Effect of cervical spinal cord stimulation on regional blood flow and oxygenation in advanced head and neck tumours

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Background: Tumour ischaemia leads to decreased delivery of oxygen, chemotherapy and radiosensitisers. Hypoxia in head and neck (H&N) tumours is an important adverse prognostic factor. Spinal cord stimulation (SCS) is a well-established neurosurgical technique in the treatment of several ischaemic syndromes. This prospective study evaluated the effect of cervical-SCS on common carotid artery (CCA) blood flow and tumour oxygenation in patients with advanced H&N cancer.

Patients and methods: Sixteen patients with advanced H&N tumours were enrolled. Cervical-SCS devices were inserted subcutaneously prior to commencement of scheduled chemoradiotherapy. Pre- and post-SCS measurements were as follows: (i) tumour oxygenation (mmHg) using polarographic probes; (ii) blood flow quantification (ml/min) and diastolic and systolic velocimetry (cm/s) in the CCA using colour Doppler.

Results: After SCS, median tumour oxygenation increased in two-thirds of patients (34%; \( P = 0.023 \)), all patients had improved CCA blood flow (50%; \( P < 0.001 \)) and almost all patients showed an increased CCA diastolic velocity (26%; \( P = 0.003 \)) and systolic velocity (20%; \( P = 0.011 \)).

Conclusions: Cervical-SCS increased tumour oxygenation and CCA blood flow, and could enhance the loco-regional delivery of oxygen, radiosensitising and chemotherapeutic drugs. Cervical-SCS as adjuvant in chemoradiotherapy of these tumours warrants further investigation.

Key words: blood flow, colour Doppler, head & neck cancer, spinal cord stimulation, transcranial Doppler, tumour oxygenation

Introduction

Tumour ischaemia leads to a compromised delivery of chemotherapy, radiosensitisers and oxygen. Tumour hypoxia is known to reduce, by up to 2.5–3 times, the effectiveness of radiation therapy [1] as well as certain drugs used in head and neck cancer [2]. Additionally, tumour hypoxia predisposes cancer cells to a physiological selection that encourages the increase in cellular variants that have lost their apoptotic potential (mutations of \( p53 \) or over-expression of the \( Bcl-2 \) genes) thus resulting in additional resistance to radiotherapy and chemotherapy [3].

In head and neck (H&N) tumours, oxygenation has been shown to be predictive of response to radiotherapy [4–6], and the polarographic probe technique has been accepted as the ‘gold standard’ for tumour pO2 measurement [7]. Improving tumour oxygenation can lead to better local control and increased overall survival rates following radiotherapy [8]. Such improvements would be highly desirable in patients with advanced H&N tumours. Similarly, promising clinical results have been described in which the lung oxygen uptake capacity has been increased using hyperbaric chambers [9] or carbogen breathing [10, 11] so as to enhance the radiation effect. However, these methods, if applied for >15–30 min, can lead to vasoconstriction secondary to hyperoxia. Only nicotinamide (usually combined with carbogen breathing) has been effective in improving tumour perfusion, although the initial gastrointestinal and renal side-effects associated with its use [12, 13] has lead to decreased dosage and appropriate co-medication being added.

Following its introduction in 1967, SCS has become a technique widely used in the treatment of ischaemic syndromes. These include vasospasm and peripheral vascular disease [14], and angina pectoris [15] as well as cancer-related pain [16]. However, there are no studies on the effect of cervical-SCS on tumour tissues, except our original results showing an increase of tumour pO2 [17] and loco-regional blood flow [18] in patients with high-grade gliomas.

The aim of this present prospective study was to assess the effect of cervical-SCS on tumour oxygenation and CCA blood flow in patients with advanced H&N cancer.
**Materials and methods**

**Patients**

Sixteen patients with advanced H&N cancer who were scheduled to undergo chemoradiotherapy participated in the present study. The experimental nature of the study was fully explained and written consent was obtained. The study had the full approval of the Institutional Ethical Committee.

The tumours were histologically confirmed and were not suitable for surgical resection. The patient group consisted of 15 males and one female with an age range of 40–70 years (mean, 57 years). On entering the study, a Karnofsky performance status >70% was required. The malignancies were advanced H&N tumours classified as T4 and/or with lymph nodes with diameter of ≥3 cm. The assessments of carotid blood flow and tumour oxygenation (without and with cervical-SCS) were performed before commencement of the scheduled treatment. Later, the cervical-SCS was performed during the course of the scheduled therapy consisting of hyperfractionated radiotherapy (120 cGy/fraction, two fractions/day) from a 60Co source, and daily chemotherapy with tegafur 800 mg (oral pro-drug of 5-fluorouracil). Table 1 summarises some of the most relevant clinical characteristics of the patients.

