Continuous perioperative apomorphine administration in deep brain stimulation (DBS) surgery for Parkinson’s disease

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Running Title: Apomorphine in DBS surgery
Abstract

Background

Patients with Parkinson’s disease and preoperative withdrawal of dopaminergic medication to facilitate awake testing are at increased risk of neurologic deterioration in the wake of DBS procedures. The aim of this survey was to demonstrate safety and efficacy in reduction of surgery related neurologic deterioration in patients undergoing deep brain stimulation surgery for Parkinson's disease by perioperative apomorphine treatment.

Methods

92 patients being subject to DBS surgery for PD in our department between 11/2007 and 10/2011 were analysed for this survey. Besides demographic data patients were analysed for apomorphine dosage, side-effects, complications and duration of hospitalization.

Results

72 out of 92 patients (78.3%) received apomorphine treatment; main reason for omission of treatment was intolerable nausea (16/92, 17.3%).

A significant difference in duration of hospitalization with a mean stay of 7.9 days (SD 4.5) in the apomorphine group versus 10.6 days (SD 2.7) in the control group (p=.015) was seen. Main reasons for prolonged stay were mainly confusion and therefore delayed mobilization.

Conclusions

Deprivation of dopaminergic medication can partly be held responsible for neurologic deterioration in PD patients receiving DBS procedures.

Apomorphine is a well adjustable and tolerated medicinal substitute in the perioperative setting. Neurological testing during electrode placement is not impaired and side effects are
mild. Our results indicate a reduction in perioperative neurologic deterioration and duration of hospitalization. We recommend perioperative apomorphine treatment for all Parkinsonian patients undergoing DBS surgery.
Introduction

Looking back on more than a decade of clinical experience deep brain stimulation has proven to be an effective and secure treatment in Parkinson’s disease (PD).

Intraoperative physiologic localization and especially awake macroelectrode test stimulation has been established to improve security and outcome in deep brain stimulation (DBS) surgery for PD and is routinely used in most centres[1]. As results of test stimulation are distorted by dopaminergic drugs these medication has to be withdrawn prior to surgery putting these patients at risk to suffer a variety of complications linked to drug withdrawal as well as the strenuous surgical procedure.

During this “off-phase” especially patients suffering from mainly akinetic-rigid symptoms are at risk to deteriorate worsening short-term outcome and frequently requiring postoperative intensive care monitoring. Additionally patients are at increased risk to develop post-surgery psychiatric disorders[2-6].

To overcome these issues in DBS surgery apomorphine is used in our department as a substitute for long-lasting Parkinsonian medication. Combining parenteral availability and short duration of effect apomorphine can be used perioperatively extenuating many of the effects linked with drug withdrawal.

Apomorphine is a non-selective dopamine receptor agonist which provides quick symptom relieve for PD symptoms when applied subcutaneously. Dose-response time median is 10.5 min (3-30 min). About 96% of apomorphine are metabolized and inactivated via hepatic pathways resulting in a half-life time median of only 61 min [7-11].

Subcutaneous application of apomorphine has shown to be reliable with little reduction of effectiveness in long-term administration [12].
Beside nausea, which is quite common, drowsiness, sedation, and arterial hypotension are known but rare systemic side effects. Adverse effects are mainly triggered by peripheral dopaminergic apomorphine effects and can be suppressed by domperidone, a purely peripheral dopamine receptor blocker [13, 14]. Local effects observed are painless skin nodules at the injection side. Long-term and high dose adverse effects include psychic alterations, hallucinations and sleep disorders and change in libido.

The aim of this survey was to demonstrate safety and efficacy in reduction of surgery related neurologic deterioration in perioperative apomorphine treated PD DBS patients.
Methods

92 consecutive patients being treated with DBS for Parkinson’s disease between 11/2007 and 10/2011 were retrospectively analysed for this survey. Indication for DBS surgery was conjointly put up by neurologists and neurosurgeons in synopsis of anamnestic, clinical and radiographic findings.

Perioperative apomorphine treatment of patients undergoing DBS for PD is constituted in intern treatment guidelines. Omission of treatment thereby had to be justified by intolerance or other significant medical reasons, including general anaesthesia for the electrode implantation procedure. Apomorphine treatment was included in written informed consent obtained from all patients. As apomorphine is approved medication in PD and the nature of this report is solely descriptive the necessity of an ethic approval was not seen.

Withdrawal of oral L-dopa and dopa-agonist medication was started 3 days prior to surgery, simultaneously apomorphine administration was started.

Medication was administered via an external pump system (Crono ApoGo, Licher Medizintechnologie, Wedemark, Germany). Subcutaneous injection site was the abdominal wall in all cases.

To avoid nausea supplemental domperidone was administered in advance at a dose of 30 mg daily (3x10mg) starting 4 to 5 days prior to surgery.

Starting base rate was 2.5 mg/h (flow delivery rate 0.5 ml/h at 5 mg/ml) in all patients. Dosage was individually increased or decreased based in clinical examination (range 0.3 – 1.0 ml/h basal rate). Testing of patient response to apomorphine withdrawal was tested one day preoperatively.

