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# Treatment of subcutaneous nodules after infusion of apomorphine; a biopsy-controlled study comparing 4 frequently used therapies

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ABSTRACT

This study aimed to provide clinical evidence for existing treatments of subcutaneous nodules after subcutaneous infusion of apomorphine, using a biopsy-controlled prospective crossover design of four treatments. We demonstrated that dilution of apomorphine significantly improved patient satisfaction, while subcutaneous hydrocortisone reduced nodule size, however with no differences in the histopathology.

Subcutaneous nodules are the most common adverse events of continuous subcutaneous apomorphine infusion used in advanced Parkinson's disease (PD) [1]. However, the histopathology of these apomorphine-induced nodules is poorly understood [2,3]. Thereabove, the current treatment modalities of subcutaneous nodules are limited and not evidence-based. Only the use of ultrasound has been studied in a small-sample randomized controlled trial, showing no significant differences on tenderness and hardness of the nodules, and is therefore not used in our daily practice. The objective of this study was to provide clinical evidence for treatment options used in daily practice, supported by biopsies, taken after every intervention.

We designed a five-way, open-label, crossover trial. Each patient received a fixed sequence of five treatment modalities, including no treatment (1), massage with a spikey ball (2), topical hydrocortisone 1% (3), dilution of apomorphine 0.5% to 0.25% (4), and subcutaneous hydrocortisone 10mg as pretreatment (5). Subcutaneous hydrocortisone was administered before the infusion of apomorphine, via the same catheter. Each treatment was applied for fourteen days, followed by a wash-out period of fourteen days to account for carryover effects. The primary outcome was patient satisfaction based on absolute change on the global perceived effect (GPE) scale which is a 7-point Likert scale, ranging from absolutely not satisfied (1) to absolutely satisfied (7). Secondary outcomes were nodule size, erythema size, change in serum eosinophilia and histological changes in subcutaneous tissue obtained by skin biopsies. Patients marked two subcutaneous nodules; after one day of treatment and after eleven days of treatment. After fourteen days of treatment a biopsy was taken of both nodules, representing a maturation of fourteen days and three days, in order to assess long-term and short-term treatment effects. The biopsy of a nodule with a maturation of 3 days was considered to be the most specific for subtyping the subcutaneous responses. A generalized linear model for repeated measures was applied with post-hoc analyses to examine treatment effects.

The study was approved by the local research Ethics Committee (University Medical Centre Groningen, the Netherlands) and registered in ClinicalTrials.gov registry (NCT02230930).

Thirteen patients were included of whom ten patients (age 68.4 ± 9.6 years, PD duration 13.4 ± 5.1 years; further details in Supplement) completed all treatment arms. One patient withdrew shortly after providing written informed consent, before administration of any active treatment. One patient passed away during the study. Her death was related to heart failure, and not to the treatment with apomorphine or topical hydrocortisone as active study drug. The last patient stopped apomorphine treatment due to a perceived lack of efficacy and decided to switch to levodopa/carbidopa intestinal gel infusion.

The primary and secondary outcomes are summarized in Supplement. A significant effect was seen of the overall treatment modalities on the GPE score ($F(4,36) = 3.938$; $p = 0.009$). Bonferroni's post-hoc testing revealed that especially dilution of apomorphine resulted in a significant improvement of the GPE score, versus no treatment ($p = 0.046$). The other treatment modalities did not show significant differences. Also the nodule size decreased significantly after three days of treatment comparing the overall active treatments versus no treatment ($F(1.717,15.454) = 4.330$; $p = 0.0037$). Post-hoc testing revealed that only subcutaneous hydrocortisone improved the nodule size significantly, as compared to no treatment ($p = 0.030$), massage ($p = 0.006$) and dilution of apomorphine ($p = 0.039$).

However, the histopathology did not show any significant differences between the four treatment modalities as compared to no treatment. The biopsies of subcutaneous tissue after three days of treatment showed a florid infiltration of eosinophils in seven patients, irrespective the treatment mode (see Fig. 1). Additionally, fat necrosis was found in all patients. In three patients infiltration of lymphocytes and histiocytes without eosinophils was found, also not related to the treatment mode. The biopsies of subcutaneous tissue after fourteen days of treatment especially showed macrophages, loaded with melanin-like pigment (a breakdown product by auto-oxidation via ortho-quinones, see Fig. 1). The amount of pigment was not significantly different between treatment modalities. Additional findings were the presence of fibrosis in patients who had been treated with apomorphine before the start of this study (>1 month).