**Cervical spinal cord stimulation procedure**

Cervical-SCS was performed using a Medtronic system (Medtronic Neurological, Minneapolis, MN, USA). This equipment consists of a tetrapolar electrode attached to an impulse generator. The 1.27 mm diameter electrode is inserted percutaneously (under local anaesthesia) on to the posterior surface of the cervical spinal cord (at position C2–C4) in the epidural space (Figure 1) and slightly displaced towards the tumour side. An external (or a subcutaneous impulse generator) is attached to the electrode to provide an adjustable range of pulse widths, intensities and frequencies of stimulation. The correct positioning and function is verified by producing brief paraesthesia in the upper extremities under test stimulation. The parameters of the stimulator are set at an intensity of 1–3 V, pulse width of 0.2 ms and a pulse rate, usually, of between 80–100 Hz. After placement of the device, the SCS system is maintained 'off' until the moment of carrying-out the measurements. Initial Doppler or pO2 evaluations are with the SCS 'off'. The SCS is then turned 'on' and Doppler or pO2 evaluations are repeated. After each study (Doppler or pO2), SCS is switched 'off' until the next set of measurements are to be performed, or the patient’s scheduled treatment is administered. During treatment, cervical-SCS was connected approximately 20–30 min before each radiotherapy session and it was disconnected approximately 20–30 min after the conclusion of each radiotherapy session.

**Measurement of pO2**

Tumour oxygenation is measured using a polarographic probe system (pO2 Histograph; Helzel Medical Systems, Kaltenkirchen, Germany). Briefly, a 0.5 mm diameter electrode (0.3 mm diameter at the tip) is inserted into the
tumour under subcutaneous anaesthesia. The movement is computer controlled and consists of a 1 mm forward motion and a 0.3 mm backward motion to avoid causing tissue compression at the measurement site. A pO₂ value is obtained every 0.7 mm. A set of 150–200 individual pO₂ measurements are recorded, pre- and post-SCS, using at least six different electrode tracks.

The above measurements were carried out in 11 patients, without imaging technique guidance, on accessible, clinically palpable, lymph-node metastases with a volume of at least 30 cm³. In one patient, measurement was in a relapsed tumour of the sub-maxillary area. Tumour oxygenation was estimated for each patient as the median of all pO₂ values. The percentage of pO₂ values ≤5 and ≤2.5 mmHg were obtained from the pooled data for each individual; these values representing the proportion of the tumour which is most poorly oxygenated.

Carotid volume and blood-flow quantification

The technique used provides a quick and non-invasive evaluation of CCA blood flow with values expressed in millilitres per minute (ml/min). It is based on time-domain processing and is performed using a Colour Doppler Philips Ultrasound P-800 unit® (Philips Ultrasound DR5312 P-SD-800; Philips, CA, USA).

The absence of significant stenoses in the extra-cranial carotid arteries is confirmed with the patient alert, relaxed and supine. A 7.5 MHz linear high-definition probe with a Doppler angle <60° is used to obtain, on the tumour side, the volume of blood flow (ml/min) together with systolic and diastolic velocities (cm/s) in the CCA at least 2 cm before the carotid bifurcation. All the measurements are performed in each patient on the same day. When an optimal and stable flow image is obtained, recordings are made over at least three cardiac cycles. Each measurement is recorded at least three times so as to reduce inaccuracy. The median value from these measurements is used in the statistical analyses. All recordings were performed by the same radiologist in order to avoid inter-observer variability.

In two patients, CCA blood flow could not be evaluated due to technical difficulties.

Statistical analyses

The software package SPSS 7.0 for Windows (SPSS-Ibérica, Madrid, Spain) was used for all analyses. Blood flow and oxygen values pre- and post-SCS were compared using the two-sided paired t-test. Data are expressed as means ± SD. Correlation analysis was performed using Pearson’s r test. Values of P < 0.05 were considered statistically significant.