Stereotactic procedure

Squared stereotactic planning MR-imaging was conducted the day before surgery in all patients. Apomorphine application was halted 2 hours prior to incision during the preoperative
CT planning. All patients received local anaesthetic infiltration of the scalp. A shallow total intravenous anaesthesia was performed using sole infusion of propofol in all patients during placement of the stereotactic ring and burr hole placement. No endotracheal intubation was necessary during this part of surgery in our patient population. Those patients were excluded from the survey. Propofol infusion was stopped following burr-hole placement. Following placement of the stereotactic frame (Riechert-Mundinger®) a thin-cut 1mm native CT was conducted and fused to MRI using STP 3.0® software (Stryker-Leibinger®, Freiburg, Germany). This setting was replaced by a Elekta-System in the beginning of 2010 using a Leksell stereotactic frame and Leksell SurgiPlan® software. Target points were based on AC-PC line calculations and refined in T2-imaging. In all cases of this series microelectrode recording was used with respect to individual anatomy (Inomed MicroMacro® electrode, Inomed GmbH, Freiburg, Germany).

Final implantation site was chosen on the basis of microrecording and awake stimulation testing for motor symptoms and adverse side effects. Macroelectrodes (DBS Lead 3389 or 3387, Medtronic Inc., Minneapolis, MN, USA) were implanted under fluoroscopic control.

Following electrode placement apomorphine medication was resumed and general anaesthesia including endotracheal intubation was induced for stimulator implantation. Stimulator implantation site was chosen with regard to the patients´ habit. Stimulator activation was performed one day after surgery. Apomorphine treatment was abruptly terminated two to three days after surgery.

Patients´ condition was analysed regarding pre- and postoperative clinical status, apomorphine dosage, related complications and exigency of ICU admittance.

Statistical analysis was performed using IBM SPSS Statistics 19. Patients not being treated with apomorphine were used as control group in the t-test. Level of significance stipulated was 0.05.
Results

Based on personal experience of the senior author perioperative use of apomorphine in DBS for PD is implemented in department guidelines. Therefore all 92 patients being subject to DBS surgery for PD in our department between 11/2007 and 10/2011 were integrated in this survey.

72 out of 92 patients (78.3%) received apomorphine treatment; main reason for omission of treatment was intolerable nausea in 16 cases (16/92, 17.3 %), two patients suffering from tremor dominant PD were operated in ITN with no apomorphine, one patients refused apomorphine treatment, in one patient the reason of apomorphine omission was not determinable.

Gender distribution was predominantly male (60.9 vs. 39.1%), median age was 43.7 years (44.5-79.7, SD 7.2 y). Therapeutic targets varied depending on leading symptoms, STN was target point in 89, Gpi in two, Vim in one patient. Median pre surgery Hoehn and Yahr scale was 2.3 (range 1.0-4.0, SD 0.6).

Monitored shallow sedation using propofol at about 60 µg/kg/min has been used during stereotactic frame placement and patient transfer in 90 patients. Median apomorphine base rate was 2.6 mg/h (range 1.0-6.0 mg/h, SD 0.82) at a median delivery rate of 0.53 ml/h. Apomorphine concentration was 5mg/ml in all patients.

An overview on epidemiological and surgical data is given in table 1.

Nausea is known to be an intractable problem in apomorphine treatment. Despite forceful domperidone medication nausea remained the main reason of apomorphine treatment cessation in our patients. Treatment had to be stopped in 16 patients due to nausea and
vomiting, four patients did not receive apomorphine treatment as they had tremor dominant PD with only little akinesia, one patient refused medication due to aversion to medication application via the pump.

Mild psychic side effects with disorientation and agitation observed in 2 cases during the beginning of treatment spontaneously dissolved within hours, no reduction of apomorphine dosage was required.

In all patients eventually treated with apomorphine medication was well tolerated apart from mild skin irritations at the injection site.

T-test comparison revealed a significant difference in duration of hospitalization with a mean stay of 7.9 days (SD 4.5) in the apomorphine group versus 10.6 days (SD 2.7) in the control group (p=0.015, 95% CI 1.013-4.326). Main reasons given for prolonged stay were mainly confusion and hindered mobilization.

Postoperative intensive care management was required in two cases, one patient suffering a small intracerebral haemorrhage during electrode placement (diameter approx. 3x2x3 cm), one patient developing a pulmonary embolism with cardiac arrest during surgery. Both patients received apomorphine, both patients recovered completely. None of the patients investigated required intensive care treatment due to neurologic deterioration linked to dopaminergic medication deprivation in our survey.

No severe complications were seen associated with apomorphine treatment.
**Discussion**

Neurologic deficits and especially awareness disorders including confusion following anaesthesia are well known and frequent complications in PD patients[15-18] not only in DBS surgery. In this context apomorphine has already been described as a substitute for oral dopaminergic medication in patients undergoing abdominal surgery requiring long-term abstinence from food[19] and accordingly oral medication.

