

HTA-Report | Summary

## Intravascular brachytherapy for peripheral vascular disease

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### Scientific background

Peripheral artery occlusive disease (PAOD) is a blood circulation dysfunction of the peripheral arterial vessels, which is caused through stenosis or occlusion of the arteries supplying the extremities. In more than 90 % of the cases, the vessels in the pelvic and/or in the legs are affected. The PAOD can pass asymptotically, refer to strain related pain in the extremities (claudicatio intermittens), pain in rest, up to necroses of the limbs with life threatening complications such as sepsis (blood poisoning).

In younger age groups, men are more frequently affected of PAOD than women. However, with increasing age women show a comparable incidence. Only approximately one-third of the PAOD patients shows clinical symptoms. The prevalence of claudicatio intermittens in over 65-year-old men is approximately 3 %. Within five years, on average 3 % of all men over 35 years newly develop symptoms of PAOD. Data about costs of PAOD in Germany are insufficient.

An important component of the therapy in PAOD is the "walking training". Additionally, medicines which influence the risk factors, improve blood flowing capacity or expand vessels (vasoactive substances) are used. Moreover, endovascular vessel expansions (percutaneous transluminal angioplasties, PTA) performed using balloon dilatation, sometimes also including stenting, i. e. implantation of small tubes, so called stents. Surgical interventions are also available (local thrombus endarterectomy, bypass surgery). In an advanced stage of PAOD, a leg amputation can serve as a final option.

The repeated stenosis of the vessels (restenosis) considered to be the Achilles' heel of the PTA (recurrence rate: 30 to 60 %). By the intravascular irradiation, called intravascular (endovascular) brachytherapy, the ray source is placed directly within the vessel close to the vessel wall that should be irradiated. The irradiation is performed with gamma or beta rays with the goal to prevent inflammatory proliferative restenosis. The intravascular brachytherapy after PTA promises a reduced restenosis and less frequently need of follow-up interventions.

It may be hypothesized that after PTA with intravascular brachytherapy treated PAOD patients show better long-term clinical results than conventionally treated PAOD patients. Systematic evaluations of the current data on clinical efficacy of this intervention are still missing. The cost-effectiveness of the intravascular brachytherapy in comparison with no brachytherapy after PTA and whether special ethical, social or legal concerns arise from the use of the intravascular brachytherapy remains questionable.

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## Research questions

### Medical evaluation

- Is the medical efficacy of intravascular brachytherapy proven in the treatment of PAOD?
- And if yes, to what extent is it efficacious and what are the possible complications in comparison with no brachytherapy?

### Health economic evaluation

- What is the cost-effectiveness of intravascular brachytherapy in PAOD in comparison with no brachytherapy?

### Ethical, social and legal evaluation

- Which specific ethical, social and legal concerns are to be considered in the use of intravascular brachytherapy in PAOD?

## Methods

A systematic literature search was performed in August 2007 in the medical electronic databases MEDLINE, EMBASE, SciSearch, BIOSIS, ETHMED, INAHTA, NHS-CRD-DARE, NHS EED, SOMED, Cochrane database etc. The search strategy was restricted on the publication data beginning from 2002 as well as on the languages German and English. The evaluation of the literature search results was performed in three steps (titles, summaries, complete publications). Two independent reviews were involved in the selection of the relevant publications.

### Medical evaluation

The medical evaluation included randomized controlled trials (RCT) on the comparison of intravascular brachytherapy with no brachytherapy or with other intervention(s). The data from the included RCT were summarized based on a prepared extraction form concerning methods of the RCT, patient's characteristic, performed interventions and investigated end points. RCT were reviewed with respect to their methodical quality and validity. In the information synthesis study results were analyzed with respect to their statistical heterogeneity and if reasonable were summarized in meta-analyses. The meta-analyses calculated relative risks (RR) using a "random-effect" model.