Results

pO₂ measurements

During cervical-SCS, mean tumour oxygenation increased by 34%, from 16.7 ± 3.6 to 22.3 ± 4.7 mmHg (P = 0.023; Figure 2). Before SCS, the percentage of values ≤5 and ≤2.5 mmHg were 28.7 ± 5.3% and 20.4 ± 5%, respectively, with no significant changes in the relative proportions following SCS. There were no statistically significant correlations between tumour oxygenation and tumour size or CCA blood flow. However, in the group of patients studied, haemoglobin concentrations correlated significantly with median pO₂ (r = 0.811; P = 0.002) and there was a trend towards an inverse correlation with the percentage of values ≤5 mmHg (r = −0.591; P = 0.055), but not with the percentage of values ≤2.5 mmHg.

Carotid volume blood flow quantification

Colour Doppler assessment following cervical-SCS administration showed a CCA blood flow increase in all patients. The individual percentage increase ranged from 6% to 108% (median, 46%; mean, 53 ± 10%). In the overall study group, CCA blood flow increased 50%, from 238 ± 20 to 357 ± 28 ml/min (P <0.001;
and 64 Gy in these two patients, respectively. The radiotherapy that had been delivered up to this point was incomplete. This was because the connection to the electrical apparatus was removed before completion of the planned treatment.

In two patients with external impulse generators (temporary devices) the SCS were occasional and transient upper limb paraesthesia. In two patients with H&N cancer [9–11], there appear to be some limitations due to a vasoconstriction effect. For this reason, carbogen breathing is usually combined with nicotinamide as a vasoactive agent.

SCS is a technique that has been validated in the treatment of ischaemic syndromes in non-cancer tissues. To the best of our knowledge, the present study is the first to report the effects of cervical-SCS on blood flow and oxygenation in H&N tumours.

All patients in this study showed a CCA blood flow increase within a few minutes of commencing cervical-SCS; the mean increase was ~50%. This remarkable level of blood-flow increase during cervical-SCS has been described previously in CCA in animal models [23] and is similar to that found in patients with high-grade gliomas [18]. This finding suggests a rapid and consistent effect that augers well for a potential clinical application during chemoradiotherapy of tumours receiving their blood supply from this artery.

We have not, as yet, been able to establish the timing of maximal effect of tumour oxygenation following the initiation of cervical-SCS. In the present study, post-SCS evaluation using Doppler was started immediately after connection of the electrodes for the SCS. The tumour pO2 measurements were started about 5–15 min after SCS connection, when the polarographic device was ready to begin the measurements. An additional 10–20 min were spent for each Doppler or pO2 measurement procedure. However, our previous experiences with photoplethysmography and contact thermography techniques in non-cancer patients [14] and contact thermography in two previous cancer patients showed higher effect 1 h later. This time-scale may be equivalent for the present situation but further studies will need to be conducted in order to establish the most appropriate schedule for cervical-SCS activation.

SCS has a low morbidity rate [16]. The present study showed that cervical-SCS could be performed safely in selected patients with advanced H&N tumours. Also, it was possible to incorporate this technique within a scheduled chemoradiotherapy programme. The effects of cervical-SCS are quite selective for brain, head & neck and upper limbs. SCS has a segmental vascular effect, depending on the part of the spinal cord receiving the stimulus and, as such, there are fewer systemic side-effects than might be encountered when using vasoactive drugs. For example, a systemic vasodilatation with an associated potential decrease in blood pressure and ‘steal effect’ can be avoided. Furthermore, SCS is a reversible procedure that can be ‘switched-on/switched-off’ at any time, and it can be activated as and when required according to the patient’s chemotherapy or radiotherapy schedule.

The vascular effect of SCS is mediated by sympatholytic mechanisms, with a segmental liberation of vasoactive substances and the activation of vasomotor centres in the brain stem [14, 24]. This can lead to increased blood flow secondary to decreases in peripheral vascular resistance. The diastolic velocity increase observed in the present study would seem to support this explanation. Our hypothesis is that this vascular effect of SCS can influence the tumour vasculature and result in an increase in tumour blood flow. Previous studies by this group using single photon emission computed tomography (SPECT) in brain tumours [18] also appear to support this reasoning. While the exact mechanism has not yet been elucidated, it may involve the alteration of blood flow.

**Figure 3.** Blood-flow quantification in CCA. Blood flow (in ml/min) in CCA on the tumour side pre- and post-SCS. All patients showed improvements in CCA blood flow with a mean increase of 50% over pre-SCS values (P < 0.001).

