td>
<td>2.6 ± 0.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Usual activities</td>
<td>1.9 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Pain / discomfort</td>
<td>1.8 ± 0.7</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anxiety / depression</td>
<td>2.5 ± 0.7</td>
<td>2.7 ± 0.6</td>
<td>2.3 ± 0.5</td>
<td>2.2 ± 0.7</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 3. Domain scores of the EuroQol questionnaire (mean ± standard deviation). Scores are on a scale of 1-3 and higher scores indicate better health. † the change between baseline and 12 months was compared between the TMLR and maximal medication group (primary outcome measure); m = months; n.s. = non-significant (p > 0.05).

**Seattle Angina Questionnaire (SAQ)**

Results of the SAQ domains are presented in figure 3. There were no baseline differences between the TMLR and the control group except for the treatment satisfaction domain where the TMLR group scored significantly higher than the control group. Physical limitation, angina frequency and disease perception were significantly more improved between baseline and 12 months in the TMLR group than in the control group (see figure 3 for p-values). In the remaining domains (angina stability and treatment satisfaction) no significant differences between the TMLR and the control group were observed.

**Discussion**

Patients with severe refractory angina are known to have a poor QOL [129]. They are heavily disabled by their angina, which not only results in a limitation of their physical possibilities, but can also negatively affect their mental state and social life (also observed in this study as indicated by the low baseline QOL scores). Therefore, when evaluating the effect of alternative therapies in these patients, QOL should be the most important endpoint and should therefore be assessed extensively using general and disease specific questionnaires.
Figure 1 A-G. Domain scores of the Medical Outcomes Study - Short Form 24. For the domains social functioning (C), energy (E), general health (F) and bodily pain (G), the change between baseline and 12 months was significantly greater in the TMLR group compared to the control group (primary outcome measure), indicating better health in the TMLR group. * = level of significance for the change in score (between baseline and 12 months) compared between the TMLR and control group. Pre = baseline assessment; m = month(s); QOL = quality of life.
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Figure 2. Scores of the EuroQol Standardised Questionnaire’s Visual Analogue Scale. The change between baseline and 12 months was significantly greater in the TMLR group compared to the control group (primary outcome measure), indicating better health in the TMLR group. † = level of significance for the change in score (between baseline and 12 months) compared between the TMLR and control group. Pre = baseline assessment; m = month(s); QOL = quality of life.

Figure 3 A-E. Domain scores of the Seattle Angina Questionnaire. For the domains physical limitation (A), angina frequency (C) and disease perception (E), the change between baseline and 12 months was significantly greater in the TMLR group compared to the control group (primary outcome measure), indicating better health in the TMLR group. † = level of significance for the change in score (between baseline and 12 months) compared between the TMLR and control group. Pre = baseline assessment; m = month(s); QOL = quality of life.
In the study presented here, significantly improved QOL was found at 12 months in the XeCl excimer TMLR group (compared to the control group). The improvement was observed in the MOS-SF24 social functioning, energy, general health and bodily pain domains, in the SAQ physical limitation, angina frequency and disease perception domains and in the EuroQol ‘usual activities’ domain and the EuroQol VAS. Five of the MOS-SF24 and SAQ domains did not improve significantly. Of these 5 domains, two already showed a significant difference at baseline (MOS-SF24 physical functioning and SAQ treatment satisfaction). Since the QOL assessment was performed after randomisation, the difference in baseline SAQ-treatment satisfaction score could express that patients were more satisfied with their treatment if they were randomised into the TMLR group. This positive bias might also have played a role in the baseline difference in the MOS-physical functioning domain. It is furthermore possible that this bias may have played a role for the control patients. With the SAQ-treatment satisfaction domain for instance, the significant baseline difference had disappeared at 12 months, when the control group came close to receiving TMLR. Therefore, the differences between the TMLR and control group might have been even greater if, at baseline, the control group had not been offered treatment one-year after randomisation.

It is interesting to see that in all three questionnaires, there is a general tendency for the differences between the two groups to be most pronounced at 3, 6 and 12 months while the 1-month results are more similar between the two groups. The absence of general improvement in the TMLR group at 1 month follow up is likely due to the recovery from the operation.