### Health economic evaluation

In the course of health economic evaluation the literature was searched for studies and systematic reviews on the health economic comparison of brachytherapy with no brachytherapy or with other intervention(s). As no relevant health economic publications could be identified, a health economic modeling with clinical assumptions derived from the meta-analyses (medical evaluation) and current economic assumptions derived from the German Diagnosis Related Groups (G-DRG, version 2007, diagnosis and resource use based classification system of medical care cases) was performed from a restricted societal perspective with a time horizon of up to one year. The base-case value was assumed to be 2,800 Euro.

## Ethic, social and legal evaluation

In course of the ethic, social and legal evaluation the literature was searched for publications with an explicit view towards ethical, social and legal aspects in the use of intravascular brachytherapy in PAOD.

## Results

### Medical evaluation

The literature search yielded 353 hits. Twelve publications about seven RCT were included into the medical evaluation.

- *Studies on the comparison of brachytherapy vs. no brachytherapy, both after successful balloon dilatation.*

Two from three RCT on the comparison of brachytherapy vs. no brachytherapy, both after successful balloon dilatation, showed a significant reduction in the rate of restenosis, both in the per protocol and in the intention-to-treat analyses (in follow-up at six and/or twelve months). The results of the RCT showed no statistical heterogeneity. The RR for restenosis was found to be 0.47 (95 % CI: 0.33 to 0.69) in the meta-analysis for the per protocol and 0.62 (95 % CI: 0.46 to 0.84) for the intention-to-treat data (significant in both analyses). Respectively, the cumulative clinical patency rate was significantly higher for brachytherapy at twelve months (73.6 % vs. 51.9 %; data only for one study).

The rate of repeated revascularisations was neither in the single study nor in the meta-analysis of the studies significantly different between the study groups at six and/or twelve months. The results of the studies for the rate of repeated revascularisations showed no evidence of statistical heterogeneity, the RR in the meta-analysis was found to be 0.63 (95 % CI: 0.38 to 1.05).

The mortality in the brachytherapy group was low in follow-up at twelve months, one patient in each of the two RCT died, respectively (mortality data for the control group only in one study).

In the subgroup analysis in one RCT for diabetic vs. non-diabetic patients, patients with de novo vs. restenotic lesions, with stenosis vs. occlusion, with 4 to 10 cm long vs. over 10 cm long lesions the recurrence rate was consistently lower in the brachytherapy group than in the control group at six months. However, significant results were found only for patients with restenotic, over 10 cm long lesions and occlusions. In a separate analysis of data for de novo and restenotic lesions from two studies significant results were found for restenotic lesions.

At 24 months in one study the rate of cumulative patency of the revascularized vessel segment was significantly higher in the brachytherapy group both in the intention-to-treat and in the as treated analyses (54 % vs. 27 % and 77 % vs. 39 %, data only for one study).

The five year results (data only for one study) showed similar rates of repeated restenosis in patients with and without performed brachytherapy (both 72.5 %). Time to recurrence after brachytherapy was significantly longer (17.5 vs. 7.4 months,  $p < 0.01$ ). The rate of repeated revascularisations of the target vessels was also similar (70.6 % vs. 72.5 %, difference was not statistically significant). From a total of 17 patients died, seven were in the brachytherapy group. The mortality and the recurrence rate of the clinical symptoms were not significantly lower in the brachytherapy group (13.7 % vs. 19.6 % and 56.6 % vs. 67.6 %).

- *Studies on the comparison of brachytherapy vs. no brachytherapy, both after PTA with optional stent implantation.*

From three RCT on the comparison of brachytherapy vs. no brachytherapy, both after PTA with optional stent implantation (in case of dissections and/or

insufficient results of the balloon dilatation) only one study showed a significant reduction in the rate of restenosis, both in the per protocol and in the intention-to-treat analyses (in follow-up at six months). Only patients with de novo lesions were included in this study. The results of all three RCT showed no statistical heterogeneity. In the meta-analysis the RR for restenosis was found to be 0.58 (95 % CI: 0.42 to 0.80) in the per protocol and 0.76 (95 % CI: 0.61 to 0.95) in the intention-to-treat analyses (significant in both cases). Respectively, the survival without claudicatio intermittens in one RCT was significantly higher after the brachytherapy at six months (77% vs. 61%,  $p < 0.05$ ). The rate of the cumulative patency of the revascularized vessels in this study was also higher after brachytherapy (significance not reported).