Diastolic velocity increased 26%, from 12.5 ± 1.4 to 15.8 ± 1.7 cm/s (P = 0.003) and systolic velocity increased 20%, from 52.9 ± 4.4 to 63.4 ± 4.4 cm/s (P = 0.011). There were no statistically significant correlations between CCA parameters and haemoglobin concentrations, tumour size or tumour oxygenation.

The adverse effects observed in relation to the use of cervical-SCS were occasional and transient upper limb paraesthesia. In two patients with external impulse generators (temporary devices) the electrode was removed before completion of the planned treatment. This was because the connection to the electrical apparatus had broken off while the procedure was being conducted in patient 12, and in patient 14 because the electrode had become displaced. The radiotherapy that had been delivered up to this point was 52 and 64 Gy in these two patients, respectively.

**Discussion**

Tumour hypoxia, as assessed by polarographic probes, is an adverse prognostic factor for response to radiotherapy in patients with H&N carcinomas [4–6]. Additionally, anaemia has an adverse effect in these tumours [19] and a relationship has been described between low concentrations of haemoglobin and tumour hypoxia in such patients [20, 21]. Blood transfusions and, more recently, erythropoietin administration have been used to improve a decrease in oxygen-carrying capacity. However, these methods are principally advocated in anaemic patients since an excessive increase in haemoglobin concentrations could be counter productive due to increases in blood viscosity and peripheral blood vessel resistance with further blood flow decrease [22].

Investigation of techniques aimed at improving tumour oxygenation have focused mainly on the use of hyperbaric chambers and carbogen breathing. These methods act by increasing the oxygen uptake in the lungs. However, although clinical improvements have been demonstrated in H&N cancer [9–11], there appear to be some limitations due to a vasoconstriction effect. For this reason,
flow in pre-existing host vessels which have been incorporated into the tumour or, alternatively, the absence of appropriate self-regulation in tumour vessels [25] could preclude opposition to local blood-flow increases produced by SCS.

Measurements using polarographic probes have indicated increases in tumour pO2 with carbogen breathing [26] and hyperbaric chambers [27]. These procedures increase arterial blood pO2. However, arterial hyperoxia beyond a period of 15–30 min can lead to an increase in peripheral vascular resistance and a general vasoconstriction in most organs [28], as well as in tumour tissue [26]. Additionally, it has been suggested that the vasoconstriction occurring upon hyperoxia could be sympathetic mediated [29]. In the advanced H&N tumours investigated in the present study (mean node-size >5.5 cm) cervical-SCS increased oxygenation by 34%, but there was not a significant modification of hypoxic fraction. Certainly this percentage of increase is modest when compared with other hyperoxia-modifying techniques, such as carbogen breathing. However, these techniques show an early vasoconstriction effect (beyond the 15–20 min period) that is not evident with cervical-SCS. As such, cervical-SCS offers a benefit over a more protracted period of time and which would be valuable if more complicated radiotherapy schedules are contemplated (such as brachytherapy) and for increasing oxygen-dependent effects of chemotherapy (as in the case of carboplatin). Considering the above mentioned vasoactive and sympatholytic effects, the results augur well for the use of cervical-SCS in combination with carbogen breathing or hyperbaric chambers. Indeed, our measurements of P02 in patients with advanced H&N cancer undergoing cervical-SCS treatment in conjunction with carbogen breathing appear to support this possibility (unpublished data, B. Clavo, F. Robaina et al.). However, because of the limited number of patients enrolled, some of the findings in this study do need to be viewed with caution. A linear correlation between haemoglobin levels and basal tumour oxygenation was found. However, other studies in our institution with a larger number of patients have shown this correlation to be non-linear [21]; a finding which is in accordance with other clinical data [20], as well as with experimental [22] and theoretical [30] models.

On the basis of the present data, further studies are warranted and which should include a greater number of patients and/or additional techniques to verify fluctuations in tumour perfusion during SCS.

In conclusion, the present study in H&N tumours showed CCA blood-flow improvement following the application of cervical-SCS. This regional blood flow increase could improve loco-regional delivery of oxygen (as indicated in the present study), radiosensitising agents and chemotherapeutic drugs. The potential usefulness of cervical-SCS as an adjuvant in chemoradiotherapy for H&N tumours merits further investigation.

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References