In conclusion, this small fixed-sequence crossover study with the control of multiple biopsies demonstrated that dilution of apomorphine subjectively improved patient satisfaction, while none of the other treatments significantly improved GPE scores. Because decreasing the

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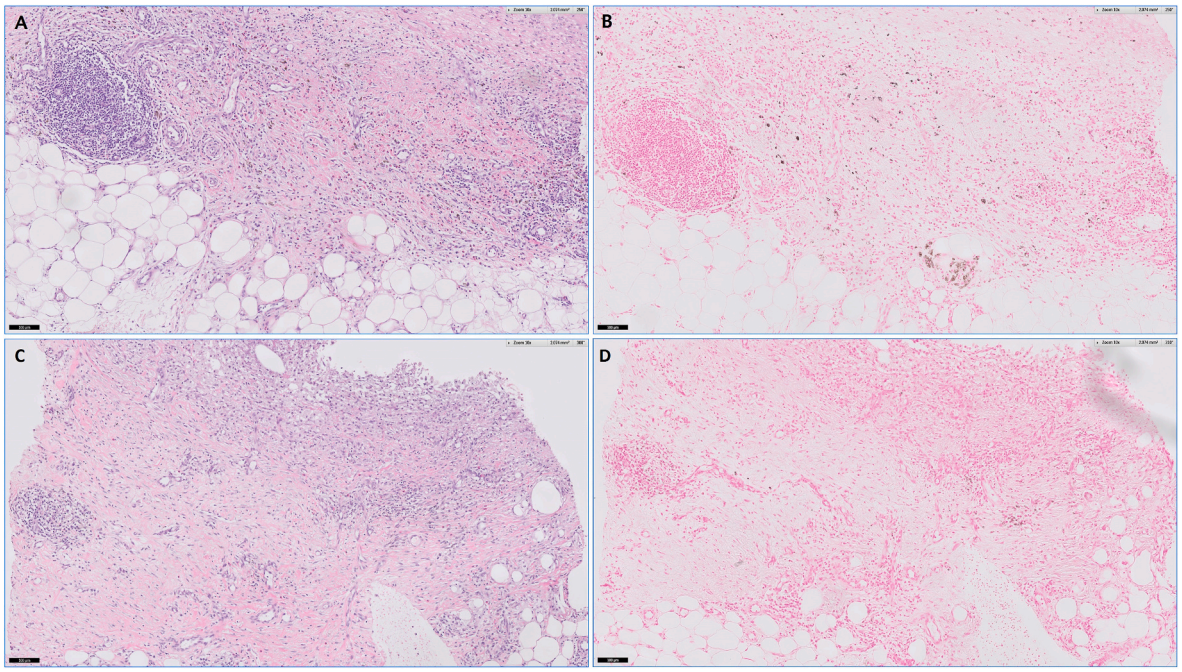


**Fig. 1.** Biopsy of a non-treated subcutaneous nodule three and fourteen days after infusion of apomorphine.
Description.
Fig. 1. Illustrative sections of a non-treated subcutaneous nodule three (a + b) and fourteen days (c + d) after infusion of apomorphine stained with hematoxylin-eosin (a + c) and Fontana-Masson to identify melanin-like pigment (b + d). Note the florid infiltration of lymphocytes and eosinophils together with fibrosis (a). After fourteen days of maturation, eosinophils have disappeared (c). In the Fontana-Masson stain (b + d), macrophages loaded with melanin-like pigment can be identified in brown (original magnification 10x).

apomorphine concentration had a good effect, even further lowering is conceivable, but at the cost of reloading apomorphine cartridges more frequently, which might be bothersome to patients and caregivers.

The objective outcome measures showed that subcutaneous hydrocortisone administered before the treatment, dramatically reduced nodules size after three days of treatment, compared to no treatment, massage and dilution of apomorphine. The effect of subcutaneous hydrocortisone is presumably related to the mode of administration, targeting the site were apomorphine is infused. Topical hydrocortisone, instead, did not improve patient satisfaction or nodule size. This is explained by the poor penetrance of topical hydrocortisone into the deeper subcutaneous layers [4].

Although PD nurses are always very positive about the effects of massage, this was not supported by our data.

A possible explanation for the lack of change in the biopsies, in contrast with the clinical observations, could be the formation of edema (by ortho-quinones) which is not visible in the biopsies. The formation of severe edema upon skin contact with ortho-quinones is well known in botany, in which poison ivy is most notorious [5]. The molecular structure of poison ivy is very similar to apomorphine, containing a catechol moiety with two hydroxyl groups, which can rapidly auto-oxidate, producing ortho-quinones [5].

Based on this study, clinical practice guidelines for the treatment of subcutaneous nodules related to apomorphine infusion should be adapted, stressing the importance of dilution of apomorphine and pre-treatment of subcutaneous hydrocortisone.

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## Author contributions

Conception and design of the study: all authors. Acquisition of data: RWKB and TvL. Analysis of biopsies: GFHD. Interpretation and analysis of data: all authors. Drafting the article: RWKB and TvL. All authors reviewed and approved the final manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.06.024.

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