The rate of repeated revascularisations was significantly different between study groups in two RCT and in the meta-analysis of all RCT. The results of the studies for the rate of repeated revascularisations showed no evidence of statistical heterogeneity, the RR in the meta-analysis was found to be 0.47 (95 % CI: 0.27 to 0.83).

One or two patients in each study group died up to follow-up at six or twelve months (difference not statistically significant). As an important complication in a study, late thrombotic occlusions after discharge of the clopidogrel treatment were observed in 27% of the stented patients after brachytherapy vs. in no stented patients without brachytherapy ( $p < 0.05$ ).

In the average follow-up of three years no significant differences in the restenosis rate, freedom from angiographic restenosis, cumulative sustained clinical success rate and in the rate of the repeated revascularisations could be found in the combined analysis of the data for one clinic from two RCT. A total of 14 patients died during this follow-up.

*- Studies on the comparison of brachytherapy vs. no brachytherapy, both after stenting.*

The single study on the comparison of brachytherapy vs. no brachytherapy, both after stenting (stenting was performed in case of insufficient results after balloon dilatation) no significant reduction in the rate of restenosis was shown both in the per protocol and in the intention-to-treat analyses in follow-up at six months. The RR for restenosis rate was found to be 0.96 (95 % CI: 0.54 to 1.72) in the per protocol analysis and 1.12 (95 % CI: 0.67 to 1.87) in the intention-to-treat analysis. Respectively, the rate of clinical patency of the revascularized vessels was not significantly different between the two groups (69 % vs. 74 %).

The rate of repeated revascularisations at six months was also not significantly different between both study groups. The RR for repeated revascularisations was found to be to 0.78 (95 % CI: 0.39 to 1.57).

Four patients died during the one-year follow-up of the study. Early thrombotic occlusions were found significantly more frequently in patients after brachytherapy (17 % vs. 4 %,  $p < 0.05$ ). Late thrombotic occlusions were also observed more frequently in the brachytherapy group (7 % vs. 0 %,  $p = 0.05$ ), in two of all three patients after discharge of clopidogrel.

In the twelve month follow-up the recurrence rate in the brachytherapy group was not significantly lower (43 % vs. 59 %), the rate of clinical patency of the revascularized vessels was not significantly higher, respectively (62 % vs. 54 %). At 24 months, the rate of cumulative patency of the vessels and the rate clinically patency of the revascularized vessels were not significantly higher in the brachytherapy group (43 % vs. 33 % and 57 % vs. 50 %).

## Health economic evaluation

The literature search yielded 73 hits. No publication concerning health economic aspects could be included into the evaluation.

### Health economic modeling

The estimated additional costs of the brachytherapy corresponding to the used G-DRG were approximately 1,655 or 1,767 Euro. Respectively, the incremental cost-effectiveness ratio (i. e. additional costs per additional effect) per avoided restenosis was found to be to

- 8,484 Euro (95 % CI: 5,970 to 20,150 Euro) or 9,058 Euro (95 % CI: 6,374 to 21,514 Euro) for the comparison of brachytherapy vs. no brachytherapy after successful balloon dilatation,
- 19,027 Euro (95 % CI: 11,709 to 91,328 Euro) or 20,314 Euro (95 % CI: 12,501 to 97,509 Euro) for the comparison of brachytherapy vs. no brachytherapy after PTA with optional stent implantation and
- -39,646 Euro (95 % CI: -5,468 to 14,417 Euro) or -48,330 Euro (95 % CI: -5,839 to 15,393 Euro) for the comparison of brachytherapy vs. no brachytherapy after stenting.