**Comparison to other randomised trials**

The improvements in QOL observed in this study are similar to the improvements reported by other randomised TMLR studies using CO$_2$ or Ho:YAG lasers. Four out of the five published randomised studies have also assessed QOL. One used the Duke Activity Status Index (Allen et al., Ho:YAG laser [72]), one used the SAQ (Burkhoff et al., Ho:YAG laser [73]), one used both the MOS-SF36 and the SAQ (March, Frazier et al., CO$_2$ laser [71,74], detailed QOL results from this last study were later published by Spertus et al. [77]) and one did not report the QOL assessment method nor its results (Schofield et al., CO$_2$ laser [75]). The first three studies reported significant improvements in the TMLR groups compared to the control groups. In the study by Burkhoff, all 5 domains of
the SAQ were significantly improved at 12 months in the TMLR group vs. the control group. When comparing the 3 improved SAQ domains of our study with the same domains of the study by Burkhoff et al., similar improvements were observed in both the TMLR and the control groups. In the study by Burkhoff et al., the remaining 2 SAQ domains (treatment satisfaction and angina stability) were also significantly improved. The absence of a difference between the two groups in the treatment satisfaction domain between baseline and 12 months in this study is likely due to the fact that the control patients also underwent TMLR shortly after their 12 months follow up. Their anticipation towards the treatment after 12 months follow up likely increased their treatment satisfaction, thus decreasing the difference in satisfaction with the TMLR group. The non-significant difference in the angina stability domain in this study may be due to the (non-significant) difference between the two groups that was already present at baseline. Spertus et al. only presented results on 3 of the 5 SAQ domains (physical limitation, angina frequency and disease perception) and showed that these were all significantly improved in the TMLR vs. the control group. Interestingly, these 3 domains were also the ones that improved significantly in the study reported here. Spertus et al. furthermore divided the MOS-SF36 domains into a physical and a mental component and found significant improvements in both components. Unfortunately, the specific MOS-SF36 domain results were not provided and could therefore not be compared to the results presented here.

Other treatments for refractory angina
Besides TMLR, several other techniques such as PMR and SCS are currently in use for the treatment of refractory angina pectoris, and studies investigating these techniques have reported improvements in QOL [130], which seem comparable to those observed in this study [40]. However, since QOL assessment was not performed as extensively as in this study and other QOL assessment methods were used, a definitive statement on which technique provides the best improvement cannot be made until the different techniques have been compared within one study.

Study limitations and placebo effect
As mentioned above, there are two important points in this study that may be considered limitations, as they could have created bias in the QOL results. The first limitation is the assessment of baseline QOL scores after randomisation. This may have created a positive baseline bias in the treatment group as well as a negative bias in the control group. The latter
could also play a role as a consequence of the study design (i.e. non-blinded). The second limitation that could have introduced a bias is the fact that at baseline, patients randomised to the control group were offered treatment after they had completed their one-year follow up. This may have introduced a positive anticipation bias, especially towards the end of the follow up period when they were about to be treated. However, although these two limitations should be considered when interpreting the results, it is also important to realise that they both tend to give an under-estimate of the actual effect (given the method of statistical analysis in this study). Therefore, since it may then be speculated that the real effect is even more pronounced than currently observed, the limitations do not change the general conclusion of this study, i.e. that patient’s QOL is significantly increased after TMLR.

A much-debated point in the clinical efficacy of TMLR has been the relevance of the placebo effect. Fuelled by the absence of (reproducible) effects of TMLR on perfusion, some believe that the improvement is mainly due to the placebo effect. Indeed, the fact that TMLR is an option for patients who thought there were no options anymore, makes them very anxious to feel better after the treatment, thus introducing a placebo bias, especially in QOL assessment. Furthermore, clinical improvements in patients who only received a thoracotomy or sternotomy without further treatment have been described. The extent of these effects will probably never be fully known since it is impossible to perform a sham operation in a fully blinded TMLR study. Despite these explanations, we believe that the improvements in QOL found in this study cannot be fully explained by placebo effects. Although it can have some effect on the clinical outcome, this is likely to be short-term (up to 6 months) and cannot explain the persistent improvement found at one-year in this and up to 5 years in other studies [109], for which TMLR-induced cardiac denervation currently appears the most likely explanation.

In conclusion, the results of this study show that XeCl excimer TMLR generally improves the QOL at 12 months follow up of patients with severe refractory angina, with results that are comparable to those after CO$_2$ or Ho:YAG TMLR. Whether these improvements are sustained at longer follow up has to be awaited.