Postoperative observation at the IMC or the ICU is frequently required in PD patients undergoing DBS surgery, mostly due to aggravation of leading parkinsonism symptoms caused by intended or accidental medication withdrawal [18, 20, 21]. Accompanying cognitive and behavioural decline has been described in up to 5% of these cases, this rate might be higher in patients with preoperative cognitive dysfunctions [22, 23].

None of our patients, neither in the apomorphine nor in the control group did require ICU attendance due to neurologic deterioration linked with drug withdrawal. Two patients required ICU attendance for complications, one suffering from an ICH and one from a pulmonary embolism.

The pathophysiological background of neurologic deterioration in PD patients undergoing DBS is only partly understood, apparently involving deprivation of dopamine and its equivalents and interference of anaesthetics like GABA agonists and opioids [2, 5]. In a large series with 258 procedures analysing perioperative complications in anaesthesia for DBS severe neurologic complications directly related to dopaminergic withdrawal were reported to be 3.2% [24]. These complications have been identified to be the main reasons for delayed discharge in DBS surgery for PD followed by intracerebral haemorrhage [25]. This corresponds to our findings.

It is accepted that neurologic deterioration following DBS cannot solely be linked to dopaminergic deprivation and hence be alleviated by apomorphine treatment. The closely
connected complex of intracranial air, brain shift and CSF-loss, anaesthetic medication and of course brain penetration (microlesion effect) including minor traumatic subarachnoid haemorrhages are also likely to induce awareness deterioration and behavioural disorders [26].

Intraoperative microelectrode recording (MER) has been established in the past years to enhance electrode placement accuracy. MER was used in all patients in our study. No influence of perioperative apomorphine treatment was detected.

Side effects in apomorphine treatment were generally infrequent. Most commonly skin irritation with small subcutaneous nodules was seen at the injection site. Treatment was generally not required. The morphologic correlate is a nodular panniculitis[27]. Exacerbation can be effectively prevented by periodically changing injection site every two days. Additionally the injection site should be chosen away from planned stimulator implantation site to reduce the risk of IPG infections. Skin irritation typically resolves completely within one week after cessation of treatment.

Derived from these observations in perioperative application apomorphine treatment should further be taken into account for acute hardware failure in PD DBS patients. Acute hardware failure in long term PD DBS patients with severe parkinsonism should generally be considered an emergency as severe akinetic syndromes with insufficient breathing and loss of consciousness are described in the literature [3, 5, 28]. Apomorphine is especially useful if levodopa treatment, which is known to have reduced rapid effect in patients with chronic STN DBS, fails [5, 29].

We are well aware of the fact that retrospective reports like this naturally entail a number of limitations; especially randomization and specific long-term follow up. Our five year
experience with perioperative apomorphine administration is excellent justifying clinical trials to generate higher levels of evidence.
Conclusion

Patients with Parkinson’s disease and preoperative withdrawal of dopaminergic medication are at increased risk of neurologic deterioration in the wake of DBS procedures. Deprivation of dopaminergic medication can partly be held responsible for these complications. Apomorphine is a well adjustable and tolerated medicinal substitute in the perioperative setting. Neurological testing during electrode placement is not impaired and side effects are mild. Our results indicate a reduction in perioperative neurologic deterioration and duration of hospitalization. We recommend perioperative apomorphine treatment for all Parkinsonian patients undergoing DBS surgery.
Conflict of interest disclosure: None of the authors has any conflict of interest in the materials investigated.

Authors contributions:
PJS: Took part in data acquisition and performed the statistical analysis, wrote the final version of the manuscript
TMK: Took part in data acquisition, concept of the study and revision of the final manuscript
CW: Drafted the manuscript and took part in data acquisition
FN: Drafted and revised the manuscript with special focus on anaesthesiological issues
JV: Initiated and designed the study, final revision of the manuscript
All authors carefully read and approved this version of the manuscript.

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References:


Table 1: Synopsis of demographic and treatment data

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<td><strong>apomorphine treatment</strong></td>
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<td>20 (21.7 %)</td>
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<tr>
<td><strong>apomorphine rate</strong></td>
<td>median 2.6 mg/h, range 1-5 mg/h, SD 0.82 mg/h</td>
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<td><strong>anesthesia</strong></td>
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<td>general anaesthesia</td>
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<td>90 (97.8%)</td>
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<td><strong>target point</strong></td>
<td>Gpi</td>
<td>STN</td>
</tr>
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<td></td>
<td>2 (2.2%)</td>
<td>89 (96.7%)</td>
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<td>7 (7.6 %)</td>
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<td>56 (60.9 %)</td>
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<td>median 64.6 yrs, range 44.5-79.7 yrs, SD 7.2</td>
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**Image 1:** Specially designed device used for continuous apomorphine application

**Image 2:** Apomorphine pump in situ (Crono ApoGo, Licher, Germany)