Using per protocol data for avoided revascularisations (no intention-to-treat data were available) and corresponding to the used G-DRG the total additional costs per patient assigned to brachytherapy were found to be

- 1,417 Euro (95 % CI: 1,256 to 1,687 Euro) or 1,529 Euro (95 % CI: 1,368 to 1,799 Euro) for the comparison of brachytherapy vs. no brachytherapy after successful balloon dilatation,
- 1,434 Euro (95 % CI: 1,350 to 1,584 Euro) or 1,546 Euro (95 % CI: 1,462 to 1,696 Euro) for the comparison of brachytherapy vs. no brachytherapy after PTA with optional stent implantation and
- 1,492 Euro (95 % CI: 1,204 to 2,076 Euro) or 1,604 Euro (95 % CI: 1,316 to 2,188 Euro) for the comparison of brachytherapy vs. no brachytherapy after stenting.

According to the used G-DRG the incremental cost-effectiveness ratio per avoided revascularization was found to be

- 14,468 Euro (95 % CI: 7,655 to -127,457 Euro) or 15,612 Euro (95 % CI: 8,338 to -135,919 Euro) for the comparison of brachytherapy vs. no brachytherapy after successful balloon dilatation,
- 15,746 Euro (95 % CI: 10,767 to 54,230 Euro) or 16,976 Euro (95 % CI: 11,660 to 58,065 Euro) for the comparison of brachytherapy vs. no brachytherapy after PTA with optional stent implantation and
- 22,287 Euro (95 % CI: 6,486 to -11,967 Euro) or 23,960 Euro (95 % CI: 7,089 to - 12,612 Euro) for the comparison of brachytherapy vs. no brachytherapy after stenting.

## Ethic, social and legal evaluation

No publication concerning ethic, social or legal aspects of the intervention could be included into the evaluation.

## Discussion

### Medical evaluation

Partially poor performing and reporting quality of the RCT hinder the interpretation and the transferability of the study results.

The study hypothesis with corresponding calculation of the participant num-

ber was reported only in four, the method of the randomization in three publications. For three RCT no data for the difference in patient characteristics between the study groups were reported. A sham irradiation for the purpose of the patients blinding was performed in three RCT. RCT presented usually only results for per protocol analysis, that means that the patients deviating from the treatment protocol were excluded from the analysis. In five study evaluations, the completeness of the data for clinical follow-ups was approximately 82 to 95 %.

The analyzed RCT differed with respect to the patient baseline characteristic (the proportion of patients in different PAOD stages, the proportion of patients with de novo or restenotic lesions, with different stenosis lengths), methods of the brachytherapy performance (irradiation dose and its homogeneity), definition of the end points, method of the end point analysis as well as the duration of the follow-up. However, no statistically significant and also no clearly visible trends could be observed if the study RR were analyzed in relation to these parameters.

### **Health economic evaluation**

Health economic modeling was performed from a restricted societal perspective. In this modeling the costs of possible rehabilitations, costs of the work loss due to illness as well as intangible costs were not considered since referring data were missing in the studies.

The use of clinical assumptions from the current meta-analysis of the RCT enabled in the health economic modeling the highest evidence level (highest reliability) for the determined results, if the results of the single studies are considered to be valid. The use of current cost assumptions for Germany from the year 2007 over the corresponding G-DRG enables a good approximation of the current brachytherapy related costs for the German health care system.

### **Ethic, social and legal evaluation**

The access of different social and ethnic groups to DES as well as independence and privacy of the patients seems not to be restricted in Germany. The informed consent of the patients and its documentation are important aspects in the use of brachytherapy in PAOD patients.

From an organizational point of view a limiting factor for the widespread use of brachytherapy with gamma irradiation is the necessity of the spatial connection of the catheter and brachytherapy departments.

### **Conclusions**

From a medical point of view the use of brachytherapy in PAOD after successful balloon dilatation can be recommended for medium-term improvement of the vessel patency (reduction of the one-year restenosis rate) and for lengthening of the time to recurrence. The possible appearance of different long-term side-effects should be proven. From a health economic point of view and based on the current data the question about the cost-effectiveness of brachytherapy after balloon dilatation is still not answered yet.

Based on the current data the use of brachytherapy after stenting in PAOD cannot be recommended neither from a medical nor from a health economic point of view. Further studies could clarify this issue.